

# Liposomal Amphotericin B: A Cost-Outcome Analysis

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## ABSTRACT

*Our objective in this study was to conduct a cost-outcome analysis of the use of liposomal amphotericin B in our institution, which is a tertiary care, adult, university-affiliated hospital. A retrospective review was carried out on 11 patients treated with liposomal amphotericin B. Criteria for use of liposomal amphotericin B were developed and implemented at our institution. Information collected included results of fungal cultures, reasons for use of liposomal amphotericin B, use of other antifungal agents, duration of therapy, total dose administered, clinical response and outcome, and acquisition cost. Four patients met the criteria for appropriate use of liposomal amphotericin B but only one of these patients survived. The total acquisition cost of using liposomal amphotericin B in the 11 patients was \$ 171,900. We conclude that the use of liposomal amphotericin B should be carefully controlled. The therapeutic role of this agent will only be defined when the results of randomized, controlled clinical trials, including pharmacoeconomic analysis, are available.*

**Key Words:** Amphotericin B, pharmacoeconomics  
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## RÉSUMÉ

*L'objectif de l'étude était d'analyser les coûts relatifs à l'utilisation de l'amphotéricine B liposomique à l'établissement, soit un hôpital universitaire de soins tertiaires pour adultes. L'analyse rétrospective a été effectuée sur 11 patients qui avaient reçu le médicament. On a élaboré des critères applicables à l'administration du produit, qui ont ensuite été respectés à l'établissement. Les renseignements recueillis comprenaient les résultats des cultures de champignons, les raisons concernant l'usage de l'amphotéricine B liposomique, l'utilisation d'autres antifongiques, la durée du traitement, la dose totale administrée, la réponse et l'issue cliniques et le coût du produit. Les critères justifiant l'emploi de l'amphotéricine B liposomique ont été respectés pour quatre malades, mais un seul a survécu. Le coût total de l'utilisation de l'amphotéricine B liposomique pour les 11 malades s'est établi à 171 900 \$. On en conclut qu'il faudrait contrôler soigneusement l'usage du médicament. Son rôle thérapeutique ne pourra être précisé que lorsqu'on connaîtra les résultats d'essais cliniques randomisés avec témoins et d'une analyse pharmacoéconomique.*

**Mots-clés:** amphotéricine B, pharmacoéconomique

## INTRODUCTION

The successful treatment of systemic fungal infections remains a considerable challenge because few antifungal agents are available and there is an increased incidence of these infections in immunocompromised patients. Amphotericin B has long been established as the "gold standard" of therapy for many fungal infections, but its utility is limited by a high incidence of significant adverse reactions such as nephrotoxicity and infusion-related reactions.<sup>1</sup> Less toxic antifungal agents such as fluconazole and itraconazole have been introduced but the

efficacy of these agents in the treatment of fungemia and in immunosuppressed patients is not well established.

In an effort to improve upon the established efficacy and diminish the toxicity of amphotericin B, a liposomal preparation has been developed.<sup>2</sup> Liposomal amphotericin B, which is currently an investigational drug in Canada, is available for the treatment of severe systemic fungal infections in patients who are unresponsive to or intolerant of conventional amphotericin B. The use of liposomal amphotericin B is limited by its cost (\$300/50 mg

vial) which is approximately nine times the cost of conventional amphotericin B. As total doses typically range from one to three grams<sup>3,4,5</sup>, the cost of using liposomal amphotericin B is considerable.

Published data on the efficacy of liposomal amphotericin B are limited to relatively small, uncontrolled studies that generally support the contention that liposomal amphotericin B provides better tolerability and/or improved efficacy compared with conventional amphotericin B.<sup>3,4,5</sup> However, one must be cautious in interpreting these data, as prelim-

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inary reports on new drugs generally tend to be positive and may overstate their role in therapy. Given the high cost of liposomal amphotericin B, our objectives were to review our experience with this agent with respect to outcome and acquisition costs.

## METHODS

All patients who received liposomal amphotericin B at the Ottawa General Hospital from September 1991 to October 1992 were included in the analysis. Patients' charts were retrospectively reviewed to obtain the following information: age, sex, underlying diagnosis, other relevant medical problems, results of fungal cultures, other antifungal drugs used, stated reason for use of liposomal amphotericin B, duration of therapy with liposomal amphotericin B, total dose administered, response of the infection and if the patient survived. The total acquisition cost of liposomal amphotericin B was calculated.

Based on our experience with the first six cases in this report, criteria for the appropriate use of liposomal amphotericin B were developed by our Subcommittee on Antibiotics and Cytokines and approved by the Medical Advisory Committee of the hospital (Table I). All cases were evaluated to determine if they met these criteria.

## RESULTS

Eleven patients were treated with liposomal amphotericin B during the period studied. There were seven males and four females ranging in age from 30 to 75 years of age. Brief summaries of the cases follow.

### Case 1

A 31 year-old female received an autologous bone marrow transplant for nonresponsive Hodgkins disease. The patient became febrile while neutropenic and blood cultures were

positive for *Candida albicans*. The blood cultures remained positive despite nine days of therapy with conventional amphotericin B. Therapy was subsequently changed to liposomal amphotericin B and the patient received a total dose of 3925 mg over 31 days. Although further blood cultures were negative, the patient developed a relapse of Hodgkin's disease, Cytomegalovirus pneumonitis, multi-organ failure and the patient's clinical condition deteriorated. All therapy was discontinued and the patient died shortly thereafter.

### Case 2

A 42 year-old male became febrile while neutropenic following chemotherapy for acute myelogenous leukemia. Blood cultures grew *Torulopsis glabrata* and *Candida krusei* and the patient was started on conventional amphotericin B. After three days of therapy the serum creatinine had increased from 111 to 159  $\mu\text{mol/L}$  whereupon the patient was switched to liposomal amphotericin B for seven days during which time the serum creatinine normalized. Conventional amphotericin B was reinstated for an additional 15 days of therapy

without a significant increase in serum creatinine. The fungemia was clinically and microbiologically cured and the patient was discharged from hospital.

### Case 3

A 41 year-old female, with a history of non-Hodgkins lymphoma refractory to chemotherapy, developed fever and oropharyngeal candidiasis while neutropenic following an autologous bone marrow transplant. After five days of conventional amphotericin B, the creatinine had increased from 97 to 206  $\mu\text{mol/L}$ . Therapy was switched to liposomal amphotericin B and the patient received a total dose of 615 mg over the following six days during which the serum creatinine continued to rise and the patient became dialysis- and ventilator-dependent. All therapy was then withdrawn and the patient died the following day.

### Case 4

A 44 year-old female became febrile while neutropenic following chemotherapy for acute myeloblastic leukemia. A nasal swab grew *Aspergillus fumigatus* and the patient was started on conventional

**Table I: Criteria for Appropriate Use of Liposomal Amphotericin B at Ottawa General Hospital.**

Restricted to the Division of Infectious diseases for patients in whom the continued use of amphotericin B is desirable but the patient has:	
1.	Persistence or progression of proven systemic fungal infection despite an adequate trial of conventional amphotericin B of at least two weeks at a dose of 0.5 - 2mg/kg/day.
	OR
2.	Evidence of rapidly deteriorating renal function occurring while receiving conventional amphotericin B. (This is defined as a doubling of pre-therapy serum creatinine and a serum creatinine of at least 250 $\mu\text{mol/L}$ ).
	OR
3.	Patients with severe hypersensitivity reactions to conventional amphotericin B, not preventable by adjunctive therapy.
	AND
4.	Patients who are not candidates for fluconazole therapy.

amphotericin B. After three days of therapy the creatinine had increased from 60 to 138  $\mu\text{mol/L}$  and the patient was switched to liposomal amphotericin B and received a total dose of 1800 mg over 12 days. The patient recovered and was discharged from hospital. She was readmitted for further chemotherapy and again developed neutropenia and fever that did not respond to 10 days of broad spectrum antibiotics. Although the creatinine was within normal limits, liposomal amphotericin B was initiated empirically and continued for 15 days to a total dose of 1500 mg. The patient remained febrile throughout treatment and all anti-infectives were discontinued when the neutropenia resolved. The patient was discharged from hospital.

#### Case 5

A 30 year-old male had an allogeneic bone marrow transplant for aplastic anemia. The patient became febrile while neutropenic and the fever persisted despite broad spectrum antibiotics. All cultures were negative. Conventional amphotericin B was initiated and continued for six days. Although the creatinine had not increased, there were concerns of additive nephrotoxicity with other drugs (acyclovir, cyclosporin, vancomycin) and the patient was switched to liposomal amphotericin B which was continued for 15 days to a total dose of 2250 mg. The patient's clinical condition improved and the liposomal amphotericin B was discontinued. However, the patient subsequently developed graft versus host disease with multiple complications which ultimately proved fatal two months after discontinuation of liposomal amphotericin B.

#### Case 6

A 47 year-old male developed a fever while neutropenic following

chemotherapy for chronic lymphocytic leukemia. All cultures were negative. As the patient did not respond to broad spectrum antibiotics and the creatinine was 185  $\mu\text{mol/L}$  the decision was made to start liposomal amphotericin B. This was only given for three days to a total of 60 mg. The patient recovered and was discharged from hospital.

#### Case 7

A 40 year-old male infected with human immunodeficiency virus (HIV) complicated by severe oral candidiasis was unresponsive to several weeks of initial therapy with fluconazole and then conventional amphotericin B. Liposomal amphotericin B was initiated and continued for 49 days to a total dose of 2010 mg. Renal function was normal throughout therapy. The candidiasis was clinically cured.

#### Case 8

A 30 year-old male became febrile while neutropenic following chemotherapy for promyelocytic leukemia. A CT scan revealed possible multiple hepatic abscesses and a liver biopsy confirmed the presence of *Candida* species. The patient received conventional amphotericin B for 16 days. Due to a lack of clinical response as evidenced by persistent fever, the patient was switched to liposomal amphotericin B which continued for 56 days to a total dose of 9100 mg. Nonetheless, the patient remained symptomatic and a follow-up CT scan was consistent with hepatic abscesses. The patient died from complications of his underlying disease one and a half months after discontinuing liposomal amphotericin B.

#### Case 9

A 75 year-old female developed a recto-vaginal fistula following a

bowel resection. Blood cultures grew *Candida albicans* and the patient was started on conventional amphotericin B. The creatinine rose from 156 to 231  $\mu\text{mol/L}$  after seven days of amphotericin B and the patient was switched to liposomal amphotericin B. The patient only received one dose of 100 mg before she died.

#### Case 10

A 39 year-old male with late stage HIV infection complicated by severe esophageal candidiasis was unresponsive to treatment with fluconazole and conventional amphotericin B. The patient was switched to liposomal amphotericin B and received a total dose of 3600 mg over 18 days before his death.

#### Case 11

A 52 year-old male sustained multiple injuries in a motor vehicle accident. During the patient's stay in the intensive care unit, cultures from bronchial washings grew *Candida tropicalis* and blood cultures grew *Candida parapsilos* and the patient was started on conventional amphotericin B. After five days of conventional amphotericin B the creatinine had risen from 128  $\mu\text{mol/L}$  to 381  $\mu\text{mol/L}$  and the patient was switched to liposomal amphotericin B. The patient received 11 days of therapy to a total dose of 2100 mg before his death due to multi-organ failure.

A summary of the cost and outcomes for patients administered liposomal amphotericin B is presented in Table II. Analysis of these cases revealed that four (Cases 7,8,10,11) met our institution's criteria for use outlined in Table I. Of these four patients, only one (Case 7) survived. The total drug acquisition costs for liposomal amphotericin B were \$12,060 in this patient compared to a total of \$71,040 for patients who

**Table II. Summary of Patient Outcomes and Cost of Therapy**

Patient	Met Criteria for Use?	Cost of Therapy (\$)	Outcome
1	No	23,550	Died
2	No	6,300	Survived
3	No	3,690	Died
4	No	19,800	Survived
5	No	13,500	Died
6	No	3,600	Survived
7	Yes	12,060	Survived
8	Yes	54,600	Died
9	No	600	Died
10	Yes	21,600	Died
11	Yes	12,600	Died
		<b>TOTAL \$171,900</b>	

did not meet our criteria for use, and \$88,800 for patients who met the criteria for use but still had a negative survival outcome.

## DISCUSSION

Our experience with the use of liposomal amphotericin B highlights the problems associated with using a new, expensive drug whose place in therapy has not yet been defined by either properly controlled clinical studies nor pharmacoeconomic evaluations.

The initial reports of the utility of new drugs are typically in the form of uncontrolled observations that tend to reflect favourably on the drug's potential. This may be because clinicians are more likely to report therapeutic success than failures, pharmaceutical manufacturers are more likely to encourage publication or presentation of favourable results, and medical journals may be more likely to publish therapeutic advances as opposed to relative failures.<sup>6,7</sup> As a result of this phenomenon, a new drug that has not yet been scrutinized through properly designed clinical trials can establish a favourable reputation and a place in some practitioners' therapeutic approach. In the case of liposomal amphotericin B and other drugs which are sold to institutions as investigational drugs on the Emergency Drug Release Program

prior to gaining regulatory approval to market, this can have considerable cost implications to hospitals.

Our initial experience with the first six patients reported in this series, caused us to examine the rationale of allowing liposomal amphotericin B to be utilized in our institution without specific criteria or restrictions. However, even with the criteria in place, the potential value of using liposomal amphotericin B must be weighed against the high cost of its use and the lack of data on its relative efficacy compared to conventional amphotericin B. It is possible that our criteria select out the most severely ill patients who are likely to have a high mortality rate regardless of which antifungal therapy is used. Conversely, liberalization of the criteria may lead to use in patients that could be more cost-effectively treated with conventional amphotericin B or triazoles.

The acquisition cost of liposomal amphotericin B in the 11 patients in our study was \$171,900 which is \$152,315 more than the cost of the equivalent amount of conventional amphotericin B. The actual benefit of using liposomal amphotericin B in these patients is not known. Given our experience with this drug, a case could be made to develop criteria for use

of all new, expensive drugs before their use is allowed within the institution.

Our study was not designed to thoroughly evaluate the clinical utility of liposomal amphotericin B, and this agent may well represent a significant advance in antifungal therapy. Four patients in our series survived and it is possible that liposomal amphotericin B contributed to their positive outcome.

Additionally, liposomal amphotericin B appeared to be well tolerated as we did not observe any significant nephrotoxicity or hypersensitivity reactions. The clinical efficacy of liposomal amphotericin B, as assessed by response rate of the infection, morbidity and mortality, will only be known when the results of controlled clinical trials are available.

Our study does raise the question, however, whether or not the extremely high cost of this agent is justified. A recent controlled, randomized trial has reported that conventional amphotericin B mixed with lipid emulsion 20% is less toxic than amphotericin B diluted with dextrose.<sup>8</sup> If the clinical efficacy of such a therapy can be demonstrated, it would likely prove to be a more cost-effective approach than liposomal amphotericin B.

Our study was also uncontrolled and was not a cost-effectiveness study. Therefore, we cannot precisely define the place of liposomal amphotericin B in the treatment of serious fungal infections. The ultimate value of liposomal amphotericin B will only be known when the results of well-designed, comparative studies to evaluate the cost-effectiveness and place in therapy of liposomal amphotericin B are

available. Until that time we would encourage physicians and pharmacists to carefully evaluate their utilization of this agent. ☒

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