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

Peter de Blank, MD, MSCE[1], Theoklis Zaoutis, MD, MSCE[2,3,4,5,6], Brian Fisher, DO, MSCE[2,3,4,5], Andrea Troxel, ScD[5,6], Jason Kim, MD, MSCE[2,3,5], and Richard Aplenc, MD, PhD[4,5,6,7]

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 *International Classification of Diseases, 9th edition-Clinical Modification* (ICD-9CM), CDI diagnostic assay billing code, and concurrent administration of a CDI-active antibiotic. HA-CDI was defined as CDI with assay occurring after the sixth hospital day.

Results A total of 1736 admissions with CDI were identified, of which 380 were HA-CDI. CDI incidence increased from 1999-2006 ($P = .01$); however, CDI testing frequency and disease decreased from 2006-2010 ($P < .05$). Admissions with HA-CDI had longer lengths of stay compared with those without HA-CDI (35 days vs 12 days, $P < .01$) and greater risk of inpatient mortality (relative risk 2.3, $P < .01$). Increased risk of HA-CDI (hazard ratio [95% CI]) 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 (1.942 [1.491-2.529]) in the 8-14 days prior to HA-CDI onset. 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. *(J Pediatr 2013;163:699-705)*.

See related articles, p 627 and p 692

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 and 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 over-represented 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 because of their underlying malignancy, exposure to chemotherapy, broad-spectrum antibiotics, and supportive medications.

CDI	*Clostridium difficile* infection
CNS	Central nervous system
DOT	Days of antibiotic therapy
H2	Histamine-2
HA-CDI	Hospital acquired CDI
HR	Hazard ratio
ICD-9CM	*International Classification of Diseases, 9th edition-Clinical Modification*
PCR	Polymerase chain reaction
PHIS	Pediatric Health Information System

From the [1]Division of Pediatric Hematology-Oncology, Department of Pediatrics, Case Western Reserve University, Cleveland, OH; [2]Division of Infectious Diseases, [3]Center for Pediatric Clinical Effectiveness, The Children's Hospital of Philadelphia; [4]Department of Pediatrics, [5]Center for Clinical Epidemiology and Biostatistics, and [6]Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine; and [7]Division of Oncology, The Children's Hospital of Philadelphia, Philadelphia, PA

P.dB. was funded by the Center for Pediatric Clinical Effectiveness (The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania) and the National Institutes of Health (T32-CA009679-18). T.Z. received research support and an honorarium from Merck, and serves as a consultant for Merck, Pfizer, Astellas, and Hemocue. J.K. has received research funding from ViroPharma. B.F. has received research funding from Pfizer Pharmaceuticals. The other authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2013.01.062

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 System (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 US affiliated with the Children's Hospital Association. Member hospitals represent 17 of the 20 major metropolitan areas across the US, and comprise 85% of the free-standing children's hospitals in the US 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 *International Classification of Diseases, 9th edition-Clinical Modification* (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 1 year old at their index hospitalization were excluded because of the high prevalence of asymptomatic *Clostridium 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 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-central nervous system (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 *Clostridium 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 nonspecific 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 1 day of exposure or no exposure within the last 7 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 7 days was also established. This variable (the total number of days of each antibiotic given within the last 7 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 included 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 χ^2 test and