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Trends in *Clostridium difficile* Infection and Risk Factors for Hospital Acquisition of *C. difficile* Among Children with Cancer

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Abstract

Objectives—To study the trend of *Clostridium difficile* infection (CDI) and risk factors for hospital acquired CDI (HA-CDI) among children with cancer.

Study design—We analyzed 33,095 first pediatric hospitalizations for malignancy among 43 pediatric hospitals between 1999 and 2011. The effect of demographics, disease characteristics, and weekly drug exposure (antibiotics, antacids and chemotherapy) on HA-CDI was assessed with multivariate Cox regression. CDI was defined by the combination of ICD-9CM code, CDI diagnostic assay billing code and concurrent administration of a CDI-active antibiotic. HA-CDI was defined as CDI with assay occurring after the 6th hospital day.

Results—1,736 admissions with CDI were identified, of which 380 were HA-CDI. CDI incidence increased from 1999–2006 (p=0.01); however, CDI testing frequency and disease

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decreased from 2006–2010 ($p<0.05$). Admissions with HA-CDI had longer lengths of stay compared with those without HA-CDI (35days vs. 12days, $p<0.01$) and greater risk of inpatient mortality (RR 2.3, $p<0.01$). Increased risk of HA-CDI (hazard ratio [95% confidence interval]) was seen after exposure to the following drugs: aminoglycoside (1.357 [1.053 – 1.749]), third generation cephalosporin (1.518 [1.177 – 1.959]), cefepime (2.383 [1.839 – 3.089]), and proton pump inhibiting agent (1.398 [1.096 – 1.784]) in the prior week, and chemotherapy in the 8–14 days prior to HA-CDI onset (1.942 [1.491 – 2.529]). Histamine-2 receptor antagonist exposure in the prior week was associated with decreased risk of HA-CDI (0.730 [0.584 – 0.912]).

Conclusions—Despite an apparent decrease in CDI incidence from 2006–2010, HA-CDI remains prevalent and morbid among children with cancer. Recent exposure to chemotherapy, proton pump inhibitor, and certain antibiotics were independent risk factors for HA-CDI.

Keywords

pediatric oncology; nosocomial infection; antibiotics; chemotherapy; epidemiology

Clostridium difficile infection (CDI) is the most common cause of nosocomial diarrhea and can lead to a range of complications from colitis to toxic megacolon, bowel perforation and death. CDI is a significant cause of nosocomial and antibiotic-associated diarrhea in adults,(1, 2) with increasing frequency and severity.(3–5) Even though the frequency of CDI in children was only 2.6 per 1000 admissions in 2001, the annual incidence of pediatric CDI increased 55% between 2001–2006.(6, 7) Recent reports have described more severe CDI in the pediatric population(8, 9) and demonstrate that 25% of pediatric CDI occurs in children with cancer.(6)

Although CDI incidence may be overrepresented among children with cancer, there have been no publications on the incidence of CDI in children with cancer since 2006 and there is a paucity of data evaluating risk factors for CDI in this population. Tai et al(10) examined demographic and healthcare utilization factors, but were unable to obtain individual medication data. We hypothesize that children with cancer may have an increased risk of CDI due to their underlying malignancy, exposure to chemotherapy, broad-spectrum antibiotics, and supportive medications. Identifying potentially modifiable risk factors could lead to a reduction in CDI in this vulnerable population. Because children with cancer have frequent and prolonged hospital exposures, evaluating risk factors specific to hospital acquired CDI (HA-CDI) may permit targeting the most effective interventions.

Using the Pediatric Health Information Systems (PHIS) database, we sought to evaluate CDI trends since 2006 among children with cancer and identify risk factors for HA-CDI in this population.

METHODS

We performed a retrospective cohort study to determine the incidence of CDI among hospitalized patients with cancer, to examine the outcomes associated with CDI during initial hospitalization for malignancy, and to identify risk factors for HA-CDI among a large cohort of children with newly diagnosed malignancy. Children with cancer entered the

cohort when they were first hospitalized for malignancy. Inpatient data were acquired for the index admission and all subsequent hospitalizations. Only index hospitalizations were used for risk factor analysis of HA-CDI. Patients were censored if they died or received a bone marrow transplant prior to CDI.

The PHIS database currently contains inpatient data from 43 not-for-profit, free-standing, tertiary care children's hospitals in the United States affiliated with the Children's Hospital Association. Member hospitals represent 17 of the 20 major metropolitan areas across the United States, and comprise 85% of the free-standing children's hospitals in the United States registered with the National Association for Children's Hospitals and Related Institutions. Data quality and reliability are ensured through a joint effort between the Children's Hospital Association, a data manager (Thompson Healthcare) and participating hospitals. Data are de-identified at time of submission and subjected to 175 reliability and validity checks. Data are accepted into the database when classified errors occur in fewer than 2% of the hospital's quarterly data. Institutional review board approval was granted prior to acquiring any data.

Inpatients at PHIS hospitals between June 1, 1999 and March 31, 2011 who received an ICD-9CM code for malignancy (140.0–209.3) were included in the cohort. To restrict our cohort to new malignancies, subjects were included only if their index hospitalization was preceded by 6 months of PHIS hospital data during which an ICD-9CM code for malignancy was not assigned. Patients less than one year old at their index hospitalization were excluded due to the high prevalence of asymptomatic *C. difficile* colonization in that age group.(11) To reduce prior knowledge that may bias physician CDI testing or medication selection, only the first cancer hospitalization was used for HA-CDI risk factor analyses. Because hospitalizations less than 7 days duration could not contribute to HA-CDI, they were excluded to ensure comparability during risk factor analysis for HA-CDI. Patients were censored from the cohort at the end of hospitalization, stem cell transplantation or death. Sex, age, malignancy, year of admission, and race were all defined at the time of the each subject's index hospitalization. Age at admission and year of index admission were analyzed continuously and categorically by quartiles (age as >1–3 years, >4–8 years, >9–14 years, and >14 years; year of admission as 1999–2003, >2004–2006, >2007–2008, >2009). Race was reported as a categorical variable (white, black, Asian, American Indian, other, and missing). Malignancies were categorized by ICD-9CM code into categories (leukemia, lymphoma, non-CNS solid tumor, CNS tumor) used in prior studies.(12)

CDI was defined by ICD-9CM code (008.45), as well as billing for a laboratory test code for a *C. difficile* toxin assay and billing for either metronidazole (oral or parenteral) or oral vancomycin within the period of 1 day before or 2 days after the toxin assay. The billing code for toxin assay is non-specific and may include enzyme immunoassay, polymerase chain reaction (PCR) or both. The date of CDI was defined as the date of the toxin assay. This definition of CDI has been previously validated in an inpatient setting with a positive predictive value of 83.0% and a negative predictive value of 99.9%.(13) HA-CDI was defined as CDI that occurred after at least 6 inpatient days.

A number of medications and co-morbid conditions were predicted *a priori* as possible contributors to HA-CDI. Antibiotics, antacids, and chemotherapeutic agents were analyzed by class. Because chemotherapy class may not correlate with extent of immunosuppression or mucositis, chemotherapeutic agents were analyzed as a single group. Disease severity was defined as a categorical variable that reported a history of vasopressor support, ventilation use, or both previously in that hospitalization.

Exposure to each potential risk factor was documented daily for each subject. For purposes of analysis, medication or medication category exposures were dichotomized as at least one day of exposure or no exposure within the last seven days. It is plausible that simply dichotomizing recent antibiotic exposures by category may underestimate the impact of total antibiotic exposure on risk for HA-CDI. Therefore, a measure of total days of antibiotic therapy (DOT) administered during the last seven days was also established. This variable (the total number of days of each antibiotic given within the last seven days) was defined categorically (no DOT, 1-3 DOT, 4-7 DOT, and >7 DOT). The DOT categorical variable was analyzed in a separate model from the model that including individual antibiotic categories. Finally, chemotherapy exposure 8 to 14 days prior was included in the analysis based on the estimated onset of immunosuppression and mucositis from those drug exposures.

Statistical analyses

Summary statistics were constructed using frequencies and proportions for categorical data elements and means and medians for continuous variables. Pearson Chi-square test and Mann-Whitney-Wilcoxon test were used when appropriate. A p-value of <0.05 was considered significant. Trends were examined using a non-parametric version of the Cochrane-Armitage test.

Bivariate analysis stratified by site was conducted to determine the association between risk factors and HA-CDI. Demographic characteristics were analyzed using a Chi-square test, and drug exposure was analyzed using a Log-rank test. A p-value of < 0.20 was used to identify covariates to be analyzed in a multivariable model.

A Cox Proportional Hazards multivariable regression was used to identify independent predictors of HA-CDI. Analysis was stratified by hospital site to allow for variability in CDI frequency and prescribing practices among hospitals. Covariates were eliminated from the multivariate model if the p-value of their association with CDI was >0.05 and if their elimination from the model did not change the hazard ratio estimates of other covariates by >15%. Because interaction between co-administered medications can cause changes in drug elimination and metabolism and result in increased medication effects and toxicity, potential drug interactions identified using a pharmaceutical database (Lexicomp: www.lexi.com) were investigated in our analysis. Additional interaction terms that modeled interactions between age at admission and malignancy category were also investigated.

In order to determine the strength of our findings, we extended our drug exposure window from the last seven days to include the prior 14 days and prior 21 days. To determine if potential data entry errors may have influenced our results, a drug index [(number of days a

drug was billed) / (number of inpatient hospital days)] for three common antibiotics (cefepime, vancomycin and ciprofloxacin) was created for each hospital site during each year. Outliers of this index were eliminated in a subsequent sensitivity analysis. Because our cohort included a wide range of hospital durations, a sub-analysis investigated whether significant differences existed between those hospitalizations that were shorter or longer than the median hospital duration. To investigate the effect of mucositis on HA-CDI risk, a sub-analysis divided chemotherapy exposure categorically into exposure to agents associated or not associated with mucositis.(14) Risk factor analysis was repeated for individual cancer diagnoses to investigate potential differences in risk between cancer types. All analyses were conducted with STATA statistical software version 11.2 (College Station, TX).

RESULTS

Between June 1, 1999 and March 31, 2011, we identified 33,095 patients who matched our inclusion criteria. Of these patients, 1,736 (5.2% of patients, 2.6% of hospitalizations) had at least one hospitalization associated with CDI. Considering all index admissions for malignancy, 574 contained a diagnosis of CDI, of which 380 were HA-CDI. The incidence of CDI and frequency of *C. difficile* toxin assays in children hospitalized for malignancy in 43 participating PHIS hospitals is seen in Figure 1. From 1999 to 2010, the incidence of CDI among children hospitalized for malignancy increased from 7.3 to 13.4 cases of CDI/10,000 inpatient days ($p=0.04$). This is despite no significant change in the frequency of *C. difficile* toxin assays from 1999 to 2010 ($p=0.93$). Because prior studies analyzed the incidence of CDI only until 2006,(6, 7, 10) a separate analysis examined trends after 2006. The incidence of CDI and the frequency of toxin assays both decreased from 2006-2010 ($p<0.05$).

To analyze risk factors for HA-CDI, only those CDI events diagnosed after the sixth hospital day of the index admission were considered. Demographics of this cohort are shown in Table I. Between patients who were diagnosed with HA-CDI during their first admission and those who were not diagnosed with HA-CDI, there were significant unadjusted differences in race, age at admission, year of admission, type of malignancy, length of stay, and inpatient mortality. In the multivariate Cox proportional hazards regression model, stratified by hospital site, recent chemotherapy exposure (8–14 days prior), exposure in the past week to certain antibiotics commonly used for febrile neutropenia (aminoglycosides, 3rd generation cephalosporins and cefepime), male sex, non-CNS solid tumor and proton pump inhibitors were each independently associated with an increased risk of HA-CDI (Table II). Notably, exposure to Histamine-2 (H2) receptor antagonists appeared protective. Among antibiotics often used in the setting of fever and neutropenia, third and fourth generation cephalosporins were associated with the greatest risk of HA-CDI (Figure 2).

Sensitivity analyses that allowed for prolonged exposure windows (up to 14 and 21 days prior) for cephalosporins and gastric acid blockade, which excluded hospital sites and admission years with potential data entry errors, or excluded hospital admissions with either longer (>11days) or shorter (≤ 11 days) hospital stays resulted in similar findings (data not shown). A sub-analysis investigating DOT in the past 7 days demonstrated that 1 to 3 DOT, 4 to 7 DOT, and greater than 7 DOT were associated with hazard ratios (HR [95% CI]) of

1.553 [1.068 – 2.257], 1.972 [1.434 – 2.710], and 1.691 [1.196 – 2.391] compared with no antibiotic exposure, respectively. Compared with no chemotherapy exposure, HR [95% CI] for chemotherapy exposure in the prior 8 to 14 days associated and not associated with mucositis were 1.971 [1.494–2.601] and 1.827 [1.186–2.813], respectively. Similar multivariate analyses performed on sub-cohorts of patients with similar cancer diagnoses and at least 20 HA-CDI events demonstrated few significant differences. These results are shown in Table III (available at www.jpeds.com).

Subjects with HA-CDI had longer length of stay for their index hospitalization compared with those patients without HA-CDI in their index admission (median 35days vs. 12days, $p<0.01$). All-cause mortality also was different between these two patients groups: 19/379 (5.0%) patients with HA-CDI died in the hospital during that visit vs. 713/32,689 (2.2%) without HA-CDI (RR 2.29, 95% confidence interval [1.47 – 3.57], $p<0.01$). Of those who died after being diagnosed with HA-CDI, 8 of 19 (42%) were not treated with vancomycin or metronidazole in the last week of their lives. The median time from HA-CDI diagnosis to death was 50 days (range 1–371 days).

DISCUSSION

We investigated both demographic and daily patient-level drug exposures in the analysis of HA-CDI risk factors in children with cancer. In this study, we found that the CDI rate in children with cancer is approximately ten times the incidence of CDI previously reported for all hospitalized children.(6) Importantly, our data identify recent chemotherapy exposure as an independently associated risk factor for HA-CDI in children, and our results suggest that patients diagnosed with HA-CDI in their index malignancy admission had significantly longer hospital stays and were twice as likely to die during that index admission.

Similar to prior studies,(6, 10) we found an overall increase in the incidence of CDI in children with cancer from 1999 to 2010 ($p=0.04$) despite a stable frequency of *C. difficile* toxin assays ordered ($p=0.93$). However, although the incidence of CDI increased 221% between 1999 and 2006 ($p=0.01$), CDI incidence and frequency of *C. difficile* toxin assays subsequently decreased from 2006 to 2010 ($p<0.05$). This may represent a plateau of CDI prevalence, as has recently been shown in the Nationwide Inpatient Sample data.(15) However, because our definition of CDI included billing for a *C. difficile* toxin assay, it is impossible to tell if this change represents a true decrease in CDI incidence, a decrease in CDI testing frequency or a change in how contemporary *C. difficile* diagnostic modalities are captured in PHIS. PCR tests for *C. difficile* toxin genes are becoming frequently utilized in many clinical laboratories. If billing for these PCR tests are not as of yet appropriately captured in PHIS, the frequency of CDI will appear artificially diminished. It will be important for future studies to investigate whether this decrease in CDI incidence is real and whether it is limited to children with cancer.

As noted above, HA-CDI during the index cancer admission was associated with prolonged hospital stays and increased overall mortality; it is difficult to quantify the direct attributable effect of HA-CDI. As the diagnosis of HA-CDI preceded death by a median of 50 days and 42% of patients who died did not receive an antibiotic active against *C. difficile* in the last

week of their lives, it is unlikely that much of the increased mortality was directly attributable to HA-CDI. However, HA-CDI may indirectly contribute to higher mortality by affecting nutritional status, requiring more invasive procedures or delaying planned chemotherapy. Alternatively, HA-CDI may be a marker of the severity of a patient's underlying malignancy and poor health status, which are the actual causes of longer hospital stays and increased mortality. Further investigation is necessary to define the association between HA-CDI and increased mortality among children with cancer.

As with many prior studies, we found that exposure to broad-spectrum antibiotics was associated with an increased risk of HA-CDI. Third and fourth generation cephalosporins were associated with the greatest risk, and fluoroquinolones and anti-pseudomonal penicillins used by some clinicians for febrile neutropenia were not associated with increased risk. However, the 95% CI was wide (0.488 — 1.142); insufficient power may have obscured a significant association. Additional investigations are necessary to corroborate these findings before endorsing certain anti-pseudomonal agents as a better option for fever and neutropenia. We also found an increasing risk of CDI associated with 1 to 3 DOT, and 4 to 7 DOT, compared with no antibiotic exposure suggesting a dose response effect for amount of antibiotic exposure, but there is no such dose response effect when considering 7 or more DOT. It may be that the risk of CDI reaches a threshold at a certain number of DOT or that patients that reached the 7 or more DOT category within the one week exposure window were treated with antibiotics associated with lower risk of CDI.

Interestingly, exposure to chemotherapy 8–14 days prior, and not in the week preceding, increased the risk of HA-CDI independent of exposures to antibiotics or other supportive care medications. This timing of increased risk (in the second week after chemotherapy exposure) coincides with the expected onset of chemotherapy-induced neutropenia and mucositis. Reports in adults have noted the association between chemotherapy and CDI, but have not been able to identify a period of greatest risk after chemotherapy.(16–19) Our analysis did not show that exposure to chemotherapy associated with mucositis increased the risk of HA-CDI compared with chemotherapy not associated with mucositis. If patients exposed to mucositis-associated chemotherapy failed to develop mucous membrane breakdown due to variable toxicity or low dosing, this difference may have been biased toward the null and concealed a real effect. However, exposure to chemotherapy that does not commonly cause mucositis was still associated with an increased the risk of HA-CDI, suggesting that neutropenia may be a more important aspect of chemotherapy risk than mucositis. In addition to neutropenia, decreased levels of anti-*C. difficile* toxin immunoglobulin G (20) has been proposed as a reason for the association between chemotherapy and increased risk for CDI. It is not clear why patients with non-CNS solid tumors had a higher risk of HA-CDI, but individual chemotherapy agents used to treat these tumors may have an increased risk of CDI.

Finally, we identified an increased risk of HA-CDI associated with exposure to proton pump inhibitors in the week prior to HA-CDI onset. Surprisingly, a decreased risk for HA-CDI was found with recent H2 receptor antagonist exposure. Although most studies of children(21, 22) and adults(23, 24) have shown that exposure to proton pump inhibiting agents increases the likelihood of developing CDI, the data regarding exposure to H2

receptor antagonists in children has been ambiguous. Studies in adults show either a modest risk(25) or no effect(26, 27) due to H2 receptor antagonists, but reports in children have shown both an increased risk(28) and a protective effect.(29) Our study supports the possibility of a protective effect from exposure to H2 receptor antagonists although the reason for the effect is not clear. Further investigations should focus on trying to delineate a mechanism for this differential effect of acid reducing agents on the risk for HA-CDI.

A limitation of our findings is that data gathered from large administrative databases are subject to data misclassification. PHIS data are subjected to numerous validity checks, and data are accepted into the database when classified errors occur in fewer than 2% of the hospital's quarterly data. We attempted to further reduce this source of error by analyzing medication classes rather than individual agents and by using a validated definition of CDI. Although it is possible that newer PCR tests for *C. difficile* may have misclassified some subjects with CDI as being free of disease, this error would have biased our results toward the null, suggesting that true hazard ratios may be even greater than reported. In order to reduce the potential impact of unknown outpatient exposures, we defined HA-CDI as occurring after six inpatient hospital days in the risk factor analysis. This approach ensured that at least one week of drug exposure information was known for each case of HA-CDI. However, previous surveillance recommendations have defined healthcare facility-onset, healthcare facility associated CDI as occurring after 48 hours of hospitalization.(30) It is possible that CDI occurring in hospital days 3–6 that were excluded from our analysis of HA-CDI may have altered reported risk factors. We also limited our risk factor analysis for HA-CDI to first hospitalizations of newly diagnosed children with cancer to reduce the chance that previous complications of their underlying malignancy would bias physician's behavior in testing for and treating HA-CDI. Risk factors for CDI occurring in the first week of hospitalization or during subsequent hospitalization may differ due to varying exposures and duration of such exposures. Additionally, risk factors examined in this study were limited to those that were measurable using data elements in PHIS. Other potentially important risk factors, such as a history of CDI, laboratory-defined neutropenia or clinically-defined mucositis, and the use of radiation were not available and should be investigated in future studies.

Nosocomial CDI threatens the health, quality of life and planned therapies for children with cancer. Despite a potential decrease in the incidence of CDI since 2006, this infection still contributes substantially to morbidity and possibly mortality in this vulnerable patient population. Our study collected the largest cohort of patient-level data in hospitalized children with malignancy at risk for CDI. Given the relative frequency of HA-CDI in pediatric oncology patients, it is imperative to follow infection control guidelines, including isolation of children suspected to have CDI and proper handwashing for caregivers and clinicians. Our data demonstrate the importance of judicious use of antibiotics even in a population at high risk for invasive bacterial infection. Of the antibiotics commonly used for febrile neutropenia, cefotaxime and cefepime were associated with the greatest risk for HA-CDI. If additional studies confirm this increased risk, hospitals should consider adjusting their empiric therapy choices for febrile neutropenia to an agent with similar broad-spectrum coverage that may provide reduced risk of HA-CDI. Additional studies also are necessary to

further investigate the role of immunosuppression, to confirm the variation in risk for HA-CDI associated with different acid blockade agents, to identify potential interventions for reducing HA-CDI risk after chemotherapy administration and to compare the effectiveness of newer *C. difficile* active agents in children with cancer.

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List of Abbreviations

CDI	*Clostridium difficile* infection
H2	Histamine-2
HA-CDI	Hospital acquired *Clostridium difficile* nfection
PCR	Polymerase Chain Reaction
PHIS	Pediatric Health Information System

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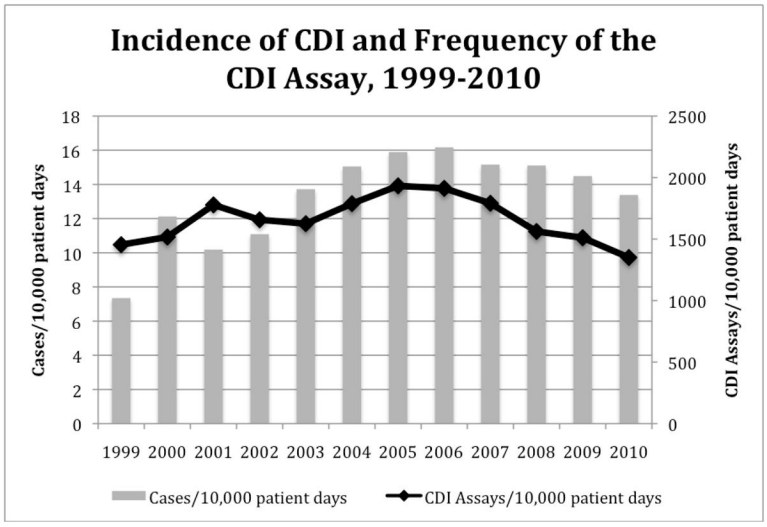

Figure 1.

Overall incidence of CDI and frequency of *C. difficile* toxin assay among children hospitalized for cancer in 43 children's hospitals in the United States, 1999–2010.

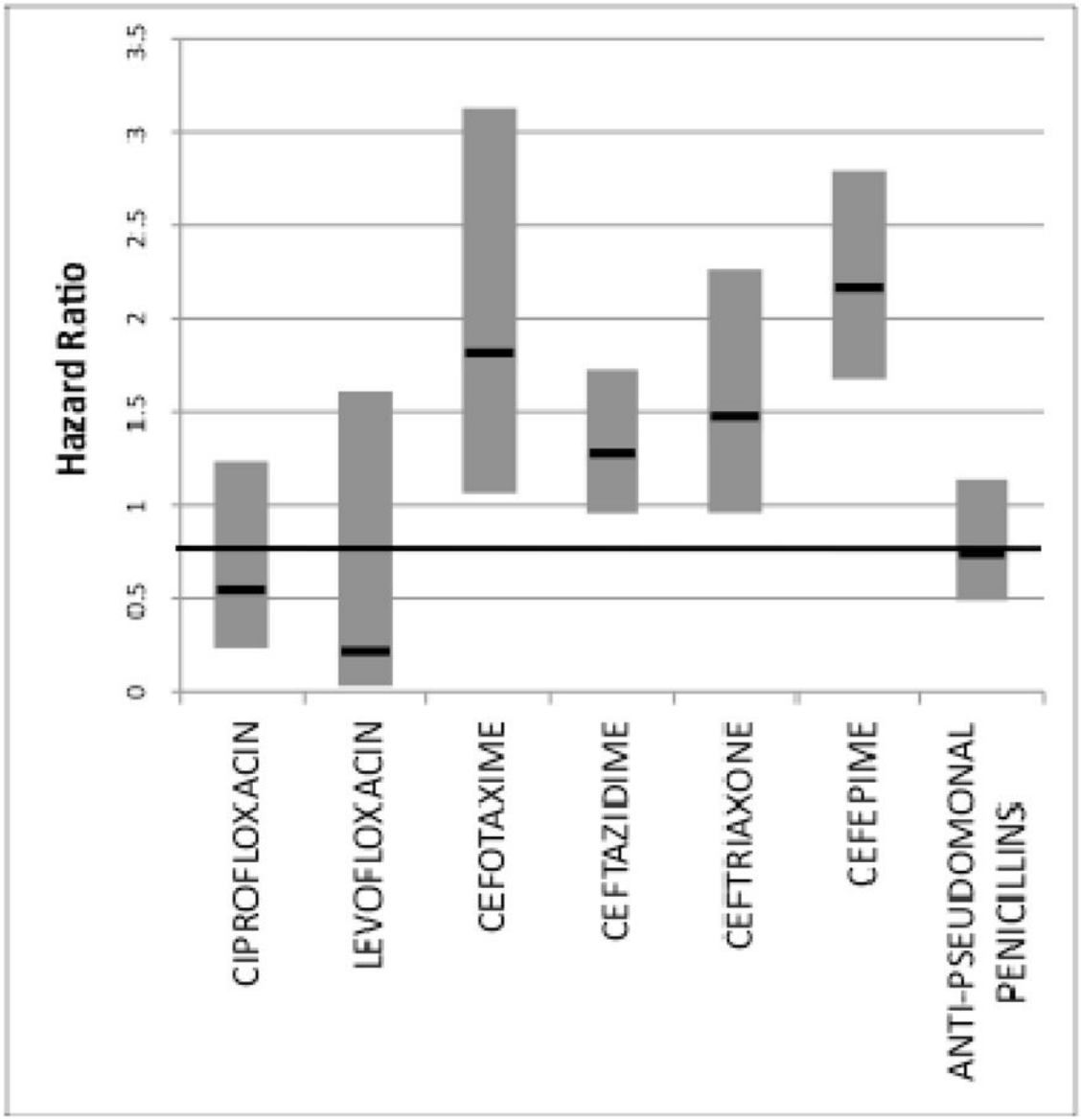

Figure 2.

Hazard ratios for exposure in the last week to individual agents used commonly for febrile neutropenia. Results are stratified by hospital site, clustered by patient, and adjusted for sex, race, age at admission, and year of admission.

Table I

Characteristics of first hospitalizations for malignancies in 43 children's hospitals in the United States, 1999–2011.

Characteristic		(−) HA-CDI 32,715 patients (%)	(+) HA-CDI 380 patients (%)	p value
Race	White	52.91	53.16	**0.02**
	Black	8.11	7.89	
	Asian	2.11	4.21	
	American Indian	0.40	1.05	
	Other	5.71	4.47	
	Missing	30.75	29.21	
Sex	Male	55.78	60.53	0.06
Admit Age Quartile	>1 – 3	27.45	33.42	**0.04**
	>4 – 8	27.38	23.16	
	>9 – 14	26.30	23.95	
	>14	18.87	19.47	
Admit Year Quartile	1999 – 2003	28.09	20.00	**<0.01**
	2004 – 2006	27.65	33.95	
	2007 – 2008	22.17	23.42	
	2009 – 2011	22.08	22.63	
Malignancy Category	Leukemia	39.83	52.63	**<0.01**
	Lymphoma	10.71	8.42	
	Solid Tumor, not CNS	22.01	19.21	
	CNS Tumor	18.94	11.05	
	Other	8.51	8.68	
Length of Stay (median days [range])		12 [7 – 545]	35 [7 – 439]	**<0.01**
Inpatient Mortality (%)		2.18	5.00	**<0.01**

Table II

Univariate and multivariate hazard ratios (HR) for HA-CDI.

Exposure*		Univariate HR (95% CI)	Multivariate HR (95% CI)
Race	White	Reference	Not Significant
	Black	0.920 (0.617–1.371)	
	Asian	1.292 (0.769–2.173)	
	American Indian	2.477 (0.895–6.855)	
	Other	0.676 (0.408–1.119)	
	Missing	0.893 (0.693–1.152)	
Sex	Male	1.246 (1.014 – 1.532)	1.272 (1.034 – 1.565)
Admit Age	1–3	1.176 (0.881 – 1.568)	Not Significant
	4–8	0.874 (0.640 – 1.193)	
	9–14	0.833 (0.612 – 1.135)	
	>14	Reference	
Admission Year	1999 – 2003	Reference	Not Significant
	2004 – 2006	1.582 (1.181 – 2.121)	
	2007 – 2008	1.249 (0.906 – 1.720)	
	2009 – 2011	1.288 (0.933 – 1.779)	
Malignanacy Category	Leukemia	Reference	Reference
	Lymphoma	0.779 (0.535 – 1.135)	0.980 (0.669 – 1.436)
	Solid, not CNS	1.066 (0.812 – 1.399)	1.467 (1.105 – 1.948)
	CNS tumor	0.554 (0.395 – 0.778)	1.073 (0.741 – 1.553)
	Other	1.038 (0.716 – 1.504)	1.434 (0.980 – 2.100)
Disease Severity	No prior ventilator or pressor use	Reference	Not Significant
	Prior ventilator use	0.820 (0.601 – 1.120)	
	Prior pressor use	0.867 (0.622 – 1.210)	
	Both ventilator and pressor use	0.785 (0.510 – 1.208)	
Aminoglycoside		1.552 (1.211 – 1.989)	1.357 (1.053 – 1.749)
Penicillins		0.901 (0.493 – 1.648)	Not Significant
Anti-Pseudomonal Penicillins		0.822 (0.550 – 1.230)	Not Significant
1st Generation Cephalosporin		0.653 (0.470 – 0.908)	Not Significant
2nd Generation Cephalosporin		1.127 (0.594 – 2.140)	Not Significant
3rd Generation Cephalosporin		1.346 (1.061 –1.708)	1.518 (1.177 – 1.959)
4th Generation Cephalosporin		2.442 (1.921 – 3.104)	2.383 (1.839 – 3.089)

Exposure*	Univariate HR (95% CI)	Multivariate HR (95% CI)
Macrolide	0.677 (0.359 – 1.275)	Not Significant
Fluoroquinolone	0.585 (0.310 – 1.106)	Not Significant
Carbapenem	1.321 (0.968 – 1.803)	Not Significant
Other Antibiotic	0.863 (0.582 – 1.281)	Not Significant
H2 Antagonist	0.645 (0.522 – 0.798)	0.730 (0.584 – 0.912)
Proton Pump Inhibitor	1.599 (1.264 – 2.023)	1.398 (1.096 – 1.784)
Chemotherapy 0–7d	1.525 (1.227 – 1.894)	Not Significant
Chemotherapy 8–14d	2.144 (1.678 – 2.740)	1.942 (1.491 – 2.529)

HR, Hazard Ratio

*Results stratified by hospital site

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Table III

Multivariate hazard ratios and 95% confidence intervals for HA-CDI among specific cancer diagnoses.

Exposure*		Full Cohort N = 33,095 380 CDI	ALL N = 10,070 92 CDI	AML N = 3,161 108 CDI	NHL N = 2,798 30 CDI	OS/EWS N = 2,132 20 CDI	CNS N = 6,238 42 CDI
Race	White	Not Significant	reference	Not Significant	Not Significant	Not Significant	Not Significant
	Black		0.346 (0.081–1.478)				
	Asian		3.190 (1.390–7.309)				
	American Indian		0.700 (0.050–9.886)				
	Other		0.595 (0.182–1.951)				
	Missing		0.940 (0.556–1.589)				
Sex	Male	1.272 (1.034–1.565)	1.701 (1.096–2.641)	Not Significant	Not Significant	Not Significant	Not Significant
Aminoglycoside		1.357 (1.053 – 1.749)	1.786 (1.079–2.956)	Not Significant	Not Significant	Not Significant	Not Significant
Penicillins		Not Significant	Not Significant	Not Significant	Not Significant	Not Significant	3.195 (1.056—9.671)
3rd Generation Cephalosporin		1.518 (1.177 – 1.959)	Not Significant	Not Significant	Not Significant	4.417 (1.230–15.860)	2.306 (1.120–4.746)
4th Generation Cephalosporin		2.383 (1.839 – 3.089)	2.166 (1.306–3.592)	2.272 (1.434–3.599)	Not Significant	4.315 (1.272–14.635)	Not Significant
Carbapenem		Not Significant	Not Significant	Not Significant	Not Significant	Not Significant	3.123 (1.146–8.515)
H2 Antagonist		0.730 (0.584 – 0.912)	0.554 (0.340–0.903)	Not Significant	Not Significant	Not Significant	Not Significant
Proton Pump Inhibitor		1.398 (1.096 – 1.784)	Not Significant	Not Significant	Not Significant	4.095 (1.270–13.205)	Not Significant
Disease Severity	No Ventilation, Pressor History	Not Significant	Not Significant	Not Significant	Not Significant	reference	Not Significant
	Ventilation History					0.855 (0.154–4.744)	
	Pressor History					3.724 (0.680–20.400)	
	Ventilator & Pressor History					34.969 (4.709– 259.703)	
Chemotherapy 7d		Not Significant	Not Significant	Not Significant	Not Significant	Not Significant	2.916 (1.435—5.925)
Chemotherapy 8–14d		1.942 (1.491 – 2.529)	2.603 (1.317—5.147)	2.248 (1.253—4.033)	Not Significant	Not Significant	Not Significant

ALL, Acute Lymphoblastic Leukemia; *AML*, Acute Myeloid Leukemia; *NHL*, Non-Hodgkins Lymphoma; *OS/EWS*, Osteosarcoma/Ewings Sarcoma; *CNS*, Central Nervous System tumors.

* Results stratified by hospital site