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A Hospital-Based Study of the Clinical Characteristics of *Clostridium difficile* Infection in Children

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Abstract

Background—*Clostridium difficile* infection (CDI) is an increasingly important cause of morbidity in hospitalized children. We describe the recent epidemiology of pediatric CDI at a children's hospital, compare community-associated (CA) and hospital-associated (HA) infections, and identify risk factors for severe disease.

Methods—Children with CDI at Texas Children's Hospital were identified from February 1, 2011 to October 31, 2011. Severe CDI was defined as the presence of a CDI-related complication or 2 clinical features: fever, bloody stools, leukocytosis, hypoalbuminemia, or elevated creatinine. Standard epidemiologic definitions were used.

Results—109 unique patients 1-21 years of age with CDI were identified throughout the study period. The proportions of CA-CDI (41%) and HA-CDI (46%) were similar, while community-onset indeterminate CDI (13%) was less common. Children with malignancy or solid organ transplantation were more likely to have HA-CDI. Conversely, all children with inflammatory bowel disease had CA-CDI. Twenty-three patients (21%) met criteria for severe disease and 8 experienced a CDI-related complication, including 1 death attributable to CDI. On multivariate analysis, the presence of a gastrostomy tube (adjusted odds ratio 3.09; 95% CI 1.07-8.94) and having community-onset indeterminate disease (adjusted odds ratio 4.62; 95% CI 1.28-16.67) were found to be associated with severe CDI.

Conclusions—A substantial proportion of pediatric CDI is community-associated and there are clinical differences between children with CA-CDI and HA-CDI. Children with CDI frequently experience severe disease, while complications are uncommon. Early identification and treatment of CDI should be pursued in children with gastrostomy tube and recent hospitalization.

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Supplemental Digital Content Supplemental Digital Content 1. Table that demonstrates the severity criteria fulfilled by severe pediatric CDI cases. doc

Keywords

Clostridium difficile; diarrhea; epidemiology

INTRODUCTION

Clostridium difficile (CD), a spore-forming, toxin-producing anaerobe, is an important cause of nosocomial and antibiotic-associated diarrhea in children [1, 2]. Hospitalized children with *Clostridium difficile* infection (CDI) have a longer length of hospital stay, greater hospital costs, and an increased risk of death than hospitalized controls [3, 4]. During the past decade, the incidence of CDI has been rising in hospitalized children [4-7].

Children were previously considered a population at low-risk for community-associated CDI, but there is growing awareness that children have community-associated infections from *C. difficile*, with recent studies reporting that 25-75% of pediatric CDI is community-associated [1, 8-10].

Severe disease from *C. difficile* has been described in children [11-14], coinciding with a well-defined increase in the severity of CDI in adults [15, 16]. Older age, poor functional status, and exposure to gastric acid suppressants or narcotic medications have been identified as risk factors for severe disease in adults [17-19].

In this study, we describe the recent epidemiology of CDI in children at a tertiary-care children's hospital. We compare children with community-associated and hospital-associated CDI and identify risk factors for severe disease in children.

MATERIALS and METHODS

Study Definitions

Individuals who tested positive for *C. difficile* were identified at Texas Children's Hospital in Houston, Texas from February 1, 2011 through October 31, 2011. The medical record of each case was manually reviewed to identify children with CDI and to collect information on demographics, clinical features, treatment, and outcomes.

Cases were defined as persons 1-21 years of age with diarrhea (≥ 3 loose bowel movements per day) who tested positive for *C. difficile*. Children under 1 year of age were excluded due to the high rates of *C. difficile* colonization in this age group. Testing was performed using an institutional real-time polymerase chain reaction (PCR) assay, which detects the *C. difficile* toxin genes, *tcdA* and *tcdB*, and has a sensitivity of 95% and specificity of 100% [20]. Severe CDI was defined by the presence of a CDI-related complication or the presence of ≥ 2 clinical criteria – a modified version of the definition developed by Kim et al [11]. CDI-related complications were defined as pneumatosis intestinalis, pseudomembranous colitis, toxic megacolon, gastrointestinal perforation, surgical intervention related to CDI, admission to an intensive care unit (ICU) on the date of CDI diagnosis, and death attributable to CDI. CDI cases found to have ≥ 2 of the following clinical features were also considered to have severe disease: fever (≥ 100.5 °F), bloody stools (grossly visible or stool

guaiac test positive), leukocytosis (white blood cell count $> 15,000/\text{dL}$), hypoalbuminemia ($< 2.5\text{mg/dL}$), or elevated age-adjusted creatinine (< 2 years old: $> 0.5\text{mg/dL}$; 2-8 years old: $> 0.7\text{mg/dL}$; 9-18 years old: $> 0.9\text{mg/dL}$). Recurrent CDI was defined as a CDI episode that occurred within 60 days after the resolution of symptoms from a previous CDI episode [21]. Refractory CDI was defined as no improvement of symptoms after 7 days of therapy.

Standard epidemiologic surveillance definitions were used as per guidelines from the 2007 *C. difficile* Surveillance Working Group [21]. Community-associated CDI (CACDI) was defined as the onset of symptoms > 12 weeks after the last discharge from a healthcare facility. Hospital-associated CDI (HA-CDI) was defined as symptom onset > 48 hours after hospital admission or < 4 weeks after the last discharge from a healthcare facility. Cases with symptom-onset between 4-12 weeks after the last discharge were defined as community-onset, indeterminate CDI (COI-CDI).

Data Analysis

A descriptive analysis was performed on patients with CDI from 1 to 21 years of age. Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using mean, median, and interquartile range (IQR).

A comparison of pediatric CA-CDI with pediatric HA-CDI was performed. CDI cases in the COI-CDI category were excluded from this analysis given the uncertainty whether individuals in this category acquired *C. difficile* in healthcare or community settings.

Comparisons of severe pediatric CDI cases with non-severe cases were performed with an initial univariate analysis followed by a multivariate analysis consisting of all variables with a $P < 0.15$ on the univariate analysis. Given its importance in the development of pediatric CDI, age was identified as a potential confounder and included in the multivariate model [22].

Categorical data were analyzed using the χ^2 test or Fisher exact test, where appropriate. Continuous variables were compared using the Student's *t* test. 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 approved this study.

RESULTS

198 positive CD tests representing 139 unique patients were identified. 12 patients were excluded due to presumed colonization - absence of diarrhea (11) or absence of change in bowel habits (1). There were 18 cases (12.9%) of children < 12 months of age who were excluded from analysis. There were 109 patients that remained eligible for analysis.

Clinical Features

In Table 1, differences in demographics, co-morbidity, medication exposure prior to CDI, and CDI treatment are shown for severe and non-severe CDI. The median age for children with CDI was 7 years (mean 8.3 years; IQR 2-13 years). The majority of patients had 1

underlying medical conditions. Only 9.2% of cases had no exposure to either an antibiotic or gastric acid suppressant in the 30 days preceding CDI.

Fever was present in 41 children (37.6%) with CDI. The median duration of fever was 2 days (mean 2.8 days; IQR 1-4 days) and the median maximum temperature during the illness was 102.9 °F (mean: 102.6 °F; IQR 101.6-103.3 °F). The median duration of diarrhea was 5 days (mean: 6.1 days; IQR 3-7 days). The median maximum number of daily stools passed during the peak of the illness was 5 per day (mean: 6.5 stools/day; IQR 4-8 stools/day). Patients experienced abdominal pain (50/109 [45.9%]) and vomiting (31/109 [28.4%]). Bloody stools were frequent (27/109 [24.8%]); 15 patients had stool with grossly visible blood while 12 had guaiac-positive stools.

Testing for additional enteropathogens was performed, at the discretion of the clinical provider, in the majority of patients (79/109 [72.5%]). Stool specimens were sent for bacterial culture (78/109 [71.6%]), viral electron microscopy (35/109 [32.1%]), rotavirus enzyme immunoassay (EIA) [18/109 [16.5%]], adenovirus PCR (16/109 [14.7%]), viral culture (10/109 [9.2%]), examination for ova and parasites (22/109 [20.2%]), and cryptosporidium/giardia EIA (14/109 [12.8%]). Three patients were identified with co-infections: two hematopoietic stem cell transplant recipients had adenovirus infection and one immunocompetent child had rotavirus. These patients were included in the analysis.

Community-associated vs. Hospital-associated

In Table 2, comparisons are provided for CA-CDI and HA-CDI. Similar proportions of CA-CDI (45/109 [41.3%]) and HA-CDI (50/109 [45.9%]) were seen. Among the 50 cases of HA-CDI, 22 were hospital-onset and 28 were community-onset. COI-CDI (14/109 [12.8%]) was the least common epidemiologic category identified.

Differences were noted between patient groups and clinical features when CACDI was compared with HA-CDI (Table 2). Fever occurred more commonly in HA-CDI patients (24/50 [48.0%] vs. 11/45 [24.4%]; $P=0.02$), while the passage of bloody stools was more common in children with CA-CDI (19/45 [42.2%] vs. 5/50 [10.0%]; $P<0.01$). Children with HA-CDI passed more unformed stools per day during the peak of illness than those with CA-CDI (7.7 vs. 5.6 stools/day; $P=0.04$). There was no difference noted in the two groups for duration of diarrhea (10.1 vs. 9.7 days), presence of abdominal pain (22/45 [44.0%] vs. 22/50 [48.9%]), or presence of vomiting (13/45 [28.0%] vs. 14/50 [28.9%]). There was no difference in the rate of severe, recurrent, or refractory CDI in the two groups, but the numbers of each were small.

Severe CDI

Twenty-three of 109 (21.1%) children with CDI met criteria for severe CDI. Eight patients (7.4%) had CDI-related complications: five were admitted to an ICU; one each with pneumatosis intestinalis, surgical intervention related to CDI, and CDI-related death. Fifteen patients had severe CDI based on clinical criteria (see Table, Supplemental Digital Content 1, that demonstrates the severity criteria fulfilled by severe pediatric CDI cases).

The mean duration of diarrhea in children with severe CDI and non-severe CDI was similar, 6.9 vs. 5.9 days ($P=0.43$). However, children with severe CDI passed a greater number of unformed stools (7.8 stools/day) during the peak of illness than children with non-severe CDI (6.1 stools/day), though this finding was not statistically significant ($P=0.12$). Leukocytosis (43.5% vs. 7.0%; $P<0.01$) and hypoalbuminemia (34.8% vs. 1.2%; $P<0.01$) were more common among children with severe CDI. However, a similar proportion of children with severe CDI had an elevated age-adjusted creatinine than children with non-severe CDI (8.7% vs. 4.7%; $P=0.60$). Children with severe CDI were more likely to receive combination therapy than children with non-severe CDI (Table 1). One patient with severe CDI improved without antibiotic therapy. The rate of recurrent and refractory disease was similar. There was no difference in the 3-month or 6-month all-cause mortality rate between children with severe and non-severe CDI.

On univariate analysis, the following risk factors were found to be associated with severe CDI: COI-CDI, presence of a gastrostomy tube, and exposure to H₂-receptor antagonist. A multivariate model was created that included age and the above variables. In the final model, having COI-CDI (OR 4.62; 95% CI 1.28-16.67; $P=0.02$) and the presence of a gastrostomy tube (OR 3.09; 95% CI 1.07-8.94; $P=0.04$) were found to be statistically significant (Table 3).

DISCUSSION

Our study highlights two important aspects of pediatric CDI – clinical differences between community-associated and hospital-associated CDI and risk factors for severe disease.

Community-associated disease, defined as symptom onset > 12 weeks following an inpatient hospital stay, represents a significant proportion of CDI in pediatric studies. A single-center, hospital-based study in 2008 found that 25% of pediatric CDI episodes were community-associated [1]. In a population-based study in Minnesota from 1991 to 2009, 75% of cases were CA-CDI [8]. Differences in the burden of community-associated CDI may reflect differences in patient populations and methods of case ascertainment. The reason for the emergence of CDI in community settings in the pediatric population is unclear. It may reflect more frequent exposure in outpatient healthcare settings, contaminated food, the emergence of the hypervirulent NAP1 strain, or increasing use of antibiotics and acid suppressants [23-25]. Further studies are needed to investigate the manner in which children acquire *C. difficile* in community settings.

Our study illustrates important differences in the epidemiology of community-associated and hospital-associated CDI in children. Children with HA-CDI passed more frequent unformed stools and were more likely to have fever than children with CA-CDI. Additionally, children with HA-CDI were more likely to have been exposed to antibiotics, immunosuppressants, or narcotics. These findings are consistent with a recent study by Tschudin-Sutter et al, where children with HA-CDI had higher rates of exposure to antibiotics, acid suppressants, and narcotics [26].

Our study found differences among patient groups relating to CA-CDI and HACDI. It was more common for children with hematologic malignancies or solid organ transplantation to have HA-CDI, likely reflecting their frequent need for hospitalization. Conversely, there were no children with inflammatory bowel disease with HA-CDI, making the community setting the most likely source of *C. difficile* acquisition. Recognition of the settings (hospital versus community) in which certain sub-groups of the pediatric population acquire *C. difficile* may allow for future individualized prevention efforts.

The recent increase in the severity of *C. difficile* infections in adults has partly been attributed to the emergence of one or more hypervirulent strains, including the BI/NAP1/027 strain [15, 16, 27]. Although an increasing trend in disease severity has not been reported in children, there is growing recognition that children experience severe and complicated disease from *C. difficile* [11-14]. Severe disease and CDI-related complications have been described in 9-59% and 3-17% of cases of pediatric CDI, respectively [8, 11].

At our institution, severe disease was frequent, involving 21% of pediatric *C. difficile* infections. CDI-related complications were uncommon, occurring in 7% of patients, including one patient whose death was attributable to CDI. For the definition of severe disease, we used a modified version of the criteria proposed by Kim et al [11]. In contrast to their definition, we chose to remove leukopenia (white blood cell count $< 5 \times 10^3$) as a criterion to improve the specificity of the definition. Although myelosuppression caused by severe bacterial infections occurs in children, including leukopenia in the definition would overestimate the incidence of severe CDI since children with hematologic malignancies compose a substantial proportion of pediatric CDI. Additional investigators have questioned the utility of the white blood cell count as a measure of CDI disease severity in patients with malignancies [28].

We identified risk factors for severe CDI in children. After adjusting for age, the presence of a gastrostomy tube and having COI-CDI remained as predictors of severe disease. The presence of a gastrostomy tube has been described as a risk factor for CDI in both children and adults, however it has not been associated previously with severe CDI [1, 29]. It has been hypothesized that frequent encounters with healthcare settings or the contamination of the hands of care providers may contribute to an increase risk of CDI in persons with assisted feeding [29]. The association of gastrostomy tubes with severe disease is less clear and may be due to the increased number of co-morbidities in children requiring assisted feeding, differences in the host pro-inflammatory and humoral immune response to CDI, or the effects of assisted feeding on the intestinal microbiota [30]. The association of gastrostomy tubes with severe pediatric CDI warrants further investigation.

Gastric acid suppressants have been associated with the development of severe-complicated CDI in adult studies [17-18]. Shivashankar and colleagues, in a population-based study, found that individuals with exposure to gastric acid suppressants were 1.8 times more likely to have severe-complicated CDI [17]. In our study, there was a trend toward an association between severe CDI and exposure to an H₂-receptor antagonist. It has been postulated that acid suppressants may inhibit the inactivation of the vegetative form of *C. difficile* within the stomach or alter bile salt concentrations in the small bowel.

Epidemiologic surveillance definitions for *C. difficile* are available from the 2007 *C. difficile* Surveillance Working Group [21]. The definitions, which standardize infection surveillance for epidemiologic studies on CDI, seek to accurately attribute the source of *C. difficile* exposure to the healthcare environment (HA-CDI) or the community (CA-CDI). COI-CDI is considered a mixed category as it may represent *C. difficile* acquisition from either the recent hospitalization or the community.

We found that having COI-CDI was associated with severe disease. This association remained after adjusting for age, the presence of a gastrostomy tube, and exposure to H₂-receptor antagonists. In adult and pediatric CDI series, cases of COI-CDI are the least common [1, 8, 25]. It is unclear why COI-CDI would be associated with severe disease in children. However, we postulate that children with COI-CDI continue to have diminished functional status, or other residual effects, related to a recent hospital stay that may predispose them to more severe disease from CDI. Support for this hypothesis is found in a recent study where children with COI-CDI had baseline comorbidities and CDI risk factors that were more comparable to HA-CDI cases than CA-CDI cases [26]. Additionally, studies in adults have shown an increased risk of severe CDI in hospitalized adults with multiple comorbidities [18-19]. Further study is needed to characterize the importance of community-onset indeterminate CDI in children.

Limitations to this study are predominantly related to its retrospective nature and reliance on medical documentation. Although a thorough review of the medical records was performed, the potential for misclassification remains. Given the association between certain *C. difficile* strains and severe CDI, the absence of molecular typing data in our study is a notable limitation. Children that met our CDI case definition may have been colonized with *C. difficile* and had an alternative, unidentified cause of diarrhea. Additionally, the absence of a validated definition for severe pediatric CDI may limit our ability to effectively identify risk factors for severe disease. Lastly, the epidemiology of pediatric CDI at our tertiary-care children's hospital may not reflect the experience at less specialized institutions.

An important strength in our study is the availability of extensive patient-specific clinical data. Using the CDC/SHEA epidemiologic definitions, we were able to distinguish community-associated and hospital-associated disease for each case of pediatric CDI. Previous studies relying on administrative databases have not had this data at their disposal. Furthermore, by excluding children with < 3 bowel movements per day, we were able to decrease the potential for including children colonized with *C. difficile*.

Clostridium difficile is an increasingly important cause of diarrhea in children. Clinical differences in community-associated and hospital-associated pediatric CDI exist. Community-based pediatric providers should consider testing for *C. difficile* in children with gastroesophageal reflux disease or inflammatory bowel disease who present with increased stool production. Severe disease is frequently encountered among children with CDI while CDI-related complications are uncommon. Early identification and treatment of CDI should be pursued in children with gastrostomy tube and recent hospitalization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Severe and Non-Severe *Clostridium difficile* Infection in Children, Texas Children's Hospital, February 2011 – October 2011

	Total Pediatric CDI (N=109) Number (%)	Severe CDI (N=23) Number (%)	Non-Severe CDI (N=86) Number (%)	P-value
Demographics				
Male Gender	66 (60.6)	12 (52.2)	54 (62.8)	0.36
Mean Age (years)	8.3	8.6	8.2	0.82
Community-Associated CDI	45 (41.3)	7 (30.4)	38 (44.2)	0.23
Community-Associated, Indeterminate	14 (12.8)	6 (26.1)	8 (9.3)	0.03 *
Hospital-Associated CDI	50 (45.9)	10 (43.5)	40 (43.5)	0.80
Co-Morbidities				
Presence of 1 Comorbid Conditions	94 (86.2)	22 (95.7)	72 (83.7)	0.17
Malignancy	38 (34.9)	9 (39.1)	29 (33.7)	0.63
Hematologic Malignancy	22 (20.2)	6 (26.1)	16 (18.6)	0.43
Solid Tumor	16 (14.7)	3 (13.0)	13 (15.1)	1.00
Gastroesophageal Reflux Disease	25 (22.9)	5 (21.7)	20 (23.3)	0.88
Presence of Gastrostomy Tube	24 (22.0)	9 (39.1)	15 (17.4)	0.03 *
Inflammatory Bowel Disease	10 (9.2)	2 (8.7)	8 (9.3)	1.0
Solid Organ Transplantation	7 (6.4)	3 (13.0)	4 (4.7)	0.16
Cystic Fibrosis	6 (5.5)	1 (4.4)	5 (5.8)	1.0
Medication Exposure [†]				
Antibiotics	88 (80.7)	19 (82.6)	69 (80.2)	0.80
Acid Suppressants	53 (48.6)	12 (52.2)	41 (47.7)	0.70
- Proton Pump Inhibitors	33 (30.3)	5 (21.7)	28 (32.6)	0.32
- H ₂ -Receptor Antagonists	21 (19.3)	7 (30.4)	14 (16.3)	0.13
Immunosuppressants	47 (43.1)	11 (47.8)	36 (41.9)	0.61
Narcotics	20 (18.4)	2 (8.7)	18 (20.9)	0.23
Treatment [‡]				
None	15 (13.8)	1 (4.4)	14 (16.3)	0.19
Metronidazole alone	68 (62.4)	11 (47.8)	57 (66.3)	0.11
Vancomycin alone	16 (14.7)	3 (13.0)	13 (15.1)	1.0
Metronidazole + Vancomycin	9 (8.3)	8 (34.8)	1 (1.2)	< 0.01 *
Probiotic	10 (9.2)	3 (13.0)	7 (8.1)	0.44
Outcomes				
Recurrence	18 (16.5)	4 (17.4)	14 (16.3)	1.0
Refractory	5 (4.6)	2 (8.7)	3 (3.5)	0.28
3 Month All-Cause Mortality	2 (1.8)	1 (4.4) [§]	1 (1.2)	0.38
6 Month All-Cause Mortality	5 (4.6)	2 (8.7) [§]	3 (3.5)	0.28

Note: Analysis was performed using Student's *t* test for continuous variable and the χ^2 or Fisher's exact tests for categorical variables, as appropriate. CDI indicates *Clostridium difficile* Infection.

* Indicates statistically significant.

[†] Within 30 days prior to CDI diagnosis.

[‡] One patient was treated with Rifaximin alone.

[§] One death attributable to CDI.

Table 2

Community- and Hospital-Associated *Clostridium difficile* Infections in Children, Texas Children's Hospital, February 2011 – October 2011

	Community-associated CDI (n=45) Number (%)	Hospital-associated CDI (n=50) Number (%)	P-value
Demographics			
Male Gender	28 (62.2)	30 (60.0)	0.83
Mean Age (years)	8.0	9.0	0.43
Co-Morbidities			
Presence of 1 Comorbid Conditions	35 (77.8)	45 (90.0)	0.10
Malignancy	4 (8.9)	28 (56.0)	<0.01 *
Hematologic Malignancy	3 (6.7)	18 (36.0)	<0.01 *
Solid Tumor	1 (2.2)	10 (20.0)	<0.01 *
Gastroesophageal Reflux Disease	10 (22.2)	13 (26.0)	0.67
Inflammatory Bowel Disease	8 (17.8)	0 (0.0)	<0.01 *
Presence of Gastrostomy Tube	10 (22.2)	11 (22.0)	0.98
Solid Organ Transplantation	1 (2.2)	4 (8.0)	0.37
Cystic Fibrosis	4 (8.9)	1 (2.0)	0.19
Medication Exposure [†]			
Antibiotics	31 (68.9)	47 (94.0)	<0.01 *
Acid Suppressants	22 (48.9)	24 (48.0)	0.93
- Proton Pump Inhibitors	14 (31.1)	13 (26.0)	0.58
- H ₂ -Receptor Antagonists	8 (17.8)	12 (24.0)	0.46
Immunosuppressants	11 (24.4)	28 (56.0)	<0.01 *
Narcotics	1 (2.2)	18 (36.0)	<0.01 *
Treatment [‡]			
None	7 (15.6)	8 (16.0)	0.95
Metronidazole alone	23 (51.1)	34 (68.0)	0.09
Vancomycin alone	12 (26.7)	3 (8.0)	0.01 *
Metronidazole + Vancomycin	2 (4.4)	5 (8.0)	0.44
Outcomes			
Severe CDI	7 (15.6)	10 (20.0)	0.57
Recurrence	5 (11.1)	9 (18.0)	0.34
Refractory	1 (2.2)	3 (6.0)	0.62
3 Month All-Cause Mortality	0 (0.0)	2 (4.0) [§]	0.50
6 Month All-Cause Mortality	1 (2.2)	3 (6.0) [§]	0.62

Analysis was performed using Student's *t* test for continuous variable and the χ^2 or Fisher's exact tests for categorical variables, as appropriate. CDI indicates *Clostridium difficile* Infection.

* Indicates statistically significant.

[†] Within 30 days prior to CDI diagnosis.

[‡] One patient was treated with Rifaximin alone.

[§] One death attributable to CDI.

Table 3 Risk Factors for Severe *Clostridium difficile* Infection in Children - Multivariate Analysis

	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (years)	1.0 (0.94-1.09)	0.82	1.02 (0.94-1.10)	0.71
Community-onset, Indeterminate CDI	3.4 (1.06-11.21)	0.03 *	4.62 (1.28-16.67)	0.02 *
Presence of Gastrostomy Tube	3.04 (1.11-8.32)	0.03 *	3.09 (1.07-8.94)	0.04 *
Exposure to H ₂ -Receptor Antagonists [†]	2.25 (0.78-6.47)	0.13	2.67 (0.85-8.44)	0.09

OR indicates odds ratio. CI indicates confidence interval. CDI indicates *Clostridium difficile* Infection.

* Indicates statistically significant.

[†] Within 30 days prior to CDI diagnosis.