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High Colonization Rate and Prolonged Shedding of *Clostridium difficile* in Pediatric Oncology Patients

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Abstract

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Surveillance testing for *Clostridium difficile* among pediatric oncology patients identified stool colonization in 29% of patients without gastrointestinal symptoms and in 55% of patients with prior *C. difficile* infection (CDI). A high prevalence of *C. difficile* colonization and diarrhea complicates the diagnosis of CDI in this population.

Keywords

Clostridium difficile; pediatric; oncology; colonization; surveillance

Clostridium difficile infection (CDI) is the most common cause of nosocomial and antibiotic-associated diarrhea in adults, with increasing frequency, morbidity, and mortality in recent years [1]. Despite a large body of literature on the incidence, risk factors, and outcomes of CDI in adults, there is less information about the pediatric population. The most common comorbid condition associated with CDI in children is cancer, with 25% of all cases of pediatric CDI occurring in children with an underlying malignancy and 5% of children with cancer developing CDI at some time during their multiple hospitalizations [2–5]. In 2012, an increase in CDI rates among children with cancer receiving care at our hospital prompted an evaluation of *C. difficile* colonization and shedding in this population.

METHODS

The Center for Cancer and Blood Disorders (CCBD) program, which includes inpatient and outpatient services for oncology, hematology, and bone marrow transplant patients, is located on a single floor of our freestanding children's hospital. To assess for continued shedding of *C. difficile*, stool and skin samples were collected on a convenience sample of CCBD patients with a recent diagnosis of CDI (45 patients eligible), who either remained hospitalized or returned to the outpatient clinic for scheduled appointments. Skin samples were obtained by sequentially swabbing a composite sample of skin from the patient's hands, groin, and abdomen with a sterile CultureSwab (Becton Dickinson). Stool samples were tested for the *C. difficile* toxin B gene by polymerase chain reaction (PCR) (Xpert *C. difficile*, Cepheid, Sunnyvale, California) and cultured for *C. difficile* (Supplementary Data). Performance characteristics of formed stools were validated on this assay by our hospital's microbiology laboratory. Sequencing was performed on the IlluminaMiSeq platform using the Nextera XT kit (Illumina Inc). Sequencing reads were mapped onto the *C. difficile* 630 (NC_009089.1) reference genome using bowtie 2.0, results converted to pileup format, and consensus genomic sequences generated using the script pile2cons.rb (www.explicet.org) (Supplementary Data). The presence or absence of diarrhea (watery or loose stools) was obtained from the medical record.

To assess prevalence of colonization upon admission, the first stool samples were collected from consecutively admitted CCBD patients with no prior history of CDI. To be eligible for analysis, the sample had to be collected within the first 72 hours of hospitalization. Stool sample consistency was documented as formed, soft, or liquid, and samples were tested by PCR. For comparison, the percentage of nonduplicate (ie, no positive *C. difficile* stool specimen within the past 2 weeks from the same patient) *C. difficile* PCR tests that were positive among symptomatic CCBD patients in 2012 was calculated.

We evaluated potential risk factors of the *C. difficile*-colonized children on admission compared with those who were not colonized. Prior antibiotic exposure was calculated as total number of days on antibiotics (equal to 1 day for every day on antibiotic irrespective of the number of antibiotics). Healthcare exposure was calculated in 2 ways: number of days hospitalized and number of overall healthcare encounters (number of independent outpatient visits to our institution). The Wilcoxon rank-sum test was used for continuous variables, and mid-*P* exact test or the χ^2 test for dichotomous variables. All analyses for this study were performed with SAS software, version 9.3.

RESULTS

Follow-up Testing of Patients With Previous CDI

Between 1 August 2012 and 7 November 2012, stool samples were collected from each of 33 patients after treatment for CDI (age range, 11 months–21 years; median 4 years; 1 patient 1 year old, 5 patients between 1 and 2 years old). Each patient had completed treatment with at least 10 days of metronidazole for CDI at time of retesting. By 20 weeks after initial CDI diagnosis, the majority of patients (18 [55%]) had at least 1 PCR- or culture-positive stool for *C. difficile*. Overall, 5 (15%) patients had persistently positive, 13 (39%) had persistently negative, and 13 (39%) had intermittently positive stool tests in the follow-up period after treatment (Supplementary Figure). Of the 5 patients who had multiple samples available for full genome sequence analysis, 3 individuals carried different strain types at sequential time points (separated by 4–6 weeks). All strains between patients were highly dissimilar (>1000 single-nucleotide polymorphisms [SNPs]), except for 1 pair that only had 330 different SNPs.

A total of 23 skin swabs from 16 patients (7 patients had duplicate samples 1 week apart) were performed. All skin swabs were negative. Of these 23 samples, 19 had concurrent stool samples, of which 5 (26%) were PCR positive for *C. difficile*.

Admission Surveillance Testing of Patients With No Previous History of CDI

From 11 October 2012 to 21 December 2012, 45 consecutively admitted CCBBD patients had stool samples collected for surveillance testing (age range, 6 months–22 years; median, 7.6 years; 3 patients 1 year old, 1 patient between 1 and 2 years old). None of these patients had documented gastrointestinal complaints (abdominal pain, cramping, diarrhea, loose stools, nausea, or emesis) at time of admission. Of these 45 patients, 34 were established CCBBD patients and 11 were children with a new oncologic diagnosis and were new to our hospital. Ten (22%) of the 45 patients were positive for *C. difficile* by PCR, all of whom were established patients, resulting in an overall colonization rate of 29% (10 of 34 patients) for established CCBBD patients. Only 1 of the *C. difficile*-positive patients was aged <2 years. The consistency of the stool samples reported by the laboratory was as follows: 7 (16%) formed, 33 (73%) soft, 4 (9%) liquid, and 1 (2%) not reported. All 10 positive samples were from soft stools. The colonized patients had an overall greater antibiotic and hospital exposure in the previous 12 weeks compared with the noncolonized patients, but these differences were not statistically significant (Table 1).

During 2012, 77 of 237 (32%) samples submitted to our clinical microbiology laboratory from CCBD patients for diagnostic (ie, from symptomatic patients) *C. difficile* testing by PCR were positive. During this time, 111 unique CCBD patients were tested, of whom 45 (41%) had at least 1 positive *C. difficile* PCR test. The median and mean PCR cycle threshold (C_t) values between the samples submitted for diagnostic purposes compared with those submitted for surveillance purposes were not significantly different (mean $C_t = 25.8$ vs 27.4; $P = .53$).

DISCUSSION

We report that approximately one-third of pediatric oncology patients tested upon hospital admission were colonized with *C. difficile*, as indicated by a positive PCR test in the absence of gastrointestinal symptoms. In addition, more than half of our oncology patients with a history of CDI who were tested during a follow-up period of up to 20 weeks after diagnosis remained intermittently or persistently colonized with *C. difficile* following treatment. Several patients had different strains over time, suggesting acquisition of new strains or carriage of multiple strains simultaneously. Although other studies have found high rates of *C. difficile* colonization in neonates and children up to 3 years of age, in older children, colonization rates are thought to decline to those found in adult populations, ranging from 5% to 15% [6–8]. The high prevalence of colonization in our pediatric oncology patients, combined with a high frequency of diarrhea due to gastrointestinal toxicity of numerous chemotherapy regimens, antibiotic exposure, and underlying disease pathology, complicates the diagnosis of CDI.

Although our numbers are small, none of the newly diagnosed oncology patients were colonized with *C. difficile*, suggesting a high acquisition rate of *C. difficile* from healthcare encounters. Multiple medications might predispose to colonization, including proton-pump inhibitors, antibiotic use, and chemotherapy, all of which have been associated with CDI in pediatric oncology patients [2]. Frequent hospitalizations and clinic visits in this patient population also provide opportunities for *C. difficile* acquisition. Given that a significant proportion of oncology care has shifted to the outpatient setting, efforts should be made to understand the potential role of the outpatient and home settings in *C. difficile* acquisition.

Our findings highlight the potential implications of using a more sensitive diagnostic test for CDI diagnosis. Others have reported that the introduction of PCR testing for *C. difficile*, at a minimum, has resulted in a >50% increase in the detection and reported CDI incidence rates [9–11]. Concerns about detection of colonization rather than true CDI have been raised with the use of molecular methods. Given the frequency of *C. difficile* colonization and diarrhea in the pediatric oncology population, there is considerable uncertainty as to the significance of a positive test result even in a symptomatic patient. Although sample size was small, quantitative PCR testing did not distinguish between colonization and symptomatic infection. Diagnosis therefore needs to be based on a thorough clinical assessment, including evaluation for other causes of diarrhea, as well as assessment of response to CDI treatment. In the future, novel diagnostic strategies, such as measures of inflammation or host immune responses combined with positive *C. difficile* test results, may improve the accuracy of diagnosis.

The high prevalence of *C. difficile* colonization in the established pediatric oncology population is likely a reflection of the multiple healthcare and environmental exposures leading to *C. difficile* acquisition, disruption of the intestinal microbiota, and immunosuppression. Greater understanding of the risk of transmission of *C. difficile* from colonized patients and the mechanism(s) by which patients transition from colonization to disease is needed. Novel interventions might focus on preventing transmission from colonized patients as well as minimizing disruption of and maintaining the protective microbiota.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Comparison of Healthcare and Antibiotic Exposures of *Clostridium difficile*–Positive and –Negative Pediatric Patients in the Preceding 12 Weeks

Exposure	<i>C. difficile</i> PCR Negative (n = 35)	<i>C. difficile</i> PCR Positive (n = 10)	P Value ^a
Age, y	7.7 (4.0–13.4)	8.5 (3.9–13.1)	.81
Total No. of healthcare encounters	22 (8–37)	34 (15–45)	.16
Total No. of hospital admissions	1 (0–2)	1 (0–2)	.86
Total No. of inpatient days	4 (0–18)	5 (0–21)	.83
Total No. of days on antibiotics	7 (2–26)	11.5 (4–26)	.45
Established CCBD patient, No. (%)	24 (68.6)	10 (100)	.04 ^b

Data are presented as median (interquartile range) unless otherwise specified. Abbreviations: CCBD, Center for Cancer and Blood Disorders; PCR, polymerase chain reaction.

^aKruskal-Wallis test (Wilcoxon rank-sum test).

^bMid-*P* exact test.