

Pharmacoeconomic Analysis of Liposomal Amphotericin B Versus Conventional Amphotericin B in the Empirical Treatment of Persistently Febrile Neutropenic Patients

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Purpose: In a randomized, double-blind, comparative, multicenter trial, liposomal amphotericin B was equivalent to conventional amphotericin B for empirical antifungal therapy in febrile neutropenic patients, using a composite end point, but was more effective in reducing proven emergent fungal infections, infusion-related toxicities, and nephrotoxicity. The purpose of this study was to compare the pharmacoeconomics of liposomal versus conventional therapy.

Patients and Methods: Itemized hospital billing data were collected on 414 patients from 19 of the 32 centers that participated in the trial. Hospital length of stay and costs from the first dose of study medication to the time of hospital discharge were assessed.

Results: Hospital costs from the time of first dose to discharge were significantly higher for all patients who received liposomal amphotericin B (\$48,962 v

\$43,183; $P = .022$). However, hospital costs were highly sensitive to the cost of study medication (\$39,648 v \$43,048 when drug costs were not included; $P = .416$). Using decision analysis models and sensitivity analyses to vary the cost of study medications and the risk of nephrotoxicity, the break-even points for the cost of liposomal therapy were calculated to range from \$72 to \$87 per 50 mg for all patients and \$83 to \$112 per 50 mg in allogeneic bone marrow transplant patients.

Conclusion: The cost of liposomal amphotericin B and patient risk for developing nephrotoxicity play large roles in determining whether liposomal amphotericin B is cost-effective as first-line empirical therapy in persistently febrile neutropenic patients.

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A RANDOMIZED, DOUBLE-blind, multicenter trial that compared liposomal amphotericin B (AmBisome; NeXstar Pharmaceuticals, Boulder, CO, and Fuji-

sawa Healthcare, Deerfield, IL) with conventional amphotericin B demonstrated that liposomal amphotericin B is as effective as conventional amphotericin B, when measured by a composite efficacy end point, but is more effective in reducing proven invasive fungal infection and infusion-related toxicity.¹ However, because the acquisition cost of liposomal amphotericin B is substantially higher than that of conventional amphotericin B, the economic value of liposomal amphotericin B for first-line empirical antifungal therapy is controversial. Therefore, a retrospective pharmacoeconomic analysis from the hospital perspective was performed of patients enrolled onto the multicenter, randomized study in order to compare the hospital costs of treating patients with liposomal amphotericin B and conventional therapy. Nineteen of the original 32 centers who participated in the multicenter study provided data for this study. Hospital billing data for 414 (60%) of 687 patients evaluated in the clinical study were obtained.

PATIENTS AND METHODS

Patient Population and Study Outcomes

Between January 1995 and May 1996, 687 patients were treated in a randomized, double-blind, multicenter study of liposomal amphotericin B versus conventional amphotericin B at 32 centers in the United States. Enrolled patients were required to have received chemotherapy and at least 5 days of broad-spectrum empirical antibacterial therapy while remaining febrile and neutropenic (absolute neutrophil count < 500). Exclusion criteria included uncontrolled bacteremia or docu-

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mented fungal infection, use of any form of parenteral amphotericin B within 10 days before the administration of the study drug, serum hepatic transaminase or alkaline phosphatase level more than 10 times the upper limit of normal (ULN), total bilirubin concentration higher than 3 mg/dL (if the transaminase level was > twice the ULN) or higher than 5 mg/dL (if the transaminase level was < twice the ULN), serum creatinine level more than twice the ULN, or a history of anaphylactic reaction to amphotericin B. Patients were initially to be treated either with conventional therapy at 0.6 mg/kg/d or liposomal amphotericin B at 3.0 mg/kg/d. To reflect clinical practice patterns, investigators were allowed to adjust the dose of the study drug for evidence of infection or toxicity. The mean duration of therapy for all patients treated in the study was 10.8 days for liposomal amphotericin B and 10.3 days for conventional therapy.

The success rate, as evaluated by a composite end point, was equivalent. However, there were fewer proven breakthrough fungal infections in patients treated with liposomal amphotericin B versus conventional therapy. There also were fewer infusion-related fevers, chills/rigors, and cardiorespiratory events in patients treated with liposomal amphotericin B.

The incidence of nephrotoxicity (defined as a doubling of baseline creatinine level and > 1.2 mg/dL creatinine in adults) was significantly lower across all patients treated with liposomal amphotericin B (64 of 343 patients), compared with conventional therapy (116 of 344 patients; *P* < .001). The incidence of renal toxicity was also lower in allogeneic bone marrow transplant (BMT) patients treated with the liposomal drug (17 of 52 patients), compared with conventional therapy (33 of 50 patients; *P* = .001).²

Data Collection and Hospital-Cost Calculations

Because hospital length of stay (LOS) and costs were not prospectively defined end points in the clinical study, a retrospective pharmacoeconomic analysis was conducted from the hospital perspective. Hospital billing data corresponding to hospital admissions during which patients received empirical antifungal therapy with the study medication were collected. Data collection was initiated before the results of the clinical study were revealed.

All 32 participating centers that enrolled patients onto the clinical study were invited to submit detailed hospital billing data for corresponding episodes of care. Nineteen of the 32 centers provided hospital billing data for pharmacoeconomic analysis. These 19 institutions enrolled a total of 429 patients, for whom 414 patient hospital bills (96.5%) were obtained. Fifteen billing records from the 19 centers were not available because participating institutions had archived patient files.

The remaining 13 centers did not participate in the pharmacoeconomic study. Two centers did not participate because hospital billing data were not generated by the hospital (for example, as in government institutions). Eleven centers were unable to provide billing data for administrative reasons.

Data on service items, dates of service, units of service, American Hospital Association departmental revenue codes, and hospital charges per service were abstracted from detailed itemized hospital bills from each of the 414 patient records. Hospital charges were converted to costs by using each hospital's ratio of cost to charges contained in each hospital's Medicare Cost Report or other hospital-specific cost accounting report. Departmental ratios of cost to charges were not available from all institutions and, therefore, were not utilized in the analysis. All hospital costs were adjusted to May 1996 dollars, using the hospital and

Table 1. Characteristics of Patients in Cost-Study Sample, by Treatment Group

Patient Demographics	Liposomal Amphotericin B (n = 206)		Conventional Amphotericin B (n = 208)	
	No.	%	No.	%
Mean age, years	40.4		41.7	
Sex, male	99	48	110	53
Stratification				
High risk	59	29	55	26
Low risk	147	71	153	74
Bone marrow transplantation	103	50	110	53
Autologous BMT	75	73	82	75
Allogeneic BMT	28	27	28	25

related-services component of the Consumer Price Index (Bureau of Labor Statistics, Washington, DC).

The analyses were limited to hospital LOS and costs from the start of study medication to the time of hospital discharge. This allowed a focused analysis of the costs associated with empirical therapy, as well as of the sequelae associated with treatment during the inpatient hospital stay. The costs of providing second-line therapy because of treatment failure or premature discontinuation of treatment with the study drug were included in hospital bills and incorporated into the analysis. Data on physician fees and consultations, outpatient follow-up care, and subsequent hospitalizations were not monitored as part of this study.

During the clinical study, study drugs were provided without cost to study participants. Therefore, these costs were added separately. The cost of study drug was calculated by multiplying the total dose per course of treatment by the average wholesale price (AWP) for that drug, as listed in the *Red Book* (Medical Economics Company, Montvale, NJ).

Statistical Analyses

Descriptive statistics are presented as percentages for discrete variables and means, SDs, and 95% confidence intervals for continuous

Table 2. Study-Drug Dosing and Cost Calculations

Group/Factor	Liposomal Amphotericin B (n = 206)	Conventional Amphotericin B (n = 208)
All patients		
Mean duration of therapy, days*	11.2	10.1
Total dose per course of treatment, mg*	2,472	409
Cost of drug per 50 mg vial, \$†	188.40	16.60
Mean cost per course of treatment, \$‡	9,315	136
Allogeneic BMT patients		
Mean duration of therapy, days*	14.0	10.1
Total dose per course of treatment, mg*	2,720	380
Cost of drug per 50 mg vial, \$†	188.40	16.60
Mean cost per course of treatment, \$‡	10,248	126

*Based on treatment duration and total dose for patients in the cost-study sample.

†Based on average wholesale price.

‡Cost per course = total dose × drug cost.

Table 3. Hospital LOS and Costs, by Treatment Group

Time Period/Factor	Liposomal Amphotericin B* (n = 206)	95% CI	Conventional Amphotericin B* (n = 208)	95% CI
Total hospitalization				
Total hospital length of stay, days	32.1 ± 14.9	30.0-34.1	32.5 ± 15.9	30.3-34.7
Total hospital costs, \$	82,075 ± 48,560	75,444-88,707	77,496 ± 53,378	70,242-84,750
Total hospital costs, excluding study drug, \$	72,761 ± 45,693	66,521-79,001	77,360 ± 53,319	70,114-84,606
From start of therapy to time of discharge				
Hospital length of stay after treatment, days†	17.5 ± 13.1	15.7-19.3	18.0 ± 13.5	16.2-19.9
Hospital costs after treatment, \$‡	48,962 ± 39,607	43,554-54,371	43,183 ± 41,339	37,565-48,801
Hospital costs after treatment, excluding study drug, \$\$	39,648 ± 36,391	34,678-44,617	43,048 ± 41,279	37,438-48,657

*Values presented as means ± SDs.

†P = .561 for comparison of LOS after start of therapy.

‡P = .022 for comparison of costs from start of therapy to time of discharge.

\$\$P = .416 for comparison of costs from start of therapy to time of discharge, excluding study drug.

variables. Hospital LOS and costs were nonparametric, and differences were tested with the Wilcoxon rank sum test. Two-sided *P* values of .05 or less were considered statistically significant. No adjustments to *P* values were made in any of the analyses. All statistical analyses were performed with the use of software from NCSS Statistical Software (Kaysville, UT).

Sensitivity Analyses

Prior studies have shown that the cost-effectiveness of liposomal amphotericin B is highly dependent on its acquisition cost.³ Therefore, the impact of the acquisition cost and dosing of the liposomal preparation on total hospital cost was assessed. Furthermore, other studies have shown that a doubling of baseline creatinine for patients treated with amphotericin B for suspected or proven fungal infection is associated with prolonged LOS, increased hospital costs, and greater mortality.^{4,5} Therefore, data were also analyzed to examine the impact of nephrotoxicity on costs, using two separate approaches. First, allogeneic BMT patients who are at high risk for nephrotoxicity were analyzed as a subgroup. Second, decision analysis models and sensitivity analyses were developed to adjust

for differences in renal toxicity and dosing between the cost sample and clinical study populations.

RESULTS

Baseline Characteristics

Table 1 summarizes the patient demographics from the pharmacoeconomic study. The population demographics in this study were similar to those of the larger clinical study.

Dosing and Drug Costs

Table 2 presents the duration of treatment, total dose of study drug, and mean cost per course of treatment across all patients and allogeneic BMT patients from the cost study sample. The mean cost of study medication for patients treated with liposomal amphotericin B was significantly greater because of higher dosing regimens (3.0 mg/kg/d v 0.6 mg/kg/d) and higher drug AWP (\$188.40 v \$16.60 per 50 mg).

Table 4. Hospital LOS and Costs for Allogeneic BMT Patients, by Treatment Group

Time Period/Factor	Liposomal Amphotericin B* (n = 28)	95% CI	Conventional Amphotericin B* (n = 28)	95% CI
Total hospitalization				
Total hospital length of stay, days	43.6 ± 17.8	36.8-50.5	36.3 ± 16.4	30.0-42.7
Total hospital costs, \$	123,219 ± 73,155	94,853-151,586	118,624 ± 70,959	91,109-146,139
Total hospital costs, excluding study drug, \$	112,971 ± 71,660	85,185-140,758	118,498 ± 70,921	90,998-145,998
From start of therapy to discharge				
Hospital length of stay after treatment, days†	26.8 ± 17.9	19.9-33.8	21.3 ± 14.9	15.5-27.0
Hospital costs after treatment, \$‡	82,909 ± 60,430	59,477-106,341	77,194 ± 55,799	55,558-98,831
Hospital costs after treatment, excluding study drug, \$\$	72,661 ± 59,114	49,739-95,583	77,068 ± 55,764	55,445-98,691

*Values presented as means ± SDs.

†P = .171 for comparison of LOS after start of therapy.

‡P = .706 for comparison of costs from start of therapy to time of discharge.

\$\$P = .544 for comparison of costs from start of therapy to time of discharge, excluding study drug.

Table 5. Hospital Costs, by Department, From First Dose to Time of Discharge for All Patients

Hospital Department	Liposomal Amphotericin B (\$)	Conventional Amphotericin B (\$)	Difference (\$)	Difference (%)
Total	39,648	43,048	3,400	100.0
Pharmacy*	13,354	14,832	1,478	43.5
Room and Board	10,646	10,862	216	6.3
Blood†	6,375	7,495	1,120	32.9
Laboratory	6,445	6,451	6	0.2
Radiology	1,356	1,476	120	3.5
Other	1,471	1,931	460	13.5

*Excluding the cost of study medications; $P = .275$ for comparison of pharmacy costs.

† $P = .089$ for comparison of blood products.

Hospital LOS and Costs, by Treatment Group

Table 3 summarizes hospital LOS and costs by treatment group for all patients. Hospital costs for all patients from the start of therapy to the time of discharge were higher for patients treated with liposomal amphotericin B (\$48,962 v \$43,183; $P = .022$). However, hospital costs were sensitive to the cost of study medication (\$39,648 v \$43,048 when drug costs were not included; $P = .416$). The cost of liposomal therapy similarly impacted hospital costs in allogeneic BMT patients (Table 4).

Table 5 presents the differences in hospital costs by revenue department by treatment group when the costs of study medications are not included. Differences in hospital costs were primarily concentrated in the pharmacy department (44%) and the blood bank (33%).

Sensitivity Analyses

Sensitivity analyses of the cost of study medication revealed that total hospital costs from the start of therapy to the time of discharge for patients treated with liposomal amphotericin B would be the same as that for conventional therapy at an acquisition cost of \$72 per 50 mg for all patients and \$83 for allogeneic BMT patients.

In addition, there were differences in the frequency of nephrotoxicity in patients within the cost study sample,

compared to the overall clinical study (Table 6). A higher percentage of patients in the cost sample developed nephrotoxicity, especially in the allogeneic BMT subgroup and in patients treated with liposomal amphotericin B. Therefore, additional sensitivity analyses were conducted to assess the impact of the differences in the rates of nephrotoxicity between samples on drug break-even points.

Hospital LOS and costs after the start of therapy were analyzed, comparing patients who did and did not develop nephrotoxicity while being treated with the study medication (Table 7) in order to develop a decision analysis model (Fig 1). Hospital costs were significantly greater for patients who developed nephrotoxicity (\$59,621 v \$34,415; $P < .001$) when the costs of study drugs were excluded from the analysis. Hospital costs also tended to be higher in allogeneic BMT patients who experienced nephrotoxicity (\$81,983 v \$65,740; $P = .111$), although these differences did not reach statistical significance because of the small sample size. Differences between hospital costs by outcome for all patients were primarily concentrated in the pharmacy (22%), blood bank products (19%), and room and board (18%). Differences for allogeneic BMT patients were seen in blood products (34%), pharmacy (31%), and laboratory (15%).

Hospital costs (excluding the cost of the study drugs) were similar between patients treated with liposomal and

Table 6. Incidence of Nephrotoxicity in the Clinical Trial and Cost-Study Populations

Incidence of Nephrotoxicity*	Clinical Trial Population				Cost-Study Sample			
	Liposomal Amphotericin B		Conventional Amphotericin B		Liposomal Amphotericin B		Conventional Amphotericin B	
	n/N†	%	n/N	%	n/N	%	n/N	%
All patients	64/343	19	116/344	34	44/206	21	70/208	34
Allogeneic BMT patients‡	17/52	33	33/50	66	12/28	43	19/28	68

*Defined as a doubling of baseline creatinine level and greater than 1.2 mg/dL creatinine concentration in adults.

†Numbers of patients in each treatment group who developed nephrotoxicity (n)/total number of patients in each treatment group (N).

‡ $P = .367$ (by χ^2 test) for comparison of the incidence of nephrotoxicity of patients treated with liposomal amphotericin B in the clinical trial and cost-study populations.

Table 7. Hospital LOS and Costs, by Nephrotoxicity Outcome

Group/Factor	No Nephrotoxicity*	95% CI	Nephrotoxicity*	95% CI
All patients				
Hospital length of stay after treatment, days†	15.8 ± 12.2 (n = 300)	14.4-17.2	22.8 ± 14.7 (n = 114)	20.1-25.6
Hospital costs after treatment, excluding study drug, \$‡	34,415 ± 31,557	30,844-37,986	59,621 ± 49,346	50,464-68,777
Allogeneic BMT patients				
Hospital length of stay after treatment, days§	24.4 ± 18.7 (n = 25)	16.7-32.1	23.8 ± 15.0 (n = 31)	18.3-29.3
Hospital costs after treatment, excluding study drug, \$	65,740 ± 61,849	40,210-91,270	81,983 ± 55,568	61,600-102,365

*Values presented as means ± SDs.

†P < .001 for comparison of LOS after start of therapy for all patients.

‡P < .001 for comparison of costs from start of therapy to time of discharge for all patients.

§P = .860 for comparison of LOS after start of therapy for allogeneic BMT patients.

||P = .111 for comparison of costs from start of therapy to time of discharge, excluding study drug, for allogeneic BMT patients.

conventional therapy when these patients were grouped by nephrotoxicity outcome. Across all patients who developed nephrotoxicity, the mean hospital costs were \$60,982 for liposomal amphotericin B patients and \$58,765 for conventional therapy patients. Across all patients who did not develop nephrotoxicity, liposomal therapy patients incurred mean costs of \$33,853, compared with \$35,075 for patients treated with conventional therapy ($P > .05$). The findings were similar for allogeneic BMT patients.

Figures 1 and 2 illustrate the decision analyses models developed across all patients and allogeneic BMT patients, respectively, to account for the variability in the rates of nephrotoxicity and dosing regimens of the cost study sample, compared with the clinical trial population. The

frequency of nephrotoxicity is determined on the basis of data found in the overall clinical study (Table 6). The cost of each outcome (that is, patients who developed or did not develop nephrotoxicity) was based on the data presented in Table 7. Conventional amphotericin B costs were held constant on the basis of an acquisition cost of \$5 per 50 mg. The analyses were performed with various liposomal amphotericin B drug acquisition costs to determine the break-even point, the point at which hospital treatment costs from the start of empirical therapy to the time of hospital discharge would be equivalent.

The sensitivity analysis conducted on the basis of the frequency of nephrotoxicity from the overall clinical trial shows that liposomal amphotericin B would be cost-

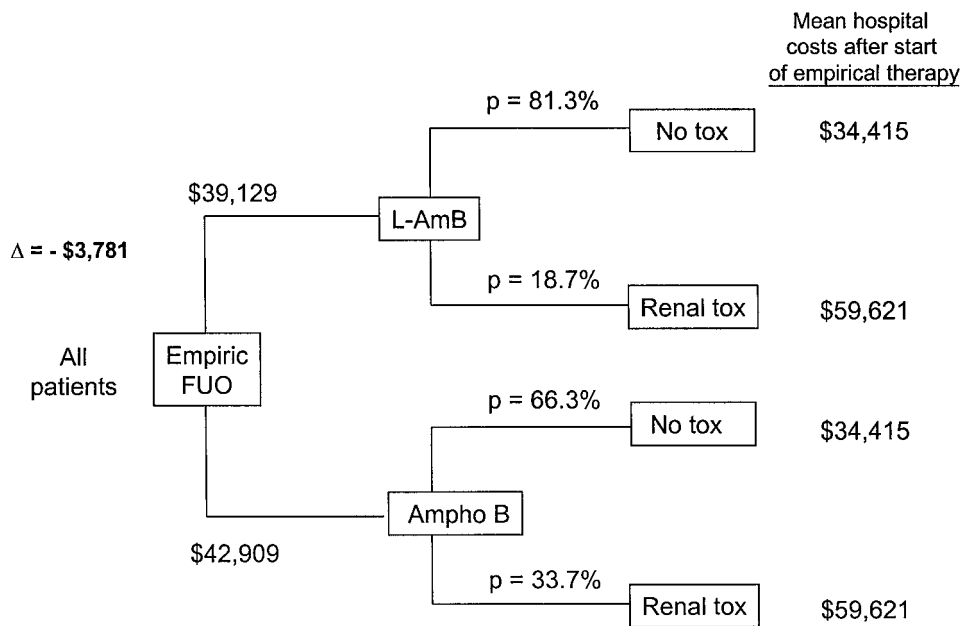
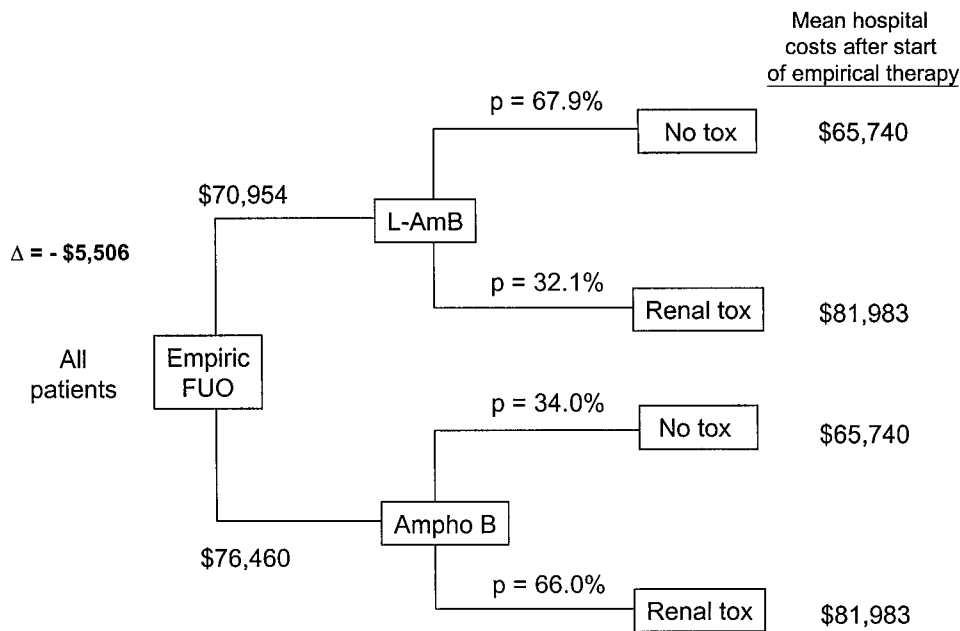


Fig 1. Decision analysis model for all patients, excluding the cost of the study drugs. Percentages indicate the frequency of nephrotoxicity development (Renal tox) or no nephrotoxicity development (No tox) across all patients treated with liposomal therapy (L-AmB) and conventional therapy (Ampho B). The mean hospital costs are based on data listed in Table 7. The total cost per treatment from first dose to the time of discharge does not include the costs of study medications.

Fig 2. Decision analysis model for allogeneic BMT patients, excluding the cost of the study drugs. Percentages indicate the frequency of nephrotoxicity development (Renal tox) or no nephrotoxicity development (No tox) across allogeneic BMT patients treated with liposomal therapy (L-AmB) and conventional therapy (Ampho B). Mean hospital costs are based on data listed in Table 7. The total cost per treatment from first dose to the time of discharge does not include the costs of study medications.

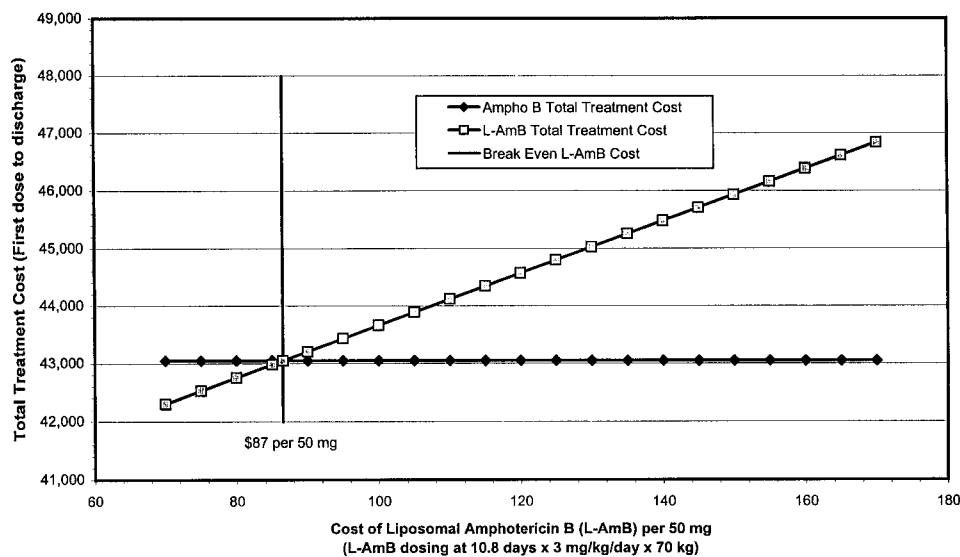


effective at an acquisition cost less than or equal to \$87 per 50 mg vial across all patients (Fig 3). For allogeneic BMT patients, liposomal amphotericin B would be cost-effective at an acquisition cost less than or equal to \$112 per 50 mg vial (Fig 4). These break-even points are more reflective of the costs associated with outcomes seen overall in the clinical study, not just the cost study sample.

DISCUSSION

The objective of this study was to examine hospital LOS and costs for patients treated empirically with liposomal amphotericin B, compared with those treated with conventional amphotericin B. At current AWP's, patients treated with liposomal amphotericin B have significantly higher hospital costs, compared with patients treated with conven-

Fig 3. Sensitivity and break-even analysis of drug costs versus total hospital costs for all patients. The study drug costs for conventional therapy (Ampho B) are held constant at \$5.00 per 50 mg. The study drug costs for liposomal therapy (L-AmB) are varied. The total treatment costs for Ampho B and L-AmB were based on the decision analysis results (Fig 1).



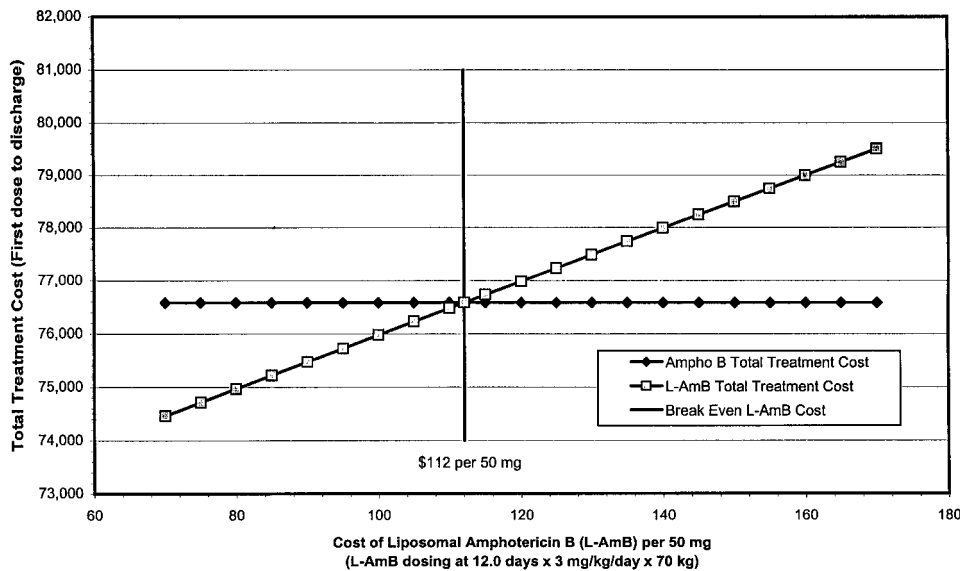


Fig 4. Sensitivity and break-even analysis of drug costs versus total hospital costs for allogeneic BMT patients. The study drug costs for conventional therapy (Ampho B) are held constant at \$5.00 per 50 mg. The study drug costs for liposomal therapy (L-AmB) are varied. The total treatment costs for Ampho B and L-AmB were based on the decision analysis results (Fig 2).

tional therapy (\$48,962 v \$43,183; $P = .022$). However, total hospital costs were greatly affected by the cost of study medications. At drug acquisition costs at or below \$72 per 50 mg across all patients and \$83 for allogeneic BMT patients, liposomal amphotericin B is less costly, compared with conventional therapy, when the total costs of hospitalization are compared for the two treatment regimens.

When the costs of study drugs are not included in the analysis, hospital costs from start of empirical therapy to the time of discharge were lower for liposomal amphotericin B across all patients and a subset of allogeneic BMT patients. This may have been due in part to costs associated with management and outcomes associated with nephrotoxicity, which occurred more frequently in patients treated with conventional therapy. Patients who developed nephrotoxicity after initiating amphotericin B therapy with either formulation stay in the hospital longer and incur higher hospital costs. When sensitivity analyses were performed to reconcile differences in the rate of nephrotoxicity between the cost sample and clinical study populations, the break-even points for liposomal amphotericin B were \$87 per 50 mg across all patients and \$112 per 50 mg for allogeneic BMT patients.

The clinical study was a double-blind trial. Thus reductions in hospital LOS and resource use are not results of investigator expectations or biases but rather of the effects of the drug and clinical outcomes. The strength of this pharmacoeconomic analysis rests on the utilization of original data from the actual costs of hospitalization without assumptions beyond what have been reported in the overall clinical study.

In some cases, hospitals and physicians have elected to reserve the use of liposomal amphotericin B as second-line therapy for patients who become refractory or intolerant to conventional drug because of toxicities.⁶ One study has attempted to quantify the cost implications of using such a protocol.⁷ This current study also has documented the costs associated with renal toxicity outcomes and with changes in therapeutic management. Although the costs of the primary study medication did not appear on hospital bills, commercially available second-line agents administered after the discontinuation of the study medication were captured in billing records. Therefore, converting patients from conventional amphotericin B to liposomal therapy after the development of toxicities may not be the most cost-effective strategy.

Several caveats to the study presented here should be considered. The extrapolation of economic data from clinical trials, especially those that are double-blinded, to noninvestigational settings has inherent limitations. Protocols may require resource consumptions that would not occur in normal practice. Also, treatment-related resource patterns and associated costs may have been different between patients for whom data were not available. The analysis was conducted solely from the hospital perspective, which ignored other potential indirect and direct medical costs related to potential outpatient utilization, hospital readmissions, and physician services.

Judgments about the preferred formulation for empirical treatment should be made on the basis of several factors, including the clinical characteristics of the patient and the morbidity and costs associated with therapeutic options. As

new therapeutic interventions are developed, their expense may be greater than that of existing, established alternatives. Clearly the acquisition cost of liposomal amphotericin B is much greater than that of conventional amphotericin B. This study indicates that assessment of the cost-to-benefit ratio of a more expensive antimicrobial agent should not be restricted solely to the acquisition cost to a pharmacy department. Instead, the impact of potential cost savings and expenditures for the entire hospital should be evaluated.^{8,9}

The findings from this study apply only to persistently febrile cancer patients with chemotherapy-induced neutropenia who undergo empirical therapy with amphotericin B. It does not address other potential indications for the use of liposomal amphotericin B, including prophylaxis therapy or for the treatment of confirmed infections. Additional research needs to be conducted to identify those patients who

are at greatest risk for developing nephrotoxicity and for whom liposomal amphotericin B as first-line therapy may provide the greatest clinical and economic benefit.

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