**EDITORIAL COMMENTARY**

*Clostridium difficile* in Pediatric Oncology Patients: More Questions Than Answers

Jason Kim¹,²

¹Perelman School of Medicine at The University of Pennsylvania, Philadelphia, and ²Division of Infectious Diseases, Children’s Hospital of Philadelphia, Pennsylvania

(See the Brief Report by Dominguez et al on pages 401–3.)

**Keywords.** *Clostridium difficile*; pediatric oncology.

During the past decade, there has been a heightened interest in *Clostridium difficile* infection (CDI) and its changing epidemiology. According to PubMed, 366 articles were published from 1994 to 2004 about CDI epidemiology, and 1667 articles over the last 9 years. A confluence of factors contributed to the increased number of articles about CDI epidemiology: the emergence of a hypervirulent *Clostridium difficile* strain (called NAP1) that caused significant morbidity and mortality among adults, a focus on patient safety and the elimination of healthcare-associated infections (HAIs), and the desire to reduce healthcare costs associated with HAI. CDI is the leading cause of HAI diarrhea, and rivals methicillin-resistant *Staphylococcus aureus* as the most common cause of HAI. During the last decade, the epidemiology of CDI in the pediatric population has only begun to become elucidated, and has been recently reviewed [1]. Thus, this commentary will focus on pediatric CDI and cancer.

Describing CDI epidemiology in persons with cancer is inherently more difficult than in the general population. A problematic issue about CDI among patients with cancer is that its presentation may be confounded by the presence of neutropenic enterocolitis or antibiotic-associated diarrhea not caused by *C. difficile*. Despite this diagnostic dilemma, a multicenter study of adult cancer centers reports that the pooled incidence rate of hospital-onset CDI was more than twice the National Healthcare Safety Network rate of 7.8 cases per 10,000 patient-days [2]. The incidence of CDI in children was reported to be >15 times greater among children hospitalized with cancer compared with those without cancer [3]. Hospitalized children with malignancy accounted for 15% of a pediatric CDI cohort from a single center, and 25% when using administrative data from multiple freestanding children's hospitals [4, 5]. Another retrospective, multicenter cohort study examining children with newly diagnosed acute myeloid leukemia (AML) found that 11% of patients had CDI, with a 14% recurrence rate [6].

As with adults with cancer, children with cancer may be more susceptible to CDI due to similar factors: increased contact with the healthcare system, immunosuppression due to chemotherapeutic agents, and repeated prolonged exposure to broad-spectrum antibiotics. In addition to broad-spectrum antibiotic exposure, there may be a differential risk of CDI among the antipseudomonal β-lactam antibiotics used in patients during febrile neutropenia, with cefepime posing a greater risk than antipseudomonal penicillins [7, 8]. Another important risk factor is length of hospital stay associated with development of CDI [3, 7]. Again, each of these studies relies on large administrative databases. A multicenter study of children with AML demonstrated that mandatory hospitalization during prolonged neutropenia was associated with a higher relative incidence rate of CDI [9]. Hospital-onset CDI leads to longer hospitalizations for children admitted for newly diagnosed cancers, similar to findings in the general pediatric population [7, 10]. All pediatric studies of CDI in children with cancer are similar in 2 aspects: There were no deaths directly attributable to CDI, and no samples were collected for molecular analysis.

Several limitations become clear when examining what is known about the epidemiology of CDI in children. With many multicenter studies examining risk factors for pediatric CDI relying on administrative databases, the conclusions are tempered by the limitations associated with such data sources: no microbiologic confirmation of laboratory tests, inferred inpatient antibiotic exposure (based on billing data and not medication administration record), and a lack of clinical information at the patient...
level. Studies with patient-level clinical data are generally from single-center studies, which may limit generalizability.

In this issue of Clinical Infectious Diseases, Dominguez and colleagues present clinical and microbiologic data garnered through a multipronged investigation into CDI at their institution [11]. Despite the small size of the study, the report produces several interesting observations about CDI in pediatric oncology patients.

An interesting facet of the article is that it is the first to collect microbiologic samples longitudinally from a variety of patients: asymptomatic patients, previously treated patients, and sequential admissions. The data hint at the dynamism of CDI in children with cancer, which may serve as a starting point for further investigations into CDI in this population.

One observation from the study is the high rate of detection of C. difficile in 18 of 33 previously treated patients (55%), which may not be surprising, but 5 patients were persistently positive over a 20-week period, and 13 more were intermittently positive. For 3 of 5 patients with multiple stool samples available for genomic analysis, the authors reported strain changes at sequential time points, raising the question, “Where does acquisition occur?” A larger cohort study in adult cancer patients from a single center found that the majority of repeat cases <8 weeks and >8 weeks following treatment were relapses of the same strain [12]. It could be that if stools were available from all patients for molecular epidemiologic analysis, persistence rather than reinfection might have been found in the present study.

Another interesting observation in this article was that 22% of asymptomatic patients had C. difficile detected in their stool during admission surveillance testing (from 45 sequential admissions), which is not particularly interesting per se in pediatric CDI. More notably, there were no positive stool samples from 11 children on their first admission to their center (new diagnoses or new transfers). The authors calculate a 29% colonization rate for established patients. However, later in the article, they report that 41% of their center’s patients had at least 1 positive C. difficile polymerase chain reaction assay for 2012, suggesting an even higher colonization rate at their center, which is significant considering that <5% of older children are colonized with CD. Despite the inconsistency of the surveillance and clinical microbiology–positive test numbers, a number of conclusions may be made. One, children with cancer may become colonized due to increased time and interaction within the healthcare system. Two, where acquisition of C. difficile occurs remains unknown. In a child rendered more susceptible to colonization as a result of underlying disease, its immunosuppressive therapy, and altered microbiota from increased antibiotic exposure, C. difficile acquisition may occur during hospitalizations, outpatient oncology visits, or in the community. The site of acquisition has significant ramifications on infection control practices surrounding the pediatric oncology patient. Three, asymptomatic children with cancer may represent a larger reservoir for healthcare-associated CDI than previously determined, with colonization rates potentially as high as 40%.

Despite the limitations of the study, the observations in this study raise questions that need to be answered in larger, multicenter studies. When does acquisition of C. difficile occur: in the hospital, clinic, or community? How would this affect infection control practices? Which modifiable risk factors lead to colonization and then to CDI? What can be done to discriminate colonization from actual infection in pediatric cancer patients? What factors are associated with reinfection vs recurrence in children with cancer? The latter is an important question, as reinfection deals with infection control issues and recurrence deals with treatment issues.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has 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