MAJOR ARTICLE

Fluoroquinolone Use and Risk Factors for *Clostridium difficile*–Associated Disease within a Veterans Administration Health Care System

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Background. Prompted by the changing profile of *Clostridium difficile* infection and the impact of formulary policies in hospitals, we performed this study when an increase in the incidence of *C. difficile*–associated disease was noted at our health care center (Veterans Administration Puget Sound Health Care System, Seattle, Washington).

Methods. A retrospective, matched case-control study of patients presenting to the Veterans Administration Puget Sound Health Care System, Seattle, Washington during 2004 was performed. Conditional logistic analysis determined risk factors for case patients, defined as individuals with diarrhea and test results (i.e., culture or toxin assay results) positive for *C. difficile*, and control subjects, defined as individuals with diarrhea and test results negative for *C. difficile*.

Results. *C. difficile*–associated disease incidence was 29.2 cases per 10,000 inpatient-days. The increase in the incidence of *C. difficile*–associated diarrhea that paralleled increased gatifloxacin use was not attributable to use of the antimicrobial but was a reflection of seasonal variation in the rate of *C. difficile*–associated disease. Multivariate analysis controlling for the time at which the assay was performed, the age of the patient, ward, and source of acquisition (community-acquired vs. nosocomial disease) found 6 significant risk factors for *C. difficile*–associated diarrhea: receipt of clindamycin (adjusted odds ratio [aOR], 29.9; 95% confidence interval [CI], 3.58–249.4), receipt of penicillin (aOR, 4.1; 95% CI, 1.2–13.9), having a lower intestinal condition (aOR, 2.8; 95% CI, 1.3–6.1), total number of antibiotics received (aOR, 1.4; 95% CI, 1.1–1.7), number of prior hospital admissions (aOR, 1.3; 95% CI, 1.1–1.6), and number of comorbid conditions (aOR, 1.3; 95% CI, 1.1–1.5).

Conclusions. The increase in the number of cases of *C. difficile*–associated disease was not attributable to a formulary change of fluoroquinolones; instead, the incidence was within expected seasonal variations for *C. difficile*–associated disease. Recognition of community-acquired cases and the use of culture may help to identify additional cases of *C. difficile*–associated disease. Early diagnosis and treatment of *C. difficile* cases may shorten the duration of hospital stays and reduce the number of outbreaks and readmissions, mortality, and other consequences of *C. difficile* infection.

The emergence of a hypervirulent strain of *Clostridium difficile* is refocusing attention on *C. difficile* and methods to control its transmission [1–3]. Control of *C. difficile*–associated disease (CDAD) may involve various strategies, including antimicrobial stewardship, prompt diagnosis and treatment, and limiting exposure to *C. difficile* organisms or spores [4, 5]. Despite our best efforts, national incidence of CDAD is steadily increasing at acute care hospitals, Veteran Administration (VA) centers, and long-term care facilities [4].

The incidence of CDAD increased at our institution, the VA Puget Sound Health Care System (VAPSHCS; Seattle, Washington), coinciding with a change in our formulary (levofloxacin was replaced with gatifloxacin). Previous studies have shown a significant impact on CDAD rates when formulary recommendations for fluoroquinolones change [6–8]. The aims of this study were to test the hypothesis that the increase in CDAD

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incidence was associated with the formulary change and to determine CDAD risk factors for our patient population.

PATIENTS AND METHODS

Study population. The study was conducted at the VAPSHCS, a large referral network that provides care to >60,000 patients. This network has 2 main campuses: Beacon Hill, which is located in Seattle, Washington, and American Lake, which is located 40 miles away, in Tacoma, Washington. The Beacon Hill campus operates 274 beds (60% of the beds are in an acute care facility, 15% are in a rehabilitative nursing home, 10% are in a critical care facility, and 15% are in transitional care and psychiatric facilities) and also provides outpatient care, whereas the American Lake campus has 58 extended-stay nursing home beds and also provides outpatient services.

This study was approved by the University of Washington Human Subjects Committee. All patients submitting diarrheal stool samples for *C. difficile* assays to the microbiology laboratory were screened.

Microbiological assays. Only diarrheal stool samples were routinely assayed for *C. difficile* using both standard culture (Difficile Agar; PML Microbiologicals) and toxin assays (EIA for toxins A or B using Premier *C. difficile* Toxins A&B EIA; Meridian Diagnostics) [9, 10]. Neither strain typing nor toxin assays of *C. difficile* isolates were routinely performed at our laboratory.

Definitions. CDAD was defined as an acute onset of diarrhea (liquid or watery stools) and either a culture positive for *C. difficile* or a positive toxin A/B result with no other documented active cause for diarrhea [11, 12]. Nosocomial cases were defined as CDAD occurring >72 h after hospital admission in patients who had no health care admissions (i.e., admission to a hospital, long-term care facility, or nursing home) within the past year. Presumptive nosocomial cases were defined as CDAD occurring ⩽72 h after admission to our institution and a history of at least 1 health care admission within the past year. Community-acquired cases were defined as CDAD occurring in patients admitted to our institution who had diarrhea or who experienced diarrhea ⩽72 h after admission who had no history of a health care admission within the past year. Only the first (index date) *C. difficile*–positive sample was counted, excluding additional samples. CDAD recurrences were defined as an onset of CDAD occurring ⩾7 days after resolution of the previous diarrheal episode and discontinuation of antimicrobial therapy. To limit misclassification bias, control subjects were required to have both a negative culture result and a negative toxin assay result. To limit ascertainment bias, control subjects were selected from patients submitting a liquid or watery stool sample for *C. difficile* testing, as done in previous studies [13, 14]. Case patients and control subjects were matched 1:1 with respect to time of *C. difficile* assay sample submission (± 6 days), age (± 15 years), and ward (and hospital) location.

Data collection. Exposure and follow-up data from June 2003 through December 2005 were collected using national and local VA databases: the VAPSHCS Infection Control database (containing information on microbiologic assay results, ward location, transfers, and admission and discharge dates) and the Veterans Integrated Service Network 20 Data Warehouse Program database (containing medical data on every inpatient and outpatient visit) [15]. Antimicrobial drugs, other medications, intestinal procedures, and surgeries were included if they were administered or performed ⩽3 months before the *C. difficile* assay date. Mortality and subsequent CDAD recurrence data were collected for 1 year after the *C. difficile* assay was performed. Data and documentation of diarrhea from all subjects with community-acquired diarrhea, deaths, and a subsample of case patients and control subjects (25%) were verified using electronic record review.

Statistical analysis. The sample size required to test the hypothesis that exposure to gatifloxacin was a significant risk factor for CDAD was 52 patients (assuming a similar rate of gatifloxacin exposure [67%] in case patients with CDAD and a 25% rate of exposure in control subjects from a study with a similar formulary change, a 1:1 ratio of case patients to control subjects, $\alpha = 0.05$, and 80% power) [6].

Univariate analysis was used to screen for potential risk factors, using Yates-corrected χ^2 test, the Student's t test, or McNemar's test. Logistic models were compared using the likelihood ratio test. Annual CDAD incidence density was calculated as the number of unique case patients with CDAD for the period 1998–2004 divided by patient-days (i.e., occupied bed-days by ward location), by year. Analysis of variance was used to analyze monthly seasonal trends. Data were analyzed using Stata software, version 9.0 (Stata). P values <.05 were considered to be significant using 2-tailed tests.

RESULTS

Descriptive epidemiology. During 2004, a total of 1348 stool samples from 723 unique individuals were tested (figure 1). Of the 723 individuals, 184 had samples that were *C. difficile* positive. Of the 184 *C. difficile*–positive patients, 147 (80%) were inpatients; 167 (91%) were from the Seattle facility, and 17 (9%) were from the American Lake facility. CDAD incidence density was 23.8 cases per 10,000 patient-days for 144 Seattle patients and 4.2 cases per 10,000 patient-days for 4 American Lake inpatients. Twenty-three of the 36 outpatients received a diagnosis while at the Seattle facility; 13 received a diagnosis as outpatients at American Lake. Because 69% of the outpatients who received a diagnosis at American Lake had been admitted (within 6 weeks) to the Seattle facility, the data was pooled. The total incidence at VAPSHCS increased from 14.0

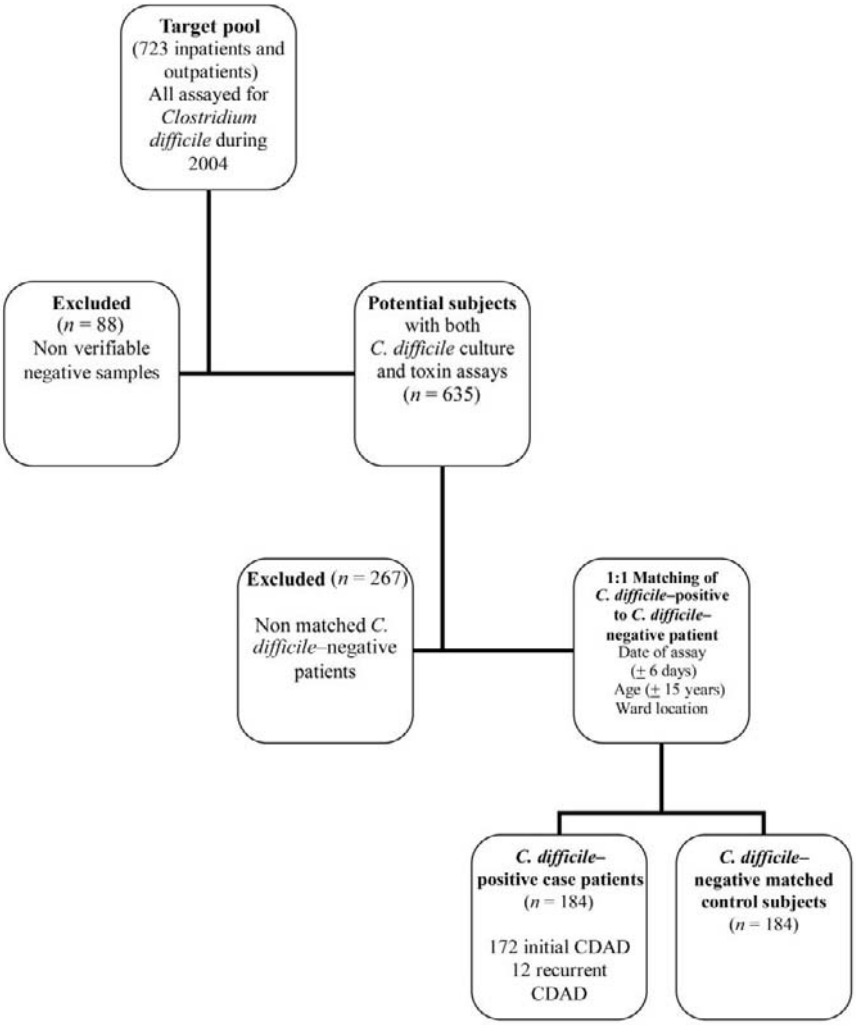

Figure 1. Consolidated Standards of Reporting Trials enrollment flow diagram for a case-control study of *Clostridium difficile*–associated disease (CDAD). Nonverifiable negative samples were defined as samples from patients with only 1 negative *C. difficile* assay result (either culture or toxin) for whom the other type of assay was not performed.

cases per 10,000 patient-days in 1998 to 29.2 cases per 10,000 patient-days in 2004 and to 32.8 cases per 10,000 patient-days in 2005.

Of the 184 patients with CDAD, 172 (93.5%) were experiencing an initial episode, and 12 (6%) had a history of recurrent CDAD. Among the case patients, 111 (60.3%) had nosocomial cases, 53 (28.8%) had presumptive nosocomial cases, and 20 (11%) had community-acquired cases. Patients with community-acquired cases of CDAD were younger, had less severe disease, and had a trend for lower intestinal conditions (table 1), with 6 (75%) of the 8 case patients with intestinal conditions having stool samples positive for toxins or toxigenic isolates. Most (60%) of the patients with community-acquired CDAD had no prior exposure to antibiotics; in contrast, only 15% of patients with nosocomial CDAD had no prior antibiotic exposure. The consequences of CDAD were significantly less severe for patients with community-acquired cases, who had a shorter mean duration of hospitalization, lower mortality, and no CDAD-related surgeries.

Overall, the 184 patients with CDAD had long durations of inpatient stays (mean duration, 45 days); 30% required intensive care unit admission, and 21% required readmission to a health care facility <1 year after hospital discharge. Two wards had significantly higher rates of CDAD (bone marrow transplant unit, 59.7 cases per 10,000 patient-days; medical intensive care unit, 50.3 cases per 10,000 patient-days), compared with other wards ($P = .002$). The consequences of CDAD included a high frequency of recurrences (occurring in 27% of patients, with a mean [± SD] time to recurrence of 49 ± 60 days) and a CDAD-attributable mortality rate of 15%; in addition, 2% of patients required gastrointestinal surgery for *C. difficile*-related complications (table 2).

Table 1. Comparison of 20 patients with community-acquired *Clostridium difficile*–associated disease (CDAD) and 164 patients with nosocomial CDAD who were treated during 2004 at the Veterans Administration Puget Sound Health Care System, Seattle, Washington.

Characteristic	Community-acquired CDAD (n = 20)	Nosocomial CDAD (n = 164)	P
Age, mean years ± SD	56.5 ± 48.5	65.9 ± 13.4	.05
Comorbid condition(s)			
Mean no. of comorbid conditions ± SD	5.3 ± 2.8	6.8 ± 2.7	.02
Anemia[a]	1 (5.0)	45 (27.4)	.03
Lower intestinal conditions[b]	8 (40.0)	37 (22.6)	.09
Antimicrobial exposure[c]			
Any	8 (40.0)	139 (84.8)	<.001
None	12 (60.0)	25 (15.2)	
Mean no. of medications ± SD[c]	5.3 ± 5.1	12.6 ± 9.7	.001
Receipt of proton pump inhibitors[c]	3 (15.0)	31 (18.9)	NS
Length of hospitalization, mean no. of days ± SD	5.4 ± 9.6	50.0 ± 36.4	.001
Mortality	1 (5.0)	53 (32.3)	.01
CDAD-related surgery	0 (0.0)	4 (2.0)	.001
Recurrent CDAD in the following year	2 (10.0)	47 (28.6)	NS

NOTE. Data are no. (%) of patients, unless otherwise indicated. NS, not significant.

[a] Anemia was defined as a hematocrit <40% in male subjects or <37% in female subjects.

[b] Lower intestinal conditions include polyps, bleeding, neurogenic bowel, inflammatory bowel disease (in remission), irritable bowel syndrome (in remission), diverticulitis, and paralytic ileus.

[c] Received ⩽3 months prior to index date.

Most patients with CDAD were treated with metronidazole (47%) or vancomycin (26%) for a mean (±SD) of 8.2 ± 5.9 days or received no antimicrobial treatment (24%). Of the 140 patients with cases of CDAD who received antimicrobials, 33 (24%) received treatment on the same day that an assay result positive for *C. difficile* was obtained, and 70 (50%) received treatment within 1 week after the assay result was obtained; however, 37 (26%) had treatment delayed for >1 week. Significantly more patients for whom treatment was delayed died (17 [46%] of 37), compared with patients who were treated rapidly (26 [25%] of 103; $P = .02$), but death was usually attributable to other comorbidities.

CDAD-attributable deaths were observed in 19% of case patients who had delayed treatment, 14% of those who had rapid treatment, and 14% of those who had no treatment ($P > .05$). Treated and untreated cases of CDAD did not differ with respect to severity, based on mortality (31% vs. 25%), mean total length of hospital stay (51 days vs. 28 days), whether the case was community acquired (10% vs. 14%, respectively), or other variables; however, significantly more patients with treated cases experienced recurrence (33% vs. 7%; $P < .001$). For patients with untreated cases of CDAD, the reason that CDAD was not treated was not reported in the medical records.

Diagnosis. Detection of *C. difficile* was increased by routine use of both culture and toxin assay (table 2); both toxin assay and culture results were positive for 96 (52%) of case patients, only culture results were positive for 65 (35%), only toxin assay results were positive for 21 (11%), and toxin assay was not performed for 1% (2 case patients). All case patients had clinical diarrhea; asymptomatic carriers were excluded. Among the 117 case patients with positive toxin assay results, toxin was found in the first sample obtained from 102 (87%), in the second sample obtained from 10 (8%), in the third sample obtained from 2 (2%), and in the fourth sample obtained from 3 (3%). Patients usually had additional samples submitted only if the initial assays had results that were negative for *C. difficile*, their diarrhea persisted despite treatment, and no other etiology was found. Cultures detected an additional 67 case patients (36%) who were missed by toxin assays alone. Of the 65 patients with positive culture results and negative toxin assay results, 6 (9%) had a CDAD recurrence with positive toxin assay results within 2 months, and only 16 (25%) had additional samples assayed for toxin. A subsample of 18 available isolates obtained from culture of stool samples that were negative for toxin were retested for toxin or the toxin B gene, and 12 (67%) had positive results. Patients with CDAD who had positive culture results and negative toxin assay results were not significantly different from patients who had positive culture and toxin assay results with respect to risk factors, demographic data, or disease severity (data not shown). The *International Classification of Diseases, Ninth Revision* (ICD-9) code for *C. difficile* (008.45) was

Table 2. Characteristics of 184 patients with cases of *Clostridium difficile*–associated disease (CDAD) who were treated during 2004 at the Veterans Administration Puget Sound Health Care System, Seattle, Washington.

Variable	No. (%) of patients (n = 184)
Type of CDAD	
Initial episode	172 (93.5)
Recurrent CDAD	12 (6.5)
Delayed complications	
Subsequent CDAD recurrence within 1 year	49 (26.6)
CDAD-attributable mortality	28 (15.2)
Subsequent surgery related to CDAD	4 (2.2)
Antimicrobial treatment of CDAD	
Metronidazole	86 (46.7)
Vancomycin	48 (26.1)
Metronidazole and vancomycin	6 (3.3)
None	44 (23.9)
Route of antimicrobial treatment	
Oral	84 (60.0)
Intravenous	55 (39.3)
Rectal tube	1 (0.7)
Delay of antimicrobial treatment, no. of days after positive assay result	
0	33 (23.6)
1–7	70 (50.0)
>7	37 (26.4)
Mortality	
Patients with delayed treatment (>7 days after positive assay result)	17 (45.0)[a]
Patients without delayed treatment	26 (25.2)
Diagnosis	
Laboratory assay result	
Positive culture and toxin assay results	96 (52.2)
Positive culture and negative toxin assay results	65 (35.3)
Negative culture and positive toxin assay results	21 (11.4)
Negative culture and negative toxin assay results	0
Positive culture result and toxin assay not done	2 (1.1)
ICD-9 code 008.45 listed, any diagnosis	64 (34.8)
Positive endoscopic examination findings	19 (10.3)
Diarrhea	184 (100)

NOTE. ICD-9, *International Classification of Diseases, Ninth Revision.*

[a] $P = .02$.

not listed for 120 (65%) of the case patients with CDAD was documented by microbiology results.

Formulary change. Previous studies have indicated that the incidence of *C. difficile* infection may be tied to changes in fluoroquinolone use [6–8]. At VAPSHCS, pharmacy records indicated that hospital-wide use of levofloxacin (calculated as dispensed-days per month) decreased from 3397 dispensed-days in January 2004 to 455 dispensed-days in December 2004 (figure 2*A*). Gatifloxacin use increased from 0 dispensed-days (in January and February 2004) to 216 dispensed-days (in March 2004) and peaked at 2640 dispensed-days in December 2004. We predicted that CDAD incidence at our facilities might increase by 2.9 times after gatifloxacin use began at our institution, on the basis of the experience at an Atlanta long-term care VA facility after its formulary switched from levofloxacin to gatifloxacin [6], but the incidence of CDAD at our facilities never reached the predicted rate (figure 2*B*). The incidence of CDAD decreased from 22 cases per 10,000 patient-days in January 2004, reached a nadir in July 2004 (12.3 cases per 10,000 patient-days), and increased again, to 35.5 cases per 10,000 patient-days in October 2004. Based on seasonal trends of CDAD incidence from 1998 through 2005 at VAPSHCS (figure

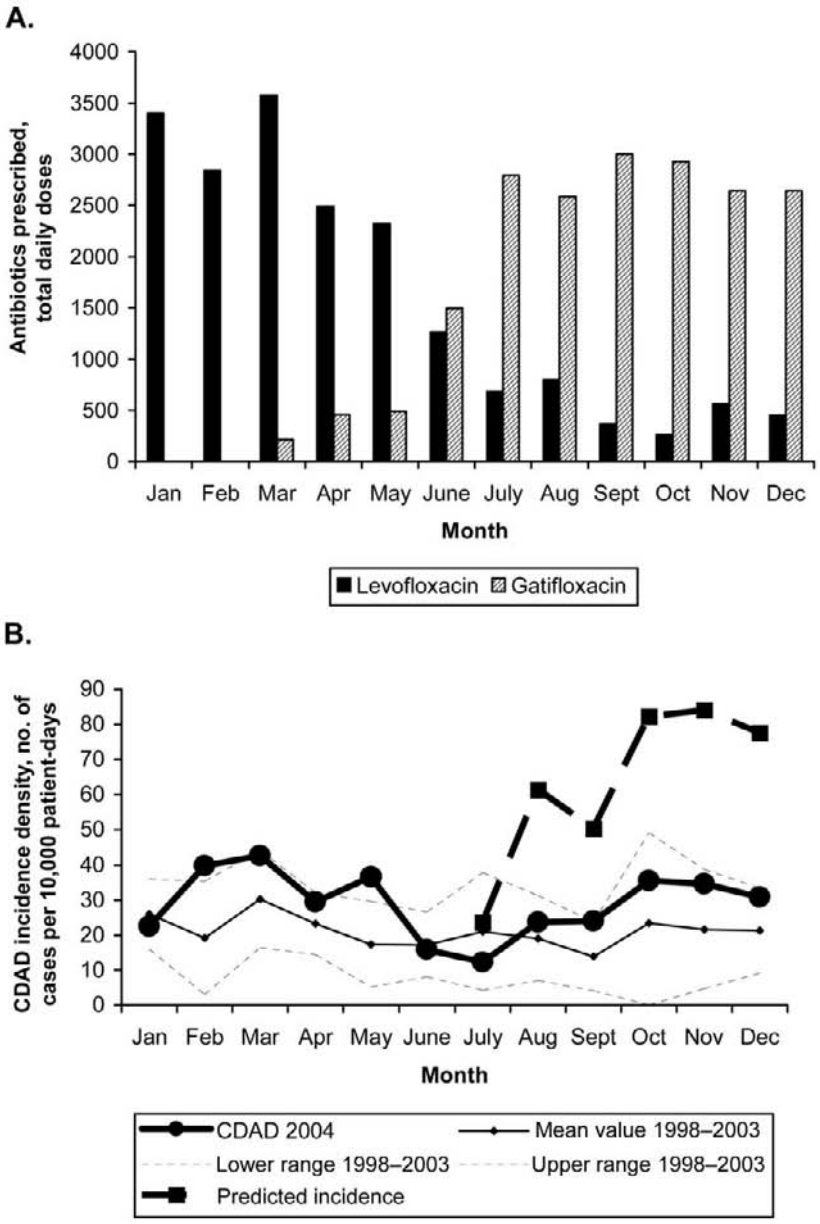

Figure 2. Fluoroquinolone use during 2004 and incidence of *Clostridium difficile* associated disease (CDAD) from 1998 through 2004 at Puget Sound Veterans Administration Health Care System (Seattle, Washington). *A,* Hospital-wide use of fluoroquinolone during 2004. *B,* Monthly incidence density of CDAD during 2004 and mean incidence density ± 2 SDs for the period 1998–2003. Predicted incidence is adapted from that reported in Gaynes et al. [6], who found that predicted incidence was 2.9 times higher among patients receiving gatifloxacin than among patients receiving levofloxacin, and applied to the incidence observed at the Puget Sound Veterans Administration Health Care System.

2*B*), CDAD incidence follows a bimodal seasonal pattern (high incidence during the fall and spring; $P = .006$), and the rates in our study in 2004 were within the expected seasonal ranges. Thus, it does not appear that the increase in CDAD incidence was explained solely by the change in formulary recommendations.

Risk factors. Among 723 patients with diarrhea who were tested for CDAD during 2004, 184 *C. difficile*–positive case patients were matched with 184 *C. difficile*–negative patients. Statistically significant differences are shown in table 3. Physical proximity to an infected case patient (either being the roommate of an infected case patient or being admitted into the room of an infected case patient within 2 weeks after the infected case patient had left) may indicate the presence of viable spores in the hospital environment after terminal room disinfection (with a 1:64 mixture of phenolic germicidal deter-

gent). Case patients with CDAD also had more comorbid conditions than did control subjects, which may explain, in part, the longer lengths of stay among patients with CDAD.

Although case patients with CDAD were prescribed significantly more medications than were control subjects (mean number of medications, 12 vs. 9), the types of medication (e.g., proton pump inhibitors, laxatives, immunosuppressives, and chemotherapeutic drugs) were not significantly different between the 2 groups (table 3). Most case patients with CDAD (147 patients; 80%) were exposed to at least 1 antibiotic during the previous 3 months, compared with significantly fewer of the control subjects (63; 34%). Fluoroquinolone use was significantly more frequent among case patients with CDAD (55 patients; 30%), compared with control subjects (24; 13%), most of which was attributable to levofloxacin use. Cephalosporins, penicillins, and clindamycins were the only other antimicrobials that were significant risk factors for CDAD. Interestingly, vancomycin and metronidazole also acted as inciting antimicrobials (45 [88%] of 51 of the indications were non-CDAD indications, and only 6 (12%) were for recurrent CDAD). Of the 35 case patients with CDAD with exposure to vancomycin, the most frequent indications were severe wound infection (e.g., decubitis ulcers, diabetic foot ulcers, and gangrene; 12 patients [34%]), bacteremia (9; 26%), or recurrent CDAD (1; 3%). Nearly one-third of these patients (32%) were exposed to intravenous vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia or wound infections, whereas none of the control subjects had infection due to methicillin-resistant *S. aureus.* In 6 (17%) of the patients with CDAD with exposure to vancomycin, vancomycin was the only antibiotic given within 3 months of the index date. Of the 16 patients exposed to metronidazole, the most common reason was to treat recurrent CDAD (5 patients; 31%).

The conditional logistic model (table 4) for all-cause CDAD (including community-acquired and recurrent cases) found 6 statistically significant risk factors for CDAD disease: clindamycin use (adjusted OR [aOR], 29.9), penicillin use (aOR, 4.1), lower intestinal conditions (aOR, 2.8), total number of antibiotics (aOR, 1.4), number of prior hospitalizations (aOR, 1.3), and number of comorbidities (aOR, 1.3). There were no significant interactions between the variables, nor were any other variables found to be statistically significant. A model limiting CDAD cases to primary episodes of health care–acquired CDAD found a similar risk factor profile (table 4), except that there was only a trend for lower intestinal conditions, mainly attributable to the exclusion of community-acquired cases.

DISCUSSION

This investigation of CDAD had several major findings: (1) the formulary change to gatifloxacin did not cause the observed increase in CDAD cases, (2) risk factors for CDAD in the veteran population are similar to those found in other populations, (3) patients with community-acquired CDAD differ from patients with nosocomial CDAD, and (4) CDAD may be underdiagnosed, depending on the assay conducted.

When a health care formulary changes antimicrobial recommendations, a fortuitous opportunity arises to observe the impact of antimicrobial use patterns on CDAD rates [6–8]. Previous case-control studies have found that gatifloxacin use increased the risk of CDAD [16], although other studies have found that it did not [8, 17, 18]. Gaynes et al. [6] found that *C. difficile* rates increased at the VA long-term care facility in Atlanta, Georgia, after a formulary change from levofloxacin (0.44 cases per 1000 patient-days) to gatifloxacin (1.3 cases per 1000 patient-days); rates then decreased after levofloxacin was reinstated (0.5 cases per 1000 patient-days), but infection-control practices also changed during this period. Our incidence of CDAD followed expected seasonal patterns and was not significantly correlated with the formulary change or changes in infection-control practices. Two other studies have also reported higher CDAD rates in spring and winter [19, 20].

Risk factors for nosocomial CDAD in our veteran population are similar to risk factors found in other studies of veteran and nonveteran patients [13, 16, 21–27]. Changela et al. [25] studied veterans at the Hines VA (Chicago, IL) and found that levofloxacin use, the presence of comorbid conditions, and a higher mortality were associated with CDAD, but they did not examine spatial or seasonal trends, and the control group was not assayed for *C. difficile,* which may have allowed misclassification to occur. Similar to other studies, our data indicate that the use of antimicrobials (e.g., clindamycin and penicillin) is associated with increased risk of CDAD [4, 5, 22–24, 27, 28]. In our study, both the number of comorbid conditions and the presence of lower intestinal conditions were significant risk factors for CDAD. Changes in intestinal morphology associated with polyps and chronic intestinal disease (even in remission) and changes in normal intestinal microflora may alter the normal colonization-resistance ability (similar to the effect of antibiotics), thereby increasing the risk of CDAD [29]. Previous studies confirm that inflammatory bowel disease may increase the risk of CDAD [7, 28, 30], and normal colonic flora are disrupted in patients with inflammatory bowel disease [31].

Community-acquired CDAD is at the forefront of clinical interest because of increasing incidences of severe community-acquired CDAD [4, 28, 30, 32]. Noren et al. [32] found that patients with community-acquired CDAD were younger than patients with nosocomial CDAD and had less antibiotic exposure and lower mortality rates. Several other studies have shown that most patients with community-acquired CDAD have not had previous exposure to antibiotics; 12 (60%) of 20

Table 3. Comparison of case patients with *Clostridium difficile*–associated disease (CDAD) with control subjects treated during 2004 at Veterans Administration Puget Sound Health Care System, Seattle, Washington.

Characteristic	CDAD-positive case patients (n = 184)	CDAD-negative control subjects (n = 184)	P
Onset of diarrhea			
Nosocomial			
Incident	111 (60.3)	143 (77.7)	.001
Previous hospitalization history	53 (28.8)	16 (8.7)	
Community acquired	20 (10.9)	25 (13.6)	
Hospital stay			
No. of prior hospital admissions[a]	1.5 ± 1.7	0.9 ± 1.2	.001
Length of stay before enrollment, mean no. of days ± SD	22.7 ± 54.3	10.8 ± 17.2	.01
Physical proximity to patient infected with CDAD[b]	15 (8.2)	4 (2.2)	.009
Comorbid condition(s)			
Mean no. of comorbid conditions ± SD	6.6 ± 2.7	4.6 ± 2.6	.001
Paralysis and/or spinal cord injury	36 (19.6)	19 (10.3)	.01
Renal	78 (42.4)	51 (27.7)	.003
Anemia	46 (25.0)	26 (14.1)	.009
Lower intestinal[c]	45 (24.5)	25 (13.6)	.008
Urinary tract infection	36 (19.6)	19 (10.3)	.01
All infections, mean no. of infections ± SD	0.7 ± 0.9	0.4 ± 0.7	.01
Arterial catheterization	35 (19.0)	18 (9.8)	.01
Transfusion	56 (30.4)	37 (20.1)	.02
Dialysis	8 (4.3)	2 (1.1)	.05
All medications,[d] mean no. of medications ± SD	11.9 ± 9.6	9.5 ± 9.6	.02
Antacids			
Any	62 (33.7)	64 (34.8)	NS
Proton pump inhibitor	34 (18.5)	39 (21.2)	NS
H_2 antagonist	24 (13.0)	23 (12.5)	NS
Other	13 (7.0)	11 (6.0)	NS
Antimicrobials			
All antimicrobials, mean no. of antimicrobials ± SD	2.9 ± 4.1	0.8 ± 1.8	.001
Any antimicrobial therapy			
Yes	147 (79.9)	63 (34.2)	.001
No	37 (20.1)	121 (65.8)	
Antimicrobial route[e]			
Intravenous	22 (15.0)	9 (14.3)	NS
Oral	125 (85.0)	54 (85.7)	
Fluoroquinolones			
Any quinolone	55 (29.9)	24 (13.0)	<.001
Levofloxacin	33 (17.9)	12 (6.5)	.001
Gatifloxacin	21 (11.4)	13 (7.1)	NS
Ciprofloxacin	8 (4.3)	2 (1.1)	.05
Cephalosporins			
Any	50 (27.2)	17 (9.2)	.001
First generation	34 (18.5)	13 (7.1)	.001
Second generation	9 (4.9)	2 (1.1)	.06
Third generation	7 (3.8)	2 (1.1)	NS
Penicillin	49 (26.6)	8 (4.3)	.001
Clindamycin	25 (13.6)	4 (2.2)	<.001
Vancomycin	35 (19.0)	1 (0.5)	.001
Metronidazole	16 (8.7)	4 (2.2)	.01

(continued)

Table 3. ***(Continued.)***

Characteristic	CDAD-positive case patients (n = 184)	CDAD-negative control subjects (n = 184)	P
Consequences of disease			
Total length of hospital stay, mean days ± SD	45.2 ± 6.3	21.1 ± 3.6	.001
Subsequent CDAD recurrence[f]	49 (26.6)	4 (2.2)	<.001
Subsequent hospitalization[g]	38 (20.6)	35 (19.0)	NS
Mortality[h]	54 (29.3)	43 (23.4)	NS

[a] No. of prior hospital admissions within 1 year of the current admission.
[b] Residency in the same room <2 weeks after the patient with CDAD.
[c] Lower intestinal comorbid conditions include polyps, bleeding, neurogenic bowel, inflammatory bowel disease (in remission), irritable bowel syndrome (in remission), diverticulitis, and paralytic ileus.
[d] No. of medications and antimicrobial drugs received within 3 months prior to the index date.
[e] Percentage of those patients receiving antimicrobial medication.
[f] Subsequent CDAD recurrence within 1 year after the index date.
[g] Subsequent hospitalization within 1 year after discharge from the hospital.
[h] Death within 1 year after index date; subsequent hospitalizations <1 month after hospital discharge.

patients in our study and 801 (65%) of 1233 patients in the study by Dial et al. [28] did not have previous antibiotic exposure. Other studies reporting high percentages of antibiotic use among patients with community-acquired CDAD either included patients with prior hospitalization or did not determine this history [33, 34]. Because patients with community-acquired CDAD generally lack several of the major risk factors (e.g., recent hospitalization, advanced age, and antibiotic exposure) that trigger physicians to order diagnostic tests for *C. difficile*, the true frequency of community-acquired cases may be underestimated.

The incidence of *C. difficile* infection also may be underestimated if only cytotoxin assays or ICD-9 codes are used for diagnosis. Reliance on positive toxin assay results alone would have missed the 35% of the CDAD cases in our study that were detected only by culture. The patients with culture-positive, stool toxin assay–negative CDAD cases were similar to patients with toxin-positive cases, except that fewer of the patients in the former group received treatment (55% vs. 87%). Further studies involving this interesting subgroup are underway. Delmee et al. [35] also found that cultures detected 56% of patients with CDAD who had stool assay results that were negative for toxin, and other studies have reported similar findings [28, 36]. False-negative stool toxin assay results can be attributable to

Table 4. Conditional logistic regression multivariate models for the association of individual risk factors with *Clostridium difficile*–associated disease (CDAD) during 2004 at the Veterans Administration Puget Sound Health Care System, Seattle, Washington.

Risk factor	Adjusted OR (95% CI)	P
Full model of all nosocomial and community-acquired CDAD[a]		
Clindamycin use	29.88 (3.58–249.4)	.002
Penicillin use	4.07 (1.19–13.87)	.020
Lower intestinal condition	2.84 (1.32–6.12)	.008
No. of antibiotics	1.39 (1.14–1.69)	.001
No. of prior hospital admissions	1.30 (1.04–1.63)	.020
No. of comorbid conditions	1.30 (1.13–1.50)	.001
Model restricted to primary episodes of nosocomial CDAD[b]		
Clindamycin use	5.62 (1.70–18.54)	.004
Penicillin use	3.57 (1.37–9.34)	.009
Lower intestinal condition	1.86 (0.94–3.69)	.076
No. of antibiotics	1.24 (1.06–1.45)	.007
No. of prior hospital admissions	1.37 (1.15–1.65)	.001
No. of comorbid conditions	1.32 (1.19–1.48)	.001

[a] Includes 184 patients with CDAD and 184 matched control subjects, matched with respect to the time of the *C. difficile* assay, age, and ward location, adjusted for community or nosocomial acquisition; log likelihood by χ^2, 67.7; $P < .001$.
[b] Includes 152 patients with CDAD and 152 matched control subjects, excluding those with community-acquired and recurrent CDAD and matched control subjects; log likelihood by χ^2, 158.9; $P < .001$.

sampling error (as a result of unequal toxin distribution in stool), the type of toxin assay used, a lack of additional samples, or the presence of other virulence factors [1, 4, 3537]. The frequency of CDAD may also be underestimated if only ICD-9 codes are used [26, 38]. We found that nearly two-thirds of patients with CDAD did not have the ICD-9 code for *C. difficile* infection noted in their electronic medical database.

This study has several strengths and limitations. By using control subjects with diarrhea, we discerned risk factors that were specifically associated with CDAD, rather than with nosocomial diarrhea in general. Wilcox et al. [39] reports that, despite using 2 types of control groups (one with diarrhea and one without), the resulting risk factor profile for CDAD was the same. Another strength of our study is that all control subjects were assayed for *C. difficile.* Having control subjects for whom no *C. difficile* assays were performed may lead to control misclassification [6, 25]. Another strength of this study was the availability of comprehensive, longitudinal electronic VA databases with complete medical information.

A limitation to this study is the generalizability of the results, because the VA population consists mostly of older male patients with significant comorbid conditions. However, epidemiologic findings from a 10-year study conducted in a VA hospital have remained valid over time and compare favorably to epidemiologic findings for other hospital populations with CDAD [40]. Another limitation of this study is that *C. difficile* isolates were not typed, because this is not routinely performed at VA hospitals; as a result, the occurrence of emerging new *C. difficile* variants (e.g., BI/NAP1/027) is not known [1, 4, 16]. Another limitation is that we did not study gatifloxacin use in the years following this study, to observe whether gatifloxacin use changed and whether CDAD rates increased above the expected seasonal rates.

The high prevalence of *C. difficile* infection will remain a major problem for VA hospitals and non-VA hospitals, because factors associated with CDAD are common (e.g., the presence of comorbid conditions, advanced age, use of antimicrobials, and difficulty in *C. difficile* spore disinfection). Changes in provider behavior (i.e., an awareness of atypical risk profiles for patients with community-acquired CDAD) and health care system interventions (i.e., diagnostic protocols and treatment) may lower CDAD rates, reduce transmission, shorten hospital stays, and reduce mortality and other consequences of *C. difficile* infection in our health care institutions.

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