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Major Article

Development of a risk prediction model for hospital-onset *Clostridium difficile* infection in patients receiving systemic antibiotics

Carrie S. Tilton PharmD [a], Steven W. Johnson PharmD, BCPS, CPP, AAHIVP [a,b,*]

[a] *Department of Pharmacy, Novant Health Forsyth Medical Center, Winston-Salem, NC*
[b] *Department of Pharmacy Practice, Campbell University College of Pharmacy & Health Sciences, Buies Creek, NC*

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Background: *Clostridium difficile* infection (CDI) is recognized as a significant challenge in health care. Identification of high-risk individuals is essential for the development of CDI prevention strategies. The objective of this study was to develop an easily implementable risk prediction model for hospital-onset CDI in patients receiving systemic antimicrobials.

Methods: This retrospective, case-control, multicenter study included adult patients admitted to Novant Health Forsyth Medical Center and Novant Health Presbyterian Medical Center from July 1, 2015, to July 1, 2017, who received systemic antibiotics. Cases were subjects with hospital-onset CDI; controls were subjects without a CDI diagnosis. Cases were matched 1:1 with controls by admitted medical unit type. Variables significantly associated with CDI were incorporated into a multivariate analysis. A logistic regression model was used to formulate a point-based risk prediction model. Positive predictive value, negative predictive value, sensitivity, specificity, and accuracy were determined at various point cutoffs of the model. A receiver operating characteristic–area under the curve was created to assess the discrimination of the model.

Results: A total of 200 subjects (100 cases and 100 controls) were included. Most patients were Caucasian and female. Risk factors for CDI identified and incorporated into the model included age ≥ 70 years (adjusted odds ratio, 1.89; 95% confidence interval 1.05-3.43; $P = .0326$) and recent hospitalization in the past 90 days (adjusted odds ratio, 3.55; 95% confidence interval 1.90-6.83; $P < .0001$). Sensitivity and specificity were 76% and 49%, respectively, for scores ≥ 2 and 20% and 93%, respectively, for a score of 6. Diagnostic performance of various score cutoffs for the model indicated that a score ≥ 2 was associated with the highest accuracy (63%). The receiver operating characteristic–area under the curve was 0.7.

Discussion: We developed a simple-to-implement hospital-onset CDI risk model that included only independent risks that can be obtained immediately on presentation to the health care facility. Despite this, the model had fair discriminatory power. Similar risk factors were found in previously developed models; however, the utility of these models is limited owing to the difficulty of assessing other included risk factors and the inclusion of risk factors that cannot be evaluated until the patient is discharged from the health care facility.

Conclusions: Identification of hospitalized patients who are receiving systemic antibiotics, are ≥ 70 years old, and were recently admitted to the hospital in the past 90 days may allow for an easily implementable hospital-onset CDI risk prevention strategy.

Clostridium difficile infection (CDI) is associated with a significant burden on the health care system. It is expected that this burden will only continue to increase as the incidence and severity of CDI continues to surge.[1,2] Several risk factors have been identified for CDI, including, but not limited to, advanced age, systemic antibiotic exposure, gastrointestinal surgery, and manipulation of the gastrointestinal tract, including tube feedings, hospitalization (recent or current), and antacid therapy with proton pump inhibitors (PPIs).[3-7] Fortunately, antibiotic stewardship efforts have aided in the reduction of antibiotic misuse and rates of CDI.[8-11] Despite these endeavors, CDI remains a significant challenge,[12] and, regrettably, the appropriate use of antibiotics is unavoidable in many hospitalized patients.[13]

*Address correspondence to Steven W. Johnson, PharmD, BCPS, CPP, AAHIVP, Department of Pharmacy Practice, Campbell University College of Pharmacy & Health Sciences, 217 Main St, Buies Creek, NC 27506.
E-mail address: johnsonsw@campbell.edu (S.W. Johnson).
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Clearly, there is a need for more effective measures to reduce CDI incidence, especially in high-risk patient populations.

To execute a targeted strategy to reduce CDI, the development of an up-to-date, easily implementable risk stratification model is necessary to identify patients at highest risk for CDI early into hospital admission. Through reviewing the literature, we identified 7 CDI risk stratification models.[4-7,14-16] There are several differences between each of these models, and each has limitations for use as an initial screening tool on hospital admission, namely, their ease of implementation into clinical practice. Some models include several variables, including those that are not routinely collected or may not be known until well into the hospitalization. Specifically, Tanner et al[6] applied the Waterlow Score technique (used frequently in nursing to identify patients at risk for pressure ulcers). Owing to common miscalculation of the Waterlow Score, the utility of this tool is questionable. Dubberke et al[7] developed a tool involving Acute Physiology Score and *C difficile* pressure, among other variables. Owing to the complexity of these 2 variables, the ability to assess a patient at bedside may be hindered.[6] Some of these studies collected data from over a decade ago.[5-7] Consequently, these models were developed prior to the implementation and heightened awareness of CDI preventative measures and the routine use of more accurate diagnostic testing modalities.[5-7]

Therefore, the objective of this study was to develop an easily implementable risk prediction model for hospital-onset CDI in patients receiving systemic antimicrobials that can be used on hospital admission. The secondary objective was to determine the all-cause mortality rate in subjects with hospital-onset CDI versus those without.

METHODS

This was a retrospective, case-control, multicenter study. Potential subjects were identified using an electronic medical record database query. Subjects were included if they were aged ≥18 years, were admitted from July 1, 2015, to July 1, 2017, to Novant Health Forsyth Medical Center (NHFMC) or Novant Health Presbyterian Medical Center (NHPMC). Novant Health is a 14-hospital health system that provides care across multiple states in the southeast region of the United States. NHFMC is a 921-bed tertiary care center located in Winston-Salem, North Carolina. NHPMC is a 622-bed tertiary care center located in Charlotte, North Carolina. Subjects were excluded if they had a CDI diagnosis prior to the index admission to the hospital; were pregnant; had incomplete medical records; had a length of stay <48 hours; had a diagnosis of irritable bowel syndrome, Crohn disease, or ulcerative colitis; or had diarrhea <48 hours into admission (to exclude community-associated CDI). Subjects were randomly screened until the desired sample population of 200 subjects was achieved. The study was approved by Novant Health's institutional review board. Case subjects were patients with hospital-onset CDI (defined as a positive *C difficile* polymerase chain reaction [PCR] test result ≥48 hours into hospital admission with signs/symptoms consistent with CDI [eg, diarrhea, leukocytosis, fever, or abdominal pain]). Novant Health uses pre-agreed institutional criteria for patient stool submission for CDI (ie, clinicians and laboratory personnel agree to not submit stool specimens on patients receiving laxatives or who have formed stools. The clinician must also have clinical suspicion of CDI based on signs/symptoms). These institutional criteria were implemented in 2014, demonstrating compliance with current Infectious Disease Society of America recommendations for molecular-based testing alone in the setting of an established agreement. Through the implementation of this CDI testing protocol, positive results secondary to colonization are less likely to occur. Additionally, patients with a past medical history of irritable bowel syndrome, Crohn disease, or ulcerative colitis were excluded to reduce the identification of colonization. Control subjects included patients without documented CDI (who had a negative CDI PCR test result or did not have a PCR obtained). Control subjects were matched to a corresponding case subject using a 1:1 ratio based on hospital ward type (critical care or medicine).

Data collected included patient age, sex, date of index admission, admission unit ward, admission from, discharge date, length of stay, most recent prior hospital admission date, outpatient antibiotics prior to index hospital admission, inpatient systemic (defined as oral or parenteral) antibiotics (≥1 dose), duration of antibiotics, diarrhea <48 hours into admission, histamine receptor antagonist use, PPI use, gastrointestinal surgery, gastrointestinal manipulation including tube feeds, and all-cause mortality.

Descriptive statistics were used to describe the study population to compare cases with controls. Continuous variables were expressed as means and were compared by the Student t test. Categorical variables were analyzed by the 2-tailed Fisher exact test. To determine the strength of any association that emerged, odds ratios and 95% confidence intervals were calculated. JMP 8 statistical software (SAS Institute, Cary, NC) was used to perform all statistical analyses. A univariate analysis was conducted to identify variables significantly more associated with cases than controls for hospital-onset CDI. Statistically significant (defined as $P < .05$) and only evaluable variables at hospital admission were then incorporated into a multivariant analysis. A logistic regression model using a backward stepwise approach was employed to identify risk factors. Variables were kept in the final model if the P value was <.05. The final regression model was transformed into a point-based tool with weighted scores assigned to the variables identified to be associated with hospital-onset CDI. The scores assigned to each variable were obtained by dividing each regression coefficient by half of the smallest coefficient and rounding to the nearest integer. The positive predictive value, negative predictive value, sensitivity, specificity, and accuracy were determined at various point cutoffs of the tool. A receiver operating characteristic–area under the curve (ROC-AUC) was also completed to assess the discrimination of the risk model. The secondary outcome assessing all-cause mortality (defined as death from all causes from the time of hospitalization until the time the data were collected) was analyzed using the Fisher exact test.

RESULTS

A total of 200 subjects were included in the study, 100 from NHFMC and 100 from NHPMC. Each institution included 50 case subjects and 50 control subjects. Table 1 compares hospital-onset CDI cases with controls. Subjects were mostly Caucasian and female in both groups. Case subjects were older, were more likely to have a prior recent hospitalization, had a longer length of stay during index hospitalization, had a longer duration of systemic antibiotic use during index hospitalization, and were more likely to receive tube feeds. Specific antibiotic use during index hospitalization was also evaluated and reported in Table 1.

Of the statistically significant variables identified in Table 1, only age ≥70 years and hospitalization in the past 90 days were characteristics that could be evaluated at admission. These variables remained statistically significant when evaluated in the multivariate logistic regression model. Table 2 summarizes the odds ratios and 95% confidence intervals for these variables in the univariate and multivariate analysis. Recent admission in the past year was not included owing to recent admission in the past 90 days being more statistically significant.

Age ≥70 years and recent hospitalization in the past 90 days were incorporated into a hospital-onset prediction scoring model (Table 3). The diagnostic performance of various score cutoffs for the hospital-onset CDI risk prediction model is summarized in Table 4. The positive predictive value, negative predictive value, sensitivity, specificity,

Table 1
Demographic characteristics of patients infected with hospital-onset *Clostridium difficile* infection versus patients without hospital-onset *Clostridium difficile* infection

Characteristic	Cases (n = 100)	Controls (n = 100)	*P* value
Patient characteristics			
Age, mean ± SD, years	**67.98 (± 14.68)**	**63.51 (± 16)**	**.0435**
Age ≥ 70 years	**52**	**38**	**.0322**
Female	59	51	.3198
Race			
Caucasian	73	74	1
African American	23	19	.6029
Other	3	4	1
Unknown	1	3	.6212
Past medical history			
Recent hospitalization within 90 days	**45**	**20**	**<.0001**
Recent hospitalization within 1 year	**45**	**29**	**.0277**
Outpatient antibiotic use prior to hospitalization*	23	18	.4839
Antacid use prior to hospitalization*	37	32	.5520
Probiotic use prior to hospitalization*	6	6	1
Gastrointestinal surgery within the past 90 days	16	14	.8433
Gastrointestinal surgery within the past year	8	5	.5679
Hospitalization			
Length of stay, mean ± SD, days	**20.25 (± 14.33)**	**6.72 (± 5.94)**	**<.0001**
Histamine receptor antagonist use during hospitalization	39	28	.1338
Proton pump inhibitor use during hospitalization	58	54	.6692
Probiotic use during hospitalization	9	4	.2507
Systemic antibiotic duration, mean ± SD, doses	**17.69 (16.60)**	**9.71 (11.8)**	**.0005**
Tube feeds during hospitalization	**34**	**4**	**<.0001**
Systemic antibiotic used, no. of subjects (total doses)			
Penicillin	0	1 (8)	1
Ampicillin	0	1 (5)	1
Cephalexin	2 (10)	1 (1)	1
Cefazolin	22 (64)	30 (83)	.2590
Cefoxitin	1 (1)	0	1
Cefuroxime	1 (10)	1 (3)	1
Ceftriaxone	35 (137)	28 (91)	.3611
Cefdinir	2 (8)	2 (2)	1
Cefepime	**30 (229)**	**4 (45)**	**<.0001**
Ceftaroline	0	3 (12)	.2462
Ertapenem	3 (5)	4 (11)	1
Meropenem	5 (30)	2 (60)	.4448
Piperacillin-tazobactam	**57 (572)**	**17 (204)**	**<.0001**
Ampicillin-sulbactam	1 (11)	2 (33)	1
Amoxicillin-clavulanate	4 (33)	1 (11)	.3687
Aztreonam	7 (47)	3 (23)	.3311
Ciprofloxacin	**28 (138)**	**11 (51)**	**.0039**
Levofloxacin	14 (40	18 (67)	.5634
Azithromycin	9 (28)	8 (28)	1
Erythromycin	0	1 (14)	1
Doxycycline	7 (39)	9 (60)	.7953
Vancomycin	**72 (260)**	**30 (118)**	**<.0001**
Linezolid	1 (1)	1 (2)	1
Daptomycin	0	3(18)	.2462
Clindamycin	3 (20)	2 (7)	1
Sulfamethoxazole-trimethoprim	4 (9)	1 (6)	.3687

NOTE. Bold values are statistically significant ($P < .05$).
SD, standard deviation.
*Received immediately prior to hospitalization.

and accuracy were calculated at each score cutoff (Table 4). A score ≥ 2 was associated with the highest accuracy (63%). Additionally, the ROC-AUC was 0.7 for the model.

All-cause mortality was higher in case subjects than in control subjects (41 subjects vs 15 subjects; $P < .05$).

DISCUSSION

Similarities and differences were discovered between our results and prior published data. Harris et al[14] similarly found that patients with CDI had an increased length of stay and increased average age. Davis et al[15] similarly found high-risk antibiotics (ie, cefepime and piperacillin/tazobactam) and advanced age to be risk factors for CDI. However, unlike our results, PPI use and specific antibiotics (ie, ceftriaxone, carbapenems, and sulfamethoxazole-trimethoprim) were identified as risks for CDI.[15] Last, Kuntz et al[16] similarly found that patients with CDI were older and more likely to have a recent stay in a hospital (or community living health care facility prior to admission of interest) and recent use of high-risk antibiotics (ie, ciprofloxacin). In contrast to our study, patients who developed CDI were also more likely to have gastric acid suppression and receive other specific antibiotics (ie, second- and third-generation cephalosporins and clindamycin).[16] Contrary to previous studies, vancomycin was found in our study to be significantly more associated with cases than controls. However, this is likely owing to the concomitant use of broad-spectrum antibiotics with vancomycin rather than increased incidence of CDI caused by vancomycin therapy alone.

Several other known risk factors for CDI could have been evaluated and potentially incorporated into the risk model. Although the incorporation of additional risk factors would have improved the performance of the model, it would also limit the utility. We attempted to make a predictive model with as few risk variables as possible that would be fairly accurate and easy to obtain on initial presentation to the hospital. Some prior published risk factors for CDI were not evaluated for various reasons. Specifically, we had hoped to identify prior antibiotic use in the past 30 days and 90 days; however, based on prior work, we discovered that this could not be reliably analyzed given the retrospective design of the study. Only institution-specific pharmacy records could be evaluated. If the patient filled prescriptions outside of Novant Health, this information would not be captured. Therefore, we evaluated admission medication reconciliation to capture prior antibiotic use. We also hoped to evaluate the role of immunosuppression on CDI risk. Based on prior work, we discovered that immunosuppression was a difficult variable to assess at hospital presentation and would not be a practical variable to use for the purpose of this model. For instance, some patients would need laboratory work to determine if they were immunocompromised (ie, an HIV-infected individual on appropriate antiretroviral therapy would need a CD4 count to determine immune status).

Based on our results, for patients receiving systemic antibiotics, only age ≥ 70 years and hospitalization in the past 90 days were characteristics that could be evaluated at admission, which were incorporated into a scoring model. This model's discrimination ability was evaluated by determining the ROC-AUC, which measures the ability of the model to correctly classify those with and without the disease.[17] This tool plots the true-positive rate against the false-positive rate for the different cut points of a diagnostic test. The interpretation of this tool includes a ROC-AUC of 0.5-0.6 indicating a poor model, 0.6-0.7 a fair model, 0.8-0.9 a good model, and 0.9-1.0 an excellent model. With the Novant Health Model having a ROC-AUC of 0.7, this model is classified as fair. Other published models resulted in ROC-AUCs of 0.71-0.88.[1,4-6,15]

The utility of this scoring model and how it should be used is yet to be determined. The first practical step to applying this model would be setting a "cutoff" score. However, the optimal cutoff score depends on the purpose of the scoring model. If the scoring model will be used as a screening tool (ie, identifying those at high risk for CDI), choosing a cutoff score with a high sensitivity with the sacrifice of a lower specificity (eg, ≥ 2) may be appropriate. Using the model in this manner would allow implementation of an intervention to reduce the chances of CDI. The score cutoff will also be affected by

Table 2
Evaluation of admission risk factors identified

Variable	Unadjusted OR (95% CI)*	Unadjusted *P* *	Adjusted OR (95% CI)†	Adjusted *P*†
Age ≥70 years	1.78 (1.01-3.10)	.0322	1.89 (1.05-3.43)	.0326
Hospitalized in the past 90 days	3.41 (1.82-6.39)	<.0001	3.55 (1.90-6.83)	<.0001

CI, confidence interval; *OR*, odds ratio.
*Obtained through univariate logistic regression.
†Obtained through multivariate logistic regression, adjusted for other factors.

Table 3
Novant Health hospital-onset *Clostridium difficile* infection risk score

Attribute	Number of points
Age ≥70 years	2
Hospitalized in the past 90 days	4

Table 4
Distribution of scores with diagnostic cutoff performance

Score	TP	FP	TN	FN	Se	Sp	PPV	NPV	Acc
≥2	76	51	49	24	76	49	60	67	63
≥4	44	20	80	56	44	80	69	59	62
6	20	7	93	80	20	93	74	54	57

Acc, accuracy; *FN*, false negative; *FP*, false positive; *NPV*, negative predictive value; *PPV*, positive predictive value; *Se*, sensitivity; *Sp*, specificity; *TN*, true negative; *TP*, true positive.

the desired intervention. If the scoring model was used to identify those who should receive prophylaxis, using a lower score cutoff will likely result in overuse of prophylactic measures. Use of a prophylactic intervention will likely require a cutoff score with a higher specificity and positive predictive value with the sacrifice of a lower sensitivity (eg, 6). Therefore, if only subjects with a score of 6 were included for prophylactic measures for CDI, only 7% of patients would receive unnecessary prophylaxis (eg, oral vancomycin or probiotics). Further studies will be conducted to apply this model and assess the utility of prophylactic antibiotics to reduce the incidence of hospital-onset CDI. The authors will continue to assess simplification and improvement of the CDI risk model.

In the meantime, the question remains: what should be done for these high-risk patients? The updated Infectious Disease Society of America guidelines do not currently recommend primary prophylaxis with probiotics or oral vancomycin. They also state that there are insufficient data to support asymptomatic isolation or discontinuation of PPIs for CDI prevention.[3] However, all institutions should employ traditional infection prevention strategies (eg, hand hygiene and the wearing of gloves and gowns when entering the room of someone with CDI). Furthermore, all institutions should implement an antimicrobial stewardship program. Until more data are available on other possible interventions to prevent CDI, it seems reasonable to have heightened antimicrobial stewardship efforts for high-risk CDI patients.

Limitations of this study include its retrospective design. Additionally, information on outpatient antibiotics prior to admission was dependent on the quality of medication reconciliation done at admission. Despite the goal of including antibiotics prior to admission, we were unable to reliably analyze this variable given the retrospective design of the study and being limited to institution-specific pharmacy records. Diarrhea, noted less than 48 hours into admission, was an exclusion factor; however, the accuracy of this (and other symptoms) was dependent on subjective documentation by a nurse or provider. Another limitation to this study is how we defined hospital-onset CDI. After the design of this study, standardized case definitions of the various types of CDI are now commonly recognized and have been published in the updated Infectious Disease Society of America CDI Treatment Guidelines.[3] Health care facility–onset CDI cases are defined by the Centers for Disease Control and Prevention and the National Healthcare Safety Network as events collected more than 3 days after admission to the health care facility.[3] This study excluded patients with documentation of diarrhea within 48 hours of admission. Despite this, no included case patients had diarrhea and were diagnosed with CDI <4 days into their hospitalization. Therefore, the results of this study would be applicable to the current Centers for Disease Control and Prevention /National Healthcare Safety Network definition of health care facility–onset CDI.

CONCLUSIONS

Age ≥70 years and hospitalizations within the past 90 days are risk factors identifiable at admission that increase the risk of hospital-onset CDI in the setting of systemic antibiotic use. Additional risk factors were identified; however, these risk factors were not identifiable at admission. The ROC-AUC of 0.7 for the Novant Health Model indicates that the model is a fair predictor of hospital-onset CDI, which may allow for primary prevention. All-cause mortality was higher in the CDI group, highlighting the urgency for preventative efforts. Additional studies are needed to validate this model.

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