Clinical and Economic Outcomes of Conventional Amphotericin B–Associated Nephrotoxicity

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A retrospective 9-year cohort study was conducted to identify the hospitalization costs, length of hospital stay, and mortality associated with nephrotoxicity (NT) among 494 inpatients who were treated with conventional amphotericin B (CAB). Survival regression methods were used to model the effect of NT. The rate of NT was 12%; the overall in-hospital mortality rate was 22%. After adjustment for confounding, NT was associated with a 2.7-fold higher risk of death (P < .001). Although the unadjusted effects of NT on length of hospital stay and hospitalization costs after the initiation of CAB were consistent with small increases, such effects were not significant in multivariate models (time ratio, 1.2 [P = .2]; cost ratio, 1.1 [P = .8]). The greater the number of days before the onset of NT that were included in the analysis, the greater the apparent effect of NT on costs. CAB-associated NT was associated with increased mortality, but it did not impact the costs and length of hospital stay.

Adverse events associated with use of medications are considered to be a major source of morbidity and mortality among hospitalized patients. Although some studies have addressed overall outcomes associated with drug-related adverse events [1, 2], there is a need to study in detail individual medications and their related toxicities. In clinical practice, drug exposure is not randomly allocated. Therefore, potential confounding variables, such as severity of illness and length of hospital stay, need to be taken into account in studies that quantify the impact of drug-related adverse events. Methodological approaches to minimize bias in the design and analysis of these types of studies have heretofore received relatively little attention.

Conventional amphotericin B (CAB) deoxycholate is an antifungal agent associated with a significant number of toxic side effects, one of the most important of which is nephrotoxicity (NT). Unfortunately, there is limited understanding of the clinical and economic impact of CAB-induced NT, although recent studies have attempted to examine this question [3–5]. In the present study, we evaluated the occurrence of NT in a large cohort of hospitalized individuals treated with varying doses of CAB to determine whether patients who had CAB-associated NT had differences in length of hospital stay, costs of hospitalization, and mortality rates when compared with patients who did not have NT. By use of survival regression methods to assess all 3 outcomes of interest, we attempted to control for confounding by use of time-varying covariables to adjust for the interval between commencement of CAB therapy and the onset of NT.
METHODS

Hospital setting, study population, and data collection.  LDS Hospital is a private, 520-bed hospital located in Salt Lake City and is a teaching affiliate of the University of Utah School of Medicine. It has ~23,000 admissions per year. The hospital has a large oncology service and includes an allogeneic bone marrow transplantation unit. The study population consisted of all adult inpatients admitted to the hospital during the period of January 1990 through September 1998 who received ≥2 doses of CAB.

With the help of computerized hospital files, we identified study subjects from the population of all inpatients. Data were extracted from administration, pharmacy, and laboratory databases and were compiled into a single data set by means of a database management system that has been described elsewhere [6].

Definitions and study design. Use of CAB formed the primary time axis. We recorded the numbers of daily, cumulative, and total CAB doses [7]. Serial serum creatinine levels during therapy with CAB were compared with the baseline creatinine level to assess the occurrence of NT. The effects of CAB-induced elevation of the creatinine level on mortality, length of hospital stay, and daily costs of hospitalization were examined in 2 ways: first, by including serum creatinine level as a continuous variable, and second, by defining the occurrence of NT as a discrete event. The criterion for NT in this analysis was doubling of the serum creatinine level during CAB therapy from baseline up to an absolute value of ≥2.0 mg/dL [5, 7, 8]. The baseline creatinine value was defined as the mean of the serum creatinine measurements during the 3-day interval before the initiation of CAB therapy.

Three outcomes were examined: in-hospital mortality rate, length of hospital stay, and daily hospitalization costs after the initiation of CAB therapy. All patients were observed until discharge from the hospital. Length of hospital stay was calculated as the number of days in the hospital. Costs were computed in 1998 US dollars by applying a yearly consumer price index for hospital services [9]. The daily costs of hospitalization were studied only for patients admitted after 1 January 1993, because such data were not available before this date. Costs were computed in 1998 US dollars by applying a yearly consumer price index for hospital services [9].

The demographic and clinical variables that we studied as potential risk factors for mortality or increased length of hospital stay were age, sex, race, body weight, baseline creatinine level, medical or surgical status, primary diagnosis, chronic comorbid conditions, type of infection, transplantation status, severity of illness (defined by daily nursing acuity scores, which were determined by nurse responses to standardized questions about the care of the patient, representing an index of the time required for each activity), treatment in the intensive care unit, and CAB-associated NT [7].

Statistical analysis. We expressed continuous variables as the mean ± SD or, if the distribution was skewed, as the median and interquartile range. Survival analytic methods were used to model the effect of NT on length of hospital stay, costs, and mortality rate after the initiation of CAB therapy. For all analyses, time 0 was considered to be the day of initiation of CAB therapy.

The use of survival analysis to analyze the impact of in-hospital events, such as NT, offered the following advantages: (1) on each day after the initiation of CAB therapy, patients with NT were compared with patients who were still receiving CAB and who had not experienced NT; (2) the relationship between change in kidney function and outcome could also be assessed by modeling the serum creatinine level as a continuous variable; (3) we could account for confounding factors in multi-variable models with time-dependent covariates [10]; and (4) for analyses of length of hospital stay and costs of hospitalization, patients who died were treated as “censored”—that is, for a patient who died, the full length of time for recovery to the point of discharge from the hospital was considered unknown. Alternative analyses that excluded patients who died were performed and yielded effect estimates similar to the main results.

For the mortality analysis, we used Cox proportional hazard regression. Patients were censored on the day of discharge from the hospital. The effect of NT on mortality was expressed as a hazard ratio (HR). Proportional hazard assumptions were examined by graphical analysis and by testing the null hypothesis that the slope of the Schoenfeld residuals was zero [11]. For continuous variables, the linearity of effect was tested by plotting β coefficients against grouped levels of the covariate and by obtaining smoothed plots of the martingale residuals [12].

An accelerated failure time model (Weibull model) was used to analyze the length of hospital stay after it was determined that the distributional fit was adequate. The Weibull model was parameterized in the form of logarithmic time, so that the exponentiated coefficients could be interpreted as multiplicative effects on length of hospital stay or time ratios [13].

We also applied a parametric survival model to the cost analysis [14, 15]; a log-normal distribution was specified on the basis of adequacy of fit. When survival analysis is applied to cost studies, cost replaces time as the dependent variable [16]. Costs accumulate on each day of hospitalization, allowing inclusion of such covariates as NT at the appropriate interval.
after initiation of CAB therapy. By use of a parametric survival model, the effect of NT could be expressed as a cost ratio. For control of confounding, diagnosis-related groups (DRGs) were stratified into 4 cost levels on the basis of mean costs for each DRG within the study population. The DRG cost level was then included in multivariable models as a covariate. To explain the observed differences between our cost estimates and those of previous reports, we conducted an additional analysis to examine the following question: are there changes in the final cost model if the effect of NT is assumed to begin before it is actually detected?

As stated above, NT was incorporated as a time-dependent covariate in all survival models so that comparisons between patients who had and patients who did not have NT were made at comparable intervals from initiation of CAB therapy [10, 17, 18]. Variables with \( P \leq .20 \) on univariable analyses were candidates for multivariable analysis, as was the main variable of interest (NT). Variables were also tested for confounding by adding them one at a time to a model and examining their effects on the \( \beta \) coefficients of the main exposure variable. Those variables that caused substantial confounding (change in \( \beta \) coefficient of \( >20\% \)) were kept in the final model. We tested for pairwise interactions between important risk factors in the multivariable models by use of appropriate multiplicative terms. These statistics were calculated by use of STATA software, version 6.0 (STATA). All statistical tests were 2 tailed. \( P < .05 \) was considered to be significant.

Finally, to corroborate the findings of the parametric survival model, mixed regression methods for longitudinal data were used to estimate the effect of NT on costs of hospitalization. Random effects were specified for the intercept term and slope, represented by days receiving CAB. Within-subject variance was fit with an unstructured correlation structure. Fixed variables that were included in this model were age, length of hospital stay, and severity of illness, expressed as year-specific DRG cost weights [5]. We used the PROC MIXED function in SAS software, version 7.0 (SAS Institute), for this analysis.

### RESULTS

A total of 494 patients were included in the study. The majority of patients (361 [73\%]) received CAB for empirical treatment. Important patient characteristics are shown in table 1. Overall, 58 patients (12\%) had NT. Initiation of hemodialysis was causally related to CAB therapy in 3 patients.

**Mortality.** One hundred eleven (22\%) of the 494 patients died in the hospital. Figure 1 illustrates the cumulative probability of survival according to the occurrence of NT. According to univariable Cox analysis, patients who experienced NT had a 2.5-fold increased hazard of death (95\% CI, 1.6–4.0). Table 2 summarizes the results of the univariable analysis for the association of different patient characteristics with mortality, and it lists the results of the multivariable Cox model constructed to control for confounding. Factors that were independently associated with mortality (\( P < .01 \) for all predictors) were age of \( \geq 65 \) years, elevated baseline creatinine level, chronic renal impairment, liver disease, increased acuity score, receipt of mechanical ventilation for \( >24 \) h, and aspergillosis (table 2). After adjustment for confounding, NT was associated with a 2.7-fold higher hazard of death (\( P < .001 \)). Models that included serum creatinine level as a continuous variable demonstrated a highly linear relationship between serum creatinine level during CAB therapy and hazard of mortality (adjusted HR, 1.4; 95\% CI, 1.3–1.6).

**Length of hospital stay.** The median time interval from initiation of CAB therapy to discharge from the hospital was 19 days (interquartile range, 8–36) for patients without renal toxicity and 23 days (interquartile range, 17–45) for those ex-
periencing NT. The median length of hospital stay for the latter
group was 9 days from initiation of CAB therapy to the oc-
currence of NT and 14 days from NT to discharge. Figure 2
demonstrates the probability of discharge after initiation of
CAB therapy, according to the presence or absence of NT. On
univariate analysis, a trend toward increased length of hospital
stay was observed in patients who experienced NT (time ratio,
1.2; \( P = .3 \)), which was most pronounced early after the com-
mencement of CAB therapy. Adjustment for important con-
founding factors, such as the nurse acuity score, did not sig-
nificantly change the time ratio (1.2; 95% CI, 0.9–1.6; \( P = .2 \)).

When examined in the model as a continuous variable, in-
creases in the serum creatinine level also were not significantly
associated with increased length of hospital stay after adjust-
ment for illness acuity (time ratio, 1.0; 95% CI, 0.9–1.1; \( P = .8 \)). In contrast, a longer duration of hospital stay was observed
for patients who had undergone surgery (time ratio, 1.4; 95%
CI, 1.2–1.7; \( P < .001 \)), who had leukemia (time ratio, 1.3; 95%
CI, 1.1–1.6; \( P = .01 \)), or who had an elevated acuity score (time
ratio per 1-point increase, 1.03; 95% CI, 1.02–1.04; \( P < .001 \)).
The results were not affected by the choice of the survival
model—that is, when a Cox proportional hazard model was
applied, the association between NT and length of hospital stay
remained statistically nonsignificant (HR, 0.8; 95% CI, 0.5–1.1;
\( P = .2 \)).

Hospital costs. Daily costs of hospitalization were available
for 292 patients admitted after 1 January 1993; 30 (10%) of
these patients developed NT. Fourteen of these 30 patients died.
The mean total costs per admission were $58,861 for patients
who experienced NT and $44,314 for those without renal tox-
icity. For patients with NT, the mean hospital costs were $28,695
before and $30,166 after the onset of NT. The mean intensive
care unit cost was $16,825, and the mean pharmacy cost was
$11,017.

The univariate cost ratio associated with NT was 0.7 (95%
CI, 0.3–1.8; \( P = .5 \)). After adjustment for different DRG-cost
quartiles, renal toxicity still was not associated with significantly
increased costs of hospitalization (cost ratio, 1.1; 95% CI,
0.7–1.8; \( P = .8 \)). Models that used DRG cost weights instead
of DRG cost quartiles produced comparable results (adjusted
cost ratio, 0.9; \( P = .8 \)). Exclusion of all 68 patients (23%) who
died in the hospital rather than treatment of these patients as
censored did not affect the results (adjusted cost ratio, 0.75;
\( P = .3 \)).

When the serum creatinine level during CAB therapy was
examined as a continuous variable, a statistically significant
effect was seen on univariate analysis (cost ratio, 1.3; \( P = .01 \)),
but not after adjusting for baseline creatinine level and DRG-
cost group (cost ratio, 1.1; \( P = .5 \)). The results were not ma-
terially affected by the choice of the model form: a statistically
significant effect of NT also was not observed when Cox pro-
portional hazard regression was used instead of the log-normal
parametric model. In addition, mixed-effect regression models
were created to evaluate the association between NT and daily
costs. After adjustment for days in the hospital, DRG weight,
and age, NT was associated with a $40 increase in per-day costs,
an effect that was not significant (\( P = .8 \)).

Finally, by use of the survival model, we assessed the mag-
nitude by which the results would be affected if costs that
occurred before the calculated onset of NT were included in


Table 2. Risk factors for mortality, assessed by means of univariate and multivariable analysis, for 494 inpatients treated with conventional amphotericin B (CAB) therapy.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Hazard ratio (95% CI)</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristic</td>
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<tr>
<td>Male sex</td>
<td>1.3 (0.9–1.9)</td>
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<tr>
<td>White race</td>
<td>1.0 (0.9–1.2)</td>
<td></td>
<td></td>
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<tr>
<td>Age of ≥65 years</td>
<td>2.1 (1.4–3.1)</td>
<td>2.4 (1.6–3.5)</td>
<td></td>
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<tr>
<td>Body weighta</td>
<td>1.1 (1.0–1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline creatinine level at the start of CAB therapy</td>
<td>1.2 (1.1–1.3)</td>
<td>1.2 (1.0–1.3)</td>
<td></td>
</tr>
<tr>
<td>Underlying condition</td>
<td></td>
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<tr>
<td>Leukemia</td>
<td>0.7 (0.4–1.2)</td>
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<tr>
<td>Solid-organ malignancy</td>
<td>1.3 (0.7–2.6)</td>
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<tr>
<td>Lymphoma</td>
<td>1.7 (0.9–2.9)</td>
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<tr>
<td>Liver disease</td>
<td>3.0 (2.1–4.4)</td>
<td>2.2 (1.4–3.5)</td>
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<tr>
<td>Cardiac disease</td>
<td>2.4 (1.5–4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>3.3 (2.2–5.1)</td>
<td>2.2 (1.3–3.5)</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>2.2 (1.4–3.6)</td>
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<td></td>
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<tr>
<td>Infection</td>
<td></td>
<td></td>
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<tr>
<td>Disseminated candidiasis</td>
<td>2.2 (1.4–3.4)</td>
<td></td>
<td></td>
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<tr>
<td>Aspergillosis</td>
<td>17.2 (4.0–72.8)</td>
<td>13.9 (2.9–66.1)</td>
<td></td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>1.4 (0.3–5.7)</td>
<td></td>
<td></td>
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<tr>
<td>Sepsis</td>
<td>1.6 (1.1–2.3)</td>
<td></td>
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<tr>
<td>Pneumonia</td>
<td>1.7 (1.2–2.6)</td>
<td></td>
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<tr>
<td>Peritonitis</td>
<td>2.2 (1.3–3.5)</td>
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<tr>
<td>Urinary tract infection</td>
<td>1.1 (0.7–1.7)</td>
<td></td>
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<tr>
<td>Events in hospital</td>
<td></td>
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<td></td>
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<tr>
<td>Any type of surgery</td>
<td>1.3 (0.9–2.0)</td>
<td></td>
<td></td>
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<tr>
<td>Bone marrow transplantation</td>
<td>0.7 (0.4–1.5)</td>
<td></td>
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<tr>
<td>Solid-organ transplantation</td>
<td>1.3 (0.7–2.6)</td>
<td></td>
<td></td>
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<tr>
<td>Intensive care unit stay</td>
<td>2.5 (1.7–3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation of ≥24 h</td>
<td>2.6 (1.6–4.2)</td>
<td>2.1 (1.3–3.6)</td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicityc</td>
<td>2.5 (1.6–4.0)</td>
<td>2.7 (1.6–4.4)</td>
<td></td>
</tr>
<tr>
<td>Mean acuity scoreb</td>
<td>1.1 (1.0–1.2)</td>
<td>1.2 (1.1–1.3)</td>
<td></td>
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</tbody>
</table>

- Per 10-kg increase.
- Per 10-point increase.
- Serum creatinine values during CAB treatment were also significantly associated with mortality when entered into the model as a continuous variable.

The principal findings of this study, which was performed with a heterogeneous patient population, are as follows: (1) NT occurred in 58 patients (12%) and was associated with a 2.7-fold higher mortality rate after controlling for underlying disease and severity of illness; (2) although the unadjusted effects of NT on length of hospital stay and hospitalization costs after the initiation of CAB were consistent with small to moderate increases, such effects were not significant in multivariate models that accounted for the interval between the commencement of CAB therapy and the onset of NT (time ratio, 1.2 \[P = .2\]; cost ratio, 1.1 \[P = .8\]); and (3) the greater the number of days before the calculated onset of CAB-associated NT that were included in the cost analysis, the greater the apparent effect of NT on costs. Thus, this study demonstrates the danger of violating basic cause-effect relations in cost analysis by attributing costs to an adverse event before the event occurs.

The results of our study extend those of previous studies about the association between medically induced renal toxicity and mortality [19–21]. The administration of nephrotoxic agents especially can result in an acute reduction in renal function and can ultimately cause the death of a patient [22]. Wiegand et al. [3] also reported an increased mortality rate associated with the toxic renal damage induced by CAB use. In particular, hemodialysis may have contributed to the observed increase in the mortality rate. However, these authors and others cautioned that the increased mortality rate among inpatients who develop acute renal failure may be determined by preexisting comorbid conditions that also predispose patients to acute renal failure and by simultaneous, nonrenal complications, which are usually related to multiple organ dysfunction [21]. An alternative interpretation of the increased mortality rate could be that some patients with NT were receiving inadequate antifungal therapy as a consequence of a dose reduction in response to NT. Although the evidence of a statistical association between CAB-induced NT and mortality does not prove causality, our multivariable analysis suggests that the association between renal toxicity and mortality cannot be attributed to comorbidities or severity of illness alone.

Our finding that NT was not significantly associated with an increased length of hospital stay and costs of hospitalization stands in contrast to other studies that found that CAB-associated renal toxicity increases costs [4, 5]. Cagnoni et al. [4], for example, calculated that the hospital costs were sig-
significant greater for patients who developed NT compared with those who did not ($59,621 vs. $34,415; P < .001), although CAB-treated patients had lower mean hospitalization costs after treatment ($43,183) than did patients treated with lipid formulations of amphotericin B ($48,962). In the context of other work on the subject, the results of a single observational study such as ours need to be interpreted with caution. For instance, the 95% CIs around the effect estimates in our analysis are still compatible with small to moderate effects of NT on costs and length of hospital stay. Yet it is important to consider methodological differences among studies that have attempted to estimate the attributable effect of adverse events, which may occur at various intervals after starting use of a medication. In their comparative analyses, previous studies have included length of stay and costs of hospitalization for patients with NT that were incurred before renal toxicity may have actually occurred [4, 5]. Adjustment for severity of illness does not adequately control for confounding due to the length of time from initiation of therapy to the occurrence of toxicity. Even patients with the same severity of illness experience a distribution of different time intervals to the adverse event; thus, patients with NT or another drug-related adverse event may have longer total lengths of hospital stay, independent of any effect of toxicity. In our analysis of costs that tested different assumptions, we showed that the greater the number of CAB-treatment days before the calculated occurrence of NT that are included, the greater the apparent effect of NT on total costs. Thus, estimation of cost effects may often be overestimated if the interval to onset of renal toxicity is not properly accounted for in the analysis.

The strengths of our study were the large sample size of our patient population and the use of analytic methods that allow for time-dependent covariates to adjust for the time interval between commencement of CAB therapy and the calculated onset of NT. Nonetheless, our study had limitations, one of which was that the cost data were not available for patients admitted to the hospital before 1993. Second, the high mortality rate among patients with NT represented a further constraint on the sample size of patients for whom costs were measurable to the point of recovery sufficient for hospital discharge. Third, our data were generated for a single tertiary care hospital; therefore, results may not be generalizable to other settings. Fourth, we cannot exclude the possibility that residual, unmeasured confounding accounted for effects noted in the study. Fifth, it is possible that NT leads to increased length of hospital stay and costs only in the subset of patients with severe renal dysfunction and great variation in serum creatinine levels, a group of patients that may have been of insufficient size in this study to observe an impact. It is also possible that a cost effect of NT may be difficult to detect in patients whose length of hospital stay is expected to be prolonged regardless of individual drug-related toxicities, as a result of the need for chemotherapy or treatment of their underlying diseases.

NT is just one of the adverse consequences of CAB use. In future studies, an analysis of outcomes associated with the full spectrum of CAB-induced toxicities is warranted. Addi-
Figure 3. Analysis of different assumptions about costs attributable to renal toxicity. The figure shows adjusted cost ratios for amphotericin B–associated nephrotoxicity for the case if hospital costs are included in the model before the calculated onset of renal toxicity.

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