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Gastrointestinal Tract Colonization With Fluoroquinolone-Resistant *Escherichia coli* in Hospitalized Patients: Changes Over Time in Risk Factors for Resistance

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Abstract

OBJECTIVE—The prevalence of fluoroquinolone (FQ) resistance in *Escherichia coli* has increased markedly in recent years. Despite the important role of gastrointestinal tract colonization with FQ-resistant *E. coli* (FQREC), the prevalence of and risk factors for FQREC colonization among the general hospitalized patient population have not been described, to our knowledge. The objective of this study was to identify the prevalence of and risk factors for FQREC colonization among hospitalized patients.

DESIGN—Three-year case-control study. Case patients (ie, all subjects with FQREC colonization) were compared with control patients (ie, all subjects without FQREC colonization).

SETTING—Two large medical centers within an academic health system.

PARTICIPANTS—All patients hospitalized at the 2 study hospitals.

MAIN OUTCOME MEASURE—Three annual fecal surveillance surveys were conducted. All patients colonized with FQREC (levofloxacin minimum inhibitory concentration, ≥ 8 $\mu\text{g/mL}$) were identified.

RESULTS—Of the 774 subjects, 89 (11.5%) were colonized with FQREC. Although there was a significant association between prior FQ use and FQREC colonization on bivariable analysis (odds ratio [OR], 2.02 [95% confidence interval {CI}, 1.14–3.46]; $P = .01$), there was statistically significant effect modification by year of study ($P = .005$). In multivariable analyses, after controlling for the hospital and for the duration of hospitalization prior to sampling, the association between FQ use and FQREC colonization was as follows: adjusted OR (aOR), 0.97 (95% CI, 0.29–3.23) in 2002; aOR, 1.41 (95% CI, 0.57–3.50) in 2003; and aOR, 9.87 (95% CI, 3.67–26.55) in 2004.

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CONCLUSIONS—The association between prior FQ use and FQREC colonization varied significantly by study year, suggesting that the clinical epidemiology of resistant organisms may change over time. Furthermore, in the context of recent work showing significant changes in FQREC prevalence as well as changes in FQ resistance mechanisms (specifically, efflux overexpression) over the same time period, these results suggest a previously unrecognized complexity in the relationship between the clinical and molecular epidemiology of FQ resistance.

The fluoroquinolone (FQ) antibiotics remain well-established agents in the treatment of many bacterial infections.¹ Indeed, FQs have emerged as the most commonly prescribed class of antibiotics in both ambulatory and healthcare settings.^{2,3} Recent reports have noted significant increases in the prevalence of FQ resistance in *Escherichia coli*, the most common gram-negative pathogen, over the past few years.^{4,5} These trends are concerning, given the association between FQ resistance and negative clinical outcomes,⁶ as well as the fact that FQ resistance often coexists with other resistance phenotypes (eg, extended spectrum β -lactamase resistance).^{7,8}

Elucidating the epidemiology of gastrointestinal tract colonization with FQ-resistant *E. coli* (FQREC) is critical, because the gastrointestinal tract of humans serves as a natural reservoir for *E. coli*.^{9,10} Furthermore, clinical *E. coli* isolates are almost always derived from an organism colonizing the gastrointestinal tract.^{11,12} Finally, the stepwise accumulation of FQ resistance determinants in *E. coli* (eg, in response to antimicrobial pressure) in the clinical setting likely occurs at the level of the gastrointestinal tract.¹³

We recently showed that nearly 20% of the patients at 2 hospitals within a single academic health system were colonized with *E. coli* that demonstrated reduced susceptibility to FQs.¹⁴ However, little is known regarding the determinants of gastrointestinal tract colonization with FQREC. The few studies that have sought to identify risk factors for FQREC gastrointestinal tract colonization have been limited by small sample size,^{15–18} a focus on only 1 specific setting (eg, long-term care facility residents, internal medicine wards, or outpatient children),^{15,19} and restriction to only patients with certain conditions (eg, malignancy or cirrhosis).^{16,18} With a focus on a study population for which the colonizing FQREC strains have previously been characterized,¹⁴ we sought to identify risk factors for FQREC colonization in a general hospital population.

METHODS

The study was performed at 2 hospitals within the University of Pennsylvania Health System: the Hospital of the University of Pennsylvania, an academic tertiary care medical center with 725 patient beds; and Penn Presbyterian Medical Center, a 344-bed urban community hospital. This study was reviewed and approved by the University of Pennsylvania committee on studies involving human beings.

As described elsewhere,¹⁴ we conducted 3 annual fecal surveillance surveys (2002–2004) at the 2 study hospitals. For each survey, all inpatient care areas of both hospitals, except psychiatric floors, were included. On the first day that a hospital floor was surveyed, all patients hospitalized on the floor at 8:00 AM were identified. All of these patients were considered eligible and enrolled if informed consent was provided. For patients unable to provide informed consent, a legal decision maker (eg, a family member) was sought to provide consent. For those subjects who agreed to participate, a fecal sample was obtained. The following day, any previously identified eligible subjects who had been unavailable were enrolled. Thus, each floor was surveyed over a period of 48 hours. All patient care areas at the 2 hospitals were sampled in the same manner, in sequential fashion. Each annual survey required approximately 3 months to complete. In the original surveillance surveys, a subject could be enrolled more

than once (ie, he or she could be enrolled more than once if eligible in multiple survey years). In the current study, a subject could be included only once (ie, the first time he or she was surveyed). The surveys took place from June through August in 2002, from March through May in 2003, and from January through March in 2004.

During the first annual survey, stool samples were requested for all eligible subjects. However, due to a low rate of sample collection, the method of fecal sample collection was changed to perirectal swab for the second and third annual surveys. Of note, culture of perirectal swab samples is highly sensitive and specific for detection of FQREC, compared with stool culture.²⁰ The same research nurse collected all stool samples during the first survey and all perirectal swabs throughout the second and third surveys.

Detection of fecal FQREC was performed as described elsewhere.¹⁴ Resistance to levofloxacin was used as a marker for resistance to the FQ antibiotics. *E. coli* isolates with a levofloxacin minimum inhibitory concentration of at least 8 µg/mL were considered resistant.²¹

To identify risk factors for FQREC colonization, we conducted a case-control study. All subjects with FQREC colonization were considered case patients, and all subjects for whom no FQREC were detected were considered control patients. All eligible case and control patients were included. Risk factors were assessed through the use of a comprehensive clinical and administrative health system database, which has been used effectively in previous studies.^{22–24}

Data obtained included age, sex, race, location within hospital at the time of fecal sampling, and number of hospital days and intensive care unit days prior to fecal sampling. All antimicrobial therapy administered in the 30 days prior to sampling was ascertained. Antimicrobials were categorized by class or by specific agent, if only 1 agent of a given class of antimicrobials was used.²⁵ Agents with antianaerobic activity were also assessed as a group.²⁵ The presence of the following comorbid conditions at the time of sampling was documented: anemia (indicated by a hemoglobin level of <10 g/dL), malignancy, diabetes mellitus, renal insufficiency (indicated by a creatinine level of >2 mg/dL or the requirement of dialysis), HIV infection, and neutropenia. Finally, the Charlson comorbidity index was calculated for each subject.²⁶

Statistical Methods

Bivariable analyses were conducted to determine the association between potential risk factors and FQREC colonization, with a focus on the relationship between FQ use and FQREC colonization as the primary association of interest. Categorical variables were compared using the Fisher exact test. An odds ratio (OR) and a 95% confidence interval (CI) were calculated to evaluate the strength of any association. Continuous variables were compared using the Student *t* test or the Wilcoxon rank-sum test, depending on the validity of the normality assumption.²⁷

Stratified analyses were then performed to identify where data were sparse and to elucidate where confounding and interactions with prior FQ exposure were likely to exist in the multivariable analysis. We explored the effect of stratifying by sex, hospital (Hospital of the University of Pennsylvania or Penn Presbyterian Medical Center), and year of study (2002, 2003, or 2004) on the association between FQ use and FQREC colonization. Interaction was assumed to be present when the results of the test for heterogeneity between the ORs for different strata were statistically significant ($P < .05$); the Mantel-Haenszel test for summary statistics was used to evaluate the effects of each variable of interest as a possible confounder.²⁸

Multivariable analysis was performed using multiple logistic regression.²⁹ Building of the multivariable model began with inclusion of the key variable of interest (ie, prior FQ use). All variables with a *P* value of less than .20 on bivariable analyses were considered for inclusion in a multivariable explanatory model,³⁰ as were variables noted to be confounders of the FQ exposure variable on stratified analysis. A variable remained in the final model if its inclusion resulted in more than a 15% change in the effect size for the primary association of interest (ie, FQ use and FQREC colonization).³¹ Colinearity and interaction between risk factor variables were also investigated.

For all calculations, a 2-tailed *P* value of less than .05 was considered significant. All statistical calculations were performed using standard programs in Stata, version 9.0 (StataCorp).

RESULTS

Over the 3-year study period, a total of 1,360 hospitalized patients were approached to enroll in the study. Of these patients, 789 (58.0%) provided consent and had a swab sample collected. As noted previously, there were no significant differences between eligible patients who enrolled in the study, compared with those who did not, except that participants were significantly older than nonparticipants (median age, 62 years vs 56 years).¹⁴ Of these 789 subjects, there were 15 who were included twice (ie, during surveillance sweeps in different years). Since only the first sample for each subject was included, a total of 774 unique subjects were included.

The median age among all 774 subjects was 62 years (interquartile range [IQR], 49–73 years), and 417 (53.9%) were male. Of the 774 total subjects, 446 (57.6%) were white, 273 (35.3%) were African-American, 9 (1.2%) were Asian, 5 (0.6%) were Latino, and 41 (5.3%) were of unknown race or ethnicity. Five hundred eighty-five patients (75.6%) were hospitalized at the Hospital of the University of Pennsylvania, and 189 (24.4%) were hospitalized at Penn Presbyterian Medical Center. At the time of study enrollment, the geographic locations of hospitalized subjects were as follows: medical floor, 245 (31.7%); surgical floor, 165 (21.3%); oncology floor, 89 (11.5%); medical and/or cardiac intensive care unit, 78 (10.1%); surgical intensive care unit, 63 (8.1%); rehabilitation floor, 42 (5.4%); transplantation floor, 39 (5.0%); neurology floor, 38 (4.9%); and obstetrics/gynecology, 15 (1.9%).

Of the 774 subjects, 89 (11.5%) were colonized with FQREC. By year, the prevalence of FQREC among fecal samples was: 15.9% (26 of 164) in 2002; 11.3% (39 of 346) in 2003; and 9.1% (24 of 264) in 2004 (*P* = .04, χ^2 test for trend). Of note, the prevalence of FQ resistance among *E. coli* isolates in clinical cultures increased steadily at both hospitals during this same time period.

On bivariable analyses, several variables were noted to be significantly associated with FQREC colonization (Table 1). FQ use within the prior 30 days was associated with FQREC colonization (OR, 2.02 [95% CI, 1.14–3.46]; *P* = .01). Although the use of several other antibiotics was also associated with FQREC colonization, use of an agent with antianaerobic activity was not (OR, 0.99 [95% CI, 0.58–1.62]; *P* > .99). Furthermore, there was no association between overall antibiotic use and FQREC colonization; the median number of antibiotic days for case patients was 2 (IQR, 0–16 antibiotic days) and for control patients was 2 (IQR, 0–8.5 antibiotic days) (*P* = .30). Neither the Charlson score (*P* = .35) nor the number of days in the intensive care unit within the previous 30 days (*P* = .55) was associated with FQREC colonization.

On stratified analysis, there was significant effect modification by year of study (*P* = .005), with a significant association between prior FQ use and FQREC colonization for subjects enrolled in 2004 but not for subjects enrolled in 2002 or 2003. The association between FQ

use and FQREC colonization in the 3 study years was as follows: OR, 0.75 (95% CI, 0.17–2.47) in 2002; OR, 1.43 (95% CI, 0.53–3.43) in 2003; and OR, 6.68 (95% CI, 2.42–17.86) in 2004.

On multivariable analysis, prior FQ use remained an independent risk factor for FQREC colonization, but this association varied significantly by year of enrollment (Table 2). After controlling for the hospital and the duration of hospitalization prior to sampling, the association between FQ use and FQREC colonization was as follows: adjusted OR (aOR), 0.97 (95% CI, 0.29–3.23), $P = .96$, in 2002; aOR, 1.41 (95% CI, 0.57–3.50), $P = .46$, in 2003; and aOR, 9.87 (95% CI, 3.67–26.55), $P < .001$, in 2004.

To explore possible explanations for the changes in the association between FQ use and FQREC colonization over time, we evaluated the potential impact of the underlying FQ resistance mechanism(s). The most common mechanism of FQ resistance in *E. coli* is chromosomal mutation of the genes that encode the 2 FQ target enzymes (ie, DNA gyrase and topoisomerase IV).^{32,33} Another mechanism of FQ resistance is increased drug efflux via the AcrAB efflux pump.^{32,33} As noted previously, the resistance mechanism(s) of the FQREC isolates recovered from subjects included in this study were characterized as part of a previous descriptive molecular epidemiological study.¹⁴ In that study, it was noted that the proportion of isolates that demonstrated efflux overexpression as a mechanism of FQ resistance varied significantly across study years (ie, 48.6% in 2002, 47.7% in 2003, and 22.4% in 2004; $P = .01$). To elucidate whether these temporal changes in underlying FQ resistance mechanisms might explain our findings of changes in risk factors over the same time period, we conducted 2 subanalyses in which case patients were divided on the basis of whether the colonizing isolate demonstrated efflux overexpression, as measured indirectly by the organic solvent tolerance assay.^{34,35} Case patients with FQREC isolates that exhibited efflux overexpression were compared with all control patients. Separately, case patients with FQREC isolates that did not exhibit efflux overexpression were compared with control patients. The results of the final multivariable models for both of these subanalyses did not differ substantively from the results of the primary model. For both models, FQ use remained a significant risk factor for FQREC colonization in 2004 only, after adjustment for the hospital and the duration of hospitalization prior to sampling.

DISCUSSION

In this 3-year, health system–wide study involving 774 patients, we found that 89 (11.5%) were colonized with FQREC. Although there was a significant association between prior FQ use and FQREC colonization on bivariable analyses, there was significant effect modification by year of study. In the final multivariable model controlling for the hospital and the duration of hospitalization prior to sampling, the association between FQ use and FQREC colonization was statistically significant for subjects enrolled in 2004 but not for subjects enrolled in 2002 and 2003. Notably, the overall prevalence of FQREC carriage was lowest in 2004.

Among the 774 subjects, 89 (11.5%) were colonized with FQREC. Of note, the overall prevalence of FQ resistance among clinically obtained isolates of *E. coli* at the 2 hospitals during the same 3-year period was 10.2% (971 of 9,515 isolates were FQ resistant). Although this relationship has not been previously investigated, these data demonstrate that the prevalence of FQ resistance is similar between colonizing isolates and clinical isolates.

Findings regarding the association between prior FQ use and FQREC colonization have been inconsistent across past studies. FQ use has been previously found to be associated with FQREC colonization in some studies.^{15,17,18} In contrast, others have not found an association between prior FQ use and FQREC colonization,^{16,19} although many studies may have been

underpowered to demonstrate such an association. Our finding, in a much larger study cohort, of an association between FQ use and FQ resistance is consistent with studies that focused on clinical *E. coli* infections that also demonstrated such an association.³⁶ The importance of more clearly defining this association is seen in recent data that show that FQs are the most commonly prescribed class of antibiotics in the outpatient and emergency department settings.³ Furthermore, numerous studies that found that FQs are often prescribed outside of guidelines^{3,37} suggest that there is much room for improvement in how FQs are used.

We noted that the association between FQ use and FQREC colonization varied significantly across study years. Although an outbreak of a specific *E. coli* strain might be one explanation for this finding, analysis of FQREC isolates from patients included in this study, by means of pulsed-field gel electrophoresis, revealed no evidence for clonal dissemination.¹⁴ Similarly, there were no substantive changes in the antimicrobial formulary or infection control protocols in the 2 hospitals during the study (another possible explanation of these results). Finally, the 3 surveillance surveys were not conducted at exactly the same time in each year. It is conceivable that these differences (perhaps through seasonal variation in antimicrobial use patterns) may have influenced FQ resistance mechanisms. Future studies should confirm these changes in the epidemiology of FQREC over time and investigate whether similar patterns occur for other antimicrobial-resistant organisms.

Another possible explanation for the differences in the clinical epidemiology of FQREC colonization across study years is that they may reflect underlying differences in the resistance mechanism(s) of the colonizing FQREC isolates over time. In assessing the findings of the current study in the context of prior work,¹⁴ it is apparent that prior FQ use was only associated with FQREC colonization during the year in which efflux overexpression was a less common mechanism of FQ resistance (ie, 2004). Overexpression of efflux pumps can be elicited by many products (eg, various antibiotics, detergents, or dyes),³⁸ and our results suggest that when efflux overexpression is less prevalent, FQ use (which elicits resistance primarily through mutations in the DNA gyrase and topoisomerase IV genes)³³ may assume a more prominent role in conferring FQ resistance. However, our subanalyses in which isolates that did and isolates that did not demonstrate efflux overexpression were analyzed separately revealed results similar to those of the primary analyses. Paterson³⁹ has suggested that, although a group of resistant organisms may appear similar phenotypically, they may harbor different mechanisms of resistance, and that different antibiotics may select for different mechanisms of resistance. Elucidating these complexities in the evolution of resistance is critical in better understanding the emergence of resistant organisms.⁴⁰⁻⁴¹

A final possible explanation for the temporal changes noted in our study is that as the prevalence of FQREC goes up in a hospital, individual-level exposure to FQs may become less important. However, as FQREC prevalence becomes less common, individual-level selection is more significant, since patients are less likely to acquire FQREC from other patients or the environment. Indeed, in the final year of this study, when prevalence of FQREC colonization was lowest, the association between FQ use and FQREC colonization was strongest.

Our study had several potential limitations. Although selection bias is of potential concern, we sought to enroll all eligible subjects. Although only approximately 60% of eligible subjects were enrolled, participants and nonparticipants were similar (except with respect to median age), suggesting no substantial bias introduced by nonparticipation. Misclassification bias was also reduced because antibiotic susceptibility profiles had been completed prior to initiation of the study, so that the distinction between case patients and control patients could not have influenced the identification of antibiotic resistance patterns. Furthermore, our inability to access data on outpatient antibiotic use raises the possible concern for misclassification of the exposure. In addition, the potential for uncontrolled confounding exists, because certain

variables (eg, presence of diarrhea or indwelling devices) were not assessed. Finally, our study was conducted in a large tertiary care medical center and a smaller urban community hospital; the results may not be generalizable to other dissimilar institutions.

In conclusion, we found that 11.5% of hospitalized patients were colonized with FQREC, which is similar to the prevalence of FQ resistance noted in clinical *E. coli* isolates. The association between prior FQ use and FQREC colonization varied significantly by study year, suggesting that the clinical epidemiology of resistant organisms may change over time. Finally, in the context of recent work that shows significant changes in FQREC prevalence as well as changes in FQ resistance mechanisms (specifically efflux overexpression) over the same time period, these results reveal a complex relationship between the clinical and the molecular epidemiology of FQ resistance.

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TABLE 1

Results of Bivariable Analysis of Risk Factors for Colonization With Fluoroquinolone-Resistant *Escherichia coli*

Variable	Case patients (n = 89)	Control patients (n = 685)	OR (95% CI)	P
Age, median (IQR), years	66 (54–74)	61 (49–73)		.07
Male sex	54 (60.7)	363 (52.9)	1.37 (0.85–2.22)	.18
White race	38 (42.7)	408 (59.6)	0.51 (0.31–0.81)	.003
Stay at Penn Presbyterian Medical Center ^a	27 (30.3)	162 (23.7)	1.41 (0.83–2.33)	.19
Time from admission to sampling, median (range), days	6.5 (2–17)	4 (2–9)		.03
Comorbidities				
Diabetes	33 (37.1)	187 (27.3)	1.57 (0.96–2.54)	.06
HIV infection	4 (4.5)	3 (0.4)	10.7 (1.77–73.82)	.004
Renal insufficiency	15 (16.9)	69 (10.1)	1.81 (0.91–3.40)	.07
Steroid use	26 (29.2)	136 (19.9)	1.67 (0.97–2.78)	.05
Antimicrobial use in prior 30 days				
Fluoroquinolone	23 (25.8)	101 (14.7)	2.02 (1.14–3.46)	.01
TMP-SMZ	14 (15.7)	68 (9.9)	1.69 (0.84–3.23)	.10
Extended-spectrum cephalosporin ^b	19 (21.4)	94 (13.7)	1.71 (0.93–3.02)	.08

NOTE. Data are no. (%) of patients, unless otherwise indicated. Only variables with $P < .20$ are shown. The Fisher exact test was used for categorical variables and the Wilcoxon rank-sum test for continuous variables. CI, confidence interval; IQR, interquartile range; OR, odds ratio; TMP-SMZ, trimethoprim-sulfamethoxazole.

^a As opposed to the Hospital of the University of Pennsylvania.

^b Ceftriaxone, ceftazidime, or cefepime.

TABLE 2

Multivariable Model of Risk Factors for Colonization With Fluoroquinolone (FQ)–Resistant *Escherichia coli*

Variable	Regression coefficient (SE)	Adjusted OR (95% CI)	P
Intercept	−2.16 (0.31)		<.001
FQ use in prior 30 days ^a	−0.03 (0.61)	0.97 (0.29–3.23)	.96
Greater median time from admission to sampling ^b	0.02 (0.01)	1.02 (1.01–1.03)	.003
Stay at Penn Presbyterian Medical Center ^c	0.94 (0.30)	2.56 (1.41–4.64)	.002
Year of enrollment ^d			
2003	−0.32 (0.34)	0.72 (0.37–1.42)	.35
2004	−1.22 (0.43)	0.30 (0.13–0.69)	.005
Interaction between FQ use and enrollment			
In 2003	0.37 (0.75)	1.45 (0.33–6.33)	.62
In 2004	2.31 (0.78)	10.16 (2.21–46.64)	.003

NOTE. CI, confidence interval; OR, odds ratio; SE, standard error.

^a Coefficient and OR reflect those subjects enrolled in 2002.^b Coefficient and OR associated with each increase of 1 hospital day.^c As opposed to the Hospital of the University of Pennsylvania.^d Coefficient and OR reflect those subjects without prior FQ use.