Variation in Risk of Hospital-Onset *Clostridium difficile* Infection Across β-Lactam Antibiotics in Children With New-Onset Acute Lymphoblastic Leukemia

Brian T. Fisher,1,4,5,6,a Julia Shaklee Sammons,1,2,4,5,a Yimei Li,3,6 Peter de Blank,7,8 Alix E. Seif,1,5 Yuan-Shung Huang,3 Marko Kavcic,3 Sarah Klieger,1 Tracey Harris,3 Kari Torp,3 Douglas Rheam,3 Ami Shah,3 and Richard Aplenc3,4,5,6

1Division of Infectious Diseases, 2Department of Infection Prevention and Control, 3Division of Oncology, and 4Center for Pediatric Clinical Effectiveness, The Children’s Hospital of Philadelphia, Pennsylvania; 5Department of Pediatrics, and 6Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia; 7Division of Pediatric Hematology and Oncology, Rainbow Babies & Children’s Hospital, and 8Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, Ohio

Corresponding Author: Brian T. Fisher, DO, MSCE, Division of Infectious Diseases, The Children’s Hospital of Philadelphia, 34th and Civic Center Boulevard, CHOP North, Room 1515, Philadelphia, PA 19104. E-mail: fisherbria@email.chop.edu.

B. T. F. and J. S. S. contributed equally to this work.

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**Background.** Antibiotic exposure is common among children with leukemia. However, limited data exist regarding the risk of *Clostridium difficile* infection (CDI) across anti-pseudomonal β-lactam antibiotics commonly used for fever and neutropenia.

**Methods.** A multicenter cohort of children with newly diagnosed acute lymphoblastic leukemia (ALL) was established from 43 freestanding children’s hospitals from 1999 to 2009. Patients were followed until their index CDI event, defined by the CDI ICD-9 code plus a *C. difficile* test charge, or until 180 days from ALL diagnosis. Cox proportional hazards models were performed to identify the hazards of CDI after exposure to anti-pseudomonal β-lactams, adjusting for demographics, other antibiotic exposures, severity of illness, antacids, gastrointestinal manipulation, and confounding by hospital.

**Results.** A cohort of 8268 ALL patients was assembled; median age was 5.5 years (interquartile range, 3.26–10.58). Two-hundred sixty-eight (3.2%) patients developed CDI within 180 days of ALL diagnosis. Each 1-day increase in exposure to an anti-pseudomonal β-lactam within the prior 30 days was associated with a significantly increased risk for CDI (hazard ratio [HR], 1.05; 95% confidence interval [CI], 1.01, 1.09). Ceftazidime (HR, 1.05; 95% CI, 1.02, 1.08) and cefepime (HR, 1.07; 95% CI, 1.02, 1.12) were each independently associated with CDI.

**Conclusions.** Efforts to reduce total exposure to anti-pseudomonal β-lactam agents may help to reduce the risk of CDI in children with newly diagnosed ALL. Cefepime and ceftazidime were independently associated with CDI, whereas anti-pseudomonal penicillins and carbapenems were not. These findings, if confirmed, have potential implications for antibiotic choice during periods of fever and neutropenia.

**Key words.** *Clostridium difficile*; leukemia; pediatrics.

The epidemiology of *Clostridium difficile* infection (CDI) has changed dramatically over the past decade, and CDI is increasingly recognized as a growing problem among hospitalized children [1]. Children with malignancy are uniquely at risk for CDI, likely reflective of increased healthcare exposure, immunosuppressive therapies, and other factors, such as antibiotics, that alter the intestinal microbiota [2–4]. Among hospitalized children in a large pediatric database, the rate of CDI was 15 times greater among children with cancer compared with all other children [5]. In addition, children with malignancy and CDI have worse outcomes, including longer lengths of stay and...
METHODS
Study Design and Data Source
We performed a retrospective cohort study of newly diagnosed ALL patients cared for at pediatric institutions contributing data to the Pediatric Health Information System (PHIS). The PHIS database is a comparative database that includes inpatient data from 43 freestanding children’s hospitals in the United States. These institutions are affiliated with the Children’s Hospital Association ([CHA] Overland Park, KS) and represent 17 of the 20 major metropolitan areas nationwide. Pediatric Health Information System data include discharge or encounter information including demographics, and ICD-9 discharge diagnosis and procedure codes (up to 41 codes per admission). Hospitals submit billing data for specific resources (eg, pharmaceutical agents) by hospital day of service. Patients are de-identified using a unique PHIS identifier that is preserved for subsequent admissions. Maintenance of PHIS data quality is a joint effort between CHA, Truven Health Analytics ([data processing partner] Ann Arbor, MI), and participating hospitals. Data are subjected to reliability and validity checks before inclusion in the database.

This study was approved by CHA and received an exemption by the Committee for Protection of Human Subjects at the Children’s Hospital of Philadelphia.

Study Population
Patients with presumed newly diagnosed ALL between January 1, 1999 and December 31, 2009 were identified in a process previously described and validated [8]. In brief, PHIS was screened for first admissions containing an ICD-9 code consistent with ALL (204.xx, excluding 204.02, relapsed ALL). Patients were excluded if data elements suggested an alternative malignancy or receipt of a stem cell transplant during the index ALL admission. Finally, an extensive manual review of chemotherapy billing data in PHIS was performed to identify patients with chemotherapy patterns consistent with ALL induction therapy.

The final cohort was limited to children aged 1 to <19 years at the time of their first admission. Patients aged less than 1 year were excluded, because asymptomatic colonization with *C difficile* is common in infants. Each patient was followed until their index CDI event, inpatient death, or until 180 days from the first admission for ALL.

Outcome
The primary study endpoint was CDI, as defined by the presence of the CDI ICD-9 code (008.45) plus a billing record for a *C difficile* test. The timing of CDI onset was defined by the *C difficile* test date. This definition has been previously validated in a multicenter comparison of administrative data to microbiology results [9].

Exposure of Interest
In the primary analysis, the association between exposure to various anti-pseudomonal β-lactam antibiotics and CDI was investigated. Four categories of β-lactam agents were considered: ceftazidime, cefepime, anti-pseudomonal penicillins (piperacillin, piperacillin plus tazobactam, ticarcillin, and ticarcillin plus clavulanate), and carbapenems (imipenem and meropenem). Billing records were used to identify exposure to each category. A patient’s total days exposed to each antibiotic was determined for each 30-day period from the time of first ALL admission to diagnosis of CDI or censorship. In the same manner, a composite exposure was determined by cumulating a patient’s exposure to all anti-pseudomonal β-lactam agents simultaneously. For this exposure, aztreonam was included along with the 4 previously mentioned β-lactam groups.

Covariates and Confounders
Demographics. Gender, age, and race were determined during each patient’s index hospitalization. Age in years was considered as a continuous and categorical (1 to <2 years, 2 to <10 years, 10 to <16 years, and >16 years) variable. Race was described categorically (white, black, Asian, Native American, other, and missing) by PHIS and analyzed dichotomously (white and non-white) in multivariable models.

higher rates of in-hospital mortality, compared with children with malignancy and no CDI [6]. The risk of CDI has also been shown to vary across different antibiotic types commonly used in hospitalized children with malignancy. In particular, fourth-generation cephalosporins have been associated with an increased risk for CDI [6].

These prior publications have highlighted the consequences of CDI and shown that risk of CDI may vary across antibiotics commonly administered to children with malignancy. However, previously assembled cohorts contained a heterogeneous mix of patients with malignancy at varying points in their treatment course. Prior studies were unable to quantify the cumulative CDI risk after specific amounts of antibiotic exposure in a cohort of patients with a single malignancy and uniform time from diagnosis. We sought to identify the variation in risk of CDI after recent exposure to anti-pseudomonal β-lactam antibiotics commonly used for febrile neutropenia among a cohort of children with newly diagnosed acute lymphoblastic leukemia (ALL), adjusting for other antibiotic exposures, non-antibiotic risk factors, and accounting for clustering by hospital. We chose to focus our cohort to ALL patients, because ALL is the most common pediatric malignancy [7].
Non-anti-pseudomonal β-Lactam Antibiotic Exposures. Although exposure to other antimicrobial agents may confound the association of anti-pseudomonal β-lactam antibiotics and development of CDI, adjustment for those exposures was necessary. Additional antibiotic exposures included the following: broad-spectrum Gram-positive agents (vancomycin, daptomycin, and linezolid), clindamycin, third-generation cephalosporins (cefotaxime and ceftriaxone), fluoroquinolones (any systemic fluoroquinolone exposure), and aminoglycosides (any systemic aminoglycoside exposure). Exposure during each 30-day period was calculated as described above.

Non-antibiotic Exposures. Non-antibiotic exposures were also captured. Billing data were used to define exposure to proton pump inhibitors (PPIs), H2 blockers, and total parenteral nutrition (TPN) described similarly as days of exposure for each 30-day period. Manipulation of the gastrointestinal tract or nasogastric or a gastrostomy tube placement were identified by ICD-9 procedure codes. Timing was based on the date of the procedure code (Appendix A). An individual’s history of gastrointestinal tract manipulation or nasogastric or gastrostomy tube placement starting from first ALL admission was recorded on each study day.

Severity of Illness. Because a patient’s clinical status may confound the association of anti-pseudomonal β-lactam antibiotics and CDI, adjustment for severity of illness was included in the final model. In the absence of a validated mechanism to identify days of severe illness from the PHIS database, we used specific billed resources as a proxy for severity of illness on a given hospital day. A severe illness day was defined by presence of 1 of the following resources: (1) vasopressor or cardiac support medication (epinephrine, dopamine, norepinephrine, dobutamine, or milrinone) on 2 consecutive days; (2) insertion of or monitoring from an arterial line; (3) respiratory support (continuous positive airway pressure, bilevel positive airway pressure, mechanical ventilation, nitric oxide, or surfactant therapy) on 2 consecutive days; (4) extracorporeal membrane oxygenation; (5) hemodialysis or peritoneal dialysis; and (6) close cardiovascular monitoring (eg, 38.91: arterial catheterization) or actual resuscitation efforts (eg, 93.93: nonmechanical methods of resuscitation). Similar to antibiotic exposure, days of severe illness were determined for each 30-day period.

In-Hospital Exposure. Similar to severe illness days, inpatient days may also confound the association of anti-pseudomonal β-lactam antibiotics and CDI. The number of inpatient days for each 30-day period was totaled and categorized as follows: 0–2 hospital days; 3–10 hospital days; 11 or more hospital days.

Statistical Analysis

Summary statistics were constructed to describe demographic characteristics using frequencies and proportions for categorical data and medians and interquartile range (IQR) for continuous variables. In bivariate analysis, we compared demographics and exposures of interest in patients with and without CDI. For demographic variables, the Wilcoxon rank-sum and χ2 tests were used. For exposure variables other than feeding tube and gastrointestinal manipulation, the rate of each exposure was described as days of exposure per 100 study days during the entire follow-up period. The incidence rate ratios for patients with versus without CDI and the corresponding 95% confidence intervals (CI) were calculated using Poisson regression. Exposures to feeding tube and gastrointestinal manipulation were described as percentage of patients who had this intervention at least once during the follow-up period and were compared between patients with and without CDI using the χ2 test.

Cox proportional hazards models were constructed to compare time to CDI in patients with and without recent exposure to anti-pseudomonal β-lactam agents. Exposure to anti-pseudomonal β-lactams was considered in the Cox model first as a single composite exposure to all β-lactam agents and then with each β-lactam individually. All medication exposures of interest are time varying and were defined as number of exposure days in the past 30 days. To account for the possibility of confounding by hospital, we decomposed the within- and among-hospital components of the effect of patient demographics and antibiotic choices at each institution by creating hospital level means of each factor [10, 11]. In addition, each of the aforementioned potential confounders (other antibiotic and nonantibiotic exposures, severity of illness, and number of recent inpatient days) was included in each of the final regression models. Finally, the Cox proportional hazards assumption was tested using Schoenfeld residuals and rank analysis time as the time scaling function. Data organization and analyses were performed using Stata statistical software, version 12.0 (College Station, TX).

RESULTS

The final assembled cohort consisted of 8268 new-onset ALL patients with a median age of 5.51 years (IQR, 3.26–10.58). The majority of the cohort was white (76.6%) and more commonly male (56.4%). Within 180 days from first ALL admission, 326 patients had at least 1 admission in which an ICD-9 code for CDI was assigned. Of these 326 patients, 268 (3.2% of the cohort) also had an order for C difficile testing, thus meeting the study criteria for CDI.
designation. The median time from first ALL admission to onset of CDI was 60 days (IQR, 23–113). CDI incidence was highest in the 3rd and 4th week after first ALL admission and decreased during the latter half of the follow-up period (Figure). Age, gender, and race were similar between patients with and without CDI (Table 1). Patients with CDI had significantly more hospital days and days of severe illness per 100 study days than patients without CDI (Table 1).

The results of bivariate analyses for each of the a priori-identified risk factors for CDI are displayed in Table 2. Recent exposure to anti-pseudomonal agents considered individually and as a composite measure was significantly associated with increased risk for CDI. Fluoroquinolones were infrequently used and so were not included in bivariate analysis nor as potential confounders in the final multivariate models. Exposure to PPIs, H2 blockers, and TPN was significantly associated with increased risk for CDI. Neither nasogastric or gastrostomy tube placement nor gastrointestinal manipulation was associated with subsequent CDI.

After adjusting for demographic characteristics, exposure to other antibiotics, and non-antibiotic risk factors, number of severe illness days, total hospital days, and accounting for confounding by center, the HR for exposure to anti-pseudomonal β-lactam agents remained significant at 1.05 (95% CI, 1.01–1.09). A 5-day increase in exposure to an anti-pseudomonal β-lactam agent has an HR of 1.29 (95% CI, 1.07–1.55).

The composite anti-pseudomonal β-lactam exposure variable was then decomposed into individual exposures to each agent. Table 3 displays the adjusted HR for each β-lactam and for aminoglycosides. After multivariable adjustment, only ceftazidime and cefepime remained significantly associated with CDI.

DISCUSSION

The incidence of pediatric CDI has increased dramatically over the past decade [4, 12, 13] and has been associated with significantly worse outcomes, including a 6-fold greater risk of in-hospital mortality [14]. Among pediatric patients, children with malignancy have been shown to be at the highest risk for CDI and its complications [5, 6]. Although the association between antibiotics and CDI is well described, there are limited data on the risk for CDI

| Table 1. Comparison of Age, Gender, Race, Hospital Days, and ICU Days for Those With and Without Clostridium difficile Infection |

<table>
<thead>
<tr>
<th></th>
<th>Patients With CDI n = 268</th>
<th>Patients Without CDI n = 8000</th>
<th>IRR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, IQR)</td>
<td>5.59 (3.06–10.79)</td>
<td>5.50 (3.27–10.57)</td>
<td>N/A</td>
<td>.775</td>
</tr>
<tr>
<td>Gender (female %)</td>
<td>112 (41.79)</td>
<td>3496 (43.70)</td>
<td>N/A</td>
<td>.532</td>
</tr>
<tr>
<td>Race (white %)</td>
<td>210 (78.36)</td>
<td>6119 (76.49)</td>
<td>N/A</td>
<td>.477</td>
</tr>
<tr>
<td>Hospital days per 100 study days</td>
<td>38.1</td>
<td>16.2</td>
<td>2.41 (2.35–2.47)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Days of severe illness per 100 study days</td>
<td>0.7</td>
<td>0.3</td>
<td>2.33 (1.94–2.77)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, Clostridium difficile infection; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; IRR, incidence rate ratio; N/A, not applicable.

| Table 2. Bivariate Associations of Exposure to Anti-pseudomonal Antibiotics and Non-antibiotic Factors With Development of CDI |

<table>
<thead>
<tr>
<th>Exposure to anti-pseudomonal β-lactam agents</th>
<th>Cohort n = 8268</th>
<th>Patients With CDI n = 268</th>
<th>Patients Without CDI n = 8000</th>
<th>IRR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-pseudomonal β-lactam antibiotics*</td>
<td>7.69</td>
<td>20.41</td>
<td>7.53</td>
<td>2.71 (2.62, 2.80)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cefepime*</td>
<td>2.21</td>
<td>9.59</td>
<td>2.12</td>
<td>4.53 (4.32, 4.76)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Ceftazidime*</td>
<td>3.39</td>
<td>6.74</td>
<td>3.34</td>
<td>2.01 (1.91, 2.13)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Carbapenems*</td>
<td>0.90</td>
<td>1.89</td>
<td>0.89</td>
<td>2.12 (1.90, 2.34)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Aminoglycosides*</td>
<td>1.93</td>
<td>4.78</td>
<td>1.90</td>
<td>2.52 (2.36, 2.70)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Anti-pseudomonal penicillins*</td>
<td>1.30</td>
<td>2.54</td>
<td>1.28</td>
<td>1.98 (1.80, 2.16)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Exposure to non-antibiotic risk factors for CDI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proton Pump inhibitors*</td>
<td>2.18</td>
<td>6.64</td>
<td>2.12</td>
<td>3.14 (2.96, 3.32)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>H2 Blockers*</td>
<td>6.43</td>
<td>16.60</td>
<td>6.29</td>
<td>2.64 (2.54, 2.74)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TPN*</td>
<td>1.45</td>
<td>3.27</td>
<td>1.43</td>
<td>2.29 (2.11, 2.48)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Feeding tube†‡ (%)</td>
<td>1.50</td>
<td>1.87</td>
<td>1.49</td>
<td>N/A</td>
<td>.616</td>
</tr>
<tr>
<td>Gastrointestinal manipulation† (%)</td>
<td>5.45</td>
<td>3.73</td>
<td>5.51</td>
<td>N/A</td>
<td>.207</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, Clostridium difficile infection; CI, confidence interval; IRR, incidence rate ratio; N/A, not applicable.

*Rate for each medication reported as days of exposure per 100 study days.
†Feeding tube and gastrointestinal manipulation reported as a percentage of patients that had this intervention at least once during the study period.
‡Includes placement of a nasogastric or gastrostomy tube.
Previous antibiotic exposure is recognized as the most important modifiable risk factor for CDI, and virtually all antibiotic agents have been associated with development of disease [15]. However, risk of CDI by antibiotic type has been challenging to define in epidemiologic studies. There are a number of patient- (eg, non-antibiotic exposures, duration of hospitalization, etc) and hospital-level factors (eg, hospital preference for antibiotic choice, concurrent infection control interventions, etc) that can confound this association. We attempted to address such confounding in our multivariable analysis by including patient-specific factors, such as frequency of inpatient stays, as well as hospital-level factors, such as hospital means for patient demographics and antibiotic choices. However, confounders such as concurrent infection control practices or local C difficile epidemics could not be accounted for in our analysis.

Variation in anaerobic activity across antibiotic agents has been proposed as a source for variation in the risk of CDI. This hypothesis is related to the concept of “colonization resistance,” which suggests that antibiotics with anti-anaerobic activity reduce obligate anaerobic commensals that otherwise help to maintain the host’s defense against colonization and overgrowth of C difficile [16, 17]. However, we did not identify an independently increased risk for CDI after exposure to anti-pseudomonal penicillins or carbapenems, agents with anti-anaerobic activity. It is possible that their broad activity against anaerobes includes some degree of growth inhibition and suppression of toxin production of many C difficile strains, which has been supported by in vitro and animal model data [18–20]. In addition, studies in adult patients have demonstrated a reduction in CDI rates after replacing cefotaxime with piperacillin-tazobactam [21] as well as a rise in CDI after unintended restriction of piperacillin-tazobactam use [22].

Evaluation of CDI incidence by distinct 2-week intervals revealed an apparent increased incidence during the 3rd and 4th week after ALL onset. This period of increased risk may represent the simultaneous impact of recent induction chemotherapy and subsequent neutropenia with increased antibiotic exposure. Previous analyses in children with cancer have identified recent chemotherapy exposure as an independent risk factor for CDI onset, thus highlighting the need for increased vigilance for CDI post-chemotherapy [6]. Although the CDI event rate appeared to decrease with time, the risk for incident CDI persisted throughout the study period.

Our study has potential limitations. Because our cohort was limited to children with ALL, our findings may not be generalizable to all hospitalized children. Still, children with ALL are among those at highest risk for CDI, thus representing an ideal population in which to study the

### Table 3. Hazard Ratios for Developing CDI After Exposure to Each Factor of Interest

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted* HR (95% CIs)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual anti-pseudomonal antibiotic exposures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime†</td>
<td>1.05 (1.02–1.08)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cefepime†</td>
<td>1.07 (1.02–1.12)</td>
<td>0.006</td>
</tr>
<tr>
<td>Anti-pseudomonal PCNs‡</td>
<td>1.02 (0.96–1.08)</td>
<td>0.52</td>
</tr>
<tr>
<td>Carbapenems†</td>
<td>0.98 (0.93–1.04)</td>
<td>0.58</td>
</tr>
<tr>
<td>Aminoglycosides†</td>
<td>1.00 (0.97–1.04)</td>
<td>0.86</td>
</tr>
<tr>
<td>Non-antibiotic exposures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitors†</td>
<td>1.01 (0.99–1.03)</td>
<td>0.32</td>
</tr>
<tr>
<td>H2 blockers†</td>
<td>1.02 (0.99–1.05)</td>
<td>0.20</td>
</tr>
<tr>
<td>Total parenteral nutrition†</td>
<td>0.98 (0.95–1.01)</td>
<td>0.15</td>
</tr>
<tr>
<td>Manipulation of the gastrointestinal tract†</td>
<td>0.91 (0.42–2.00)</td>
<td>0.82</td>
</tr>
<tr>
<td>Placement of a nasogastric and/or a gastrostomy tube†</td>
<td>1.85 (0.75–4.51)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, Clostridium difficile infection; CI, confidence interval; HR, hazard ratio; PCN, penicillin.

*Adjusted for age (categorized as 1 to 2 years, 3 to 10 years, >10 years); race (dichotomized as white or non-white); gender; number of days in past 30 days exposed to other antibiotics (clindamycin, aminoglycosides, cefotaxime/ceftriaxone, and broad-spectrum Gram-positive agents); number of severe illness days in past 30 days; number of hospital days in past 30 days (categorized as 0–2 days, 3–10 days, or >11 days); and variability of each covariate by hospital.

†Indicated variables were dichotomized as yes or no exposure before CDI onset or completion of follow-up.

Across antibiotics commonly used in children with malignancy. Our study shows that among anti-pseudomonal β-lactams commonly used for febrile neutropenia, cefepime and ceftazidime are independently associated with CDI in children with ALL. Furthermore, our results indicate that even 1 additional day of exposure to anti-pseudomonal β-lactams in the last 30 days significantly increases the risk for CDI. These data suggest that reducing a patient’s total exposure to anti-pseudomonal β-lactams even by 1 day can reduce the risk of CDI.

These findings are consistent with recent work by de Blank et al. [6] that showed that exposure to fourth-generation cephalosporins in the preceding week was associated with an increased risk of CDI in children with any malignancy and specifically in ALL patients. However, our current study has important advantages that expand on these findings. We utilized a validated process to establish an ALL-specific cohort that leveraged ICD-9 codes and chemotherapy exposure and followed patients for up to 180 days from their index admission. Patients were therefore similar with regards to malignancy type and time of follow-up after ALL diagnosis. Furthermore, exposure to each antibiotic of interest was quantified as total number of days exposed in the last 30 days. This analysis allowed for interpretation of the potential impact of each additional day of antibiotic exposure.
variation in risk of CDI across antibiotics. Likewise, our study was limited to children receiving care at freestanding children’s hospitals; therefore, our results may not be generalizable to all facilities providing pediatric care. However, children with ALL are more likely to be cared for at tertiary care centers similar to our nationwide sample of hospitals, particularly in the setting of fever and neutropenia. The use of administrative data may also lead to misclassification of exposure (anti-pseudomonal β-lactam antibiotics) or outcome (CDI), due to inaccurate billing data or miscoding for diagnoses. However, PHIS data are subject to frequent audit checks for valid entries, and known data quality issues are transparently communicated to all PHIS data users. Furthermore, the use of PHIS data to identify hospitalized children with CDI has previously been validated and found to be both sensitive and specific, making misclassification of CDI less likely [9]. Finally, we were only able to capture exposures and outcomes that happened in the inpatient setting. It is possible that patients were exposed to some of these antibiotic agents via home healthcare or experienced CDI that was managed in an outpatient clinic.

Our study demonstrates that each 1-day increase in exposure to anti-pseudomonal β-lactam antibiotics resulted in a significantly increased risk for CDI. Although existing guidelines direct appropriate use of antimicrobial therapy in patients with febrile neutropenia [23, 24], there is significant variability in antibiotic use for patients with ALL across pediatric institutions, suggesting some degree of antibiotic overutilization [25]. Clinicians can reduce the risk of CDI in this patient population by discontinuing these broad-spectrum agents as soon as clinically appropriate. Among anti-pseudomonal agents, cefepime and ceftazidime were each independently associated with CDI, raising questions about the optimal antibiotic choice for management of febrile neutropenia. Although switching local practice from cephalosporins to anti-pseudomonal penicillins may seem reasonable, such practice changes could have unintended consequences. Of particular concern is the association between broad-spectrum antibiotics and other opportunistic infections, such as candidemia [26]. This finding should therefore be interpreted in the context of local epidemiology. Centers with both increased CDI rates and high cephalosporin utilization may consider changing their empiric anti-pseudomonal β-lactam choice to an anti-pseudomonal penicillin and monitor subsequent CDI incidence.

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**Potential conflicts of interest.** All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**


