Clostridium difficile in the Pediatric Population of Monroe County, New York

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Presented in part: The International Conference on Emerging Infectious Diseases in Atlanta, GA.

Received August 12, 2013; accepted November 27, 2013; electronically published January 15, 2014.

Background. *Clostridium difficile* infection (CDI) incidence in hospitalized children has increased over the past decade and disease has been reported in the community. Therefore, population surveillance that includes nonhospitalized cases is important to accurately estimate the burden of CDI in children. We describe the epidemiology of CDI in the pediatric population of Monroe County, New York.
Methods. Active, laboratory, and population-based surveillance for CDI has been ongoing in Monroe County through the Emerging Infections Program of the Centers for Disease Control and Prevention since 2010. Infants less than 12 months of age are excluded.
Results. In 2010, the incidence of CDI in the pediatric population was 33.8 per 100 000 population, which increased to 45.8 in 2011and remained stable in 2012. Seventy-one percent of the CDI cases were community-associated, 60% had an underlying medical condition, and 71% received antibiotics before their illness. The North American pulsed-field gel electrophoresis type 1 (NAP1) epidemic strain was identified in 27% of cultured stool specimens.
Conclusions. *Clostridium difficile* infection has emerged as a disease affecting children in both the community and hospital settings, with a higher proportion of community illness in our population. The majority of children with CDI had chronic underlying conditions and prior antibiotic exposure. To prevent CDI in this population, the judicious use of antibiotics, especially in the outpatient setting, may be the best strategy. Further population-based studies are warranted to determine preventable risk factors for CDI in the pediatric population.

Key words. children; *Clostridium difficile*; pediatric; population surveillance.

INTRODUCTION

The epidemiology of *Clostridium difficile* infection (CDI) has changed over the past decade, and this change is manifested by (1) an increase in the incidence and severity of illness in the adult population and (2) the occurrence of disease in the community setting in patients without the traditional risk factors [1]. This change also occurred concomitantly with the emergence of a new hypervirulent strain referred to as North American pulsed-field gel electrophoresis (PFGE) type 1 or NAP1 [2]. In the pediatric population, several studies in the United States reported an increase in CDI-related hospitalizations [3–6] over the past decade, but few studies reported disease in the community setting [7, 8]. Most of these studies are either single center studies or based on large administrative databases and therefore focus on hospitalized cases and patients seeking emergency room care. Population surveillance for CDI in children is limited [9], but it is important in assessing the incidence and the spectrum of disease by including nonhospitalized cases. In this study, we describe the epidemiology and clinical characteristics of CDI in children, aged 1 to 17 years, residing in Monroe County, New York, in both the inpatient and outpatient settings.

MATERIALS AND METHODS

Since 2009, active laboratory and population-based surveillance for CDI has been conducted in Monroe County, New York as part of the Centers for Disease Control and Prevention's Emerging Infections Program. The surveillance methods have been described elsewhere [10, 11]. In brief, all positive *C difficile* stool assays from Monroe County residents are reported to the surveillance staff. This study describes the characteristics of the pediatric CDI cases, aged 1 to 17 years, reported between January 2010 and December 2011. Cases occurring in 2012 were not included, but the number of cases was used to compare the incidence over a 3-year time period. Children less than 12 months of age were excluded due to the high rate of colonization in that population [12].

Clostridium difficile infection cases were defined as (1) incident: positive *C difficile* specimen without a previous positive in the past 8 weeks; or (2) recurrent: positive *C difficile* specimen collected 2–8 weeks after the last positive specimen. Cases without diarrhea, defined as unformed or watery stool, were excluded. The frequency and duration of diarrhea was not included in the case definition, because this information is often not well documented in the medical record. We classified cases with stool collected as outpatient or $\leq$3 days after hospital admission and no overnight healthcare facility stay in the prior 12 weeks as community-associated (CA), otherwise cases were healthcare-associated (HA) and included cases diagnosed during their hospitalization (>3 days of admission) or in the community within 12 weeks of discharge from a hospital [13]. Data for CDI cases reported in 2010 and 2011 were abstracted by clinical staff from electronic medical records or outpatient providers. Exposure to antibiotics was collected for the 12 weeks before CDI; other medication usage was collected for the 2 weeks before CDI. Incidence of CDI was calculated using publicly available US Census Bureau/National Center for Health Statistics bridged-race population estimates. Incidence for the pediatric population was divided into 4 age groups and compared to the incidence in adults. Univariate analysis was conducted to summarize the demographic and clinical characteristics of cases. Bivariate analyses were used to compare these characteristics across age and classifications using the χ^2 test and Fisher's Exact test as appropriate. All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC). The study was approved by New York State Department of Health and the local hospitals' human subject review boards.

Laboratory Methods

Only unformed stool samples were tested for *C difficile* toxin or molecular assays at the 3 clinical laboratories servicing the Monroe County population. In 2010, 2 laboratories used toxins A and B enzyme immunoassay (EIA), and 1 laboratory used a 2-step testing method with glutamate dehydrogenase in combination with toxin EIA. Discrepant glutamate dehydrogenase-positive/EIA-negative samples underwent nucleic acid amplification test (NAAT) for the toxin B gene (GeneXpert *C difficile* assay; Cepheid). In 2011, the 2 laboratories using toxin EIA changed their testing method; 1 adopted the 2-step method with reflex to NAAT, and 1 switched to NAAT testing alone (GeneOhm Toxin B gene NAAT; Becton Dickinson).

A random sample of specimens (50% of CA cases and 10% of HA cases) from 2 of 3 laboratories were submitted to the New York State Public Health Laboratory for culture of *C difficile*. Isolates were shipped to the Centers for Disease Control and Prevention for molecular typing by PFGE. Pulsed-field gel electrophoresis banding patterns were analyzed by using BioNumerics version 5.10 (Applied Maths, Austin, TX) and grouped into PFGE types using Dice/UPGMA (Unweighted Pair-Group Method with Arithmetic mean) clustering. North American PFGE types were assigned to patterns with 80% similarity to established clusters.

RESULTS

Incidence

Of the 5080 CDI cases detected during the 3 years of the surveillance, 197 occurred in children, representing approximately 4% of total CDI cases in Monroe County. Pediatric incidence rates by age group are summarized in Table 1. The annual pediatric incidence was 33.8 cases per 100 000 population in 2010 and increased to 45.8 in 2011, which remained stable in 2012 at 45.8 cases per 100 000 population. Comparatively, the adult incidence increased from 262.2 to 294.1 cases per 100 000 population in 2011 and was 285.0 cases per 100 000 population in 2012. The highest incidence was in cases aged 1 year.

Clinical Characteristics

One hundred twenty-six cases reported in 2010–2011 were reviewed. The median age was 5 years (interquartile range, 2–11). The majority of cases were males (56%) and white race (78%) (Table 2). Seventy-one percent of cases were classified as CA.

The majority of cases, across all age groups, had an underlying medical condition with many having multiple comorbidities requiring medical devices such as feeding

Table 1. Incidence of Pediatric *Clostridium difficile* Cases, 2010–2012 Monroe County, NY

		Age Group			
	Total (n=197)	1 Year[a] (n=43)	2–3 Years (n=24)	4–9 Years (n=56)	10–17 Years (n=74)
Incidence					
2010					
Cases	54	12	8	14	20
Incidence per 100 000 population	33.79	142.48	45.54	26.04	24.97
(95% confidence interval)	(25.4–44.1)	(73.6–248.9)	(19.7–89.8)	(14.2–43.7)	(15.3–38.6)
2011					
Cases	72	17	9	23	23
Incidence per 100 000 population	45.82	199.13	52.43	43.27	29.38
(95% confidence interval)	(35.8–57.7)	(116–318.8)	(24–99.5)	(27.4–64.9)	(18.6–44.1)
2012					
Cases	71	14	7	19	31
Incidence per 100 000 population	45.79	162.23	41.12	35.96	40.49
(95% confidence interval)	(35.8–57.8)	(88.7–272.2)	(16.5–84.7)	(21.7–56.2)	(21.5–57.5)

[a]≥12 months to <24 months of age.

Table 2. Characteristics of Pediatric *Clostridium difficile* Infection Cases by Age Group and Epidemiologic Classification, 2010–2011

		Age Group					Epidemiologic Classification		
Characteristic	Total (n=126) n (%)	1 Year[a] (n=29) n (%)	2–3 Years (n=17) n (%)	4–9 Years (n=37) n (%)	10–17 Years (n=43) n (%)	*P* Value	CA (n=89) n (%)	HA (n=37) n (%)	*P* Value
Sex						.39			.54
Male	70 (56)	20 (69)	9 (53)	20 (54)	21 (49)		51 (57)	19 (51)	
Race						.66			.12
White	98 (78)	21 (72)	13 (76)	27 (73)	37 (86)		71 (80)	27 (73)	
Black	21 (17)	6 (21)	3 (18)	7 (19)	5 (12)		11 (12)	10 (27)	
Other	5 (4)	2 (7)	0 (0)	2 (5)	1 (2)		5 (6)	0 (0)	
Unknown	2 (2)	0 (0)	1 (6)	1 (3)	0 (0)		2 (2)	0 (0)	
Epidemiologic classification						.12			
Community-associated	89 (71)	23 (79)	8 (47)	26 (70)	32 (74)		89 (100)	0 (0)	
Healthcare-associated	37 (29)	6 (21)	9 (53)	11 (30)	11 (26)		0 (0)	37 (100)	
Comorbidities						.64			<.0001
Underlying comorbidities (any)	76 (60)	15 (52)	10 (59)	22 (59)	29 (67)		43 (48)	33 (89)	
None	47 (37)	14 (48)	6 (35)	14 (38)	13 (30)		43 (48)	4 (11)	
Unknown	3 (2)	0 (0)	1 (6)	1 (3)	1 (2)		3 (3)	0 (0)	
Comorbidities by type									
Pulmonary disease	34 (27)	7 (24)	4 (24)	8 (22)	15 (35)	.55	21 (24)	13 (35)	.18
Gastrointestinal	26 (21)	7 (24)	3 (18)	7 (19)	9 (21)	.94	15 (17)	11 (30)	.10
Inflammatory bowel disease	6 (5)	0 (0)	0 (0)	1 (3)	5 (12)	.11	6 (7)	0 (0)	.18
Other gastrointestinal	20 (16)	7 (24)	3 (18)	6 (16)	4 (9)	.37	9 (10)	11 (30)	.006
Neurological	24 (19)	6 (21)	6 (35)	7 (19)	5 (12)	.21	12 (13)	12 (32)	.01
Medical devices	20 (16)	6 (21)	3 (18)	6 (16)	5 (12)	.75	7 (8)	13 (35)	.0001
Renal or urologic	18 (14)	3 (10)	2 (12)	9 (24)	4 (9)	.28	6 (7)	12 (32)	.0002
Solid and hematologic malignancy	13 (10)	2 (7)	2 (12)	3 (8)	6 (14)	.74	3 (3)	10 (27)	.0003
Cardiovascular	11 (9)	2 (7)	3 (18)	4 (11)	2 (5)	.38	3 (3)	8 (22)	.002
Hematologic disorder or immunodeficiency	9 (7)	0 (0)	2 (12)	5 (14)	2 (5)	.10	5 (6)	4 (11)	.45
Transplant	8 (6)	0 (0)	0 (0)	5 (14)	3 (7)	.12	4 (4)	4 (11)	.23
Diabetes	2 (2)	0 (0)	0 (0)	0 (0)	2 (5)	.50	1 (1)	1 (3)	.50
Hemi/paraplegia	1 (1)	0 (0)	0 (0)	0 (0)	1 (2)	1.0	1 (1)	0 (0)	1.0
Premature (<37 weeks, 1 year only)	7 (6)						4 (4)	3 (8)	
Outcome									
Recurrence	33 (26)	10 (34)	4 (24)	12 (32)	7 (16)	.26	23 (26)	10 (27)	.89
Severe disease[b]	9 (7)	1 (3)	0 (0)	2 (5)	6 (14)	.24	5 (6)	4 (11)	.45
C difficile test method						.02			.53
NAAT toxin B gene positive	60 (48)	15 (52)	4 (24)	24 (65)	17 (40)		44 (49)	16 (43)	
EIA toxins A and B positive	66 (52)	14 (48)	13 (76)	13 (35)	26 (60)		45 (51)	21 (57)	

Abbreviations: CA, community-associated; HA, healthcare-associated; EIA, enzyme immunoassay; NAAT, nucleic acid amplification test.

[a]≥12 months to <24 months of age.

[b]Severe disease is defined as radiology showing ileus or toxic megacolon, white blood cell count 15 000/μL or higher, pseudomembranous colitis, or intensive care unit admission.

tubes (Table 2). The most common underlying medical conditions were pulmonary disease (27%) including disease related to prematurity and asthma; gastrointestinal disease (21%), with inflammatory bowel disease noted in a small percentage of the older age group; and neurological conditions (19%) including cerebral palsy, seizures, and developmental delays. When comparing the cases by epidemiologic classification, the CA cases were less likely to have an underlying condition than the HA cases (48% vs 89%; $P < .0001$).

Outcomes

Twenty-six percent of cases had a recurrence. Twenty-seven percent of cases were hospitalized, and 7% of cases had severe disease with an elevated white blood cell count (above 15,000/μL) or intensive care admission. There were no other severe disease outcomes such as colectomy or death.

Exposures

Exposure to antibiotics within 12 weeks of CDI diagnosis was noted in 71% of the cases (Table 3). Thirty-nine percent had more than 1 antibiotic; the most common were cephalosporins, primarily 3rd-generation cephalosporins, followed by penicillins. Exposure to antibiotics was more common in the HA cases compared with the CA cases (89% vs 64%; $P = .01$), but antibiotic exposure was unknown in 12% of the CA cases. Antibiotic indications included: upper respiratory tract or ear infection (26%), chronic prophylaxis for infection or preoperatively (16%), renal or urologic infection (13%), pulmonary infection (11%), skin and soft tissue infection (8%), neutropenic fever (6%), other reasons (11%), and in 11% the indication was unknown. Exposure to gastric acid reducers, immunosuppressants, and emergency room visits are listed in Table 3.

Table 3. Medications and Emergency Room Visits Prior to *Clostridium difficile* Infection in Pediatric Cases, 2010–2011

		Age Group					Epidemiological Classification		
Exposures	Total (n=126) n (%)	1 Year[a] (n=29) n (%)	2–3 Years (n=17) n (%)	4–9 Years (n=37) n (%)	10–17 Years (n=43) n (%)	*P* Value	CA (n=89) n (%)	HA (n=37) n (%)	*P* Value
Medications (12 weeks)									
Antibiotics						.31			.01
Yes	90 (71)	17 (59)	13 (76)	28 (76)	32 (74)		57 (64)	33 (89)	
No	25 (20)	7 (24)	2 (12)	6 (16)	10 (23)		21 (24)	4 (11)	
Unknown	11 (9)	5 (17)	2 (12)	3 (8)	1 (2)		11 (12)	0 (0)	
Antibiotic classification[b]									
Cephalosporins	48 (38)	8 (28)	8 (47)	14 (38)	18 (42)		26 (29)	22 (59)	
First generation	17 (13)	1 (3)	2 (12)	4 (11)	10 (23)		12 (13)	5 (14)	
Second generation	2 (2)	0 (0)	0 (0)	1 (3)	1 (2)		2 (2)	0 (0)	
Third generation	31 (25)	7 (24)	6 (35)	9 (24)	9 (21)		16 (18)	15 (41)	
Fourth generation	7 (6)	1 (3)	2 (12)	2 (5)	2 (5)		0 (0)	7 (19)	
Penicillins	22 (17)	8 (28)	4 (24)	8 (22)	2 (5)		18 (20)	4 (11)	
β-lactamase inhibitors combination	20 (16)	6 (21)	6 (35)	5 (14)	3 (7)		10 (11)	10 (27)	
Trimethoprim-sulfamethoxazole	10 (8)	1 (3)	3 (18)	3 (8)	3 (7)		2 (2)	8 (22)	
Macrolides	8 (6)	1 (3)	1 (6)	4 (11)	2 (5)		4 (4)	4 (11)	
Quinolones	7 (6)	0 (0)	1 (6)	2 (5)	4 (9)		1 (1)	6 (16)	
Clindamycin	6 (5)	0 (0)	2 (12)	1 (3)	3 (7)		2 (2)	4 (11)	
Metronidazole	4 (3)	0 (0)	2 (12)	0 (0)	2 (5)		0 (0)	4 (11)	
Vancomycin (intravenous)	4 (3)	0 (0)	2 (12)	1 (3)	1 (2)		0 (0)	4 (11)	
Other	8 (6)	2 (7)	0 (0)	4 (11)	2 (5)		2 (2)	6 (16)	
Antibiotic name unknown	9 (7)	1 (3)	1 (6)	3 (8)	4 (9)		7 (8)	2 (5)	
Medications (2 weeks)									
Proton Pump Inhibitors						.39			<.0001
Yes	19 (15)	3 (10)	2 (12)	7 (19)	7 (16)		4 (4)	15 (41)	
No	102 (81)	24 (83)	13 (76)	29 (78)	36 (84)		80 (90)	22 (59)	
Unknown	5 (4)	2 (7)	2 (12)	1 (3)	0 (0)		5 (6)	0 (0)	
H2 Blocker						.16			.07
Yes	16 (13)	2 (7)	4 (24)	5 (14)	5 (12)		8 (9)	8 (22)	
No	105 (83)	25 (86)	11 (65)	31 (84)	38 (88)		76 (85)	29 (78)	
Unknown	5 (4)	2 (7)	2 (12)	1 (3)	0 (0)		5 (6)	0 (0)	
Immunosuppressant (any)						.12			.0001
Yes	28 (22)	3 (10)	3 (18)	7 (19)	15 (35)		11 (12)	17 (46)	
No	95 (75)	25 (86)	13 (76)	29 (78)	28 (65)		75 (84)	20 (54)	
Unknown	3 (2)	1 (3)	1 (6)	1 (3)	0 (0)		3 (3)	0 (0)	
Emergency room visit (12 weeks)	44 (35)	15 (52)	8 (47)	8 (22)	13 (30)	.05	19 (21)	25 (68)	<.0001

Abbreviations: CA, community-associated; HA, healthcare-associated.

[a] ≥12 months to <24 months of age.

[b] Cases may have multiple antibiotic exposures.

Laboratory Testing

In 2010, 43% of CDI cases were diagnosed by NAAT, which increased to 52% in 2011 after all laboratories implemented more sensitive testing. For the combined 2 years of surveillance, 48% of cases were diagnosed by NAAT without any apparent trend for the different age groups. In addition, no difference in the diagnostic testing was noted when the 1-year-old cases were compared with the combined 2- to 17-year-old cases (NAAT positive, 52% vs 46%; $P = .61$).

Testing for coinfection with other pathogens was done across the 4 age groups; 64% had additional stool bacterial cultures, 34% were tested for *Giardia* and *Cryptosporidium* antigen, 14% were tested for ova and parasites, and 10% were tested for rotavirus. All stool tests were negative.

Fifty (40%) stool samples were submitted for *C difficile* culture and molecular testing, and *Clostridium difficile* was recovered from 41 (82%) of the toxin-positive specimens submitted. The NAP1 epidemic strain was identified in 11 (27%) of stool specimens, 32% of CA cases, and 10% of HA cases.

DISCUSSION

This population surveillance shows that CDI has emerged as a disease affecting children in both the community and hospital settings in Monroe County, NY. We determined that the 2011 incidence is similar to the incidence in 0- to 18-year-olds reported in 2009 in Olmstead County, MN [9]. We noted an increase in the CDI incidence between 2010 and 2011 and hypothesize that this increase is partially due to the adoption of more sensitive diagnostic testing across all laboratories in 2011. This hypothesis is supported by the subsequent relatively stable incidence of CDI in 2012 determined by the ongoing Monroe County surveillance. Likewise, the recent study in Olmstead County [9] showed an increased incidence after adopting more sensitive testing methods. We found the highest incidence rate in children aged 1 year old with a much lower rate in the older age groups. Similar trends in children less than 5 years old have been reported [3, 6, 9]. Many of the similarities between the younger and older age groups (such as the type of diagnostic testing, clinical characteristics, outcomes, and the exposure to antibiotics) suggest that most of the diarrhea in the younger cases is likely due to CDI rather than colonization. However, a recent American Academy of Pediatrics' policy statement cautioned about interpreting positive *C difficile* testing in children aged 1–3 years due to a high rate of colonization and suggested testing for other etiologies, particularly viral causes [14]. One study of 62 children with a positive NAAT for *C difficile* showed that 24% of the children had concomitant viral infection, but coinfection was not exclusive for the younger age group [15]. In addition, the clinical features were similar between the coinfected and the *C difficile*-infected patients, making it difficult to determine the role of *C difficile* in the coinfected children. Further investigation into the reasons for the high incidence in the younger age group is needed.

The majority (71%) of our pediatric CDI cases were classified as CA, similar to another study that reported that 75% of their cases were CA [9]. Studies conducted in tertiary care centers report a lower proportion of CA cases (25%–41%) [16, 17], highlighting the need for population-based surveillance to accurately describe the burden of disease in the pediatric community.

The majority (89%) of the HA CDI case patients and approximately 50% of CA CDI patients had at least 1 underlying illness, and several had complex medical conditions. It is theorized that complex chronic medical conditions increase pediatric CDI risk due to antibiotic exposure, longer hospitalizations, and frequent outpatient contact with healthcare settings [5]. For instance, 21% of the CA CDI cases and 68% of the HA CDI cases had an emergency visit within 12 weeks of their CDI diagnosis. Because our surveillance included nonhospitalized patients, the percentage of patients with cancer, organ transplant, or immunosuppression was not as large as other reports. Gastrostomy or jejunostomy tube use has also been reported to be a risk factor in the pediatric population [16], and in our surveillance 16% of CDI cases had a chronic medical device in place including tracheostomy tubes.

Antibiotic exposure, a known risk factor for CDI, was common (71%) and was similar to other reports of 57%–78% antibiotic exposure among pediatric CDI cases [8, 9, 16, 17]. Reasons for antibiotic use were similar to prior studies, with most antibiotics taken for upper respiratory and ear infections. Proton pump inhibitor (PPI) exposure in the 2 weeks before CDI occurred in 15% of cases, with most of the use occurring in HA cases. Although evidence for an association between PPI and CDI in children is limited, PPI use was an important additional risk factor in adults in a recent meta-analysis [18].

Twenty-seven percent of our CDI cases were hospitalized, but none experienced a severe outcome. The percentage of severe disease was similar to the Olmstead County study [9] (7% and 8.7% respectively) but lower than a pediatric study focused on hospital-onset CDI [5].

Thirty-two percent of the CA isolates were NAP1, demonstrating that this strain causes disease in children in the community. Previous studies in hospitalized children found the percentage of NAP1 to be between 10%–19% [19–21]. This strain is potentially associated with worse

outcomes [12]; however, we were unable to link disease severity to strain type due to the small number of stool specimens that underwent molecular typing.

Our study's major strengths are the performance of surveillance on a population level and inclusion of CDI cases that are both community and HA. In addition, we completed detailed medical record review for underlying conditions and medication exposure. Previous literature has relied on administrative data that lacks information from outpatient medical charts. Limitations include the small number of cases and the inability to definitely differentiate between colonization and disease. We attempted to exclude colonized patients by only including patients with diarrhea and by the laboratory policy of testing only unformed stool. Although additional diagnostic tests were done to exclude other etiologies, the majority of the cases were not tested for viruses such as rotavirus and norovirus, which have been shown to occur concurrently with *C difficile* [12, 15].

This population-based surveillance highlights that CDI has emerged as a significant disease in the pediatric population, although the incidence is lower compared to adults. The majority of disease is CA, and most of the children had chronic underlying conditions and prior antibiotic exposure. Strategies to prevent CDI in this population should focus on judicious use of antibiotics, especially in the outpatient setting. Further population-based studies are warranted to determine additional preventable risk factors for CDI in the pediatric population.

Disclaimer: The funding agencies had no role in the preparation, review or approval of the manuscript.

Financial support. This work was supported by a collaborative agreement with the Centers for Disease Control and Prevention's Emerging Infections Program.

Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflict of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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