Application of Fluoroquinolone Resistance Score in Management of Complicated Urinary Tract Infections

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ABSTRACT The fluoroquinolone resistance score (FQRS) predicts the probability of fluoroquinolone resistance with good discrimination. The score has been derived from patients with bloodstream infections caused by Gram-negative bacteria and is based on fluoroquinolone use within the past 6 months, among other clinical and health care exposure criteria. This study aims to examine the utility of the FQRS in patients with complicated urinary tract infections (cUTI) and determine whether extension of prior fluoroquinolone use to 12 months improves model discrimination. Adults with cUTI at Palmetto Health in central South Carolina, USA, from 1 April 2015 through 31 July 2015 were prospectively identified. Multivariate logistic regression was used to examine the association between prior fluoroquinolone use and resistance. Among 238 patients, 54 (23%) had cUTI due to fluoroquinolone-resistant bacteria. Overall, the median age was 66 years, 162 (68%) patients were women, and 137 (58%) patients had cUTI due to *Escherichia coli*. Prior exposure to fluoroquinolones within 3 months (adjusted odds ratio [aOR], 23.4; 95% confidence interval [CI], 8.2 to 76.8; $P < 0.001$) and within 3 to 12 months (aOR, 13.2; 95% CI, 3.1 to 68.4; $P < 0.001$) was independently associated with fluoroquinolone resistance compared to no prior use. The area under the receiver operating characteristic curve for the FQRS increased from 0.73 to 0.80 when prior fluoroquinolone use was extended from 6 to 12 months. FQRSs of ≥ 2 and ≥ 3 had negative predictive values of 91% and 90%, respectively. The modified FQRS stratifies patients with cUTI on the basis of the predicted probability of fluoroquinolone resistance with very good discrimination. Application of the modified FQRS may improve antimicrobial utilization in patients with acute pyelonephritis.

KEYWORDS risk factors, ciprofloxacin, levofloxacin, pyelonephritis, sepsis, bacteremia, bloodstream infections

Complicated urinary tract infections (cUTI) are a leading cause of hospitalization due to infections in the United States (1, 2). Increasing rates of antimicrobial resistance have limited the options for oral empirical therapy of cUTI (3–5). The rates of resistance to fluoroquinolones (FQ), trimethoprim-sulfamethoxazole, and amoxicillin-clavulanate among *Escherichia coli* isolates have exceeded 20% in multiple geographical settings in North America (6–8). Despite increasing rates of antimicrobial resistance, fluoroquinolones remain among the antimicrobial agents most commonly prescribed for the treatment of cUTI (9).

The fluoroquinolone resistance score (FQRS) was recently developed by our group to predict the probability of fluoroquinolone resistance in bloodstream Gram-negative isolates. The score is based on male sex (1 point), diabetes mellitus (1 point), residence

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TABLE 1 Demographics and clinical characteristics of patients with cUTI and risk factors for fluoroquinolone resistance in univariate model^a

Variable	Value for patients infected with:		OR	95% CI	P value
	FQ-NS bacteria (n = 54)	FQ-S bacteria (n = 184)			
Median (IQR) age (yr)	69 (59–81)	65 (54–76)	1.18 ^b	0.98–1.43	0.09
No. (%) of male subjects	21 (39)	55 (30)	1.49	0.79–2.94	0.22
No. (%) of subjects of white race	29 (53)	83 (45)	1.41	0.77–2.61	0.27
No. (%) of subjects with:					
Diabetes mellitus	21 (39)	71 (39)	1.01	0.54–1.88	0.97
Cancer	13 (24)	33 (18)	1.45	0.68–2.96	0.32
Hospital-acquired infection	9 (17)	38 (21)	0.77	0.33–1.65	0.51
Recent hospitalization ^c	25 (46)	61 (33)	1.74	0.93–3.22	0.08
Residence at a skilled nursing facility	10 (19)	18 (10)	2.10	0.88–4.79	0.09
Recent outpatient procedure ^d	6 (11)	5 (3)	4.48	1.30–16.13	0.02
Prior fluoroquinolone use					
None	21 (39)	171 (93)	1	Referent	Referent
Within 3 mo	18 (33)	6 (3)	24.43	9.18–73.91	<0.001
Within 3–12 mo	15 (28)	7 (4)	17.45	6.60–50.47	<0.001

^acUTI, complicated urinary tract infections; OR, odds ratio; CI, confidence interval; IQR, interquartile range.^bPer decade.^cWithin 3 months of infection.^dWithin 1 month of infection.

at a skilled nursing facility (2 points), recent outpatient procedures (3 points), and prior fluoroquinolone use (within 3 months, 5 points; within 3 to 6 months, 3 points). The FQRS stratifies patients with bloodstream infections caused by Gram-negative bacteria according to the predicted risk of fluoroquinolone resistance with good discrimination on the basis of an area under a receiver operating characteristic curve (AUC) of 0.73 (10).

The aim of this study was to prospectively examine the utility of the FQRS in the management of patients with cUTI and examine whether extension of fluoroquinolone use up to 12 months prior to infection improves model discrimination.

(The preliminary results of this study were presented, in part, at IDWeek, 26 to 30 October 2016, New Orleans, LA, USA [11].)

RESULTS

During the 4-month study period, 238 patients with cUTI were included. Overall, the median age was 66 years, and 76 (32%) of the patients were men. *Escherichia coli* was the most common pathogen ($n = 137$ patients; 58%), followed by *Klebsiella pneumoniae* ($n = 37$; 16%), *Pseudomonas aeruginosa* ($n = 14$; 6%), *Enterobacter cloacae* ($n = 13$; 5%), *Proteus mirabilis* ($n = 10$; 4%), *Serratia marcescens* ($n = 10$; 4%), *Enterobacter aerogenes* ($n = 7$; 3%), and others ($n = 10$; 4%). Among the patients in this cohort, 54 (23%) had cUTI due to fluoroquinolone-nonsusceptible (FQ-NS) Gram-negative bacilli. The baseline demographics and clinical characteristics of the patients with cUTI due to FQ-NS and fluoroquinolone-susceptible (FQ-S) bacteria are shown in Table 1.

Univariate logistic regression results for risk factors for infection with FQ-NS bacteria are demonstrated in Table 1. In the multivariate model, male sex, residence at a skilled nursing facility, outpatient procedures within 1 month of the index infection, and prior fluoroquinolone use within 3 months and within 3 to 12 months of the index infection were independently associated with fluoroquinolone resistance (Table 2).

On the basis of multivariate logistic regression results, the FQRS was modified by extending prior fluoroquinolone exposure from 6 to 12 months (Table 3). The AUC for the FQRS model increased from 0.73 to 0.80 when prior fluoroquinolone use was extended from 6 months (not shown) to 12 months (Fig. 1). The performance characteristics of the modified FQRS as a binary classification test are demonstrated in Table 4. The negative predictive values (NPVs) were 94%, 91%, and 90% when FQRS cutoff

TABLE 2 Independent risk factors for fluoroquinolone resistance in multivariate logistic regression model^a

Variable	aOR	95% CI	P value
Male sex	2.22	1.00–5.34	0.049
Diabetes mellitus	1.48	0.71–3.14	0.29
Residence at a skilled nursing facility	2.80	1.02–7.25	0.046
Outpatient GI/GU procedure within 1 mo	6.65	1.47–29.78	0.01
Prior fluoroquinolone use within 12 mo			
None	1	Referent	Referent
Within 3 mo	23.35	8.20–76.85	<0.001
Within 3–12 mo	13.16	3.11–68.43	<0.001

^aaOR, adjusted odds ratio; CI, confidence intervals; GI, gastrointestinal; GU, genitourinary.

points of ≥ 1 , ≥ 2 , and ≥ 3 were used to indicate a high risk of fluoroquinolone resistance.

The risk of fluoroquinolone resistance in patients with cUTI predicted using the modified FQRS is shown in Fig. 2. Patients with FQRSs of 0 and 1 have relatively low predicted probabilities of fluoroquinolone resistance of 6% and 10%, respectively. The estimated risk of fluoroquinolone resistance increases to 31% in patients with an FQRS of 3 and to 60% in patients with an FQRS of 5.

DISCUSSION

This study supports the use of the FQRS for the management of patients with cUTI. On the basis of prior and current results, the FQRS predicts the risk of fluoroquinolone resistance with good discrimination both in patients with bloodstream infections caused by Gram-negative bacteria and in patients with cUTI, respectively (AUC = 0.73 for both) (10). Modification of the FQRS by extension of fluoroquinolone use up to 12 months prior to infection improves the discriminative ability of the model (AUC = 0.80).

It is alarming that fluoroquinolone use in patients with cUTI predisposes these patients to an increased risk of fluoroquinolone resistance up to 1 year after exposure. This is supported by the results of a recent study which demonstrated the persistent impact of antimicrobials on the intestinal flora up to 1 year after exposure (12). This highlights the significance of antimicrobial stewardship efforts to reduce the unnecessary use of fluoroquinolones for the treatment of mild infections, e.g., upper respiratory tract infections and uncomplicated cystitis. The risks of fluoroquinolone therapy, including the induction of antimicrobial resistance, in patients with these minor infections exceed the potential benefits (13). Fluoroquinolones are potentially life-saving antimicrobial agents. Due to recent safety concerns and updates to fluoroquinolone labels by the U.S. Food and Drug Administration, fluoroquinolone use should be reserved for patients with potentially life-threatening infections (13). Narrower-spectrum antimicrobial agents are more appropriate for less serious infections. Fluoroquinolone therapy is not appropriate in patients with uncomplicated cystitis when other treatment options (e.g., nitrofurantoin, fosfomycin, and trimethoprim-sulfamethoxazole) are available (2, 14).

TABLE 3 Modified FQRS^a

Risk factor for fluoroquinolone resistance	Point allocation
Male sex	1
Diabetes mellitus	1
Residence in a skilled nursing facility	2
Outpatient GI/GU procedure within past 1 mo	3
Prior fluoroquinolone use within past 12 mo	
None	0
Within 3 mo	5
Within 3–12 mo	3

^aFQRS, fluoroquinolone resistance score; GI, gastrointestinal; GU, genitourinary.

FIG 1 Receiver operating characteristic plot of the modified fluoroquinolone resistance score. The black line indicates the receiver operating characteristic curve. The light color tangent line highlights the point in the curve that represents the best performance of the model. The area under the curve was 0.80.

In the era of increasing antimicrobial resistance, creative solutions to maintain the adequacy of antimicrobial therapy in patients with serious infections by optimizing the utilization of currently available resources are of paramount importance. Fluoroquinolones are among the most effective oral antimicrobial agents for the treatment of acute pyelonephritis due to their excellent oral bioavailability and high urinary and tissue concentrations (15). However, increasing rates of fluoroquinolone resistance have complicated the management of acute pyelonephritis, particularly in outpatient settings. The current national guidelines recommend using oral fluoroquinolones in patients with acute pyelonephritis not requiring hospitalization in settings with a <10% overall prevalence of fluoroquinolone resistance among uropathogens (2). However, geographical locations with a <10% overall prevalence of resistance to fluoroquinolones hardly exist these days in North America or elsewhere (3–8). This forces the administration of intravenous ceftriaxone to most patients with acute pyelonephritis prior to discharge from the emergency room or other outpatient settings on oral fluoroquinolones (2). The FQRS presents health care providers with opportunities to improve antimicrobial utilization in acute pyelonephritis by categorizing patients on the basis of the predicted probability of fluoroquinolone resistance into 3 groups: low, moderate, and high risk (Fig. 3). These categories are based on the performance characteristics of the modified FQRS using cutoff points of ≥ 2 and ≥ 3 to optimize the NPV and positive predictive value (PPV), respectively. Patients with an FQRS of 0 and 1 have a 6% and 10% predicted probability of fluoroquinolone resistance, respectively (Fig. 2), corresponding to a NPV of 91% for an FQRS of ≥ 2 . Since the predicted rate of resistance to fluoroquinolones is <10% in this low-risk group, patients with an FQRS of <2 are eligible for empirical oral fluoroquinolone therapy without the need for administration of intravenous ceftriaxone, in concordance with the national management guidelines (2). Application of the FQRS may simplify antimicrobial management in the majority of patients with acute pyelone-

TABLE 4 Performance of modified FQRS as a binary classification test^a

FQRS cutoff point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥ 1	93	33	29	94
≥ 2	76	68	41	91
$\geq 3^b$	69	84	56	90

^aFQRS, fluoroquinolone resistance score; PPV, positive predictive value; NPV, negative predictive value.

^bThe use of a cutoff score of ≥ 3 to indicate a high predicted risk of fluoroquinolone resistance provides the best performance in the statistical model.

FIG 2 Predicted probability of fluoroquinolone resistance by modified fluoroquinolone resistance score. The size of the marker for point estimates is weighted approximately by the relative number of subjects with the corresponding score.

phritis, since 60% of patients in the current study met the criteria for the low-risk category (no prior fluoroquinolone use, outpatient procedures, or residence at a skilled nursing facility). The management of patients in the moderate-risk group (FQRS = 2) remains unchanged from current guidelines since the predicted probability of fluoroquinolone resistance in this group is comparable to the overall resistance rate in the study (19% and 23%, respectively). The FQRS also identifies patients in whom fluoroquinolone therapy is most likely inadequate. If fluoroquinolones were initially prescribed to patients with acute pyelonephritis in the high-risk category, the majority would undergo revision of antimicrobial therapy when *in vitro* antimicrobial susceptibility testing results become available, given a PPV of 56% for an FQRS of ≥ 3 . Unfortunately, current data are insufficient to recommend alternative oral antimicrobial agents in this group. It would be valuable to develop clinical scores to predict resistance to other oral antimicrobial agents with a high efficacy in the treatment of cUTI, e.g., trimethoprim-sulfamethoxazole, in future studies. That would help identify other potential oral options for patients with a high risk of fluoroquinolone resistance and may diversify antimicrobial prescriptions overall.

In the inpatient setting, utilization of the FQRS may allow the early discharge of hospitalized patients with cUTI who demonstrate clinical improvement prior to the availability of urine culture and *in vitro* antimicrobial susceptibility testing results. If used properly, this may confer significant cost savings for the health care system. However, the FQRS should not replace *in vitro* antimicrobial susceptibility testing.

FIG 3 Proposed algorithm for application of the modified FQRS in the outpatient management of acute pyelonephritis. FQRS, fluoroquinolone resistance score; IV, intravenous.

Antimicrobial therapy should be adjusted, if needed, on the basis of organism identification and *in vitro* antimicrobial susceptibility testing results.

In addition to its clinical applications, the FQRS may also be used in clinical research studies. Increasing rates of fluoroquinolone resistance limited the utility of fluoroquinolones as comparators to a new antimicrobial agent for cUTI in a recent clinical trial (16). Exclusion of patients with a high predicted risk of fluoroquinolone resistance, such as those with an FQRS of ≥ 3 , would make comparisons between fluoroquinolones and new antimicrobial agents more meaningful.

This study has strengths and limitations. The identification of cases and risk factors for antimicrobial resistance was facilitated by having a centralized microbiology laboratory and access to both inpatient and outpatient records from several affiliated medical facilities in the region. The patients' prior antimicrobial treatment histories were available, for the most part, in electronic medical records, including medication administration records and electronic prescriptions. Utilization of the FQRS in settings that lack access to prior records would heavily depend on patients' recall of their prior use of antimicrobial agents and providers' efforts to ascertain medical records. In addition, the case-control section of the current study was not powered to demonstrate an association between fluoroquinolone resistance and each individual component of the FQRS. Rather, it was focused on examining the risk of fluoroquinolone resistance on the basis of fluoroquinolone exposure within the past 12 months. Four of the variables in the FQRS were identified as independent risk factors for fluoroquinolone resistance in the current study. The role of diabetes mellitus in predicting fluoroquinolone resistance remains unclear on the basis of the current results. Moreover, although the impact of gender on antimicrobial resistance was statistically significant, it warrants further explanations in populations with different antimicrobial consumption and dietary habits.

In summary, the modified FQRS stratifies patients with cUTI on the basis of the predicted probability of fluoroquinolone resistance with very good discrimination. Application of the modified FQRS may simplify antimicrobial management in patients with acute pyelonephritis and improve the design of future clinical trials.

MATERIALS AND METHODS

Setting. The study was conducted at Palmetto Health inpatient and outpatient facilities in central South Carolina, USA. These facilities included three large community hospitals with a combined capacity of nearly 1,200 licensed beds, three emergency rooms, several affiliated urgent treatment centers, and ambulatory care clinics. The Institutional Review Board at Palmetto Health approved the study.

Definitions. Patients were considered to have cUTI if they had urinary symptoms or signs and monomicrobial growth of Gram-negative bacilli in urine cultures in the presence of complications such as obstructive uropathy, indwelling urinary catheters, urinary retention from neurologic disease, or bladder outlet obstruction (17, 18). Patients with clinical manifestations of acute pyelonephritis (temperature of $>38^{\circ}\text{C}$, unilateral flank pain, or costovertebral angle tenderness) and monomicrobial growth of Gram-negative bacilli in urine cultures were also included among those with cUTI (19). Outpatient procedures included both invasive procedures (e.g., bladder, colon, and prostate biopsies) and noninvasive procedures (e.g., colonoscopy, cystoscopy, and duodenoscopy) (10). Fluoroquinolone-nonsusceptible (FQ-NS) isolates were defined as Gram-negative bacilli that had intermediate *in vitro* susceptibility to ciprofloxacin ($\text{MIC} = 2\text{ }\mu\text{g/ml}$) or were resistant *in vitro* to ciprofloxacin ($\text{MIC} \geq 4\text{ }\mu\text{g/ml}$) according to Clinical and Laboratory Standards Institute guidelines.

Case ascertainment. All adult patients ≥ 18 years old with growth of Gram-negative bacilli in urine cultures from 1 April 2015 to 31 July 2015 were prospectively identified through a real-time alert system which interfaced with the central microbiology laboratory at Palmetto Health ($n = 582$). Patients with polymicrobial growth of bacteria in urine cultures ($n = 56$) or recurrent episodes of positive urine cultures during the study period ($n = 11$) and those with positive urine cultures who did not meet the predefined criteria for cUTI ($n = 277$) were excluded. Patients with recurrences and polymicrobial growth of bacteria in urine cultures were excluded to avoid enrolling the same patient as a case and a control. A total of 238 unique adults with cUTI were included in the study. Demographic, microbiology, and clinical data, including potential risk factors for antimicrobial resistance, were collected from electronic medical records. The receipt of fluoroquinolones in the 12 months preceding the cUTI was ascertained from medication administration records, electronic prescriptions, and clinical notes from current and prior hospitalizations and visits to affiliated emergency rooms or other ambulatory care settings.

Statistical analysis. Logistic regression was used to examine the association between fluoroquinolone resistance and fluoroquinolone exposure up to 12 months prior to the index cUTI in a case-control design. For the simplification of statistical analysis, Gram-negative bacilli that were

resistant or intermediate to ciprofloxacin *in vitro* were analyzed as FQ-NS isolates. Demographics and clinical variables were collected for patients with cUTI due to FQ-NS (cases) and fluoroquinolone-susceptible (FQ-S) Gram-negative bacilli (controls). Variables included age, sex, ethnicity, diabetes mellitus, cancer, nosocomial acquisition, recent hospitalization within 3 months, residence in a skilled nursing facility, and outpatient procedures within 1 month. Fluoroquinolone use within 12 months prior to the cUTI was analyzed as a categorical variable: none and within 3 months and within 3 to 12 months of the time of the index infection. The individual components of the FQRS, in addition to other variables associated with fluoroquinolone resistance in the univariate logistic regression model with a *P* value of <0.05, if any, were included in the multivariate logistic regression model to identify independent risk factors for fluoroquinolone resistance. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) were reported to demonstrate the strength of the association between each variable and fluoroquinolone resistance.

The area under a receiver operating characteristic curve (AUC) was used to quantify the discriminative ability of the FQRS using fluoroquinolone exposure up to 6 and 12 months prior to the cUTI. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for fluoroquinolone nonsusceptibility were calculated from the receiver operating characteristic curve for the best cutoff points in the FQRS.

JMP Pro (version 12.1; SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. The level of significance for statistical testing was defined as a *P* value of <0.05 (2-sided) unless otherwise specified.

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A.S. and M.N.A.-H. have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis.

A.S., J.A.J., J.K., and H.A. have no conflicts of interest. M.N.A.-H. is on the Continuing Medical Education Steering Committee for Rockpointe Corporation, Columbia, MD, USA. P.B.B. is on the Research Advisory Board for Actavis Pharmaceuticals (now Allergan), has received research funding from Actavis Pharmaceuticals (now Allergan), and is on the Continuing Medical Education Steering Committee for Rockpointe Corporation, Columbia, MD, USA.

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