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Antibiotic Exposure and Risk for Hospital-Associated *Clostridioides difficile* Infection

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ABSTRACT *Clostridioides difficile* infection (CDI) is a health care-associated infection associated with significant morbidity and cost, with highly varied risk across populations. More effective, risk-based prevention strategies are needed. Here, we investigate risk factors for hospital-associated CDI in a large integrated health system. In a retrospective cohort of all adult admissions to 21 Intermountain Healthcare hospitals from 2006 to 2012, we identified all symptomatic (i) hospital-onset and (ii) health care-facility-associated, community-onset CDI. We then evaluated the risk associated with antibiotic exposure, including that of specific agents, using multivariable logistic regression. A total of 2,356 cases of CDI among 506,068 admissions were identified (incidence, 46.6 per 10,000). Prior antibiotic use was the dominant risk factor, where for every antibiotic day of therapy prior to the index admission, the odds of subsequent CDI increased by 12.8% (95% confidence interval [CI], 12.2 to 13.4%; $P < 0.0001$). This was a much stronger association than was inpatient antibiotic exposure (odds ratio [OR], 1.007 [95% CI, 1.005 to 1.009]; $P < 0.0001$). The highest-risk antibiotics included second-generation and later cephalosporins (especially oral), carbapenems, fluoroquinolones, and clindamycin, while doxycycline and daptomycin were associated with a lower CDI risk. We concluded that cumulative antibiotic exposure prior to admission is the greatest contributor to the risk of subsequent CDI. Most classes of antibiotics carry some risk, which varies by drug and route. This information may be useful for antimicrobial stewardship efforts.

KEYWORDS antibiotics, *Clostridioides difficile* infection, antibiotic stewardship, health care associated

Clostridioides difficile infection (CDI) remains one of the most significant infectious causes of morbidity and mortality and is often health care associated (1, 2). The annual incidence of CDI in the United States exceeds half a million cases (3) and represents a major contributor to health care costs at up to $10,000 per episode (4–6). Considering projections that the incidence of CDI may increase by up to 40% in the next 10 years (7), CDI is considered an urgent threat by the Centers for Disease Control and Prevention (8), and controlling this infection is a top priority for health care institutions in order to prevent unfavorable clinical and financial outcomes. Antibiotics disrupt the protective microdiversity of the gastrointestinal microbiome (GIMb), which plays a central role in the pathophysiology of CDI (9). Accordingly, one of the most effective strategies to prevent CDI is antimicrobial stewardship (10–12). However, the

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TABLE 1 Demographics and characteristics by *Clostridioides difficile* infection group[a]

Patient characteristic[b]	Data for infection group[c]:	
	CDI (n = 2,356)	No CDI (n = 503,712)
No. with hospital onset	1,655	
No. with community onset, health care facility associated (within 30 days of discharge)	701	
Age (mean [SD]) (yr)	62.95 (17.84)	60.21 (18.87)
Male	1,127 (47.8)	231,215 (45.9)
1-yr mortality	704 (29.9)	62,461 (12.4)
30-day readmission	148 (6.3)	11,390 (2.3)
Length of stay (mean [SD]) (days)	14.72 (15.74)	3.84 (4.54)
Current ICU admission	928 (39.4)	80,623 (16.0)
Medical-surgical ward admission within 90 days	896 (38.0)	120,212 (23.9)
ICU admission, prior 90 days	315 (13.4)	33,480 (6.6)
Antibiotic use, prior 60 days	1,931 (82.0)	80,379 (16.0)
Gastric acid suppression	1,645 (69.8)	225,061 (44.7)
Steroids	652 (27.7)	62,285 (12.4)
Nonsteroidal immunosuppression	232 (9.8)	13,631 (2.7)
White blood cell count (median [IQI]) (cells/mm^3)	6.8 (4.7–9.3)	7.2 (5.6–9.3)
Absolute neutrophil count (median [IQI]) (cells/mm^3)	5.5 (3.4–8.5)	5.4 (3.8–7.8)
Serum creatinine concn (median [IQI]) (mg/dl)	1.26 (0.88–2.20)	1.00 (0.80–1.32)
Gastrointestinal procedure, prior 90 days	756 (32.1)	36,353 (7.2)
Charlson comorbidity score (median [IQI])	6.00 (4.0, 9.0)	4.00 (2.0, 8.0)
No. of comorbidities (mean [SD])	3.42 (2.37)	2.42 (2.24)
Connective tissue disease	151 (6.4)	17,337 (3.4)
Human immunodeficiency virus	7 (0.3)	446 (0.1)
Inflammatory bowel disease	84 (3.6)	6,836 (1.4)
Solid organ transplant recipient	29 (1.2)	2,360 (0.5)
Hematological malignancy	108 (4.6)	3,188 (0.6)
Hematopoietic stem cell transplant recipient	57 (2.4)	646 (0.1)
History of malignancy	655 (27.8)	86,524 (17.2)
Cerebrovascular disease	554 (23.5)	96,899 (19.2)
Chronic pulmonary disease	1,125 (47.8)	209,408 (41.6)
Congestive heart failure	866 (36.8)	128,003 (25.4)
Cognitive impairment	92 (3.9)	16,481 (3.3)
Diabetes mellitus without complications	838 (35.6)	152,933 (30.4)
Diabetes mellitus with complications	340 (14.4)	49,779 (9.9)
Metastatic cancer	175 (7.4)	25,576 (5.1)
Mild hepatic disease	665 (28.2)	76,608 (15.2)
Severe hepatic disease	193 (8.2)	11,704 (2.3)
Myocardial infarction	440 (18.7)	81,554 (16.2)
Paraplegia	159 (6.7)	19,511 (3.9)

[a]Data are reported as the no. (%), unless otherwise noted.
[b]IQI, 25% to 75% interquartile interval.
[c]CDI, *Clostridioides difficile* infection.

degree to which various antibiotic classes are associated with the risk of CDI (especially after controlling for other risk factors) is not fully understood yet could be very important in making effective stewardship recommendations. Here, we explore predictive risk factors for health care-associated CDI, including antibiotic exposure before and during the index hospitalization.

RESULTS

During the study period, 506,068 unique admissions were identified. Among these, 2,356 cases of CDI occurred (1,655 hospital onset [HO] and 701 community onset, health care-facility associated [CO-HCFA]), for an overall incidence of 46.6 per 10,000 admissions. Incidences ranged from 51.8/10,000 in 2006 to 38.1/10,000 in 2010 and increased to 51.9/10,000 in 2011 to 2012 after changing CDI laboratory assays. Clinical and demographic data stratified by the presence or absence of CDI are detailed in Table 1. Age and Charlson comorbidity scores were greater in the CDI group than in the non-CDI group. Antibiotic administration within the 60 days prior to the index admission was far more common (94.7%) in the CDI group than in the non-CDI group (16.0%), as were immunosuppression, gastric acid suppression, and recent gastrointestinal procedures. Antibiotics by agent and CDI group are displayed in Tables S1 and S2 in the

TABLE 2 Adjusted risk of CDI and individual antibiotics within 60 days prior to index admission in final model[a]

Antibiotic	Odds ratio	95% CI[b]	*P*[c]
Ampicillin	1.6	1.1–2.4	0.039
Ampicillin-sulbactam	1.6	1.1–2.3	0.044
Cefazolin	2.3	1.9–2.6	0.013
Cefdinir	3.5	1.8–6.7	0.036
Cefepime	2.8	2.1–3.6	0.017
Cefoxitin	4.8	3.8–6.3	0.011
Ceftriaxone	4.0	3.5–4.6	0.005
Cefuroxime	6.4	5.1–7.9	0.009
Cephalexin	2.1	1.5–3.0	0.03
Clindamycin	1.9	1.5–2.5	0.022
Daptomycin	0.4	0.2–0.6	0.034
Doxycycline	0.6	0.3–1.0	0.05
Ertapenem	2.5	2.0–3.2	0.016
Antipseudomonal carbapenem	5.1	4.4–6.0	0.003
Fluoroquinolone	3.0	2.7–3.5	0.008
Linezolid	1.2	1.0–1.5	0.047
Nafcillin	2.1	1.4–3.1	0.038
Piperacillin-tazobactam	5.1	4.4–6.0	0.002
Trimethoprim-sulfamethoxazole	2.0	1.6–2.6	0.019

[a]Continuation of multivariable logistic regression model in Table 4, with individual antibiotics replacing the cumulative 60-day antibiotic variable.
[b]CI, confidence interval.
[c]*P* values adjusted for a 5% false-discovery rate via the Benjamini-Hochberg method.

supplemental material. Seventy-one percent of patients who received antibiotics in the prior 60 days also had a hospital admission during that time period prior to the index admission. Outcomes were worse in CDI cases, including mortality, proportion admitted to an intensive care unit (ICU), and hospital length of stay.

In the multivariable regression model adjusting for demographic and other CDI risk factors, any antibiotic administered prior to the index admission was the predominant risk factor for CDI, contributing far more risk than antibiotics received during the hospital stay (Table 1). Using the variables for any antibiotic given resulted in a better fit model (adjusted $R^2 = 0.34$) than using the days of therapy (DOT) antibiotic use variable (adjusted $R^2 = 0.2$). For every day of antibiotic therapy received prior to the index admission, the odds of CDI were higher by 12.8% (odds ratio [OR], 1.128; 95% confidence interval [CI], 1.122 to 1.134; $P < 0.0001$).

The adjusted odds of CDI by individual antibiotic given prior to the index admission are shown in Table 2. Notably, a risk of CDI was observed with nearly all classes included in the model, with the exception of daptomycin and doxycycline, which may have been associated with a lower risk of CDI. Significant associations with CDI were observed with both prior azithromycin and vancomycin in the original model; however, in sensitivity analyses, neither of these remained associated with CDI when accounted for in the absence of any other concomitant antibiotic coadministration. The odds of CDI were greatest with the cephalosporin class, particularly second- and third-generation cephalosporins, with oral cefuroxime, cefdinir, and intravenous ceftriaxone and cefoxitin associated with the greatest risk. Antipseudomonal carbapenems were also associated with elevated risk, as were fluoroquinolones. The adjusted odds of CDI by antibiotic given during the index admission are shown in Table 3. Of the antibiotics administered during the admission, carbapenems and cefoxitin were associated with the greatest risk, followed by cefuroxime, piperacillin-tazobactam, and cefepime.

Recent hospitalization or ICU stay (within 60 days of index admission) were significantly associated with CDI in multivariable models before inclusion of the variable for antibiotics within 60 days. There was a clear interaction between recent hospitalization and prior antibiotic use (*P* value for interaction term < 0.001); in that model, prior hospital admission was associated with higher risk of CDI, as was true in the base model. The estimates of association on stratified models were as follows: for prior

TABLE 3 Adjusted risk of CDI and individual antibiotics during index admission[a]

Antibiotic (index admission)	Odds ratio	95% CI[b]	*P*[c]
Amoxicillin-clavulanate	0.6	0.4–0.8	0.039
Cefepime	1.3	1.0–1.7	0.048
Cefoxitin	1.9	1.5–2.4	0.023
Ceftriaxone	1.4	1.2–1.6	0.025
Cefuroxime	1.6	1.3–1.9	0.033
Daptomycin	0.3	0.2–0.5	0.027
Doxycycline	0.5	0.3–0.8	0.041
Antipseudomonal carbapenem	2.1	1.8–2.4	0.014
Piperacillin-tazobactam	1.5	1.3–1.7	0.020

[a]Continuation of multivariable logistic regression model in Tables 2 and 4, with individual antibiotics given during the index hospital admission.
[b]CI, confidence interval.
[c]*P* values adjusted for a 5% false-discovery rate via the Benjamini-Hochberg method.

antibiotics (DOT), OR, 1.43 (95% CI, 1.41 to 1.45); and for inpatient antibiotics (DOT), OR, 1.003 (95% CI, 1.001 to 1.006). Other risk factors for CDI in the final multivariable regression model including all individual antibiotics are listed in Table 4. The discrimination of the final logistic regression model by the area under the receiver operator characteristic curve (AUROC) was excellent, at 0.91 (95% CI, 0.90 to 0.92), with an adjusted R^2 of 0.36.

DISCUSSION

This study reports one of the largest CDI cohorts to date, clarifying the epidemiology of hospital-associated CDI and confirming the association of multiple previously identified risk factors for CDI. While many previous studies have evaluated the risk of antibiotics independently of other factors (13, 14), the large size of our study cohort permitted an examination of the relative risks of antibiotic classes after adjustment for many other risk factors, giving a more accurate picture. Consequently, these data further help inform antimicrobial stewardship decisions with respect to antimicrobial choice and duration as they relate to CDI.

Perhaps most interesting was the observation that while antibiotics administered

TABLE 4 Multivariable logistic regression for factors associated with CDI

Variable	Odds ratio	95% CI[a]	*P*
Age	1.01	1.006–1.013	<0.0001
Charlson comorbidity score	1.05	1.02–1.07	<0.0001
Chronic pulmonary disease	0.85	0.76–0.95	0.005
Diabetes mellitus	0.73	0.65–0.83	<0.0001
Malignancy	0.83	0.71–0.96	0.012
Hepatic disease	1.3	1.1–1.4	<0.0001
Hematological malignancy	3.1	2.3–4.1	<0.0001
Hematopoietic stem cell transplant	5.7	3.8–8.4	<0.0001
Corticosteroids	1.2	1.1–1.4	0.001
Gastric acid suppression	1.4	1.3–1.6	<0.0001
Recent hospitalization (past 60 days)[b]	2.2	1.5–3.4	<0.0001
Recent intensive care unit stay (past 60 days)[c]	6.5	3.8–11.3	<0.0001
Intensive care unit (current admission)	1.9	1.6–2.1	<0.0001
Gastrointestinal procedure (prior 90 days)	3.1	2.7–3.5	<0.0001
Absolute neutrophil count	1.02	1.01–1.03	<0.0001
Serum creatinine concn	1.004	1.001–1.007	0.006
Antibiotic DOT during index admission[e]	1.007	1.005–1.009	<0.0001[d]
Antibiotic DOT in the prior 60 days[e]	1.128	1.122–1.134	<0.0001[d]

[a]CI, confidence interval.
[b]OR after introducing a multiplicative interaction term between recent hospitalization and any antibiotic received in the prior 60 days.
[c]OR after introducing a multiplicative interaction term between recent intensive care unit stay and any antibiotic received in the prior 60 days.
[d]*P* values adjusted for a 5% false-discovery rate via the Benjamini-Hochberg method.
[e]Individual prior antibiotics were substituted for cumulative antibiotics in the final model. See Table 2 for individual antibiotics.

during the index hospitalization are associated with an increased risk of CDI, the predictive contributions of this and other traditional risk factors are minimal compared to that of antibiotics administered in the 60 days prior to admission. While our observations are not themselves causal, they are consistent with observations from previous studies suggesting that the CDI risk of antecedent antibiotic use is both cumulative (15), with odds increasing by 12.8% with every day of individual antibiotic exposure in our data, and greatest within 60 days of antibiotic administration (16, 17). These observations lend support to antimicrobial stewardship interventions that avoid unnecessary antibiotics and limit an excessive duration of therapy. Because much of the prior antibiotic use in this cohort occurred during a preceding hospitalization, these results do not depreciate the importance of inpatient stewardship; they simply suggest that antibiotic reductions during a given admission may have additional benefit if a patient is later readmitted.

Second, our data confirm that even after adjusting for other risk factors, nearly all commonly prescribed classes of antibiotics, except daptomycin and tetracyclines, portend some risk of CDI (14, 18). While some classes had predictably higher risk, such as late-generation cephalosporins and carbapenems (19), even relatively narrow-spectrum antibiotics, such as ampicillin, nafcillin, and cefazolin, were associated with CDI. This supports the underrecognized principle that the clinical spectrum of an antibiotic is distinct from its risk for CDI (20). The clinical spectrum of an antibiotic, commonly referred to in terms of "narrow" or "broad," represents the variety of bacterial pathogens for which achievable serum or tissue drug levels are sufficiently greater than the MIC. In contrast, the risk of CDI as defined in preclinical models for any given antibiotic is dependent on the following three distinct factors: (i) *in vitro* susceptibility of *C. difficile* to the agent (21), (ii) collateral impact of the agent on the GIMb, an important ecological deterrent to *C. difficile* (22, 23), and (iii) the intraluminal gastrointestinal concentrations achieved by the antibiotic (20). Culture-based susceptibility studies suggest that second- and third-generation cephalosporins have the poorest activity against *C. difficile* isolates, up to 3 times less active than first-generation cephalosporins, for example (21). This is consistent with our observations, in which oral cefuroxime and cefdinir were among the highest-risk agents, perhaps because of their poor *C. difficile* activity or limited oral bioavailability. This is an interesting observation with respect to the implications of the common practice of intravenous-to-oral beta-lactam switch and may merit further study. Conversely, we observed a possible association between doxycycline and daptomycin use and decreased risk of CDI. This association has been previously reported for doxycycline (24) and is biologically plausible for daptomycin considering that this agent is active against *C. difficile* but has little effect on the GIMb (25, 26). We acknowledge that this finding may also reflect confounding by indication.

The strengths of this study include the very large cohort and availability of granular, patient-level data from multiple hospitals representing a cross-section of health care spanning small critical access hospitals to tertiary-care academic centers. The large number of cases available facilitated an evaluation of risk factors, including many different individual antibiotics. As noted above, an important limitation includes the likely incompleteness of data regarding prior antibiotics prescribed or filled outside our system. Another important limitation was the frequent overlap between previous antibiotic use and prior hospitalization, which may represent a collider variable; we are reassured by the stratified analyses that show that both prior antibiotic use and prior hospitalization are associated with a higher risk of CDI. We note that we did not employ causal inference methods because our inferential target was predictive association rather than causation. We are careful not to make causal claims about our findings. We do, however, identify the reality that risk prediction models for CDI will likely need to incorporate data on the individual agents used in order to optimize predictive accuracy. Finally, although most CDI cases in our cohort were identified by toxin-positive status by immunoassay plus documented diarrhea, it is still possible that we included some patients with colonization with *C. difficile* rather than invasive infection with the use of

a nucleic acid amplification test (NAAT). Because *C. difficile* screening is not employed, we were unable to validate interesting data suggesting that asymptomatic carriage during a hospitalization was associated with postdischarge CDI (27).

Our results confirm the importance of prior antibiotic use and demonstrate the relative differences in risk between classes in terms of CDI risk among hospitalized patients. These data can be taken into consideration by antimicrobial stewardship teams in the identification of patients at risk for CDI.

MATERIALS AND METHODS

Study design. We conducted a retrospective cohort study with model derivation and independent hold-out validation. The study was approved by the Intermountain Healthcare institutional review board with a waiver of informed consent. Our study population included all consecutive adult admissions to an inpatient medical, surgical, or medical-surgical unit or intensive care unit (ICU) at any of 21 Intermountain Healthcare hospitals in Utah and Idaho. We excluded admissions from the following units: emergency department observation, inpatient behavioral health, inpatient rehabilitation, same-day surgery, and labor and delivery. The study period was 1 January 2006 to 31 December 2012. During the study period, the diagnostic test for *C. difficile* was enzyme-linked immunoassay for toxin B (without two-step glutamate dehydrogenase [GDH] antigen) from January 2006 to November 2010 and nucleic acid amplification test (NAAT) for toxin A from November 2010 to December 2012.

Data collection and definitions. Intermountain Healthcare is an integrated health network with 22 adult hospitals and 200 clinics in Utah and southern Idaho. Most clinical laboratory testing for patients within the network is done at local hospital laboratories or referred to the Intermountain central laboratory. All cases and admission data were acquired through electronic query of the Intermountain enterprise data warehouse. Antibiotic administration data were limited to outpatient prescriptions documented in the electronic health record and medications administered in network hospitals and infusion centers. During the study period, paper prescriptions were common in the ambulatory setting and not reliably captured electronically, nor was it possible to verify actual antibiotic consumption. Antibiotic use was quantified using the days of therapy (DOT) metric (each unique antibiotic administered during a 24-h calendar day period was defined as 1 day of therapy). International Classification of Diseases, Ninth Edition (ICD-9) codes were used to identify comorbidities using the Charlson comorbidity index (28). Procedure codes were used to identify intra-abdominal surgeries and intestinal endoscopic procedures, defined collectively as gastrointestinal procedures. *C. difficile* infection was defined as a positive enzyme-linked immunoassay or NAAT result in the setting of more than three stools per day, determined by querying the electronic health record (EHR) stool count, which is routinely documented at study hospitals, or evidence of toxic megacolon. Routine stool *C. difficile* screening is not performed at our facility, so asymptomatic carriage rates were not available. Hospital-onset (HO) CDI was defined as CDI not present on admission and diagnosed by positive CDI assay ordered at least 72 h after admission but before discharge. All community-acquired CDI cases during our study period were previously manually determined to be present on admission as part of a separate, unpublished study and were excluded. Community-onset, health care facility-associated (CO-HCFA) CDI was defined as a positive diagnosis within 30 days after discharge from the index hospitalization; confirmation by strain typing was not performed to confirm association with prior admission. These two definitions were combined to define our outcome of hospital-associated CDI in all models.

Statistical analysis. Our primary aim was to explore the predictive association between antibiotics and risk of CDI rather than to draw causal inferences about specific mechanisms. We thus conducted a risk factor analysis by fitting a multivariable logistic regression model for CDI using a purposeful variable selection strategy including variables previously associated with CDI as identified by a literature search. First, a base model was developed with clinical variables but excluding antibiotic variables. We then developed a model by introducing antibiotic variables into the base model. First, we introduced variables for any antibiotic administered in the 60 days prior to the index admission and any antibiotic given during the index admission, respectively. We then replaced these with variables for overall cumulative antibiotic DOT given prior to and/or during the index admission and verified the fit of these two models.

In further modeling, we replaced the cumulative antibiotic variables with all individual antibiotics administered prior to (Table S1) and individual antibiotics administered during (Table S2) the index admission and reduced the model to only those agents that remained significantly associated with CDI. To assist with this step, we also used a collinearity matrix to identify clinical characteristics that were collinear with specific antibiotics and where necessary excluded collinear variables from the model. We identified high collinearity between oral penicillin VK mucositis prophylaxis and hematological malignancy, a known independent risk factor for CDI; we thus removed penicillin VK from analysis. We also identified modest collinearity between antibiotics that are frequently coadministered, such as ceftriaxone and azithromycin (for community-acquired pneumonia) and vancomycin plus either piperacillin-tazobactam or carbapenems (for severely ill patients). To address, this we conducted a sensitivity analysis in a stratified cohort consisting only of patients for whom vancomycin or azithromycin was used, in the absence of any other antibiotics, and a second sensitivity analysis in which variables for vancomycin and azithromycin were coded only when used independently of any other antibiotics, either prior to admission or during the admission, respectively. We intentionally did not include metronidazole or oral vancomycin in any models because of the confounding for CDI treatment. Final model relevance and fit were explored using adjusted R^2, and model discrimination was measured by the area under the receiver

operator characteristic curve (AUROC). All analyses were considered significant at a two-tailed *P* value of <0.05. To account for multiple comparisons, we adjusted the *P* value for all antibiotics in the final model for a 5% false-discovery rate using the Benjamini-Hochberg method (29). Finally, anticipating that prior hospitalization might introduce bias via ascertainment and/or collider bias, we performed sensitivity analyses to investigate the relationship between recent hospitalization and the association between antibiotics and CDI. First, we introduced multiplicative interaction terms for prior "antibiotic use × prior hospitalization" and "prior antibiotic use × prior ICU stay." Based on the results of the interaction analysis, we also conducted separate stratified analyses for patients with and without a recent hospitalization before the index hospitalization.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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B.J.W. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. B.J.W., J.F., and A.S. developed the study concept and design. All authors participated in acquisition, analysis, or interpretation of the data. B.J.W., S.M.B., J.F., and A.S. drafted the manuscript. B.J.W., S.M.B., and J.F. performed statistical analysis. All authors participated in critical review of the manuscript for important intellectual content.

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