MAJOR ARTICLE

Risk Estimation for Recurrent *Clostridium difficile* Infection Based on Clinical Factors

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Background. The incidence of *Clostridium difficile* infection (CDI) has risen dramatically during the last decade. Although patients respond well to medical therapy such as vancomycin, 20%–30% of patients treated suffer a recurrence of CDI.

Methods. We developed a simple/practical scoring rule (logistic regression model) for recurrent CDI using data from 2 large phase 3 clinical trials. Seventy-seven baseline CDI factors were classified: demographics, comorbidity, medications, vital signs, laboratory tests, severity, and symptoms. Predictors with the highest discrimination in each class (using receiver operating characteristics curve) were selected. For the final model, stepwise selection was performed. Discrimination, calibration, and internal validation were used to assess the model.

Results. The final model with a simple scoring rule was developed. It includes 4 independent risk factors that are readily available when the patient makes initial contact: age (<75 vs ≥75 years), number of unformed bowel movements during previous 24 hours (<10 vs ≥10), serum creatinine leves (<1.2 mg/dL vs ≥1.2 mg/dL) and prior episode of CDI (yes vs no). In addition, the model includes choice of treatment (vancomycin or fidaxomicin).

Conclusions. The prediction model for recurrence may be useful for treatment decision.

Clinical Trials Registration. NCT00314951 and NCT00468728.

Keywords. *Clostridium difficile* infection; CDI; fidaxomicin; vancomycin.

The incidence of *Clostridium difficile* infection (CDI) has risen dramatically during the last decade [1, 2]. Although most patients respond well to medical therapy such as vancomycin and metronidazole, 20%–30% of patients treated with these agents suffer a recurrence of CDI [3]. Recurrent CDI remains a substantial therapeutic challenge as an initial recurrence is often followed by a succession of recurrences. Research on the prediction of incidence and recurrence of CDI is sparse. A systematic review article identified 13 studies on the derivation of clinical prediction rules on unfavorable outcomes in CDI. These prediction rules have had limited use in clinical practice due to several methodological limitations in deriving the rules including large heterogeneity in the variables analyzed as well as small sample sizes [4].

Fidaxomicin, a newly licensed macrocyclic antibiotic, is approved to treat intestinal infections caused by *Clostridium difficile.* Approval was based on 2 large clinical trials [5, 6]. In the aforementioned clinical trials, fidaxomicin was compared to treatment with oral vancomycin in 1105 patients with recently diagnosed *C. difficile*–associated diarrhea (CDI). It proved to have similar efficacy for cure: 88% for fidaxomicin and 86% for vancomycin. However, fidaxomicin reduced the recurrence rate to 14% compared to 26% with vancomycin treatment [5, 6].

A simple scoring rule would be useful to predict the risk of developing recurrence based on clinical features apparent on presentation of the patient to the healthcare worker. This rule could be used to predict the risk of recurrence when choosing either vancomycin or fidaxomicin as treatment of this episode.

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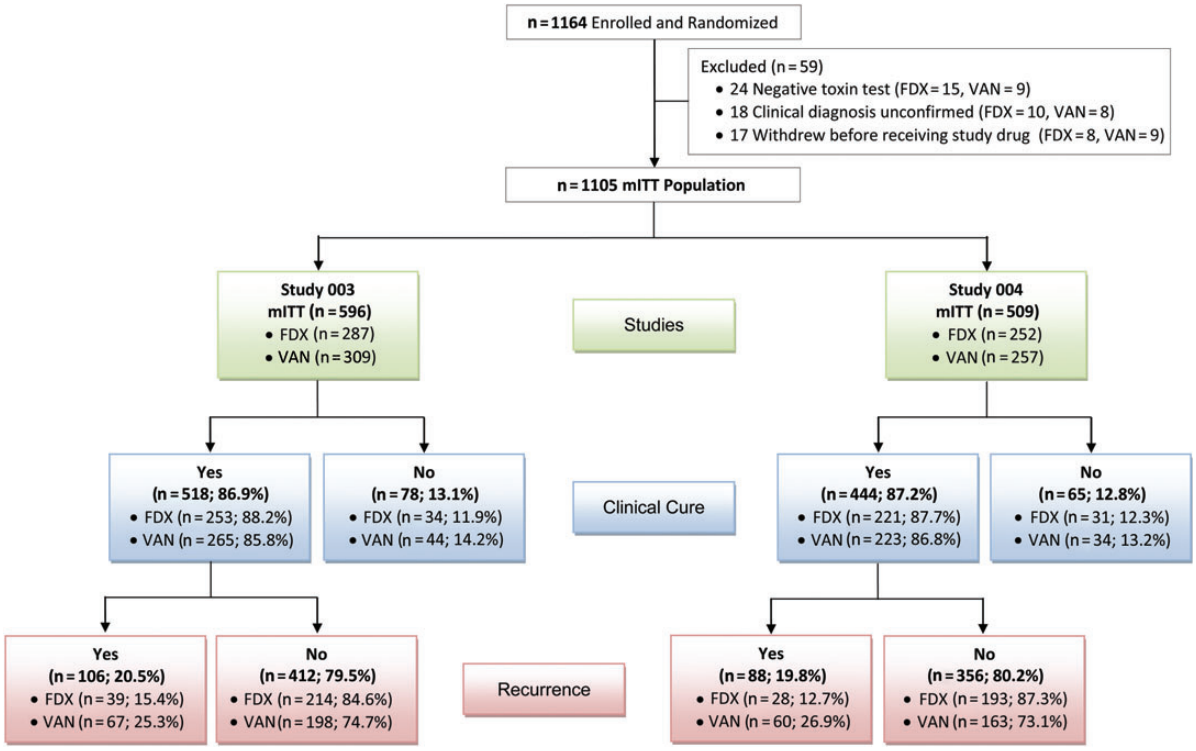

Figure 1. Patient disposition. Abbreviations: FDX, fidaxomicin; mITT, modified intent to treat; VAN, vancomycin.

METHODS

Data Sources and Study Population

We derived and validated the clinical prediction rule from data collected in 2 large double-blind, randomized clinical trials comparing the efficacy and safety of 400 mg/day fidaxomicin with 500 mg/day vancomycin in adult patients with CDI. The majority of the patients enrolled in the 2 trials had no prior episode of CDI, and a subset of patients (16%) had a single episode of CDI during the 3 months prior to enrollment. The first study was conducted in the United States and Canada (study 003, April 2006–July 2008), and the second study was conducted in the United States, Canada, and Europe (study 004, April 2007–November 2009).

Patients were evaluated for clinical cure or failure at the end of 10-day drug therapy. Patients who were cured were subsequently followed up for 28 days for an assessment of recurrence. The modified intent-to-treat (mITT) patient population (n = 1105) consisted of patients who took at least 1 dose of the study treatment. Patients who were cured and eligible for the assessment of recurrence in the mITT population (n = 962) were used in the derivation of the prediction rule in this paper (Figure 1). The studies are reported in full else where [5, 6].

Statistical Analysis

Derivation of the Multivariable Model

The risk prediction function for recurrence of CDI was developed using the multivariable logistic regression model [7]. All analyses were conducted separately for study 003, study 004, and both studies combined among patients who were cured with fidaxomicin or vancomycin. Only variables with <5% missing records in at least 1 of the 2 studies were included in this analysis.

The selection of risk factors started with dividing 77 baseline predictors into 7 clinically meaningful classes to avoid potential overfitting: demographic, comorbidity, medications, vital signs, laboratory tests at baseline, severity of CDI, and symptoms of CDI. Table 1 summarizes the variables that were considered in building the model.

Univariate logistic regressions were performed on all variables within each class, separately for each study (003, 004, and combined) and treatment combination (fidaxomicin or vancomycin). Predictors with the highest discriminatory potential in each class, as determined by the area under the curve of the receiver operating characteristic (AUC of ROC, also known as C-statistic) [8], were selected as candidates for the final model [9, 10]. When 2 or more variables had similar magnitude of

Table 1. Variables Included in the Univariate Analysis

Demographic	Laboratory Tests at Baseline
Age (continuous)	Absolute neutrophil count $<500 \times 10^9$/L
Age (<60, ≥60 y)	Alkaline phosphatase (U/L)
Age (<65, ≥65 y)	Albumin (continuous)
Age (<75, ≥75 y)	Albumin <2.5 g/dL
Age (<55, 55–74, ≥75 y)	Albumin <2.7 g/dL
Age (in decades)	Albumin <3.2 g/dL
Age (<65, 65–74, ≥75 y)	Blood urea nitrogen (mg/dL)
Country	Blood urea nitrogen-to-creatinine ratio
Ethnicity	Calcium (mg/dL)
Patient status (inpatient/outpatient)	Cholesterol (mg/dL)
Race	Chloride (mmol/L)
Sex	Creatinine clearance (continuous)
Stratum (single prior episode/no)	Creatinine clearance <50 mL/min/1.73 m^2
Comorbidity	Creatinine clearance <60 mL/min/1.73 m^2
Cancer (solid tumor or hematologic)	Creatinine clearance <75 mL/min/1.73 m^2
Cancer (solid tumor and hematologic)	Creatinine (mg/dL; continuous)
Cancer (hematologic only)	Creatinine (<1.2 mg/dL, ≥1.2 mg/dL)
Cancer (solid tumor only)	Potassium (mmol/L)
Cancer (had chemotherapy)	Globulin (g/dL)
Colitis	Glucose (mg/dL)
Hemodialysis-dependent chronic kidney disease (creatinine >2 mg/dL)	Phosphate (mg/dL)
HIV/AIDS	Protein (g/dL)
Inflammatory bowel disease	Sodium (mmol/L)
Immunosuppression (broad definition)	Triglycerides (mg/dL)
Immunosuppression (corticosteroids/HIV/AIDS/ chemotherapy)	Urate (mg/dL)
Renal disease (defined by creatinine clearance)	Severity of CDI
Toxic megacolon, ileus, hypotension, shock	ESCMID severity[a] (severe, not severe)
Transplant (SOT/HSCT)	Severity[b] (mild/moderate vs severe)
Medications	Severity[b] (mild, moderate, severe)
Con Abx at enrollment	Symptoms of CDI
High-risk Con Abx at enrollment	No. of unformed bowel movements (continuous)
Con Abx among patients with prior episode of CDI	No. of unformed bowel movements (<10, ≥10)
CDI antibiotic within 24 h of randomization	No. of unformed bowel movements (0–5, 6–9, ≥10)
Immunomodulating agent use	Severe abdominal pain/tenderness/distention
Metronidazole failure	Vital signs
PPI/H2 inhibitor or H2 blocker use at any time	Body mass index (kg/m^2)
PPI/H2 during treatment or follow-up period	Diastolic blood pressure (mm Hg)
P-glycoprotein inhibitor use	Height (cm)
Vancomycin use prior to study treatment	Pulse rate (beats/min)
	Systolic blood pressure (mm Hg)
	Temperature (°C)
	Temperature ≥38.5°C (fever)
	Weight (kg)

Abbreviations: CDI, *Clostridium difficile* infection; Con Abx, concomitant antibiotics; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; PPI, proton pump inhibitor; SOT, solid organ transplant.

[a] Severe = creatinine ≥1.5 mg/dL or leukocytes >15 cells/μL or temperature >38.5°C.

[b] Mild CDI = 4-5 unformed bowel movements (UBMs)/day or white blood cells (WBCs) ≤12 000 cells/μL; moderate CDI = 6–9 UBMs/day or WBCs 12 001–15 000 cells/μL; severe CDI, ≥10 UBMs/day or WBCs ≥15 001 cells/μL.

AUC, within a given class, the most clinically important variable was chosen. On these variables, stepwise selection was performed with entry and stay criteria of $P = .2$. This process led to 6 multivariable models (Supplementary Table 1), 1 for

Table 2. Demographics and Baseline Characteristics, Modified Intent-to-Treat and Clinical Cure (N = 962)

Characteristic	Study 003 (n = 518)	Study 004 (n = 444)	Total (N = 962)
Age, y			
<75	386 (74.5%)	298 (67.1%)	684 (71.1%)
≥75	132 (25.5%)	146 (32.9%)	278 (28.9%)
Sex			
Female	292 (56.4%)	272 (61.3%)	564 (58.6%)
Male	226 (43.6%)	172 (38.7%)	398 (41.4%)
Country/Region			
Canada	225 (43.4%)	145 (32.7%)	370 (38.5%)
Europe	0	171 (38.5%)	171 (17.8%)
US	293 (56.6%)	128 (28.8%)	421 (43.8%)
Patient status			
Inpatient	282 (54.4%)	293 (66.0%)	575 (59.8%)
Outpatient	236 (45.6%)	151 (34.0%)	387 (40.2%)
Stratum			
No prior episode	428 (82.6%)	375 (84.5%)	803 (83.5%)
Single prior episode	90 (17.4%)	69 (15.5%)	159 (16.5%)
Concomitant antibiotics at enrollment			
No	457 (88.2%)	384 (86.5%)	841 (87.4%)
Yes	61 (11.8%)	60 (13.5%)	121 (12.6%)
Baseline CDI severity[a]			
Mild	127 (24.5%)	167 (37.6%)	294 (30.6%)
Moderate	190 (36.7%)	130 (29.3%)	320 (33.3%)
Severe	201 (38.8%)	147 (33.1%)	348 (36.2%)
Unformed bowel movement			
<10	360 (69.5%)	336 (75.9%)	696 (72.4%)
≥10	158 (30.5%)	107 (24.2%)	265 (27.6%)
Creatinine clearance			
<75 mL/min/ 1.73 m^2	196 (39.0%)	181 (43.1%)	377 (40.9%)
≥75 mL/min/ 1.73 m^2	306 (61.0%)	239 (56.9%)	545 (59.1%)
Creatinine			
<1.2 mg/dL	388 (77.3%)	335 (79.6%)	723 (78.3%)
≥1.2 mg/dL	114 (22.7%)	86 (20.4%)	200 (21.7%)

Abbreviations: CDI, *Clostridium difficile* infection.

[a] Mild CDI = 4-5 unformed bowel movements (UBMs)/day or white blood cells (WBCs) ≤12 000 cells/μL; moderate CDI = 6–9 UBMs/day or WBCs 12 001–15 000 cells/μL; Severe CDI ≥10 UBMs/day or WBCs ≥15 001 cells/μL.

each study (003, 004, and combined) and treatment combination (fidaxomicin or vancomycin). In addition to the risk factors contained by these 6 models, "prior episode" was considered a highly important clinical variable related to the outcome. All these variables were chosen for selection of the final model if they were statistically significant after stepwise procedure at the .05 level.

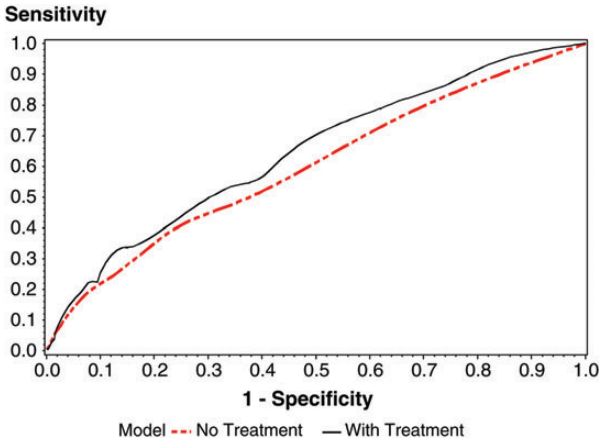

Figure 2. Comparison of receiver operating characteristic for model with treatment (C-statistic = 0.64) and without treatment (C-statistic = 0.60).

Assessment of the Model Performance

The ability of the model to discriminate between patients with and without recurrence of CDI was assessed by using the C-statistic. The influence of treatment (fidaxomicin vs vancomycin) on the prediction of CDI recurrence was evaluated by the C-statistic for the prediction models with and without treatment. The relative integrated discrimination improvement (rIDI) measure was used [11] to assess the relative difference between the discrimination slopes of these 2 models. Discrimination slope was calculated as the difference in means of model-based predicted risk for those with and without recurrence of CDI. Change in discrimination slope divided by the slope of the baseline model defines the rIDI.

The calibration of multivariable model was quantified by the Hosmer-Lemeshow goodness-of-fit test [7]. Calibration plots were constructed to compare the actual and observed risks of CDI recurrence.

Validation and consistency of the results were assessed by comparing the performance of the final model (C-statistics, *P* values, and β coefficients) on the 2 independent samples from study 003 and study 004 as well as on the combined sample. The results were also cross-validated to correct for overfitting: the final model applied on study 003 was validated on study 004, and the final model applied on study 004 was validated on study 003. The cross-validated C-statistic was computed as the average of the C-statistics from those 2 models. The purpose of this validation was not to validate variable selection but to quantify degree of overoptimism when using factors from the final model.

Recurrence Prediction Score Sheet

Two simple scoring sheets were derived from the predictive probability of the model to calculate the estimated risk of CDI

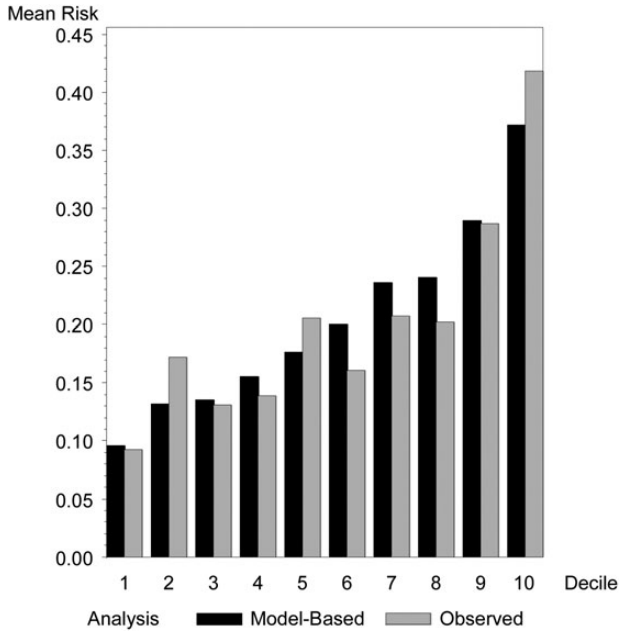

Figure 3. Calibration plot for the model with treatment variable ($\chi^2 = 4.499$, $P = .810$). Mean risk of recurrence (observed vs model based).

recurrence for a given patient [12, 13] to aid clinicians to identify high-risk patients likely to benefit from interventions to prevent the recurrence of CDI. Risk scores were derived from the same final model and were presented in 2 separate tables: one sheet is for patients with no prior episode of CDI and the other for patients with a prior episode.

RESULTS

Data Source

After 10 days of treatment, 962 patients were cured, 518 patients from study 003 and 444 patients from 004. Baseline characteristics of the patients in the cured population were similar in the 2 trials (Table 2). The univariate analyses in this article were based on these 962 patients; however, the final model was derived from 922 participants, due to missing records. In the first trial, 15.4% of the fidaxomicin patients compared with 25.3% of the vancomycin patients experienced clinical recurrence (difference = 9.9%, $P = .005$). In the second trial, 12.7% of the fidaxomicin patients compared with 26.9% of the vancomycin patients experienced recurrence (difference = 14.2, $P < .001$).

Multivariable CDI Recurrence Prediction Models

Four statistically significant dichotomous predictors were selected: age (<75 vs ≥75 years), number of unformed bowel movements during the previous 24 hours (<10 vs ≥10); serum creatinine at baseline (<1.2 mg/dL vs ≥1.2 mg/dL) and prior episode of CDI (no vs yes). In addition to these predictors, treatment (fidaxomicin vs vancomycin) was included in the final model. Addition of the treatment variable was justified by the high ability of this single predictor to discriminate patients with recurrence (C-statistic = 0.59, $P < .01$). Figure 2 presents the comparison of the ROC curves for the models with and without the treatment variable. After adding treatment, the magnitude of model discrimination increased (C-statistic: 0.64, 95% confidence interval [CI], .60–.69 vs C-statistic: 0.60,

Table 3. Validation of the Prediction Model for *Clostridium difficile* Infection Recurrence

Study	Model	No.	β	Odds Ratio	*P* Value	C-Statistic (95% CI)	Cross-validated C-Statistic (95% CI)
003	Age (<75 vs ≥75 y)	502	0.21	1.23	.11	0.65 (.59–.71)	0.64 (.57–.70)
	UBMs per day (<10 vs ≥10)		0.12	1.13	.35		
	Serum creatinine (<1.2 vs ≥1.2 mg/dL)		0.34	1.40	.01		
	Prior episode (no vs yes)		0.19	1.21	.17		
	Treatment (fidaxomicin vs vancomycin)		0.30	1.35	.01		
004	Age (<75 vs ≥75 y)	420	0.17	1.19	.21	0.64 (.58–.71)	0.62 (.55–.69)
	UBMs per day (<10 vs ≥10)		0.30	1.35	.04		
	Serum creatinine (<1.2 vs ≥1.2 mg/dL)		0.19	1.21	.21		
	Prior episode (no vs yes)		0.26	1.30	.11		
	Treatment (fidaxomicin vs vancomycin)		0.42	1.52	<.01		
003[a] + 004	Age (<75 vs ≥75 y)	922	0.18	1.20	.05	0.64 (.60–.69)	0.63 (.56–.69)
	UBMs per day (<10 vs ≥10)		0.19	1.21	.04		
	Serum creatinine (<1.2 vs ≥1.2 mg/dL)		0.28	1.32	<.01		
	Prior episode (no vs yes)		0.21	1.23	.04		
	Treatment (fidaxomicin vs vancomycin)		0.35	1.42	<.01		

Abbreviations: CI, confidence interval; UBM, unformed bowel movement.

[a] Intercept for this model is equal to −1.03.

95% CI, .55–.64). Furthermore, the rIDI of 0.73 suggested strong discriminatory potential in relation to other predictors already in the model [11]. In both models, parameter estimates and *P* values for age, number of unformed bowel movements per day, serum creatinine at baseline, and prior episode of CDI were similar.

Performance of CDI Recurrence Prediction Model

The predictive accuracy of the final model with 5 factors (4 risk factors and treatment) was assessed using the goodness-of-fit test. The small value of the calibration χ^2 statistic and high *P* value indicating excellent goodness of fit ($P = .81$, $\chi^2 = 4.50$). The calibration plot that provides a graphical display of goodness-of-fit of the model shows that the means of the predicted probabilities from the model were very similar to the means of actual outcomes in each decile bin (Figure 3).

The multivariable model with 5 risk factors was applied to the 2 independent samples from study 003 and study 004. Table 3 provides the comparison of the results for the model performance on study 003 and study 004. The C-statistics of the final model applied to each sample were identical with slight differences in the ranges of confidence intervals (.59–.71 vs .58–.71 vs .60–.69 for study 003, study 004, and both studies combined, respectively), which is explained by differing sample sizes. There were no meaningful differences in the parameter estimates across the 3 samples considered. In addition, the cross-validated C-statistic for the model was 0.63, similar to the C-statistic from the model developed on combined samples (0.64), indicating limited amount of overfitting.

Derivation of CDI Recurrence Prediction Score

The risk score sheet for estimation of CDI recurrence was constructed using the multivariable logistic model, which includes 4 independent risk factors that are readily available to the healthcare worker when the patient makes initial contact: age (<75 vs ≥75 years), number of unformed bowel movements during the previous 24 hours (<10 vs ≥10), serum creatinine level (<1.2 mg/dL vs ≥1.2 mg/dL), and prior episode of CDI (no vs yes). In addition, the model includes choice of treatment as a factor and the scoring rule provides risk of recurrence when choosing vancomycin or fidaxomicin. Analogous to multivariable logistic model, performance of the scoring tool was assessed, proving good fit of risk scores to the data (calibration χ^2 $P = .70$, AUC = 0.64).

Table 4 provides the point system and the score sheet based on predicted probabilities obtained from the same model. Table 4*A* is for patients with no prior history of CDI and Table 4*B* is for those with a prior history. Upon presentation of the patient to the healthcare worker, the risk of recurrence could be predicted based on clinical risk factors and the choice of treatment. The use of the risk score is illustrated with an example—that of a 79-year-old patient with 10 unformed bowel movements with serum creatinine level 1.5 mg/dL and with a prior history of CDI. Using the point system in Table 4*B*, the risk of CDI for this patient is computed as follows: 1 point is assigned for age, 1 point for number of unformed bowel movements, and 2 points for serum creatinine. If fidaxomicin is selected for therapy, the risk of recurrence is 37% whereas with vancomycin treatment, the risk of recurrence is 54%.

Table 4. Predicted Risk of *Clostridium difficile* Infection Recurrence[a]

	Points for Each Risk Factor			Predicted Risk of Recurrence	
No. of Risk Factors	Age ≥75 y	UBM ≥10/d	Cr ≥1.2 mg/dL	FDX	VAN
(A) Score sheet for people with no prior episode					
No risk factors	0	0	0	10%	18%
1 Risk factor					
Age	1	0	0	13%	24%
UBM	0	1	0	13%	24%
Cr	0	0	2	17%	29%
2 Risk factors					
Age and UBM	1	1	0	17%	29%
Age and Cr	1	0	2	21%	35%
UBM and Cr	0	1	2	21%	35%
3 Risk factors					
Age, UBM, and Cr	1	1	2	28%	44%
(B) Score sheet for people with prior episode					
No risk factors	0	0	0	14%	25%
1 Risk factor					
Age	1	0	0	19%	32%
UBM	0	1	0	19%	32%
Cr	0	0	2	24%	39%
2 Risk factors					
Age and UBM	1	1	0	24%	39%
Age and Cr	1	0	2	29%	45%
UBM and Cr	0	1	2	29%	45%
3 Risk factors					
Age, UBM, and Cr	1	1	2	37%	54%

Abbreviations: Cr, creatinine; FDX, fidaxomicin; UBM, unformed bowel movement; VAN, vancomycin.

[a] Predicted risks in both (A) and (B) were derived from the same model with age (<75 vs ≥75 y), unformed bowel movements (<10 vs ≥10), serum creatinine level (<1.2 vs ≥1.2 mg/dL), prior episode of CDI (no vs yes), and treatment (vancomycin or fidaxomicin).

DISCUSSION

Oral vancomycin and fidaxomicin have similar success rates (88% and 86% for fidaxomicin and vancomycin, respectively)

in achieving clinical cure of CDI after 10 days of treatment [5, 6]. Metronidazole has a similar cure rate for cases with mild to moderate degrees of illness but in more severe cases, metronidazole has been shown to have reduced efficacy compared with vancomycin [14, 15]. The situation for risk of recurrence is somewhat different as the 2 phase 3 trials have shown that initial treatment with vancomycin produces a recurrence rate of 26% vs 14% recurrence with fidaxomicin. Therefore, it is clear that for CDI patients, the advantage of using fidaxomicin in the initial episode is based on a reduction in recurrence rate.

Many factors have been alleged to play a role in risk of recurrence. We analyzed 77 risk factors in this study, which were derived from our phase 3 trials and supplemented by an extensive search of the literature and by personal inquiries of clinicians for risk factors developed from their own experience. The benefit of this model is that it found 4 independent factors with the best predictive value derived from the largest prospective database of acute CDI available in current times to study risk of recurrence. Although we agree that an AUC of 0.64 indicates that there is ample room for improvement in model performance, we submit that our work offers the first scoring algorithm that is based on such a large sample.

It has been shown in our phase 3 studies as well as in reports in the literature that the major onset of recurrence is 2–3 weeks after cessation of the initial treatment regimen with vancomycin or metronidazole. Recurrence of CDI is associated with substantial morbidity and mortality and increased medical costs [16–20]. It represents an unresolved area of concern in the management of CDI. Recurrence of CDI can develop as a relapse of the previously treated infection or a new episode ("reinfection") [21, 22]. A true recurrence of the original infection is usually caused by the original infecting strain; however, a later onset reinfection is often related to a new strain from the environment often acquired in a long-term healthcare facility or nursing home [23–25].

Another risk factor for recurrent CDI is a history of a previous episode of this disease, especially within the previous 3 months. A review of research on this topic was published by Johnson [34], who reported that the risk of a subsequent episode of CDI in a patient who has already had 1 recurrence is approximately 45% and that a subset of these patients will have multiple recurrences. The 2 phase 3 trials from which the database is derived for this analysis had relatively few recurrent CDI cases, but even with only 16% having prior CDI, this variable did add significantly to the model. Table 4 shows that there is a substantial increase in the risk of another CDI if the patient has a history of CDI. It should be noted that the decrease in the risk of CDI recurrence associated with the use of fidaxomicin over vancomycin is maintained even for those with a previous history.

Dysbiosis within the gastrointestinal tract and exposure to *C. difficile* are the primary determinants of late-onset CDI. These factors continue to exist among patients following successful therapy of CDI [26–31]. The gut flora can be abnormal for weeks after the discontinuation of CDI therapy [32, 33]. Many patients require concomitant antibiotics for new infections, further impairing their gut flora.

The proposed risk assessment model can be used when the patient makes initial contact with a healthcare worker to estimate risk of recurrent infection within the 25 days of stopping CDI treatment. The 4 risk factors—age, number of unformed bowel movements during the previous 24 hours, renal status (serum creatinine), and history of a previous CDI episode—are readily available. In addition, inclusion of treatment in the model provides a guide to risk of recurrence when choosing vancomycin or fidaxomicin. It is likely that use of metronidazole would entail a similar recurrence risk as vancomycin [14]. The final choice of treatment is dependent on an array of issues, and risk of recurrence would fit into this matrix of considerations.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. R. B. D. and K. M. P. performed the statistical analysis for this work. All authors have full access to the study data.

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Potential conflicts of interest. S. H. C. is an employee of Cubist Pharmaceuticals, Inc. Y. K. is a former employee of Optimer Pharmaceuticals, Inc (recently acquired by Cubist Pharmaceuticals, Inc). S. G. is an employee of Cubist Pharmaceuticals, Inc, and a consultant for Cempra Pharmaceuticals, Inc.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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