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A Clinical Prediction Rule for Fluoroquinolone Resistance in Healthcare-Acquired Gram-Negative Urinary Tract Infection

Pinyo Rattanaumpawan, MD, MSCE¹, Pam Tolomeo, MPH¹, Warren B. Bilker, PhD^{1,2,3}, and Ebbing Lautenbach, MD, MPH, MSCE^{1,2,3,4}

¹Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

²Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

³Center for Education and Research on Therapeutics and University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

⁴Division of Infectious Diseases of the Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Abstract

Data from a case-control study were used to derive and internally validate a prediction rule for identifying fluoroquinolone resistance in healthcare-acquired gram-negative urinary tract infection. This prediction rule has an excellent sensitivity and specificity (C-statistic, 0.816). External validation is necessary before implementing this rule to optimize empirical antibiotic use in clinical practice.

Because of an increasing prevalence of fluoroquinolone (FQ) resistance among gram-negative uropathogens, use of FQs as empirical therapy for healthcare-acquired gram-negative urinary tract infection (HA-GNB-UTI) may be inadequate.¹ Overuse of broad-spectrum antibiotics to avoid inadequate coverage would increase antibiotic cost and lead to the emergence of antimicrobial resistance.^{1,2} Development of a clinical prediction score to identify those patients who are most likely to be infected with an FQ-resistant GNB would be useful for optimizing empirical antibiotic therapy.

METHODS

We used a retrospective case-control study to build a predictive model for FQ resistance in patients with HA-GNB-UTI. We subsequently developed a scoring system by simplifying coefficients of each independently predictive factor. We then validated our clinical prediction rule in a hypothetical cohort that was derived from the case-control population. The University of Pennsylvania Institutional Review Board reviewed and approved this study.

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Address correspondence to Ebbing Lautenbach, MD, MPH, MSCE, University of Pennsylvania School of Medicine, Center for Clinical Epidemiology and Biostatistics, 825 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021 (ebbing@mail.med.upenn.edu).

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We enrolled all patients who were admitted to the hospital from January 2003 through March 2005 at 2 medical centers within the University of Pennsylvania Health System (UPHS): the Hospital of University of Pennsylvania (HUP), a 725-bed academic tertiary and quaternary medical center, and Penn Presbyterian Medical Center (PPMC), a 324-bed urban community hospital center. Both centers are located in Philadelphia.

To determine the case-control population (derivation population), all patients with urine culture results positive for GNB who met the Centers for Disease Control and Prevention (CDC) definition for HA-UTI³ were prospectively identified from the clinical microbiology laboratory database. From this population, all patients who had FQ-resistant GNB-UTI (case patients) were included, whereas patients with FQ-susceptible GNB-UTI were randomly selected to equal the number of case patients. Frequency matching on month of isolation and species of infecting organism was used to sample control subjects. Frequency matching was separately performed within each medical center. Only the first episode of infection in a given patient was included.

The hypothetical cohort population (validation population) was derived from the case-control population. All case patients were included, whereas control subjects were randomly sampled on the basis of a frequency weighting scheme. The probability for a control subject to be sampled was equal to a ratio of the number of FQ-susceptible UTIs to FQ-resistant UTIs for each particular organism in the source population. The frequency weighting scheme was performed to make the causative pathogen distribution and prevalence of FQ resistance for each particular organism similar to that for the source population.

We performed chart review to obtain data, including baseline demographic characteristics, hospital service, hospital location, number of hospital-days (before the onset of UTI), comorbidities, the presence of a urinary catheter, and receipt of inpatient antimicrobial therapy within the preceding 30 days.

An isolate was considered to be resistant if it demonstrated a minimum inhibitory concentration (MIC) of greater than or equal to 8 $\mu\text{g/mL}$ to levofloxacin. Susceptibilities to levofloxacin were determined according to existing criteria established by the Clinical and Laboratory Standards Institute.⁴

Bivariable analysis was performed to determine the unadjusted association between FQ resistance and potential risk factors. Categorical variables were compared using the χ^2 test. Continuous variables were compared using the Student's t test. Multiple logistic regression analysis was subsequently performed by the forward stepwise method to build a final model. We included all variables with P less than .05 in the final model. A simplified scoring system was developed by simplifying coefficients of each independent predictor variable. The simplified model was built by including a summation of scores from the presence of all independent predictor variables as a continuous variable.

The Hosmer-Lemeshow χ^2 goodness-of-fit test was performed to determine the accuracy of the models. The C-statistic or area under the receiver operating characteristic (ROC) curve was used to evaluate the discrimination ability (sensitivity and specificity).

Both models (the final model and the simplified model) were internally validated by the optimism adjustment method.⁵ Our models may not be fitted to other populations, and the sensitivity and specificity obtained from our study may be overly optimistic. Therefore, we calculated the adjusted sensitivity and specificity of the clinical prediction rule from 10,000 bootstrap data sets.

A 2-tailed *P* value of less than .05 was considered significant. All statistical calculations were performed using STATA software, version 10 (StataCorp).

RESULTS

During the study period, there were a total of 1,691 episodes of HA-GNB-UTI, and 263 episodes (15.6 %) of these were caused by FQ-resistant pathogens. Only 95% of case patients (251 of 263) had complete medical records available for abstraction; therefore, we enrolled a total of 251 case patients and 263 control subjects to the study.

Full details of organism distribution, baseline characteristics, comorbidities, and recent antibiotic exposure of case patients and control subjects have been published elsewhere.⁶ Each variable of case patients and control subjects was compared in a bivariate analysis to identify the significant association. We subsequently performed multiple logistic regression to identify the independent predictors. A simplified scoring system was developed on the basis of the magnitude of the coefficient for each variable. Specifically, a scoring point of each variable is equal to a rounded number of its coefficient divided by the smallest coefficient in the final model. Table 1 shows the regression coefficient, the adjusted odds ratio (OR), and the simplified scoring points of each independent predictor. The clinical prediction score is a summation of scores from the presence of each independent predictor variable. The possible score ranges from 0 to 18.

Our clinical prediction rule performed well in the validation cohort. It showed good calibration (Hosmer-Lemeshow χ^2 test, 1.16; *P* = .76) and good discrimination (C-statistic, 0.816). The ROC curve is shown in Figure 1. At the cutoff score of 2 or greater, the clinical prediction score demonstrated 75% sensitivity and 73% specificity to identify FQ-resistant UTI (Table 2). The overoptimism-adjusted C-statistic was 0.815.

We also evaluated the coefficient model (the final model) in the validation cohort and obtained similar results, including good calibration (Hosmer-Lemeshow χ^2 test, 4.02; *P* = .67) and good discrimination (C-statistic, 0.820). The overoptimism-adjusted C-statistic was 0.819.

DISCUSSION

Our clinical prediction rule has several important features. First, the simplified scoring system provided an excellent C-statistic (0.815) and acceptable sensitivity and specificity to predict FQ resistance in patients with HA-GNB-UTI. Second, it also has good calibration, which indicates the accuracy of the predicted probabilities of the event of interest. Third, this scoring system is simple and requires only information regarding 9 predictive factors. Finally, implementation of this score in clinical practice would likely be less costly than that of other antibiotic stewardship strategies, which typically require higher financial and human resources.⁷

Despite those important features, our prediction rule has several potential limitations. First, our validation population was derived from the case-control study. This method may lead to overestimation of sensitivity and specificity. However, the sensitivity and specificity estimates with or without adjustment for over optimism were comparable. Second, this prediction rule is applicable only to HA-UTIs associated with a urine culture positive for GNB. Third, it is well known that a clinical prediction rule may have reduced accuracy when it is used in different populations or different time periods. Our study was conducted within UPHS during the period 2003–2005; therefore, temporal and domain validation are still necessary.

In conclusion, this clinical prediction score is a promising tool for prediction of FQ resistance in patients with HA-GNB-UTI and provides the opportunity to optimize empirical antibiotic therapy. External validation of this score is necessary before we implement this tool in clinical practice.

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Figure 1.
Receiver operating characteristic (ROC) curve.

TABLE 1

Regression Coefficient, Adjusted Odds Ratio (OR), and Simplified Scoring Points of Each Independent Predictor

Variable	Coefficient (β)	Adjusted OR (95% CI)	P	Scoring points
Male sex	0.63 (2.11–4.16)	1.88 (1.16–3.04)	.01	1
Recent metronidazole exposure ^a	0.80 (0.22–1.39)	2.23 (1.24–8.88)	.007	1
Medicine service	0.84 (0.36–1.31)	2.30 (1.44–3.70)	.001	1
Recent trimethoprim-sulfamethoxazole exposure ^a	1.03 (0.23–1.83)	2.79 (1.25–6.23)	.012	2
Chronic respiratory disease ^b	1.06 (0.34–1.79)	2.90 (1.40–6.00)	.004	2
Residence in a long-term care facility	1.20 (0.22–2.18)	3.32 (1.24–8.88)	.017	2
Hydronephrosis	1.51 (0.06–2.95)	4.51 (1.06–19.18)	.042	2
Renal insufficiency ^c	1.56 (0.67–2.44)	4.74 (1.95–11.52)	.001	2
Recent FQ exposure ^a	3.14 (2.11–4.16)	23.02 (8.24–64.27)	<.001	5

NOTE. CI, confidence interval; FQ, fluoroquinolone.

^aInpatient antibiotic exposure in the preceding 30 days.

^bChronic obstructive pulmonary disease or chronic bronchitis.

^cA creatinine clearance of less than 50 mL/min and/or requirement of hemodialysis or peritoneal dialysis.

TABLE 2

Sensitivity and Specificity for Each Cutoff Value of Simplified Scoring System

Score cutoff value	Sensitivity, %	Specificity, %
≥0	100.00	0.00
≥1	92.03	31.47
≥2	75.30	73.01
≥3	63.35	89.06
≥4	51.79	95.67
≥5	44.22	98.11
≥6	39.84	98.51
≥7	31.47	98.98
≥8	21.51	98.98
≥9	14.34	100.00