Derivation and Validation of a *Clostridium difficile* Infection Recurrence Prediction Rule in a National Cohort of Veterans

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Abstract

Study Objective—Prior studies have identified risk factors for recurrent *Clostridium difficile* infection (CDI), but few studies have integrated these factors into a clinical prediction rule that can aid clinical decision making. The objective of this study was to derive and validate a CDI recurrence prediction rule to identify patients at risk for first recurrence in a national cohort of veterans.

Design—Retrospective cohort study.

Data Source—Veterans Affairs Informatics and Computing Infrastructure.

Patients—A total of 22,615 adult Veterans Health Administration beneficiaries with first-episode CDI between October 1, 2002, and September 30, 2014; of these patients, 7,538 were assigned to the derivation cohort and 15,077 to the validation cohort.

Measurements and Main Results—A 60-day CDI recurrence prediction rule was created in a derivation cohort using backward logistic regression. Those variables significant at p<0.01 were assigned an integer score proportional to the regression coefficient. The model was then validated in the derivation cohort and a separate validation cohort. Patients were then split into three risk categories, and rates of recurrence were described for each category. The CDI recurrence prediction rule included the following predictor variables with their respective point values: prior third-and fourth-generation cephalosporins (1 point), prior proton pump inhibitors (1 point), prior

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antidiarrheals (1 point), nonsevere CDI (2 points), and community-onset CDI (3 points). In the derivation cohort, the 60-day CDI recurrence risk for each score ranged from 7.5% (0 points) to 57.9% (8 points). The risk score was strongly correlated with recurrence (R^2=0.94). Patients were split into low-risk (0-2 points), medium-risk (3-5 points), and high-risk (6-8 points) classes and had the following recurrence rates: 8.9%, 20.2%, and 35.0%, respectively. Findings were similar in the validation cohort.

Conclusion—Several CDI and patient-specific factors were independently associated with 60-day CDI recurrence risk. When integrated into a clinical prediction rule, higher risk scores and risk classes were strongly correlated with CDI recurrence. This clinical prediction rule can be used by providers to identify patients at high risk for CDI recurrence and help guide preventive strategy decisions, while accounting for clinical judgment.

Keywords

Clostridium difficile; epidemiology; prediction rule

Clostridium difficile infection (CDI) is the main cause of bacterial infectious diarrhea in nosocomial settings, accounting for 90–100% of antibiotic-associated pseudomembranous colitis cases.[1] Importantly, 14–26% of individuals experience CDI recurrence despite successful treatment of the initial episode.[2–5] In those patients who have already experienced one recurrence, the risk of additional recurrences may be as high as 65%.[6] Recurrent CDI places a heavy burden on patients, as it increases morbidity and mortality and diminishes quality of life associated with repeated episodes of diarrhea.[7, 8] Patients with recurrent CDI experience prolonged symptoms and repeated courses of antibiotics.[8] This can lead to increased risk of adverse effects, rehospitalization, and development of multidrug-resistant pathogens. Additionally, patients with recurrent CDI continue to serve as a reservoir that can lead to infection in other vulnerable patients.[9]

Prior clinical trials identified several patient-specific factors that increase the risk for recurrent CDI.[7, 10–13] These include advanced age, immunosuppression, persistent disruption of the intestinal flora, concomitant use of non-CDI antibiotics, concomitant use of gastric acid–suppressing (GAS) drugs, prolonged hospital stays, and severity of illness. Although several studies have identified risk factors for recurrent CDI, few studies have integrated these factors into a tool that can be readily used by clinicians to identify patients at low and high risk for CDI recurrence. Clinical prediction rules combine medical signs, symptoms, and other patient-specific findings into a simple rule that can be used to predict the probability of a specific disease or outcome.[14] They serve as a method of translating key research findings into routine clinical practice by aiding practitioners in making better health care decisions.

Available studies provide some evidence for the effectiveness of clinical prediction rules for CDI recurrence; however, these rules have only demonstrated modest discriminatory power.[4, 11, 15, 16] This is likely due to small sample size, variable selection, and study design limitations. The objective of this study was to derive and validate a clinical prediction rule to identify patients at risk for first CDI recurrence. This rule can be used to help guide clinical

decision making after an initial CDI episode. It can also be used by researchers who wish to measure and balance the risk of CDI recurrence among the various groups in their studies.

Methods

Study Design

This was a national, retrospective cohort study of all patients with CDI receiving care at any of the approximately 150 Veterans Health Administration (VHA) hospitals and 820 VHA clinics in the United States. Data for this study were obtained from the Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI), which includes administrative, clinical, laboratory, and pharmacy data repositories that are linked using unique patient identifiers. All data collection and analyses were performed at the South Texas Veterans Health Care System, Audie L. Murphy Memorial VA Hospital (San Antonio, TX). This study was approved by the Institutional Review Boards at UT Health San Antonio and the South Texas Veterans Health Care System Research and Development Committee.

Study Population

The cohort was created by including all adult patients (aged 18–89 years) with any inpatient or outpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code for CDI (008.45) plus any positive laboratory value (e.g., glutamate dehydrogenase, enzyme immunoassay, polymerase chain reaction) for CDI during the visit or within 7 days of the visit from October 1, 2002, through September 30, 2014. The cohort was limited to patients with first-episode CDI by excluding those patients with an ICD-9-CM code for CDI (008.45) in the year prior to study inclusion. We also excluded those who died within 60 days of the end of treatment discontinuation for the initial episode to capture only those patients at risk for 60-day recurrence.

Study Definitions

A first recurrence was defined as a second outpatient or inpatient visit during which a patient received an ICD-9-CM code for CDI, plus a minimum 3-day gap between the visit and the end of active CDI therapy for the initial episode. For those in whom CDI therapy was not provided, the gap was defined from the day of the outpatient encounter or hospital discharge to a second outpatient or inpatient visit. Recurrent CDI typically occurs within one to three weeks post-treatment discontinuation, but late recurrences, occurring up to 60 days post-treatment discontinuation, are frequent.[2] The mean relapse time is approximately 14.5 days, whereas mean reinfection time is 42.5 days.[2] We chose 60-day recurrence as our primary dependent variable because it is likely to capture the majority of CDI recurrences. This definition has been used as the primary outcome in other studies evaluating CDI recurrence risk.[11]

Patient demographics included age during the initial CDI episode, sex, race, and ethnicity. Sex, race, and Hispanic ethnicity were defined as the most frequent reporting of each characteristic over the study period. Principal CDI was defined as ICD-9-CM code 008.45 in the first position. This often indicates that CDI was the primary contributor to hospitalization. Secondary CDI was defined as ICD-9-CM code 008.45 in any position

except first. Community-onset CDI was defined based on the presence of CDI therapy initiated in the outpatient setting or on days 1 or 2 of hospitalization. Hospital-onset CDI was defined based on the presence of CDI therapy beginning on day 3 or later of hospitalization.

Data on the Charlson Comorbidity Index score as modified by Deyo et al.,[17] Charlson comorbidities, and other relevant diagnoses were collected in the year prior to the first CDI episode (Appendix 1). Data on other markers of CDI severity that occurred at any time during a CDI encounter (from hospital admission or outpatient visit to end of CDI therapy) were also captured, including intensive care unit admission, sepsis/septicemia, shock, acute renal failure, megacolon, prolonged ileus, perforated intestine, colectomy, and white blood cell count, and C-reactive protein, serum creatinine, and albumin concentrations. For prediction rule simplicity, these were combined into one "severe CDI" category, meaning the patient experienced at least one of these severity indicators.

Data on prior (90 days prior to a CDI encounter) non-CDI antibiotics (excluding oral vancomycin, metronidazole, fidaxomicin, rifaximin, and nitazoxanide since they may also be used to treat CDI), GAS drugs (antacids, histamine$_2$ receptor antagonists, proton pump inhibitors), antidiarrheal medications, narcotics, and laxatives and stool softeners were collected.

Data and Statistical Analyses

Data extraction and variable creation were conducted by using SAS version 9.2 (SAS Corp., Cary, NC). All other data and statistical analyses were conducted by using JMP 13.0 (SAS Corp.).

The cohort was randomized, using a random number generator, to either the derivation or validation cohort. The derivation cohort consisted of one third of the total cohort, whereas the remaining two thirds were assigned to the validation cohort. The validation cohort was assigned a larger sample size to more accurately test the generalizability of the prediction rule. Similar methodology was used by Fine et al[18] for deriving and validating a prediction rule for community-acquired pneumonia.

Each variable collected was first tested for its relationship with 60-day CDI recurrence using bivariable analyses (χ^2, Fisher exact test, t test, or Wilcoxon rank sum test). A backward stepwise logistic regression model was then performed using all candidate variables that were present in at least 5% of the sample. Antibiotics and GAS drugs were entered into the model in classes rather than combined groups. Only variables with a p value <0.01 were retained in the final model.

Each significant predictor variable was assigned an integer score proportional to the regression coefficient derived in the final model. We assigned one point to the smallest regression coefficient, using it as the least common denominator for assigning point values for the score items. All other variables were assigned integer scores proportional to the regression coefficient.[19, 20] Patients were then assigned a risk score according to the variables present and their respective integer scores.

The Spearman rank correlation test was used to test the correlation between patient scores and recurrence rates. Next, scores were divided into thirds to represent low-, medium-, and high-risk groups; recurrence rates were calculated for each group.

In the separate validation cohort, predictor variables were collected, and each patient was assigned a risk score. The analyses described above were repeated in the validation cohort. Finally, because the time to recurrence varied, we conducted sensitivity analyses. We used the prediction rule derived for 60-day recurrence and repeated the correlation analysis of risk score with 30- and 90-day recurrence as the dependent variables.

Results

Overall, 22,615 patients met study inclusion criteria, of whom 7,538 were assigned to the derivation cohort and 15,077 to the validation cohort. Baseline characteristics of patients randomized to the derivation and validation cohorts were similar; no significant differences were noted in demographics, CDI characteristics, comorbidities, concomitant infections, medications, or CDI severity.

Table 1 describes the patients' baseline characteristics stratified by presence or absence of 60-day CDI recurrence. Baseline characteristics of patients with 60-day CDI recurrence significantly differed from those of patients without a recurrence with respect to demographics, CDI characteristics, comorbidities, medications, and CDI severity.

In the logistic regression model, the following were identified as independent predictors of 60-day recurrence and assigned points (Table 2): prior third- and fourth-generation cephalosporins (1 point), prior proton pump inhibitors (1 point), prior antidiarrheals (1 point), nonsevere CDI (2 points), and community-onset CDI (3 points). The total score ranged from 0–8 points.

In the derivation cohort, the 60-day CDI recurrence risk for each score ranged from 7.5% (0 points) to 57.9% (8 points). The risk score was strongly correlated with 60-day recurrence ($R^2=0.94$) (Figure 1). Correlation was similar in the sensitivity analysis for 30-day ($R^2=0.95$) and 90-day ($R^2=0.94$) recurrence. Patients were split into low-risk (0-2 points), medium-risk (3-5 points), and high-risk (6-8 points) classes and had the following recurrence rates: 8.9% in the low-risk class, 20.2% in the medium-risk class, and 35.0% in the high-risk class (Figure 2). Findings were similar in the validation cohort and when the derivation and validation cohorts were combined to reflect the overall population.

Discussion

CDI recurrence is a common and challenging health problem. Prior studies have identified several clinical and host risk factors for CDI recurrence; however, few have integrated these factors into a tool that can help guide clinical decision making. Our study developed a clinical prediction rule for recurrent CDI using a robust split-cohort design and, to our knowledge, the largest CDI cohort for this purpose. Antibiotic and proton pump inhibitor use have been widely reported as a predictor of recurrent CDI,[11, 15, 21–24] whereas other predictor variables have not been extensively studied.

Antidiarrheals have not been previously associated with CDI recurrence; however, these agents are largely avoided during active CDI due to the risk of worsening clinical outcomes. [25, 26] Antidiarrheals, such as loperamide, slow fecal transit time,[27] which could delay elimination of *C. difficile* through the bowel and result in absorption of *C. difficile* toxins into the gut mucosa. This could increase the likelihood of recurrent episodes due to relapse and accumulation of *C. difficile* in the gastrointestinal tract.

The remaining variables included in the prediction rule all seem to reflect "healthier" patients with CDI. Patients with community-onset, nonsevere CDI might be discharged on outpatient therapy more quickly than those who develop CDI in the hospital or who have other comorbid conditions that necessitate inpatient treatment.[28] CDI treatment regimens typically include antibiotics taken 3–4 times daily, which could limit patient adherence in the outpatient setting, thus reducing the likelihood of *C. difficile* eradication. Furthermore, strict precautions are taken to prevent the spread of spores in a patient's hospital environment compared to home, which could play a role in the association between duration of hospitalization and CDI recurrence.[6]

To our knowledge, four prior prediction rules for CDI recurrence have been published. Similar to our study, antibiotic use[11, 15] and community-onset CDI[4, 15] have been previously included in these rules. Variables that were commonly found in other rules, but not our rule, included older age and severe CDI as measured by subjective or objective measures. [4, 11, 15, 16] The fact that these variables were not significant predictors of recurrence in our population could reflect the generally older age and poorer health of the VHA population, which would limit the variation in these variables and the likelihood of detecting differences between those who did and did not have 60-day CDI recurrence.

The use of a simple, objective clinical prediction rule for recurrent CDI has several possible implications for public health. The rule could potentially define a high-risk population in whom awareness of the risk would facilitate more prompt recognition, diagnosis, and treatment of recurrent CDI. These patients could also be targeted for specific interventions aimed at preventing recurrence, including infection control precautions, judicious use of antibiotics, appropriate duration of antibiotic therapy, and use of other preventive measures. Additionally, certain risk factors might also be mitigated prior to CDI recurrence, thus limiting the risk of recurrence. Lastly, a prediction rule could be of value in selecting high-risk patients for clinical trials of novel agents to prevent recurrent CDI, such as fidaxomicin.

This study has some potential limitations. First, we used a retrospective cohort study design that includes data collection from electronic medical records. Cohort studies might be subject to misclassification bias and confounding by unmeasured variables. Additionally, electronic medical data are created for the purpose of patient care, rather than research, which could lead to information bias. Similarly, administrative codes might not entirely capture all of a given patient's comorbidities and, therefore, cannot be considered equivalent to a medical chart review. Although we included several CDI recurrence risk factors, there might be other factors that are not included that could aid in the predictive model of CDI recurrence. These include processes of care, patient frailty, medication adherence, and infecting C. *difficile* strain. CDI therapies could have also impacted recurrence risk;

however, we did not include these in our model, such that the rule can be used to guide initial selection of therapy in high-risk patients. Our predominately elderly, male veteran CDI population might not be representative of all CDI populations; thus, potentially limiting the generalizability of our epidemiologic findings to other settings. Validation of the prediction rule in a cohort more inclusive of women, who are generally at higher risk for initial CDI, is needed. Next, some CDI episodes could have been missed, as veterans could have been treated at non-VHA facilities, especially those with severe CDI who might have needed a higher level of care. We attempted to limit study survival bias by excluding patients with CDI who died prior to assessing for recurrence; however, survival bias cannot be ruled out. It is also important to note the large population of patients who received laxatives/stool softeners prior to the initial CDI episode. This could have increased the misclassification of CDI due to colonization, especially in patients who were diagnosed by the more sensitive nucleic acid amplification tests.

Prediction rules themselves also have inherent limitations. They are developed using clinical information to predict an outcome in a population of patients; therefore, application of the rule to an individual patient could be problematic. Because of this limitation, the prediction rule is intended to supplement, not supersede, a clinician's clinical judgment. Our prediction rule is designed to predict CDI recurrence, not to drive decisions on implementing specific preventive or treatment measures. Whether this rule can be applied in conjunction with different management strategies to improve clinical outcomes and health service utilization requires further study.

Conclusion

Several CDI and patient-specific factors were independently associated with 60-day CDI recurrence risk. When integrated into a clinical prediction rule, increasing risk score was strongly correlated with CDI recurrence. This clinical prediction rule can be used by providers to identify patients at high risk for CDI recurrence and help guide preventive strategy decisions, while accounting for clinical judgment.

Acknowledgments

Appendix 1. Study Comorbidity Definitions

Comorbidity	ICD-9-CM code(s)
Comorbidities in year prior to CDI encounter	
Hypertension	401-405

Comorbidity	ICD-9-CM code(s)
Dyslipidemia	272
Obesity	278
Myocardial infarction	410, 412
Congestive heart failure	428
Peripheral vascular disease	441, 443.9, 785.4, V43.4
Cerebrovascular disease	430-438
Dementia	290
COPD	490-496, 500-505, 506.4
Rheumatologic disease	710.0-710.1, 710.4, 714.0-714.2, 714.81, 725
Peptic ulcer disease	531.0-531.9, 532.0-532.9, 533.0-533.9, 534.0-534.9
Liver disease	571.2, 571.4, 571.5, 571.6, 572.2-572.8, 456.0-456.21
Diabetes	250.0-250.3, 250.4, 250.5, 250.6, 250.7, 250.8, 250.9
Hemiplegia or paraplegia	342, 344.1
Renal disease	582, 583, 585, 586, 588
Neoplastic disease	140-172, 174-208
HIV/AIDS	42-44, V08
Bacteremia	790.7
Pneumonia	480.0-483.99, 485–487
Skin infection	680-686
Endocarditis	421.0, 421.1, 421.9, 424.9
Urinary tract infection	590-599
Device-related infection	996.31, 996.62, 996.64, 999.31
Acute respiratory infection	460-466
GERD	530.11, 530.81
Transplant	V42, E878.0
Inflammatory bowel disease	555, 556
CDI severity indicators	
Shock	639.5, 785.52, 785.59
Sepsis/septicemia	020.2, 038.0-038.9, 995.91, 995.92
Perforation of intestine	569.83
Prolonged ileus	560.1
Megacolon	558.2, 564.7
Acute renal failure	584, 586

AIDS = acquired immune deficiency syndrome; CDI = *Clostridium difficile* infection; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; HIV = human immunodeficiency syndrome; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*.

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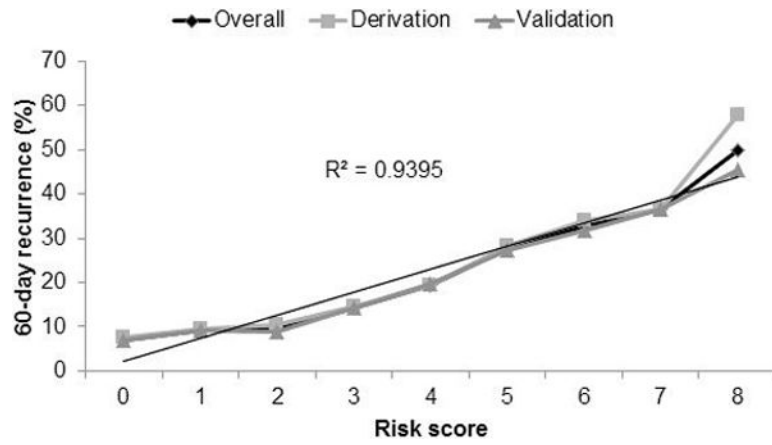
Figure 1.
Correlation of risk score and 60-day *Clostridium difficile* infection recurrence in the
derivation (n=7538) and validation (n=15,077) cohorts, and in the overall population
(derivation and validation cohorts combined).
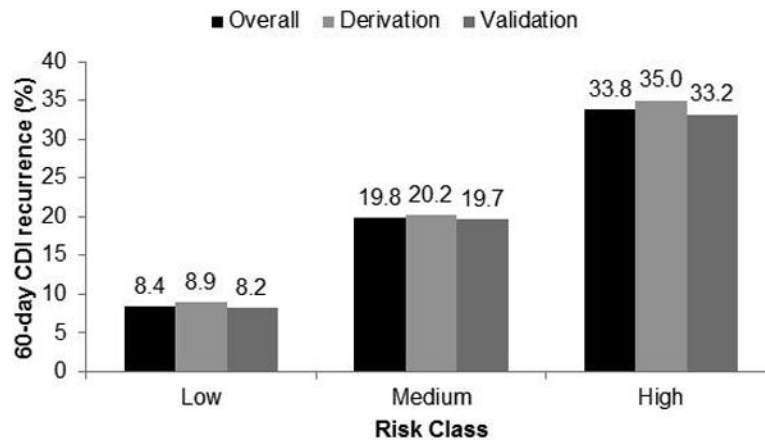
Figure 2.
Sixty-day *Clostridium difficile* infection (CDI) recurrence by risk class in the derivation (n=7538) and validation (n=15,077) cohorts, and in the overall population (derivation and validation cohorts combined).

Table 1

Association between Baseline Characteristics and 60-Day CDI Recurrence in the Derivation Cohort (n=7538)

Characteristic	No 60-Day CDI Recurrence (n=6315)	60-Day CDI Recurrence (n=1223)	p Value
Age (yrs), median (IQR)	65 (59 – 76)	66 (60 – 76)	0.1195
Age 65 yrs	3347 (53.0)	681 (55.7)	0.0845
Male sex	6031 (95.5)	1151 (94.1)	0.0357
Race-ethnicity			0.0007
Non-Hispanic white	4092 (64.8)	863 (70.6)	
Non-Hispanic black	1459 (23.1)	248 (20.3)	
Hispanic	379 (6.0)	48 (3.9)	
Other	221 (3.5)	37 (3.0)	
Missing	164 (2.6)	26 (2.1)	
Principal CDI diagnosis	1768 (28.0)	433 (35.4)	<0.0001
Hospital LOS 14 days	3094 (49.0)	632 (51.7)	<0.00763
Community-onset CDI	2463 (39.0)	795 (65.0)	<0.0001
Comorbidities			
Hypertension	4913 (77.8)	936 (76.5)	0.3043
Dyslipidemia	3524 (55.8)	733 (59.9)	0.0062
Obesity	1175 (18.6)	247 (20.2)	0.2055
Prior myocardial infarction	701 (11.1)	125 (10.2)	0.3446
Congestive heart failure	1522 (24.1)	295 (24.1)	0.9921
Peripheral vascular disease	1194 (18.9)	230 (18.8)	0.8928
Cerebrovascular disease	1250 (19.8)	220 (18.0)	0.1213
Dementia	208 (3.3)	27 (2.2)	0.0429
COPD	2235 (35.4)	461 (37.7)	0.1196
Rheumatologic disease	158 (2.5)	42 (3.4)	0.0766
Peptic ulcer disease	278 (4.4)	49 (4.0)	0.5038
Liver disease	417 (6.6)	84 (6.9)	0.6607
Diabetes mellitus	2633 (41.7)	495 (40.5)	0.4277
Hemiplegia or paraplegia	284 (4.5)	38 (3.1)	0.0222
Renal disease	1661 (26.3)	333 (27.2)	0.4892
Cancer	1604 (25.4)	300 (24.5)	0.5207
HIV/AIDS	114 (1.8)	21 (1.7)	0.8537
GERD	1749 (27.7)	388 (31.7)	0.0048
Transplant	114 (1.8)	34 (2.8)	0.0270
Inflammatory bowel disease	139 (2.2)	57 (4.7)	<0.0001
Irritable bowel syndrome	76 (1.2)	20 (1.6)	0.2793
Charlson Comorbidity Index score, median (IQR)	3 (1 – 6)	3 (1 – 5)	
Any severe CDI	4098 (64.9)	564 (46.1)	<0.0001

Characteristic	No 60-Day CDI Recurrence (n=6315)	60-Day CDI Recurrence (n=1223)	p Value
CDI severity indicators			
ICU admission	158 (2.5)	12 (1.0)	0.0004
Sepsis/septicemia	871 (13.8)	108 (8.8)	<0.0001
Shock	189 (3.0)	21 (1.7)	0.0070
Acute renal failure	1711 (27.1)	227 (18.6)	<0.0001
Megacolon	19 (0.3)	1 (0.1)	0.1292
Prolonged ileus	272 (4.3)	32 (2.6)	0.0022
Perforated intestine	25 (0.4)	4 (0.3)	0.6744
White blood cell count $15 \times 10^3/mm^3$	2305 (36.5)	286 (23.4)	<0.0001
C-reactive protein 160 mg/L	95 (1.5)	7 (0.6)	0.0027
Albumin < 2.5 g/dL	1749 (27.7)	146 (11.9)	<0.0001
Serum creatinine >1.5 mg/dL	1377 (21.8)	249 (20.4)	0.2477
Colectomy	6 (0.1)	0 (0.0)	0.2129
Prior medications			
Antibiotics	3404 (53.9)	758 (62.0)	<0.0001
Penicillins	1478 (23.4)	338 (27.6)	0.0018
First- and second-generation cephalosporins	644 (10.2)	149 (12.2)	0.0021
Third- and fourth-generation cephalosporins	720 (11.4)	196 (16.0)	<0.0001
Carbapenems	227 (3.6)	56 (4.6)	0.0932
Macrolides	512 (8.1)	122 (10.0)	0.0372
Fluoroquinolones	1718 (27.2)	408 (33.4)	<0.0001
Aminoglycosides	145 (2.3)	43 (3.5)	0.0191
Tetracyclines	202 (3.2)	45 (3.7)	0.4141
Clindamycin	474 (7.5)	114 (9.3)	0.0298
Other	1465 (23.2)	330 (27.0)	0.0044
High-risk antibiotics	2248 (35.6)	543 (44.4)	<0.0001
Narcotics	2450 (38.8)	505 (41.3)	0.1073
Antidiarrheals	461 (7.3)	150 (12.3)	<0.0001
Laxatives	2431 (38.5)	488 (39.9)	0.3428
GAS	3499 (55.4)	459 (62.1)	<0.0001
PPIs	2924 (46.3)	669 (54.7)	<0.0001
H_2RAs	916 (14.5)	179 (14.6)	0.9080
Other	701 (11.1)	158 (12.9)	0.0729
CDI therapies			
Metronidazole	4831 (76.5)	631 (51.6)	<0.0001
Vancomycin	2172 (34.4)	350 (28.6)	<0.0001
Fidaxomicin	44 (0.7)	49 (4.0)	0.1788
Probiotics	1572 (24.9)	171 (14.0)	<0.0001

Data are no. (%) of patients unless otherwise specified.

AIDS=acquired immune deficiency syndrome; CDI=*Clostridium difficile* infection; CI=confidence interval; COPD=chronic obstructive pulmonary disease; GAS=gastric acid–suppressing; GERD=gastroesophageal reflux disease; HIV=human immunodeficiency syndrome; H_2RAs=histamine$_2$ receptor antagonists; ICU=intensive care unit; IQR=interquartile range; LOS=length of stay; PPIs=proton pump inhibitors.

Table 2

Results of Backward Stepwise Logistic Regression Model and Integer Score Assignment

Variable	Regression coefficient	p value	Integer score
Prior third- or fourth-generation cephalosporins	0.1346	0.0030	1
Prior proton pump inhibitors	0.1460	0.0002	1
Prior antidiarrheals	0.1889	<0.0001	1
Nonsevere CDI	0.3277	<0.0001	2
Community-onset CDI	0.4761	<0.0001	3

CDI = Clostridium difficile infection.