MAJOR ARTICLE

Emergence of Fluoroquinolones as the Predominant Risk Factor for *Clostridium difficile*–Associated Diarrhea: A Cohort Study during an Epidemic in Quebec

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Background. Since 2002, an epidemic of *Clostridium difficile*–associated-diarrhea (CDAD) associated with a high case-fatality rate has involved >30 hospitals in the province of Quebec, Canada. In 2003, a total of 55% of patients with CDAD at our hospital had received fluoroquinolones in the preceding 2 months. It has been suggested that massive use of proton pump inhibitors might have facilitated this epidemic.

Methods. To delineate the risk of CDAD associated with specific classes of antibiotics and whether this is modulated by concomitant use of proton pump inhibitors and other drugs altering gastric acidity or gastrointestinal motility, we conducted a retrospective cohort study of patients hospitalized in a teaching hospital in Sherbrooke, Canada, during the period of January 2003 through June 2004. We obtained data on 7421 episodes of care corresponding to 5619 individuals. Patients were observed until they either developed CDAD or died or for 60 days after discharge from the hospital. Adjusted hazard ratios (AHRs) were calculated using Cox regression.

Results. CDAD occurred in 293 patients. Fluoroquinolones were the antibiotics most strongly associated with CDAD (AHR, 3.44; 95% confidence interval [CI], 2.65–4.47). Almost one-fourth of all inpatients received quinolones, for which the population-attributable fraction of CDAD was 35.9%. All 3 generations of cephalosporins, macrolides, clindamycin, and intravenous β-lactam/β-lactamase inhibitors were intermediate-risk antibiotics, with similar AHRs (1.56–1.89). Proton pump inhibitors (AHR, 1.00, 95% CI, 0.79–1.28) were not associated with CDAD.

Conclusions. Administration of fluoroquinolones emerged as the most important risk factor for CDAD in Quebec during an epidemic caused by a hypervirulent strain of *C. difficile*.

Since the end of 2002, many hospitals in the province of Quebec have been struggling with an epidemic of *Clostridium difficile*–associated diarrhea (CDAD), with >7000 cases of nosocomial CDAD reported in 2003 [1]. During January 2005, a total of 30 hospitals in Quebec reported an incidence of ⩾15 cases per 10,000 patient-days, which was 5 times higher than the historic incidence [2, 3]. Concurrently, an increase in the proportion of patients with CDAD who developed complications or who died ⩽30 days after diagnosis was noted [4]. The predominant clone in Quebec is identical to a *C. difficile* strain with novel virulence factors found in the United States [1]. These virulence factors may be associated with more-severe disease and diarrhea, which in turn facilitate transmission of the pathogen within hospitals. Other factors that may have contributed to the rapid spread of this strain within Quebec include the substantial aging of the population of inpatients with numerous comorbidities; a lack of investment in hospital infrastructures, resulting in a shortage of private and semiprivate rooms (so that prevention of cross-transmission is more difficult); and, possibly, the introduction of alcohol-based hand washing. Finally, there appears to be a suboptimal response

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of this strain to metronidazole treatment, accompanied by frequent recurrences, which might have an impact on transmission dynamics [4, 5].

In our hospital, the proportion of patients with CDAD who had received fluoroquinolones in the preceding 2 months increased from ~10% in 1991–1996 to 55% in 2003 [4], but it remained unclear to what extent this reflected changes in prescription practices. Furthermore, it has been suggested that the use of proton pump inhibitors (PPIs) might increase the risk of CDAD [6, 7]. In Canada, use of PPIs has increased exponentially in recent years: up to 50% of inpatients now receive PPIs at some point during their hospitalization [6]. If this association were causal, restriction of PPI use might be considered as a control measure for CDAD. To delineate the risk of CDAD associated with specific classes of antibiotics in the context of this epidemic, and to measure the effect of PPIs and other drugs that alter gastric acidity or gastrointestinal motility, we undertook a retrospective cohort study of patients hospitalized at the Centre Hospitalier Universitaire de Sherbrooke (Sherbrooke, Quebec), a 683-bed secondary and tertiary care hospital, during the peak of the *C. difficile* infection epidemic.

METHODS

We reviewed the records of all adult patients hospitalized at least once in the internal medicine, family medicine, or gastroenterology wards during the period of 1 January 2003 through 30 June 2004, as well as a random sample of 50% of patients hospitalized in the general surgery unit. For each individual, we reviewed all hospital admissions during that period, regardless of the admitting service. Hospitalizations for which the primary reason for admission was CDAD were excluded. Multiple hospitalizations for the same patient were considered to represent a single episode of care if the interval between the date of discharge from the hospital and the date of subsequent readmission was $\leq$60 days; in such cases, we tabulated the total number of days actually spent in the hospital as the sum of the durations of each hospitalization within that episode of care. Hospitalizations separated by >60 days were considered to be distinct events and were analyzed as 2 (or more) episodes of care. This approach was based on the maximum incubation period for CDAD, generally thought to be 60 days, and it aimed to consider multiple hospitalizations with short intervals as a single exposure, whereas hospitalizations separated by more than the maximum incubation period were analyzed as distinct exposures.

Sociodemographic, clinical, pharmaceutical, and laboratory data were extracted from the medical records (part of which are computerized, whereas medical and nursing notes remain handwritten). We collected data on level of care, use of antibiotics (during the hospital admissions, data were derived from the computerized medical records; for the 2 months prior to the episode of care, data were derived from medical notes) or other drugs (during hospital admissions), and procedures performed. To quantify the overall burden of comorbidities, we used the Charlson comorbidity index [8]; because this index is based essentially on chronic diseases, we reviewed for each patient all discharge diagnoses during all hospital admissions up to the one that constituted the beginning of an episode of care. For patients who developed CDAD, data were collected from hospital admission up to the date of diagnosis of CDAD. We excluded colonoscopies during which a diagnosis of CDAD was made, because these procedures clearly did not antedate acquisition of *C. difficile*.

A patient was considered to have developed CDAD if (1) diarrhea developed during the episode of care or within 60 days after last discharge, and (2) either a stool specimen was found to have *C. difficile* toxin by the cytotoxicity assay, and/or colonoscopy revealed changes typical of pseudomembranous colitis, and/or histopathology supported that diagnosis [4]. Centre Hospitalier Universitaire de Sherbrooke is the only hospital in our region that performs *C. difficile* toxin assays (smaller hospitals forward their samples to our laboratory), so our measure of the outcome must have been fairly accurate. The probability of developing CDAD was measured using Kaplan-Meier analyses, in which day 0 corresponded to the date of first hospital admission for an episode of care, and data were censored when the patient died or 60 days after the date of the last hospital discharge within that episode of care, whichever came first. Crude and adjusted hazard ratios (AHRs) were measured using Cox regression. Variables significantly associated with CDAD in univariate analyses were then tested in Cox multivariate models, which were built up sequentially, starting with the variable most strongly associated with CDAD and continuing until no other variable reached significance or altered the AHR of variables already in the model. When the final model was reached, each variable was dropped in turn to assess its effect, different models being compared with the likelihood ratio test. We kept in the final model variables that were significant at the $P = .05$ level. Interactions were sought between variables other than antibiotics. The proportional hazards assumption was verified by comparing the Kaplan-Meier curve to the Cox predicted curve for a given variable, and by assessing the parallel nature of curves in log-log plots.

RESULTS

We obtained data on 7421 episodes of care corresponding to 5619 individuals; 4181 patients contributed to 1 episode of care, 1119 contributed to 2 episodes of care, 281 contributed to 3 episodes of care, and 38 patients contributed to $\geq$4 episodes of care. Of these 7421 episodes of care, 5091 corresponded to a single hospital admission, 1620 to 2 hospital admissions, and 710 to $\geq$3 hospital admissions. All analyses consider episodes

of care as the unit of analysis. As shown in table 1, almost two-thirds of patients were aged ⩾65 years, and only one-fifth of them had no comorbidity present. The most prevalent comorbidities were coronary heart disease (37.5% of patients), chronic lung disease (27.3%), peripheral vascular disease (24.8%), diabetes mellitus (23.7%), and cancer (17.9%). Antibiotics, PPIs, and laxatives were administered to 46.2%, 42.2%, and 41.1% of patients, respectively, while they were in the hospital. The most commonly used antibiotics were fluoroquinolones and cephalosporins.

A total of 293 incident cases of CDAD occurred (148 [50.5%] in individuals aged ⩾80 years, and 186 [63.5%] among patients who had received fluoroquinolones). Sixty-four patients with CDAD (21.8%) died within 30 days after diagnosis. Table 2 shows the factors associated with CDAD in univariate analyses. Older age, a high Charlson score, and a longer duration of hospitalization were strongly associated with CDAD. Among antibiotics, those with the highest univariate hazard ratios were fluoroquinolones and third-generation cephalosporins. Administration of PPIs, H_2-blockers, laxatives, nonsteroidal anti-inflammatory drugs, and corticosteroids was associated with CDAD, but less strongly so. Antacids and antimotility drugs were not associated with CDAD (data not shown). Many of these variables were confounded by each other, and the results of the multivariate Cox regression are also shown in table 2. The independent risk factors for CDAD were age, duration of hospitalization, a previous episode of CDAD independent of the current one, and having received fluoroquinolones, cephalosporins, macrolides, clindamycin, or intravenous β-lactam/β-lactamase inhibitors. The adjusted hazard ratios were very similar for first-, second-, and third-generation cephalosporins. The Charlson score was strongly confounded by age and duration of hospital stay and was no longer significant after adjustment. The use of PPIs, laxatives, H_2 blockers, and tube feeding; having undergone surgery or endoscopy; and having received intensive care were confounded by the same factors and were not significantly associated with CDAD in multivariate analysis. No interaction was found between age, Charlson score, and duration of hospital stay.

To examine whether the risk of inducing CDAD was modulated by duration of antibiotic therapy, we compared (for those antibiotics independently associated with CDAD) the AHRs according to whether the drugs were given for 1–3 days, 4–6 days, or ⩾7 days, adjusting for the other independent correlates of CDAD (table 3). Although the 95% CIs often overlapped, it can be seen that for quinolones, first-generation cephalosporins, cefuroxime, clindamycin, and macrolides, a longer duration of use tended to enhance the risk of CDAD, whereas for cefoxitin, the risk was paradoxically higher when used as a single dose for perioperative prophylaxis.

Table 1. Baseline characteristics of participants in 7421 episodes of care of *Clostridium difficile*–associated diarrhea (CDAD).

Characteristic	Value
Sex	
Male	3451 (46.5)
Female	3970 (53.5)
Age, years	
18–64	2667 (35.9)
65–79	2457 (33.1)
⩾80	2297 (31.0)
Median years	72
Charlson comorbidity index	
0	1573 (21.2)
1–3	3426 (46.2)
4–6	1761 (23.7)
⩾7	661 (8.9)
Level of care	
Intensive care unit stay	1579 (21.3)
Surgery	1473 (19.8)
Oesophagogastroduodenoscopy	565 (7.7)
Colonoscopy prior to CDAD	474 (6.3)
Drugs received	
Any antibiotic	3432 (46.2)
Fluoroquinolones	1708 (23.0)
Second-generation cephalosporins	1001 (13.5)
First-generation cephalosporins	661 (8.9)
Narrow-spectrum penicillins	587 (7.9)
Third-generation cephalosporins	581 (7.8)
Metronidazole	535 (7.2)
Macrolides	376 (5.1)
Intravenous β-lactam/β-lactamase inhibitors	355 (4.8)
Aminoglycosides	278 (3.7)
Intravenous vancomycin	217 (2.9)
Trimethoprim-sulfamethoxazole	199 (2.7)
Amoxicillin–clavulanic acid	147 (2.0)
Clindamycin	147 (2.0)
Carbapenems	61 (0.8)
Nonsteroidal anti-inflammatory drugs	4088 (55.1)
Proton pump inhibitors	3134 (42.2)
Laxatives	3050 (41.1)
Corticosteroids	1389 (18.7)
H_2 blockers	1199 (16.2)
Antacids	756 (10.2)
Antimotility drugs	644 (8.7)
Immunosuppressive drugs	288 (3.9)
Enteral feeding	237 (3.2)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

To further characterize the risk associated with fluoroquinolones, we measured the drug-specific AHRs, which tended to be lower among the 368 patients given levofloxacin (AHR, 2.52; 95% CI, 1.68–3.79) than among the 1153 patients given ciprofloxacin (AHR, 3.74; 95% CI, 2.81–4.97) or in the 127 pa-

Table 2. Crude and adjusted hazard ratios for development of *Clostridium difficile*–associated diarrhea (CDAD), according to demographic, clinical, and pharmaceutical characteristics during 7421 episodes of care.

Characteristic	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Age, per additional year	1.04 (1.03–1.05)	1.04 (1.03–1.05)[a]
Duration of stay in hospital (all admissions during that episode of care), days		
1–3	1.00	1.00
4–7	7.41 (3.39–16.19)[a]	4.69 (2.14–10.28)[a]
8–14	11.24 (5.18–24.39)[a]	5.11 (2.34–11.18)[a]
⩾15	14.20 (6.63–30.44)[a]	3.35 (1.53–7.34)[b]
Charlson comorbidity index		
0	1.0	1.0
1–3	2.35 (1.49–3.70)[a]	0.91 (0.56–1.45)
4–6	4.09 (2.58–6.49)[a]	1.11 (0.68–1.80)
⩾7	5.25 (3.18–8.68)[a]	1.56 (0.92–2.64)
Past history of CDAD[c]	3.22 (1.97–5.25)[a]	2.04 (1.24–3.34)[b]
Antibiotic received		
Quinolones	5.43 (4.28–6.90)[a]	3.44 (2.65–4.47)[a]
Cephalosporins		
First-generation	1.76 (1.29–2.39)[a]	1.78 (1.28–2.46)[b]
Second-generation	3.20 (2.51–4.07)[a]	1.89 (1.45–2.46)[a]
Third-generation	4.02 (3.08–5.24)[a]	1.56 (1.15–2.12)[b]
Macrolides	2.97 (2.12–4.16)[a]	1.65 (1.15–2.39)[b]
Clindamycin	2.70 (1.65–4.41)[a]	1.77 (1.06–2.96)[b]
Intravenous β-lactam/β-lactamase inhibitors	3.75 (2.75–5.10)[a]	1.88 (1.35–2.63)[b]
Amoxicillin–clavulanic acid	1.76 (0.99–3.14)	0.91 (0.50–1.66)
Carbapenems	3.90 (2.07–7.36)[a]	1.52 (0.79–2.94)
Narrow-spectrum penicillins	2.32 (1.73–3.13)[a]	1.37 (1.00–1.86)
Aminoglycosides	1.74 (1.11–2.71)[b]	1.34 (0.84–2.14)
Trimethoprim-sulfamethoxazole	1.52 (0.89–2.61)	0.88 (0.51–1.53)
Metronidazole	2.07 (1.50–2.85)[a]	1.12 (0.79–1.59)
Intravenous vancomycin	2.27 (1.46–3.52)[a]	1.10 (0.70–1.75)
Other drugs received while in the hospital		
Proton pump inhibitors	1.67 (1.32–2.10)[a]	1.00 (0.79–1.28)
H_2 blocker	1.53 (1.17–2.01)[a]	1.07 (0.80–1.43)
Laxatives	1.91 (1.51–2.42)[a]	1.11 (0.86–1.42)
Nonsteroidal anti-inflammatory drugs	1.32 (1.04–1.67)[b]	0.93 (0.73–1.19)
Corticosteroids	1.90 (1.48–2.44)[a]	1.16 (0.89–1.52)
Procedures and level of care		
Intensive care unit stay	2.02 (1.59–2.56)[a]	1.20 (0.92–1.57)
Surgery	1.33 (1.02–1.72)[b]	1.21 (0.89–1.63)
Tube feeding	2.59 (1.73–3.89)[a]	1.32 (0.85–2.06)
Oesophagogastroduodenoscopy	1.35 (0.94–1.95)	1.22 (0.84–1.77)
Colonoscopy prior to CDAD diagnosis	1.22 (0.81–1.86)	1.37 (0.90–2.10)

[a] $P < .001$.
[b] $P < .05$.
[c] That is, an episode of CDAD occurred at least 3 months prior to the episode of care.

tients given both drugs (AHR, 4.55; 95% CI, 2.90–7.14). Among the small number of patients who received newer respiratory fluoroquinolones, the risk seemed higher in those who received gatifloxacin (AHR, 6.10; 95% CI, 2.22–16.74; $n = 22$) than in those given moxifloxacin (AHR, 2.04; 95% CI, 0.50–8.31; $n = 27$). Among patients who received ciprofloxacin, those who were given metronidazole concomitantly were less at risk (AHR, 2.21; 95% CI, 1.33–3.65; $n = 370$) than were those who were not (AHR, 3.71; 95% CI, 2.70–5.11; $n = 707$).

The risk of CDAD tended to be higher for ticarcillin/clavulanic acid (AHR, 2.62; 95% CI; 1.51–4.56; $n = 96$) than for piperacillin/tazobactam (AHR, 1.83; 95% CI, 1.24–2.72; $n = 220$); for cefoxitin (AHR, 3.32; 95% CI, 2.06–5.35; $n = 218$) than for cefuroxime and oral second-generation cephalosporins

Table 3. Adjusted hazard ratios of developing *Clostridium difficile*–associated diarrhea (CDAD), according to the duration of use of each class of antibiotics.

Antibiotic class	Adjusted hazards ratio (95% CI),[a] by duration of therapy		
	1–3 days	4–6 days	⩾7 days
Fluoroquinolones	2.42 (1.62–3.62)	2.99 (2.06–4.35)	4.33 (3.21–5.84)
First-generation cephalosporins	1.07 (0.66–1.75)	2.61 (1.28–5.31)	3.14 (1.98–4.98)
Cefuroxime and oral second-generation cephalosporins	1.20 (0.73–1.98)	1.80 (1.17–2.76)	1.80 (1.20–2.69)
Cefoxitin	3.41 (2.07–5.60)	2.58 (0.36–18.63)	2.14 (0.29–15.54)
Third-generation cephalosporins	1.41 (0.94–2.10)	1.53 (0.93–2.53)	1.75 (1.08–2.83)
Macrolides	1.38 (0.80–2.40)	1.62 (0.88–2.97)	2.09 (1.12–3.90)
Clindamycin	1.15 (0.47–2.83)	2.35 (0.86–6.43)	2.38 (1.15–4.93)
Intravenous β-lactam/β-lactamase inhibitors	1.75 (0.96–3.18)	1.98 (1.13–3.50)	1.82 (1.15–2.88)

[a] Adjusted for the independent correlates of CDAD shown in table 2.

(AHR, 1.65; 95% CI, 1.24–2.21; $n = 768$); and for clarithromycin (AHR, 2.51; 95% CI, 1.28–4.93; $n = 91$) than for azithromycin (AHR, 1.43; 95% CI, 0.90–2.28; $n = 215$) or erythromycin (AHR, 1.71; 95% CI, 0.54–5.36; $n = 40$).

DISCUSSION

Among patients who receive antibiotics, several risk factors have been identified as potentially enhancing the risk of developing CDAD: advanced age, comorbidities, duration of hospitalization, stay in intensive care units, administration of antiulcer medications, use of laxatives, tube feeding, a poor immune response to toxin A, surgery, and nonsurgical gastrointestinal procedures [9–21]. Most of these risk factors are related to each other. Unfortunately, many previous studies with a limited sample size investigated a single risk factor without adjusting for confounders. Others used the case-control approach, which is prone to biases associated with the selection of control subjects [18, 19, 21]. Prior cohort studies that did not take survival into consideration had a biased estimate of the effect of variables themselves associated with death (such as age). They included <400 patients and <40 outcomes [12, 14–16]. Our study, conducted during an epidemic of nosocomial CDAD, included nearly 300 outcomes and had sufficient statistical power to adjust for numerous risk factors.

Duration of hospitalization, a strong risk factor for CDAD, must be viewed as a proxy for exposure to *C. difficile* spores in the hospital environment. Age was also a strong risk factor, but the presence of comorbidities (summarized by the Charlson score) was confounded by the former two (older, sicker patients were hospitalized for longer periods of time than were younger ones), with AHRs approaching the null value. Prior studies that identified comorbidities as a risk factor for CDAD did not adjust for both age and duration of hospital stay [10, 12, 15, 21]. Given the senescence of immunity [22], it seems plausible that older individuals develop a less effective immune response against *C. difficile* toxins than do younger patients, but this remains to be confirmed [10, 11, 23]. Similarly, the finding that a prior episode of CDAD >3 months before the beginning of an episode of care was a risk factor for a new, independent episode may indicate that some individuals are intrinsically more at risk, perhaps because of a suboptimal immune response.

Several risk factors identified in prior studies were found to be unrelated to CDAD after adjustment for confounders. Use of PPIs was more common among older patients and among patients who were hospitalized for long periods of time and was not associated with CDAD in multivariate analysis. Previous reports implicating PPIs had little opportunity to adjust for confounders [6, 7]. Inpatients are exposed to *C. difficile* vegetative forms and spores, and we speculate that gastric acidity and its iatrogenic suppression have little impact on the natural course of infection with spores. Use of laxatives was also not associated with CDAD in multivariate analysis. Thus, a reduction in the use of PPIs and laxatives, although perhaps advisable for other reasons, would not be expected to impact on the incidence of CDAD.

Fluoroquinolones were the class of antimicrobials most prone to induce CDAD. This represents a major change in the epidemiology of hospital-acquired CDAD, which is historically associated with use of cephalosporins and clindamycin [9, 13, 24–28]. Almost one-fourth of inpatients received fluoroquinolones, and it can be calculated that their population-attributable fraction of CDAD was 35.9%. This finding goes a long way in explaining the explosive spread of *C. difficile* in Quebec hospitals in 2003–2004: the introduction of a novel strain—which, at the same time, caused more-severe diarrhea (and enhanced transmission by incontinent patients) and was highly resistant to quinolones—in an environment of massive use of fluoroquinolones among elderly patients must have created a vicious circle further compounded by frequent postmetronidazole relapses. Several other classes of antimicrobials (all 3 generations of cephalosporins, macrolides, clindamycin, and β-

lactam/β-lactamase inhibitors) were independently associated with CDAD with lower (and very similar) AHRs, constituting an intermediate-risk category. Their population-attributable fraction varied according to frequency of use from 10.7% for second-generation cephalosporins to as little as 1.5% for clindamycin. These findings differ somewhat from those of our previous study [4], in which the risk associated with various classes of antimicrobials was assessed by a different method (number of patients who had received a given antibiotic divided by number of patient-days of use), which corresponded to a univariate analysis, with no adjustment for major confounders, such as age, duration of hospital stay, or the administration of other antibiotics.

Traditional infection-control measures have limited efficacy in reducing nosocomial transmission of *C. difficile,* the spores of which can survive for months in the hospital environment [19, 29]. Shortening the duration of hospitalization (by facilitating the transition from hospital care to home-based care in elderly patients) would reduce exposure, but this might have little impact, because the risk of CDAD did not increase linearly with longer durations of hospitalization, perhaps because a selection process occurs. Ultimately, control of nosocomial CDAD depends primarily on more judicious use of antimicrobial agents: sparing use of fluoroquinolones, substitution of intermediate-risk antibiotics with aminoglycosides when feasible (for instance in patients with intra-abdominal infections or pyelonephritis who have a normal renal function), and administration of trimethoprim-sulfamethoxazole to patients with urinary tract infections caused by a susceptible pathogen. For patients with community-acquired pneumonia requiring hospital admission, the risk of CDAD associated with a combination of ceftriaxone and azithromycin (the product of their AHRs is 2.57) is identical to that of levofloxacin (AHR, 2.52); the risk could be reduced by obtaining appropriate specimens and rapidly narrowing the spectrum, rather than relying on syndromic management. Duration of antimicrobial therapy is based more on tradition than evidence. For the first time, we were able to document that, for some antibiotics, the risk of CDAD was influenced by duration of use. Shorter courses of antibiotic therapy should be considered—for instance, for patients with pneumonia or intra-abdominal infections [30, 31].

A limitation of our study is that its findings are relevant mostly to hospitals where this novel, hypervirulent, quinolone-resistant strain of *C. difficile* has emerged. However, this strain has been found in at least 6 US states [32], and a recent report from Pittsburgh, Pennsylvania, described a large outbreak of CDAD related mostly to fluoroquinolones (with an etiologic fraction similar to ours), and a high proportion of patients needed a colectomy [33]. Other reports from the United States and Canada linking use of fluoroquinolones with CDAD [21, 34–38] and from Europe, where resistance to moxifloxacin has emerged [39, 40], suggest that, although not necessarily caused by the same strain, fluoroquinolone-induced CDAD is widespread.

In conclusion, fluoroquinolones were the most important risk factor for CDAD during a large epidemic caused by a hypervirulent strain of *C. difficile.* Control of CDAD requires a reduction in the use of fluoroquinolones and of intermediate-risk antibiotics and shorter durations of therapy for common infections. Fluoroquinolones have become the most widely prescribed class of antibacterials in the United States [41]. Future guidelines for the use of antimicrobial agents need to take into consideration the risk of inducing CDAD.

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