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Risk Factors for Renal Failure in Pediatric Patients With Acute Myeloid Leukemia: A Retrospective Cohort Study

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Abstract

Background—In children receiving treatment for acute myeloid leukemia (AML) there is often concern for the development of acute renal failure (ARF). Despite this, data are limited to define the incidence of ARF in this population. This study aims to evaluate the rate of ARF in AML patients and to delineate the impact of age, race, various co-morbid conditions and antimicrobial agents on the development of ARF.

Methods—A cohort of newly diagnosed AML patients from children's hospitals across the United States was identified using the Pediatric Health Information Systems database. Information regarding demographics, discharge diagnoses, pharmaceutical exposures, and hospital resource utilization were collected for each hospitalization for up to 1 year from AML diagnosis. Cox regression analysis was used to define the hazard ratios for development of ARF by demographic variables, co-morbid conditions, and exposure to various antimicrobial agents.

Results—Within 1 year of AML diagnosis, 135 (16.2%) patients were diagnosed with ARF. After adjustment for the presence of co-morbid conditions, the risk for ARF was greater in older patients and in black patients. Vancomycin exposure duration of greater than 48 hr and carbapenem exposure duration greater than 10 days were associated with an increased risk for ARF.

Conclusion—ARF is a relatively common problem in children with AML. Future studies should address the different risks of ARF by age and race. Empiric therapy with potentially nephrotoxic

agents did not increase the risk of nephrotoxicity. Patients on prolonged vancomycin therapy should be monitored closely for development of ARF.

Keywords

antimicrobials; epidemiology; leukemia; pediatrics; renal failure

INTRODUCTION

In the United States, there are approximately 3,250 newly diagnosed cases of childhood leukemia each year [1,2]. Acute myeloid leukemia (AML) accounts for 15–20% of these leukemia cases. During the past 25 years advances in the use of intensified chemotherapy, bone marrow transplant, and improvements in supportive therapy have resulted in increased survival rates to 40–60% [2–8].

Unfortunately, the intensification of chemotherapy has resulted in the frequent occurrence of infection during all phases of AML chemotherapy [9]. In an effort to reduce the mortality rate secondary to infection, AML patients are often started on empiric broad-spectrum antibiotics, antifungal agents, or antiviral agents at the early signs of infection [10].

As a result of these medication exposures, clinicians are constantly concerned about the risk for acute renal failure (ARF). To date there have been no definitive estimates of ARF in pediatric AML patients and there are limited data on risk factors for ARF, particularly with exposure to antimicrobial agents. This lack of knowledge exists because no prior data sets have collected information on ARF and concomitant medication exposures and co-morbid conditions in a sample set large enough for robust statistical analysis. Such data are currently available via the Pediatric Health Information System (PHIS), a database which contains inpatient data from 41 free-standing children's hospitals affiliated with the Child Health Corporation of America (CHCA, Overland Park, Kansas). The contributing hospitals account for 85% of all freestanding children's hospitals in the United States (data from the National Association of Children's Hospitals and Related Institutions, Alexandria, VA). Using this database, we sought to test the hypothesis that exposure to various antimicrobial medications (aminoglycosides, vancomycin, amphotericin B, and antiviral agents) and co-morbid conditions would be associated with development of ARF.

METHODS

Study Design

We performed a retrospective cohort study to identify risk factors for ARF among a large cohort of children with newly diagnosed AML. Children entered the cohort on the day of AML diagnosis and were followed for 1 year or until ARF onset. Patients were censored if they died prior to the onset of ARF.

Data Source

The PHIS database has been used to study other clinically important medical conditions such as meningitis, osteomyelitis, appendicitis, and methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections [11–14]. Data are de-identified at the time of submission and they are subjected to a program that performs 175 reliability and validity checks. The data checks range from confirming demographic data (i.e., date of birth) to validating clinical data (i.e., validating the admission and discharge dates). The program identifies definite errors that the submitting hospital is then required to repair and warns a hospital of possible errors that may need to be repaired. Data are only accepted from a

participating hospital when classified errors occur in fewer than 2% of a hospital's quarterly data.

Data contained in the database include the following: patient identification, demographics, dates of admission and discharge, all International Classification of Diseases-9-Clinical Modification (ICD-9-CM) diagnosis and procedure codes, and specific financial/utilization data (which include pharmacy, imaging, and clinical services). Included in the medication data are the date, type, and route of administration of any medication administered. Member hospitals have access to the multicenter database via a virtual private network.

The PHIS database was queried to extract data on each of the variables described below. Once data were extracted, SAS version 9.1 (Cary, NC) and Stata statistical software version 10.0 (College Station, TX) were used to convert the PHIS data into a survival database. The survival database contained one line representing each of the 365 days after a patient's AML diagnosis. For each inpatient day, information on the medications administered and hospital resources utilized was available. ICD-9-CM discharge diagnoses and discharge disposition were available on the day of discharge for each hospitalization. The code written to convert the PHIS data into a survival database was validated in a 5% random sample of the cohort.

Defining the Study Cohort

The source population for our study was children aged 0–18 years with a hospital discharge date in the PHIS database between January 1, 2002 and December 31, 2006. Children were considered for study cohort inclusion if their index hospitalization in the database was assigned an ICD-9-CM code for any type of myeloid or unspecified leukemia at one of the 21 ICD-9-CM diagnosis fields. In addition, children were excluded if they were admitted to a hospital during time periods when CHCA deemed that hospital's data invalid or missing.

In order to further restrict our cohort to children with newly diagnosed AML, an analysis of the specific chemotherapy regimen administered to each patient in their index admission was performed. Using Stata statistical software version 10.0, code was written to recognize standard AML induction chemotherapy regimens, defined by a pediatric oncologist (R.A.), based on chemotherapeutic agents administered and the pattern of the regimen. A random sample of regimens identified by the Stata code was manually reviewed to validate the code. All chemotherapy regimens not identified by the Stata code were manually reviewed and, if consistent with an AML induction chemotherapy regimen, marked as identifiable. Patients with an induction chemotherapy regimen that was identifiable by Stata code or manual review were included in the study cohort. Those receiving a regimen not consistent with AML induction therapy were said to be misclassified by ICD-9 CM codes and were excluded from the final study cohort. Lastly, any patients with a diagnosis of trisomy 21 (ICD-9-CM code 758.0 “Down's syndrome”) were excluded. These children were excluded because they receive substantially different chemotherapeutic regimens and therefore are not necessarily comparable to the rest of the AML cohort.

Variable Definitions

Demographics—The following variables were defined at the time of AML diagnosis for each patient: gender, age, and race. Age was analyzed as a continuous and a categorical variable (0–2 years, >2–10 years, >10–16 years, and >16–18 years) consistent with prior AML cohort publications [9]. Race was reported as a categorical variable (white, black, Asian, other, and missing). For the purposes of the final analysis race was dichotomized as black compared to non-black. The decision to dichotomize race in this manner was based on prior literature that suggests black patients have a poorer overall prognosis after leukemia diagnosis [15].

Risk factors for ARF—A number of medications and co-morbid conditions were predicted a priori as possible contributors to ARF. AML chemotherapy certainly places a patient at risk for developing ARF. However, all patients will have undergone similar chemotherapy regimens and therefore their baseline risk for ARF relative to chemotherapy should be comparable at specific time points from initial diagnosis. Adjustment of time since diagnosis in a survival analysis thus acted as a proxy for chemotherapy exposure.

Other medications associated with ARF will have been administered to patients based on clinical scenarios specific to the patient. Most important are the following antimicrobial medications: aminoglycosides (amikacin, gentamicin, kanamycin, netilmicin, streptomycin, and tobramycin), vancomycin, amphotericin B (conventional and lipid formulations), and antiviral agents (acyclovir, valacyclovir, famciclovir, ganciclovir, valganciclovir, cidofovir, and foscarnet). Data were too sparse to evaluate aminoglycosides, amphotericin products, and antiviral agents separately. Therefore, a composite variable for each was created for final analysis.

Additionally, it was postulated that patients receiving broad-spectrum antibiotics were likely to be generally more ill and therefore more likely to develop ARF even if the agent administered was not typically thought to be nephrotoxic. This is otherwise referred to as confounding by indication [16]. To assess for this possibility, the association of carbapenems (ertapenem, meropenem, and imipenem) with ARF was also analyzed in a similar manner to the above potentially nephrotoxic medications.

Poor clinical status of a patient would also likely contribute to an increased risk for ARF. Specific clinical conditions included the following: respiratory decompensation, cardiac failure, liver failure, and presence of hypotension or shock. Time-dependent identification of these co-morbid conditions was thought to be important in assessing their association with onset of ARF (see below). Therefore, use of ICD-9-CM discharge codes was not ideal to define the timing of these co-morbid conditions. Instead, medications administered or hospital resources often utilized by patients with the respective condition were used as a proxy to define the presence of a co-morbid condition at a specific time point (Table I).

To account for a patient's severity of illness, we created a proxy severity of illness measure for each hospitalization day. A daily composite severity of illness variable was created to define the presence of any of the above co-morbid conditions. If on a particular hospital day a patient utilized at least one of the medications or hospital resources used to define each co-morbid condition then that day was considered a day of severe illness (Table I).

Exposure to each of the above potential risk factors was documented daily for each patient. The total number of days exposed to each of these risk factors was calculated for each 30-day period that the patient was contributing to the survival data set. Each 30-day period was then categorized for each risk factor as no exposure, 1–2 days exposure in a 30-day period, 3–10 days exposure in a 30-day period, or >10 days exposure in a 30-day period. Amphotericin B product exposure was the only exception as this risk factor was categorized as no exposure, 1–6 days exposure in a 30-day period, and >6 days exposure in a 30-day period. These categorizations were deemed appropriate as they would mirror clinically important durations of antimicrobial agents and clinically important durations of the need for certain medical interventions. Furthermore, it would allow for evaluation of potential dose–response outcomes with regard to ARF.

Outcome—The primary outcome for this study is the new onset of ARF during any hospitalization within 1 year from AML diagnosis. ARF was defined as the presence of an ICD-9-CM code for ARF at one of the 21 ICD-9-CM diagnosis fields. The date of

assignment of the ICD-9-CM code for ARF is not available in the PHIS database. Therefore, in the analysis the date of ARF onset will be assumed to be the hospital discharge date for the hospitalization during which ARF was first identified.

Statistical Analysis

Summary statistics were constructed using frequencies and proportions for categorical data elements and means and medians for continuous variables. Pearson's chi-square test was used when appropriate. A *P*-score <0.05 was considered significant.

Cox proportional hazards models were performed to compare the time to ARF in patients with each risk factor compared to those without. A priori identified exposures (aminoglycosides, amphotericin B, vancomycin, and antivirals) and co-morbidities (respiratory decompensation, liver failure, cardiac failure, and hypotension/shock) thought to be associated with ARF were first analyzed one at a time. Those variables found to have a significant association with ARF were included in a final multivariable Cox regression model including age, race, and gender. The unadjusted and adjusted associations for each risk factor with ARF are reported as hazard ratios (HR) with 95% confidence intervals.

We performed additional analyses to determine the within and among hospital effects. Confounding by hospital can occur when both the exposure of interest and outcome are clustered by hospital. To address this potential problem, we decomposed the within- and among-hospital components of the effect of patient demographics and antimicrobial agent choices at each institution [17,18].

Calculation of the cumulative HR using Cox regression analysis assumes that there is conservation of proportional hazards throughout the study period of interest. If there is variation of the proportional hazards from one time period of the study to another, then there is likely a violation of the proportional hazards assumption. The proportional hazard assumption was tested by evaluating the Schoenfeld residuals and using rank of analysis time as the time scaling function. In the setting that the proportional hazards assumption was violated, identification of the timing of the proportional hazard variation was explored by interacting the exposure variables of interest and confounders of interest with time. All analyses were conducted with Stata statistical software version 10.0.

Human Subject's Oversight

The conduct of this study was approved by the Child Health Corporation of America and the Committee for the Protection of Human Subjects at the Children's Hospital of Philadelphia.

RESULTS

Between January 1, 2002 and December 31, 2006 we identified 2,135 patients with a hospital admission that included an ICD-9-CM discharge diagnosis code for myeloid or unspecified leukemia. Patients were then excluded if the induction chemotherapy regimen was inconsistent with AML, an AML hospital admission was identified prior to the study period, or an ICD-9-CM code for trisomy 21 was present. Additionally, during certain time points in the study period, some hospitals contributed only demographic data and not pharmaceutical level data to the PHIS database. If an identified patient was admitted during one of these periods then they were excluded from the final cohort. This resulted in a final study cohort of 831 patients who were admitted to 37 of the 41 PHIS contributing hospitals (Fig. 1). Consistent with prior literature on pediatric AML, the median age of this cohort was 9.14 years (IQR: 2.9–14.0 years), showed a slight male predominance, and had an in-hospital mortality rate at 1 year from diagnosis of 14.4% (Table II).

Each patient was followed until development of ARF, in hospital death, or until 1 year from the date of AML diagnosis. Within 1 year of initiation of AML chemotherapy, 135 (16.2%) patients were diagnosed with ARF. The median age of patients diagnosed with ARF was 13.1 years (IQR: 4.7–15.8 years). Males accounted for 45% of ARF cases and 20% were black. More than half (56.3%) of the incident ARF diagnoses were made during a patient's first AML admission, 11.1% during the second admission, and the remaining were diagnosed during the third through fourteenth admissions. Patients diagnosed with ARF versus those without a diagnosis of ARF were more likely to suffer in-hospital mortality (30% vs. 10.1%, Pearson's chi-square, P -value < 0.001).

The unadjusted analysis suggested that patients diagnosed with ARF were older, more likely to be female, and were more commonly black. Additionally, there appeared to be a dose–response association for each of the antimicrobial, antiviral, and antifungal agents evaluated (Table III). At short durations of exposure (1–2 days) none of the antimicrobial agents were associated with a significant increased risk in ARF. Each of the defined resources used as a proxy for co-morbid illnesses was associated with an increased risk for ARF even if only present for short time periods (1–2 days). With the exception of respiratory decompensation, all co-morbid conditions showed an increasing risk for ARF with prolonged presence of the co-morbid condition. For respiratory decompensation, the risk for ARF actually decreased when respiratory decompensation was present for 3–10 days and then increased again when present for 10 or greater days (Table III).

Recognizing that each of the nephrotoxic associated antimicrobial agents and co-morbid conditions was associated with an increased risk of ARF with longer exposures, they were all included in a multivariate Cox regression analysis along with age, gender, and race. In an attempt to limit the number of variables in this final model, the composite severity of illness variable was used alone to account for presence of the co-morbid conditions (cardiac failure, respiratory decompensation, liver failure, and hypotension/shock). This same model included mean use of each antimicrobial agent and mean presence of severity of illness for each hospital to account for variation of each of these variables by hospital.

The results of this multivariable model are shown in Table IV. Both age and black race were associated with a higher risk of ARF. A majority of the antimicrobial agents that were associated with ARF in the univariate analyses were no longer associated with ARF in this comprehensive model. Only vancomycin (exposure durations of 3–10 days and >10 days) and carbapenem exposure (>10 days) were associated with ARF.

Finally, simultaneous exposure to vancomycin and aminoglycosides during any 30-day period was tested in a multivariate model analyzing the combined exposure of the two antimicrobials. Whether alone (HR: 3.38, 95% CI: 1.45–7.91) or in combination with aminoglycosides (HR: 3.71, 95% CI: 1.47–9.39), vancomycin had a similarly significant association with ARF relative to no exposure to either vancomycin or aminoglycosides. However, aminoglycosides alone was not significantly associated with ARF (HR: 2.13, 95% CI: 0.59–7.72) as compared to no exposure to either antibiotic.

DISCUSSION

This is the first report on the frequency of ARF from a national cohort of children treated for AML. ARF was an unexpectedly common (16.2%) co-morbid condition, most frequently presenting during the first or second AML hospitalization. In the adjusted analysis, increasing age, black race, and prolonged duration of vancomycin were each independently associated with a significantly increased risk for development of ARF.

The etiology for an increase in risk relative to an increase in age is not currently known. Certainly, the prognosis in the treatment of AML has been documented to be worse with increasing age [19]. Moreover, older children may be more susceptible to the development of co-morbid conditions or an elevated baseline susceptibility to renal damage from nephrotoxic agents. Work by other investigators has shown that amphotericin B causes less nephrotoxicity among younger children [20]. However, even after control for exposure to such nephrotoxic agents, the association between increasing age and ARF was observed.

Of concern was the increased risk for development of ARF in black children compared to all other children in the cohort. Prior published literature has documented a worse overall outcome in AML patients who are black or Hispanic [15]. Since AML therapy is primarily inpatient, the increased risk of AML treatment-related toxicity is not thought to be related to differential access to medical care resources. The increased risk of ARF may be due to pharmacogenetic variations conferring an increased susceptibility to toxicity from nephrotoxic agents. Davies et al. [21] have previously demonstrated that the GSTT1 homozygous deletion has been associated with an increased risk of AML treatment-related toxicity. Interestingly, two reports have noted that GSTT1 deletions are also a risk factor for end-stage renal disease [22,23]. Thus, the GSTT1 gene may be a potential candidate for investigation.

We evaluated the association of a number of antimicrobials that are commonly thought to be nephrotoxic (aminoglycosides, vancomycin, amphotericin B products, and antiviral agents) as well as agents not thought to be routinely nephrotoxic (carbapenems). In the unadjusted analysis each of these agents was shown to have a dose-response relationship with longer durations of exposure resulting in a higher risk for ARF. We were concerned that such associations were the result of confounding by indication. That is, more severely ill patients were more likely to receive antimicrobials and thus more likely to develop ARF as a result of their severe illness. Therefore, we incorporated a composite severity of illness variable into the final model. This resulted in a reduction in the association of each of the antimicrobial agents and ARF. Thus, even after prolonged exposure to aminoglycosides, there still did not appear to be an increased risk of ARF. However, an association of vancomycin exposure (beyond 48 hr duration) with ARF persisted in this analysis.

This study has several strengths that support the validity of the described associations. First, the study cohort is a nationally representative sample identified from 85% of free-standing pediatric hospitals in the United States. Thus, the results are likely very generalizable to all pediatric AML patients. Second, the study cohort is the largest reported to date with a validated measure of renal failure. This large sample size enables an accurate estimation of ARF risk and a comprehensive evaluation of potential risk factors. To our knowledge, no other data set has allowed the estimation of ARF during AML therapy or risk factors for ARF in children with AML.

However, a number of limitations should also be acknowledged. The identification of the cohort was based on the presence of an ICD-9-CM code consistent with an AML diagnosis and receipt of chemotherapy consistent with AML chemotherapy. While this two-stage process was likely specific in identifying patients with AML it did not differentiate patients with newly diagnosed AML from those with relapsed AML.

The study outcome (ARF) was also based on the presence of ICD-9-CM codes that resulted in at least two limitations. First, ICD-9-CM codes may not identify all patients experiencing the outcome of interest. Work by other investigators has shown that ICD-9 codes are specific but not sensitive for ARF [24]. Therefore, the frequency of ARF may be under-reported in this cohort. Additionally, data specific to chemotherapy toxicity criteria grading

of the ARF events were not available, limiting our ability to quantify severity and duration of ARF.

Second, the ICD-9-CM codes were assigned on the day of discharge rather than the day of ARF development. Unfortunately, a pharmaceutical intervention or hospital resource that could reasonably act as a proxy for ARF could not be identified. Therefore, the results should be interpreted with the knowledge that the timing of ARF is likely delayed relative to the exposures. This delay likely limits the ability of the study to identify an association between a particular antimicrobial agent and ARF. However, since both of these limitations should produce a bias toward the null, neither should decrease the validity of the associations of age and black race with an increased risk of ARF.

In summary, ARF is a relatively common and early onset problem in children receiving therapy for AML. The risk increases with age and is greater in black children than non-black children. There does not appear to be a significant association between short empiric therapies (48 hr or less) of potentially nephrotoxic antimicrobial agents and ARF. Therefore, physicians should feel comfortable in administering these agents in children who present with fever and suspicion of infection while culture results are pending. Clinicians should be cautious in the use of vancomycin for extended periods of time and closely monitor vancomycin levels and renal function. Future studies of ARF should focus on pharmacogenomic determinants of differential toxicity.

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Fig. 1.

Flow diagram describing identification of 831 patients receiving chemotherapy consistent with new onset pediatric AML. *At the time of these admissions, these hospitals were only contributing demographic and not pharmaceutical level data so these patients were excluded from the final cohort.

TABLE I**Medications and Hospital Resources Used as Proxy Measures of Co-Morbid Conditions**

Co-morbid condition^a	Medication or hospital resource
Cardiac failure	Milrinone, dopamine, dobutamine, or epinephrine
Respiratory failure	CPAP, BiPAP, mechanical ventilation (conventional or HFOV), or ECMO
Liver failure	Ursodiol, factor VII, factor VIII, or factor IX replacement
Shock	Dopamine, dobutamine, epinephrine, or norepinephrine
Composite severity of illness measure	Daily presence considered if at least one of the co-morbid conditions above existed

CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; HFOV, high flow oscillatory ventilation; ECMO, extracorporeal membrane oxygenation.

^aPresence of each co-morbid condition was defined on a daily basis based on the presence of at least one of the listed medications or hospital resources.

TABLE II**Demographic Characteristics and In-Hospital Mortality**

Age in years (median; IQR)	9.14 (2.9–14.0)
Age in years categorized	
0–2 years	165 (19.9)
>2–10 years	273 (32.9)
>10–16 years	280 (33.7)
>16–18 years	113 (13.6)
Gender	
Male	468 (56.3)
Race	
White	587 (70.6)
Black	109 (13.1)
Asian	27 (3.3)
Other	76 (9.1)
Missing	32 (3.9)
Number of hospitalizations (median; IQR)	6 (3–7)
Length of first hospitalization (median; IQR)	33 (23–42)
In-hospital mortality	120 (14.4)

TABLE III

Unadjusted Cox Proportional Hazards Model With Resultant Hazard Ratios and 95% Confidence Intervals for Each a Priori Identified Risk Factor for ARF

Risk factor	Hazard ratios (95% confidence intervals)		
Demographic variables			
Age	1.07 (1.03–1.10)		
Female gender	1.58 (1.13–2.22)		
Black race	1.72 (1.13–2.62)		
	1–2 days ^a exposure	3–10 days ^a exposure (1–6 days for amphotericin)	>10 days ^a exposure (>6 days for amphotericin)
Medications			
Aminoglycosides ^b	1.84 (0.87–3.91)	3.05 (1.99–4.66)	3.23 (1.99–5.26)
Vancomycin	2.21 (0.73–6.68)	6.58 (3.67–11.78)	11.10 (6.14–20.06)
Amphotericin B ^c	—	2.20 (1.31–3.70)	3.75 (2.50–5.64)
Antivirals ^d	2.12 (0.78–5.79)	2.32 (1.35–3.98)	3.60 (2.38–5.43)
Carbapenems ^e	1.28 (0.40–4.06)	1.84 (1.09–3.10)	3.81 (2.49–5.84)
Clinical co-morbidities ^f			
Cardiac failure	2.95 (1.75–4.98)	10.98 (6.92–17.42)	18.84 (10.09–35.16)
Respiratory failure	12.87 (6.70–24.70)	4.06 (1.49–11.04)	20.97 (10.10–43.55)
Liver failure	5.77 (3.51–9.45)	8.04 (4.92–13.14)	12.90 (7.95–20.93)
Hypotension/shock	2.99 (1.77–5.05)	12.78 (8.20–19.93)	19.78 (10.05–38.92)
Composite of severe illness ^f	5.17 (3.15–8.50)	8.61 (5.30–14.00)	17.89 (11.30–28.32)

^aEach compared to baseline of no exposure in the preceding 30-day period;

^bAmikacin, gentamicin, kanamycin, netilmicin, streptomycin, and tobramycin;

^cConventional and lipid formulations; categories were based on 0, 1–6, and >6 days;

^dAcyclovir, valacyclovir, famciclovir, ganciclovir, valganciclovir, cidofovir, and foscarnet;

^eErtapenem, imipenem, meropenem;

^fSee Table I for description of how each co-morbidity and composite severity of illness was defined.

TABLE IV

Adjusted* Cox Proportional Hazards Model With Resultant Hazard Ratios and 95% Confidence Intervals for Each a Priori Identified Risk Factor for ARF

Risk factor	Hazard ratios (95% confidence intervals)		
Demographic variables			
Age	1.04 (1.01–1.08)		
Female gender	1.39 (0.94–2.04)		
Black race	1.67 (1.11–2.51)		
	1–2 days ^a exposure	3–10 days ^a exposure (1–6 days for amphotericin)	>10 days ^a exposure (>6 days for amphotericin)
Anti-infective agents			
Aminoglycosides ^b	0.99 (0.44–2.23)	1.26 (0.77–2.06)	1.03 (0.56–1.90)
Vancomycin	1.29 (0.47–3.58)	3.04 (1.67–5.52)	3.15 (1.37–7.24)
Amphotericin B ^c	—	1.11 (0.68–1.80)	1.30 (0.82–2.04)
Antivirals ^d	1.78 (0.68–4.70)	1.39 (0.88–2.18)	1.60 (0.96–2.67)
Carbapenems ^e	1.05 (0.29–3.82)	1.12 (0.63–1.99)	1.83 (1.14–2.96)
Composite of severe illness ^f	3.36 (2.02–5.58)	4.91 (2.89–8.33)	8.83 (5.42–14.37)

* Each hazard ratio is adjusted for all other variables as well as the variability for each covariate by hospital site;

^a Each compared to baseline of no exposure in the preceding 30-day period;

^b Amikacin, gentamicin, kanamycin, netilmicin, streptomycin, and tobramycin;

^c Conventional and lipid formulations; categories were based on 0, 1–6, and >6 days;

^d Acyclovir, valacyclovir, famciclovir, ganciclovir, valganciclovir, cidofovir, and foscarnet;

^e Ertapenem, imipenem, meropenem;

^f See Table I for description of how composite severity of illness was defined.