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ORIGINAL RESEARCH & CONTRIBUTIONS

# Predicting the Risk of *Clostridium difficile* Infection upon Admission: A Score to Identify Patients for Antimicrobial Stewardship Efforts

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## ABSTRACT

**Introduction:** Increasing morbidity and health care costs related to *Clostridium difficile* infection (CDI) have heightened interest in methods to identify patients who would most benefit from interventions to mitigate the likelihood of CDI.

**Objective:** To develop a risk score that can be calculated upon hospital admission and used by antimicrobial stewards, including pharmacists and clinicians, to identify patients at risk for CDI who would benefit from enhanced antibiotic review and patient education.

**Methods:** We assembled a cohort of Kaiser Permanente Northwest patients with a hospital admission from July 1, 2005, through December 30, 2012, and identified CDI in the six months following hospital admission. Using Cox regression, we constructed a score to identify patients at high risk for CDI on the basis of preadmission characteristics. We calculated and plotted the observed six-month CDI risk for each decile of predicted risk.

**Results:** We identified 721 CDIs following 54,186 hospital admissions—a 6-month incidence of 13.3 CDIs/1000 patient admissions. Patients with the highest predicted risk of CDI had an observed incidence of 53 CDIs/1000 patient admissions. The score differentiated between patients who do and do not develop CDI, with values for the extended C-statistic of 0.75. Predicted risk for CDI agreed closely with observed risk.

**Conclusion:** Our risk score accurately predicted six-month risk for CDI using preadmission characteristics. Accurate predictions among the highest-risk patient subgroups allow for the identification of patients who could be targeted for and who would likely benefit from review of inpatient antibiotic use or enhanced educational efforts at the time of discharge planning.

## INTRODUCTION

*Clostridium difficile* infection (CDI) is a leading cause of health care-associated gastrointestinal illness and places a high burden on the US health care system, resulting in more than 14,000 deaths and costing more than $2.1 billion annually.[1] Common risk factors for CDI include advanced age, severe underlying comorbidity, and prolonged hospitalization; however, antibiotic use remains the primary risk factor for CDI.[2-7] Numerous studies have shown that monitoring and restriction of offending antimicrobials are effective in CDI prevention.[8] Thus, antimicrobial stewardship in the prevention and management of CDI during and after hospitalization is essential.

Stratification of patients based on CDI risk would enable pharmacists and other clinicians to identify and focus on patients for whom enhanced stewardship efforts, such as antimicrobial review and education, may be beneficial. These efforts have the potential to reduce morbidity and health care costs associated with CDI. However, a tool is needed to easily calculate an individual patient's risk on the basis of patient characteristics and medical history, including drug therapies and comorbid conditions, and to identify high-risk patients most likely to benefit from antimicrobial stewardship intervention and education. The primary objective of this study was to develop a prognostic risk score to identify patients at risk for CDI upon hospital admission and in the six months following admission, using patient characteristics documented during routine practice and collected before hospitalization.

## METHODS

We developed a risk score using a retrospective cohort of Kaiser Permanente Northwest (KPNW) members who had one or more hospital admissions for any reason from July 1, 2005, through December 31, 2012. We restricted the study cohort to patients with an admission to one hospital owned by KPNW. For patients with more than one hospital admission during the study period, to help ensure a uniform distribution of visits over time, we randomly selected 1 admission to serve as the index encounter. We included patients if they were at least 20 years old, had at least one year of continuous Health Plan enrollment and prescription drug coverage before the index hospital admission, and had no history of a CDI (eg, CDI diagnosis code, positive *C difficile* toxin test result, outpatient dispensing for oral vancomycin) in the 180 days up to and including the date of the index hospital admission. Patients were allowed to have up to a 90-day gap in their

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enrollment and still be considered "continuously" enrolled. The study was reviewed and approved by KPNW's Human Subjects Committee.

We identified the first occurrence of CDI in the 6 months (180 days) following index admission date through 1) an International Classification of Diseases, Ninth Revision, diagnosis code 008.45 for "Intestinal infection due to *C difficile*" from an outpatient encounter or hospitalization or 2) a positive *C difficile* toxin test in the outpatient setting. We also required that positive toxin tests be associated with outpatient dispensing for oral metronidazole or vancomycin in the 7 days before or after the positive toxin test result. We followed up patients only until their first observed CDI or the end of the 6-month follow-up period. Patients were censored upon death or discontinuation of enrollment in the Health Plan.

We examined patient characteristics available in the electronic medical record (EMR) during the 1-year baseline period before the admission date of the index hospitalization for comorbid conditions and from 1 to 60 days before admission for medication use. The International Classification of Diseases, Ninth Revision, procedure and diagnosis codes and specific medications used to identify risk score characteristics are available upon request. We classified antibiotic use in the 60 days before admission into 4 mutually exclusive groups: 1) use of high-risk antibiotics, including second- and third-generation cephalosporins, fluoroquinolones, and clindamycin; 2) medium-risk antibiotic use, including amoxicillin/clavulanic acid and macrolides; 3) low-risk antibiotic use, including all antibiotics not considered to be high-risk or medium-risk; and 4) no antibiotic use. Antibiotic exposure was categorized in a hierarchical order, from high to low. For example, if a patient received a dispensing of a low-risk antibiotic in the 60 days prior and no dispensing of a medium- or high-risk antibiotic, then antibiotic use was classified as "low-risk." Accordingly, if a patient received a dispensing of a medium-risk antibiotic in the previous 60 days without a dispensing of a high-risk antibiotic, then antibiotic use was classified as "medium-risk." Finally, any dispensing of a high-risk antibiotic in the previous 60 days led to a "high-risk" antibiotic use classification.

We used Cox regression to evaluate baseline patient characteristics that might predict CDI during the six months after the date of the index hospital admission. We selected patient characteristics to include in the risk score on the basis of evidence in the scientific literature, how easily and reliably we could measure the characteristics in retrospective EMR databases, and the prevalence of the characteristics in our population. We modeled categorical variables, such as the presence or absence of comorbid conditions or medication exposure, using indicator variables. To account for nonlinear relationships between a predictor and outcome, we modeled continuous variables, such as age, using a restricted cubic spline. To avoid overfitting, we limited the number of candidate characteristics and their degrees of freedom; specifically, we required at least ten CDIs per degree of freedom.[9] We translated the coefficients from the Cox regression into a points-based risk score in which a higher number of points indicates a higher risk of CDI.[10] To accomplish this, the linear predictor in the Cox model was mapped to the corresponding six-month CDI risk. The components of the linear predictor were then rescaled to an arbitrary axis in which a score of

**Table 1. Baseline characteristics for patients who did and did not experience *Clostridium difficile* infection during the six months following hospital admission**

| Characteristic | Patients, no. (%) | |
|---|---|---|
| | Without CDI n = 53,465 | With CDI n = 721 |
| Age in years | | |
| 20 to 29 | 4709 (8.8) | 16 (2.2) |
| 30 to 39 | 6890 (12.9) | 27 (3.7) |
| 40 to 49 | 6796 (12.7) | 57 (7.9) |
| 50 to 59 | 9990 (18.7) | 103 (14.3) |
| 60 to 69 | 10,911 (20.4) | 162 (22.5) |
| 70 to 79 | 7713 (14.4) | 148 (20.5) |
| 80 to 89 | 5090 (9.5) | 163 (22.6) |
| ≥ 90 | 1366 (2.6) | 45 (6.2) |
| Female sex | 33,788 (63.2) | 410 (56.9) |
| Days of hospitalization in the previous 60 days | | |
| 0 | 47,101 (88.1) | 526 (73.0) |
| 1-6 | 5149 (9.6) | 110 (15.3) |
| ≥ 7 | 1215 (2.3) | 85 (11.8) |
| Stay in a communal-living health care facility in previous 60 days | 248 (0.5) | 24 (3.3) |
| Chronic kidney disease | | |
| No diagnosis of CKD and no history of dialysis | 50,263 (94.0) | 581 (80.6) |
| CKD diagnosis *and* no history of dialysis | 2432 (4.5) | 88 (12.2) |
| History of dialysis | 770 (1.4) | 52 (7.2) |
| Inflammatory bowel disease | 583 (1.1) | 19 (2.6) |
| Immunosuppression in previous 60 days | 5471 (10.2) | 186 (25.8) |
| Chronic pulmonary disease | 10,357 (19.4) | 187 (25.9) |
| Rheumatologic disease | 1274 (2.4) | 33 (4.6) |
| Diabetes mellitus | 9703 (18.1) | 197 (27.3) |
| Cardiovascular disease | 9784 (18.3) | 257 (35.6) |
| Liver disease | 512 (1.0) | 24 (3.3) |
| Malignancy and metastatic solid tumor | 6230 (11.7) | 154 (21.4) |
| Chemotherapeutic procedures or therapies in previous 60 days | 4266 (8.0) | 112 (15.5) |
| Antibiotic use[a] | | |
| No antibiotic use | 42,661 (79.8) | 450 (62.4) |
| Low-risk antibiotic use | 2690 (5.0) | 30 (4.2) |
| Medium-risk antibiotic use | 3010 (5.6) | 39 (5.4) |
| High-risk antibiotic use | 5104 (9.5) | 202 (28.0) |
| Use of gastric acid suppressants in previous 60 days | 9237 (17.3) | 218 (30.2) |

[a] We classified antibiotic use in the 60 days before admission into four mutually exclusive groups: 1) use of high-risk antibiotics, including second- and third-generation cephalosporins, fluoroquinolones, and clindamycin; 2) medium-risk antibiotic use, including amoxicillin/clavulanic acid and macrolides; 3) low-risk antibiotic use, including all antibiotics not considered to be high-risk or medium-risk; and 4) no antibiotic use.

CDI = *Clostridium difficile* infection; CKD = chronic kidney disease.

zero points was assigned to the lowest-risk category for each variable, with increasing points representing proportionate increases in the linear predictor. The relative distance between risk score points approximates the hazard ratio for CDI.

## RESULTS

We identified 721 CDIs following 54,186 randomly selected hospital admissions during the study period—an overall 6-month incidence of 13.3 CDIs per 1000 patient admissions. Compared with the patients who did not develop CDI following hospital admission, patients who developed CDI were older and were more likely to have a recent stay in a hospital or communal-living health care facility before the index admission (Table 1). All comorbid conditions occurred more frequently among patients who developed CDI than among patients who did not develop CDI. Patients who developed CDI were also more likely to have a history of immunosuppression (25.8% vs 10.2% among patients without CDI), chemotherapy (15.5% vs 8.0%) or gastric acid suppression (30.2% vs 17.3%). Finally, patients with CDI were also much more likely to have recently received a high-risk antibiotic (28% vs 9.6%), although low- or medium-risk antibiotics were used slightly less often among patients who developed CDI than among those who did not (Table 1).

Table 2 shows the risk score points; each 25 points indicates an approximate doubling of CDI risk. The patient characteristics that contributed more than 25 points to the risk score were age 40 years or older (31-100 points, depending on age category), recent use of high-risk antibiotics (32 points), chronic kidney disease requiring dialysis (28 points),

**Table 2. Points assigned to patient characteristics by the Cox regression model to predict *Clostridium difficile* infection in the six months following hospital admission**

| Characteristic | Risk score points |
|---|---|
| Age in years | |
| 20 to 29 | 0 |
| 30 to 39 | 16 |
| 40 to 49 | 31 |
| 50 to 59 | 39 |
| 60 to 69 | 46 |
| 70 to 79 | 57 |
| 80 to 89 | 71 |
| 90 to 99 | 85 |
| ≥ 100 | 100 |
| Sex | |
| Men | 0 |
| Women | 0 |
| History of a stay in a communal-living health care facility in the previous 60 days | |
| No stay | 0 |
| History of stay | 12 |
| Days of hospitalization in the previous 60 days | |
| 0 | 0 |
| 1-6 | 7 |
| ≥ 7 | 26 |
| Inflammatory bowel disease | |
| No IBD | 0 |
| History of IBD | 26 |
| Cardiovascular disease | |
| No CVD | 0 |
| History of CVD | 3 |
| Chronic pulmonary disease | |
| No CPD | 0 |
| History of CPD | 0 |

| Characteristic | Risk score points |
|---|---|
| Rheumatologic disease | |
| No rheumatologic disease | 3 |
| History of rheumatologic disease | 0 |
| Diabetes | |
| No diabetes | 0 |
| History of diabetes | 1 |
| Liver disease | |
| No liver disease | 0 |
| History of liver disease | 31 |
| Malignancy or metastatic tumor | |
| No malignancy | 0 |
| History of malignancy | 7 |
| Chronic kidney disease[a] | |
| No CKD | 0 |
| CKD diagnosis and no history of dialysis | 14 |
| CKD diagnosis history of dialysis | 28 |
| Antibiotic use[b] | |
| No use | 6 |
| Low-risk antibiotic use | 0 |
| Medium-risk antibiotic use | 3 |
| High-risk antibiotic use | 32 |
| Gastric acid suppressant use | |
| No use | 0 |
| History of use | 7 |
| Immunosuppression | |
| No immunosuppression | 0 |
| History of immunosuppression | 21 |
| Chemotherapy | |
| No use | 0 |
| History of chemotherapy | 6 |

[a] Defined as CKD diagnosis or history of dialysis.

[b] We classified antibiotic use in the 60 days before admission into 4 mutually exclusive groups: 1) use of high-risk antibiotics, including second- and third-generation cephalosporins, fluoroquinolones, and clindamycin; 2) medium-risk antibiotic use, including amoxicillin/clavulanic acid and macrolides; 3) low-risk antibiotic use, including all antibiotics not considered to be high-risk or medium-risk; and 4) no antibiotic use.

IBD = Inflammatory bowel disease; CVD = Cardiovascular disease; CPD = Chronic pulmonary disease; CKD = Chronic kidney disease.

liver disease (31 points), and 7 or more days of hospitalization within the previous 60 days (26 points) (Table 2). The 16 characteristics in the score accounted for 23 degrees of freedom. The slope-shrinkage statistic was 0.97 (on a scale from 0 to 1 where 1 indicates no overfitting).

Risk score points, observed risk during the 6-month follow-up period, and sensitivity and specificity based upon patient deciles of predicted risk are shown in Table 3. Patient scores ranged from 0 to 244. Observed infection rates ranged from 2 cases per 1000 patient admissions in the low-risk group to 53 cases per 1000 patient admissions in the very high-risk group (Table 3). The score differentiated between patients who do and do not develop CDI, with values for the extended C-statistic of 0.75. Predicted risk for CDI agreed closely with observed risk in the highest decile; calibration was less optimal in lower deciles (Figure 1).

When applying this model to patient care, a pharmacist or clinician might choose a threshold of predicted risk that, in his/her judgment, indicates a patient's need for antibiotic review or enhanced education. For example, if the 90th percentile of the risk score (ie, the top decile, or the 10% of patients at highest risk) was chosen as a threshold, s/he would focus attention on those patients who account for 36% of the CDIs. The specificity for that threshold is 90.2% (95% confidence interval [CI], 90.0%-90.5%). Nearly 5% of patients in the top decile developed CDI (positive predictive value, 4.84%; 95% CI, 4.28%-5.54%). The negative predictive value was 99.1% (95% CI, 99.0%-99.1%).

To have a score in the top decile of predicted risk, a patient would require at least 103 risk points (Table 3). For example, a patient aged 75 years with inflammatory bowel disease and recent fluoroquinolone use would score 115 points (age 75 [57 points] + history of inflammatory bowel disease [26 points] + high-risk antibiotic use [32 points] = 115 points).

## DISCUSSION

Our risk score accurately predicts the risk for CDI during and following hospitalization and identifies patients who are at the highest risk for CDI and who could be targeted for intervention, such as pharmacist review of inpatient antibiotic use or enhanced educational efforts at the time of discharge planning. In fact, using our risk score could better direct antimicrobial stewardship to the 10% of patients who will experience 36% of the CDIs; therefore, we suggest that using predicted risk of CDI generated from our score could represent an improvement over current strategies to identify patients at risk for CDI and stratify patients by that risk.

Prognostic risk scores have most commonly been developed for the identification of populations at high risk for the development of chronic disease or its complications.[11-13] Prognostic risk modeling has been used less frequently for infectious diseases; however, a number of risk prediction scores have been created to identify risk for incident and recurrent CDI among hospitalized patients.[14-19] In contrast to previous efforts, our risk score was developed to predict risk upon admission specifically to aid in decision making and targeting of antimicrobial stewardship efforts. This simple, reliable, and accurate tool will enable antimicrobial stewardship programs to use combinations of predictors to estimate the probability that CDI will occur in the next six months, and to identify patients for whom intensive antimicrobial review and stewardship efforts may be beneficial.

**In contrast to previous efforts, our risk score was developed to predict risk upon admission specifically to aid in decision making and targeting of antimicrobial stewardship efforts.**

Antibiotics are the most recognized, and likely the most modifiable, risk factor for CDI, as well as for antibiotic resistance.[20] Recognizing this, antimicrobial stewards may conduct antibiotic review for all hospitalized patients using antibiotics. However, because more than 50% of patients receive an antibiotic during hospitalization,[21-24] choosing "any antibiotic use" as the sole indicator for antibiotic review is impractical and resource intensive and does not capture the patient's underlying risk for CDI or rank patients by that risk.

Our risk stratification approach can be implemented at the time of hospital admission to rank patients by their pre-admission risk for CDI. The score was developed as a tool that could be used by pharmacists to 1) identify patients who will most benefit from review of inpatient antibiotic use, 2) communicate patient risk and inform prescribers of

**Table 3. Range of risk score points, corresponding observed risk of *Clostridium difficile* infection in the six months following hospital admission, and sensitivity and specificity by decile of predicted *Clostridium difficile* infection risk**

| Decile of predicted risk (from lowest to highest risk) | Risk score point cut-off | Observed CDI risk (CDI cases per 1000 patient admissions) | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|---|---|---|---|---|
| 10th percentile | 30 | 3 | 98.6 (97.5-99.3) | 10.2 (9.9-10.4) |
| 20th percentile | 44 | 6 | 96.4 (94.8-97.6) | 21.5 (21.1-21.8) |
| 30th percentile | 51 | 7 | 91.3 (89.0-93.2) | 32.0 (31.6-32.4) |
| 40th percentile | 56 | 6 | 87.1 (84.4-89.5) | 40.9 (40.4-41.3) |
| 50th percentile | 62 | 8 | 83.4 (80.4-86.0) | 49.9 (49.5-50.4) |
| 60th percentile | 69 | 13 | 77.5 (74.3-80.5) | 59.7 (59.3-60.1) |
| 70th percentile | 78 | 17 | 68.7 (65.1-72.0) | 69.8 (69.4-70.2) |
| 80th percentile | 88 | 27 | 55.5 (51.8-59.1) | 80.2 (79.9-80.5) |
| 90th percentile (top decile) | 103 | 53 | 36.3 (32.8-40.0) | 90.2 (90.0-90.5) |

CDI = *Clostridium difficile* infection; CI = confidence interval.

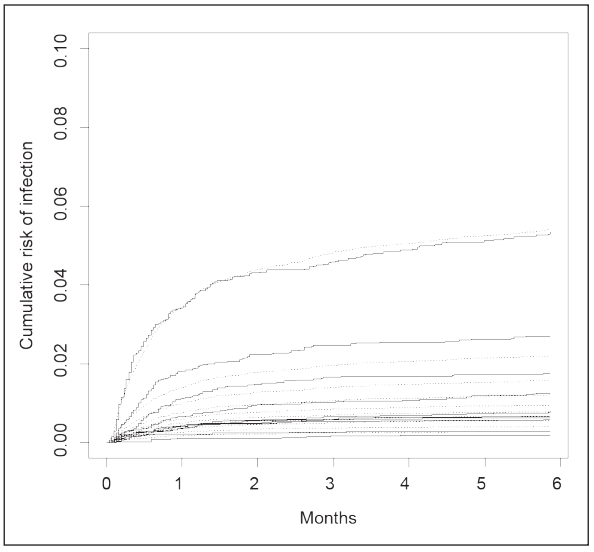


Figure 1. Failure curves showing the observed risk (solid lines) and the predicted risk (dotted lines) of *Clostridium difficile* infection in the six months following hospital admission according to deciles of predicted risk, as determined by the risk score.

the rationale for pharmacist intervention on antibiotic use, and/or 3) identify patients who may benefit from enhanced educational efforts at the time of discharge planning. In the first scenario, on the basis of patient risk for CDI upon admission, the antimicrobial steward would review the patient's medication use and other variables and decide whether to intervene by, for example, stopping or preventing the use of a potentially inciting antibiotic before CDI develops. If an intervention is necessary and performed, the steward may then use the risk score information as a resource when discussing antibiotic treatment changes with prescribing physicians. Finally, high-risk patients who have either received an antibiotic during their hospitalization or are being discharged with an antibiotic prescription would be given additional information about postdischarge CDI risk and symptoms, which may lead to earlier recognition of disease by patients and potential reductions in severe and prolonged disease and rehospitalization.

To discern the potential for additional applications of the tool, we applied our risk score to patients hospitalized at KPNW from January 1 to January 31, 2013, and categorized patients by their predicted CDI risk. Infectious disease pharmacists then reviewed medical records for a subset of patients who developed CDI in the six months following their hospital admission. Although the pilot chart review was not intended to be definitive, pharmacists who conducted the review were able to note opportunities for improved care including, but not limited to, antibiotic prescribing intervention and clinician and patient education (the original intended applications of this score). Additional opportunities include using the predicted CDI risk: 1) to reduce antibiotic use that may increase CDI risk during care transitions (eg, closer follow-up to discontinue ciprofloxacin prophylaxis after absolute neutrophil count targets are met for a neutropenic cancer patient) or 2) as a catalyst for communication and education of clinicians about antibiotic prescribing issues (eg, use of broad- versus narrow-spectrum agents). Notably, these points suggest that knowledge about predicted CDI risk not only would be valuable to pharmacists but also would serve as a tool to raise awareness and alter decision making among other health care workers, such as nurses and physicians.

We developed our risk score to be pragmatic, meaning that this score identified patients at risk for CDI on the basis of the available clinical and nonclinical information present in the patient medical record at the time of admission. Although the inclusion of numerous other risk factors for CDI, such as genetic and immune response markers,[25-28] may improve the stratification of patients into risk groups, this information is not widely available and its inclusion would greatly increase the complexity of the score and its calculation. In addition, pharmacist review is typically focused on the absolute presence or absence of antibiotic use, whereas our risk score offers a tool that can accurately assess risk by taking multiple risk factors and patient characteristics into account. Finally, our risk score does not require laboratory data or other EMR data. Although we designed our score to be calculated automatically using our EMR, any health care system could categorize its patients by CDI risk on the basis of administrative claims data alone.

Our study has a number of limitations. First, we did not include patients with a history of CDI in the 180 days before an index encounter, thus the risk score is not tailored to estimate risk of CDI recurrence. However, patients with a history of CDI would likely be flagged for antibiotic review and close monitoring in the inpatient setting and after discharge on the basis of their history of infection alone. Second, we did not measure antimicrobial or other medication use that occurred during hospitalizations before the index admission. In addition, we acknowledge that alternative methods to measure antibiotic use (eg, number or cumulative exposure to antibiotics rather than categorization of antibiotics by CDI risk) may refine the predictive value of the score. Different methods could be examined in future applications. Finally, on the basis of the accuracy of the risk score's predictions and the low incidence of CDI, the positive predictive value is low—that is, most patients designated as "high-risk" will not go on to develop CDI in the 6 months following a hospital admission.

## CONCLUSION

Our risk score successfully discriminated between patients at the highest and lowest risk for CDI following a hospital admission. Thus, our risk score can help pharmacists and other clinicians identify high-risk patients who would benefit from additional medication management during and after their hospital admission or from education at the time of discharge. Pharmacists who wish to use this risk score may want to validate its predictive ability in their populations

and health care setting. Future efforts may also want to focus on determining the impact of the risk score on inpatient pharmacy and infection control management and outcomes, compared with usual care.[29] ❖

**Disclosure Statement**

*The author(s) have no conflicts of interest to disclose.*

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## Heaven

Bacteria keep us from heaven and put us there.

— Martin H Fischer, 1879-1962, German-American physiologist