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Major Article

Antibiotic exposure and risk of community-associated *Clostridium difficile* infection: A self-controlled case series analysis

Giulio DiDiodato, MD, PhD [a], Lauren Fruchter, MD [b]

[a] *Department of Pharmacy, Royal Victoria Regional Health Centre, Barrie, Ontario, Canada*
[b] *Family Medicine Teaching Unit, Royal Victoria Regional Health Centre, Barrie, Ontario, Canada*

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Background: Community-associated *Clostridium difficile* infection is inconsistently associated with antibiotic exposure. This study uses a self-controlled case series (SCCS) design to estimate antibiotic exposure effect sizes and compare them with those estimated from previous case-control studies.

Methods: We estimated the association between antibiotic exposure and community-associated *Clostridium difficile* infection among 139,000 patients registered to the Barrie Family Health Team from January 1, 2011, to May 1, 2017, using an SCCS design. Poisson regression analysis was used to estimate the incidence rate ratio (IRR) between antibiotic exposure versus nonexposure periods within individuals. Antibiotic exposure was categorized as either high risk (fluoroquinolone, clindamycin, or cephalosporin) or low risk (all other antibiotic classes).

Results: The final analysis included 189 cases. The pooled IRR for high-risk antibiotics was 2.26 (95% confidence interval [CI] 1.29, 3.98) and 2.03 (95% CI 1.19, 3.47) for lower-risk antibiotics. There was no difference between high-risk and lower-risk antibiotics (IRR 1.11, 95% CI 0.53, 2.36).

Interpretation: The IRRs were smaller than the odds ratios reported in previous case-control studies, suggesting a less biased estimate because SCCS designs control for time-invariant confounders. Compared with case-control studies, SCCS designs are underused in infection prevention and control studies.

Clostridium difficile is an anaerobic bacterium that has been associated with mild to life-threatening diseases of the intestine.[1] The most consistently reported risk factors are age over 65 years, prolonged hospitalization, and recent antibiotic exposure.[2] Research has suggested that these risk factors disrupt the intestinal flora and predispose patients to opportunistic infections with *C difficile*.[1] The estimated incidence of community-associated *C difficile* infection (CA-CDI) ranges from 10.0 to 60.5 cases per 100,000 populations, accounting for 25% to 35% of all *C difficile* cases.[3,4] Unlike hospital-associated CDI (HA-CDI), antibiotic exposure is not as consistently associated with CA-CDI with up to 50% of cases reporting no exposure in the 3-month period preceding the diagnosis.[5,6]

Two recent meta-analyses estimated odds ratios (ORs) for the association between antibiotic exposure and CA-CDI.[7,8] The pooled ORs were 3.55 (95% confidence interval [CI] 2.56, 4.94) and 6.91 (95% CI 4.17, 11.44). The antibiotics with the strongest association were fluoroquinolones (ORs 5.50 and 5.65), clindamycin (ORs 16.8 and 20.43), and cephalosporins (ORs 5.68 and 4.47). These ORs are several-fold larger than the corresponding ORs for HA-CDI. For example, the OR for clindamycin use and risk of HA-CDI was estimated to be 2.31 (95% CI 1.84, 2.91), or 15% of the effect seen for CA-CDI.[9] This discrepancy is a consistent finding across all antibiotic classes, with ORs for CA-CDI far exceeding those for HA-CDI, suggesting confounding bias may be inflating the association between antibiotic exposure and CA-CDI.

Case-control studies have been used to estimate these ORs. Like all observational studies, case-control studies cannot account for unobserved confounders resulting in significant bias in OR estimates. SCCS designs represent "an alternative epidemiologic study design" that can be used "to investigate an association between a transient exposure and an outcome event."[10] Unlike case-control studies, SCCS designs can account for unobserved, time-invariant confounders because each individual acts as their own control. By dividing each case's observation period into exposure-risk and nonexposure-risk periods, an incidence rate ratio (IRR) can be estimated. The advantages of SCCS over case-control designs include the elimination of the need for separate matched controls, that time-invariant confounders

Address correspondence to Giulio DiDiodato MD, PhD, Department of Pharmacy, Royal Victoria Regional Health Centre, 201 Georgian Dr, Barrie, Ontario, Canada, L4M 6M2.
E-mail address: didiodatog@rvh.on.ca (G. DiDiodato).
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are automatically accounted for in the design, that time-varying confounders can be included in the model, that multiple exposure periods within the same individual can be included, and that there is no requirement that the exposure must precede the outcome, only that the observation includes both the exposure and outcome.[10] The primary objective of this study was to estimate the strength of association between antibiotic exposure and CA-CDI and compare this with ORs estimated from case-control studies.

METHODS

Study setting and population

The Barrie and Community Family Health Team (BCFHT) is the largest integrated community-based primary practice in Ontario, Canada's most populous province. The BCFHT consists of 86 physician practices with more than 139,000 registered patients. The BCFHT serves the city of Barrie with a population of 146,000. The Royal Victoria Regional Health Centre is the only hospital in Barrie. From January 1, 2011, to May 1, 2017, all adults over 18 years old registered with the BCFHT who were diagnosed with CA-CDI and exposed to any antibiotic therapy were eligible for inclusion. An incident case of CA-CDI was defined by a positive stool culture or any diagnostic test for *C difficile* in the community or within 3 days of admission to a health care facility, with no previous history of an overnight stay in any health care facility in the preceding 12 weeks, and with no previous CDI in the preceding 8 weeks.[4] Antibiotic exposure was defined as any antibiotic prescription ≥1 dose that was documented in the patient's electronic medical record.

Since 2011, the BCFHT has used the Accuro electronic medical record system (QHR Technologies Incorporated, Toronto, Ontario) for all registered patients. For identification of adult patients with an incident case of CA-CDI and antibiotic exposure, the system administrator queried the database. CA-CDI cases were identified using the public health laboratory reports directly inputted into the electronic medical record. All stool testing for *C difficile* infection is done by the public health laboratory. Health care exposure in the 12 weeks preceding the diagnosis of CA-CDI was available through a link between the BCFHT and Royal Victoria Regional Health Centre databases. Research ethics approval was obtained from the institutional review boards of both the Royal Victoria Regional Health Centre and the BFCHT.

Study design and outcomes

This was a retrospective, observational study using the SCCS design. The SCCS design divided each CA-CDI case's observation period into antibiotic-exposure and nonexposure periods (Fig 1).

The start of each CA-CDI case's observation period was defined as January 1, 2011, if the patient was registered before this date and was also ≥12 weeks after any health care–related exposure and ≥8 weeks after a previous case of *C difficile* infection and ≥ 62 days after any antibiotic prescription. For those patients registered at a later date, this date was defined as the start date as long as all the other aforementioned conditions were met. The observation period end date was defined as the day of the last recorded BCFHT clinic visit regardless of the reason (eg, death vs moving out of the BCFHT catchment area) and ≥122 days after the last antibiotic prescription to ensure that the entire exposure period was accounted for in the analysis. The antibiotic exposure period was defined as starting 2 days after an antibiotic was prescribed and continued until 62 days after that prescription. This interval was chosen because it represents the highest risk period for CDI after antibiotic exposure and was consistently included in previous case-control studies.[7,8] In addition, to account for unobserved time-varying confounders, the observation period was further divided into yearly intervals (Fig 1). The final number of intervals (n) and interval lengths for each CA-CDI case (j) were unique and dependent on the duration of the observation period (k), the number of antibiotic prescriptions, and the yearly intervals (Fig 1).

Antibiotic exposure was categorized a priori as "high risk," "low risk," and no exposure (i) (3 categories: high risk = 2; low risk = 1; no exposure = 0). Specifically, "high-risk" antibiotic exposure included any prescriptions for fluoroquinolones (moxifloxacin, levofloxacin, or ciprofloxacin), clindamycin, or cephalosporins (cephalexin, cefprozil, or cefuroxime). These antibiotics were categorized as "high-risk" from their estimated effect size ORs from the 2 previous meta-analyses.[7,8] They were combined into a single "high-risk" exposure category on the assumption that their effect sizes overlapped given their estimated 95% CIs.[7,8] The same rationale was used to create the "low-risk" exposure category. If there were overlapping intervals due to multiple antibiotic exposures, the intervals were categorized as the higher-risk antibiotic exposure. For example, if a patient had received a low-risk antibiotic, but 32 days after this prescription they were prescribed another course of antibiotics with a high-risk agent, then

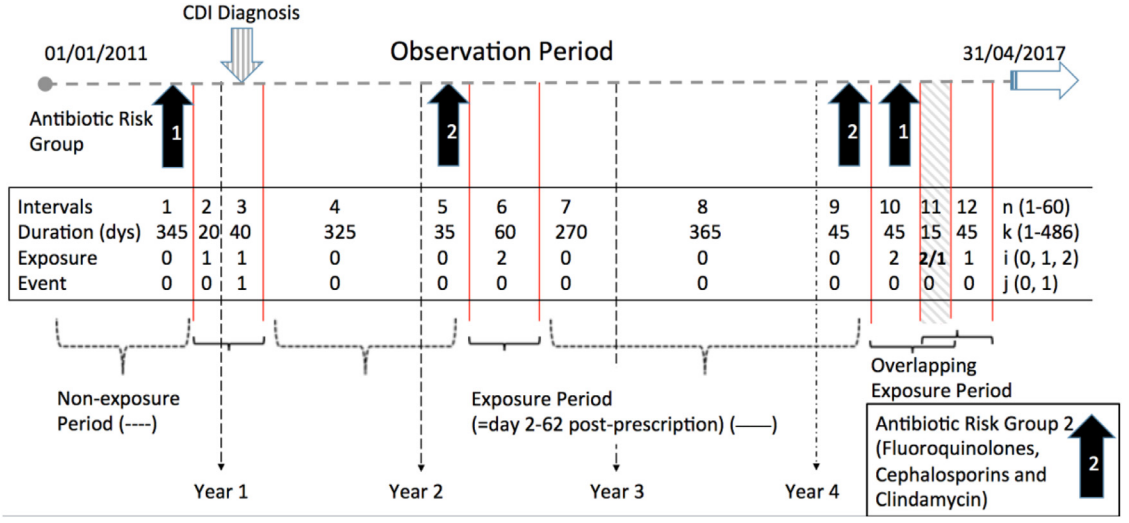

Fig 1. Schematic of observation period for a hypothetical community-associated *Clostridium difficile* infection (CA-CDI) case (see main text for a detailed explanation of the design). *i*, antibiotic exposure (0, nonatibiotic; 1, low-risk antibiotic; 2, high-risk antibiotic); *j*, case of CA-CDI (0, negative; 1, positive); *k*, duration of each interval; *N*, interval number. (See Supplemental Table for description of antibiotic risk groups).

the last 30 days of the first low-risk antibiotic exposure interval were categorized as a high-risk exposure interval (Fig 1).

Proton pump inhibitor (PPI) use was included as a covariate in the final model, along with its interaction with antibiotic exposure to detect evidence for effect modification of the association between antibiotics and CA-CDI. Patients prescribed any PPI (omeprazole, esomeprazole, lansoprazole, rabeprazole, or pantoprazole) at any time during the observation period were categorized as having been exposed to PPIs.

Statistical analysis

Conditional Poisson regression analysis was used to estimate the overall IRR for the risk of CA-CDI after exposure to antibiotics.[10] The overall IRR is a ratio of the incidence rate of CA-CDI in the exposure period compared with the incidence rate of CA-CDI in the nonexposure period. The SCCS design permits multiple exposure periods and incident CA-CDI cases to be included in the final model. An IRR > 1 implies an increased risk of CA-CDI after antibiotic exposure, an IRR < 1 implies a reduced risk of CA-CDI after antibiotic exposure, and an IRR = 1 implies no difference in risk of CD-CDI after antibiotic exposure. In addition, the laboratory tests used for the diagnosis of *C difficile* infection have changed over the years of the study from those based on enzyme-linked immunosorbent assays to DNA-based assays.[11] The DNA-based tests are more sensitive than their predecessors and have been demonstrated to increase the detection of *C difficile* toxin by up to 2-fold.[12] The year variable was included in the final model to account for possible confounding bias due to this temporal change in laboratory tests and to account for changes in the age of patients. In addition to estimating the IRR, the attributable proportion of CA-CDI due to antibiotic exposure was estimated by using the following formula = [(IRR − 1)/IRR]* 100%, along with 95% CIs. Sample size needed to demonstrate an IRR 2 with 90% power and type 1 error rate of $\alpha = 0.025$ was calculated as 172 CA-CDI cases, for a ratio of exposure to nonexposure risk period durations of 0.1.[13] To test the SCCS independence assumption between outcome and subsequent exposure, we will estimate the marginal difference in the mean interval lengths (days) between CD-CDI−antibiotic exposures versus antibiotic-antibiotic exposures using nonparametric regression analysis using the *npregress* command in STATA 15.0. The standard error will be estimated using resampling and adjusted for clustering within individuals. STATA/MP 15.0 (Statacorp LLC, Austin, Texas) for Mac (64-bit Intel) was used for all statistical analyses.

RESULTS

There were 189 CA-CDI cases included in the final analysis (Fig 2). The average age was 57.5 years (standard deviation [SD] 18.0), with females accounting for 75% of cases. The number of antibiotic prescriptions ranged from 1 to 13 per individual, with an average of 2.7 (SD 2.1) (Supplemental Table). The intervals between antibiotic courses ranged from 1 to 2,162 days, with a median of 249 days (interquartile range [IQR] 113-492). The number of intervals per patient's observation period ranged from 1 to 60. These interval durations ranged from 1 to 486 days, with a median of 60 days (IQR 34-338). The total duration of all the observation periods was 415,338 days, with 10.2% of the days apportioned to exposure periods. Approximately 25% of patients were prescribed a PPI. The IRR for high-risk versus low-risk antibiotic exposure was estimated to be 1.11 (95% CI 0.53, 2.36) (Table 1).

There was no evidence for any effect of PPI use on increased risk of CA-CDI in any antibiotic risk category. The attributable proportion of CA-CDI due to antibiotic exposure exceeded 50% (Table 2) for both antibiotic classes.

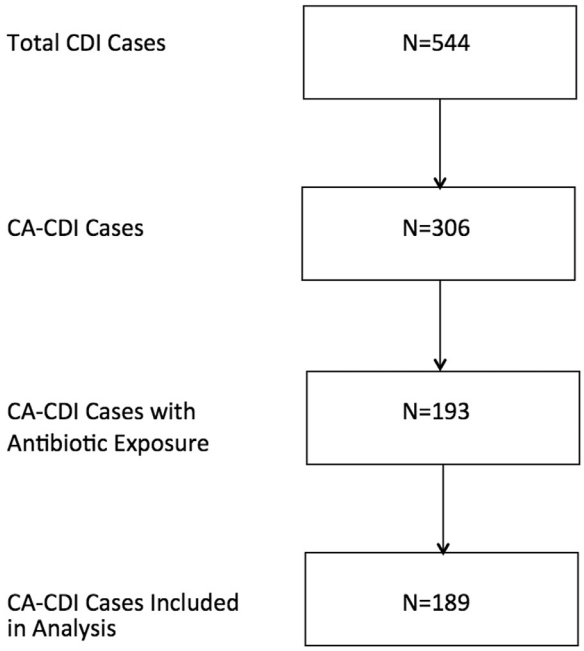

Fig 2. Flow diagram for cases of community-associated *Clostridium difficile* infection (CA-CDI).

Table 1
CA-CDI IRR estimates for high- and low-risk antibiotic exposures

Antibiotic exposure group	IRR	95% CI	*P* value
0	Baseline	N/A	N/A
1	2.03	1.19, 3.47	.009
2	2.26	1.29, 3.98	.005

CA-CDI, community-associated *Clostridium difficile* infection; *CI*, confidence interval; IRR, incidence rate ratio; *N/A*, not applicable.

Table 2
The attributable proportion of community-associated *Clostridium difficile* infection due to antibiotic exposure (using irr estimates and 95% confidence intervals (CIs) from Table 1)

Antibiotic exposure group	Attributable proportion (%)	95% CI
0	Baseline	Not applicable
1	50.7	16.0, 71.2
2	55.7	22.5, 74.9

In a sensitivity analysis using an exposure risk interval of 120 days (starting 2 days after prescription and continuing until 122 days after prescription) to account for both prolonged courses of antibiotic use or prolonged periods of risk, the results remained relatively unchanged, with a nonstatistically significant trend to lower IRRs for each antibiotic risk category (Table 3). The overall mean interval

Table 3
CA-CDI IRR estimates using an exposure risk interval of 120 days (instead of 60 days) after antibiotic prescription

Antibiotic exposure	IRR	95% CI	*P* value
0	Baseline	N/A	N/A
1	1.61	1.00, 2.57	.048
2	2.12	1.32, 3.41	.002

CA-CDI, community-associated *Clostridium difficile* infection; *CI*, confidence interval; *IRR*, incidence rate ratio; *N/A*, not applicable..

between outcome-exposure and exposure-exposure was approximately 156 days (95% CI 143, 170). The marginal difference between the mean interval lengths between CA-CDI–antibiotic exposures and antibiotic-antibiotic exposures was estimated at approximately 5 days (95% CI 3, 8) longer in the CA-CDI–antibiotic exposure group.

INTERPRETATION

Compared with the ORs from the previous case-control studies, the IRRs estimated using the SCCS design were significantly different and suggested a much weaker association between antibiotic exposure and CA-CDI. Unlike the results from previous case-control studies, the IRRs for high-risk and low-risk antibiotic exposures estimated by the SCCS design did not demonstrate any statistically significant differences, with both groups increasing the overall risk of CA-CDI by approximately 2-fold. This may represent an important finding that may help inform antimicrobial stewardship efforts in primary care practices, suggesting that there may be no such a thing as a "safer" antibiotic class for minimizing the risk of CA-CDI. This might help "nudge" physicians to be more prudent in prescribing antibiotics to patients with minimal symptoms because they may feel less reassured by the notion that there is a "safer" antibiotic alternative. More prudent prescribing may also lead to a reduction of 50% of CA-CDI cases in the population according to our results.

These IRRs are much more consistent with previous ORs estimated for HA-CDI associated with antibiotic exposure. Many methodologic issues plague the results from the 2 meta-analyses. In these meta-analyses, 5 and 8 observational studies, respectively, were used to calculate a pooled OR to estimate the association between antibiotic exposure and CA-CDI.[7,8] All the individual studies were either case-control or nested case-control studies. The matching criteria varied significantly among studies but were limited to age, clinic site, date of diagnosis, comorbidities, and medications used for gastric acid suppression. The quality scores of the included studies ranged from 3 to 7 (out of a maximum score of 7). Significant heterogeneity of effect sizes ($I^2 = 90.6\%$ and $I^2 = 95\%$, respectively) was demonstrated between studies in both meta-analyses.[7,8] Even after stratifying the results by antibiotic class, overall effect heterogeneity was reduced by 55%, but this reduction varied across antibiotic classes. For example, effect heterogeneity remained high for clindamycin ($I^2 = 76\%$), cephalosporins ($I^2 = 97\%$), penicillins ($I^2 = 85\%$), and macrolides ($I^2 = 42\%$). For other antibiotic classes, effect heterogeneity was eliminated (fluoroquinolones, sulfonamides, and tetracyclines).

The advantage of the SCCS design over case-control studies includes improved efficiency owing to the elimination of the need for separate controls. SCCS designs are also able to control for all unobserved time-invariant confounders, while still being able to incorporate time-varying confounders in the model. This is especially important for the case of CA-CDI because there are many nontraditional risk factors that are hypothesized to contribute to an increased risk of disease, such as diet, exposure to infants younger than 2 years of age, and job occupation.[5]

This is an observational study, so we cannot be certain that any association demonstrated to exist between antibiotic exposure and CA-CDI is causal in nature. We are assuming that an antibiotic prescription implies medication compliance. SCCS designs assume that the outcome will not affect subsequent exposures. We examined this independence assumption by comparing the marginal difference in mean interval lengths (days) between CA-CDI–antibiotic exposures versus antibiotic-antibiotic exposures. While the mean interval lengths were longer in the CA-CDI–antibiotic exposures group compared with those in the antibiotic-antibiotic exposures group, the difference of 5 days is unlikely to be clinically significant given this represents less than 3% of the overall mean length of the intervals. However, we cannot be certain that the independence assumption has not been violated given these results. Because of its retrospective design, the potentially important confounder of exposure to household members who may have had or have ongoing health care exposure or who were diagnosed with *C difficile* infection will remain unobserved, potentially leading to unobserved confounder bias. We only had data on health care facility exposure for the Royal Victoria Regional Health Centre, so it could be possible that some of these cases had other health care–related exposures that we would not have detected.

In summary, we demonstrated that the association between antibiotic exposure and CA-CDI estimated from case-control studies may be upwardly biased and may be more consistently measured by using an SCCS design. The SCCS design is a relatively novel epidemiologic model that provides infection prevention and control practitioners the opportunity to test hypotheses using observational data in a more efficient and consistent manner than is currently available through case control studies. The SCCS design should be incorporated as a standard feature in the education curriculum for IPAC practitioners and epidemiologists.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ajic.2018.06.016.

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