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The Association Between the Frequency of Interruptions in Antibiotic Exposure and the Risk of Health Care-Associated *Clostridiodes difficile* Infection

Jiyoun Song, MPhil, AGACNP-BC, RN[1,*], Bevin Cohen, PhD, RN[1], Jianfang Liu, PhD[1], Elaine Larson, PhD, FAAN, CIC, RN[1,2], Philip Zachariah, MD, MS[3,4]

[1] *Columbia University School of Nursing, New York, New York*
[2] *Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York*
[3] *Department of Pediatrics, Columbia University Irving Medical Center, New York, New York*
[4] *Department of Infection Prevention & Control, New York-Presbyterian Hospital, New York, New York*

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ABSTRACT

Background: Although antibiotic use is an established risk factor for health care-associated *Clostridiodes difficile* infection, estimates of the association between infection and antibiotic use vary, depending upon how antibiotic exposure is measured.
Objectives: The purpose of this study was to explore the association between the frequency of interruptions in antibiotic exposure and the risk of health care-associated *C difficile* infection.
Methods: A retrospective chart review cohort study was conducted of all inpatients between 2011and 2016 from a single academic health center who received at least 1 dose of a systemic antibacterial for a cumulative duration of >3 days and ≤30 days. The measures of antibiotic exposure examined were duration—cumulative total calendar days of antibiotics therapy—and continuity—the frequency of interruptions in antibiotic exposure that was defined as the number of antibiotic treatment courses.
Results: A total of 52,445/227,967 (23%) patients received antibacterial therapy for >3 days and ≤30 days during their hospitalization. Of these, 1161 out of 52,445 (2.21%) were patients with health care-associated *C difficile* infection. An adjusted multivariable logistic regression analysis revealed that the risk of *C difficile* increased with longer cumulative days (odds ratio = 2.7; comparison of >12 days to ≤5 days) and fewer interruptions of antibiotic treatment (odds ratio = 0.78; comparison of >3 discrete antibiotic treatment courses to 1 course or continuous antibiotic treatment course; all *P* values < 0.05).
Conclusions: For patients who received the same number of cumulative days of therapy, the patients who had more frequently interrupted courses of antibiotic therapy were less likely to experience health care-associated *C difficile* infection. (*Curr Ther Res Clin Exp*. 2020; 81:XXX–XXX)

Introduction

Cumulative antibiotic exposure is a well-described risk factor for health care-associated *Clostridiodes difficile* infection (HA-CDI).[1-3] Antibiotic stewardship programs (ASP) primarily focus on decreasing the quantity of antibiotics administered, and the Centers for Disease Control and Prevention uses summative measures of antibiotic exposure (days of therapy per 1000 patient-days) as an antibiotic stewardship programs quality measure.[4] However, patients receive similar amounts of antibiotics in diverse ways, either continuously or interrupted by antibiotic- free days (called antibiotic holidays), and antibiotic exposure can be conceptualized in multiple ways.[5–7] The influence of the dynamics of antibiotic exposure, specifically the role of interruptions in courses of antibiotics on the risk of HA-CDI has not been fully described. Further defining this association would facilitate accurate risk modeling for HA-CDI and the design of effective antibiotic stewardship interventions. In this study, we examined the association between the frequency of interruption of antibiotic therapy and the risk of HA-CDI in hospitalized inpatients. We hypothesized that in a cohort

* Address correspondence to: Jiyoun Song, MPhil, AGACNP-BC, RN, Columbia University School of Nursing, 560 W 168th St, New York, NY 10032.
E-mail address: js4753@cumc.columbia.edu (J. Song).

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Table 1
Comparison of characteristics between patients with and without health care-associated Clostridiodes difficile infection (HA-CDI); preliminary bivariate analysis.

Characteristic	Total patients (N = 52,445)	Patients with HA-CDI (n = 1161)	Patients without HA-CDI (n = 51,248)	*P* value*
Age, y†	50.04 (28.77)	59.86 (23)	49.82 (28.85)	< 0.0001
Male sex‡	47.55	52.8	47.43	< 0.001
Charlson Index score†	4.12 (3.63)	5.97 (3.39)	4.08 (3.62)	< 0.0001
Hospitalized days†	8.64 (9.78)	10.51 (8.99)	8.6 (9.79)	< 0.0001
Solid organ transplantation‡	4.47	9.13	4.37	< 0.0001
Malignancy‡	12.98	21.53	12.78	< 0.0001
PPI use‡	51.19	74.5	50.66	< 0.0001
High-risk CDI antibiotics‡	66.36	71.23	66.25	< 0.001

PPI = proton pump inhibitor.
* Student *t* test or χ^2 test.
† Values are presented as mean (SD).
‡ Values are presented as %.

of hospitalized patients who received similar cumulative antibiotic exposure, more frequent interruptions antibiotic treatment would be associated with lower HA-CDI risk when adjusted for other risk factors.

Methods

Description of dataset and study population

The dataset is derived from a federally funded grant from the Agency for Healthcare Research and Quality (R01 HS024915), which included data from 2006 to 2016. Data were extracted from various electronic databases (eg, admission-discharge-transfer system, electronic health records, a clinical data warehouse, and medication administration records) of 3 hospitals within a single academic health center in New York City.

In the study institution, the laboratory diagnostic test for CDI was changed in 2011 to the more sensitive polymerase chain reaction test for toxin B. Therefore, to eliminate the possibility of any effect caused by the change of diagnostic tests, our study population was selected from a cohort of adult and pediatric inpatients hospitalized between 2011 and 2016.

The hospitalized patients who were prescribed at least 1 dose of a systemic antibacterial agent for a cumulative duration of >3 days and ≤30 days in the hospital were included in this study. The use of metronidazole (intravenous or oral route) and vancomycin (oral route) were excluded from the analysis because those agents are used to treat CDI. The lower cut point (ie, >3 days) was used because this was our recommended time out period for reviewing empiric antibiotic prescribing once a course started.[4] The higher cut point of 30 days was chosen to limit the presence of confounders with longer cumulative durations of therapy (eg, unmeasured outpatient antibiotic exposure).

The Centers for Disease Control and Prevention definition of HA-CDI (a positive laboratory test 3 or more calendar days after admission) was used to assign the diagnosis.

The Columbia University Institutional Review Board approved this study.

Attributes of antibiotic exposure

The total duration of antibiotic exposure was measured as the number of calendar days that each patient received an antibiotic agent regardless of daily dose or number of antibiotic agents; if the patient received 2 antibiotic agents on a specific day, this was counted as 1 antibiotic day. Antibiotics were classified into high versus low risk of CDI based on previous reports,[8,9] and the proportion of antibiotic days that a patient received a high-risk antibiotic agent was determined for each patient. The list of antibiotics included in this study is presented in Supplemental Table 1 in the online version at doi:XXXXXXXXXX).

A 48-hour antibiotic-free interval between antibiotic exposures was defined as an antibiotic holiday. We used the 48-hour window to limit the influence of specific dosing schedules (eg, renal adjustment) within a specified antibiotic course.[10] For each patient, we calculated the number of antibiotic treatment courses that occurred during the total cumulative exposure to antibiotic agents. Therefore, the continuity of antibiotic therapy was defined as the number of discrete antibiotic treatment courses separated by an antibiotic holiday (eg, 2 courses would have 1 antibiotic holiday between them).

Additional predictors of CDI risk

Additional variables for each patient were extracted for the time period preceding the first diagnosis of CDI for HA-CDI cases or final captured hospitalization for others. These included demographic characteristics, indexes of severity of illness during the hospitalization(s), medical comorbidities, and previously described risk factors for HA-CDI.[11,12] Specifically, these covariates included age at end of follow-up period, sex, mean Charlson Index calculated at hospital admission, total number of days spent in an intensive care unit, International Classification of Diseases diagnoses compatible with malignancy and/or solid organ transplantation, and the use of proton pump inhibitors (PPIs).[13]

Statistical analysis

Covariates were compared between the HA-CDI and non–HA-CDI groups using Student *t* test for continuous variables and χ^2 test for categorical variables. Following this a multivariable logistic model was constructed to predict the outcome HA-CDI versus non–HA-CDI for each patient.

Both cumulative duration and continuity of antibiotic exposure (ie, number of antibiotic treatment courses) were categorized into quartiles with the reference category as the lowest quartile. Covariates significant ($P < 0.05$) in bivariate analysis between the HA-CDI and non–HA-CDI groups were also assessed for inclusion in the model. An alpha of 0.05 was set as the threshold for significance. The model was built in a stepwise manner using the likelihood ratio test to indicate the need for additional variables. The outcome of interest was the differential influence of the frequent interruption in antibiotic courses on HA-CDI risk when adjusted for the cumulative duration. Odds ratios were calculated for outcomes of interest along with 95% CI. All analyses were done using R (R Foundation for Statistical Computing, Vienna, Austria).

Table 2
Significant variables in multivariable regression predicting health care-associated *Clostridiodes difficile* infection

Predictor	Odds ratio	95% CI
Charlson Index at admission*	1.13	1.09–1-1.14
Solid organ transplantation, %*	2.01	1.63–2.48
PPI use (%)*	2.48	2.15–2.85
Antibiotic cumulative duration, d*,†		
6–7	1.44	1.17–1.75
8–12	2.06	1.72–2.45
>12	2.7	2.28–3.19
No. of courses§		
2	0.85	0.73–0.99
3	0.67	0.56–0.81
>3	0.78	0.65–0.92

‡Reference: 1 course.
* Adjusted for age and sex.
† Reference: ≤5 days.
§ Adjusted for age, sex, and cumulative duration of antibiotic exposure.

Results

Among 227,967 hospitalized patients, 52,445 patients (23%) received systemic antibiotics for >3 and ≤30 days. Among these patients, 1161/52,445 (2.2%) developed HA-CDI. Patients with HA-CDI diagnosis were more likely to be older, have higher indexes of illness severity, have malignancy or be posttransplant, and receive a PPI before diagnosis compared with patients without a diagnosis of HA-CDI (Table 1). Overall, patients with HA-CDI received more antibiotic agents, but they also did so with fewer interruptions. There were also more likely to receive high-risk antibiotic agents.

Antibiotic exposure and CDI

In multivariable regression analysis, cumulative duration and continuity of antibiotic therapy were both independently associated with HA-CDI diagnosis (Table 2). Adjusting for the cumulative duration of antibiotics and other CDI risk factors, patients who had more frequent interruptions of their course of antibiotics were less likely to have HA-CDI compared with those who received antibiotics continuously. The other strong modifiable risk factor for HA-CDI was PPI use.

Discussion

In this large cohort of hospitalized patients who received antibiotic agents during a hospital admission, we demonstrated that the patients who had more frequently interrupted courses of antibiotic therapy were less likely to experience HA-CDI. For patients who received similar cumulative days of therapy, the patients with an uninterrupted course of therapy were much more likely to have been diagnosed with HA-CDI compared with patients who had antibiotic-free intervals. The presence or absence of at least 48-hour interruptions in antibiotic administration appears to play a role in HA-CDI.

There is biological plausibility for why this may be the case. Interrupted antibiotic courses (ie, antibiotic-free days) temporarily decrease the selective pressure on the intestinal flora narrowing the window for CDI to occur in patients who are colonized with *C difficile*. When antibiotic pressure resumes, the mucosal flora may be more adapted to compete with *C difficile*, decreasing overgrowth and toxin production.

These findings have clinical implications. Prediction models for HA-CDI should take into account the dynamics of antibiotic exposure over time, in addition to cumulative exposure. Antibiotic stewardship teams that review prescriptions are often faced with the dilemma of requesting antibiotic discontinuation in patients who have a low threshold for restarting these antibiotics. These data suggest that from the perspective of HA-CDI prevention antibiotic-free intervals could minimize risk.

Our study has limitations. We were not able to include outpatient antibiotic use. Also, the types of antibiotic agents, the number of different types of antibiotics, and the dosage of antibiotics, which were not considered in this study, may affect the results. Therefore, further study is warranted to take into account other aspects of antibiotic exposure. In addition, patients who received more frequently interrupted courses of antibiotics could have differed in risk profile from those who received continuous therapy in unmeasured ways, but we did adjust for severity of illness and major comorbidities previously described as CDI risk factors. We did not adjust for every predictor for HA-CDI, particularly environmental colonization in the specific hospital unit. Lastly, there could have been a testing bias in that patients on long courses of antibiotic agents may have been more likely to have been tested frequently for CDI.

Conclusions

More frequent interruption of courses of antibiotic treatment was associated with a lower risk of developing HA-CDI. Current antibiotic stewardship metrics that focus exclusively on cumulative antibiotic exposure may not sufficiently capture the risk for CDI; therefore, other metrics of antibiotic use should be studied to identify possible targets for CDI risk mitigation. These findings suggest that interruption of antibiotic treatment courses should be examined as a possible way to mitigate the risks of HA-CDI in hospitalized patients.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

CRediT authorship contribution statement

Jiyoun Song: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Bevin Cohen:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Jianfang Liu:** Conceptualization, Data curation, Formal analysis, Writing - review & editing. **Elaine Larson:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Philip Zachariah:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2020.100600.

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