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Electronically available comorbid conditions for risk prediction of healthcare-associated *Clostridium difficile* infection

Anthony D. Harris, MD, MPH¹, Alyssa N. Sbarra, BS², Surbhi Leekha, MBBS, MPH¹, Sarah S. Jackson, MPH¹, J. Kristie Johnson, PhD^{1,3}, Lisa Pineles, MA¹, and Kerri A. Thom, MD, MS^{*,1}

¹Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland ²Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, Connecticut ³Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland

Abstract

Objective—To analyze whether electronically-available comorbid conditions are risk factors for Centers for Disease Control and Prevention (CDC)-defined, hospital-onset *Clostridium difficile* infection after controlling for antibiotic and gastric acid suppression therapy use.

Patients—Patients, aged ≥18 years, admitted to the University of Maryland Medical Center between November 7, 2015 and May 31, 2017.

Methods—Comorbid conditions were assessed by the Elixhauser Comorbidity Index. The Elixhauser Comorbidity Index and the comorbid condition components were calculated using the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes extracted from electronic medical records. Bivariate associations between CDI and potential covariates for multivariable regression, including antibiotic use, gastric acid suppression therapy use, as well as comorbid conditions, were estimated using log binomial multivariable regression.

Results—After controlling for antibiotic use, age, proton-pump inhibitor use, and histamine-blocker use, the Elixhauser Comorbidity Index was a significant risk factor for predicting CDI. There was an increased risk of 1.26 (95% CI: 1.19, 1.32) of having CDI for each additional Elixhauser point added to the total Elixhauser score

Conclusions—An increase in Elixhauser score is associated with CDI. Our study and other studies have shown that comorbid conditions are important risk factors for CDI. Electronically available comorbid conditions and scores like the Elixhauser Index should be considered for risk-adjustment of CDC *C. difficile* infection rates.

Keywords

Clostridium difficile; Comorbidities; Risk Adjustment; Hospital Epidemiology

*Corresponding author: Kerri A. Thom, MD, MPH, 655 W. Baltimore Street, Bressler Hall M-021, Baltimore, MD 21201, kthom@som.umaryland.edu.

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Although healthcare-associated infection rates have decreased dramatically for a number of infections, this has not been the case for *Clostridium difficile* infection (CDI).¹ Hospital-onset *C. difficile* infection (CDI) rates decreased by eight percent from 2011 to 2014, 22% short of the U.S. Department of Health and Human Services (HHS) goal of a 30% decrease¹ and *C. difficile* has been labeled as “an urgent threat” by the CDC.² In an effort to reduce CDI, hospital-onset CDI is a publicly reported, pay-for-performance metric.

Risk factors for CDI have been previously described in the literature.³ Important risk factors that have been identified in many studies include the use of both antibiotics and gastric acid suppression therapy, which includes proton pump inhibitors and histamine blockers.^{4,5} These are potentially preventable risk factors where interventions targeting a decrease in unnecessary use of these medications could lead to decreased *C. difficile* rates. Other risk factors for CDI such as age and comorbid conditions are not usually preventable.² Comorbid conditions identified as risk factors for CDI in various studies include liver disease, organ transplant, weight loss, inflammatory bowel disease, recent bowel surgery, congestive heart failure, renal failure, coagulopathy, and malignant tumors.^{2,6-9} However, no U.S. studies have assessed whether these comorbidities as captured by *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) codes are risk factors for CDI. If comorbid conditions captured by ICD-10-CM codes are identified as CDI risk factors, these could eventually be used for risk adjustment and prediction rules. The aim of the current study was to investigate whether comorbid conditions captured by ICD-10-CM codes are risk factors for CDI after controlling for important risk factors such as antibiotic and gastric acid suppression therapy use and thus determine whether electronically available comorbid conditions may be candidates for risk adjustment.

Methods

We performed a retrospective cohort study among all adult patients admitted to the University of Maryland Medical Center (UMMC), a 755-bed tertiary care hospital located in Baltimore, MD. The University of Maryland, Baltimore Institutional Review Board approved this study.

The cohort was created using the hospital’s central data repository, which is a relational database containing administrative, pharmacy, clinical, and laboratory data from electronic medical records. The cohort included all adult patients (aged ≥ 18 years) admitted to UMMC between November 7, 2015 and May 31, 2017. Data extracted included age, gender, race/ethnicity, ICD-10-CM codes, medication administration, length of stay, *C. difficile* test date, and *C. difficile* test result. Validation of a random sample of the fields used was performed by chart review. In this study and in prior studies, the positive and negative predictive values of the fields in the electronic medical record/central data repository were greater than 99%.
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Per CDC NHSN case definition, a patient was considered to have hospital-onset CDI if the patient tested positive for *C. difficile* at least 3 days after hospital admission and had no prior positive in the preceding 14 days.¹⁴ Throughout the study period, testing for toxigenic *C. difficile* in liquid stool samples was performed using a nucleic acid amplification test

(NAAT, Illumigene *C. difficile* assay, Meridian Bioscience, Cincinnati, OH). The laboratory did not test stool specimens that were formed. Best practice alerts recommending against *C. difficile* in the presence of diarrhea due to laxative use, and avoiding repeat testing, went into effect in the electronic medical record on December 20, 2016.

ICD-10-CM codes were mapped to appropriate comorbid components of the Elixhauser Comorbidity Index as outlined by Quan et al.¹⁵ The Elixhauser Comorbidity Index is a sum of 30 unweighted comorbid conditions in which possible scores range from 0 to 30.¹⁶ Multiple ICD-10-CM codes were used in defining each comorbidity component, but the components were operationalized as binary variables. For example, a person was considered to be positive for the lymphoma component binary variable if he or she had any of the following ICD-10-CM codes: 200.x-202.3x, 202.5-203.0, 203.8, 238.6, 273.3, V10.71, V10.72, V10.79.¹⁵ Patients were considered to have received antibiotic or gastric acid suppression therapy if they had received at least one dose from the time of hospital admission until the time of a positive *C. difficile* test or until discharge for patients who did not develop the outcome. Antibiotic use was analyzed in individual classes in the bivariate analysis and in 1 of the multivariable models. Histamine blocker and proton pump inhibitors were analyzed as separate classes. In the primary multivariable model, antibiotic use was analyzed as a binary variable defined as whether patients received or did not receive any systemic antibiotic in order to analyze whether comorbid conditions were risk factors above and beyond all antibiotic use. Antibiotic therapy and gastric acid suppression therapy use were analyzed because of their association with *C. difficile* in prior studies.^{4,5}

Bivariate associations were performed using a log binomial regression. Age was considered a continuous covariate in bivariate analysis due to its previously established linear associations with CDI.¹⁷ Candidacy for covariates in a multivariable analysis was determined by the significance of association in the bivariate approach as indicated by a p-value of less than 0.10. The linearity of association between CDI and total Elixhauser score was assessed and due to its linear association, the Elixhauser was analyzed as a continuous variable. Age was assessed for linear association with CDI and also was analyzed as a continuous variable. Tests for effect modification and confounding between antibiotic use and Elixhauser score were conducted. A multivariable log binomial regression was used to assess the risk of CDI. We conducted a likelihood ratio test to assess model fit for models with and without the Elixhauser Index. A second multivariable logistic regression model was done to analyze individual antibiotics, individual comorbid conditions, age, and gastric acid suppression. Step-wise regression was used for variable selection. As the outcome was rare, we interpreted the odds ratios as risk ratios. Analyses were performed using SAS version 9.4 software (The SAS Institute, Cary, NC).

Results

Of 37,246 patient admissions that met entry criteria, 3,001 had a *C. difficile* test performed, of which 257 (8.5%) were positive and met the CDC definition for hospital-onset *C. difficile* infection (CDI). The CDI incidence rate for our hospital was 9.5 per 10,000 patient days in calendar year 2015 and 9.1 per 10,000 patient days in calendar year 2016. Among patients with CDI, the average length of stay in the hospital was 10.8 days (standard deviation [SD],

10 days) before a positive result. Among all patients in the cohort, the mean age was 52.7 years (SD, 18 years) (Table 1). Among patients with CDI, 80% had gastric acid suppression therapy use compared to 54% of those without CDI ($p<0.001$), and 88% of persons with CDI had antibiotic use compared to 58% of persons without CDI ($p<0.001$). The mean Elixhauser score among all patients in the cohort was 3.4 (SD, 2). Patients with CDI had a mean Elixhauser score of 5.3 (SD, 2) and those without CDI had a mean score of 3.4 (SD, 2; $p<0.001$).

In the bivariate analysis, age, antibiotic use for all antibiotic classes, gastric acid suppression therapy use, and Elixhauser score were significantly related to CDI (Table 2). After controlling for any antibiotic use, age, and gastric acid suppression in a multivariable log binomial regression, for every one-point increase in Elixhauser score, there was 1.26 times the odds of having CDI (95% CI, 1.21-1.33) in model 1 (Table 3). We compared this model to one without the Elixhauser Index and found that the model with the index was a better fit ($p<0.0001$). Individual antibiotic and individual comorbid condition multivariable model is presented in model 2 (Table 3). Carbapenem, vancomycin, piperacillin-tazobactam, and cefepime were individual antibiotics statistically associated with CDI. Malnutrition, coagulopathy, lymphoma, renal failure and neurological conditions were statistically associated with CDI. Complicated hypertension was statistically protective.

Discussion

Patients with comorbid conditions identified by ICD-10-CM codes had a greater risk of hospital-onset *C. difficile* infection. Specifically, we identified that patients with higher Elixhauser scores (representing greater number of comorbidities) had a greater risk of CDI. This association remained strong even when controlling for important confounding variables of antibiotic therapy, age, and gastric acid suppression therapy.

A nested case-control study among French patients using ICD-10 codes found that chronic renal or liver disease and malnutrition were comorbid conditions that were risk factors for CDI while controlling for other confounding variables.⁶ Two of these comorbid conditions were found in our study as well. The French study measured these comorbid conditions by chart review whereas in our study, electronically available ICD-10 codes were used which has practical implications for broader application of such risk adjustment. In a study in Boston, a secondary analysis of an existing dataset was performed specifically to assess the risk of gastric acid suppression therapy for nosocomial CDI.⁷ Using ICD-9 codes mapped to Elixhauser Index components to control for possible confounding and similarly to our study, investigators found that an increase in the number of comorbid conditions was associated with an increased risk of CDI.

Current CDC NHSN hospital-onset CDI models adjust for the following variables: a) academic or non-academic affiliation; b) bed size; c) type of *C. difficile* testing, d) community-onset prevalence, and e) number of ICU beds. However, none of these variables are patient-level risk factors and therefore may not completely account for the patient case-mix and associated non-modifiable CDI risk at different hospitals.¹⁸ Our group has demonstrated that comorbid conditions identified by ICD codes are significant risk factors

for surgical site infections and central-line associated bloodstream infections.^{19,20} We also showed that risk adjustment models using ICD codes and accounting for comorbidity had better predictive discrimination and calibration than the current CDC models for these infections.²¹ A study in California showed substantial variation in hospital rankings when adjusting for group level hospital characteristics including comorbid conditions.²² These outlined issues lead to the desire among many hospital epidemiologists to have better risk adjustment modeling assessed before national reporting of outcomes occurs.²²⁻²⁴

The major limitation of this study is that it is a single center study, which impacts the generalizability. This work needs to be repeated at multiple institutions including hospitals with distinct characteristics such as non-academic and non-urban hospitals. Another limitation is that our work did not adjust for the severity of illness of patients. Further work is needed in this area as evidenced by a study that showed that a hospital's case mix index, reflecting severity of illness, was a risk factor for CDI.²⁵ A criticism of the use of ICD codes in research is that they fail to capture all patient comorbidities or could reflect codes that maximize reimbursement.^{26,27} Research comparing the Charlson and Elixhauser Comorbidity Indices derived from ICD-9-CM codes to those same scores extracted from chart review has found that the sensitivity of the individual components varies greatly but that specificity is nearly 100%.^{28,29} Future work could further elucidate the association between comorbid condition scores such as the Elixhauser Comorbidity Index and the Charlson Comorbidity Index and their association with CDI. As well, different results could be obtained if antibiotics were based on duration received and not just as a categorical variable. Another limitation is that we did not control for hospital admission source because it was not available in our database. It has been shown that transfers from long-term care facilities are at increased risk of CDI. However, the prevalence of community-onset CDI (i.e., CDI cases diagnosed within the first 3 days of hospital admission) did not change during the study period.

In conclusion, if our work is repeated at multiple institutions and shows that electronically-available comorbid conditions are risk factors for CDI, the CDC and the Centers for Medicare and Medicaid Services (CMS) should strongly consider adding comorbidity-based risk adjustment to publicly reported *C. difficile* infection rates.

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Table 1

Selected characteristics of patients admitted to University of Maryland Medical Center in Baltimore, MD between November 7, 2015 and May 31, 2017 by *C. difficile* infection status

Characteristic	<i>C. difficile</i> PCR result		Total	p ^a
	Positive (N =257)	Negative (N =36985)		
Age, in years, Mean (SD)	59.1 (16.2)	52.7 (18.3)	52.7 (18.3)	<0.001
Male, n (%)	140 (54.5)	18814 (50.9)	18954 (50.9)	0.509
Use of antibiotics, n (%)	219 (85.2)	20843 (56.4)	21062 (56.6)	<0.001
Use of gastric acid suppression therapy, n (%)	205 (79.8)	19889 (53.8)	20094 (54.0)	<0.001
Elixhauser Index, Mean (SD)	5.3 (2)	3.4 (2)	3.4 (2)	<0.001
Total length of hospital stay, in days, Mean (SD)	25.5 (23.1)	6.6 (8.8)	6.8 (9.1)	<0.001

^aP-value is for t-test or χ^2 test as appropriate for continuous and categorical variables, respectively.

Table 2

Risk ratios and 95% confidence intervals for the associations between selected covariates and *C. difficile* infection

	Risk Ratio Estimate^a	95 % CI^b	p-value
Age (in years)	1.02	(1.01, 1.03)	<0.001
Male	1.15	(0.90, 1.47)	0.250
Race			
Black	0.92	(0.71, 1.18)	0.510
Hispanic	1.05	(0.55, 1.99)	0.882
Other race	1.44	(0.71, 2.93)	0.314
Use of antibiotics	4.27	(3.02, 6.05)	<0.001
Cephalosporins, first generation	0.94	(0.68, 1.28)	0.688
Cephalosporins, second generation	1.48	(0.37, 5.89)	0.580
Cephalosporins, third generation	1.91	(1.38, 2.65)	<0.001
Vancomycin IV	3.49	(2.73, 4.45)	<0.001
Piperacillin-tazobactam	4.67	(3.66, 5.95)	<0.001
Cefepime	3.71	(2.73, 5.03)	<0.001
Fluoroquinolones	1.86	(1.36, 2.54)	<0.001
Carbapenems	5.13	(3.78, 6.95)	<0.001
Cephalosporins	1.79	(1.40, 2.28)	<0.001
Use of gastric acid suppression therapy			
H2 Blockers	1.60	(1.23, 2.08)	<0.001
Proton pump inhibitors	2.66	(2.07, 3.43)	<0.001
Total Elixhauser score	1.33	(1.28, 1.39)	<0.001
Congestive heart failure	1.84	(1.38, 2.44)	<0.001
Cardiac arrhythmia	1.82	(1.41, 2.34)	<0.001
Valvular	1.51	(1.08, 2.12)	0.017
Pulmonary circular	2.27	(1.67, 3.09)	<0.001
Peripheral vascular	1.70	(1.20, 2.41)	0.003
Hypertension, uncomplicated	1.14	(0.89, 1.46)	0.301
Hypertension, complicated	1.41	(0.93, 2.15)	0.105
Paralysis	1.13	(0.56, 2.27)	0.742
Other neuro	2.48	(1.85, 3.31)	<0.001
Chronic pulmonary	1.30	(0.98, 1.71)	0.070
Diabetes, uncomplicated	0.92	(0.63, 1.35)	0.671
Diabetes, complicated	2.18	(1.64, 2.89)	<0.001
Hypothyroidism	1.58	(1.10, 2.28)	0.014
Renal failure	2.33	(1.79, 3.04)	<0.001
Liver	1.99	(1.41, 2.80)	<0.001
Peptic ulcer	0.90	(0.23, 3.61)	0.884
AIDS	1.41	(0.59, 3.41)	0.442
Lymphoma	4.44	(2.98, 6.62)	<0.001

	Risk Ratio Estimate^a	95 % CI^b	p-value
Metastatic cancer	0.89	(0.46, 1.73)	0.728
Solid tumor	1.23	(0.82, 1.84)	0.3186
Rheumatoid arthritis	1.34	(0.71, 2.51)	0.363
Coagulopathy	3.71	(2.89, 4.76)	<0.001
Obesity	1.12	(0.80, 1.57)	0.516
Weight loss	3.81	(2.85, 5.09)	<0.001
Fluid electrolyte	3.72	(2.86, 4.84)	<0.001
Anemia, blood loss	4.09	(2.19, 7.63)	<0.001
Anemia, deficiency	0.80	(0.36, 1.80)	0.597
Alcohol abuse	1.47	(1.02, 2.12)	0.037
Drug abuse	0.76	(0.51, 1.14)	0.183
Psychoses	1.01	(0.48, 2.14)	0.973
Depression	1.11	(0.79, 1.56)	0.554

^aEstimates are obtained from a log binomial regression.

^bWald 95% confidence intervals.

Table 3Multivariable regression to assess risk of *C. difficile* infection

Model 1			
	Risk Ratio Estimate ^a	95% CI^b	p-value
Age, in years	1.01	(1.00, 1.01)	0.198
Antibiotics	3.22	(2.26, 4.58)	<0.001
H2 Blockers	1.45	(1.11, 1.91)	0.007
Proton pump inhibitors	1.59	(1.21, 2.08)	<0.001
Elixhauser score ^c	1.26	(1.19, 1.32)	<0.001
Model 2			
	Risk Ratio Estimate ^a	95% CI^b	p-value
Age, in years ^d	1.01	(1.00, 1.02)	0.004
Carbapenem	1.58	(1.11, 2.25)	0.011
Vancomycin IV	1.38	(1.01, 1.89)	0.043
Piperacillin-tazobactam	2.05	(1.51, 2.78)	<0.001
Cefepime	1.42	(1.00, 2.00)	0.048
Proton pump inhibitors	1.32	(1.00, 1.73)	0.018
Hypertension complicated	0.55	(0.34, 0.90)	<0.001
Other neurological	1.72	(1.27, 2.33)	<0.001
Renal failure	1.93	(1.40, 2.65)	<0.001
Lymphoma	3.80	(2.47, 5.86)	<0.001
Coagulopathy	1.70	(1.29, 2.24)	<0.001
Weight loss	1.93	(1.42, 2.64)	<0.001
Fluid and Electrolyte disorders	1.73	(1.29, 2.33)	0.006
Blood loss anemia	2.54	(1.31, 4.91)	0.050

^aEstimates are obtained from a logistic regression.^bWald 95% confidence intervals.^cFor each additional comorbidity the risk of CDI increases by 26%.^dFor each 1 year in age, the risk of CDI increases by 1%.