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Outcomes associated with conventional versus lipid-based formulations of amphotericin B in propensity-matched groups

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Background: Lipid-based formulations of amphotericin B (LF-AMB) are indicated for treatment of invasive fungal infections in patients intolerant to conventional amphotericin B (CAB) or with refractory infections. Physicians still may choose to administer CAB to such patients. We described the use of CAB and LF-AMB in this population and quantified differences in post-amphotericin B length of stay (LOS) among survivors and hospital mortality in matched patients.

Methods: Data were extracted from *Health Facts* (Cerner Corporation, Kansas City, MO, USA) for a retrospective cohort analysis. Inpatients aged ≥18 years with evidence of fungal infection and with orders for LF-AMB or CAB on ≥2 days from January 2001 to June 2010 were identified. Patients were required to have renal insufficiency or other relative contraindications to use of CAB, exposure to nephrotoxic agents, or evidence of a CAB-refractory infection. Multilevel (hierarchical) mixed-effects logistic regression was used to determine factors associated with initial exposure to LF-AMB versus CAB. Multivariate adjustment of outcomes was done using propensity score matching.

Results: 655 patients were identified: 322 patients initiated therapy with CAB and 333 initiated treatment with LF-AMB. Compared to those initiating CAB, patients initiating LF-AMB had greater acuity and underlying disease severity. In unadjusted analyses, hospital mortality was significantly higher in the LF-AMB group (32.2% versus 23.7%; $P = 0.02$). After propensity score matching and covariate adjustment, mortality equalized and observed differences in LOS after amphotericin B initiation decreased.

Conclusion: Among patients at risk for amphotericin B toxicity, differences between CAB and LF-AMB seen in crude outcomes analyses relate to channeling of sicker patients to initiate treatment with LF-AMB. Failing to account for differences among patients that drive clinical decision-making will result in inaccurate conclusions about the real-world effectiveness of different amphotericin B formulations.

Keywords: amphotericin, outcomes, mortality, hospitalization

Introduction and objectives

Amphotericin B is commonly the treatment of choice in invasive fungal infections (IFIs). Clinicians may choose among amphotericin B deoxycholate (conventional amphotericin B [CAB]) or a number of lipid-based formulations (LF-AMB), such as liposomal amphotericin B and amphotericin B lipid complex. Many factors influence the treatment decision, including the patient's current clinical condition and the potential to experience and/or tolerate adverse effects, cost of the drugs, and formulary specifications. The indications for LF-AMB, in part, include patients who are

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refractory to or intolerant of CAB therapy.[1,2] This potential for toxicity associated with CAB – including infusion-related reactions acutely, and nephrotoxicity associated with chronic use – and the lower risks associated with LF-AMB are well documented.[3–10] However, in "real world" clinical practice, hospitals and/or physicians may reserve LF-AMB for the sickest patients and chance administering CAB to only the lower acuity patients perceived to be at low risk for adverse consequences.[11] These underlying differences in patients' clinical characteristics are likely to affect outcomes, potentially skewing the results of effectiveness research efforts.

Few real-world data are available on the use of CAB and LF-AMB and associated outcomes among patients with conditions precluding the use of CAB. Alvarez-Lerma et al conducted a subanalysis on 49 critically ill patients with elevated serum creatinine (greater than 1.5 mg/dL) at initiation of treatment in an observational study of liposomal AMB.[12] There was minimal effect on renal function, though overall in-hospital mortality was 67.3%. However, the study did not compare amphotericin B formulations in this population. The aims of the current study were to examine the use and outcome of CAB and LF-AMB therapies in patients with known renal disease or other potential contraindications to CAB and to determine factors associated with LF-AMB initiation vs (versus) CAB, using a large, multicenter database.

Methods

Study design and data source

This was a retrospective cohort study using data collected from hospitals in the *Health Facts* electronic health record (EHR) database (Cerner Corporation, Kansas City, MO, USA). Cerner Corporation develops, implements, and supports EHR software for hospitals and health systems globally. US-based institutions using Cerner's comprehensive suite of solutions can opt to contribute their EHR data to a database for use in research and quality improvement initiatives. *Health Facts* contains a comprehensive clinical record for each encounter and includes pharmacy, clinical and microbiology laboratory, admission, and billing information from affiliated patient care locations. Clinical information is date- and time-stamped, providing a temporal relationship between clinical information relating to the drugs dispensed and the results of diagnostic laboratory testing. Cerner Corporation has established Health Insurance Portability and Accountability Act-compliant operating policies to establish deidentification for *Health Facts*.

Population selection

Patients were selected if they were hospitalized between January 2001 and June 2010, aged 18 years or older upon admission and had orders for LF-AMB or for CAB on 2 or more calendar days. Additional requirements to capture patients with conditions that may constitute a relative contraindication to the use of CAB were the presence of at least one of the following: evidence of renal insufficiency or other conditions and characteristics such as a history of organ transplant or advanced age (Appendix A), exposure to nephrotoxic agents during the index encounter (Appendix B), or CAB exposure within 90 days prior to the admission date (suggesting a CAB-refractory infection). Finally, evidence of infection with *Aspergillus*, *Candida*, and/or *Cryptococcus* during the index encounter or within 90 days prior to the index encounter was required, as indicated by a positive blood culture and/or relevant International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes as a discharge diagnosis. For patients with multiple eligible encounters in *Health Facts*, only the first encounter was considered.

Study group definitions and other measures

All patients had exposure to amphotericin B. The two study groups were defined by having a first amphotericin B order for CAB or for LF-AMB and were required to have an active order for this first formulation on at least 2 calendar days. Patients could have subsequent orders for the alternate amphotericin B formulation or for other antifungal agents. Patient clinical characteristics and comorbidities of interest were derived from administrative (eg, ICD-9-CM codes) and clinical (eg, pharmacy, laboratory) records of encounters within the previous 12 months, including the current encounter. The diagnosis-related group (DRG) classified the patient as surgical or medical. Evidence of impaired immune function comprised medications (eg, systemic corticosteroids, chemotherapy) and discharge diagnoses (eg, autoimmune diseases, certain malignancies). Organ dysfunction was identified within a 48-hour window surrounding the time of admission using measures modeled after and intended to equate to a Sepsis-related Organ Failure Assessment score ≥ 2.[13] Critical care exposure was defined as having two or more orders from an intensive care unit 12 or more hours apart, mechanical ventilation, or orders for vasopressors.

Predicting initial exposure

To determine the predictors most strongly associated with initial exposure to LF-AMB vs CAB, we used a multilevel (ie,

hierarchical) mixed-effects logistic regression model structure with random intercepts at the hospital level to allow for the fact that the choice of drugs given to patients within each hospital (but not between hospitals) may not be independent (eg, influenced by hospital formulary).[14] To avoid including potential complications of amphotericin B use, we limited the candidate variables to chronic comorbidities and events that occurred prior to amphotericin B initiation. We also ensured that each potential predictor had face validity for affecting treatment choice. The final model was chosen based on a stepwise bootstrapping procedure[15] combined with an analysis of the Bayesian Information Criterion among nested models.[16] The influence of hospital on treatment choice was assessed using a likelihood ratio test for the significance of random intercepts.

Outcomes analysis

Outcomes of interest were length of stay (LOS) following the first order for amphotericin B (post-amphotericin B LOS) among survivors, and in-hospital mortality. Bivariate differences by amphotericin B type were assessed with either a chi-square test or a t-test, with P values <0.05 being considered statistically significant.

The primary analysis was performed using propensity score matching. Five patients with missing mortality data were excluded. A logistic regression model that adjusted for serial correlation at the hospital level was used to generate a propensity score with the outcome of initiation on CAB vs LF-AMB. The primary propensity score model included all possible predictors (Appendix C). Namely, patient demographics, comorbid conditions, encounter events, microbiology results, laboratory values prior to initiation of amphotericin B, and pre-amphotericin B LOS were included in the propensity score. Variables that showed colinearity were removed (and this was only true for hepatic organ dysfunction, which was collinear with laboratory measures of bilirubin or aspartate aminotransferase). Baseline total bilirubin and aspartate aminotransferase were defined as binary variables (normal vs abnormal) and missing values in these variables were assumed to be normal. For the small number of patients with missing values for mechanical ventilation (7.9%) or organ dysfunction (1.2%), ventilation or organ dysfunction was also assumed to be absent. For baseline serum creatinine, a univariate imputation sampling method was used, which predicted missing values based on all other predictor variables used in the propensity score. No other imputation was necessary.

The primary matching algorithm was kernel matching, a one-to-many approach in which patients with smaller propensity score differences were weighted more heavily in deriving matched estimates. Two sensitivity analyses were then done.[17] The first used the propensity scores based only on predictors that entered the model with a P value <0.25 after a stepwise regression procedure. In the second sensitivity analysis, a 5:1 greedy matching algorithm was applied to the non-parse- and stepwise-regression-based propensity scores.

Nested variable analysis of mortality

To explore which categories of variables most explained differences in mortality between the CAB and LF-AMB initiator groups, we created a series of multilevel (ie, hierarchical) mixed-effects logistic regression models of increasing size. We sequentially added variables representing "chronic" to "acute" conditions. Namely, the variable order was demographics, chronic comorbidities, surgical vs medical DRG, laboratory values, and finally clinical variables indicating acuity. For each model, we present the odds ratio (OR) related to treatment choice (LF-AMB vs CAB) and its adjusted P value with 95% confidence intervals (CIs).

Results

Patient and clinical characteristics

A total of 655 patients from 53 hospitals were identified; 333 patients' first amphotericin B order was for LF-AMB and 322 were initiated on CAB. Of these, 81% and 70%, respectively, also received another systemic antifungal agent during their hospitalization. Fifty-three percent of patients were identified during the first half of the study period. Clinically, the cohorts were heterogeneous: LF-AMB patients were younger and more likely to be male, and had greater underlying disease severity (Table 1). Mean Charlson Comorbidity Index score was higher among LF-AMB initiators, as was the frequency of several individual comorbidities: hematologic malignancy, solid tumor, human immunodeficiency syndrome or acquired immunodeficiency syndrome, and history of solid organ transplant. LF-AMB patients were far more likely to have any evidence of impaired immune function. During the hospital encounter itself, multiple measures of patient acuity were more common among LF-AMB initiators: organ dysfunction upon admission, bacteremia, diagnosis of sepsis, critical care use, and use of systemic corticosteroids or chemotherapy. Exposure to nephrotoxic drugs was similar across groups. More CAB initiators had an ICD-9-CM discharge diagnosis of candidiasis during the encounter, while more LF-AMB patients were diagnosed with aspergillosis. Rates of candidemia were similar

Table 1 Patient and clinical characteristics

Variable	CAB N = 322 %	LF-AMB N = 333 %	*P* value
Patient and encounter characteristics			
Male	44.4	53.8	0.02
Age, years, mean (SD)	60.1 (20.0)	53.1 (18.5)	<0.001
Surgical type DRG (versus medical or unknown)	38.2	38.4	0.88
Urgent or emergent admission status	75.5	67.0	0.02
Comorbid conditions			
Charlson comorbidity index score, mean (SD)	2.7 (2.4)	3.2 (2.5)	0.02
Hypertension	38.8	29.7	0.01
Diabetes	31.7	19.8	0.001
Dyslipidemia	9.6	12.9	0.01
Heart failure	20.2	12.3	0.01
Chronic kidney disease	18.6	19.2	0.85
Chronic respiratory condition	29.2	27.0	0.54
Impaired immune function	55.0	78.4	<0.001
Hematologic malignancy	18.3	30.6	<0.001
Solid tumor	9.0	13.8	0.05
Aplastic anemia, pancytopenia, and other blood dyscrasias	11.8	30.0	<0.001
HIV/AIDS	11.2	16.2	0.06
History of solid organ transplant	7.8	14.7	0.005
History of stem cell transplant	6.2	5.1	0.54
Encounter events			
Organ dysfunction within 48 hours of admission (any)	50.6	58.3	0.05
Respiratory	11.8	14.4	0.32
Hematologic	15.2	28.8	<0.001
Hepatic	5.0	13.2	<0.001
Cardiovascular	9.6	13.5	0.12
Renal	25.8	22.8	0.38
Critical care exposure – any time	48.8	59.8	0.005
Critical care exposure – pre-amphotericin	28.6	33.0	0.22
Bacteremia	10.9	24.3	<0.001
Diagnosis of sepsis/septic shock	23.0	31.8	0.01
Total parenteral nutrition	15.8	18.6	0.35
Diagnosis of candidiasis	69.3	45.3	<0.001
Disseminated candidiasis	18.9	16.5	
Candidiasis of mouth	14.9	15.9	
Candidiasis of other urogenital sites	27.6	2.1	
Esophageal candidiasis	3.4	2.7	
Candidal endocarditis	0.6	2.1	
Candidiasis of lung	2.5	3.6	
Candidiasis (other specified sites)	6.2	6.0	
Diagnosis of aspergillosis	10.6	19.8	0.001
Diagnosis of cryptococcosis	15.5	19.5	0.18
Blood culture positive for *Candida*[a]	63.6	58.2	0.41
Blood culture positive for *Cryptococcus*[a]	8.0	10.8	0.48
Drug exposure during encounter			
Time to first amphotericin B order, days, mean (SD)	9.9 (11.8)	13.5 (17.4)	0.002
Total days with amphotericin B exposure, mean (SD)	10.6 (10.7)	9.8 (9.4)	0.34
Exposure to any nephrotoxic agent	75.8	80.5	0.33
Number of nephrotoxic agents, mean (SD)	1.7 (1.6)	1.8 (1.4)	0.44
Total number of days with ≥1 nephrotoxic agent, mean (SD)	16.2 (17.1)	18.2 (17.3)	0.21
Any antibacterial agent orders	95.0	95.5	0.78
Number of antibacterial classes, mean (SD)	3.9 (2.3)	4.1 (2.3)	0.19
Systemic corticosteroid exposure	55.0	68.8	<0.001
Chemotherapy exposure	10.6	18.0	0.01
Immunosuppressive agents commonly associated with transplant[b]	13.0	16.2	0.25

(*Continued*)

Table 1 (*Continued*)

Variable	CAB N = 322 %	LF-AMB N = 333 %	*P* value
Baseline laboratory values			
Serum creatinine, mg/dL, mean (SD)[c]	1.8 (1.9)	1.5 (1.3)	0.03
Total bilirubin, mg/dL, mean (SD)[d]	0.8 (1.0)	1.8 (3.9)	<0.001

Notes: [a]Denominators are patients with any blood culture obtained. CAB, N = 88; LF-AMB, N = 158; [b]examples: cyclosporine, tacrolimus, mycophenolic acid. Evidence of transplant not required; [c]CAB, N = 296; LF-AMB, N = 305; [d]CAB, N = 223; LF-AMB, N = 238.
Abbreviations: CAB, conventional amphotericin B; DRG, diagnosis-related group; HIV/AIDS, human immunodeficiency syndrome/acquired immunodeficiency syndrome; LF-AMB, lipid-based formulation of amphotericin B; SD, standard deviation.

across groups. CAB initiators were more likely to have a history of diabetes, hypertension, or heart failure and to have higher mean baseline serum creatinine values.

Predictors of LF-AMB initiation

We found several clinical factors that were significantly associated with starting LF-AMB rather than CAB (Table 2). Patients with critical care exposure prior to amphotericin B, impaired immune function, liver dysfunction upon admission, or aplastic anemia/pancytopenia were more likely to be started on LF-AMB. Diabetes, cryptococcosis, candidiasis, and history of stem cell transplant were associated with starting on CAB. The specific hospital had a strong influence, perhaps driven by formulary guidelines, on the choice of amphotericin B formulation, as allowing each hospital to have its own intercept significantly improved model fit ($P < 0.001$).

Outcomes

Crude analysis of in-hospital mortality favored initiation of CAB, with an OR of 1.53 for initiating LF-AMB ($P = 0.02$) (Table 3). Among survivors, the observed point-estimate of post-amphotericin B LOS was nonsignificantly shorter in the CAB group (difference in LOS = 2.5 days shorter for CAB group, 95% CI: –6.1–1.1; $P = 0.17$).

The primary propensity score model and the less parse, secondary model based on stepwise regression both exhibited good calibration (Hosmer–Lemeshow statistics were either borderline significant [$P = 0.03$] for the primary model or nonsignificant [$P = 0.16$] for the stepwise model). The mean propensity scores for the CAB and LF-AMB groups were 0.35 and 0.66, respectively. While not a goal of the propensity score modeling, we did observe relatively strong discrimination (high area under the receiver-operating characteristic curve values) of 0.83 and 0.82 for the primary and secondary models, respectively. Matching on the propensity to receive LF-AMB eliminated the significant differences in odds of mortality (OR = 1.05, 95% CI: 0.62–1.77; $P = 0.85$) and reversed the directionality of observed differences in post-amphotericin B LOS (difference in LOS = 2.6 days longer in the CAB group, 95% CI: –2.6–7.9; $P = 0.32$). Sensitivity analyses using the secondary propensity score based on stepwise regression and the alternative matching procedure based on greedy matching produced similar findings (results not shown).

Table 2 Patient factors significantly associated with amphotericin formulation

Factor	Odds ratio[a]	95% CI	*P* value
Critical care use, pre-amphotericin	2.40	1.43–4.02	0.001
Impaired immune function	2.13	1.28–3.54	0.004
Hepatic dysfunction within 48 h of admission	2.09	0.98–4.42	0.06
Aplastic anemia, pancytopenia, and other blood dyscrasias	1.84	1.03–3.26	0.04
Diabetes	0.59	0.36–0.97	0.04
Discharge diagnosis of cryptococcosis	0.55	0.30–1.01	0.05
Discharge diagnosis of candidiasis	0.48	0.31–0.74	0.001
Stem cell transplant	0.32	0.12–0.84	0.02

Note: [a]Odds ratio >1 indicates a positive association with LF-AMB initiation.
Abbreviations: CI, confidence interval; LF-AMB, lipid-based formulation of amphotericin B.

Nested model analysis

Sequentially adding covariates into our models for hospital mortality "explained" the effect of initial treatment (Table 4). Addition of variables for demographics and baseline clinical status to the models had little impact, but addition of acuity variables eliminated differences in the odds of mortality across the treatment groups.

Discussion

To our knowledge, this is the first study to use real-world data to compare LOS and mortality in patients with IFIs initiated on CAB vs LF-AMB with clinical conditions warranting the

Table 3 Outcomes before and after propensity score matching, CAB vs LF-AMB initiators

Outcome	CAB before matching	LF-AMB before matching	Unadjusted effect size; 95% CI	Unadjusted *P* value	CAB after matching	LF-AMB after matching	Effect estimate; 95% CI	*P* value
Mortality, %	23.7	32.2	OR[a] 1.53 (1.08–2.17)	0.02	30.5	31.6	OR[a] 1.05 (0.62–1.77)	0.85
Post amphotericin B LOS for survivors, mean (SD), days	16.7 (18.7)	19.2 (21.1)	Difference −2.5 (−6.1–1.1)	0.17	21.3 (18.7)	18.6 (19.7)	Difference 2.6 (−2.6–7.9)	0.32

Note: [a]Referent: CAB.

Abbreviations: CAB, conventional amphotericin B; CI, confidence interval; LF-AMB, lipid-based formulation of amphotericin B; LOS, length of stay; OR, odds ratio; SD, standard deviation.

Table 4 Sequential modeling of mortality

Model (name)	Odds ratio for LF-AMB vs CAB	95% CI	*P* value
LF-AMB vs CAB (referent) (M1)	1.53	1.10–2.13	0.01
M1 + Age, gender, race, insurance status (M2)	1.76	1.22–2.55	0.003
M2 + comorbidities (M3)	1.44	0.96–2.15	0.08
M3 + patient type (medical vs surgical) + admission type (M4)	1.46	0.97–2.21	0.07
M4 + baseline lab values (M5)	1.36	0.91–2.04	0.13
M5 + critical care before ampho B and time to first ampho B (M6)	1.19	0.80–1.79	0.40
M6 + organ dysfunction and other acuity variables (M7)	0.91	0.52–1.59	0.75

Abbreviations: CAB, conventional amphotericin B; CI, confidence interval; LF-AMB, liposomal amphotericin B.

use of LF-AMB. In evaluating 10 years of data on hospitalized patients with IFIs and evidence of renal impairment or other comorbidities or exposures that might put them at risk for CAB-associated toxicity, we found that approximately half were started on CAB. When physicians believe amphotericin B treatment is needed for patients with serious fungal infections, they have a choice between CAB and LF-AMB. The risk of nephrotoxicity associated with CAB is well documented,[4,18] and thus, particularly in patients with renal compromise or otherwise at risk for toxic effects, LF-AMB may be more appropriate.[19,20]

Preliminary descriptive analysis demonstrated that patients initiated on LF-AMB were generally sicker than those initiated on CAB. The multivariate model predicting LF-AMB initiation (vs CAB) extended this, and showed that critical care exposure and impaired immune function both doubled the odds of receiving LF-AMB. Based on the inclusion criteria (eg, history of kidney disease), all patients in the study were at risk for adverse effects of CAB. Absent these restrictions, we would have expected to see even more pronounced differences between the treatment groups, with greater acuity and comorbidity burden – particularly related to renal disease – among LF-AMB patients. We observed no clear trend toward certain types of variables (eg, higher baseline serum creatinine or a diagnosis of end-stage renal disease) being associated with LF-AMB. Most striking was the clustering of amphotericin B formulation by hospital, which may indicate that formulary requirements or other institutional practices are important drivers of amphotericin

B choice. This implies that the clinical drivers of choice were very powerful to have emerged in the setting of apparently common administrative constraints. As many of the patients included here were from early in the study period, further research should examine trends in choice of formulation over time.

Raw hospital mortality was significantly higher and observed post-amphotericin B LOS nonsignificantly longer among patients initiated on LF-AMB prior to adjustment. Absent further analysis, a naïve interpretation would be that LF-AMB was inferior, with increased mortality potentially due to toxicity or to limited effectiveness in treating the fungal infection. However, the LF-AMB patients were sicker. Propensity score matching eliminated the differences in both acuity and effect, indicating that outcomes were driven by factors affecting choice of therapy. This was confirmed by the nested model exercise, which demonstrated that acuity variables accounted for the differences in mortality between the groups. These findings suggest that, contrary to the impression given by naïve analyses, the real-world effectiveness of the treatments is consistent with that found in randomized clinical trials.[9,21–24]

A strength of our analysis is that our EHR-based data source includes clinical characteristics that are not available in administrative claims-based data, such as laboratory results. We attempted to minimize confounding in our multivariate adjustment by including numerous demographic characteristics, comorbidities, and encounter events in the propensity score and regression models. Nevertheless, we acknowledge that unmeasured variables may be causing residual bias. For example, we did not collect data on antifungal exposure subsequent to the amphotericin B orders, which may have provided further insight into patients' course of illness and, indirectly, severity of the fungal infection. Future analyses should investigate use of additional antifungals to better understand treatment sequencing and duration following initiation of amphotericin B. Information on specific institutional formulary policies would have been useful in controlling for a patient's potential to be treated with CAB vs LF-AMB, but was not available in *Health Facts* at the time this study was conducted. However, we observed in our analyses that a given hospital influenced its patients' starting formulations, and accounted for this in our outcomes analysis.

Conclusion

In an EHR database of patients with IFIs and contraindications to use of CAB, clinical factors appeared to drive therapeutic decisions regarding initiation of LF-AMB or CAB. Real-world outcomes may initially appear to contradict what has been demonstrated in clinical trials. Proper adjustment for underlying patient acuity is needed to accurately estimate comparative effectiveness between CAB and LF-AMB.

Disclosure

Samuel A Bozzette, Rebecca S Campbell, Harlen D Hays, and Robert J Taylor are employees and stockholders of Cerner Corporation, which received payment for consulting services delivered to Astellas in connection with the conduct of this study and the development of this manuscript. Cerner Corporation owns the *Health Facts* database and provides consulting services to pharmaceutical and biotechnology companies, including Astellas. Paresh Chaudhari is an employee of Astellas Scientific and Medical Affairs, Inc. Brian H Nathanson's company, OptiStatim, LLC, has a paid consulting agreement with Cerner Corporation. David Horn served as a paid consultant to Astellas during the study and manuscript preparation.

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Appendix tables

Appendix A Clinical conditions or circumstances suggesting intolerance to CAB treatment

ICD-9-CM discharge diagnosis codes for chronic kidney disease, end-stage renal disease or other form of nephritis, nephritic syndrome, or nephrosis during index admission or 12 months prior
ICD-9-CM discharge diagnosis codes for acute renal failure or acute glomerulonephritis during index admission
Abnormal baseline renal function,[25] defined in our study as serum creatinine (prior to first amphotericin B order) >1.5 mg/dL
Exposure to any nephrotoxic drug during the encounter and prior to initiation of amphotericin B (Appendix B)
Baseline hypokalemia,[25] defined in our study as a potassium value (prior to first amphotericin B order) less than the institution's laboratory-defined lower limit of normal
Baseline hypomagnesemia,[25] defined in our study as a magnesium value (prior to first amphotericin B order) less than the institution's laboratory-defined lower limit of normal
Polyuria,[25] defined in our study by an ICD-9-CM discharge diagnosis during the index encounter
Diuretic use during the index encounter and prior to initiation of amphotericin B[18,26]
Patient location within the ICU at or before initiation of first amphotericin B[27]
Major solid organ transplantation or bone marrow transplant[25,27–29]
Advanced age,[25] defined in our study as ≥65 years

Abbreviations: CAB, conventional amphotericin B; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICU, Intensive Care Unit.

Appendix B Directly nephrotoxic drugs and other agents

Antiviral agents
Acyclovir
Adefovir
Adefovir dipivoxil
Cidofovir
Efavirenz/emtricitabine/tenofovir
Emtricitabine-tenofovir
Emtricitabine/lopinavir/ritonavir/tenofovir
Emtricitabine/nelfinavir/tenofovir
Foscarnet
Ganciclovir
Tenofovir
Valacyclovir
Valganciclovir
Aminoglycosides
Gentamicin
Netilmicin
Streptomycin
Tobramycin
Amikacin
Other antibiotics
Colistin
Vancomycin
Teicoplanin
Calcineurin inhibitors
Cyclosporine
Tacrolimus
Anticancer drugs
Carboplatin
Carmustine
Cisplatin
Cyclophosphamide
Ifosfamide
Ifosfamide-mesna
Methotrexate
Streptozocin

(*Continued*)

Appendix B (*Continued*)

Radiocontrast agents
Amidotrizoate
Ioxithalamate
Ioxaglate
Iopamidol
Iohexol
Iomeprol
Iopentol
Ioversol
Iopromide
Iobitridol
Iodixanol
Iotrolan
Miscellaneous
Pentamidine

Note: Systemic routes only, including oral/nasogastric tube/feeding tube, intramuscular, and intravenous.[3,18,30]

Appendix C Propensity score model

Variable	Odds ratio	95% CI	*P*-value
Patient and encounter characteristics			
Age	0.992	0.974–1.011	0.412
Male gender	1.345	0.935–1.934	0.110
White race	1		
Black	1.615	0.869–3.003	0.130
Hispanic	1.863	0.607–5.717	0.277
Asian	0.432	0.073–2.550	0.354
Other/unknown race	0.740	0.256–2.142	0.579
Medicare	1		
Commercial	3.985	1.093–14.526	0.036
Medicaid	4.547	1.742–11.870	0.002
Other/unknown insurance	1.086	0.617–1.913	0.774
Medical versus surgical (referent)	1.002	0.643–1.561	0.993
Admit from emergency room	1		
Hospital admission	1.140	0.541–2.401	0.730
Other/unknown admission	1.387	0.822–2.341	0.221
Urgent or emergent admission status	0.857	0.510–1.438	0.558
Encounter events			
Mycosis, any of the below (ICD-9 codes)			
(some variables were too uncommon to be used)			
Candidiasis	0.475	0.281–0.802	0.005
Histoplasmosis	2.323	0.556–9.714	0.248
Aspergillosis	1.432	0.464–4.417	0.533
Pneumonia in aspergillosis	1.119	0.482–2.596	0.794
Cryptococcosis	0.912	0.355–2.344	0.848
Other and unspecified mycoses	4.451	0.965–20.530	0.056
Bacteremia	1.448	0.626–3.350	0.387
Parenteral nutrition	0.819	0.444–1.510	0.522
Critical care use, pre-amphotericin B	1.423	0.756–2.676	0.274
ICU care setting	0.917	0.414–2.035	0.832
Mechanical ventilation	0.863	0.533–1.397	0.549
Vasopressor use	1.500	1.005–2.239	0.047
Ventricular shunt	1.092	0.256–4.667	0.905
Central catheter use	1.233	0.853–1.783	0.265
Presumed new-onset dialysis	0.848	0.389–1.853	0.680
Immunosuppressive therapy	0.648	0.390–1.075	0.093
Post-transplant immunosuppressive therapy	0.623	0.325–1.193	0.154
Corticosteroid therapy	1.226	0.759–1.978	0.405
Chemotherapy	1.206	0.610–2.382	0.590
Sepsis/septic shock	1.162	0.766–1.762	0.479
Organ system dysfunction upon admission (first 48 hours) – any	0.429	0.227–0.812	0.009
Respiratory dysfunction	1.660	0.789–3.492	0.182
Hematologic dysfunction	1.512	0.832–2.749	0.175
Hepatic dysfunction	1.512	0.832–2.749	0.175
Cardiovascular dysfunction	1.648	0.829–3.275	0.154
Renal dysfunction	2.538	1.254–5.137	0.010
Comorbid conditions			
Hematologic malignancy	1.163	0.550–2.461	0.693
Solid tumor	1.394	0.730–2.663	0.314
Impaired immune function	3.092	1.897–5.038	<0.001
CCI score per unit	1.044	0.888–1.227	0.601
Diabetes	0.579	0.387–0.865	0.008
Hypertension	0.727	0.436–1.213	0.222
Dyslipidemia	1.305	0.576–2.955	0.524
Coronary artery disease	0.977	0.436–2.190	0.954
Cardiomyopathy	0.323	0.101–1.039	0.058
Congestive heart failure	0.838	0.523–1.343	0.463

(*Continued*)

Appendix C (*Continued*)

Variable	Odds ratio	95% CI	*P*-value
Atrial fibrillation	0.993	0.415–2.380	0.988
Cardiac dysrhythmias (other than AF)	0.824	0.473–1.433	0.492
Valvular heart disease	3.077	0.883–10.721	0.078
Peripheral arterial disease	0.436	0.117–1.627	0.217
Stroke/TIA	0.951	0.457–1.978	0.893
Chronic kidney disease	2.542	0.998–6.475	0.051
Dialysis dependence	0.471	0.143–1.550	0.215
Chronic respiratory conditions – any	0.461	0.237–0.897	0.023
COPD/bronchiectasis	2.083	1.171–3.704	0.013
Asthma	2.177	0.741–6.390	0.157
Cystic fibrosis	3.072	1.027–9.190	0.045
Chronic respiratory, primary pulmonary hypertension, and cardiopulmonary obesity	1.316	0.531–3.261	0.553
Alveolitis, pneumonitis, pneumoconiosis, pulmonary fibrosis, and idiopathic pulmonary hemosiderosis	1.157	0.484–2.768	0.742
Cirrhosis/chronic liver disease	1.011	0.164–6.253	0.990
HIV/AIDS	0.403	0.097–1.665	0.209
Other disorders involving the immune mechanism	0.546	0.158–1.891	0.340
Autoimmune disorders	0.743	0.347–1.594	0.446
Blood dyscrasias	2.248	1.145–4.413	0.019
Major solid organ transplantation	1.549	0.542–4.424	0.414
Stem cell transplant	0.268	0.092–0.781	0.016
Microbiology			
Blood culture obtained	1.432	0.664–3.087	0.360
Fungal pathogens isolated, final report			
Candida	1.180	0.507–2.746	0.701
Cryptococcus	1.299	0.314–5.374	0.718
Laboratory values			
Serum creatinine, baseline, mg/dL (imputed)	0.774	0.649–0.923	0.004
Total bilirubin, baseline >2.0 mg/dL	1.968	0.778–4.978	0.153
Cirrhosis/chronic liver disease and total bilirubin, baseline >2.0 mg/dL	1.041	0.031–35.400	0.982
AST, prior to initiation of amphotericin B therapy (pre-amphotericin B AST) was above ULN	1.367	0.838–2.233	0.211
Cirrhosis/chronic liver disease and AST, prior to initiation of amphotericin B therapy (pre-amphotericin B AST) was above ULN	1.618	0.056–46.595	0.779
Time to first amphotericin B (per hour)	1.000	1.000–1.001	0.211

Abbreviations: AF, atrial fibrillation; AST, aspartate aminotransferase; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; ICD-9, International Classification of Diseases, Ninth Revision; ICU, intensive care unit; TIA, transient ischemic attack; ULN, upper limit of normal.