Evaluation of a risk assessment model to predict infection with healthcare facility–onset *Clostridioides difficile*

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**Purpose.** We evaluated a previously published risk model (Novant model) to identify patients at risk for healthcare facility–onset *Clostridioides difficile* infection (HCFO-CDI) at 2 hospitals within a large health system and compared its predictive value to that of a new model developed based on local findings.

**Methods.** We conducted a retrospective case-control study including adult patients admitted from July 1, 2016, to July 1, 2018. Patients with HCFO-CDI who received systemic antibiotics were included as cases and were matched 1 to 1 with controls (who received systemic antibiotics without developing HCFO-CDI). We extracted chart data on patient risk factors for CDI, including those identified in prior studies and those included in the Novant model. We applied the Novant model to our patient population to assess the model’s utility and generated a local model using logistic regression–based prediction scores. A receiver operating characteristic area under the curve (ROC-AUC) score was determined for each model.

**Results.** We included 362 patients, with 161 controls and 161 cases. The Novant model had a ROC-AUC of 0.62 in our population. Our local model using risk factors identifiable at hospital admission included hospitalization within 90 days of admission (adjusted odds ratio [OR], 3.52; 95% confidence interval [CI], 2.06-6.04), hematologic malignancy (adjusted OR, 12.87; 95% CI, 3.70-44.80), and solid tumor malignancy (adjusted OR, 4.76; 95% CI, 1.27-17.80) as HCFO-CDI predictors and had a ROC-AUC score of 0.74.
Conclusion. The Novant model evaluating risk factors identifiable at admission poorly predicted HCFO-CDI in our population, while our local model was a fair predictor. These findings highlight the need for institutions to review local risk factors to adjust modeling for their patient population.

Keywords: antimicrobial stewardship, *Clostridioides difficile*, *Clostridium* infections, pharmacists, risk factors, ROC curve
*Clostridioides difficile* infection (CDI) is a significant challenge to the healthcare system.\(^1\)-\(^3\) Healthcare facility–onset CDI (HCFO-CDI) leads to considerable patient morbidity and mortality, increased length of stay, and increased healthcare costs.\(^1\)-\(^4\) As a result, both risk factors for HCFO-CDI and prevention measures are topics of study. Previously identified risk factors include the number and duration of antibiotics that a patient receives, use of high-risk antibiotics classes (third- and fourth-generation cephalosporins, fluoroquinolones, carbapenems, and clindamycin), chronic kidney disease and end-stage renal disease, advanced age, duration of hospitalization, human immunodeficiency virus, chemotherapy, and gastrointestinal surgery or manipulation of the gastrointestinal tract.\(^3\)

Antimicrobial stewardship efforts are an area of focus, as they have aided in a reduction in the incidence of HCFO-CDI.\(^3\) Pharmacists have direct and indirect roles in antimicrobial stewardship and are well positioned to have a critical role in preventing HCFO-CDI by identifying patients at high risk and implementing prevention strategies. Researchers have studied models to predict CDI (including the Waterlow score technique, acute physiology score, *C. difficile* pressure, etc); however, there are several limitations to these models, most notably that they are difficult to implement because they include risk factors for which data may not be present, routinely collected, or known on admission.\(^5\)-\(^11\) Additionally, some of these models were developed from 2008 to 2011, necessitating the inclusion of more recent data since the advent of heightened CDI awareness and preventative measures.\(^6\)-\(^8\) More recently, Novant Health developed a model that fairly predicted HCFO-CDI for patients receiving systemic antibiotics using 2 variables, age 70 years or greater and hospitalization within the previous 90 days, which are easy to identify at admission.\(^12\)
This type of model offers the advantage of identifying high-risk patients early in their course but needs to be validated at other health systems with diverse patient populations before it can be implemented routinely. This specific model was chosen here for comparison because it was developed and evaluated by pharmacists and focuses on identifying risk factors at admission. Some gaps in the Novant model include its definition of HCFO-CDI by a positive PCR result at 48 hours or later during hospital admission and its lack of assessment for chronic kidney disease and immunosuppression, which are CDI risk factors.\textsuperscript{3,12}

We therefore sought to evaluate the Novant model in a patient population that includes large numbers of oncology, transplant, and dialysis patients to determine the model’s accuracy and compared its performance with that of a new model generated from local risk factors. The primary objective for the study was to determine whether the Novant model accurately identified patients at risk for HCFO-CDI at admission. The secondary objectives were to identify local risk factors available at admission that are associated with HCFO-CDI and to determine whether including these new risk factors improved the model’s predictive value. Additionally, variables not identifiable at admission were also assessed in an effort to identify areas for future research and pharmacist-driven antibiotic stewardship initiatives.

**Methods**

**Study design.** This was a multicenter, retrospective, case-control study conducted at 2 hospitals, a 733-bed academic medical center and a 531-bed not-for-profit community teaching hospital. All included patients admitted to one of these hospitals between July 2016 and July 2018 were 18 years or older and received one or more doses of systemic antibiotics during their hospitalization (Appendix). Patients were excluded if they had a CDI
diagnosis within 90 days of index admission to the hospital; were pregnant; were discharged from the hospital in 72 hours or less; had an International Statistical Classification of Diseases and Related Health Problems (ICD)-10 code indicating a past medical history of irritable bowel syndrome, Crohn’s disease, or ulcerative colitis; received metronidazole or oral vancomycin before their CDI diagnosis; or had diarrhea before day 4 of their hospital admission. Cases had a diagnosis of HCFO-CDI, defined as a positive CDI PCR result on or after day 4 of hospital admission, in the setting of receiving systemic antibiotics. This time frame for defining HCFO-CDI is consistent with the National Healthcare Safety Network (NHSN) definition. Controls were patients without a CDI diagnosis, who either had a negative PCR result within 90 days of admission or did not have a CDI test performed within the health-system network and had received systemic antibiotics. The health-system network includes multiple hospitals and clinics, and laboratory results within the system are accessible electronically. A unique control was matched to a corresponding case using a 1 to 1 ratio on the basis of admission hospital ward type (acute care or intensive care unit [ICU]). The primary endpoints included the positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, and accuracy of using the risk factor variables in the Novant model at each weighted score to predict CDI. The secondary endpoints included PPV, NPV, sensitivity, specificity, and accuracy calculated at each weighted score for a local risk factor model. The study was approved by the Emory University institutional review board.

Data collection. We utilized an electronic data warehouse and electronic medical record query based on a positive PCR result to identify CDI cases. The Novant model also used positive PCR results to identify CDI cases. We collected the following data in Microsoft
Excel (Microsoft Corporation, Redmond, WA): age, sex, date of admission, admission hospital ward type (acute care vs ICU), discharge date, length of stay, date of the most recent prior hospital admission, outcome (survival to discharge vs mortality), outpatient antibiotic administration recorded on medication history at admission (when available), outpatient probiotic use recorded on medication history at admission (when available), systemic antibiotics administered, use of histamine H$_2$-receptor antagonist (H2RA) or proton pump inhibitor (PPI) before admission (when available) and during the hospitalization, inpatient probiotic use, gastrointestinal surgery documented in the electronic medical record within 90 days of admission (control group) or CDI diagnosis (case group), presence of chronic kidney disease based on ICD-10 codes, and immunosuppression. Information on medication administration for antibiotics, PPIs, H2RAs, and probiotics was collected before CDI diagnosis for cases. Patients with immunosuppression were identified by having an ICD-10 code for one or more of the following: hematologic or solid tumor malignancy, history of solid organ or bone marrow transplant, a connective tissue disorder, acquired immunodeficiency syndrome, symptomatic liver failure, chronic kidney disease, and/or diabetes mellitus.

**Statistical analysis.** Descriptive statistics were used to identify potential variables associated with HCFO-CDI. A Student’s t test was used for continuous variables, and a $\chi^2$ test was used for categorical data. Variables identified as statistically significant ($P < 0.05$) in a univariable analysis were included in a multivariable analysis for development of the local model. A variable was kept in the final multivariable model if its $P$ value was less than 0.05. A point-based tool with weighted scores was developed using risk factors. Risk factors were defined as the remaining predictor variables in multivariable logistic regression after backward selection using a $P$-value threshold of 0.05. The weighted score for risk factors
was obtained by dividing the adjusted odds ratio (OR) by the smallest OR and rounding to the nearest integer. The PPV, NPV, sensitivity, specificity, and accuracy were determined at point cutoffs for both the Novant model and the local model, and a receiver operating characteristic area under the curve (ROC-AUC) value was calculated to evaluate the degree of discrimination for each model. Accuracy was defined as the overall probability that a patient was correctly classified (sensitivity × prevalence + specificity × [1 – prevalence]). All-cause mortality (defined as death from all causes from the time of hospitalization until the time of discharge) was analyzed using a Fisher’s exact test. Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics. A total of 362 patients were included in the study, with 161 controls and 161 cases (Table 1). The average age was similar in both groups, and the majority of patients were female and African American. During their hospitalization, significantly more patients in the case group received H2RAs (78 cases [48.45%] vs 57 controls [35.40%]; $P = 0.018$), PPIs (101 cases [62.73%] vs 72 controls [44.72%]; $P = 0.001$), and probiotics (26 cases [16.15%] vs 7 controls [4.35%]; $P < 0.001$). Antibiotic classes associated with HCFO-CDI included cephalosporins (116 cases [72.05%] vs 22 controls [13.66%]; $P < 0.001$), carbapenems (42 cases [26.09%] vs 11 controls [6.83%]; $P < 0.001$), and glycopeptides (136 cases [84.47%] vs 77 controls [47.83%]; $P < 0.001$). Multiple combinations of broad-spectrum antibiotics were associated with increased rates of HCFO-CDI, including intravenous (IV) vancomycin and piperacillin-tazobactam (53 cases [32.92%] vs 7 controls [4.35%]; $P < 0.001$), IV vancomycin and ceftriaxone (36 cases [22.36%] vs 4 controls [2.48%]; $P < 0.001$).
controls [2.48%]; \( P < 0.001 \), IV vancomycin and cefepime (42 cases [26.09%] vs 7 controls [4.35%]; \( P < 0.001 \), IV vancomycin and ceftazidime (28 cases [17.39%] vs 3 controls [1.86%]; \( P < 0.001 \), IV vancomycin and levofloxacin (33 cases [20.50%] vs 3 controls [1.86%]; \( P < 0.001 \), IV vancomycin and meropenem (41 cases [25.47%] vs 1 control [0.62%]; \( P < 0.001 \), and IV vancomycin and aztreonam (12 cases [7.45%] vs 3 controls [1.86%]; \( P = 0.017 \). IV vancomycin monotherapy was not associated with an increased risk of HCFO-CDI. Mean length of stay was longer in the case group than in the control group (21.27 days vs 9.19 days; \( P < 0.001 \).

**Primary endpoint.** When using the Novant model to predict HCFO-CDI with risk factors available at admission, a score of 4 or greater was associated with the highest accuracy (Table 2). A score of 6 or greater was associated with an improved PPV but a lower NPV, while a score of 2 or greater was associated with an improved NPV but a lower PPV. The Novant model demonstrated poor discrimination with a relatively low ROC-AUC of 0.62 when directly applied to our health-system facilities (Figure 1).

**Secondary endpoints.** To evaluate our local model, we included the 3 variables available at hospital admission that were significant in univariable analyses: hematologic malignancy, solid tumor malignancy, and a hospitalization within 90 days of admission. The adjusted OR for hematologic malignancy as a predictor of HCFO-CDI was 12.87 (95% confidence interval [CI], 3.70-44.80). The adjusted OR for solid tumor malignancy was 4.76 (95% CI, 1.27-17.80), and the adjusted OR for hospitalization within 90 days of admission was 3.52 (95% CI, 2.06-6.04) (Table 3). When included in the multivariable analysis, all 3 variables remained statistically significant (\( P < 0.05 \)).
Hematologic malignancy, solid tumor malignancy, and a hospitalization within 90 days of admission were then assigned weighted scores (Table 4), and diagnostic performance was assessed at various point cutoffs (Table 5). A score of 1 or more was associated with the highest accuracy. A score of 6 or more was associated with an improved PPV but with a lower NPV within the model. The model had fair discrimination with a ROC-AUC of 0.74 (Figure 2).

Discussion

Our local model performed better than the Novant model in predicting risk of HCFO-CDI at admission. Hematologic malignancy, solid tumor malignancy, or hospitalization within the previous 90 days significantly predicted risk of HCFO-CDI when a patient received systemic antimicrobials. The poor performance of the Novant model when applied to our patient population highlights the need for institutions to evaluate local risk factors that predict HCFO-CDI. Our patient population included a large number of patients with immunosuppression, which was not assessed by the Novant model, possibly explaining the differences in performance of the models. Studies have suggested that there is a multifactorial increase in risk of CDI for immunosuppressed patients, with frequent healthcare contacts and exposures to antibiotics and other medications as potential contributors. For example, malignancy was a significant predictor in our model, which is supported by prior evidence of chemotherapy-associated dysregulation of the gut microbiome.

A hospitalization in the previous 90 days was predictive of HCFO-CDI in both models, which highlights its importance as a more universal risk factor. This may be driven by the potential for the patient having received antibiotics during a prior hospitalization but also
could reflect the risks of exposure to CDI and resultant colonization in a healthcare setting. Studies have shown an increased risk of CDI if the prior patient in a hospital room either had CDI or received antibiotics, as well as a risk for patient-to-patient transmission via contaminated equipment or staff.\textsuperscript{16,17}

However, despite utilizing local risk factors, our model only offered fair discrimination between HCFO-CDI cases and controls, which was similar to the performance of the Novant model when applied to a local patient population. This may reflect the difficulty in utilizing only risk factors for which data are available upon admission to the hospital. Using risk factors present at admission is ideal from the standpoint of early intervention, but the results suggest that in-hospital risk factors likely have a significant role in contributing to HCFO-CDI. Before implementing the local model, a cutoff score would need to be defined. The cutoff score could vary depending on how the model is applied. A lower cutoff score, such as 1 or greater, would have high sensitivity and identify more patients at risk for HCFO-CDI. This might be an effective strategy for low-risk interventions like deescalating antibiotics or assessing the need for acid suppression. A higher cutoff score may be warranted if prophylactic vancomycin is being considered. Future studies should include hospital-associated variables present early in an admission, including those that had statistically significant associations with HCFO-CDI in the univariable analysis here.

The 2018 Infectious Diseases Society of America guidelines acknowledge an association between use of PPIs and CDI and recommend discontinuation of PPIs for patients without a clinical need for them. However, they also state that there is insufficient evidence to recommend discontinuation of PPIs as a strategy for CDI prevention,\textsuperscript{3} and this uncertainty is evident in the conflicting results that we observed. In the Novant model, use
of PPIs and H2RAs during hospitalization was similar between the case group and the control group, but in our study both medication types were more commonly prescribed during hospitalization for patients who developed HCFO-CDI. The univariable analysis from this study showed that more patients in the case group were prescribed H2RAs and PPIs during their hospitalization than patients in the control group. While the use of inpatient H2RAs and PPIs was not included in the multivariable analysis because it is not necessarily identifiable at admission, not initiating or discontinuing H2RAs and PPIs when they are not clinically indicated may be one way for pharmacists to decrease the probability of HCFO-CDI for high-risk patients.

There are also conflicting data in the literature about which antibiotic classes are most strongly associated with CDI, with third- and fourth-generation cephalosporins, fluoroquinolones, carbapenems, and clindamycin commonly referenced as high-risk antibiotics. Use of cefepime, piperacillin-tazobactam, ciprofloxacin, and IV vancomycin was associated with HCFO-CDI at Novant Health. In our patient population, use of cephalosporins, carbapenems, and glycopeptides, as well as some combinations of antibiotic classes, was found to be significantly associated with HCFO-CDI. One explanation for the differences in systemic antibiotics associated with HCFO-CDI could be a national shortage of piperacillin-tazobactam during the time of our study, with resultant increased use of carbapenems. Glycopeptides were associated with HCFO-CDI in both studies, and thus further analysis was completed to determine whether this appeared to be due to IV vancomycin use alone or reflected a high likelihood of using IV vancomycin in combination with another antibiotic class as part of empiric broad-spectrum coverage. Commonly used antibiotic combinations for broad-spectrum coverage within our system were included. IV
Vancomycin given in combination with piperacillin-tazobactam, ceftriaxone, cefepime, ceftazidime, levofloxacin, meropenem, and aztreonam was significantly associated with HCFO-CDI, while IV vancomycin monotherapy was not. It therefore appears that receiving more than one class of antibiotics may increase CDI risk, which is an important point for future consideration.

The evidence to recommend probiotics for the prevention of CDI is insufficient. In our study, there were significantly more cases than controls who received probiotics during admission. Of note, there was no difference between the case group and the control group in the use of probiotics before admission. Therefore, on the basis of the inconclusive literature and our study results, we would not recommend probiotics to prevent HCFO-CDI at this time.

The main limitation of this study was its retrospective design. All variables were identified from the electronic health record and data warehouse and thus rely on the accuracy of the documentation. As a result, some variables had to be excluded: for example, we were unable to assess the impact of tube feeds on the risk of HCFO-CDI owing to inconsistent documentation in the electronic health record. Additionally, the evaluation of previous hospitalizations and laboratory results was limited to cases and controls within our healthcare system, and so some patients may have had an admission or a diagnosis of CDI within the previous 90 days at another facility, which could have biased the results.

Another limitation may have been the method used to define CDI. A positive PCR result was used to identify patients with CDI in the case groups of both the local model and the Novant model. Many facilities, including the study institution, have since transitioned to
a 2-step testing method with PCR and a *C. difficile* toxin enzyme immunoassay (EIA) to better differentiate asymptomatic carriers from patients with an active infection.

The 2 models also differed in their definitions of HCFO-CDI. The local model used the updated NHSN time frame for HCFO-CDI in contrast to the older definition of 48 hours or more into hospital admission, which was used in the Novant model.\(^3\) The different definitions may have contributed to the poor performance of the Novant model in our patient population. Ideally, the Novant model would have been cross-validated on a separate dataset derived from the same population instead of a new patient population.

Although patients were included from 2 different hospitals within our health system, the specific hospital was not assessed as a potential risk factor for CDI. In addition, the antibiotic combinations may have had increased potential for false positives, as the statistical analysis was not adjusted for multiple comparisons. Finally, the study could have been underpowered. We initially calculated the need for a sample size of 408 patients on the basis of the use of age 70 years or older as a significant predictor of CDI in the Novant study, in which 52% of cases vs 38% of controls were in this category.\(^{12}\) However, as age was not a significant predictor of CDI in our cohort, the utility of this power calculation is unclear.

Despite the only fair discrimination ability of the local model and these limitations, the results suggest that some patients at risk for HCFO-CDI can be identified at hospital admission, which offers a target for preventive interventions that should be a focus of future studies. Pharmacists are uniquely positioned to implement these interventions because they review both antibiotic orders and orders for other medications that may increase the risk of HCFO-CDI. Pharmacists could use these models to identify those at highest risk for HCFO-CDI, which would put pharmacists on the frontline of preventing
HCFO-CDI. An electronic version of this tool could be developed, with a data query performed when a patient is started on antibiotics to evaluate whether they have risk factors for HCFO-CDI, such as a recent hospitalization or an underlying malignancy. This could generate a list of patients at risk for HCFO-CDI that would necessitate pharmacist review and intervention, such as by evaluating opportunities to deescalate broad-spectrum antibiotics and to discontinue unnecessary acid suppression agents. On the basis of new research, pharmacists could recommend prophylactic oral vancomycin in patients at the highest risk for HCFO-CDI who are receiving antibiotics.18

**Conclusion**

A local model performed better than the previously published Novant model in predicting HCFO-CDI risk in our patient population, suggesting the critical importance of evaluating risk factor models in unique patient groups, including those with significant underlying immunosuppression. A hospitalization within the previous 90 days was associated with increased risk of HCFO-CDI in both models in the setting of systemic antibiotic use, while hematologic malignancy and solid tumor malignancy were associated with increased risk locally. Further research efforts should be devoted both to improving the performance of HCFO-CDI risk prediction models within institutions and to evaluating the efficacy of preventative interventions targeted to the highest-risk patients.

**Disclosures**

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Figure 1. Performance of the Novant model in a different patient population.

Figure 2. Performance of a local model in predicting risk of healthcare facility–onset *Clostridioides difficile* infection.

**Key Points**

- The Novant model to predict a patient’s risk for healthcare facility–onset *Clostridioides difficile* infection (HCFO-CDI) at admission performed poorly when applied to a health system with more immunosuppressed patients.

- A new, local model was developed to improve the ability to identify patients at high risk for HCFO-CDI.

- The local model identified significant risk factors at admission for HCFO-CDI, including the presence of a hematologic malignancy or a solid tumor malignancy and a hospitalization within the previous 90 days.
Table 1. Demographic Characteristics and Risk Factors of Cases vs Controls\(^a\)

| Characteristic\(^b\) | Controls  | Cases       | P Value |
|----------------------|-----------|-------------|---------|
|                      | \(n = 161\) | \(n = 161\) |         |
| Demographic factors  |           |             |         |
| Age, mean (SD), years| 62.17 (15.69) | 61.04 (16.07) | 0.524   |
| Age ≥70 years        | 53 (32.92)  | 53 (32.92)  | 1.000   |
| Female               | 85 (52.80)  | 85 (52.80)  | 1.000   |
| Race                 |           |             | 0.363   |
| Caucasian            | 67 (41.61)  | 72 (44.72)  |         |
| African American     | 89 (55.28)  | 82 (50.93)  |         |
| Asian                | 3 (1.86)    | 2 (1.24)    |         |
| Other                | 1 (0.62)    | 0 (0)       |         |
| Unknown              | 1 (0.62)    | 5 (3.11)    |         |
| Ethnicity            |           |             | 0.154   |
| Non-Hispanic         | 150 (93.17) | 144 (89.44) |         |
| Hispanic             | 1 (0.62)    | 6 (3.73)    |         |
| Unknown              | 10 (6.21)   | 11 (6.83)   |         |
| Comorbidities at admission |         |             |         |
| Solid tumor malignancy | 3 (1.86)  | 32 (19.88)  | <0.001\(^d\) |
| Hematologic malignancy | 3 (1.86)  | 46 (28.57)  | <0.001\(^d\) |
| Solid organ or bone marrow transplant | 22 (13.66) | 25 (15.53)  | 0.636   |
| Connective tissue disorder | 6 (3.73)  | 8 (4.97)    | 0.585   |
| AIDS\(^c\)           | 6 (3.75)    | 3 (1.86)    | 0.306   |
| Symptomatic liver failure | 6 (3.73)  | 4 (2.48)    | 0.521   |
| Chronic kidney disease | 66 (40.99) | 71 (44.10)  | 0.573   |
| Diabetes mellitus    | 62 (38.51)  | 67 (41.61)  | 0.570   |
| Hospitalization within 90 days of admission | 30 (18.63) | 72 (44.72)  | <0.001\(^d\) |
| Surgery 90 days before admission or CDI diagnosis | 4 (2.48)  | 6 (3.73)    | 0.521   |
| Home medications\(^b\) |         |             |         |
| PPI                  | 49 (30.43)  | 58 (38.93)  | 0.116   |
| H2RA                 | 12 (7.45)   | 17 (11.41)  | 0.232   |
| Probiotics           | 6 (3.73)    | 8 (5.37)    | 0.487   |
| Hemodialysis         | 26 (16.15)  | 25 (15.53)  | 0.879   |
| Medication during hospitalization |         |             |         |
| H2RA                 | 57 (35.40)  | 78 (48.45)  | 0.018\(^d\) |
| PPI                  | 72 (44.72)  | 101 (62.73) | 0.001\(^d\) |
| Probiotics           | 7 (4.35)    | 26 (16.15)  | <0.001\(^d\) |
| Classes of antibiotics during hospitalization |         |             |         |
| Aminoglycosides      | 5 (3.11)    | 7 (4.35)    | 0.556   |
| Penicillins          | 47 (29.19)  | 62 (38.51)  | 0.077   |
| Cephalosporins       | 22 (13.66)  | 116 (72.05) | <0.001\(^d\) |
| β-lactamase inhibitor| 1 (0.62)    | 0 (0)       | 0.317   |
| Macrolides           | 19 (11.80)  | 14 (8.70)   | 0.358   |
| Fluoroquinolones     | 37 (22.98)  | 38 (23.60)  | 0.895   |
| Carbapenems          | 11 (6.83)   | 42 (26.09)  | <0.001\(^d\) |
| Antibiotic Class            | Cases     | Controls   | p-value |
|-----------------------------|-----------|------------|---------|
| Tetracyclines               | 2 (1.24)  | 2 (1.24)   | 1.000   |
| Glycopeptides               | 77 (47.83)| 136 (84.47)| <0.001d|
| Monobactam                  | 8 (4.97)  | 11 (6.83)  | 0.478   |
| Lincosamide                 | 9 (5.59)  | 8 (4.97)   | 0.803   |
| Lipopeptide                 | 2 (1.24)  | 5 (3.11)   | 0.252   |
| Oxazolidinone               | 2 (1.24)  | 3 (1.86)   | 0.652   |

Combinations of antibiotics during hospitalization

| Combinations of Antibiotics            | Cases     | Controls   | p-value |
|----------------------------------------|-----------|------------|---------|
| Vancomycin/amikacin                    | 0 (0)     | 1 (0.62)   | 0.317   |
| Vancomycin/gentamicin                  | 0 (0)     | 2 (1.24)   | 0.156   |
| Vancomycin/tobramycin                  | 1 (0.62)  | 4 (2.48)   | 0.176   |
| Vancomycin/piperacillin-tazobactam     | 7 (4.35)  | 53 (32.92) | <0.001d|
| Vancomycin/ampicillin-sulbactam        | 0 (0)     | 3 (1.86)   | 0.082   |
| Vancomycin/ceftriaxone                 | 4 (2.48)  | 36 (22.36) | <0.001d|
| Vancomycin/avibactam-ceftazidime       | 1 (0.62)  | 0 (0)      | 0.317   |
| Vancomycin/cefepime                    | 7 (4.35)  | 42 (26.09) | <0.001d|
| Vancomycin/ceftazidim                  | 3 (1.86)  | 28 (17.39) | <0.001d|
| Vancomycin/ciprofloxacin               | 0 (0)     | 1 (0.62)   | 0.317   |
| Vancomycin/levofloxacin                | 3 (1.86)  | 33 (20.50) | <0.001d|
| Vancomycin/ertapenem                   | 0 (0)     | 1 (0.62)   | 0.317   |
| Vancomycin/meropenem                   | 1 (0.62)  | 41 (25.47) | <0.001d|
| Vancomycin/aztreonam                   | 3 (1.86)  | 12 (7.45)  | 0.017d  |
| Vancomycin monotherapy                 | 3 (1.86)  | 6 (3.73)   | 0.310   |

Outcomes

| Outcome                      | Cases     | Controls   | p-value |
|------------------------------|-----------|------------|---------|
| Admission to ICU             | 56 (34.78)| 56 (34.78) | 1.000   |
| Length of stay, days         | 9.19      | 21.27      | <0.001d|

Abbreviations: AIDS, acquired immunodeficiency disease; H2RA, histamine H2-receptor antagonist; ICU, intensive care unit; PPI, proton pump inhibitor.

aCases were patients who developed healthcare facility–onset *Clostridioides difficile* infection, while controls were patients who did not develop healthcare facility–onset *Clostridioides difficile* infection.

bData are reported as number of patients (%) unless indicated otherwise.

cVariable with missing data.

dStatistically significant difference between cases and controls.
Table 2. Model Performance With the Novant Health Model<sup>a</sup>

| Score | TP  | FP   | TN   | FN  | Sensitivity | Specificity | PPV  | NPV  | Accuracy |
|-------|-----|------|------|-----|-------------|-------------|------|------|----------|
| ≥2    | 56.82 | 43.18 | 57.69 | 42.31 | 60.24       | 54.22       | 56.82 | 57.69 | 57.23    |
| ≥4    | 70.75 | 29.25 | 59.73 | 40.27 | 45.18       | 81.33       | 70.75 | 59.73 | 63.25    |
| ≥6    | 76.92 | 23.08 | 53.58 | 46.42 | 18.07       | 94.58       | 76.92 | 53.58 | 56.33    |

Abbreviations: TP, true positive; FP, false positive; TN, true negative; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.

<sup>a</sup>The distribution is shown for patients who met risk factor score cutoffs of 2, 4, and 6 based on their age and whether they had a prior hospitalization within 90 days of admission, using the previously developed Novant Health model.<sup>12</sup>
Table 3. Local Risk Factors Predictive of HealthCare Facility–Onset *Clostridioides difficile* Infection Present on Admission

| Risk Factor                  | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | Adjusted P Value |
|------------------------------|------------------------|----------------------|------------------|
| Hematologic malignancy       | 21.06 (6.39-69.36)     | 12.87 (3.70-44.80)   | <0.0001          |
| Solid tumor malignancy       | 13.06 (3.91-43.64)     | 4.76 (1.27-17.80)    | 0.0206           |
| Prior hospitalization within 90 days | 3.53 (2.13-5.85) | 3.52 (2.06-6.04) | <0.0001 |

Abbreviations: CI, confidence interval; OR, odds ratio.

*Results are shown from univariable and multivariable analysis of risk factor association with development of *C. difficile* infection.*
Table 4. Point-Based System for the Local Model of Risk\textsuperscript{a}

| Attribute                                      | No. of Points |
|------------------------------------------------|---------------|
| Hematologic malignancy                        | 4             |
| Solid tumor malignancy                        | 1             |
| Hospitalization within 90 days of admission   | 1             |

\textsuperscript{a}A point-based tool with weighted scores was developed using risk factors identified by the multivariable logistic regression model (hematologic malignancy, solid tumor malignancy, and recent hospitalization). These scores were then used to create risk factor cutoffs (eg, ≥1 point, ≥2 points, ≥4 points, etc) as shown in Table 5.
**Table 5.** Model Performance for the Local Model$^a$

| Score | TP    | FP    | TN    | FN    | Sensitivity | Specificity | PPV   | NPV   | Accuracy |
|-------|-------|-------|-------|-------|-------------|-------------|-------|-------|----------|
| ≥1    | 74.26 | 25.73 | 67.74 | 32.26 | 62.73       | 78.26       | 74.26 | 67.74 | 70.50    |
| ≥2    | 94.64 | 5.36  | 59.40 | 40.60 | 32.92       | 98.14       | 94.64 | 59.40 | 65.53    |
| ≥4    | 93.88 | 6.12  | 57.88 | 42.12 | 28.57       | 98.14       | 93.88 | 57.88 | 63.35    |
| ≥5    | 97.30 | 2.70  | 56.14 | 43.86 | 22.36       | 99.38       | 97.30 | 56.14 | 60.87    |
| ≥6    | 100   | 0     | 50.95 | 49.05 | 3.73        | 100         | 100   | 50.95 | 51.86    |

Abbreviations: TP, true positive; FP, false positive; TN, true negative; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.

$^a$The distribution of risk scores is shown with diagnostic cutoff performance for the local model.
Figure 2

Area Under the Curve = 0.7361