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Clinical Research in Infectious Diseases

Review Article

Antibiotic Exposure and Risk of Community-Associated Clostridium difficile Infection in Adult Patients Registered with Ontario's Largest Family Medicine Health Team: A Study Protocol for a Self-Controlled Case Series Analysis

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Submitted: 25 January 2017

Accepted: 02 March 2017

Published: 05 March 2017

ISSN: 2379-0636

Keywords

- *Clostridium difficile*
- Gastrointestinal illness

Abstract

Rationale: CA-CDI is an infectious gastrointestinal illness whose incidence is estimated to be between 10 to 61 cases per 100 000 population, with up to 50% of cases requiring hospitalization due to the severity of the disease. While antibiotic exposure and age≥65 years are known risk factors for healthcare-associated *Clostridium difficile* infection (HA-CDI), the importance of antibiotic exposure in CA-CDI is less well defined. In addition, previous case-control studies have demonstrated a potential association between antibiotic exposure and subsequent risk of CA-CDI, they did not account for important time-invariant confounders because of the limitations of matching potentially leading to a biased estimate of the antibiotic-CA-CDI association.

INTRODUCTION

Background

Clostridium difficile is a toxin-producing, spore-forming bacterium that can cause mild to severe and life-threatening diseases of the intestine [1]. *Clostridium difficile* infection is the most common healthcare-associated infection, but recent epidemiologic studies have demonstrated a significant burden of disease even among patients with no obvious healthcare-related exposures [2,3]. These cases are referred to as community-associated *Clostridium difficile* infection [4]. Since 2009, the surveillance definition of CA-CDI has been a patient with diarrhea whose stool specimen tests positive for *Clostridium difficile* toxin or culture in the community or within 3 days after admission to hospital in the absence of either any overnight stay in any healthcare facility during the previous 12 weeks or a previous CDI diagnosis during the previous 8 weeks [3]. The estimated incidence of CA-CDI ranges from 10.0 to 60.5 cases per 100 000 population, accounting for 25% to 35% of all CDI cases [2,3]. Unlike HA-CDI, antibiotic exposure is not consistently associated with CA-CDI with up to 46% of CA-CDI cases reporting no antibiotic exposure in the 3-month period preceding the diagnosis [5,6].

In 2 recent meta-analyses, 5 and 8 observational studies, respectively, were used to calculate a pooled odds ratio (OR) to estimate the association between antibiotic exposure and CA-CDI [7,8]. All CA-CDI cases were diagnosed using either a positive stool assay for *Clostridium difficile* toxin or International Statistical Classification of Diseases and Related Health Problems (ICD-9 008.45) coding on hospital admission. The observation period started from 0 days (same day as antibiotic prescription) up to 2 days after antibiotic prescription, and continued for the following 30 days up to 180 days. All studies were retrospective and either case-control or nested case-control studies. The

number of CA-CDI cases ranged from as low as 40 to as high as 1,223, with the ratio of cases to controls ranging from 1:2 to 1:10. The matching criteria varied significantly between studies but were limited to age, clinic site, date of diagnosis, comorbidities, and/or medications used for gastric acid suppression. The quality scores ranged from 3 to 7 (out of a maximum score of 7). The study periods reported cases from 1994 to 2007. The pooled OR from each study was 3.55 (95% CI 2.56 to 4.94) and 6.91 (95% CI 4.17 to 11.44), respectively, with significant heterogeneity of effect sizes (I^2 = 90.6% and I^2 = 95%, respectively) demonstrated between studies in both meta-analyses. By 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 antibiotic classes with the strongest association with CA-CDI included fluoroquinolones (OR=5.50; 95% CI 4.26 to 7.11 and OR=5.65; 95% CI 4.38 to 7.28, respectively), clindamycin (OR=16.80; 95% CI 7.48 to 37.76 and OR=20.43; 95% CI 8.5 to 49.09, respectively), and cephalosporins (OR=5.68; 95% CI 2.12 to 15.23 and OR=4.47; 95% CI 1.60 to 12.50, respectively). Only tetracyclines did not demonstrate any association with CD-CDI, and the weakest positive association was seen with sulfonamides/trimethoprim (OR=1.81; 95% CI 1.34 to 2.43 and OR=1.84; 95% CI 1.48 to 2.29). Comparing these antibiotic class effect ORs for CA-CDI to their corresponding ORs for HA-CDI demonstrates significant differences between effect sizes. For example, for clindamycin exposure and subsequent incidence of HA-CDI, the estimated OR = 2.31 (95% CI 1.84 to 2.91) which is less than 15% of the effect size seen for CA-CDI [9]. This is a consistent finding among all the other antibiotic classes, with antibiotic class ORs for CA-CDI being significantly greater than for HA-CDI, suggesting confounding bias may be inflating the association between antibiotic exposure and CA-CDI.

The evidence for other risk factors in CA-CDI is equivocal and has been recently reviewed [5]. Unlike HA-CDI, CA-CDI cases appear to be younger in age and have fewer comorbid illnesses. The role of proton pump inhibitors (PPI), a class of broadly prescribed therapeutics used for gastric acid suppression, may be less important in CA-CDI compared to their weak but established association in HA-CDI [10]. Exposure to infants ≤ 2 years old, who are frequently asymptomatically colonized with *Clostridium difficile* and believed to be potential reservoirs in the community, has been associated with CA-CDI, especially in younger women without any other risk factors. Other potential risk factors include exposure to household pets colonized with *Clostridium difficile*, ingestion of retail meats that have been shown to be contaminated with *Clostridium difficile* spores, and contact with household members who have had healthcare-related exposures or previous *Clostridium difficile* infection. Apart from this last exposure, all the other potential risk factors are assumed to be time-invariant because they would tend to remain unchanged over the period of observation commonly used for case-control studies (Figure 1).

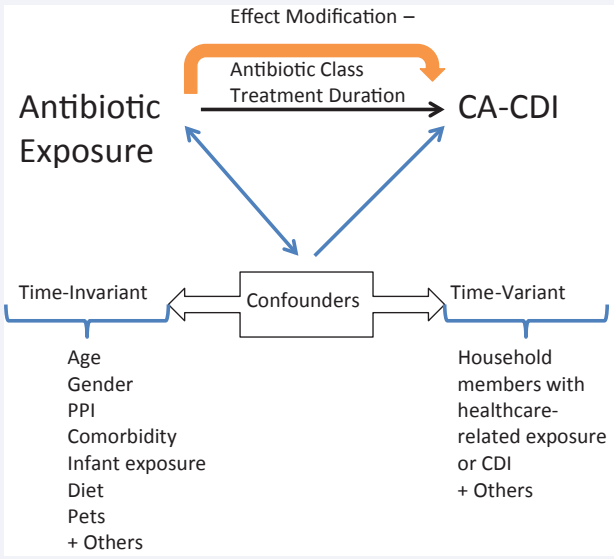

Figure 1 Antibiotic exposure and subsequent risk of CA-CDI accounting for potential confounders and effect modification.

RESEARCH QUESTION

For adult patients (≥18 years old) registered with the Barrie and Community Family Health Team who were diagnosed with community-associated *Clostridium difficile* infection and exposed to antibiotic therapy between January 1, 2011 and December 31, 2016, was the 60-day exposure-risk period after antibiotic prescription associated with an increased risk of *Clostridium difficile* infection compared to the remainder of the observation period for each case?

Relevance

Antibiotics, along with immunization, have transformed the public health by reducing premature deaths due to infectious diseases. Over 80% of all antibiotics prescribed for human illness occurs in outpatient settings, and it is estimated that up to 50% of these prescriptions are medically unnecessary and contribute to the emergence of antibiotic resistance. By demonstrating the potential harm associated with antibiotic exposure, this study may help nudge physician prescribing behaviour and result in improved antibiotic utilization, better patient outcomes, and reduction in the emergence of antibiotic resistance.

STUDY DESIGN

Target population

All adults (≥18 years old) diagnosed with an incident case of CA-CDI who have been exposed to antibiotics, where the inclusion criteria are defined as follows:

1) an incident case of CA-CDI is defined as any patient with diarrhea whose stool specimen tests positive for *Clostridium difficile* toxin or culture in the community or within 3 days after admission to hospital in the absence of either any overnight stay in any healthcare facility during the previous 12 weeks or a previous *Clostridium difficile* infection diagnosed during the previous 8 weeks, and

2) antibiotic exposure is defined as any antibiotic prescription ≥1 dose that is documented in a patient's medical record

Accessible population

All adults (≥18 years old) diagnosed with an incident case of CA-CDI who have been exposed to antibiotics, and

1) are registered patients with the Barrie and Community Family Health Team (BCFHT) in Barrie, Ontario, Canada, and

2) met the inclusion criteria between January 1, 2011 and December 31, 2016

The Barrie and Community Family Health Team is composed of 86 physician practices, six allied health clinics and four walk-in clinics. As of June 30, 2016, there were 139,670 registered BCFHT patients. Since 2011, the BCFHT has utilized the *Accuro*® electronic medical record system for all registered patients. For identification of adult patients with an incident case of CA-CDI and antibiotic exposure, the database will queried by the system administrator. In general, CA-CDI cases will be identified using the public health laboratory (PHL) reports directly inputted into the EMR since all stool testing for *Clostridium difficile* infection is done by the PHL. Healthcare-exposure in the 12 weeks preceding the diagnosis of CA-CDI will be available through a link between the BCFHT and Royal Victoria Hospital (RVH) databases. The RVH is a 399-bed acute care, large community hospital, and is the only hospital in Barrie, Ontario.

Model

This is a retrospective, analytical observational study using the self-controlled case series model. Self-controlled case series (SCCS) method represents "an alternative epidemiologic study design" that can be used "to investigate an association between a transient exposure and an outcome event" [11]. By dividing each case's observation period into exposure-risk and non-exposure-risk periods, a relative incidence rate ratio for outcome between exposed and non-exposed periods can be determinedwhile taking into account the effect of time-varying confounders.

The advantages of this design include the following:

1) no separate matched controls are needed for the cases because comparisons are made within individuals and not between individuals.

2) time-invariant confounders are automatically accounted for in the design because they cancel out of the final model.

3) time-variant confounders, such as season or year, can be included in the model through further division of the observation periods according to these potential confounders.

4) multiple exposure-risk periods of varying length can be included in the model.

5) all exposure periods occurring within the observation period are included in the model regardless of their temporal relationship to the outcome since patients are not censored at the time of the outcome event, potentially leading to a less biased exposure effect size.

The assumptions of the SCCS model include the following:

1) occurrence of any *Clostridium difficile* infection does not affect the probability of subsequent antibiotic exposure. This assumption will likely be violated since physicians' tendency to prescribe antibiotics after an episode of either HA-CDI or CD-CDI will be restrained. For this reason, apre-exposure period will be incorporated into the model to offset this potential source of bias.

2) after accounting for time-variant confounders, such as season, year of diagnosis, or effect modifiers, such as antibiotic class or treatment duration, event rates are assumed to be constant within each defined interval.

3) recurrent CA-CDI cases are independent. Only incident CA-CDI cases (see surveillance definition) will be included as outcome events in this study since recurrent CA-CDI ≤ 8 weeks of an incident CA-CDI are assumed to be related.

METHODOLOGY

Data collection period

The BCFHT database will be the source of all patient data. The data collection will be limited to January 1, 2011 to December 31, 2016. Healthcare exposure will be determined by linking the BCFHT database to the Royal Victoria Hospital (RVH) database. The RVH is the sole hospital in Barrie, Ontario, and is assumed to be the primary site of acute healthcare for all the BCFHT patients. The observation period is not fixed, but will be determined by the period of patient registration with the BCFHT, along with healthcare exposureand *Clostridium difficile* infection (Figure 2).

Data elements

The data elements, their descriptions and their definitions are described in Table (1). Antibiotic exposure will be categorized *a priori* as "high risk", "low risk" and no exposure (3 categories). Specifically, "high risk" antibiotic exposure includes any prescriptions for fluoroquinolones (moxifloxacin, levofloxacin or ciprofloxacin), clindamycin or cephalosporins (cephalexin, cefprozil, or cefuroxime). These antibiotics have been categorized as "high risk" from their estimated effect size ORs from the 2 previous meta-analyses [7,8]. They have been combined into a single "high risk" exposure category on the assumption that their effect sizes overlap given their estimated 95% confidence intervals [7,8]. The same rationale was used to create the "low risk" exposure category.

Sample size calculation

Sample size calculations for SCCS are dependent on the effect size, and the ratio of the duration of exposure to non-exposure periods [12]. In addition, the exposure variable has two independent categories ("high risk" vs none and "low risk" vs none) that will require separate hypothesis testing resulting in a multiplicity effect that may inflate the Type I error rate [13]. As a result, multiplicity adjustments using the Hochberg procedure will be applied to preserve the error rate at the nominal Type I error rate = 0.05 [13]. This multiplicity adjustment requires that the sample size calculation be estimated using a Type 1 error rate (α) = 0.05/2. Assuming a conservative effect size OR of 1.8 [7,8], the number of CA-CDI cases needed to detect this effect are estimated in Table (2).

Apreliminary screen of the BCFHT identified approximately 2,000 *Clostridium difficile* cases from January 2011 to December 2016, suggesting that 500 to 700 CA-CDI cases will be available

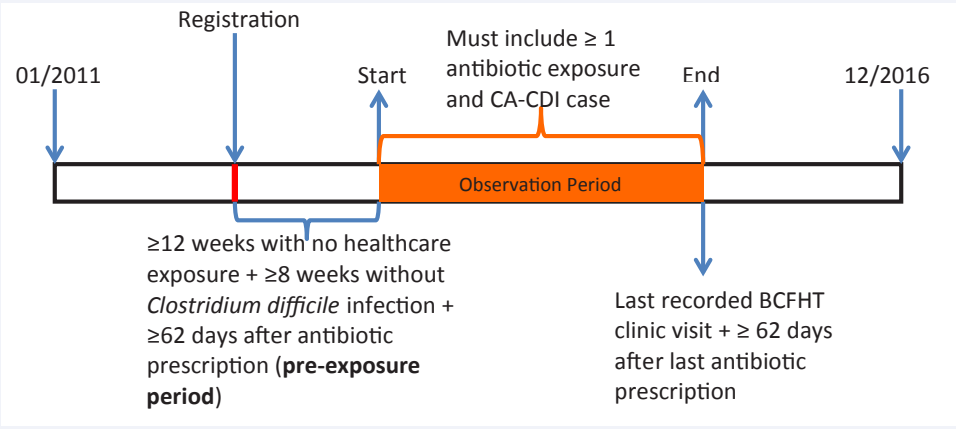

Figure 2 Schematic of the observation period (start and end points) for a hypothetical patient.

Table 1: Data dictionary.

Variable	Definition	Type	Categories
CA-CDI	PHL positive assay + no healthcare exposure ≥ 12 weeks + no previous *Clostridium difficile* infection ≥ 8 weeks	Outcome	0=no; 1=case
CA-CDI Date	Date of CA-CDI diagnosis	Outcome	DDMMYY
Antibiotic	Any prescription ≥1 dose	Exposure	2 = high risk (fluoroquinolones, clindamycin, cephalosporins); 1 = low risk (penicillins, amoxicillin, amoxicillin-clavulinate, macrolides, sulfonamides, tetracyclines, nitrofurantoin, fosfomycin, metronidazole); 0 = none
Antibiotic Date	Date of prescription	Exposure	Start and end dates (DDMMYY)
Duration	Days of antibiotic prescription	Effect modifier	0=less than 5 days; 1=5 days or more
Age	Years at time of diagnosis	Confounder	0=younger than 65 years old; 1=65 years and older
Season	Season at time of diagnosis	Confounder	Winter, spring, summer, fall
Year	Year at time of diagnosis	Confounder	2011-2016

Table 2: Estimated sample sizes needed to detect an effect size OR of 1.8 for different ratios of exposure:non-exposure risk periods, powers, type I error rate and the multiple hypothesis testing problem [12,13].

Power (%)	Type I error (α)	Ratio (exposure/Non-exposure)	Sample size (CA-CDI cases)
90	0.025	0.6	161
90	0.025	0.4	148
90	0.025	0.2	203
90	0.025	0.1	344
90	0.025	0.05	636
80	0.025	0.6	121
80	0.025	0.4	114
80	0.025	0.2	159
80	0.025	0.1	274
80	0.025	0.05	509

for analysis (assuming 25% to 35% of all *Clostridium difficile* infections are due to CA-CDI).

Data analysis

Conditional poisson regression analysis will be used to estimate the overall relative incidence rate ratio (IRR) for the risk of CA-CDI following exposure to antibiotics. The overall relative IRR is a ratio of the incidence rate of CA-CDI in the exposure period compared to the incidence rate of CA-CDI in the non-exposure period. The exposure period is defined as the interval starting 2 days after an antibiotic prescription (date of prescription in EMR) and continuing forthe next 60 days. The non-exposure periods are defined as the remaining intervals in the observation period [=Total observation period (days) – exposure period (days)]. The observation period start date is defined as the day after the pre-exposure period ends (Figure

2). The pre-exposure period is defined as the time after patient registration with BCFHT that is also ≥ 12 weeks after any healthcare-related exposure and ≥ 8 weeks after a previous case of *Clostridium difficile* infection and ≥ 62 days after any antibiotic prescription.The observation period end date is defined as the day of the last recorded BCFHT clinic visit regardless of the reason (eg, death versus moving out of the BCFHT catchment area) (Figure 2). The observation period end date must also be ≥ 62 days after the last antibiotic prescription to ensure that the entire exposure period is accounted for in the analysis (Figure 2). 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 following antibiotic exposure, an IRR < 1 implies a reduced risk of CA-CDI following antibiotic exposure and an IRR = 1 implies no difference in risk of CD-CDI following antibiotic exposure.Antibiotic exposure will be categorized as "high risk", "low risk" and no exposure.The null hypothesis for the high-risk antibiotic exposure category (IRR=1) will be rejected, according to the Hochberg procedure, if $p_{High\ Risk} \leq \alpha/2$ OR ($p_{High\ Risk} \leq \alpha$ and $p_{Low\ Risk} \leq \alpha$), where α=0.05 (Type I error rate)[13]. The null hypothesis for the low risk antibiotic exposure category (IRR=1) will also be rejected, using Hochberg's procedure, if $p_{Low\ Risk} \leq \alpha/2$ OR ($p_{Low\ Risk} \leq \alpha$ and $p_{High\ Risk} \leq \alpha$), where α=0.05.Duration of antibiotic therapy will be incorporated as an effect modifier in the final model by creating an interaction term with antibiotic exposure and including this interaction term as a separate variable. Temporal trends will be accounted for by the season variable given the known seasonal variation that exists with *Clostridium difficile* infection [14]. In addition, the laboratory tests used for the diagnosis of *Clostridium difficile*infection have changed over the years of the study from those based on enzyme-linked immunosorbent assays to DNA-based assays [15]. The DNA-based tests are more sensitive than their predecessors, and have been demonstrated to increase the detection of *Clostridium difficile*toxin by up to 2-fold [16]. The year variable (Table 1) will be included as a confounder in the final model to account for this temporal change in laboratory tests. While age will be included as a time-variant confounder, it is unlikely that any significant proportion of the cases will transition between the dichotomous categories during the observation period, thus making age more similar to a time-invariant confounder that will be eliminated as a result of the SCCS design.

EXPECTED OUTCOMES

Given the results from the previous observational studies, the investigator expects that the "high risk" antibiotic exposure category will be associated with an increased risk of CA-CDI but the effect size will be much more moderate (IRR 2-3). This less biased effect size is expected because the SCCS design should reduce the bias associated with both observed and unobserved time-invariant confounders, given that they are eliminated in the final model. In addition, the investigator expects that the "low risk" antibiotic exposure effect size will trend to the null, and may eventually demonstrate no association with CA-CDI. The investigator also expects that prolonged courses of antibiotic treatment duration will increase the risk of CA-CDI, regardless of the risk category of antibiotic exposure. Both of these findings should nudge physician-prescribing behaviour to promote the use of less risky antibiotics for shorter treatment durations, both of which have been recommended to reduce the risk of adverse patient outcomes and minimize the emergence of antibiotic resistance.

In the future, it would be ideal to conduct a prospective observational study using the SCCS design and incorporating the time-invariant confounder of household member exposure to any healthcare facility so that the effect size of this potential risk factor could be estimated. These results could be used to develop a simple screening risk tool that could be validated for predicting the risk of CA-CDI given both antibiotic exposure and household member exposure, and subsequently used by both family physicians and their patients to help make informed decisions about treatment. In addition, the impact of preventative measures such as probiotic administration or environmental cleaning strategies for the household could be tested in randomized controlled studies for those patients who require antibiotic treatment with a high-risk class antibiotic and are exposed to household members who increase their risk of CA-CDI.

STUDY LIMITATIONS

This is an observational study, so we cannot be certain that any association that may be demonstrated to exist between antibiotic exposure and CA-CDI is causal in nature. We are assuming that an antibiotic prescription implies medication compliance, thus potentially leading to definition bias. Because of it's retrospective design, the potentially important confounder of exposure to household members who may have had or have ongoing healthcare exposure or who were diagnosed with *Clostridium difficile* infection will remain unobserved, potentially leading to unobserved confounder bias. Detection and selection bias may be important limitations given that only patients who present to the BCFHT with diarrheal symptoms may be diagnosed with CA-CDI, thus potentially underestimating the true incidence of disease in this target population. In addition, given the change in diagnostic testing strategies, this may also contribute to detection bias with a lower incidence of CA-CDI expected in the early years of the study period compared to the more contemporaneous period even after accounting for year of diagnosis. Definition bias may result from limiting the definition of healthcare exposure to the Royal Victoria Hospital, given that these CA-CDI cases may have had healthcare exposures in other acute healthcare facilities. Assumptions of the SCCS design may be violated (see ***Model*** section), leading to concept bias. The sample size calculations assume a consistent exposure: non-exposure ratio for each case, but this ratio is likely to be quite variable across cases and may result in underestimation of the required number of cases needed, potentially leading to an underpowered study and false negative effect size. In addition, the power to detect antibiotic class effect sizes may not be possible due to an insufficient number of cases, thus limiting conclusions about associations between exposure and cases to groups of antibiotic classes. While the exposure risk period has been defined to include the majority of CA-CDI cases associated with antibiotic exposure, there may be cases that occur within 90 to 180 days after antibiotic exposure that may be misclassified as non-exposure-related CA-CDI cases, thus contributing to definition bias.

ETHICS

The study requires both examination of personal health information and database linkage across healthcare institutions, and so research ethics approval will be required. However, a complete waiver of informed consent will be requested from both the BCFHT research ethics board and the Royal Victoria Hospital research ethics board on the basis that this is a retrospective study that involves no more than minimal risk to the subjects, the waiver would not adversely affect the rights and welfare of the subjects, and the research could not practicably be carried out without the waiver given informed consent would have to be sought from each registered BCFHT patient from 2011 to 2016 who met the inclusion criteria, thus potentially requiring the investigator to contact hundreds, perhaps even thousands, of patients.

DATABASE SECURITY

While cases will only be identified using a unique random number and none of the data elements are direct identifiers, given the limited number of cases, the CA-CDI date variable may be considered a quasi-identifier [17]. Despite the absence of any other quasi-identifiers, it is likely that each case will represent an equivalence class of size one [17], potentially increasing the risk of re-identification. To this end, only the investigator will have access to the database through a data sharing agreement with the BCFHT, and the database will be kepton a password-protected USB memory stick that will be stored in a locked cabinet in a locked office. Once the study is complete, the USB memory stick will be returned to the BCFHT to be kept in a secured environment for 10 years, subsequent to which the data will be permanently erased.

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Cite this article

Di Diodato G (2017) Antibiotic Exposure and Risk of Community-Associated Clostridium difficile Infection in Adult Patients Registered with Ontario's Largest Family Medicine Health Team: A Study Protocol for a Self-Controlled Case Series Analysis.Clin Res Infect Dis 4(1): 1049.