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

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Objective To characterize the medication and other exposures associated with pediatric community-associated *Clostridium difficile* infections (CA-CDIs).

Study design We performed a case-control study using billing records from the US military health system database. CA-CDI cases included children 1-18 years of age with an outpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic code for *Clostridium difficile* infection (CDI) from 2001 to 2013. Each case was matched to 3 controls without CDI by age and sex. Children hospitalized at any time before their CDI were excluded. Outpatient pharmacy records were used to identify medication exposures in the preceding 12 weeks. In addition, we evaluated recent outpatient healthcare exposure, exposure to a sibling younger than 1 year of age, or to a family member with CDI.

Results A total of 1331 children with CA-CDI were identified and 3993 controls were matched successfully. Recent exposure to fluoroquinolones, clindamycin (OR 73.00; 95% CI 13.85-384.68), third-generation cephalosporins (OR 16.32; 95% CI 9.11-29.26), proton pump inhibitors (OR 8.17; 95% CI 2.35-28.38), and to multiple classes of antibiotics, each was associated strongly the subsequent diagnosis of CA-CDI. Recent exposure to outpatient healthcare clinics (OR 1.35; 95% CI 1.31-1.39) or to a family member with CDI also was associated with CA-CDI.

Conclusions CA-CDI is associated with medications regularly prescribed in pediatric practice, along with exposure to outpatient healthcare clinics and family members with CDI. Our findings provide additional support for the judicious use of these medications and for efforts to limit spread of CDI in ambulatory healthcare settings and households. *(J Pediatr 2017;186:105-9).*

Clostridium difficile is a spore-forming, toxin-producing, anaerobic bacillus responsible for a variety of gastrointestinal manifestations ranging from asymptomatic carriage to mild diarrhea, pseudomembranous colitis, and, very rarely in children, toxic megacolon, bowel perforation, and death. *Clostridium difficile* infection (CDI) is increasing among hospitalized children,[1] leading to increased mortality, longer length of stay, and greater hospitalization costs.[2] In recent years, however, the epidemiology of this infection has shifted as CDI cases in both adults and children increasingly have been originating in the community.[3,4] These community-associated *Clostridium difficile* infections (CA-CDIs) now account for nearly one-third of all *C difficile* cases.[5] Although previous antibiotic exposure is a well-established risk factor for the development of CDI, there are limited data on which antibiotic class exposures precede CDI in children and few studies evaluating these exposures in CA-CDI.[6] In addition, studies of CA-CDI in both adult and pediatric populations have identified a large subset of patients without preceding antibiotic exposures.[4,5] These findings highlight the need to identify additional exposures contributing to this increase in community transmission of CDI. Two recent small studies of CA-CDI in children identified use of gastric acid-suppression therapy[7] and the presence of a gastrointestinal feeding device[6] as additional risk factors for CA-CDI; however, the epidemiologic exposures and underlying risk factors leading to CA-CDI in children remain largely unknown. Using the large US military health system (MHS) database, we sought to characterize medication and other potential exposures associated with CA-CDI in the pediatric population.

Methods

We performed a case-control study using billing records from the TRICARE Management Activity MHS database, which includes all eligible military dependents cared for both in military and civilian facilities. Cases were selected from among children ages 1-18 years old who received care during the time period spanning October 1, 2001, to September 30, 2013, with an *International Classification of*

CA-CDI	Community-associated *Clostridium difficile* infection
CDI	*Clostridium difficile* infection
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
MHS	Military health system

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Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic code 008.45. This is the only code representing CDI and has been validated previously in pediatric billing records.[8] Children younger than 1 year old were excluded as *C difficile* frequently colonizes the intestine in healthy infants.[9-11] In addition, to evaluate only CA-CDI, children hospitalized at any time before their CDI were excluded from the analysis. Cases were then matched by age (date of birth) and sex with 3 controls without an ICD-9-CM code for CDI. We used outpatient pharmacy records for the selected cases and controls to identify medication exposures in the 12 weeks preceding the date of the first CDI among cases, including 10 classes of oral antibiotics (clindamycin, fluoroquinolones, sulfonamides, macrolides, penicillins, amoxicillin/clavulanate, tetracyclines, and first-, second-, and third-generation cephalosporins), 2 gastric acid-suppression medications (proton pump inhibitors, H2 receptor antagonists), and corticosteroids. Dosing or patient weight information was not available. All medication exposures were categorized as binary variables. In addition, we calculated the odds of CA-CDI with exposure to multiple classes of antibiotics. During the same 12-week time period, we also evaluated exposures to outpatient healthcare settings, siblings younger than 1 year of age, or to family members with a diagnosis of CDI. Each TRICARE dependent (either child or spouse) is tied to their sponsor in the MHS database by a unique identifier, which was used to identify and evaluate family member CDI exposures.

Univariate and multivariable conditional logistic regression were performed to calculate unadjusted and adjusted OR and 95% CIs. The dependent variable was CDI, and the independent variables were various medication exposures, family exposures, and the number of outpatient healthcare encounters. In addition, 2-way interactions between all independent variables were evaluated and included in the final multivariable model if significant. The Cochran-Armitage test for trend was used to analyze the trend in CA-CDI during the 13-year study period. *P* values less than .05 were considered statistically significant. All analyses were performed with SAS 9.3 (SAS Institute, Cary, North Carolina). The study was approved by our institutional review board.

Results

A total of 1331 children with CA-CDI and 3993 controls were identified and matched successfully by sex and exact date of birth from the MHS database during the study period (**Table I**). The median (IQR) age in years of CA-CDI cases and controls was 7.0 (3.3-13.4). Cases were divided evenly between male (50.3%) and female (49.7%) children. A total of 163 (12.2%) of children with CA-CDI were hospitalized on the same day as their outpatient encounter for CDI, and an additional 55 (4.1%) were hospitalized within the following week. The majority (59.7%) of the 1331 children with CA-CDI was prescribed at least 1 antibiotic in the 12 weeks preceding their diagnosis; however, 40.3% had no preceding antibiotic exposure. Of the 795 children with an identified antibiotic exposure preceding their CA-CDI, 319 (40.1%) were prescribed multiple classes of antibiotics, including 252 (31.6%) with exposure to 2, and 68 (8.6%) with exposure to 3 or more different antibiotic classes. The median (IQR) time to CA-CDI after an antibiotic prescription was 33 days (17-54). Pediatric CA-CDI cases demonstrated a significantly increasing trend during the 12-year study period with an average annual increase of 47.9% ($P < .001$) (**Figure 1**).

Table I. Exposures preceding community-associated *C difficile* infection in pediatric cases compared with controls

Exposures	Cases (n = 1331), n (%)	Controls (n = 3993), n (%)
Family member with CDI	8 (0.60)	0 (0)
Fluoroquinolones	51 (3.83)	0 (0)
Clindamycin	103 (7.74)	8 (0.20)
Third-generation cephalosporins	223 (16.75)	50 (1.25)
Proton pump inhibitors	143 (10.74)	19 (0.48)
Second-generation cephalosporins	41 (3.08)	20 (0.50)
H2 receptor antagonist	69 (5.18)	13 (0.33)
Sulfonamides	167 (12.55)	39 (0.98)
First-generation cephalosporins	62 (4.66)	37 (0.93)
Amoxicillin/clavulanate	194 (14.58)	88 (2.20)
Macrolides	131 (9.84)	161 (4.03)
Penicillins	206 (15.48)	282 (7.06)
Corticosteroids	201 (15.10)	133 (3.33)
Tetracyclines	17 (1.28)	30 (0.75)
Sibling younger than 1 y of age	98 (7.36)	343 (8.59)

The antibiotic class exposures associated most strongly with CA-CDI included fluoroquinolones (OR could not be calculated as 51 cases were exposed compared with 0 controls) (**Table I**), clindamycin (OR 73.00; 95% CI 13.85-384.68), and third-generation cephalosporins (OR 16.32; 95% CI 9.11-29.26) (**Table II**). In addition, children with recent exposure to multiple classes of antibiotics carried increased odds of developing CA-CDI, compared with those exposed to only 1 class of antibiotic (**Figure 2**). The odds of CA-CDI following exposure to proton pump inhibitors (OR 8.17; 95% CI 2.35-28.38) was comparable with that of antibiotic class exposures. Outpatient healthcare clinic visits also were associated with CA-CDI in children, with a 35% increase in the odds of CDI of

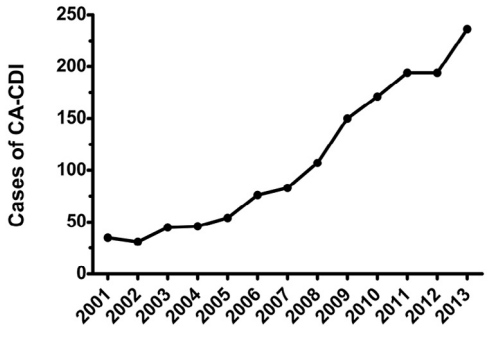

Figure 1. Trend in pediatric community-associated *C difficile* infections.