RESEARCH BRIEF

Pediatric *Clostridium difficile* Infection: 6-Year Active Surveillance in a Defined Patient Population

Clostridium difficile infection (CDI), once considered uncommon in children, is now regarded as an emerging infection.[1,2] The objective of this study was to document the epidemiology of CDI from 2007 to 2012 at the Children's Hospital of Eastern Ontario (CHEO), a tertiary care 120-bed pediatric hospital in Ottawa, Canada, and the only area hospital that admits children.

Since 2007, a designation of CDI required a stool specimen positive for *C. difficile* toxin; inpatients required new onset of at least 3 diarrheal stools in 24 hours, and outpatients required new-onset diarrhea as the major reason for presentation. Cases were reviewed when reports were received, and patients were identified as colonized if another potential cause for diarrhea was present. Only the first occurrence was included. CDI cases were classified as community associated (CA; onset prior to hospital admission or up to 72 hours after hospital admission and no prior discharge within 12 weeks); hospital onset, healthcare facility associated (HO-HCFA; onset more than 72 hours after admission); community onset, healthcare facility associated (CO-HCFA; onset up to 4 weeks after discharge); or community onset, indeterminate (CO-I; discharge more than 4 and up to 12 weeks prior to symptoms). Recurrence was defined as a subsequent episode more than 2 and up to 8 weeks after the initial diagnosis.[3]

Clostridium difficile TOX A/B II enzyme immunoassay was used from 2007 until June 30, 2011, after which stool specimens were screened for the presence of the *C. difficile* common antigen glutamate dehydrogenase, and positive samples underwent polymerase chain reaction testing for the toxin B gene. Only specimens from HCFA CDI cases were routinely sent to the National Microbiology Laboratory for determination of North American pulsed-field (NAP) types.[4]

The antimicrobials received by patients were verified using medication records and charts and grouped: narrow-spectrum β-lactams (cefazolin/cephalexin, cloxacillin, ampicillin, amoxicillin, and amoxicillin-clavulinate), broad-spectrum β-lactams (ceftriaxone, cefotaxime, ceftazidime, piperacillin, piperacillin-tazobactam, and meropenem), quinolones, aminoglycosides, metronidazole, clindamycin, vancomycin, trimethoprim-sulfamethoxazole, or unknown. A "course" of antimicrobials was defined as at least 5 days long.

Included cases were summarized descriptively using mean, standard deviation, median, interquartile range (IQR), frequency, and percentage, as appropriate. Incidence densities were estimated on the basis of the number of hospital admissions, using total number of hospital-days of stay as the denominator for HCFA infections (CO and HO) and total number of admissions as the denominator for CA infections. Exact Poisson 95% confidence intervals were computed. Changes in CDI rates were estimated with a negative binomial model to account for overdispersion. Analyses were performed in SPSS 21.0[5] and R 3.0.2.[6] Two-sided *P* values less than 0.05 were deemed to be statistically significant. This study was approved by the CHEO Research Ethics Board.

In total, 87 patients were included: 39 (44.8%) with CA CDI, 13 (14.9%) with CO-HCFA CDI, 30 (34.5%) with HO-

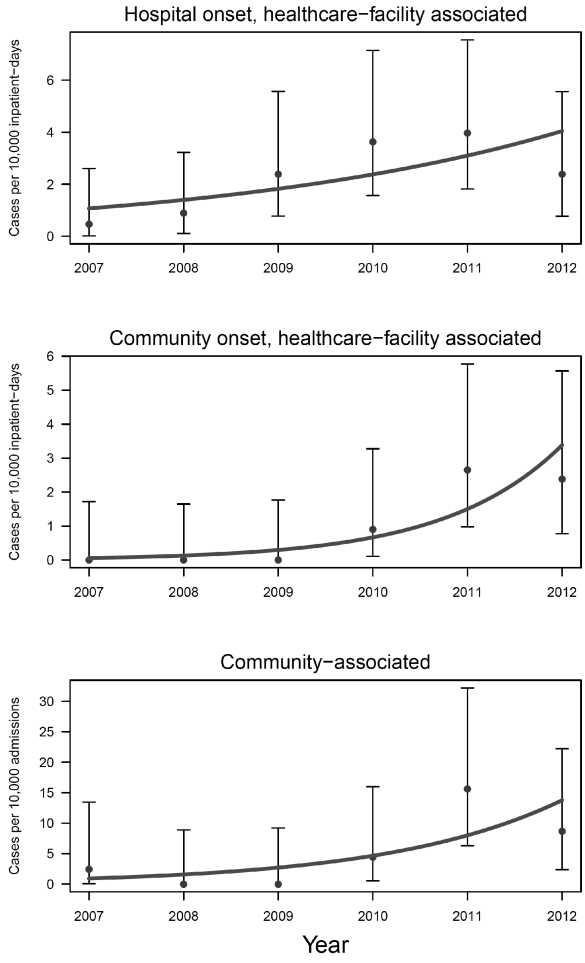

FIGURE 1. Annual incidence of *Clostridium difficile* infections (CDIs) from 2007 to 2012. *Top*, hospital onset, healthcare facility–associated cases per 10,000 inpatient-days; *middle*, community onset, healthcare facility–associated cases per 10,000 inpatient-days; *bottom*, community-associated CDIs per 10,000 admissions; error bars represent 95% confidence intervals. The superimposed curves are negative binomial model fits of the mean incidence by year.

https://doi.org/10.1086/676875 Published online by Cambridge University Press

HCFA CDI, and 5 (5.7%) with CO-I CDI. Bacterial and viral diagnostic testing was concurrently performed on 34 (87.2%) and 22 (56.4%) patients with CA CDI, 7 (53.8%) and 8 (61.5%) patients with CO-HCFA CDI, 20 (66.7%) and 20 (66.7%) patients with HO-HCFA CDI, and 5 (100%) and 2 (40%) patients with CO-I CDI, respectively.

Figure 1 illustrates the annual incidence of CDI. Rates of HCFA CDI (combining HO and CO) ranged from 0.5 to 6.6 per 10,000 inpatient-days, and rates for CA CDI varied between 0 and 15.6 per 10,000 admissions. There was a significant increase in the number of HO-HCFA CDI ($P = 0.02$) and CO-HCFA CDI ($P = 0.002$) cases and CA CDI admissions ($P = 0.01$) over the years 2007–2012. Overall, the hospitalization rates for CDI (both CA and HCFA) ranged from 4.8 to 49.1 per 10,000 admissions, with the highest rates occurring in 2011.

Characteristics of patients are described in Table 1. The median number of days from hospital admission to diagnosis for HO-HCFA was 18.0 (IQR, 8.8–77.3). Eighteen (46.1%) CA CDI patients were admitted to hospital. Overall, there

TABLE 1. Characteristics of Patients within the Study Population, Stratified by *Clostridium difficile* Infection (CDI) Type

	CA CDI ($N = 39$)	CO-HCFA CDI ($N = 13$)	HO-HCFA CDI ($N = 30$)	CO-I CDI ($N = 5$)
Mean age (SD), years	8.8 (5.5)	9.1 (5.3)	8.6 (5.8)	8.3 (5.9)
Male sex	17 (43.6)	8 (61.5)	16 (53.3)	3 (60.0)
Health status				
Malignancy or immunosuppressed	2 (5.1)	7 (53.8)	10 (33.3)	1 (20.0)
Ortho, trauma, surgical	0 (0.0)	2 (15.4)	9 (30.0)	1 (20.0)
Complex pediatric	6 (15.4)	2 (15.4)	7 (23.3)	1 (20.0)
Primary bowel disorder	7 (17.9)	0 (0.0)	1 (3.3)	1 (20.0)
Generally healthy	24 (61.5)	2 (15.4)	3 (10.0)	1 (20.0)
Other	12 (30.8)	2 (15.4)	4 (13.3)	2 (40.0)
Duration of symptoms before diagnosis, days				
Mean (SD)	14.1 (18.1)	1.9 (1.3)	10.2 (23.7)	6.4 (7.4)
Median (IQR)	8 (2.8–20.3)	2.0 (1.0–2.5)	2.5 (1.0–8.5)	2.0 (0.5–14.5)
Hospital encounters in prior 6 months				
Admitted to hospital	5 (12.8)	13 (100.0)	10 (33.3)	5 (100.0)
Seen as outpatient at CHEO	21 (53.8)	13 (100.0)	18 (60.0)	5 (100.0)
Surgery	3 (7.7)	10 (76.9)	21 (70.0)	5 (100.0)
Any of the above	21 (53.8)	13 (100.0)	30 (100.0)	5 (100.0)
Acid-suppressant medication				
H_2 receptor antagonist	0 (0.0)	3 (23.1)	16 (53.3)	1 (20.0)
Proton pump inhibitor	8 (20.5)	6 (46.2)	10 (33.3)	0 (0.0)
Antimicrobials at time of diagnosis	9 (23.1)	9 (69.2)	18 (60.0)	3 (60.0)
Antimicrobial treatment within 2 months	15 (38.5)	12 (92.3)	23 (76.7)	3 (60.0)
Number of total courses documented	31	34	104	13
Number of courses by antimicrobial class[a]				
Narrow-spectrum β-lactam	18 (58)	10 (29)	32 (31)	5 (38)
Extended-spectrum β-lactam	1 (3)	7 (21)	29 (28)	2 (15)
Aminoglycosides	0 (0)	5 (15)	9 (9)	1 (8)
Vancomycin (intravenous)	0 (0)	3 (9)	9 (9)	2 (15)
Trimethoprim-sulphamethoxazole	3 (10)	6 (18)	6 (6)	1 (8)
Metronidazole (intravenous)	2 (6)	2 (6)	7 (7)	1 (8)
Ciprofloxacin	0 (0)	1 (3)	4 (4)	1 (8)
Clindamycin	4 (13)	0 (0)	8 (8)	0 (0)
Unknown	3 (10)	0 (0)	0 (0)	0 (0)
Initial treatment for CDI				
Metronidazole	34 (87.2)	11 (84.6)	24 (80.0)	5 (100.0)
Vancomycin	2 (5.1)	2 (15.4)	4 (13.3)	0 (0.0)
Vancomycin (oral) and metronidazole (IV)	1 (2.6)	0 (0.0)	1 (3.3)	0 (0.0)
None	2 (5.1)	0 (0.0)	1 (3.3)	0 (0.0)

NOTE. Data are number (%) of patients, unless otherwise noted. CA, community-associated; CHEO, Children's Hospital of Eastern Ontario; CO-HCFA, community onset, healthcare facility associated; CO-I, community onset, intermediate; HO-HCFA, hospital onset, healthcare facility associated; IQR, interquartile range; IV, intravenous.

[a] Under this heading, percentages are based on the number of total courses documented.

https://doi.org/10.1086/676875 Published online by Cambridge University Press

were 14 recurrences (16.1%). Of 43 HCFA infections, 23 (53.5%) had specimens that were available for NAP testing. Among these, *C. difficile* could not be grown from 1, and 2 revealed nontoxigenic strains. Of the 20 specimens with NAP typing, 7 were NAP4, 4 were NAP10, 2 were NAP1, 1 was NAP2, 1 was NAP6, and 5 did not cluster in an existing NAP type designation.

In summary, we found, using case-validation strategies, a significant increase in the incidence of both CA and hospital-acquired CDI in an area servicing a defined pediatric patient population. Since ours is the only admitting hospital in the area, it is not subject to admission or referral bias, and although year-to-year variability is substantial, the increasing trend is unmistakable and statistically significant. Although it is possible that the higher testing sensitivity in the latter half of 2011 and 2012 contributed to higher rates, the same personnel and case-capture methodology were used, thereby giving some assurance of consistency. Other studies, using a discharge-coding methodology from multiple hospital databases, found similar rates.[2,7,8]

Among those with CA CDI, more than half had had at least 1 encounter with a healthcare facility within 6 months, whereas the HA CDI and CO-I group all had prior healthcare exposure. The high rate of healthcare encounters (ranging from 40.7% to 85.5%) was also seen in 2 prior studies of CA CDI.[1,9] Similar to a study from the Netherlands, we found that narrow-spectrum penicillins were the most commonly prescribed antibiotics.[10] The use of acid-suppressant medication was frequent, but its role as an independent or synergistic risk factor is yet to be determined.[9,11]

Although we used consistent real-time case-assignment strategies, the major limitation of this study is its retrospective and cohort nature. Whether concerted efforts to decrease antimicrobial and acid-suppressant medication will decrease this trend should be examined.

ACKNOWLEDGMENTS

Financial support. Children's Hospital of Eastern Ontario Research Institute Capacity Building award.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

Nicole Le Saux, MD;[1] Denise Gravel, BScN, MSc;[2] Michael R. Mulvey, PhD;[3] Judy Dennis, RRT, CIC;[1] Abdool S. Yasseen III, MSc;[4] Nicholas Barrowman, PhD;[4] Jennifer Bowes, MSc[4]

Affiliations: 1. Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada; 2. Center for Communicable Diseases and Infection Control, Public Health Agency of Canada, Ottawa, Ontario, Canada; 3. National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba, Canada; 4. Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada.

Address correspondence to Nicole Le Saux, MD, Division of Infectious Diseases, Children's Hospital of Eastern Ontario, Ottawa, Ontario K1H 8L1, Canada (lesaux@cheo.on.ca).

Received December 13, 2013; accepted March 15, 2014; electronically published May 19, 2014.

Infect Control Hosp Epidemiol 2014;35(7):904-906

 0899-823X/2014/3507-0024$15.00. DOI: 10.1086/676875

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