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Summary

Lipid-based amphotericin B agents have been studied in a number of clinical settings and patient populations, most notably as empirical therapy for patients at-risk for systemic fungal infection and for patients with documented invasive disease. In clinical practice, lipid-based therapies have been considered second- or even third-line therapy due to concerns about costs. However, few analyses have been conducted to determine those factors associated with empirical antifungal therapy and lipid-based agents that are most likely to influence hospital costs and length of stay.

The purpose of this analysis is to determine which demographic, treatment, and clinical outcome factors contribute to increased hospital costs and length of stay in patients treated empirically with a lipid-based amphotericin B agent.

A retrospective analysis of 89 patients enrolled in the clinical study was performed to assess hospital costs and length of stay following the start of empirical antifungal therapy. Bivariate and multivariate regressions were performed to identify variables most likely to affect hospital costs and length of stay.

Allogeneic bone marrow transplant (BMT) status, days of treatment, doubling of baseline creatinine, and dialysis were found to be predictive both of increased hospital costs and length of stay. Length of stay and number of concomitant

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nephrotoxic agents also were found to affect hospital costs.

Overall, risk factors and clinical outcomes associated with nephrotoxicity increased hospital costs and length of stay in patients treated empirically with lipid-based antifungal agents. Renal dialysis also increased hospital cost significantly. For empirical antifungal therapy, providers should consider both patient-specific risk factors and product-specific outcomes in selecting an appropriate agent.

Introduction

Amphotericin B-based therapy is the standard of care for the treatment of neutropenic patients with fever unresponsive to broad-spectrum antibacterial therapy[1,2]. Unfortunately, amphotericin B is associated with numerous dose-related side effects, which compromise its effectiveness. One adverse event of greatest concern associated with conventional amphotericin B is nephrotoxicity, which can delay or impede treatment, and result in clinically meaningful comorbid conditions[3].

As a result, lipid-based formulations of amphotericin B have been developed with the promise of reducing the toxicities associated with amphotericin B. Recently, Wingard and colleagues compared the safety of two such formulations — liposomal amphotericin B (L-AmB, AmBisome*, Fujisawa Healthcare, Deerfield, IL, Gilead Sciences, Foster City, CA, USA) at two different doses (3 mg/kg per day and 5 mg/kg per day) to amphotericin B lipid complex (ABLC, Abelcet*) at 5 mg/kg per day — when used as firstline empirical therapy[4].

The study was conducted at 18 centres in the United States between October 1997 and August 1998. The treatment protocol was similar to that used in other studies of empirical antifungal therapy in terms of identifying patients who necessitated treatment in the empirical setting.

Neutropenic patients (absolute neutrophil count < 500/mm^3) more than 2 years of age were enrolled in this study if they had a suspected fungal infection as demonstrated by fever after at least 72 hours of broad spectrum antibacterial therapy. Fever for the purposes of study entry was defined as two oral equivalent temperatures of >38°C taken at least 4 hours apart or a single oral equivalent temperature of >38.5°C. In addition, patients were required to have a central venous catheter or sufficient venous access to permit administration of study drug and monitoring of safety variables.

Patients were to be withdrawn from the study if unacceptable toxicity developed, the patient required an alternative systemic antifungal agent due to clinical or mycological evidence of worsening fungal infection, the investigator decided it was in the patient's best interest to discontinue, or the patient declined further study participation.

Nearly half of the patients enrolled in the

* AmBisome and Abelcet are the registered trademarks of of Fujisawa Healthcare, Deerfield, IL, USA, Gilead Sciences, Foster City, CA, USA and The Liposome Company, Princeton, NJ, USA, respectively.

study had received a bone marrow transplant (BMT), and nearly two-thirds received at least one concomitant nephrotoxic agent. Patients were excluded from the study if they had baseline serum creatinine levels > 3 mg/dl or had more than two doses of amphotericin B (conventional or lipid preparation) within ten days of enrolment in the clinical study. The mean serum creatinine value at baseline was 0.7 mg/dl.

One of several primary comparative assessments for the study was the incidence of nephrotoxicity, which was defined prospectively as a 100% increase in the baseline serum creatinine value (which ranged upwards to a maximum value of 3 mg/dl at baseline). Adult patients also had to have a creatinine value of at least 1.2 mg/dl to be considered to have experienced nephrotoxicity. The clinical study found that significantly less nephrotoxicity was observed for patients administered L-AmB at either dose (roughly 14%) compared with those treated with ABLC (42%) ($p<0.01$).

The purpose of this analysis is to determine which demographic, treatment, and clinical outcome factors contribute to increased hospital costs and length of stay. Previous studies have found that nephrotoxicity, as defined by elevated serum creatinine, in oncology and bone marrow transplant populations increases the possibility of requiring renal dialysis, and is associated with prolonged hospital length of stay, increased resource utilisation, and greater mortality[3,5,6]. We sought to build upon prior analyses by examining a host of patient- and treatment-related variables. We used a sample of patients from the Wingard study and reanalysed them specifically to determine which factors contributed to their hospital length of stay after initiation of empirical antifungal therapy. Understanding these factors may assist healthcare providers to select patients who are most likely to derive the most clinical and economic benefits associated with lipid-based amphotericin B therapy.

Methods

Economic analyses were not incorporated prospectively into the original clinical study protocol. Therefore, all hospital institutions that enrolled patients in the clinical study[4] were contacted to provide retrospective hospital billing and accounting data for the economic analysis. Of the original 18 centres, six participated in the economic analyses. Most non-participating centres cited administrative reasons for not taking part in the study.

Hospital billing data were collected on 89 of 244 (36.5%) patients from the clinical study. The primary economic outcome of interest was hospital costs from the first day of lipid-based empirical antifungal therapy to hospital discharge. This allowed for an emphasis of costs associated with empirical therapy, as well as sequelae associated with treatment during the inpatient hospital stay. Hospital charges were converted to costs by multiplying charges by institution-specific ratio of cost to charges (RCC) for each hospitalisation.

Table 1. Patient demographics and outcomes from the cost study sample

	L-AmB 3 mg/kg (n=32)	*L-AmB 5 mg/kg (n=27)*	*ABLC 5 mg/kg (n=30)*	*Total (n=89)*
Gender: male (%)	16 (50.0%)	8 (29.6%)	12 (40.0%)	36 (40.4%)
Bone marrow transplant type				
Non-BMT patient (%)	15 (46.9%)	11 (40.7%)	11 (36.7%)	37 (41.6%)
Autologous (%)	12 (37.5%)	11 (40.7%)	11 (36.7%)	34 (38.2%)
Allogeneic (%)	5 (15.6%)	5 (18.5%)	8 (26.7%)	18 (20.2%)
Discontinuation due to toxicity (%)	6 (18.8%)	3 (11.1%)	13 (43.3%)	22 (24.7%)
Death due to fungal infection (%)	0 (0.0%)	0 (0.0%)	2 (6.7%)	2 (2.2%)
Nephrotoxicity (%)[a]	5 (15.6%)	4 (14.8%)	13 (43.3%)	22 (24.7%)
2 times baseline creatinine value				

All patient demographics and outcomes were not statistically significant when compared between the original clinical study and cost sample using χ^2 or Fisher's (two-tailed) exact tests with an alpha value of 0.05.

[a] $p<0.05$, χ^2 test for comparison of either L-AmB group or both L-AmB groups combined with ABLC

Hospital charges and costs did not include drug costs for L-AmB or ABLC, which were provided free of charge to hospital institutions during the clinical study. These costs could be "modelled" into the analysis using average wholesale prices. In many instances, however, hospital costs for pharmacy items can vary considerably from one institution to another. Therefore, the study does not attempt to include standardised costs for the comparative agents used in the study. Data on physician fees and consultations, outpatient follow-up care, and subsequent hospitalisations were not monitored as part of this study. Costs of providing second-line therapy due to treatment failure or premature discontinuation of study drug were included in hospital bills and incorporated into the analysis.

Mean and frequencies were calculated for relevant variables. Patient demographics and outcomes between the original clinical study and cost sample were compared using χ^2 or Fisher's (two-tailed) exact tests with an alpha value of 0.05. Student *t*-test, Mann–Whitney and Wilcoxon analyses were used to compare distributions of treatment days, hospital length of stay, and costs.

To determine the predictors of hospital costs and length of stay, several regression analyses were performed. Hospital costs underwent a log transformation to produce more normally-distributed regression residuals. Dichotomous variables were coded using "0" or "1" to represent the absence or presence of the variable. Bivariate analyses were first performed at a significance level of p value <0.10. Variables that were statistically significant ($p<0.10$) in the bivariate analyses were retained for a stepwise (forward and backward) multiple regression analysis[8]. Models examining hospital costs as the dependent variable

Table 2. Comparison of average days of treatment, mg of drug used, and total drug costs

	L-AmB 3 mg/kg (n=32)	*L-AmB 5 mg/kg (n=27)*	*ABLC 5 mg/kg (n=30)*
Mean days of treatment with study drug[a]	9.00	9.59	6.87
Mean mg of study drug administered	1,760	3,216	2,143
Mean length of stay (days)[b]	31.4	30.5	32.3
Mean length of stay (days), day of first study drug to discharge[b]	19.8	17.0	18.6
Mean costs after first dose of study drug to discharge, excluding study drug costs[b]	$48,971	$34,323	$45,526

[a] $p<0.05$, Student *t*-test for comparison of L-AmB groups combined with ABLC

[b] p=ns, Wilcoxon rank sum test, across treatment groups

included length of stay as an independent variable. However, a second model examining hospital length of stay as the dependent variable excluded hospital costs. All statistical analyses were conducted using SPSS statistical software version 10.0[9].

Results

The population demographics in this study were similar to those of the overall clinical study (Table 1). Chi-square and Fisher's exact tests of patient demographics and treatment outcomes showed no differences between the clinical study and cost study populations. Similar comparisons yielded no differences between patients included and excluded from the cost study.

For all patients included in the study, total hospital length of stay averaged 31 days and total hospital costs averaged over $137,000 (data not shown). No statistical differences were observed in total length of stay or costs between groups.

In parallel with patients in the clinical study, the overall duration of treatment in the sample population was longer in the L-AmB groups because a significantly higher percentage of ABLC patients discontinued treatment earlier as a result of adverse events ($p<0.01$). Rates of nephrotoxicity in the sample of 89 patients closely matched rates from the clinical study, with significantly higher rates of nephrotoxicity being observed in ABLC patients ($p<0.05$). Nonetheless, no differences were found in overall hospital length of stay, length of stay after first dose of study medication, and hospital costs between treatment groups (Table 2).

A bivariate analysis was performed to assess correlations between hospital costs after first dose of lipid-based antifungal therapy and patient demographics, clinical outcomes, and risk variables (Table 3). Variables that were statistically significant

Table 3. Bivariate correlations of variables affecting log-adjusted hospital costs after first dose of lipid-based antifungal therapy

	Coefficients Correlation	*p value*
Length of stay following first dose of therapy[a]	0.702	<0.001
Treatment group (ABLC5, LAMB3, LAMB5)	–0.114	0.288
Gender (male, female)	–0.053	0.707
Age[a]	–0.208	0.051
Days of treatment with study drug[a]	0.470	<0.001
Risk group (low risk, high risk)[a]	0.334	0.001
Allogeneic BMT[a]	0.417	<0.001
Persistent fever[a]	0.265	0.012
Emergent fungal infection	0.127	0.234
Drug withdrawn because of toxicity[a]	0.244	0.021
Death related to fungal infection	0.042	0.693
Successful response[a]	–0.344	0.001
Nephrotoxicity[a]	0.303	0.004
Dialysis[a]	0.298	0.005
Number of concomitant nephrotoxic medications[a]	0.414	<0.001

[a] Variables with $p<0.10$ and therefore retained for the multiple regression model; p values based on bivariate analyses of variance or Student t-tests

($p<0.10$) in the bivariate analyses were retained for stepwise regression models. The stepwise regression model of hospital costs after a first dose of lipid-based antifungal therapy subsequently found six independent variables positively associated with hospital costs: (1) length of stay following first dose; (2) nephrotoxicity; (3) number of concomitant medications; (4) dialysis; (5) allogeneic BMT; and (6) days of treatment with study drug (Table 4).

Not surprisingly, length of stay was found to have a large impact on hospital costs. Therefore, a second stepwise model was developed using the same variables from the bivariate analysis with length of stay as the dependent variable. The results of this model revealed four independent variables most highly associated with hospital length of stay following the start of therapy: (1) days of treatment with study drug; (2) dialysis; (3) allogeneic BMT; and (4) nephrotoxicity (Table 5).

Discussion

This study found that a number of factors affect hospital costs following the initiation of empirical antifungal therapy with a lipid-based amphotericin B agent (either ABLC or L-AmB). Not surprisingly, length of stay was the primary factor affecting hospital costs as determined by stepwise regression modelling. However, several other variables were identified and most

Table 4. Stepwise regression model with log-adjusted hospital costs after first dose of lipid-based antifungal therapy as the dependent variable

	Standardised coefficients	*Adjusted R2*	*p value*
Intercept	9.081		
Length of stay following first dose of therapy	0.031	0.590	<0.001
Nephrotoxicity	0.350	0.628	0.005
Number of concomitant nephrotoxic medications	0.165	0.680	0.005
Dialysis	0.589	0.697	0.003
Allogeneic BMT	0.324	0.710	0.018
Days of treatment with study drug	0.020	0.721	0.041

relate in some way to renal toxicity that may be caused or exacerbated by amphotericin B therapy. Allogeneic BMT, days of antifungal drug treatment, doubling of baseline creatinine, and dialysis were found to increase length of stay and costs for patients receiving lipid-based empirical antifungal therapy.

It is of no surprise that allogeneic BMT patients have increased hospital stays and costs compared with autologous BMT or non-BMT cancer chemotherapy patients. Overall, these patients experience longer durations of neutropenia, have increased risk of infection, are more likely to experience graft failure, and suffer from increased risks of other comorbidities (e.g. graft-versus-host disease). Subsequently, these patients often undergo treatment with cyclosporine or tacrolimus, which increases the likelihood of developing nephrotoxicity[10]. The overall clinical study did not include a large number of solid organ transplant patients, although we might expect similar results in those patient populations due to the use of these immunosuppressive agents.

The effect of days of treatment on hospital costs should be interpreted with caution. Although prolonged drug exposure potentially could increase the likelihood of renal toxicity, it could also be associated with higher costs due to underlying fungal infection or other comorbidities which necessitate continued treatment. Although L-AmB patients in the study were treated

Table 5. Stepwise regression model with log-adjusted hospital length of stay after first dose of lipid-based antifungal therapy as the dependent variable

	Standardised coefficients	*Adjusted R2*	*p value*
Intercept	9.466		
Days of treatment with study drug	0.541	0.238	<0.001
Dialysis	0.356	0.400	<0.001
Allogeneic BMT	0.237	0.462	0.004
Nephrotoxicity	0.189	0.488	0.028

on average 2–3 days longer than ABLC patients (9.0 and 9.6 days for L-AmB versus 6.9 days for ABLC, $p<0.05$), the total hospital stay after the start of therapy was similar across treatment groups (p=ns) (Table 2).

All other variables associated with increased hospital stays and costs directly relate to risk factors or indicators of renal toxicity. These include the number of concomitant nephrotoxic agents, doubling of baseline creatinine, and dialysis. These findings are consistent with other reports highlighting the importance of renal toxicity on the economics of antifungal therapy[3,5].

In many cases, patients were already being treated with one or more concomitant nephrotoxic agents prior to the initiation of lipid-based amphotericin B therapy. The necessity of maintaining these patients on prescribed drug regimens with known renal toxicities reinforces the importance of managing patient safety, treatment efficacy, and costs combined.

In this study, the specific lipid-based amphotericin B agent was not found to be significantly associated with hospital costs in any of the bivariate or multivariate models. This may be in part due to the small samples available in this study. Unfortunately, large sample sizes often exceeding the total enrolment of the clinical study generally are required to power studies comparing economic endpoints. Therefore, we would not expect to see differences in economic outcomes from an intent-to-treat perspective.

Nonetheless, the relationship between nephrotoxicity and economics found in this study reinforces the concept that outcomes associated with treatment can have profound effects on hospital costs[6]. It is also interesting to note that traditional indicators of failure of empirical therapy (persistent fever, emergent fungal infection, discontinuation of therapy due to toxicity, and death due to fungal infection) were not predictive of hospital costs in our models.

To quantify the additional costs associated with nephrotoxicity and dialysis, all patients were categorised based on the appearance of one or both of these two outcomes (Table 6). Because creatinine values for nephrotoxicity were recorded only during treatment with study medication through a 7-day follow-up period, 2 out of 67 patients (3%) who did not experience a twofold increase in serum creatinine on study, nonetheless required dialysis in subsequent days during their hospitalisations. This compared to 6 of 16 patients (27%) requiring dialysis in the nephrotoxicity population ($p<0.05$).

When examining patients based on these outcomes, hospital costs were significantly higher for patients who developed nephrotoxicity compared to patients who did not ($62,004 versus $37,246, $p<0.05$). One explanation for the increased costs associated with nephrotoxicity may be found in the subset of patients who developed nephrotoxicity and required treatment with dialysis. In these patients, mean hospital costs exceeded $100,000. In patients who did not experience dialysis,

Table 6. Mean hospital costs by outcome (combined data across treatment groups; lipid drug costs excluded)

	No dialysis[a]	*Dialysis*[b]	*Total*[c]
Patients with no doubling of baseline creatinine while on study drug	$36,879 (n=65)	$49,161 (n=2)	$37,246 (n=67)
Patients with doubling of baseline creatinine	$45,797 (n=16)	$105,222 (n=6)	$62,004 (n=22)

[a] $p=0.073$, Mann–Whitney test for comparison of hospital costs between patients who did and did not develop nephrotoxicity

[b] $p<0.05$, χ^2 test for comparison of frequency of dialysis between patients with and without doubling of baseline creatinine

[c] $p<0.05$, Wilcoxon rank sum test for comparison of hospital costs between patients who did and did not develop nephrotoxicity

hospital costs were still greater in patients who developed nephrotoxicity ($45,797 versus $36,879) although differences were not statistically significant (p=0.073). Nonetheless, the overall differences observed in this study, as they pertain to the impact of nephrotoxicity in patients with persistent fever and neutropenia, are consistent with findings from other populations that amphotericin B-related nephrotoxicity is both clinically and economically meaningful.

The findings from this study are limited to patients who were treated with ABLC or L-AmB as first line empirical antifungal therapy. They would not apply to other indications where these agents may be used.

Unfortunately, economic data were not available for all patients from the original clinical study. In some instances, patient consent could not be obtained for the retrospective study because patients had died or were lost to follow-up. Other institutions could not participate because data had been archived or were not available for administrative reasons. The data available to us may be representative of the entire study population.

The overall clinical study by Wingard and colleagues found dramatic differences in nephrotoxicity between ABLC and L-AmB nephrotoxicity. This analysis indicates that risk factors and outcomes associated with nephrotoxicity can have profound effects on hospital costs and length of stay, although differences in hospital costs were not observed from an intent-to-treat perspective due to the small sample sizes.

These findings are particularly relevant to infectious disease physicians, bone marrow transplant specialists, pharmacists, and other audiences with clinical and financial stakes in the outcomes of patients at-risk for systemic fungal infections. Although the clinical study was completed several years ago, the findings are still relevant in today's healthcare environment given fiscal constraints.

Beyond the costs of these agents, risk factors and outcomes are important considerations in helping clinicians

identify when and how to start empirical therapy for patients at-risk for developing life threatening invasive fungal infections[11]. Additional research on the predictors of nephrotoxicity would enable hospitals and physicians to identify patients for whom less nephrotoxic agents would most likely be most cost effective.

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