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Risk Factors for Community-Associated *Clostridium difficile* Associated Diarrhea in Children

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Abstract

Background—*Clostridium difficile*-associated diarrhea (CDAD) is increasingly diagnosed in children in community settings. This study aims to assess recent antibiotic use and other risk factors in children with community-associated (CA-) CDAD compared with children with other diarrheal illnesses in a tertiary care setting.

Methods—Children with CA-CDAD evaluated at Texas Children's Hospital (Houston, Texas) from January 1, 2012 through June 30, 2013 were identified. Two control subjects with community-associated diarrhea who tested negative for *C. difficile* were matched to case subjects. Data on demographics, medication exposure, and outpatient healthcare encounters were collected from medical records. Multivariate logistic regression was performed to identify predictors of pediatric CA-CDAD.

Results—Of 69 CA-CDAD cases, most (62.3%) had an underlying chronic medical condition and 40.6% had antibiotic exposure within 30 days of illness. However, no traditional risk factor for CDAD was identified in 23.2% and 15.9% of CA-CDAD cases within 30 and 90 days of illness onset, respectively. Outpatient healthcare encounters within 30 days were more common among CA-CDAD cases than control subjects (66.7% vs. 48.6%; $P=0.01$). In the final multivariate model, CA-CDAD was associated with cephalosporin use within 30 days (OR 3.32; 95% CI 1.10–10.01) and the presence of a gastrointestinal feeding device (OR 2.59; 95% CI 1.07–6.30).

Conclusions—Recent use of cephalosporins and the presence of gastrointestinal feeding devices are important risk factors for community-associated CDAD in children. Reduction in the use of outpatient antibiotics may decrease the burden of CA-CDAD in children.

Keywords

Clostridium difficile; diarrhea; pediatric; antimicrobial stewardship; tube feeding

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INTRODUCTION

Clostridium difficile is an important cause of antibiotic-associated diarrhea and the most widely recognized diarrheal pathogen acquired in healthcare settings.¹ During the past 10 years, there has been a notable increase in the incidence of *C. difficile*-associated diarrhea (CDAD) in the United States and the emergence of disease in community settings and in individuals previously considered low-risk.^{2,3}

The incidence of CDAD in hospitalized children has been increasing since 1997.⁴⁻⁶ Accompanying this trend are studies indicating that the burden of pediatric CDAD in the community is substantial and rising.⁷⁻¹¹ Utilizing a population-based surveillance program in 10 states, a recent report found that 71% of pediatric CDAD cases are community-associated (CA-).⁹ Additionally, a study from Olmstead County, Minnesota found that their rate of CA-CDAD in children increased 10.5-fold from 1991 to 2007.⁷ Given these findings, ascertaining the factors associated with CA-CDAD in children is essential to guide future prevention strategies.

Antibiotic or gastric acid suppressant exposure, gastrointestinal feeding devices, and certain medical conditions, such as malignancy and inflammatory bowel disease, are recognized to be associated with CDAD in children.^{12,13} However, the risk factors specific to community-associated CDAD in children remain unclear. Herein, we describe the clinical characteristics and risk factors of pediatric CA-CDAD at a free-standing children's hospital.

MATERIALS AND METHODS

Study Design and Setting

This is a retrospective, hospital-based, case-control study. Study subjects included children, both inpatients and outpatients, who received medical care at Texas Children's Hospital (Houston, Texas) from January 1, 2012 through June 30, 2013.

Identification of Case and Control Subjects

The Texas Children's Hospital Molecular Microbiology Database was used to identify individuals who were tested for *C. difficile*. An institutional real-time polymerase chain reaction assay that detects toxin genes, *tcdA* and *tcdB*, with a sensitivity of 95% and specificity of 100% was used during the study period.¹⁴

The study population consisted of children 1 through 18 years of age with community-associated diarrhea who underwent testing for *C. difficile*. Community-associated diarrhea was defined, as per the recommendations of the *C. difficile* Surveillance Working Group, as symptom onset in the community or within 48 hours after hospital admission provided that symptom onset was more than 12 weeks after the last hospital discharge.¹⁵ Diarrhea was defined as the passage of 3 or more loose bowel movements per day. Individuals with diarrhea exceeding 4 weeks of duration were excluded. Due to high rates of *C. difficile* colonization in neonates and infants, individuals under 1 year of age were excluded from the study.¹⁶ Community-associated CDAD cases consisted of children with community-associated diarrhea who tested positive for *C. difficile*. Control subjects were selected among

children with community-associated diarrhea who tested negative for *C. difficile*. Children who tested positive for *C. difficile* and were found to have an alternative enteric pathogen, as identified by routine clinical testing, were excluded from the case group. For individuals with more than 1 CA-CDAD episode during the study period, only the first episode was selected for analysis.

Control subjects were frequency matched by age group (1–2 years, 3–5 years, 6–11 years, 12–18 years) and randomly selected to achieve a 1:2 ratio with CA-CDAD cases. Individuals who tested negative for *C. difficile* and had an alternative enteric pathogen identified were eligible to be selected as a control.

Data Collection

Using a standardized abstraction form, the medical record of each case and control subject was reviewed to collect data on demographics, clinical presentation, and potential risk factors for CA-CDAD. The type and frequency of antibiotic and gastric acid suppressant use were examined within 30 days and 90 days of illness onset. Additionally, we examined the type and frequency of exposure to outpatient healthcare settings within 30 days and 90 days of illness onset.

Data Analysis

Summary statistical analyses were computed for demographic, clinical characteristics, and potential risk factors for CA-CDAD. Categorical variables were summarized using frequencies and percentages.

To compare differences between CA-CDAD cases and control subjects, a univariate analysis was performed, stratified by the timing of exposure – within 30 days or 90 days of illness. The univariate analysis was performed using the X^2 test or Fisher's exact test for all variables. Two multivariable logistic regression analyses were performed to identify risk factors for CA-CDAD, stratified according to the predetermined exposure periods. Variables with a $P < 0.20$ on the univariate analysis were eligible for the multivariable models. Non-significant variables ($P > 0.10$) were removed in an iterative fashion to construct the most parsimonious model. To account for any residual confounding following frequency matching, age was included in both final multivariate models. A two-tailed $P < 0.05$ defined statistical significance.

Stata 12 (Statacorp, College Station, TX) was used for all statistical analyses. The Baylor College of Medicine Institutional Review Board and the University of Texas Health Sciences Center Committee for the Protection of Human Subjects approved this study.

RESULTS

There were 291 individuals who tested positive for *C. difficile* during the 18-month study period (see Figure, Supplemental Digital Content 1, a flowchart illustrating the identification of case subjects). Following exclusions based on the requirement for community-associated diarrhea and the absence of co-pathogens, 73 pediatric CA-CDAD episodes, occurring in 69 patients, remained. Among the 1338 individuals who tested negative for *C. difficile*, 403

unique children, aged 1 through 18 years of age, were identified with a non-*C. difficile* community-associated diarrheal illness (see Figure, Supplemental Digital Content 2, a flowchart illustrating the identification of control subjects).

Demographics and Clinical Characteristics

Baseline demographic information is provided in Table 1. The median age for children with CA-CDAD was 8 years (mean 8.1 years; IQR 3–13 years). No differences were noted between cases and controls in race, insurance status, or season of illness. The presence of an underlying chronic medical condition was common and not different among CA-CDAD cases (62.3%) and control subjects (68.1%) (see Table, Supplemental Digital Content 3, a table showing the clinical characteristics of CA-CDAD case subjects and control subjects). Gastrointestinal disorders were common in both groups, occurring in 39.1% of all study subjects; inflammatory bowel disease was the most prevalent condition, occurring in 15.9% of subjects. The presence of a gastrointestinal feeding device was more common among CA-CDAD cases than controls (14/69 [20.3%] vs. 11/138 [8.0%]; $P=0.01$). Assessment of the clinical and laboratory features of the diarrheal illness found no differences between CA-CDAD cases and controls.

The majority of CA-CDAD cases had stool specimens tested for additional enteric pathogens (see Table, Supplemental Digital Content 3, a table showing the clinical characteristics of CA-CDAD case subjects and control subjects). However, differences were seen in the testing patterns of CA-CDAD cases and controls. CA-CDAD cases were less likely to have their stool tested for parasites (27/69 [39.1%] vs. 74/138 [53.6%]; $P=0.05$) when compared with control subjects. Similarly, testing for viruses was less common among CA-CDAD cases than control subjects, though this finding was not statistically significant (17/69 [24.6%] vs. 52/138 [37.7%]; $P=0.06$).

Risk Factors – 30 Days Prior to Illness

The use of antibiotics within 30 days of illness was more common among CA-CDAD cases (28/69 [40.6%]) than controls (38/138 [27.5%]), although this difference was not statistically significant ($P=0.06$) (see Table, Supplemental Digital Content 4, a table showing exposures to medications and outpatient healthcare settings within 30 days of illness onset in CA-CDAD case subjects and control subjects). When assessed according to antibiotic class, CA-CDAD cases were more likely to have received cephalosporins (9/69 [13.0%] vs. 6/138 [4.4%]; $P=0.02$) and clindamycin (4/69 [5.8%] vs. 1/138 [0.7%]; $P=0.04$). The use of gastric acid suppressants was frequent among CA-CDAD cases, yet there was no difference in the proportion of case and control subjects that used them.

CA-CDAD cases were more likely to have visited an outpatient healthcare setting in the 30 days prior to illness than controls (46/69 [66.7%] vs. 67/138 [48.6%]; $P=0.01$). CA-CDAD cases were more likely to have 1–2 outpatient encounters (OR 2.06, 95% CI 1.09–3.87) and 3 outpatient encounters (OR 2.37, 95% CI 0.92–6.13), although a trend was not detected (Chi-square test for trend, $P=0.09$). When stratified based on type of outpatient healthcare setting, no difference was noted between cases and controls. Only 16 (23.2%) CA-CDAD

cases, compared to 58 (42.0%) controls, had no evidence of exposure to antibiotics, acid suppressants, or outpatient healthcare settings in the 30 days prior to illness ($P=0.008$).

In the final multivariate model of exposures within 30 days of illness, when controlling for age, cephalosporin use (OR 3.32; 95% CI 1.10–10.11; $P=0.03$) and the presence of a gastrointestinal feeding device (OR 2.59; 95% CI 1.07–6.30; $P=0.04$) were found to be significantly associated with CDAD (Table 2).

Risk Factors – 90 Days Prior to Illness

The use of antibiotics within 90 days was more common among CA-CDAD cases (34/69 [49.3%]) than controls (47/138 [34.1%]) ($P=0.05$) (see Table, Supplemental Digital Content 5, a table showing exposures to medications and outpatient healthcare settings within 90 days of illness onset in CA-CDAD case subjects and control subjects). When examined according to antibiotic class, CA-CDAD cases were more likely to have received cephalosporins (14/69 [20.3%] vs. 11/138 [8.0%]; $P=0.04$) and clindamycin (7/69 [10.1%] vs. 4/138 [2.9%]; $P=0.04$). Additionally, CA-CDAD cases were more likely to have received 2 or more antibiotic classes within 90 days, compared to controls (OR 2.25, 95% CI 0.97–5.21; $P=0.05$). No difference was noted in the proportion of cases and controls that used gastric acid suppressants in the 90 days prior to illness.

Exposure to outpatient healthcare settings within 90 days of illness was common among both CA-CDAD cases and controls. No differences were noted in the type and frequency of outpatient healthcare encounters between CA-CDAD cases and controls. Eleven (15.9%) CA-CDAD cases, compared to 42 (30.4%) controls, were not exposed to antibiotics, acid suppressants, or outpatient healthcare settings in the 90 days prior to illness ($P=0.02$).

In the final multivariate model for exposures within 90 days of illness, when controlling for age, we observed that exposure to cephalosporins (OR 1.95, 95% CI 0.68–4.95; $P=0.16$), exposure to clindamycin (OR 2.70, 95% CI 0.70–10.39; $P=0.15$), and the presence of a gastrointestinal feeding device (OR 2.27, 95% CI 0.92–5.60; $P=0.08$) were more common among CA-CDAD cases than controls, however none of these associations were statistically significant (Table 2).

DISCUSSION

We compared 69 children with CA-CDAD to 138 children with non-*C. difficile*, community-associated diarrhea, and found that cephalosporin use within 30 days and the use of gastrointestinal feeding devices were independently associated with pediatric CA-CDAD. This study is the first to identify risk factors for CA-CDAD in a pediatric population.

C. difficile is increasingly implicated as a cause of pediatric diarrhea in community settings. Hospital-based studies have reported that 19–41% of pediatric CDAD is community-associated.^{10–12} Recent population-based studies suggest that CA-CDAD, composing 71–75% of pediatric CDAD, is more prevalent than hospital-associated CDAD.^{7,9} While studies vary as to the amount of pediatric CDAD is community-associated, these results indicate that pediatric CA-CDAD is not insignificant.

Several studies have described the clinical features of CA-CDAD in children.^{7,9–11} Tschudin-Sutter *et al* examined the records of children hospitalized with CDAD at the Johns Hopkins Children's Center from 2003–2012 and found that children with CA-CDAD, when compared to children with hospital-associated CDAD, were older (12.3 vs. 7.57 years; $P=0.03$), less likely to have co-morbidities (73.7% vs. 97.6%; $P<0.001$), and less likely to have exposure to antibiotics (42.1% vs. 76.8%; $P<0.001$).¹⁰ Based on 2011 data from our institution, we reported that children with CA-CDAD had a lower rate of fever (24.4% vs. 48.0%; $P=0.02$) and had less severe diarrhea (5.6 vs. 7.7 stools/day; $P=0.04$) than children with hospital-associated CDAD.¹¹

Antibiotics are the most important risk factor for CDAD since they disrupt the intestinal flora, thereby permitting toxin-producing *C. difficile* to establish and proliferate. In a 2008 study, Sandora *et al* reported an association between antibiotics and pediatric CDAD, showing that children with CDAD were more likely than control subjects to have received fluoroquinolone (OR 17.04; 95% CI 5.86–49.54) or non-fluoroquinolone antibiotics (OR 2.23; 95% CI 1.18–4.20) within 4 weeks than controls.¹² In the adult population, antibiotics are also an established risk factor for CA-CDAD, and differences in the strength of the association have been described between classes of antibiotic. A meta-analysis of 8 studies ($n=30,184$ patients) found that clindamycin (OR 20.43; 95% CI 8.50–49.09), fluoroquinolones (OR 5.65; 95% CI 4.38–7.28), and cephalosporins (OR 4.47; 95% CI 1.60–12.50) were the antibiotic classes with the strongest association with CA-CDAD in adults.¹⁷

We found that cephalosporin use within 30 days was associated with pediatric CA-CDAD and found a trend toward an association with clindamycin use within 30 days. Both of these agents are commonly used in pediatrics, and there is evidence suggesting that their use is increasing among children. Cephalosporins comprise approximately 15% of antibiotic use in outpatient pediatric settings where they are frequently prescribed for upper respiratory tract infections in children.¹⁸ Additionally, the use of the broad-spectrum, third-generation cephalosporins increased in outpatient settings during the 2000s.¹⁹ Clindamycin is predominantly used in children to treat infections from methicillin-resistant *Staphylococcus aureus*. While an increase in clindamycin use in hospitalized children has been demonstrated,²⁰ whether a similar trend has occurred in pediatric outpatient settings is less clear and warrants future investigation. Fluoroquinolones, which represent 25% of antibiotics prescribed to adults during ambulatory visits,²¹ are an important risk factor for CDAD given the emergence of *C. difficile* strains resistant to these agents.²² While they were rarely used in our study, increasing fluoroquinolone use in children may cause the incidence of CA-CDAD to rise.

The presence of a gastrointestinal feeding device was associated with CA-CDAD in our study. Gastrostomy tubes have been found to be a risk factor for CDAD in children¹² and adults,²³ and recently were reported to be associated with severe CDAD in children.¹¹ The reason for their association with CDAD is unclear, though several possibilities exist. Tube feeding may disturb the composition of the intestinal flora and may allow for the bypass of host defense mechanisms present in the oropharynx and stomach (in the case of jejunostomy

tubes). Additionally, the association between pediatric CA-CDAD and gastrointestinal feeding devices may be due to frequent visits to healthcare facilities.

Our finding that a substantial proportion of CA-CDAD cases had recent exposure to outpatient healthcare settings is consistent with previous studies in children^{9–10} and adults^{24,25}. Although it was not retained in our final multivariate model, we did find, on the univariate analysis, that a higher proportion of pediatric CA-CDAD cases had an outpatient healthcare encounter within 30 days of illness than control subjects. Outpatient healthcare settings may be a source of CDAD for children through contact with contaminated environmental surfaces or through receipt of medical interventions that alter the intestinal microbiota. Support for the potential role of outpatient healthcare settings in the transmission of *C. difficile* is derived from studies in adults where outpatient healthcare environments are contaminated by patients with CDAD and asymptomatic carriers of *C. difficile*.^{26,27} The role of outpatient pediatric settings in the emergence and propagation of pediatric CA-CDAD remains unclear and warrants further investigation.

A notable aspect of our results is the difference in association that exists between the 30-day period and the 90-day period. For example, while a significant difference was noted for exposure to an outpatient healthcare encounters within 30 days (66.7% in CA-CDAD cases vs. 48.6% in controls; $P=0.01$), no difference was noted when the period of exposure was extended to 90 days (75.4% in CA-CDAD cases vs. 65.2% in controls; $P=0.14$). Additionally cephalosporin use was associated with CA-CDAD in the 30-day multivariate model, while the association in the 90-day model was not statistically significant. This indicates that the risk for CA-CDAD in children is higher within the first 30 days of antibiotic exposure, a finding consistent with studies of CA-CDAD in the adult population.²⁸

Gastric acid suppressants have been implicated in CDAD in children²⁹ and in CA-CDAD in adults.^{28,30} The results from our study, however, suggest that they do not contribute to pediatric CA-CDAD.

An appreciable number of children with CA-CDAD had no identifiable traditional risk factors. Among CA-CDAD cases, 23.2% and 15.9% had no evidence of exposure to antibiotics, acid suppressants, or outpatient healthcare settings within 30 and 90 days of illness, respectively. Similarly, in a recent population-based study, among 84 pediatric CA-CDAD cases who completed telephone interviews, seven (8.3%) reported no exposure to an antibiotic or outpatient healthcare setting.⁹ The absence of identifiable risk factors in our study may reflect incomplete information from the medical records. Although every effort was made to ensure comprehensive data was recorded, including reviewing records from hospital-affiliated clinics, the potential for incomplete information remains. Further study is needed focusing on non-traditional factors influencing the development of CDAD in children.

There are several limitations in this study. The reliance on retrospective abstraction of medical records may have led to underestimation of some of the exposures under investigation, though it's unlikely this resulted in differential misclassification. Additionally,

available *C. difficile* diagnostics are unable to reliably discriminate between carriers and those with clinical disease. The diagnostic test used at our institution, a polymerase chain reaction assay, is highly sensitive and may give a positive result in *C. difficile* carriers who have diarrhea from an alternative etiology. To minimize the risk of including children in our study who were colonized, we excluded those who were under 12 months of age or had fewer than 3 loose bowel movements per day. Lastly, due to differences in patient populations, there may be differences in risk factors at our institution compared with other facilities that provide pediatric medical care.

Antibiotics are an important risk factor for CDAD. We found that recent cephalosporin use posed the greatest risk for CA-CDAD in children. Gastrointestinal feeding devices were also associated with pediatric CA-CDAD, though the mechanism for their relationship with CDAD between remains unclear. This study suggests that programs focused on decreasing outpatient antibiotic use may decrease the burden of CA-CDAD in children.

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References

1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010; 31:431–455. [PubMed: 20307191]
2. Lessa FC, Gould CV, McDonald LC. Current status of *Clostridium difficile* infection epidemiology. *Clin Infect Dis*. 2012; 55:S65–S70. [PubMed: 22752867]
3. Elixhauser, A.; Jhung, MA. Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality; Rockville, MD: *Clostridium difficile*-associated disease in U.S. Hospitals, 1993–2005. Statistical brief #124.
4. Zilberberg MD, Tillotson GS, McDonald LC. *Clostridium difficile* infections among hospitalized children in the United States, 1997–2006. *Emerg Infect Dis*. 2010; 16:604–609. [PubMed: 20350373]
5. Kim J, Smathers S, Prasad P, et al. Epidemiological Features of *Clostridium difficile*-associated Disease Among Inpatients at Children's Hospitals in the United States, 2001–2006. *Pediatrics*. 2008; 122:1266–1270. [PubMed: 19047244]
6. Nyland CM, Goudie A, Garza JM, et al. *Clostridium difficile* Infection in Hospitalized Children in the United States. *Arch Pediatr Adolesc Med*. 2011; 165:451–457. [PubMed: 21199971]
7. Khanna S, Baddour LM, Huskins WC, et al. The epidemiology of *Clostridium difficile* infection in children: a population-based study. *Clin Infect Dis*. 2013; 56:1401–1406. [PubMed: 23408679]
8. Benson L, Song X, Campos J, Singh N. Changing epidemiology of *Clostridium difficile*-associated disease in children. *Infect Control Hosp Epidemiol*. 2007; 28:1233–1235. [PubMed: 17926272]
9. Wendt JM, Cohen JA, Mu Y, et al. *Clostridium difficile* infection among children across diverse US geographic locations. *Pediatrics*. 2014; 133:651–658. [PubMed: 24590748]
10. Tschudin-Sutter S, Tamma PD, Naegeli AN, Speck KA, Milstone AM, Perl TM. Distinguishing community-associated from hospital-associated *Clostridium difficile* infections in children: implications for public health surveillance. *Clin Infect Dis*. 2013; 57:1665–1672. [PubMed: 24046303]
11. Crews JD, Koo HL, Jiang ZD, Starke JR, DuPont HL. A hospital-based study of the clinical characteristics of *Clostridium difficile* infection in children. *Pediatr Infect Dis J*. 2014; 33:924–928. [PubMed: 25361022]

12. Sandora TJ, Fung M, Flaherty K, et al. Epidemiology and risk factors for *Clostridium difficile* infection in children. *Pediatr Infect Dis J*. 2011; 30:580–584. [PubMed: 21233782]
13. Tamma PD, Sandora TJ. *Clostridium difficile* infection in children: current state and unanswered questions. *J Pediatric Infect Dis Soc*. 2012; 1:230–243. [PubMed: 23687578]
14. Luna RA, Boyanton BL, Mehta S, et al. Stool-based diagnosis of *Clostridium difficile* infection by real-time PCR in a children's hospital. *J Clin Microbiol*. 2011; 49:851–857. [PubMed: 21209161]
15. McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kutty PK. Recommendations for surveillance of *Clostridium difficile*-associated disease. *Infect Control Hosp Epidemiol*. 2007; 28:140–145. [PubMed: 17265394]
16. Enoch DA, Butler MJ, Pai S, Aliyu SH, Karas AJ. *Clostridium difficile* in children: colonisation and disease. *J Infect*. 2011; 63:105–113. [PubMed: 21664931]
17. Deshpande A, Pasupuleti V, Thota P, et al. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. *J Antimicrob Chemother*. 2013; 68:1951–1961. [PubMed: 23620467]
18. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics*. 2011; 128:1053–1061. [PubMed: 22065263]
19. Vaz LE, Kleinman KP, Raebel MA, et al. Recent trends in outpatient antibiotic use in children. *Pediatrics*. 2014; 133:375–385. [PubMed: 24488744]
20. Herigon JC, Hersh AL, Gerber JS, Zaoutis TE, Newland JG. Antibiotic management of *Staphylococcus aureus* infections in US children's hospitals, 1999–2008. *Pediatrics*. 2010; 125:e1294–e1300. [PubMed: 20478934]
21. Shapiro DJ, Hicks LA, Pavia AT, Hersh AL. Antibiotic prescribing for adults in ambulatory care in the USA, 2007–09. *J Antimicrob Chemother*. 2014; 69:234–240. [PubMed: 23887867]
22. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med*. 2005; 353:2433–2441. [PubMed: 16322603]
23. Simor AE, Yake SL, Tsimidis K. Infection due to *Clostridium difficile* among elderly residents of a long-term care facility. *Clin Infect Dis*. 1993; 17:672–678. [PubMed: 7903557]
24. Chitnis AS, Holzbauer SM, Belflower RM, et al. Epidemiology of community-associated *Clostridium difficile* infection, 2009 through 2011. *JAMA Intern Med*. 2013; 173:1359–1367. [PubMed: 23780507]
25. Kutty PK, Woods CW, Sena AC, et al. Risk factors for and estimated incidence of community-associated *Clostridium difficile* infection, North Carolina, USA. *Emerg Infect Dis*. 2010; 16:197–204. [PubMed: 20113547]
26. Jury LA, Sitzlar B, Kundrapu S, et al. Outpatient healthcare settings and transmission of *Clostridium difficile*. *PLoS One*. 2013; 8:e70175. [PubMed: 23894609]
27. Riggs MM, Sethi AK, Zabarsky TF, Eckstein EC, Jump RL, Donskey CJ. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. *Clin Infect Dis*. 2007; 45:992–998. [PubMed: 17879913]
28. Kuntz JL, Chrischilles EZ, Pendergast JF, Herwaldt LA, Polgreen PM. Incidence of and risk factors for community-associated *Clostridium difficile* infection: a nested case-control study. *BMC Infect Dis*. 2011; 11:194. [PubMed: 21762504]
29. Turco R, Martinelli M, Miele E, et al. Proton pump inhibitors as a risk factor for paediatric *Clostridium difficile* infection. *Aliment Pharmacol Ther*. 2010; 31:754–759. [PubMed: 20047577]
30. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA*. 2005; 294:2989–2995. [PubMed: 16414946]

Table 1

Demographics of Pediatric CA-CDAD Cases and Control Subjects

Variable	Total* (n=207)	CA-CDAD Cases* (n=69)	Controls* (n=138)	P-value
Gender (male)	126 (60.9)	41 (59.4)	85 (61.6)	0.76
Age in Years				
1–2 years	48 (23.2)	16	32	
3–5 years	42 (20.3)	14	28	
6–11 years	36 (17.4)	12	24	
12–18 years	81 (39.1)	27	54	
Race				0.13
White	74 (35.8)	28 (40.6)	46 (33.3)	
Black	35 (16.9)	9 (13.0)	26 (18.8)	
Hispanic	86 (41.6)	25 (36.2)	61 (44.2)	
Other	12 (5.8)	7 (10.1)	5 (3.6)	
Insurance Status				0.38
Medicaid	111 (53.6)	34 (49.3)	77 (55.8)	
Private	96 (46.4)	35 (50.7)	61 (44.2)	
Month of Illness (by season)				0.35
December – February	59 (28.5)	20 (29.0)	39 (28.3)	
March – May	72 (34.8)	23 (33.3)	49 (35.5)	
June – August	39 (18.8)	17 (24.6)	22 (15.9)	
September – November	37 (17.9)	9 (13.0)	28 (20.3)	

* Data represent number observed (%).

CA-CDAD indicates community-associated *Clostridium difficile*-associated diarrhea.

Table 2

Multivariate Analysis of Risk Factors for CA-CDAD in Children

Variable	Exposure Within 30 Days		Exposure Within 90 Days	
	Adjusted Odds Ratio ^a (95% CI)	P-value	Adjusted Odds Ratio ^a (95% CI)	P-value
Presence of Gastrointestinal Feeding Tube	2.59 (1.07–6.30)	0.04	2.27 (0.92–5.60)	0.08
Cephalosporin Use	3.32 (1.10–10.01)	0.03	1.95 (0.68–4.95)	0.16
Clindamycin Use	7.66 (0.80–73.38)	0.08	2.70 (0.70–10.39)	0.15

CA-CDAD indicates community-associated *Clostridium difficile*-associated diarrhea.^aOdds ratios were adjusted for patient age, presence of gastrointestinal feeding tube at time of illness, cephalosporin use, and clindamycin use.