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Major Article

Correlation between hospital-level antibiotic consumption and incident health care facility-onset *Clostridium difficile* infection

Page E. Crew PharmD, MPH [a,b], Nathaniel J. Rhodes PharmD, MSc [a,b], J. Nicholas O'Donnell PharmD, MSc [a,b], Cristina Miglis PharmD, MSc [a,b], Elise M. Gilbert PharmD [b,c], Teresa R. Zembower MD, MPH [d,e], Chao Qi PhD [f], Christina Silkaitis MT (ASCP), CIC, FAPIC [e], Sarah H. Sutton MD [d,e], Marc H. Scheetz PharmD, MSc [a,b,*]

[a] *Department of Pharmacy Practice, Chicago College of Pharmacy, Midwestern University, Downers Grove, IL*
[b] *Department of Pharmacy, Northwestern Memorial Hospital, Chicago, IL*
[c] *Department of Pharmacy Practice, College of Pharmacy, Chicago State University, Chicago, IL*
[d] *Department of Internal Medicine, Division of Infectious Diseases, Feinberg School of Medicine, Northwestern University, Chicago, IL*
[e] *Department of Healthcare Epidemiology and Infection Prevention, Northwestern Memorial Hospital, Chicago, IL*
[f] *Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago, IL*

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Background: The purpose of this single-center, ecologic study is to characterize the relationship between facility-wide (FacWide) antibiotic consumption and incident health care facility-onset *Clostridium difficile* infection (HO-CDI).

Methods: FacWide antibiotic consumption and incident HO-CDI were tallied on a monthly basis and standardized, from January 2013 through April 2015. Spearman rank-order correlation coefficients were calculated using matched-months analysis and a 1-month delay. Regression analyses were performed, with $P < .05$ considered statistically significant.

Results: FacWide analysis identified a matched-months correlation between ceftriaxone and HO-CDI ($\rho = 0.44$, $P = .018$). A unit of stem cell transplant recipients did not have significant correlation between carbapenems and HO-CDI in matched months ($\rho = 0.37$, $P = .098$), but a significant correlation was observed when a 1-month lag was applied ($\rho = 0.54$, $P = .014$).

Discussion: Three statistically significant lag associations were observed between FacWide/unit-level antibiotic consumption and HO-CDI, and 1 statistically significant nonlagged association was observed FacWide. Antibiotic consumption may convey extended ward-level risk for incident CDI.

Conclusions: Consumption of antibiotic agents may have immediate and prolonged influence on incident CDI. Additional studies are needed to investigate the immediate and delayed associations between antibiotic consumption and *C difficile* colonization, infection, and transmission at the hospital level.

Clostridium difficile infection (CDI) is a major source of infectious disease-related morbidity and mortality. During 2011, there were an estimated 453,000 incident CDI events in the United States.[1] Almost one-quarter (24.2%) of those cases were classified as hospital-onset.[1] One particularly important patient-level risk factor for CDI is exposure to antimicrobial agents.[2] Several classes of antibiotics are believed to confer a higher risk for CDI relative to other antibiotics, although study findings vary.[3,4] High-risk antibiotics for CDI include fluoroquinolones,[4,5] second-, third-, and fourth-generation cephalosporins,[3,6,7] carbapenems,[3] β-lactam/β-lactamase inhibitor combinations,[6] and clindamycin.[7] Virtually all antibiotics have been associated with the development of CDI, and even a single

* Address correspondence to Marc H. Scheetz, PharmD, MSc, Midwestern University Chicago College of Pharmacy, 555 31st St, Downers Grove, IL 60515.
E-mail address: mschee@midwestern.edu (M.H. Scheetz).

PEC is currently with Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD.

EMG is currently with Janssen Scientific Affairs, LLC, Titusville, NJ.

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dose of an antibiotic may increase a patient's risk of *C difficile*.[2,5,8] According to estimates by the Centers for Disease Control and Prevention (CDC), more than half of hospitalized patients receive at least 1 antibiotic during their hospitalization.[9] Further, it is estimated that 30%- 50% of antibiotic use in hospital settings is inappropriate or unnecessary.[10,11]

The relationship between CDI and antimicrobial consumption is well established at the patient level,[2] but institution-level risk factors for CDI are emerging. Several studies have shown that antimicrobial stewardship initiatives targeting a reduction in high-risk antibiotics use are associated with a corresponding reduction in CDI.[12-14] Further, a mathematical modeling study conducted by CDC among 26 medical/surgical wards in the United States predicted that by decreasing the consumption of broad-spectrum antibiotics by 30%, hospitals could subsequently reduce the incidence of CDI by 26%.[15] Collectively, these studies suggest that changing antibiotic consumption at the population level can influence health care facility-onset CDI (HO-CDI) incidence.

A patient generally develops CDI following exposure to *C difficile* in the setting of antibiotic-related disruption of his or her microbial flora or other patient-level risk factors.[2,16] Transmission of CDI between patients or via fomites is of particular concern within hospital settings. A recent retrospective cohort study[16] explored the hypothesis that sharing the same physical unit with patients taking antibiotics may be a risk factor for CDI, even among patients without recent exposure to antibiotic agents. The study found that for each 10% increase in unit-level antimicrobial use, there was an associated 2.1 per 10,000 increase in CDI incidence ($P < .001$).[16] This association maintained statistical significance even among patients without recent antimicrobial agent use and also after adjustment for patient-level risk factors.[16]

Environment factors such as occupying a hospital room where the previous occupant had CDI[17] have been associated with increased risk for acquisition of CDI. Asymptomatic carriers of *C difficile* by stool culture are more likely to have detectable *C difficile* on their skin samples and environment samples versus noncarriers, representing a potential fomite source for transmission.[18] In addition, recurrent or persistent *C difficile* shedding and contamination of a patient's environment can persist for up to 6 weeks after CDI treatment is complete, posing a potential risk for future patients.[19]

Our study aimed to characterize the association between HO-CDI and hospital-level antibiotic consumption, both facility-wide (FacWide) and at the unit-level. Defining the association between antibiotic consumption at the hospital level and the unit level relative to HO-CDI rates will provide data that can be used to inform antimicrobial stewardship interventions and generate new hypotheses for exploration.

MATERIAL AND METHODS

A single-center, retrospective, ecologic study was conducted to evaluate the relationship between antibiotic consumption and the incidence of HO-CDI (CDI diagnosed > 3 calendar days following admission[20]) at our center between January 2013 and April 2015. The study was conducted at an 894-bed academic medical center located in Chicago, IL. The center is a level-I trauma center with 5 intensive care units. During fiscal year 2015 there were more than 44,000 inpatient admissions, and the center performs more than 250 hematopoietic stem cell transplants (SCTs) per year. The study was approved by the Northwestern University and Midwestern University Institutional Review Boards.

Antibiotic consumption data were measured in antibiotic days (ADs), standardized to 1,000 days present (DP), and tallied on a monthly basis for FacWide and for 3 individual hospital units.[21-23] Due to the low prevalence of HO-CDI overall, we selected the top-3 most prevalent units for our epidemiologic investigation to increase signal detection: the SCT unit population, the medicine/oncology (med/onc) unit population, and the medical intensive care unit (MICU) population. Each of these patient populations is geographically distinct, and all patient rooms at our center are private rooms.

Antibiotics and antibiotic classes carrying previous associations with CDI were preferentially selected for our epidemiologic analysis,[3-7] but a broad range of antibiotics from our hospital formulary were reviewed overall for signal identification. A complete list of the antibiotics that were evaluated can be found in supplementary Table S1. Of note, ciprofloxacin is the most commonly used fluoroquinolone at our center; however, we also wanted to evaluate all fluoroquinolone use as a group given the established relationship between this antibiotic class and CDI.[4,5] Furthermore, our center has a robust antimicrobial stewardship program that consistently works to promote appropriate antibiotic use through various methods. However, our analysis evaluated associations over time, so we do not anticipate that changes in consumption would invalidate our findings because an increase or decrease in consumption would yield an opportunity to assess for a corresponding increase or decrease in HO-CDI.

All antibiotic consumption data were collected in aggregate, deidentified form from all patient locations (excluding neonates) and standardized per CDC National Healthcare Safety Network (NHSN) methodology.[21] Antibiotic consumption data (ie, ADs) were obtained via TheraDoc (Premier, Charlotte, NC), which extracts use data directly from administration records (using bar code medication administration records in electronic medical records). System mapping is regularly performed to ensure that the ADs correspond to a physical location and data were manually validated for each of the units reported here.

Two units (ie, SCT and med/onc units) only had reliable antibiotic consumption and CDI data between January 2013 and September 2014 because of incomplete patient mapping and uncertain antibiotic consumption data. The analysis of these units was thus limited to that time period. Sensitivity analyses that limited FacWide data analyses to that time period and to the entire time period were performed.

HO-CDI incident events were similarly compiled on a monthly basis FacWide and for the same 3 units. HO-CDI cases were standardized to 10,000 DP.[20] Incident HO-CDI events were obtained from the Infection Prevention Department using aggregate data previously submitted to the CDC NHSN. HO-CDI incident events were defined according to NHSN criteria:[20] A positive polymerase chain reaction (PCR) result for *C difficile* toxin, known as a LabID event, collected >3 days after hospital admission was considered to be an HO-CDI incident event. Throughout the duration of the study, our center used PCR testing to identify CDI cases and our microbiology lab maintained a policy to reject formed stool samples to reduce inappropriate testing. During the study period our center had a policy restricting CDI testing to a maximum of once weekly per patient. Our CDI-positive rate was tested monthly and remained stable during the study period.

Before data collection for the study, the NHSN data portal automatically deduplicated the data to exclude recurrent CDI cases (within 8 weeks of a previous CDI episode) and to exclude repeat PCR tests conducted within 14 days after an incident positive PCR test was detected.[20] A limitation of the HO-CDI metric is that the data portal cannot recognize a positive repeat CDI test within 14 days if a patient changes location. Although acknowledging this limitation and the lack of patient-level data, we also recognize that HO-CDI is a nationally recognized and utilized metric for measuring incident CDI in health care settings.

DP, the denominator used for both antibiotic consumption and HO-CDI incidence standardized rates, were obtained from the Infection Prevention Department. HO-CDI incidence metrics were