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Risk Factors for Community-Associated *Clostridium difficile* Infection in Adults: A Case-Control Study

Alice Y. Guh,[1] Susan Hocevar Adkins,[1] Qunna Li,[1] Sandra N. Bulens,[1] Monica M. Farley,[2,3,4] Zirka Smith,[3,4,5] Stacy M. Holzbauer,[6,7] Tory Whitten,[6] Erin C. Phipps,[8] Emily B. Hancock,[8] Ghinwa Dumyati,[9] Cathleen Concannon,[9] Marion A. Kainer,[10] Brenda Rue,[10] Carol Lyons,[11] Danyel M. Olson,[11] Lucy Wilson,[12] Rebecca Perlmutter,[12] Lisa G. Winston,[13] Erin Parker,[14] Wendy Bamberg,[15] Zintars G. Beldavs,[16] Valerie Ocampo,[16] Maria Karlsson,[1] Dale N. Gerding,[17,18] and L. Clifford McDonald[1]

[1]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Emory University Department of Medicine, Atlanta, Georgia; [3]Georgia Emerging Infections Program, Decatur, Georgia; [4]Atlanta Veterans Affairs Medical Center, Atlanta, Georgia; [5]Atlanta Research and Education Foundation, Decatur, Georgia; [6]Minnesota Department of Health, St Paul, Minnesota; [7]Career Epidemiology Field Officer Program, Centers for Disease Control and Prevention, Atlanta, Georgia; [8]University of New Mexico, New Mexico Emerging Infections Program, Albuquerque, New Mexico; [9]New York Emerging Infections Program and University of Rochester Medical Center, Rochester, New York; [10]Tennessee Department of Health, Nashville, Tennessee; [11]Yale School of Public Health, Connecticut Emerging Infections Program, New Haven, Connecticut; [12]Maryland Department of Health and Mental Hygiene, Baltimore, Maryland; [13]University of California, San Francisco, School of Medicine, San Francisco, California; [14]California Emerging Infections Program, Oakland, California; [15]Colorado Department of Public Health and Environment, Denver, Colorado; [16]Oregon Health Authority, Portland, Oregon; [17]Loyola University Chicago Stritch School of Medicine, Maywood, Illinois; [18]Edward Hines, Jr. Veterans Affairs Hospital, Hines, Illinois

Background. An increasing proportion of *Clostridium difficile* infections (CDI) in the United States are community-associated (CA). We conducted a case-control study to identify CA-CDI risk factors.

Methods. We enrolled participants from 10 US sites during October 2014–March 2015. Case patients were defined as persons age ≥18 years with a positive *C. difficile* specimen collected as an outpatient or within 3 days of hospitalization who had no admission to a health care facility in the prior 12 weeks and no prior CDI diagnosis. Each case patient was matched to one control (persons without CDI). Participants were interviewed about relevant exposures; multivariate conditional logistic regression was performed.

Results. Of 226 pairs, 70.4% were female and 52.2% were ≥60 years old. More case patients than controls had prior outpatient health care (82.1% vs 57.9%; $P < .0001$) and antibiotic (62.2% vs 10.3%; $P < .0001$) exposures. In multivariate analysis, antibiotic exposure—that is, cephalosporin (adjusted matched odds ratio [AmOR], 19.02; 95% CI, 1.13–321.39), clindamycin (AmOR, 35.31; 95% CI, 4.01–311.14), fluoroquinolone (AmOR, 30.71; 95% CI, 2.77–340.05) and beta-lactam and/or beta-lactamase inhibitor combination (AmOR, 9.87; 95% CI, 2.76–340.05),—emergency department visit (AmOR, 17.37; 95% CI, 1.99–151.22), white race (AmOR 7.67; 95% CI, 2.34–25.20), cardiac disease (AmOR, 4.87; 95% CI, 1.20–19.80), chronic kidney disease (AmOR, 12.12; 95% CI, 1.24–118.89), and inflammatory bowel disease (AmOR, 5.13; 95% CI, 1.27–20.79) were associated with CA-CDI.

Conclusions. Antibiotics remain an important risk factor for CA-CDI, underscoring the importance of appropriate outpatient prescribing. Emergency departments might be an environmental source of CDI; further investigation of their contribution to CDI transmission is needed.

Keywords. community-associated *Clostridium difficile* infection.

Although predominantly associated with inpatient health care, *Clostridium difficile* infection (CDI) originating from the community has been increasingly reported. In 2011, an estimated 159 000 community-associated (CA) CDI occurred in the United States, representing 35% of the total CDI burden [1]. As of 2014, the proportion of CDI that was community-associated increased to 41% [2].

Several previous studies reported that ≥40% of patients with CA-CDI were not exposed to antibiotics [3–6], suggesting other exposures such as use of proton pump inhibitors (PPIs) or contact with infants might contribute to infection [4, 7, 8]. In addition, a high prevalence of outpatient health care exposures was noted in patients with CA-CDI [3, 6]. However, the magnitude of association between specific outpatient exposures and CA-CDI is not well described. We sought to determine whether exposures to particular outpatient settings and antibiotic classes might be independently associated with CA-CDI. We also evaluated additional potential CA-CDI risk factors such as exposures to other medications as well as various household and food exposures.

METHODS

Active population-based CDI surveillance is conducted through the Centers for Disease Control and Prevention's (CDC's) Emerging Infections Program (EIP). As of 2014, 35 counties in 10 US states (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee) participate in CDI surveillance, comprising a total population of approximately 11.6 million persons [2]. This

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Correspondence: A. Y. Guh, MD, MPH, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS A-31, Atlanta, GA 30329 (ggt4@cdc.gov).

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study protocol was approved by the institutional review boards of the CDC and all 10 EIP sites.

Case Definition and Enrollment

Laboratories serving the surveillance catchment areas report all positive *C. difficile* test results to EIP personnel. For the purpose of this study, a case patient was defined as a person age ≥18 years with a positive *C. difficile* stool specimen collected as an outpatient or within 3 days of hospitalization who had no overnight stay in a health care facility (hospital, nursing home, or any other long-term care health care setting) in the prior 12 weeks and no prior CDI diagnosis. Enrollment of case patients occurred during October 2014–March 2015. Case patients were excluded from the study if they did not report diarrheal illness (≥3 watery stools in a 24-hour period) associated with the positive stool specimen or could not be interviewed or matched to a control within 90 days of the specimen collection date.

Control Enrollment

Each case was matched to one control by sex and age group (18–29, 30–39, 40–49, 50–59, 60–69, ≥70 years). Controls were randomly selected from a commercially available database of residential telephone numbers. To be eligible for the study, controls had to be a resident within the same surveillance catchment area as their matched case patient on the date of collection of the case patient's positive specimen. Exclusion criteria for controls included ever having a diagnosis of CDI, having a diarrheal illness (as defined above), or an overnight stay in a health care facility in the 12 weeks prior to their matched case patient's illness onset date.

Data Collection

Study participants were interviewed by telephone following verbal consent for participation. Trained interviewers used a standardized questionnaire to collect demographic and clinical information, underlying comorbidities, medication use, outpatient health care visits, and household and dietary exposures. The overall exposure period of interest was the 12 weeks before the case patient's illness onset date, or the specimen collection date if the illness onset date was unknown. Participants were asked whether any medication or outpatient health care exposures occurred in the preceding 2 weeks, 2–4 weeks, or 4–12 weeks. Additional information about case patients' clinical course was collected as part of routine surveillance [1, 2].

Isolate Collection and Molecular Characterization

Stool specimens from a convenience sample of case patients were submitted to one of two laboratories (Edward Hines, Jr. Veterans Affairs Hospital, Minnesota Department of Health Public Health Laboratory) for *C. difficile* culture. Recovered isolates were submitted to the CDC for detection of *tcdA*, *tcdB*, *cdtA*, and *cdtB* toxin genes by polymerase chain reaction (PCR) and assessment of deletions in the *tcdC* gene by fragment analysis. Strain typing was performed using capillary-based PCR ribotyping; results were analyzed against a library of standard profiles using BioNumerics.

Statistical Analyses

Univariate analyses were performed using exact conditional logistic regression. Candidate variables for potential inclusion in a multivariate model included underlying conditions, individual outpatient health care exposures, antibiotic classes, gastric acid suppressant classes, antidepressant classes, household contacts, frequently consumed food products (consumed more than five times per week), and the source of drinking water around the time of illness onset. The Charlson comorbidity index and all aforementioned variables for which the univariate test yielded a P value < .10 were entered into an initial multivariate conditional logistic regression model using stepwise selection. The final model included variables that had a P value < .05; adjusted matched odds ratios (AmOR) and 95% confidence intervals (CIs) were calculated. We assessed collinearity between relevant variables and interaction between antibiotic classes and PPI use. SAS statistical software version 9.3 (SAS Institute Inc, Cary, NC) was used for the analysis.

RESULTS

In total, 452 participants (226 matched pairs) were enrolled in the study. The median number of participants per EIP site was 45 (range, 6–90) (Table 1); 52.2% were age ≥60 years, and 70.4% were female. Of the 226 case patients, 201 (88.9%) knew the onset date of their diarrheal illness. In addition to diarrhea, the most frequently reported symptoms included abdominal pain (74.8%), nausea (54.0%), and fever (37.2%). Twenty-nine

Table 1. Age, Sex, and State of Residence of Study Participants

Characteristic	Study Participants (n = 452), No. (%)
Age group, y	
18–29	30 (6.6)
30–39	28 (6.2)
40–49	58 (12.8)
50–59	100 (22.1)
60–69	104 (23.0)
≥70	132 (29.2)
Sex	
Female	318 (70.4)
State of residence	
California	20 (4.4)
Colorado	18 (4.0)
Connecticut	38 (8.4)
Georgia	90 (19.9)
Maryland	28 (6.2)
Minnesota	72 (15.9)
New Mexico	66 (14.6)
New York	62 (13.7)
Oregon	6 (1.3)
Tennessee	52 (11.5)

percent of case patients were hospitalized within 7 days of diagnosis. None of the case patients developed toxic megacolon or required a colectomy due to CDI.

Hypertension, obesity, and depression were the most frequently reported medical conditions (Table 2), with hypertension (50.0% vs 35.4%; $P = .0003$) and depression (26.2% vs 16.8%; $P = .02$) being more common among case patients than controls. Other conditions that were more frequent among case patients than controls included inflammatory bowel disease (9.3% vs 1.8%, $P = .0009$); chronic kidney disease (6.7% vs 0.4%, $P = .0005$); and cardiac disease (11.5% vs 4.9%, $P = .01$).

Outpatient medical care in the 12 weeks preceding illness onset was more common among case patients, with 82.1% reporting at least one such exposure, compared with 57.9% of controls ($P < .0001$) (Table 2). Case patients were also more likely than controls to have an outpatient health care exposure in the 2 weeks preceding illness onset (55.7% vs 37.2%; $P = .03$). The most common outpatient exposures were to doctors' and dentists' offices. Of reported dental procedures, dental surgery was more common in case patients than controls (16.9% vs 4.6%; $P = .0009$), compared with dental cleaning, which was not significantly different (24.2% vs 32.6%; $P = .24$). Case patients were also more likely than controls to have received care at an emergency department (11.2% vs 1.4%; $P < .0001$), outpatient procedure center (15.7% vs 6.7%; $P = .007$), outpatient surgery center (7.2% vs 1.8%; $P = .008$), or urgent care clinic (9.9% vs 1.8%; $P = .0003$); including hemodialysis and hospital-based outpatient settings, 38.1% of cases were exposed to one or more of these settings, whereas only 14.4% of controls were so exposed (mOR, 4.19; 95% CI, 2.40–7.42; $P < .0001$).

Antibiotic use in the preceding 12 weeks was reported in 62.2% of case patients compared with 10.3% of controls ($P < .0001$) (Table 2); more than half of the case patients received antibiotics within 2 weeks prior to illness onset. The most frequently reported antibiotic classes among case patients were beta-lactam and/or beta-lactamase-inhibitor combination (17.8%), clindamycin (12.4%), fluoroquinolone (10.7%), and cephalosporin (7.6%). The most common indications for antibiotic therapy included ear, sinus, or upper respiratory infection, skin infection, dental procedure, and urinary tract infection (Table 3). Exposure to PPI (28.8% vs 16.5%, $P = .004$) and antidepressants (29.3% vs 16.8%, $P = .002$) were more common among case patients than controls (Table 2).

Case patients were not more likely than controls to have worked or volunteered in a health care facility or to have a household member of any age who wore diapers or attended daycare (Tables 2 and 4). However, there was a trend toward increased frequency of having a household member who was ≤3 years old (ie, child who wore diapers) (8.1% vs 3.7%; $P = .08$). No significant difference was detected in the proportion of case patients and controls who had a diverse diet or a high frequency of consumption of various food types.

Of the 226 matched pairs, 207 (91.6%) matched cases and controls had provided a response to all of the selected variables (ie, no missing or unknown data) for inclusion in the final multivariate model. In multivariate analysis, white race (AmOR, 7.67; 95% CI, 2.34–25.20), cardiac disease (AmOR, 4.87; 95% CI, 1.20–19.80), chronic kidney disease (AmOR, 12.12; 95% CI, 1.24–118.89), and inflammatory bowel disease (AmOR, 5.13; 95% CI, 1.27–20.79) were significantly associated with CA-CDI (Table 5). Receipt of care in an emergency department (AmOR, 17.37; 95% CI, 1.99–151.22) and exposures to cephalosporin (AmOR, 19.02; 95% CI, 1.13–321.39), clindamycin (AmOR, 35.31; 95% CI, 4.01–311.14), fluoroquinolone (AmOR, 30.71; 95% CI, 2.77–340.05), and beta-lactam and/or beta-lactamase-inhibitor combination (AmOR, 9.87; 95% CI, 2.76–340.05) in the preceding 12 weeks were also significantly associated with CA-CDI. No significant interaction was detected between PPI and any of the antibiotic classes.

Isolates were available from 56 (24.8%) of 226 case patients. Twenty-eight distinct ribotypes were detected, with the most common being ribotype 106 (14.3%), followed by 020 (12.5%), 056 (8.93%), 015 (5.4%), and 046 (5.36%). Only one isolate of ribotype 027 was detected. Seven isolates (12.5%) comprising 6 different ribotypes (including 027, 078, and 019) were binary toxin-positive.

DISCUSSION

This is the largest case-control study performed to date to assess various CA-CDI risk factors across geographically diverse US locations. Similar to previous studies [3, 6, 9], large percentages of case patients had prior outpatient health care exposure (82.1%) and antibiotic use (62.2%). We confirmed that exposure to antibiotic classes commonly associated with CDI was a risk factor for CA-CDI. Notably, receipt of care in an emergency department (ED) within the previous 12 weeks was also significantly associated with CA-CDI, independent of the receipt of antibiotics, suggesting that the ED environment might be a reservoir for CDI. Although this was the only significant outpatient exposure in multivariate analysis and was present in only 11% of cases, several other outpatient exposures were also more common in cases than controls and might share characteristics with EDs that contribute to *C. difficile* transmission. A detailed assessment of other medication and household and dietary exposures did not reveal any novel risk factors for CA-CDI.

C. difficile environmental contamination in hospitals is well described, with growing evidence for a role in hospital-onset CDI [10–13]. Although less commonly described, *C. difficile* has also been detected in the outpatient health care environment [14, 15]. In one study, 14% of examination rooms in EDs and outpatient clinics were positive for toxigenic *C. difficile* [15]. In the same study, 81% of hospitalized patients with CDI had an outpatient visit following discharge, and approximately one-third of these patients were shedding spores at the time of

Table 2. Univariate Analysis: Select Demographic and Clinical Characteristics and Health Care and Medication Exposures Among Study Participants

Variable	Cases (n = 226), No. (%)	Controls (n = 226), No. (%)	Unadjusted Matched Odds Ratio (95% CI)	*P* Value
Demographic information				
White race	202/222 (91.0)	181/222 (81.5)	2.67 (1.34–5.69)	.004
Select medical conditions				
Charlson comorbidity index				
0	147 (65.0)	163 (72.1)	Referent	
1	35 (15.5)	28 (12.4)	1.41 (0.78–2.58)	.28
≥2	44 (19.5)	35 (15.5)	1.45 (0.83–2.57)	.21
Cardiac disease[a]	26 (11.5)	11 (4.9)	2.67 (1.20–6.52)	.01
Chronic kidney disease	15/225 (6.7)	1 (0.4)	15.00 (2.31–631.5)	.0005
Depression	59/225 (26.2)	38 (16.8)	1.84 (1.11–3.13)	.02
Diabetes mellitus	29 (12.8)	32 (14.2)	0.89 (0.48–1.61)	.78
Hypertension	113 (50.0)	80 (35.4)	2.43 (1.47–4.15)	.0003
Inflammatory bowel disease	21/225 (9.3)	4 (1.8)	5.25 (1.77–21.04)	.0009
Malignancy, any	20 (8.9)	18 (8.0)	1.13 (0.53–2.44)	.86
Pulmonary disease[b]	40 (17.7)	35/225 (15.6)	1.19 (0.69–2.06)	.60
Obese (body mass index ≥ 30 kg/m^2)	68/225 (30.2)	86/223 (38.6)	0.70 (0.47–1.06)	.10
Health care exposures[c]				
Received any outpatient care	183/223 (82.1)	129/223 (57.9)	3.94 (2.33–7.03)	<.0001
Dentist's office	71/222 (32.0)	58/222 (26.1)	1.38 (0.87–2.22)	.18
Doctor's office	131/223 (58.7)	95/223 (42.6)	1.92 (1.27–2.94)	.001
Emergency department	25/223 (11.2)	3/222 (1.4)	22.00 (3.56–907.95)	<.0001
Hemodialysis	5/223 (2.2)	0/223 (0)	6.73 (1.22–undefined)	.06
Hospital-based outpatient setting	19/223 (8.5)	11/223 (4.9)	1.64 (0.73–3.83)	.26
Outpatient lab	40/220 (18.2)	25/223 (11.2)	1.64 (0.94–2.92)	.09
Outpatient procedure center	35/223 (15.7)	15/223 (6.7)	2.46 (1.26–5.11)	.007
Outpatient surgery center	16/223 (7.2)	4/223 (1.8)	5.00 (1.41–26.9)	.008
Physical therapy center	12/223 (5.4)	15/223 (6.7)	0.73 (0.30–1.71)	.56
Urgent care	22/223 (9.9)	4/223 (1.8)	7.00 (2.09–36.65)	.0003
Volunteered or worked in a health care facility	23 (10.2)	33 (14.6)	0.64 (0.33–1.20)	.18
Visited or accompanied a person to a health care facility	70/224 (31.3)	68/222 (30.6)	1.00 (0.64–1.56)	1.00
Medication exposures[c]				
Any antibiotic use	140/225 (62.2)	23/223 (10.3)	15.25 (7.50–36.11)	<.0001
Aminoglycoside	1/225 (0.4)	0/223 (0)	1.00 (0.05–undefined)	1.00
Trimethroprim/sulfamethoxazole	8/225 (3.6)	0/223 (0)	11.05 (2.20–undefined)	1.00
Cephalosporin	17/225 (7.6)	1/223 (0.5)	15.00 (2.31–631.47)	.0005
Clindamycin	28/225 (12.4)	1/223 (0.5)	28.00 (4.63–1144.94)	<.0001
Fluoroquinolone	24/225 (10.7)	1/223 (0.5)	24.00 (3.91–986.95)	<.0001
Macrolide	7/225 (3.1)	1/223 (0.5)	7.00 (0.90–315.48)	.07
Metronidazole	16/225 (7.1)	2/223 (0.9)	15.00 (2.31–631.47)	.0005
Beta-lactam and/or beta-lactamase inhibitor combination	40/225 (17.8)	6/223 (2.7)	7.80 (3.07–25.35)	<.0001
Tetracycline	5/225 (2.2)	5/223 (2.2)	1.00 (0.23–4.35)	1.00
Vancomycin (intravenous)	2/225 (0.9)	1/223 (0.5)	2.00 (0.10–117.99)	1.00
Any acid reducing medication	93 (41.2)	59/224 (26.3)	1.80 (1.22–2.71)	.003
Proton pump inhibitor	65 (28.8)	37/224 (16.5)	2.00 (1.24–3.30)	.004
H2 blocker	15 (6.6)	16/224 (7.1)	0.93 (0.42–2.07)	1.00
Other acid reducer	23 (10.2)	10/224 (4.5)	2.30 (1.05–5.41)	.04
Any antidepressant	66/225 (29.3)	38 (16.8)	2.12 (1.29–3.56)	.002
Bupropion	12/225 (5.3)	6 (2.7)	2.00 (0.70–6.50)	.24
SNRI	9/225 (4.0)	7 (3.1)	1.29 (0.43–4.06)	.80
SSRI	38/225 (16.9)	20 (8.9)	2.06 (1.12–3.92)	.02
TCA	2 (0.9)	5 (2.2)	0.40 (0.04–2.44)	.45
Trazodone	13/225 (5.8)	1 (0.4)	13.00 (1.95–552.47)	.002

Any missing response to a variable was excluded from the denominator. Abbreviations: CI, confidence interval; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]Defined as having congestive heart failure and/or history of myocardial infarction.

[b]Defined as having asthma and/or chronic obstructive pulmonary disease.

[c]Exposure period was during the 12 weeks preceding illness onset.

Table 3. Reported Indications for Antibiotic Use among Study Participants

Indications for Antimicrobial Use[a]	Cases (n = 140), No. (%)	Controls (n = 23), No. (%)
Ear, sinus, or upper respiratory tract infection	31 (22.1)	4 (17.4)
Skin infection	27 (19.3)	4 (17.4)
Dental surgery	22 (15.7)	3 (13.0)
Dental cleaning	5 (3.6)	2 (8.7)
Urinary tract infection treatment	17 (12.1)	0 (0)
Urinary tract infection prophylaxis	6 (4.3)	0 (0)
Bronchitis or pneumonia	13 (9.3)	1 (4.4)
Surgery	4 (2.9)	3 (13.0)
Eye infection	2 (1.4)	1 (4.4)
Acne	0 (0)	2 (8.7)
Other	29 (20.7)	4 (17.4)
Unknown reason	1 (0.7)	0 (0)

[a]A study participant can indicate more than one indication for antibiotic use.

Table 4. Univariate Analysis: Select Household and Dietary Exposures Among Study Participants

Variable	Cases (n = 226), No. (%)	Controls (n = 226), No. (%)	Unadjusted Matched Odds Ratio (95% CI)	*P* Value
Household exposures[a]				
Any household member wore diapers	25 (11.1)	14 (6.2)	1.79 (0.89–3.72)	.11
Household member ≤3 years old (eg, child who wore diapers)	18 (8.1)	8 (3.7)	2.25 (.93–5.98)	.08
Household member attended child or adult daycare	15 (6.6)	9 (4.0)	1.67 (0.68–4.32)	.31
Household member had diarrhea	21/218 (9.6)	15/216 (6.9)	1.23 (0.56–2.78)	.71
Household member with overnight stay in a hospital	9/224 (4.0)	5 (2.2)	2.25 (0.63–10.00)	.27
Household member with overnight stay in a nursing home	2 (0.9)	2 (0.9)	1.00 (0.07–13.80)	1.00
Household member volunteered or worked in a health care facility	20 (8.9)	18/224 (8.0)	1.12 (0.55–2.78)	.71
Dietary exposures[b]				
Eggs	25 (11.1)	26 (11.5)	0.96 (0.50–1.82)	1.00
Dairy	125 (55.3)	129 (57.1)	0.93 (0.62–1.38)	.77
Fresh raw vegetables	73 (32.3)	87 (38.5)	0.77 (0.52–1.15)	.21
Plant-based protein	19 (8.4)	19 (8.4)	1.00 (0.48–2.08)	1.00
Red meat	33 (14.6)	27 (12.0)	1.27 (0.70–2.33)	1.00
Poultry	51 (22.6)	48 (21.2)	1.09 (0.67–1.77)	.82
Seafood	11 (4.9)	10 (4.4)	1.10 (0.42–2.89)	1.00
Diverse diet[c]	130 (57.5)	138 (61.1)	0.85 (0.56–1.29)	.48
Well or spring water[d]	22/221 (10.0)	33/219 (15.1)	0.54 (0.25–1.11)	.10

Any missing response to a variable was excluded from the denominator. Abbreviation: CI, confidence interval.

[a]Exposure period was during the 12 weeks preceding illness onset.

[b]Unless otherwise specified, dietary exposure is defined as the consumption of a food product with a frequency of more than 5 times during a typical week.

[c]Defined as any food product except for plant-based protein consumed during a typical week, regardless of the frequency of consumption.

[d]Source of drinking water around the time of illness onset.

their outpatient visit. *C. difficile* has also been cultured from the hands of health care personnel in wound care clinics; in one study, hand cultures were positive in 15% of 45 encounters [16].

In outpatient settings where procedures are performed or there is long duration and high frequency of patient contact with health care providers and the environment, such as EDs, outpatient procedure and surgical centers, hemodialysis, hospital-based outpatient settings, and urgent care, *C. difficile* transmission might be more likely to occur. Overall, we found that a significantly higher proportion of case patients (38.1%) than controls (14.4%) were exposed to one or more of these settings. In particular, our finding of a recent ED visit as a risk factor for CA-CDI suggests that EDs might be a reservoir for CDI. Compared with other outpatient settings, EDs might handle a higher volume of patient visits, including the potential for more encounters with symptomatic CDI patients with increased environmental shedding. EDs also have more frequent patient turnovers, which limits the ability to perform environmental cleaning and disinfection between patients. EDs are also uniquely situated at the interface of the community and hospital; given their high frequency of hospital admissions and discharges back to the community, they might be an important amplifier of *C. difficile* transmission in both settings. In fact, increasing evidence indicates that importation of *C. difficile* strains into hospitals might be contributing to a large portion of hospital-onset CDI [10, 13, 17].

Consistent with previous studies [4, 18, 19], exposures to fluoroquinolones, cephalosporins, and clindamycin were significantly associated with CA-CDI. We also found a significant association with beta-lactams (ie, penicillins) and/or beta-lactamase-inhibitor combinations, which have inhibitory activity against *C. difficile* but can also disrupt the indigenous microbiota, thus increasing the risk of *C. difficile* acquisition following exposure [20, 21]. Similar to previous studies [6, 9], two of the most frequently reported indications for antibiotic treatment were ear, sinus, or upper respiratory infections and dental procedures. In an assessment of antibiotic prescribing practices among US ambulatory care visits, half of the antibiotic prescriptions for acute respiratory conditions appeared unnecessary [22]. In addition, a statewide survey of Minnesota dentists revealed that up to 59% reported indications for prescribing antibiotic prophylaxis that were inconsistent with existing guidelines [23]. These data, combined with our findings, underscore the importance of outpatient antibiotic stewardship, where it has been estimated that a 10% decrease in outpatient antibiotic use could lead to a 17% decrease in CA-CDI rates [24]. To improve outpatient prescribing, the CDC released guidance that outlines the core elements of outpatient antibiotic

Table 5. Multivariate Analysis: Factors Associated With Community-Associated *Clostridium difficile* Infection

Variable[a]	Adjusted Matched Odds Ratio (95% CI)	*P* Value
White race	7.67 (2.34–25.20)	.0008
Cardiac disease	4.87 (1.20–19.80)	.03
Chronic kidney disease	12.12 (1.24–118.89)	.03
Inflammatory bowel disease	5.13 (1.27–20.79)	.02
Received care in emergency department	17.37 (1.99–151.22)	.01
Cephalosporin	19.02 (1.13–321.39)	.04
Clindamycin	35.31 (4.01–311.14)	.001
Fluoroquinolone	30.71 (2.77–340.05)	.005
Beta-lactam and/or beta-lactamase inhibitor combination	9.87 (2.76–340.05)	.0004

Abbreviation: CI, confidence interval.

[a]Exposure period for receipt of care in emergency department and antibiotic exposure was during the 12 weeks preceding illness onset. Cardiac disease was defined as having congestive heart failure and/or history of myocardial infarction.

stewardship [25]. Continued efforts to optimize antibiotic use for acute respiratory infections and stewardship efforts focusing on dental prophylaxis and other indications that commonly lead to outpatient antibiotic use may be instrumental in decreasing community-associated CDI.

Although antibiotic use remains an important risk factor, 38% of case patients did not report recent antibiotic use, similar to previous studies [3–6]. We found that 36% of case patients without recent antibiotic use also had no recent outpatient health care exposure, suggesting there might be other unidentified CA-CDI risk factors. We did not assess for more distant antibiotic use, which could have lasting impact on the microbiome, facilitating CDI development following subsequent *C. difficile* exposure.

Neither PPI nor antidepressant use was significantly associated with CA-CDI in multivariate analysis. While limited data have suggested a possible role for antidepressant use in CDI pathogenesis [26], more evidence exists linking PPI use to CDI, although results have varied [3, 5, 7, 8, 18, 19, 27]. In our study, 91% of the case patients who reported PPI use had exposure to the medication only during the two weeks prior to CA-CDI onset. The short duration of PPI use might partially explain why we did not detect an association, given that the disruption of the intestinal microbiome could be more pronounced with prolonged PPI use [28].

Previous studies of hospitalized patients demonstrated that concomitant use of PPI and antibiotics increases risk of CDI; risk might also differ by level of antibiotic exposure [27, 29]. However, we did not detect a significant interaction between PPI and antibiotics, suggesting that unaccounted factors related to hospitalization (eg, more virulent strain, exposure to other medications) might contribute to the additive effect of concomitant PPI and antibiotic use seen in some studies.

Our findings confirm inflammatory bowel disease (IBD) as a risk factor for CA-CDI [19]. Increasing incidence and severity of CDI have been described among IBD patients, with the majority of diagnosed CDI being community-associated [30]. Patients with IBD can have dysbiosis of the intestinal microbiota and altered bile salt composition that can facilitate CDI development [31]. Cardiac disease and chronic renal failure were also significantly associated with CA-CDI and can lead to severe illness that might predispose patients to CDI.

Prior studies found that contact with infants and having a household member with CDI are significantly associated with CA-CDI [4, 32]. Few of our study participants reported such exposures, which might have limited our assessment. We also did not find any association with consumption of red meat, poultry, or fresh vegetables, although toxigenic *C. difficile* has been isolated from these food products [33, 34]. Identical *C. difficile* strains have been identified in humans and food animals [35], and recent data indicate that transmission can occur between animals and humans [32]. Further studies are needed to determine if animals are an important reservoir for CA-CDI, particularly among persons without any health care exposures, and whether *C. difficile* can be transmitted by the foodborne route.

As expected, we found diverse strain types causing CA-CDI, with rare detection of ribotype 027. This is consistent with a small portion of case patients requiring hospitalization and no occurrence of severe complications (eg, colectomy). Among the predominant strains in this study, ribotypes 020, 056, and 015 were also detected among CA-CDI in England [36], whereas ribotype 106 was more prevalent overall in Scotland [37]. Notably, high frequencies of resistance to clindamycin, fluoroquinolones, and cephalosporins in ribotype 106 and associated outbreaks have been described [37, 38], indicating the need for continued surveillance for changes in the molecular epidemiology of CA-CDI to help guide prevention efforts.

Our study had several limitations. Because molecular assays used for CDI diagnosis do not distinguish between colonization and disease, some of the case patients diagnosed by a positive molecular assay may have been colonized and had diarrhea due to other factors. However, testing of other enteric pathogens was performed at the same time as the CDI diagnosis in 121 (54%) of 226 case patients; of the 121 case patients, only 2 (2%) had tested positive for another enteric organism, suggesting that *C. difficile* was likely the causative agent of the diarrheal illness in most case patients. Study participants could have been interviewed up to 6 months after their last exposure, which might affect response accuracy. Case patients might be more likely than controls to remember certain exposures around the time of their illness, leading to recall bias. In addition, although medical records were available for case patients as part of routine surveillance, documentation could have been incomplete with respect to outpatient health care exposures. Furthermore, pharmacy records were not obtained to confirm medication exposures for all participants. However, interviewers directed participants to utilize calendars and medication bottles, which might have

mitigated these limitations. The exclusion of individuals from the study who could not be interviewed by telephone might have introduced a selection bias by enrolling more nonworking participants who might be older. However, attempts were made to call during nonworking hours, that is, evenings and weekends, to identify a more representative sample of eligible participants. Approximately 29% of the participants lived alone, which might have limited our ability to evaluate household exposures. Given the wide confidence intervals of several variables in our multivariate analysis, due partly to the small sample size, our estimates might not be precise. Lastly, isolates were collected from a subset of case patients; therefore, the observed strain types might not be representative of all patients with CA-CDI.

In conclusion, antibiotic use remains a primary risk factor for CA-CDI, indicating the critical need for continued efforts to promote outpatient antibiotic stewardship. EDs could be a reservoir for CA-CDI, and a better understanding of the extent to which transmission can occur from exposures to EDs and similar types of outpatient settings is needed to help inform prevention strategies. Further efforts are also needed to identify risk factors that may explain CA-CDI among patients without any recent antibiotic or health care exposures.

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