Evaluation of *Clostridium difficile*–Associated Disease Pressure as a Risk Factor for *C difficile*–Associated Disease

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Background: Colonization pressure has been identified as an important risk factor in the transmission of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* species, but the role of colonization pressure in the transmission of *Clostridium difficile*–associated disease (CDAD) is unclear. The purpose of this study was to evaluate CDAD pressure, a modified form of colonization pressure based on symptomatic CDAD cases, as a risk factor for CDAD.

Methods: Retrospective cohort and nested case-control studies of patients admitted to Barnes-Jewish Hospital from January 1, 2003, through December 31, 2003. Univariate analysis and multivariate logistic regression models were used to evaluate the role of CDAD pressure as a risk factor for CDAD.

Results: A total of 36 275 patients were included in the cohort, of which 382 had CDAD. The median CDAD pressure was higher for case patients than noncase patients (1.4 vs 0.3; $P<.001$), and only 1 patient with CDAD had a CDAD pressure of 0. In the nested case-control study, CDAD pressure remained an independent risk factor for CDAD after adjustment for demographics, severity of illness, medications received (chemotherapy, gastric acid suppressors, antidiarrheals or narcotics, and antibiotics), and abdominal procedures or surgery performed.

Conclusions: The results of this study suggest that CDAD pressure may be an independent risk factor for CDAD. Future studies that evaluate risk of CDAD should control for CDAD pressure.

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CLOSTRIDIUM DIFFICILE–associated disease (CDAD) is the most common cause of infectious hospital-associated diarrhea.[1] Increasing age, increasing length of hospital stay, high severity of illness, and prior antibiotic use are well established as important risk factors for the development of CDAD.[1-9]

Colonization pressure is a recognized risk factor for several important hospital pathogens. Multiple studies have identified colonization pressure as an important risk factor for methicillin-resistant *Staphylococcus aureus* (MRSA)[10-15] and vancomycin-resistant *Enterococcus* (VRE) carriage.[16-18] Because *C difficile* is transmitted in a manner similar to VRE, it is likely that colonization pressure is an important, unmeasured risk factor for CDAD.

The objective of this study was to determine if the burden of concurrent inpatients with CDAD on the same ward changes a patient's risk of developing CDAD. Previous studies of MRSA and VRE have included both asymptomatic carriers and clinical cases in colonization pressure estimates. However, screening for asymptomatic *C difficile* carriers is not part of most routine infection-control practices. Therefore, this study measured a modified form of colonization pressure, CDAD pressure, in which only clinically symptomatic cases of CDAD were included.

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METHODS

This study was conducted at Barnes-Jewish Hospital (BJH), a 1250-bed, tertiary care, academic hospital. All patients admitted to BJH for more than 48 hours from January 1, 2003, through December 31, 2003, were included. The following data were collected retrospectively from the hospital's medical informatics database: patient demographics; *International Classification of Diseases, Ninth Revision, Clinical Modification*[19] *(ICD-9-CM)* discharge and procedure codes; admission, discharge, and in-hospital transfer dates; hospital ward locations; inpatient medications received; vital signs; and laboratory results, including *C difficile* toxin assay results. A modified Acute Physiology Score (APS) was calculated for each patient based on laboratory results and vital signs collected within

24 hours of admission.[20] The APS was modified because data for respiratory rate and Glasgow Coma Scale were unavailable electronically. The *ICD-9-CM* discharge codes were used to classify comorbidities by the Deyo adaptation of the Charlson Comorbidity Index.[21,22] The *ICD-9-CM* procedure codes were used to identify patients who had undergone intra-abdominal and/or gastrointestinal surgery or procedures.

A case patient was defined as any inpatient with diarrhea and a positive stool toxin assay result for *C difficile* (Techlab, Blacksburg, Va). According to the manufacturer, the sensitivity of this assay compared with tissue culture was 92.2% and the specificity was 100%. Because the hospital laboratory performs a test for *C difficile* only on unformed stool samples from patients clinically suspected of having CDAD, all patients with positive toxin results were considered case patients. Once a patient had a positive stool toxin assay result for *C difficile* and was defined as a case patient, any subsequent admissions that patient had to BJH during the study period were excluded to limit bias from recurrent or relapsed CDAD cases. Patients who had a history of a positive toxin assay result in the 60 days before January 1, 2003, were assumed to have recurrent CDAD and were excluded. A noncase patient (and control for the nested case-control study) was defined as any inpatient who did not have a positive stool toxin assay result for *C difficile* during the study period. For case patients, length of stay at risk was the time from admission to first positive *C difficile* stool toxin assay result. For noncase or control patients (in the nested case-control study), length of stay at risk was the entire hospitalization period.

CDAD PRESSURE CALCULATIONS

Data were collected for each patient regarding the hospital ward(s) where the patient stayed during admission, admission and discharge dates from each ward, and for CDAD cases, the collection dates of stool toxin assays with positive results. The patients with CDAD were considered infectious and contributing to CDAD pressure for 14 days after the collection date of their stool sample that produced positive results (or until discharge if the patient was discharged before the end of the 14-day period). Patients with multiple stool samples with positive results in a 14-day period were considered infectious from the collection date of the first stool sample with a positive result until 14 days from the collection date of the last stool sample with a positive result. Patients with stool samples with positive results more than 14 days apart during the same hospitalization period were considered to have had separate episodes of CDAD, and separate periods of infectivity were calculated. The patients with CDAD contributed to daily CDAD pressure on the ward where they were located each day they were considered infectious. If a patient with CDAD was transferred to a different ward before the end of the 14-day period, that patient's CDAD pressure contribution transferred to the second ward. The patients with CDAD admitted to the hospital for less than 48 hours and patients with recurrent CDAD were included in the CDAD pressure calculations but excluded from risk factor analysis. The number of infectious patients with CDAD was determined per calendar day for each ward. Each patient's exposure to infectious patients with CDAD was calculated by adding the daily number of infectious patients with CDAD present on the same ward during the time the patient was present on the ward (sum CDAD pressure). The mean CDAD pressure was calculated by dividing each patient's sum CDAD pressure by his or her length of stay at risk:

$$\text{Mean CDAD Pressure} = \frac{\sum \text{Daily Exposure to Infectious CDAD Patients (ie, Sum CDAD Pressure)}}{\text{Length of Stay at Risk}}$$

DATA ANALYSIS

A nested case-control study was performed with a sample of patients from the primary cohort to assess the effect of CDAD pressure after adjustment for demographics and other previously described CDAD risk factors. The nested case-control design allowed the evaluation of CDAD pressure before data collection and verification were complete for the entire cohort. Each case patient was included in the nested case-control study, and because only first episodes of CDAD were included in the cohort, no relapsed or recurrent CDAD cases were included. Controls were randomly selected from the noncases for a 1:4 case-control ratio. No patient had more than 1 admission included in the nested case-control study. Other variables included were age, sex, admissions in the previous 60 days, comorbidity as measured by the Charlson Comorbidity Index, severity of illness on admission as measured by the modified APS, hypoalbuminemia, abdominal surgery or an abdominal procedure, and receipt of various medications, including a gastric acid suppressor (histamine$_2$ receptor blocker or proton pump inhibitor), a narcotic or antidiarrheal agent, chemotherapy, and certain antimicrobials (amoxicillin or ampicillin, clindamycin, third- or fourth-generation cephalosporins, or fluoroquinolones).[1,2,4,7-9,23-25] The patients with CDAD were considered exposed to a medication if the order start date preceded the date of the patient's first positive stool toxin assay result.

On univariate analysis, χ^2 tests were used for categorical variables and Mann-Whitney *U* tests were used for continuous variables. Logistic regression was used for multivariate analysis of the nested case-control study. Several models were compared to assess the impact that length of stay at risk, sum CDAD pressure, sum CDAD pressure plus length of stay at risk, and mean CDAD pressure had on the performance of the model. Model fit was assessed using –2 log likelihood ratio and C-statistic comparisons. All tests were 2-tailed, and $P \leq .05$ was considered statistically significant. Statistical analyses were performed with SPSS statistical software for Windows, version 12.0 (SPSS Inc, Chicago, Ill). The Washington University Human Studies Committee approved this project.

RESULTS

The cohort included 36 275 admissions, 382 of which were associated with a positive *C difficile* toxin assay result and were considered case patients. The remaining 35 893 admissions were considered noncase patients. Demographic characteristics of case and noncase patients are given in **Table 1**. Case patients were significantly older, more likely to be male, and more likely to be white than noncase patients ($P < .001$ for all). Case patients had a significantly higher mean CDAD pressure, sum CDAD pressure, and length of stay at risk ($P < .001$ for all).

Length of stay at risk and sum and mean CDAD pressure were categorized for multivariable analysis, since they were not normally distributed (**Table 2**). Only 1 case patient had a sum and mean CDAD pressure of 0 compared with 47.0% of the noncase patients; therefore, a CDAD pressure of 0 could not be used as the reference category. Because a threshold for increasing risk was identified at a mean CDAD pressure of 0.3, a mean CDAD pressure less than 0.3 was used as the reference category. The rest of the population was split based on the 50th percentile of CDAD pressure for the entire population after the reference category was removed; thus, mean CDAD pressure was categorized into increments

Table 1. Univariate Analysis of Demographic Characteristics and Risk Factors for *Clostridium difficile*–Associated Disease (CDAD) in the Admission Cohort of 36 275 Patients*

Characteristic	Case Patients, No. (%) (n = 382)	Noncase Patients, No. (%) (n = 35 893)	*P* Value
Age, median (range), y	64 (18-99)	55 (12-106)	<.001
Male	204 (53.4)	15 042 (41.9)	<.001
White	278 (72.8)	22 598 (63.0)	<.001
Hospital ward†			
Medicine	227 (59.4)	15 750 (43.9)	<.001
Surgical	139 (36.4)	11 134 (31.0)	.02
Intensive care unit	179 (46.9)	5689 (15.8)	<.001
Obstetrics-gynecology	15 (3.9)	5323 (14.8)	<.001
Neurology	18 (4.7)	3072 (8.6)	.007
Leukemia or stem cell transplantation	47 (12.3)	508 (1.1)	<.001
Long-term ventilation	27 (7.1)	160 (0.4)	<.001
Length of stay at risk, median (range), d‡	8.4 (2.1-117.0)	4.4 (2.0-289.8)	<.001§
Sum CDAD pressure, median (range)‖	13 (0-322)	1 (0-491)	<.001§
Mean CDAD pressure, median (range)¶	1.4 (0-15.6)	0.3 (0-54.9)	<.001§

*Data are presented as number (percentage) unless otherwise indicated.
†Patients may have stayed on more than 1 ward during admission.
‡Length of stay at risk is defined for case patients as the length of stay until the date of collection of the stool sample positive for a *Clostridium difficile* toxin assay. For noncase patients, the length of stay at risk is defined as the entire length of stay.
§Comparison made using the Mann-Whitney test.
‖Sum CDAD pressure is defined as the total number of CDAD cases that a case or noncase patient was exposed to during his or her length of stay at risk.
¶Mean CDAD pressure is defined as the sum CDAD pressure for a case or noncase patient divided by his or her length of stay at risk.

Table 2. Risk of *Clostridium difficile*–Associated Disease (CDAD) by Length of Stay at Risk, Sum CDAD Pressure, and Mean CDAD Pressure on Univariate Analysis of Cohort*

Variable	Case Patients, No. (%) (n = 382)	Noncase Patients, No. (%) (n = 35 893)	Relative Risk (95% Confidence Interval)
Length of stay at risk, d			
<4.5	90 (23.6)	18 069 (50.3)	1 [Reference]
4.5-7.5	79 (20.7)	8972 (25.0)	1.8 (1.3-2.4)
>7.5	213 (55.8)	8852 (24.7)	5.1 (4.0-6.5)
Sum CDAD pressure			
≤1	51 (13.3)	18 182 (50.7)	1 [Reference]
2-8	107 (28.0)	9652 (26.9)	3.9 (2.8-5.5)
>8	224 (58.6)	8059 (22.5)	9.7 (7.1-13.1)
Mean CDAD pressure			
<0.3	46 (12.0)	18 386 (51.2)	1 [Reference]
0.3-1.4	142 (37.2)	8754 (24.4)	6.4 (4.6-8.9)
>1.4	194 (50.8)	8753 (24.4)	8.7 (6.3-12.0)

*Length of stay at risk is defined for case patients as the length of stay until the date of collection of the stool sample positive for a *Clostridium difficile* toxin assay. For noncase patients, the length of stay at risk is defined as the entire length of stay. Sum CDAD pressure is defined as the total number of CDAD cases that a case or noncase patient was exposed to during his or her length of stay at risk. Mean CDAD pressure is defined as the sum CDAD pressure for a case or noncase patient divided by his or her length of stay at risk.

of less than 0.3, 0.3 to 1.4, and greater than 1.4. The variables for sum CDAD pressure and length of stay at risk were categorized to match the overall population distribution of the categorized mean CDAD pressure variable. A dose-response relationship was evident with increasing mean CDAD pressure, sum CDAD pressure, and length of stay at risk. The relative risk of CDAD associated with a mean CDAD pressure of 0.3 to 1.4 was 6.4, and the relative risk of CDAD associated with a CDAD pressure greater than 1.4 increased to 8.7.

As described previously, a nested case-control study was performed to assess the impact of length of stay at risk and sum and mean CDAD pressure in multivariate models. All of the CDAD cases (N=382) and 1518 controls were included in this analysis. All potential risk factors were significantly associated with CDAD on univariate analysis with the exceptions of receiving amoxicillin or ampicillin, receiving clindamycin, and undergoing abdominal surgery (**Table 3**). The results of the multivariate analyses are given in **Table 4**. Significant risk factors for CDAD in the baseline model without any CDAD pressure or length of stay at risk included age of 45 years or older, having an admission to BJH in the previous 60 days, Charlson Comorbidity Index of 1 to 2, modified APS of 3 to 5, receiving a gastric acid suppressor, receiving a narcotic or antidiarrheal agent, hypoalbuminemia, receiving a third- or fourth-generation cephalosporin, or receiving a fluoroquinolone. Increasing length of stay at risk was not a significant risk factor for CDAD whether it was modeled with or without sum CDAD pressure. Both sum CDAD pressure and mean CDAD pressure were significant risk factors for CDAD, and dose-response relationships were evident with increasing levels of risk associated with increasing sum or mean CDAD pressure.

The –2 log likelihood ratio and C-statistic are given for each of the models evaluated. On the basis of –2 log likelihood ratio comparisons, the models with sum CDAD pressure, sum CDAD pressure plus length of stay at risk, and mean CDAD pressure fit the data significantly better than the baseline model ($P<.001$ for all). The model with length of stay at risk did not fit the data significantly better than the baseline model ($P=.60$), and the model with sum CDAD pressure and length of stay at risk did not fit the data better than the model with sum CDAD pressure alone ($P=.94$). The model that fit the data best was the one with mean CDAD pressure (C-statistic=0.88).

COMMENT

The results of this study suggest that CDAD pressure is an important risk factor for CDAD. Sum and mean CDAD pressures were significantly higher among cases than controls in univariate and multivariate analyses and when CDAD pressure was compared categorically and as a continuous variable. Notably, only 1 case patient had a CDAD pressure of 0, compared with almost half of the noncase patients. When modeled with known risk factors for CDAD, CDAD pressure (either mean or sum) remained a significant risk factor for CDAD. In fact, the odds ratios (ORs) associated with mean CDAD pressure (OR=3.9

for mean CDAD pressure of 0.3-1.4 and OR=5.4 for mean CDAD pressure >1.4) were higher than the OR for all other variables. Dose-response relationships were evident on multivariable analysis for sum and mean CDAD pressure.

It is possible that unmeasured confounders in our multivariate analyses existed. This study examined whether CDAD pressure influenced the odds of developing CDAD after controlling for other, previously described risk factors for CDAD and did not determine a best-fit model. Significant differences were found in the full cohort between CDAD cases and noncases and hospital wards (Table 1). Hospital ward is a variable that takes into account patient characteristics, ward size, and health care professional practices, all of which may influence the risk of developing CDAD. Hospital ward was not included in multivariate models because these characteristics were captured by other independent variables and, because the ward a patient was admitted to was included in the CDAD pressure calculations, ward and CDAD pressure exhibit colinearity. However, to investigate the possibility that the ward was an unmeasured confounder, the mean CDAD pressure multivariate model was rerun with the hospital wards added. Mean CDAD pressure remained the patient characteristic associated with the greatest odds of developing CDAD, and the dose-response relationship persisted (OR=3.3 [95% confidence interval, 2.2-5.0] for mean CDAD pressure of 0.3-1.4 and OR=4.3 [95% confidence interval, 2.9-6.5] for mean CDAD pressure >1.4).

In the only previous study on colonization pressure and CDAD, Lawrence et al[26] used a colonization pressure measurement based on symptomatic patients with CDAD, similar to the sum CDAD pressure described herein, to evaluate the risk of CDAD in a medical intensive care unit. They found their variable to be a risk factor for CDAD in univariate analysis (case patients had 5.5 case-days of exposure vs 2.0 days for controls; $P<.001$) and determined on subsequent sequential logistic regression that an exposure level of 10.0 was necessary before it would be an independent risk factor for CDAD. In the evaluation of CDAD pressure presented herein, the median sum CDAD pressure for cases was 13.0, higher than the 10.0 exposure threshold, and this difference may explain why CDAD pressure remained an independent risk factor for CDAD in our multivariate models. Alternatively, CDAD transmission patterns may differ between intensive care units and general hospitalized patients.

Previous studies[5,27,28] have identified increasing length of stay as a risk factor for CDAD. Possible biological explanations for this include increased exposure to *C difficile* spores in the patient's physical hospital environment or increased exposure to spores transmitted by the hands of health care workers.[29-33] Another possibility is that length of stay is confounded by severity of illness. The results of this study support the hypothesis that the primary reason why increased length of stay is a risk factor for CDAD is an increased chance of exposure to *C difficile* from concurrently admitted patients with CDAD.

A high degree of similarity was found between models with mean CDAD pressure and sum CDAD pressure. This finding raises the question of whether a sum is a better measure of CDAD pressure than a mean. Both models were significantly better than the baseline model and were comparable in terms of model discrimination. Use of a sum CDAD pressure instead of a mean CDAD pressure presupposes that exposure to patients with CDAD for a long period is as hazardous to a patient's

Table 3. Univariate Analysis of Nested Case-Control Study

Variable	Case Patients, No. (%) (n = 382)	Control Patients, No. (%) (n = 1528)	Odds Ratio (95% Confidence Interval)
Age, y			
<45	46 (12.0)	516 (33.8)	1 [Reference]
45-64	161 (42.1)	529 (34.6)	3.4 (2.4-4.8)
≥65	175 (45.8)	483 (31.6)	4.1 (2.9-5.8)
Male	204 (53.4)	659 (43.1)	1.5 (1.2-1.9)
≥1 Admission in previous 60 days	161 (42.1)	359 (23.5)	2.4 (1.9-3.0)
Charlson Comorbidity Index			
0	68 (17.8)	633 (41.4)	1 [Reference]
1-2	192 (50.3)	580 (38.0)	3.1 (2.3-4.2)
≥3	122 (31.9)	315 (20.6)	3.6 (2.6-5.0)
Modified Acute Physiology Score			
0-2	66 (17.3)	576 (37.7)	1 [Reference]
3-5	151 (39.5)	606 (39.7)	2.2 (1.6-3.0)
≥6	165 (43.2)	346 (22.6)	4.2 (3.0-5.7)
Gastric acid suppressors			
$Histamine_2$ blocker	206 (53.9)	426 (27.9)	3.0 (2.4-3.8)
Proton pump inhibitor	267 (69.9)	552 (36.1)	4.1 (3.2-5.2)
Received chemotherapy	20 (5.2)	41 (2.7)	2.0 (1.2-3.5)
Received narcotic or antidiarrheal	171 (44.8)	324 (21.2)	3.0 (2.4-3.8)
Low albumin level (<3.5 mg/dL)	187 (49.0)	342 (22.4)	3.3 (2.6-4.2)
Antibiotics			
Amoxicillin or ampicillin	14 (3.7)	87 (5.7)	0.6 (0.4-.1)
Clindamycin	21 (5.5)	57 (3.7)	1.5 (0.9-2.5)
Third-generation cephalosporin	65 (17.0)	99 (6.5)	3.0 (2.1-4.1)
Fourth-generation cephalosporin	186 (48.7)	170 (11.1)	7.6 (5.9-9.8)
Fluoroquinolone	143 (37.4)	279 (18.3)	2.7 (2.1-3.4)
Abdominal procedure performed	53 (13.9)	98 (6.4)	2.4 (1.7-3.4)
Abdominal surgery performed	34 (8.9)	95 (6.2)	1.5 (1.0-2.2)
Length of stay at risk, d*			
<4.5	90 (23.6)	786 (51.4)	1 [Reference]
4.5-7.5	79 (20.7)	368 (24.1)	1.9 (1.4-2.6)
>7.5	213 (55.8)	374 (24.5)	5.0 (3.8-6.6)
Sum CDAD pressure†			
≤1	51 (13.4)	806 (52.7)	1 [Reference]
2-8	107 (28.0)	390 (25.5)	4.3 (3.0-6.2)
>8	224 (58.6)	332 (21.7)	10.7 (7.7-14.8)
Mean CDAD pressure‡			
<0.3	46 (12.0)	802 (52.5)	1 [Reference]
0.3-1.4	142 (37.2)	364 (23.8)	6.8 (4.8-9.7)
>1.4	194 (50.8)	362 (23.7)	9.3 (6.6-13.2)

Abbreviation: CDAD, *Clostridium difficile*–associated disease.

*Length of stay at risk is defined for case patients as the length of stay until the date of collection of the stool sample positive for a *Clostridium difficile* toxin assay. For noncase patients, the length of stay at risk is defined as the entire length of stay.

†Sum CDAD pressure is defined as the total number of CDAD cases that a case or noncase patient was exposed to during his or her length of stay at risk.

‡Mean CDAD pressure is defined as the sum CDAD pressure for a case or noncase patient divided by his or her length of stay at risk.

Table 4. Multivariate Analysis of Risk Factors for CDAD and Comparison of Models With or Without LOS at Risk, Sum CDAD Pressure, or Mean CDAD Pressure*

Characteristic†	No CDAD Pressure or LOS at Risk	LOS at Risk	Sum CDAD Pressure	Sum CDAD Pressure and LOS at Risk	Mean CDAD Pressure
Age, y					
<45	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
45-64	2.1 (1.4-3.2)	2.1 (1.4-3.2)	2.1 (1.4-3.2)	2.1 (1.4-3.2)	2.2 (1.4-3.4)
≥65	2.7 (1.8-4.1)	2.7 (1.8-4.1)	2.8 (1.8-4.2)	2.8 (1.8-4.3)	2.9 (1.9-4.4)
Male	0.7 (0.6-1.0)	0.7 (0.6-1.0)	0.8 (0.6-1.0)	0.8 (0.6-1.0)	0.8 (0.6-1.0)
≥1 Admission in previous 60 days	2.1 (1.6-2.8)	2.1 (1.6-2.8)	2.2 (1.7-3.0)	2.1 (1.7-3.0)	2.3 (1.7-3.0)
Charlson Comorbidity Index					
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1-2	1.8 (1.3-2.5)	1.8 (1.2-2.5)	1.6 (1.1-2.2)	1.6 (1.1-2.2)	1.5 (1.1-2.2)
≥3	1.4 (0.9-2.8)	1.4 (0.9-2.1)	1.2 (0.8-1.9)	1.3 (0.8-1.9)	1.2 (0.8-1.9)
Modified Acute Physiology Score					
0-2	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
3-5	1.8 (1.2-2.6)	1.8 (1.3-2.6)	1.8 (1.2-2.5)	1.7 (1.2-2.5)	1.7 (1.2-2.5)
≥6	1.4 (1.0-2.1)	1.4 (1.0-2.1)	1.2 (0.8-1.8)	1.2 (0.8-1.8)	1.2 (0.8-1.8)
Gastric acid suppressors					
Histamine$_2$ blocker	3.1 (2.3-4.2)	3.0 (2.2-4.0)	2.8 (2.1-3.8)	2.9 (2.1-3.9)	3.0 (2.2-4.0)
Proton pump inhibitor	2.6 (1.9-3.4)	2.5 (1.8-3.3)	2.2 (1.6-2.9)	2.2 (1.6-3.0)	2.3 (1.7-3.1)
Received chemotherapy	1.3 (0.7-2.6)	1.3 (0.7-2.5)	1.3 (0.7-2.6)	1.3 (0.7-2.6)	1.5 (0.7-2.9)
Received narcotic or antidiarrheal	1.9 (1.4-2.5)	1.8 (1.4-2.5)	1.8 (1.3-2.4)	1.8 (1.3-2.4)	1.9 (1.4-2.6)
Low albumin level (<3.5 mg/dL)	1.8 (1.3-2.4)	1.8 (1.3-2.4)	1.7 (1.3-2.3)	1.7 (1.3-2.3)	1.7 (1.3-2.3)
Antibiotics					
Third-generation cephalosporin	2.1 (1.4-3.2)	2.0 (1.3-3.1)	2.1 (1.3-3.2)	2.1 (1.3-3.2)	2.2 (1.4-3.3)
Fourth-generation cephalosporin	3.9 (2.9-5.4)	3.7 (2.7-5.1)	3.4 (2.5-4.7)	3.5 (2.5-4.8)	3.6 (2.6-4.9)
Fluoroquinolone	1.5 (1.1-2.1)	1.5 (1.1-2.0)	1.4 (1.0-1.9)	1.4 (1.0-1.9)	1.4 (1.1-1.9)
Abdominal procedure performed	1.2 (0.8-1.9)	1.2 (0.8-1.9)	1.1 (0.7-1.8)	1.1 (0.7-1.8)	1.2 (0.8-1.9)
Length of stay at risk, d	NA		NA		NA
<4.5		1 [Reference]		1 [Reference]	
4.5-7.5		1.0 (0.7-1.5)		0.9 (0.6-1.3)	
>7.5		1.3 (0.9-1.8)		0.9 (0.6-1.3)	
Sum CDAD pressure	NA	NA			NA
≤1			1 [Reference]	1 [Reference]	
2-8			2.9 (1.9-4.3)	2.9 (2.0-4.3)	
>8			3.9 (2.7-5.7)	4.0 (2.7-6.0)	
Mean CDAD pressure	NA	NA	NA	NA	
<0.3					1 [Reference]
0.3-1.4					3.9 (2.6-5.8)
>1.4					5.4 (3.4-8.0)
C-statistic (95% confidence interval)	0.85 (0.83-0.87)	0.85 (0.83-0.87)	0.87 (0.85-0.89)	0.87 (0.85-0.89)	0.88 (0.86-0.89)
–2 log likelihood ratio	1357	1355	1302	1302	1273

Abbreviations: CDAD, *Clostridium difficile*–associated disease; LOS, length of stay; NA, not applicable.

*Data are presented as odds ratio (95% confidence interval). Length of stay at risk is defined for case patients as the length of stay until the date of collection of the stool sample positive for a *Clostridium difficile* toxin assay. For noncase patients, the length of stay at risk is defined as the entire length of stay. Sum CDAD pressure is defined as the total number of CDAD cases that a case or noncase patient was exposed to during his or her length of stay at risk. Mean CDAD pressure is defined as the sum CDAD pressure for a case or noncase patient divided by his or her length of stay at risk.

†Models also adjusted for amoxicillin or ampicillin, clindamycin, and abdominal surgery ($P>.05$ for all).

health as exposure to an equal number of patients with CDAD for a shorter period. For example, a patient with a length of stay at risk of 10.0 days and a sum CDAD pressure of 5 would have a mean CDAD pressure of 0.5, vs 2.5 for a patient with a length of stay at risk of 2.0 days. Use of the mean CDAD pressure controls for intensity of CDAD exposure and also for the likelihood that a patient is being cared for by a health care worker who is also caring for a patient with CDAD. Thus, the mean may be a better measure of CDAD exposure than a sum. Additional studies are needed to confirm this hypothesis.

There are some limitations to this study. This was a hypothesis-generating study to determine whether CDAD pressure may be a risk factor for developing CDAD. Several assumptions had to be made when defining CDAD pressure. First, patients colonized with *C difficile* but not experiencing symptomatic CDAD were not captured in the CDAD pressure measurement. In contrast, previous studies of VRE and MRSA colonization pressure have included both symptomatic cases and asymptomatic carriers. Asymptomatic patients can transmit *C difficile*,[29] so lack of inclusion of asymptomatic *C difficile* carriers in CDAD pressure calculations may have biased this study toward the null, attenuating the size of the relationship between CDAD pressure and risk of CDAD. The relative importance of symptomatic patients with CDAD vs asymptomatic carriers in the transmission of CDAD is unknown; however, symptomatic patients may shed more spores in their stool or be more likely to contaminate their surroundings. Similarly, patients with severe CDAD and

profuse diarrhea may contaminate their surroundings more than patients with mild CDAD. Second, the period of infectivity used in this analysis (14 days) was based on the collection date of a case patient's first positive stool toxin assay result, not clinical symptoms. Patients with CDAD may have had symptoms before stool collection, and some may have had resolution of symptoms before the 14-day period ended; thus, the true period of infectivity may be shorter or longer than 14 days. Studies are needed to determine the period that patients with CDAD are truly infectious. Because of these limitations, CDAD pressure should be considered a surrogate marker of colonization pressure until data become available to address these limitations.

This study opens many avenues for future research. A truly accurate measure of *C difficile* colonization pressure would require active surveillance for asymptomatic carriers and molecular typing of isolates. The transmission dynamics of *C difficile* are not completely understood, particularly the importance of asymptomatic *C difficile* carriers and mild vs severe CDAD cases on *C difficile* transmission and rates. Even without a clear understanding of how *C difficile* is transmitted or a measure of asymptomatic carriers, this study demonstrates that the presence of concurrently admitted patients with CDAD on the same ward increases patients' risk of developing CDAD. Future studies on risk factors for CDAD should adjust for CDAD pressure.

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