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Characteristics and Antibiotic Use Associated With Short-Term Risk of *Clostridium difficile* Infection Among Hospitalized Patients

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Abstract

Objectives—Polymerase chain reaction (PCR) has been shown to have an excellent sensitivity and specificity for the detection of Clostridium difficile infection (CDI). Little is known about risk factors for CDI within 14 days of an initial negative test. We sought to determine the characteristics among hospitalized patients associated with risk of short-term acquisition of CDI.

Methods—A case-control study was conducted. Cases were patients who converted from PCR negative to positive within 14 days. Each case was matched with three controls. Conditional logistic regression was used to estimate the association between patient characteristics and CDI.

Results—Of the 30 patients in our study who had a positive PCR within 14 days of a first negative PCR (cases), 15 (50%) occurred within 7 days of the initial test. Cases had a higher proportion of intravenous vancomycin use in the previous 8 weeks (odds ratio [OR], 3.38; 95% confidence interval [CI], 1.34-8.49) and were less likely to have recent antiviral agent use (OR, 0.30; 95% CI, 0.11-0.83) compared with controls.

Conclusions—In hospitalized patients, treatment with intravenous vancomycin within the prior 8 weeks of a first negative PCR test for C difficile is a risk factor for short-term risk for hospital-acquired CDI. Repeat testing guidelines for C difficile PCR should take into consideration patients who may be at high risk for short-term acquisition of CDI.

Keywords

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Clostridium difficile was not identified as the causative bacterial agent for antibiotic-related diarrhea until the late 1970s[1-3] and is now recognized as the leading cause of infectious nosocomial (hospital-acquired) diarrhea.[3,4] The median onset of symptomatic infection after colonization with toxigenic *C difficile* spores is typically 2 to 3 days.[5] Recently, molecular testing has been recognized as an important tool for *C difficile* infection (CDI) diagnosis, with a sensitivity and specificity of 73% to 100% and 91% to 100%, respectively.[6] Due to the high specificity of the test, most institutions using polymerase chain reaction (PCR) to diagnose CDI advocate against repeat testing within 7 days of an initial negative test.[7] Short-term acquisition of CDI, meaning a positive PCR test on repeat testing after an initial negative test within 14 days, is rare, but it does occur in 1% to 4% of patients who undergo repeat testing, and the specific risk factors are unknown.[7-12] Patients with short-term acquisition of CDI are exclusively inpatients since they are most likely to undergo expedited repeated testing.[7,8] Since repeat PCR testing for *C difficile* is costly, determining which patients would likely benefit from repeat testing could be used to guide laboratory policies.[13]

The overall goal of this study was to determine if identifiable patient characteristics would improve the efficiency of a short-term repeat testing protocol for detecting *C difficile*. The objectives of this study were to determine the rate of short-term acquisition (within 14 days) of CDI after an initial negative PCR in our institution and to determine patient characteristics and antibiotic regimens associated with acquisition.

Materials and Methods

This case-control study was conducted at a university-affiliated health care system in a large metropolitan area in the Southeast United States. Adult patients (aged   18 years) had a feces sample ordered in any clinical setting (if the clinician had any concern that the patient may have had CDI based on the presence of fever, leukocytosis, abdominal pain, diarrhea, or ileus). All PCR tests sent for testing for *C difficile* from November 2010 to September 2012 were eligible for the study. From the total pool of PCR tests, those that were repeated within 14 days were identified. Cases were defined as patients with an initially negative PCR test followed by a subsequent positive PCR test within 14 days of the previous negative test. Controls were chosen from the same pool of repeat PCR testing but remained negative during the entire hospital stay **Figure 1**.

Cases were matched to three randomly selected controls by (1) days of hospitalization to first *C difficile* PCR test (±1 day) and (2) age (range ±10 years). Two of the cases needed to be paired with two controls outside the age range (±15 years). These variables were selected for matching because they are established confounders for risk of CDI.[14,15]

All cases had diarrheal disease indicative of CDI confirmed by chart review and were not considered colonized by *C difficile*. Retrospective chart reviews were performed to obtain patient information on baseline demographics, clinical characteristics, and comorbidities from the electronic medical record. We chose the following patient characteristics to abstract based on the literature, including age,[14] immunosuppression (chemotherapy[16], neutropenia[17], human immunodeficiency virus[18]), recent gastrointestinal (GI) surgery,[19]

tube feeding,[20] use of proton pump inhibitors (PPIs),[21] and duration of hospitalization.[22,23] Antimicrobial use was collected for the following medication classes (both 8 weeks before and 14 days after first negative test): β-lactam, macrolide, quinolone, aminoglycoside, trimethoprimsulfamethoxazole, metronidazole, intravenous vancomycin, oral vancomycin, antifungal, antiviral (acyclovir prophylaxis), linezolid, tetracycline, clindamycin, aztreonam, daptomycin, and an "other" category. Other clinical variables collected included if the patient had a GI procedure 8 weeks prior to the first negative test, PPI therapy use within 7 days prior to the first negative test, chronic steroid use (10 mg daily prednisone for 3 months), intensive care unit (ICU) admission within 7 days prior to testing and/or 48 hours after testing, and concurrent coinfections (either GI or systemic).

Variables that were collected specifically *after* the first negative test include ICU admission as listed above, antibiotics during the 14-day time period after the first negative test, and treatment for CDI. All data were entered into a REDCap electronic database.[24]

Laboratory Measures

All feces samples sent to the clinical microbiology laboratory for *C difficile* testing were processed according to the manufacturer's instructions for the Xpert *C difficile* test (Cepheid, Sunnyvale, CA), which detects the presence of the toxin B gene by real-time PCR.[25]

Statistical Analyses

Data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC) and OpenEpi 2.3.1 (Open Source Epidemiologic Statistics for Public Health, Atlanta, GA). The underlying rate for the health care system of short-term acquisition of CDI after a first negative test was calculated using the number of new CDI cases divided by the person days of hospitalized patients who were tested for *C difficile*. This calculation assumed that all other individuals in the hospital were not tested and did not have CDI. Those at risk included the sum of the person days of the cases until their positive PCR and the total hospital days of the individuals who had repeat testing but did not become PCR positive. The χ^2 test (for categorical variables) or Wilcoxon rank-sum test (for continuous variables) was used to assess the association between patient characteristics and incident CDI. A two-sided *P* value less than .05 was considered statistically significant. Conditional logistic regression was used to estimate the adjusted association (adjusted odds ratios [ORs] and 95% confidence intervals [CIs]) between covariates and acquisition of *C difficile*, controlling for the matched patient characteristics (age and days of hospitalization to first PCR test).

Ethical Review

The Emory University Institutional Review Board reviewed the study protocols with expedited approval for minimal risk.

Results

During the study period, a total of 12,021 *C difficile* PCR tests were performed, and of those, 9,312 PCR tests were excluded because those patients received only a single test (Figure 1). Of the 2,709 tests that remained, 430 PCR tests were further excluded because

the repeated testing was performed after a first positive test. Of the 2,279 that had a repeat PCR test after a first negative PCR, 1,500 were within 14 days. From these, we identified 60 PCR tests or 30 cases of patients with short-term CDI acquisition who had an initial negative PCR followed by a positive PCR within 14 days. Fifteen (50%) of the 30 cases acquired CDI within 7 days of the first negative PCR, which is within the window that repeat testing is typically rejected from the laboratory.[7] The rate of short-term acquisition of CDI in the study population was 142 per 100,000 person years (95% CI, 97-200 per 100,000 person years).

The patients' clinical characteristics are shown in **Table 1**. In total, 120 patients were included (30 cases and 90 controls), 52.5% (63/120) were male, median age was 60 (range, 25-88) years, and the median hospital stay was 24 (range, 4-143) days. Sixty-one percent (73/120) had diarrheal disease during the first PCR test; of the cases, 13 (43.3%) had diarrhea before the first test, and 20 (66.6%) had diarrhea before the second test. There were no significant differences between cases and controls in patient characteristics and comorbidities. Compared with controls, cases were more likely to be male (63.3% vs 48.9%), have had a recent GI procedure (26.7% vs 13.3%), and were less likely to have leukemia (23.3% vs 35.6%), although these differences were not statistically significant.

Table 2 shows antibiotic use. In the 8 weeks prior to the first negative PCR test, cases were more likely than controls to be receiving intravenous vancomycin (66.7% vs 38.9%; $P = .009$) and less likely to be taking antiviral medication (20.0% vs 44.4%; $P = .02$). In the 14 days after the first negative PCR test, cases were more likely than the controls to be taking oral vancomycin (16.7% vs 3.3%; $P = .01$) or metronidazole (33.3% vs 16.7%; $P = .05$), which are the treatments for CDI.[23]

After adjusting for age and days of hospitalization prior to first PCR, no patient characteristics were strongly associated with cases or controls **Table 3**. In adjusted analysis, cases were more likely to have end-stage renal disease (ESRD) (OR, 1.71; 95% CI, 0.60-4.19) and be patients with a recent GI procedure (OR, 2.41; 95% CI, 0.84-6.88), but the detected differences were not statistically significant.

When comparing antibiotic use before the first performed PCR test (Table 3), the odds of previous intravenous vancomycin was more common among cases than controls (OR, 3.38; 95% CI, 1.34-8.49), while the use of acyclovir for prophylaxis was more common among the controls (OR, 0.30; 95% CI, 0.11-0.83). When comparing antibiotic use 14 days after the first PCR test, the odds of taking metronidazole or oral vancomycin (which are established treatments for CDI) were more common among cases.

When combining antibiotic classes **Table 4**, intravenous vancomycin therapy with a β-lactam antibiotic in the 8 weeks prior to the first PCR test showed an increased odds in cases (OR, 2.72; 95% CI, 1.10-6.72). The same effect was seen when combining intravenous vancomycin, a β-lactam, and a quinolone (OR, 2.60; 95% CI, 1.05-6.46). No antibiotic combination 14 days after the first test showed statistical significance.

Discussion

The rate of short-term acquisition in this study is comparable to the crude incidence rates in other studies,[26] and the percentage of PCR tests (4.2%) that were initially negative and subsequently positive within 14 days is similar to other studies (2.1%-3.4%).[7,8,12]

In this case-control study of short-term acquisition of CDI among hospitalized patients, we found that intravenous vancomycin (within 8 weeks prior to the first PCR-negative test) was significantly more common among cases than among controls (OR, 3.38; 95% CI, 1.34-8.49), even after adjusting for age and length of hospitalization. In addition, we found that compared with controls, cases were significantly less likely to have a history of acyclovir prophylaxis (OR, 0.30; 95% CI, 0.11-0.83).

The finding that intravenous vancomycin was associated with short-term acquisition of CDI could be partially explained by the fact that more cases were highly health care experienced and also had substantial underlying comorbidities such as immunosuppression and ESRD. This finding has been described before,[15] and one study attributed an adjusted OR of 1.9 for incident CDI (95% CI, 1.7-2.7) if administered for more than 7 days.[27] Intravenous vancomycin can be used for surgical prophylaxis, but in this study, it was used in patients with culture-directed infections or as empirical treatment for febrile syndromes in complicated (immuno-compromised, long-term steroid use, or critically ill) patients (data not shown). In this patient population, almost half were in the ICU during their hospitalization.

Intravenous vancomycin is not indicated as a therapy for *C difficile* due to poor GI penetration (ie, low concentrations found in feces of patients receiving intravenous vancomycin).[28] However, intravenous vancomycin is associated with altered microbiota, specifically selecting for vancomycin-resistant enterococci.[29] While intravenous vancomycin may not be in the causal pathway of short-term acquisition of *C difficile*, it is clearly important.

Two recent meta-analyses of antibiotic classes and their risk of incident CDI focused exclusively on community-associated CDI[30,31]; our hospitalized patient cohort is different, with almost no patients receiving antimicrobials (such as clindamycin), which are typically given on an outpatient basis. Our patients tended to be taking intravenous antibiotics and were being exposed to the hospital reservoir of *C difficile*. Given this finding, the assumption was that the increased odds associated with intravenous vancomycin might have been a surrogate for poly-antimicrobial use. Previous research demonstrated that antibiotic perturbation is necessary for dysbiosis that allows *C difficile* to causes disease.[32,33] Therefore, chronic comorbidities that may require frequent antibiotic use (and, consequently, hospital exposure to *C difficile* spores) or that result in immune compromise may place individuals at increased risk for short-term acquisition of CDI. The strong association with intravenous vancomycin reported in our study may be a surrogate for individuals who are more chronically ill.[34]

We think that the estimated protective effect of acyclovir was biased due to a higher proportion of patients with hematologic malignancy in the control population. Our cohort of

750 individuals from which we drew the cases and controls were hospitalized for lengthy periods (such as hematopoietic stem cell transplant patients), and we randomly oversampled a group that used acyclovir for prophylaxis.

Our study was subject to limitations. First, systematic error due to residual confounding may have occurred due to the limited covariates from study patients that were available for collection during chart review. Second, chart reviews performed could not determine the exact indications for previous antibiotic use. If the indication for antibiotic use was causally related to short-term CDI risk and associated with other patient covariates used in this study, confounding by indication could result in biased estimates.[35] However, we do not believe this to be a major problem because most of the time, antibiotics were used for culture-directed infections or as empirical use in febrile syndromes in complicated patients. Another limitation is that we were unable to determine if patients had previously had CDI. Our institution used a different test to diagnose CDI (enzyme immunoassay alone) before November 2010, so it would be very difficult to compare previous diagnosed cases with our current highly sensitive molecular method.[36] Third, the study's laboratory policy is to automatically reject feces submitted within 7 days of an initial negative test unless the practitioner requests a test to be performed again, which means we could have missed some cases/controls due to the clinician not being concerned enough to request a repeat test.

The purpose of this study was to delineate a subgroup of patients who would assist laboratorians in determining a clinical history that may be associated with a short-term risk of CDI. Given that short-term acquisition while in the hospital is relatively rare, this group of patients has not been studied to determine if there is a characteristic associated with CDI. While the standard practice in the clinical microbiology laboratory is to reject feces samples that are sent for *C difficile* PCR within 7 days,[7] this interval is not derived from biologic studies that show that *C difficile* can be detected within 3 to 7 days of infection.[5] Although it is clear that most patients do not need repeated *C difficile* testing within 14 days, there are still individuals who test positive within this time frame, and this is an important diagnosis to make from an individual's standpoint.[3]

In conclusion, intravenous vancomycin use within the 8 weeks prior was predictive of short-term acquisition of *C difficile* in hospitalized patients. The practical implications for this in terms of repeated testing may include eliciting this antibiotic history when clinicians request repeat testing earlier than 7 days in a hospitalized patient.

Acknowledgments

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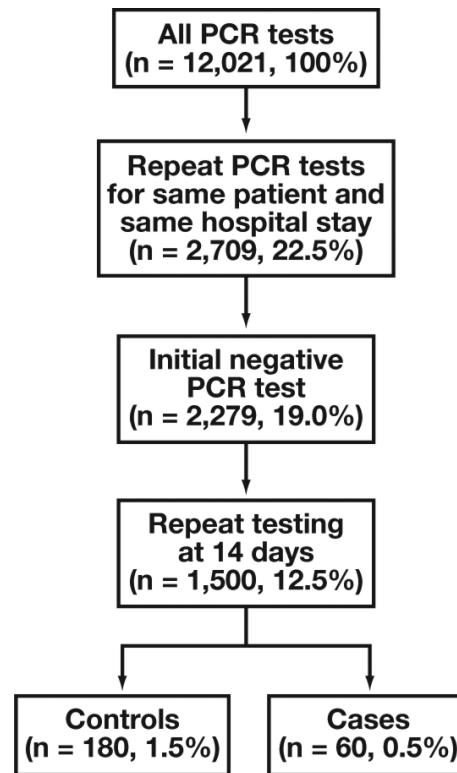
Figure 1.

Cases and controls selected from the total cohort of polymerase chain reaction (PCR) tests performed from November 2010 to September 2012. n represents the number of PCR tests (not patients), and % represents the percentage in comparison to the total cohort of PCR tests (100% cohort = 12,021 PCR tests).

Table 1

Baseline Characteristics of Cases and Controls[a]

Characteristic	Cases (n = 30)	Controls (n = 90)	P Value
Days to first test,[b] median (IQR)	7.8 (5.8)	7.8 (5.7)	.95
Age, median y (IQR)	58.8 (13.5)	58.6 (13.5)	.98
Sex			
Female	11 (36.7)	46 (51.1)	.17
Male	19 (63.3)	44 (48.9)	
Hospital stay, median d (IQR)	27.0 (18.0)	22.5 (18.0)	.39
Death (all causes)	5 (16.7)	9 (10.0)	.33
Intensive care unit stay[c]	11 (36.7)	43 (47.8)	.29
Diabetes mellitus[d]	7 (23.3)	22 (24.4)	.90
Coinfection[e]	18 (60.0)	47 (52.2)	.46
Proton pump inhibitor	26 (86.7)	76 (84.4)	.77
Recent GI procedure[f]	8 (26.7)	12 (13.3)	.09
End-stage renal disease	6 (20.0)	11 (12.2)	.29
Leukemia	7 (23.3)	32 (35.6)	.22
Solid tumor	5 (16.7)	9 (10.0)	.33
Chemotherapy[g]	10 (33.3)	31 (34.4)	.91
Stem cell transplant	1 (3.3)	1 (1.1)	.41
Solid organ transplant	2 (6.7)	9 (10.0)	.58

GI, gastrointestinal; IQR, interquartile range.

[a]Values are presented as number (%) unless otherwise indicated.

[b]Days of hospitalization prior to first *Clostridium difficile* polymerase chain reaction (PCR) test.

[c]Intensive care unit stay within 7 days before or 48 hours after first PCR test.

[d]Defined as HbA1c of more than 6.5%.

[e]Infection of any type and any source at the time of PCR testing.

[f]GI procedure of any type within 8 weeks prior to first PCR test.

[g]Received chemotherapy for malignancy within the past 8 weeks.

Table 2

Antibiotics Used 8 Weeks Prior to First PCR Test[a]

Antibiotic	No. (%)		
	Cases (n = 30)	Controls (n = 90)	P Value[b]
β-Lactam	22 (73.3)	50 (55.6)	.09
Quinolone	14 (46.7)	40 (44.4)	.83
Aminoglycoside	1 (3.3)	6 (6.7)	.50
Metronidazole (PO/IV)	2 (6.7)	9 (10.0)	.58
Vancomycin IV	20 (66.7)	35 (38.9)	**.009**
Acyclovir prophylaxis	6 (20.0)	40 (44.4)	**.02**
Antibiotic use 14 days after first PCR test			
β-Lactam	19 (63.3)	62 (68.9)	.58
Quinolone	12 (40.0)	33 (36.7)	.75
Aminoglycoside	3 (10.0)	6 (6.7)	.55
Metronidazole (PO/IV)	10 (33.3)	15 (16.7)	**.05**
Vancomycin IV	9 (30.0)	43 (47.8)	.09
Vancomycin PO	5 (16.7)	3 (3.3)	**.01**
Acyclovir prophylaxis	8 (26.7)	37 (41.1)	.16

IV, intravenous; PCR, polymerase chain reaction; PO, oral.

[a]Other antibiotics analyzed but not shown (as total number of patients receiving them 5) were macrolides, trimethoprim-sulfamethoxazole, antifungals, linezolid, tetracyclines, clindamycin, aztreonam daptomycin, and "others" (carbapenem, dapsone, meropenem, nitrofurantoin, and tigecycline). None was statistically significant.

[b]Bold signifies statistical significance, two-sided $P < .05$.

Table 3

Conditional Logistic Regression Matched Odds Ratios for Patient Characteristics and Antibiotic Use Associated With Short-Term Acquisition of *Clostridium difficile*[a]

Characteristic	OR (95% CI)[b]
Male sex	1.87 (0.76-4.18)
Death (all causes)	1.85 (0.54-6.28)
Intensive care unit stay[c]	0.59 (0.24-1.45)
Diabetes mellitus[d]	0.94 (0.35-2.47)
Coinfection[e]	1.49 (0.58-3.82)
Proton pump inhibitor	1.18 (0.37-3.73)
Recent GI procedure[f]	2.41 (0.84-6.88)
End-stage renal disease	1.72 (0.60-4.19)
Leukemia	0.49 (0.17-1.38)
Solid tumor	1.85 (0.54-6.28)
Chemotherapy[g]	0.94 (0.37-2.40)
Stem cell transplant	3.00 (0.19-47.96)
Solid organ transplant	0.67 (0.14-3.09)
Antibiotic use 8 weeks prior to first PCR test[h]	
β-Lactam	2.35 (0.91-6.07)
Quinolone	1.10 (0.47-2.59)
Aminoglycoside	0.50 (0.06-4.15)
Metronidazole	0.67 (0.14-3.09)
Vancomycin IV	**3.38 (1.34-8.49)**
Acyclovir prophylaxis	**0.30 (0.11-0.83)**
Antibiotic use 14 days after first PCR test[h]	
β-Lactam	0.81 (0.36-1.81)
Quinolone	1.18 (0.47-2.98)
Aminoglycoside	1.50 (0.38-6.00)
Metronidazole	2.39 (0.95-6.06)
Vancomycin IV	0.47 (0.19-1.16)
Vancomycin PO	**6.63 (1.27-34.74)**
Acyclovir prophylaxis	0.51 (0.20-1.29)

CI, confidence interval; GI, gastrointestinal; IV, intravenous; OR, odds ratio; PCR, polymerase chain reaction; PO, oral.

[a] OR matched on age and days to first PCR test.

[b] Bold signifies statistical significance.

[c] Intensive care unit stay within 7 days before or 48 hours after first PCR test.

[d] Defined as HbA1c of more than 6.5%.

[e] Infection of any type and any source at the time of PCR testing.

[f] GI procedure of any type within 8 weeks prior to first PCR test.

[g] Received chemotherapy for malignancy within the past 8 weeks.

[h] Other antibiotics analyzed but not shown were macrolides, trimethoprim-sulfamethoxazole, antifungals, linezolid, tetracyclines, clindamycin, aztreonam, daptomycin, and "others" (carbapenem, dapsone, meropenem, nitrofurantoin, and tigecycline). None was statistically significant.

Table 4

Matched Odds Ratio for Combined Antibiotic Classes Associated With Short-Term Acquisition of *Clostridium difficile*[a]

Antibiotic	OR (95% CI)[b]
Antibiotic class administered 8 weeks prior to first test	
β-Lactam	2.35 (0.91-6.07)
Quinolone	1.10 (0.47-2.59)
Vancomycin IV	**3.38 (1.34-8.49)**
β-Lactam + vancomycin IV	**2.72 (1.10-6.72)**
β-Lactam + vancomycin IV + quinolone	**2.60 (1.05-6.46)**
Antibiotic class administered 14 days after first test	
β-Lactam	0.81 (0.36-1.81)
Quinolone	1.18 (0.47-2.98)
Vancomycin IV	0.47 (0.19-1.16)
β-Lactam + vancomycin IV	0.49 (0.20-1.22)
β-Lactam + vancomycin IV + quinolone	0.78 (0.35-1.73)

CI, confidence interval; IV, intravenous; OR, odds ratio.

[a] OR matched on age and days to first test.

[b] Bold signifies statistical significance.