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Risk factors for fluoroquinolone resistance in Gram-negative bacilli causing healthcare-acquired urinary tract infections

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SUMMARY

The prevalence of urinary tract infections caused by fluoroquinolone-resistant Gram-negative bacilli (FQ-resistant GNB-UTIs) has been increasing. Previous studies that explored risk factors for FQ resistance have focused only on UTIs caused by *Escherichia coli* and/or failed to distinguish colonisation from infection. We conducted a case–control study at two medical centres within the University of Pennsylvania Health System to identify risk factors for FQ resistance among healthcare-acquired GNB-UTIs. Subjects with positive urine cultures for GNB and who met Centers for Disease Control and Prevention criteria for healthcare-acquired UTI were eligible. Cases were subjects with FQ-resistant GNB-UTI, controls were subjects with FQ-susceptible GNB-UTI matched to cases by month of isolation and species of infecting organism. In total, 251 cases and 263 controls were included from 1 January 2003 to 31 March 2005. Independent risk factors (adjusted odds ratio; 95% confidence interval) for FQ resistance included male sex (2.03; 1.21–3.39; $P = 0.007$), African-American race (1.80; 1.10–2.94; $P = 0.020$), chronic respiratory disease (2.58; 1.18–5.62); $P = 0.017$], residence in a long term care facility (4.41; 1.79–10.88; $P = 0.001$), hospitalisation within the past two weeks (2.19; 1.31–3.64; $P = 0.003$), hospitalisation under a medical service (2.72; 1.63–4.54; $P < 0.001$), recent FQ exposure (15.73; 6.15–40.26; $P < 0.001$), recent cotrimoxazole exposure (2.49; 1.07–5.79; $P = 0.033$), and recent metronidazole exposure (2.89; 1.48–5.65; $P = 0.002$).

Keywords

Fluoroquinolone; Gram-negative bacilli; Resistance; Risk factors; Urinary tract infection

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Conflict of interest statement

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Introduction

Fluoroquinolone (FQ) antibiotics were introduced in the mid-1980s and have been widely used against various infectious diseases including urinary tract infections (UTIs).[1] Both chromosomally mediated and plasmid-mediated FQ resistance emerged rapidly and have since progressed. The increasing prevalence of FQ resistance among uropathogens in hospitals and long term care facilities (LTCFs) is a threat to the use of FQs as empirical therapy for UTI.[2–7]

Lack of knowledge on risk factors for FQ resistance is an obstacle to controlling the emergence of FQ resistance.[8] There are several limitations to the current literature. First, several studies have explored risk factors for FQ resistance generally but risk factors may differ across sites. Second, some studies have focused only on uropathogens but failed to distinguish infection from colonisation when risk factors for colonisation and infection are likely to be different.[5,9,10–12] Additionally, most studies have investigated FQ resistance in only a few specific Gram-negative pathogens.[5,10,11,13–17] This study is, to our knowledge, the first specifically designed to identify risk factors for FQ resistance in Gram-negative bacilli (GNB) causing healthcare-acquired UTI.

Methods

This retrospective case–control study was conducted at two medical centres within the University of Pennsylvania Health System (UPHS): the Hospital of University of Pennsylvania (HUP), a 725 bed academic tertiary and quaternary medical centre, and Penn Presbyterian Medical Center (PPMC), a 324 bed urban community hospital centre.

Cases and controls were prospectively identified from the records of the clinical microbiology laboratory. From 1 January 2003 to 31 March 2005, all patients from whom urine cultures yielded GNB and who met the Centers for Disease Control and Prevention definition for healthcare-acquired UTI were eligible for this study.[18]

A patient was considered as having UTI if one of the following criteria was met: (1) presence of at least one of the signs or symptoms of UTI (fever >38°C, urgency, frequency, dysuria or suprapubic tenderness) without other recognised cause plus a positive urine culture $\geq 10^5$ cfu/mL with no more than two species of micro-organisms; (2) presence of at least two of the signs or symptoms of UTI without other recognised cause plus at least one of the following: (a) dipstick positive for leucocyte esterase and/or nitrate, (b) pyuria, (c) organisms seen on Gram stain of unspun urine, (d) at least two urine cultures with repeated isolation of the same uropathogen $\geq 10^2$ cfu/mL in non-voided specimens, (e) $\leq 10^5$ cfu/mL of a single uropathogen in a patient being treated with an effective antimicrobial agent for UTI, (f) physician diagnosis of UTI, and (g) physician institutes appropriate therapy for UTI.[18]

UTI was considered to be healthcare-acquired if one of the following was true: (1) UTI occurred ≥48 h after hospital admission and was not present or incubating at the time of admission; (2) UTI presented on admission but the patient had been admitted from another medical centre or long term care facility having spent ≥48 h in the other facility; (3) UTI present on admission but the patient had been hospitalised within the past two weeks.

Resistance to levofloxacin was considered an indicator of resistance to FQ antibiotics: an isolate was considered resistant if it demonstrated a minimum inhibitory concentration (MIC) of ≥8 μg/mL levofloxacin. Levofloxacin susceptibility was determined according to criteria established by the Clinical and Laboratory Standards Institute.[19]

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Patients with UTI caused by FQ-resistant GNB were selected as cases whereas patients with UTI caused by FQ-susceptible GNB were eligible to be controls. Controls were matched by the month of isolation and the species of the infecting organism. If GNB were isolated on multiple occasions in the same patient, only the first episode of infection was reviewed for inclusion. Potential risk factors for FQ resistance were retrospectively obtained by review of medical records. Data obtained included age, sex, race, hospital service (department), hospital location, number of hospital days both before and after the diagnosis of UTI, comorbid conditions, presence of a urinary catheter and use of inpatient antimicrobial therapy in the preceding 30 days.

We categorised antimicrobial use by the individual agent and also by the class, as follows: (1) aminoglycosides; (2) β-lactam and β-lactamase inhibitors; (3) carbapenems; (4) cephalosporins; (5) fluoroquinolones; (6) penicillins; (7) macrolides; (8) others (clindamycin, doxycycline, metronidazole, nitrofurantoin, linezolid, cotrimoxazole and vancomycin).[20,21]

Statistical analysis

Categorical variables were expressed as proportions whereas continuous variables were expressed in terms of mean (±SD) or median (range) depending on the sample distribution. Comparative analyses were performed with the Mantel–Haenszel test or the Wilcoxon rank sum test as appropriate.

To estimate the association between FQ-resistant infection and potential risk factors we performed multiple logistic regression analysis including all variables associated with FQ-resistance on bivariable analysis ($P \leq 0.20$), matching categories (the month of isolation and the species of infecting organism) and the number of days in hospital before diagnosis of UTI (as the estimate of time at risk). A two-tailed *P*-value of <0.05 was considered significant. Statistical calculations were performed using STATA, version 10 (Stata Corp, College Station, TX, USA).

Results

During the study period there were 1691 episodes of healthcare-acquired UTI caused by GNB, 263 (15.6%) of which were caused by FQ-resistant GNB. The prevalence of FQ resistance was 15.8% (135 of 852) in *E. coli*, 8.3% (22 of 264) in *Klebsiella* spp., 25.7% (58 of 226) in *P. aeruginosa*, 11.4% (16 of 140) in *Proteus* spp., 20.2% (18 of 89) in *Enterobacter* spp. and 57.4% (8 of 14) in *Acinetobacter baumannii*. Controls were randomly selected to equal the number of cases by frequency matching. However, only 251 of the 263 cases (95.4%) had complete medical records available for abstraction so the number of cases was slightly less than the number of controls (251 cases and 263 controls).

Among these 251 cases, the main causative pathogens were *E. coli* (51.0%), *P. aeruginosa* (21.5%), *Klebsiella* spp. (9.2%), *Enterobacter* spp. (6.8%), *Proteus* spp. (6.4%) and other GNB (5.1%). Baseline characteristics and comorbid conditions of cases and controls are shown in Table I. When the antibiotic exposures of the two groups were compared, cases had significantly greater overall antibiotic exposure as well as greater exposure to aminoglycosides, cephalosporins, fluoroquinolones, macrolides, clindamycin, cotrimoxazole, metronidazole and vancomycin (Table II). Although exposure to any kind of cephalosporin was more common among cases, controls had significantly greater exposure to cefazolin.

The variables that remained independent risk factors for FQ resistance after multivariable analysis are shown in Table III. Independent risk factors for FQ resistance included male sex, African-American race, chronic respiratory disease, residence in a long term care facility, hospitalisation within the past two weeks, hospitalisation under a medicine service, recent FQ

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exposure, recent cotrimoxazole exposure and recent metronidazole exposure. Recent cefazolin exposure appeared to be protective.

Discussion

Our study demonstrated a high prevalence of FQ resistance among GNB, ranging from 15.8% among *E. coli* to 57.4% among *A. baumannii*. A survey of US emergency departments during 2000–2004 reported 7% FQ resistance among patients with complicated pyelonephritis, and the North American UTI Collaborative Alliance (NAUTICA) study revealed approximately 5% FQ resistance among outpatient *E. coli* urinary isolates during 2003–2004.[16,22] However, both studies were conducted in the outpatient setting and NAUTICA did not distinguish colonisation from infection. Our results emphasise the magnitude of FQ resistance among patients with healthcare-acquired GNB UTI.

Our study found male sex to be an independent risk factor for FQ-resistant UTI. This association has not previously been demonstrated for UTIs specifically. It is possible that the male urological system is more likely to acquire FQ-resistant uropathogens; for instance, studies have shown a high prevalence of FQ resistance in the organisms responsible for acute prostatitis after transrectal prostate biopsy.[23,24] However, FQs are widely used as prophylactic agents in prostate biopsy, so the apparent association between male sex and FQ resistance may be due in part to higher antibiotic exposure among males.[25] Unfortunately our study did not identify the specific anatomic site of the UTI (e.g. bladder, prostate), any recent procedures or antibiotic exposure prior to admission.

African-American race was also an independent risk factor according to our study. This racial disparity has been described in various infections caused by antibiotic-resistant pathogens but has never been reported for FQ-resistant UTI.[26,27] The reasons for this finding are not clear, but may be related to differences in rates of antibiotic exposure, comorbidities and/or differences in antibiotic metabolism across different patient populations.

In assessing the association between FQ resistance and chronic respiratory disease, it is notable that patients who have chronic respiratory disease are more likely to be exposed to various antibiotics, especially respiratory FQs. However, we could not fully adjust for this possible confounder because of lack of data on antibiotic exposure prior to admission.

LTCF residence was also identified as a risk factor in our study. A previous case–control study found an association between LTCF residence and FQ resistance in nosocomial *E. coli* and *K. pneumoniae* infections.[5] Colonised patients who are admitted may be at greater risk of subsequent FQ-resistant UTI.[28] These results suggest that FQ resistance may be spreading across different types of healthcare facilities. Indeed, a recent study investigated the epidemiology of antimicrobial resistance among Gram-negative urinary isolates recovered from patients in a multistate network of LTCFs and found that FQ resistance in GNB uropathogens was highly prevalent and varied by facility type, size and geographic location.[7]

Previous hospitalisation is a well-known risk factor for emergence of resistance to FQ and other antibiotics.[29,30] Hospitalisation under a medicine service may be a particular risk factor due to the greater antibiotic consumption in such facilities and perhaps also because patients with more comorbidities are admitted.[31] Both of these variables were also confirmed as risk factors in our study.

Several studies have demonstrated association between previous FQ exposure and infection caused by FQ-resistant GNB in the acute care setting.[5,9,14] Prior FQ use was noted to be a strong risk factor for FQ-resistant *E. coli* UTIs in the LTCF setting.[15] Our study also found that recent FQ use was an independent risk factor for FQ-resistant GNB-UTI. However, we

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also identified recent cotrimoxazole and metronidazole exposure as independent risk factors, which has not been previously noted in community settings and or for other infection sites. Therefore we should not assume that the epidemiology of FQ resistance is similar across different settings. It is not clear whether the associations with cotrimoxazole and metronidazole use are causally related, but perhaps reducing unnecessary prescribing of these agents would benefit FQ resistance.

Recent cefazolin exposure was unexpectedly identified as a protective factor. In our institutions this agent is often used for elective surgical prophylaxis, so recent cefazolin exposure may be a proxy for patients who were recently admitted for elective surgery and are therefore generally healthier. However, the effect did not disappear after adjustment for the indication for admission and other comorbidities.

Our study has several strengths compared with previous studies. Whereas other studies failed to distinguish between UTIs and colonisation, ours included only patients who met the Centers for Disease Control and Prevention definition for UTI.[18] In addition, the mechanism of FQ resistance might be different between the hospital setting and community setting, and our study focused exclusively on healthcare-acquired UTIs. We used frequency matching by month of isolation to sample the controls: because the percentage of organisms resistant to FQs is likely to increase with time, failure to match according to this parameter might result in a greater number of controls enrolled in the early study period and a greater number of cases enrolled in the later study period. We also frequency-matched according to the species of infecting organisms: failure to do so might result in a greater number of cases infected by species with a high prevalence of FQ resistance and a greater number of controls infected by species with a low prevalence of FQ resistance.

Our study has several potential limitations. The lack of data on antibiotic exposure before hospitalisation may result in information bias, although it is unlikely that this would result in differential bias. Furthermore this study was conducted at HUP and PPMC in 2003–2005: the results may be inapplicable in other settings or in other time periods.

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Table I

Baseline characteristics and comorbid conditions of cases and controls

Characteristics	Cases (*N* = 251)	Controls (*N* = 263)	OR (95% CI)	*P*-value
Median (range) age (years)	69 (21–95)	68 (23–91)	1.01 (1.00–1.02)	0.225
Mean (range) no. of hospital days prior to UTI	8 (2–120)	5 (2–68)	1.03 (1.01–1.04)	<0.001
Male sex	101 (40.2)	70 (26.6)	1.86 (1.26–2.74)	0.001
African-American	106 (42.2)	94 (35.7)	1.31 (0.91–1.91)	0.131
Residence in a long term care facility	38 (15.1)	11 (4.2)	4.09 (1.98–9.07)	<0.001
Previous hospitalisation (within 2 weeks)	110 (43.8)	67 (25.5)	2.28 (1.55–3.38)	<0.001
Admitted for elective surgery	118 (47.0)	151 (57.4)	0.70 (0.52–0.94)	0.013
Medicine services	141 (56.2)	93 (35.4)	2.34 (1.62–3.40)	<0.001
Underlying diseases	194 (56.9)	147 (43.1)	2.69 (1.80–4.02)	<0.001
Hepatic dysfunction	11 (4.4)	5 (1.9)	2.37 (0.74–8.80)	0.105
Diabetes	88 (35.1)	59 (22.4)	1.87 (1.24–2.81)	0.002
Cardiovascular diseases	75 (29.9)	58 (22.1)	1.51 (0.99–2.29)	0.043
Chronic respiratory diseases	42 (16.7)	15 (5.7)	3.32 (1.74–6.63)	<0.001
Chronic renal insufficiency	18 (7.2)	6 (2.3)	3.31 (1.23–10.34)	0.009
Structural kidney diseases	23 (9.2)	18 (6.8)	1.37 (0.69–2.77)	0.332
Malignancy	40 (15.9)	44 (16.7)	0.94 (0.57–1.55)	0.808
Transplant recipient	11 (4.4)	3 (1.1)	3.97 (1.03–22.38)	0.024
Steroid use	36 (14.3)	13 (4.9)	3.22 (1.61–6.78)	<0.001
Immunosuppressive agents treatment	9 (3.6)	3 (1.1)	3.22 (0.79–18.68)	0.067
Indwelling urinary catheters	172 (68.5)	150 (57.0)	1.64 (1.12–2.39)	0.007
Invasive urinary devices	9 (4.8)	2 (0.8)	4.85 (0.99–46.47)	0.031

OR, odds ratio; CI, confidence interval; UTI, urinary tract infection.

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Table II

Recent antibiotic exposure of cases and controls

Characteristic	Cases (*N* = 251)	Controls	OR (95% CI)	*P*-value
All antibiotics	188 (74.9)	142 (54.0)	2.54 (1.72–3.77)	<0.001
Aminoglycosides	32 (12.7)	15 (5.7)	2.42 (1.23–4.93)	0.006
β-Lactamase inhibitors	35 (13.9)	24 (9.1)	1.61 (0.90–2.93)	0.087
Carbapenems	6 (2.4)	3 (1.1)	2.12 (0.45–13.24)	0.280
Cephalosporins	60 (23.9)	95 (36.1)	0.56 (0.37–0.83)	0.003
Cefazolin	30 (12.0)	80 (30.4)	0.31 (0.19–0.50)	<0.001
Third and fourth generation cephalosporins[a]	32 (12.7)	23 (8.7)	1.52 (0.84–2.82)	0.142
Fluoroquinolones	97 (38.6)	6 (2.3)	26.98 (11.50–76.72)	<0.001
Penicillin	14 (5.6)	14 (5.3)	1.05 (0.45–2.43)	0.898
Macrolides	11 (4.4)	2 (0.8)	5.98 (1.28–55.90)	0.009*
Others				
Clindamycin	17 (6.8)	8 (3.0)	2.32 (0.92–6.31)	0.049
Cotrimoxazole	41 (16.3)	15 (5.7)	3.23 (1.69–6.45)	<0.001
Linezolid	6 (2.4)	3 (1.1)	2.12 (0.45–13.24)	0.280
Metronidazole	86 (34.3)	37 (14.1)	3.18 (2.02–5.06)	<0.001
Vancomycin	79 (31.5)	37 (14.1)	2.81 (1.78–4.47)	<0.001

OR, odds ratio; CI, confidence interval.

[a] Included ceftriaxone, ceftazidime and cefepime.

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Table III

Risk factors for fluoroquinolone resistance (multivariable analysis)

Risk factors	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*-value
No. of hospital days prior to UTI	1.03 (1.01–1.04)	1.01 (0.99–1.02)	0.224
Male sex	1.86 (1.26–2.74)	2.03 (1.21–3.39)	0.007
African-American	1.31 (0.91–1.91)	1.80 (1.10–2.94)	0.020
Chronic respiratory disease	3.32 (1.74–6.63)	22.58 (1.18–5.62)	0.017
Residence in a long term care facility	4.09 (1.98–9.07)	4.41 (1.79–10.88)	0.001
Previous hospitalisation within 2 weeks	2.28 (1.55–3.38)	2.19 (1.31–3.64)	0.003
Hospitalisation under a medicine service	2.34 (1.62–3.40)	2.72 (1.63–4.54)	<0.001
Recent antibiotic exposure			
Fluoroquinolones	26.98 (11.50–76.72)	15.73 (6.15–40.26)	<0.001
Cotrimoxazole	3.23 (1.69–6.45)	2.49 (1.07–5.79)	0.033
Metronidazole	3.18 (2.02–5.06)	2.89 (1.48–5.65)	0.002
Cefazolin	0.31 (0.19–0.50)	0.53 (0.29–0.97)	0.039

OR, odds ratio; CI, confidence interval; UTI, urinary tract infection.