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Major article

Investigation of a cluster of *Clostridium difficile* infections in a pediatric oncology setting

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Background: We investigated an increase in *Clostridium difficile* infection (CDI) among pediatric oncology patients.

Methods: CDI cases were defined as first *C difficile* positive stool tests between December 1, 2010, and September 6, 2012, in pediatric oncology patients receiving inpatient or outpatient care at a single hospital. A case-control study was performed to identify CDI risk factors, infection prevention and antimicrobial prescribing practices were assessed, and environmental sampling was conducted. Available isolates were strain-typed by pulsed-field gel electrophoresis.

Results: An increase in hospital-onset CDI cases was observed from June-August 2012. Independent risk factors for CDI included hospitalization in the bone marrow transplant ward and exposure to computerized tomography scanning or cefepime in the prior 12 weeks. Cefepime use increased beginning in late 2011, reflecting a practice change for patients with neutropenic fever. There were 13 distinct strain types among 22 available isolates. Hospital-onset CDI rates decreased to near-baseline levels with enhanced infection prevention measures, including environmental cleaning and prolonged contact isolation.

Conclusion: *C difficile* strain diversity associated with a cluster of CDI among pediatric oncology patients suggests a need for greater understanding of modes and sources of transmission and strategies to reduce patient susceptibility to CDI. Further research is needed on the risk of CDI with cefepime and its use as primary empirical treatment for neutropenic fever.

Clostridium difficile is an anaerobic, spore-forming bacillus whose presentation in children ranges from asymptomatic colonization to severe colitis and death.[1] Host factors, including cancers, can predispose to *C difficile* infection (CDI).[2,3] Among U.S. children hospitalized with cancer, CDI incidence between 1999 and 2010 increased from 7.3-13.4 infections per 10,000 inpatient days.[4]

In June 2012, an increase in CDI was noted in a children's hospital among patients in the Center for Cancer and Blood Disorders (CCBD) program (hematology, oncology, and bone marrow transplant [BMT]). Public health officials were notified, and enhanced infection prevention measures were implemented (Table 1). However, by August 2012, CDI rates remained persistently elevated, and a formal investigation by the Colorado

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Conflicts of interest: None to report.

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Table 1
Infection prevention policies implemented immediately before CDPHE-CDC investigation

Category	Intervention
Environmental cleaning	• Universal sodium hypochlorite (1:10 solution) disinfection in all CCDB areas instead of just contact isolation rooms. • Increased frequency of environmental cleaning to 2-3 times daily and between each patient in outpatient clinic. • Cleaning of family lounge after each family use.
Personal protective equipment	• Universal glove use. • Continue contact precautions for all patients with current or prior CDI.
Isolation policies	• Closure of playrooms. • Restriction of family lounge to a single family at a time. • Cessation of group and communal gathering activities for CCBD patients and families. • Family education regarding hand hygiene and other infection control policies. • Dedicated patient equipment in each room (eg, medication barcode scanners, scales, stethoscopes). • Electronic alert for providers in medical records for all patients with CDI. • Storage of multidose containers (eg, nasal spray) in individual plastic bags in shared refrigerator for individual patients in isolation.

CCBD, Center for Cancer and Blood Disorders; *CDC*, Centers for Disease Control and Prevention; *CDI*, *Clostridium difficile* infection; *CDPHE*, Colorado Department of Public Health and Environment.

Department of Public Health and Environment and Centers for Disease Control and Prevention (CDC) was requested.

The primary objectives of this investigation were to determine the nature and extent of CDI in CCBD patients, evaluate risk factors for CDI in CCBD patients, determine potential modes of transmission, and implement interventions to stop transmission.

METHODS

Case finding

Results of inpatient and outpatient *C difficile* stool tests performed during routine clinical care from December 1, 2010-September 6, 2012, were reviewed. The hospital switched from stool toxin enzyme immunoassay testing to polymerase chain reaction (PCR) testing (Xpert; Cepheid, Sunnyvale, CA) on December 1, 2010.

Case definitions

First incident cases were defined as first *C difficile* positive stool tests (CDPSTs) collected between December 1, 2010, and September 6, 2012, from a CCBD patient.

Duplicate cases were defined as CDPSTs collected $\leq$14 days after a prior CDPST.

Recurrent cases were defined as CDPSTs collected $>$14 to $\leq$56 days after a prior CDPST.

Subsequent incident cases were defined as CDPSTs collected $>$56 days after a prior CDPST that were not duplicates.

Incident cases were further classified as hospital onset (HO) if stool was collected on or after hospital day 4 (day of admission being hospital day 1) and as community onset (CO) if stool was collected as an outpatient or prior to hospital day 4, consistent with CDC definitions.[5]

CO cases were further classified as either hospital associated if case patients had an overnight hospital stay $\leq$4 weeks before the CDPST, ambulatory care associated if the case patient had any outpatient visit $\leq$4 weeks before the CDPST, or both.

Cases considered to represent asymptomatic colonization were excluded if medical records documented formed stools on the test date. The laboratory rejected formed stools per policy unless overridden by a physician.

Case description

A detailed review of medical records and parent-caregiver interviews were conducted for case patients with first incident CDI occurring between June 1 and September 6, 2012. Medical records were reviewed for the 12 weeks before the case patient's first CDPST. All data were collected using standardized abstraction forms, including patient demographics, comorbidities, hospital locations, invasive devices, procedures, medications, diarrheal symptoms, outcomes of infection, and patient disposition. Parents-caregivers or patients (if $\geq$18 years old) were interviewed using standardized questionnaires to collect additional exposure data from the 12 weeks before the first CDPST.

Case-control study

Case patients with first incident CDI occurring between June 1 and September 6, 2012, were included in a case-control study to evaluate risk factors. Approximately 3 CCBD controls per case were randomly selected and not matched to individual cases. Because nearly all cases had an inpatient admission in the 12 weeks before diagnosis, controls were required to have a history of an overnight hospital stay from May 1-September 6, 2012. Because cases were distributed throughout June-August 2012, a random incident date was selected from June 1-September 6, 2012, for each control for data abstraction purposes. Eligible controls were excluded if new diarrhea ($\geq$3 loose or liquid stools/24 hours) was documented in the medical record $\leq$3 days before the incident date.

Statistical analysis

Cases and controls were compared using logistic odds ratios for dichotomous or categorical variables and the Wilcoxon rank-sum test for continuous variables. Statistical significance was defined as a $P < .05$.

Variables with $P < .10$ were incorporated into a multivariable logistic regression model in a forward, step-wise fashion. Variables were retained if their P value remained $<.05$ or if they significantly improved the model's fit by likelihood-ratio testing ($P < .05$). Analyses were performed in Stata 11.1 (StataCorp, College Station, TX).

Setting and infection prevention assessment

The children's hospital contained a single, dedicated floor for the CCDB outpatient clinic and the 24-bed inpatient ward. BMT inpatients occupied 4-12 beds in a closed section at the end of the ward. Each inpatient room had a dedicated bathroom. The BMT and regular inpatient areas had separate nursing staff, family rooms, kitchen, playrooms, and family bathrooms. When the inpatient ward was at capacity, additional patients were housed in an overflow ward.

Observations and staff interviews were conducted on the CCBD outpatient clinic, inpatient ward, and overflow ward. This included interviews of managers, nurses, and environmental cleaning staff; observations of staff workflow; hand hygiene and personal protective equipment use; staff and patient-family use of common areas; and environmental cleaning.