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Impact of Antibiotic Use during Hospitalization on the Development of Gastrointestinal Colonization with *Escherichia coli* with Reduced Fluoroquinolone Susceptibility

Jennifer H. Han, MD, MSCE[1,2,3], **Warren B. Bilker, PhD**[2,3], **Irving Nachamkin, DrPH, MPH**[4], **Pam Tolomeo, MPH**[2], **Xiangqun Mao, PhD**[4], **Neil O. Fishman, MD**[1], and **Ebbing Lautenbach, MD, MPH, MSCE**[1,2,3]

[1]Division of Infectious Diseases, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[2]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania

[3]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania

[4]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

OBJECTIVE—Infections due to fluoroquinolone-resistant *Escherichia coli* (FQREC) are associated with significant morbidity and mortality. Fluoroquinolone resistance likely arises at the level of gastrointestinal colonization. The objective of this study was to identify risk factors for the development of FQREC gastrointestinal tract colonization in hospitalized patients, including the impact of antibiotics prescribed during hospitalization.

DESIGN—A prospective cohort study was conducted from 2002 to 2004 within a university health system.

METHODS—Hospitalized patients initially colonized with fluoroquinolone-susceptible *E. coli* were followed up with serial fecal sampling for new FQREC colonization or until hospital discharge or death. A Cox proportional hazards regression model was developed to identify risk factors for new FQREC colonization, with antibiotic exposure modeled as time-varying covariates.

RESULTS—Of 395 subjects, 73 (18.5%) became newly colonized with FQREC. Length of stay before sampling (hazard ratio [HR], 1.02 [95% confidence interval (CI), 1.1–1.03]; $P = .003$) and malignancy (HR, 0.37 [95% CI, 0.21–0.67]; $P = .001$) were significantly associated with the

Address correspondence to Jennifer H. Han, MD, MSCE, Division of Infectious Diseases, Department of Medicine, Hospital of the University of Pennsylvania, 3400 Spruce Street, 3rd Floor, Silverstein Building, Suite E, Philadelphia, PA 19104 (jennifer.han@uphs.upenn.edu)..

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development of FQREC colonization. In addition, receipt of a first-generation cephalosporin (HR, 1.19 [95% CI, 1.10–1.29]; $P < .001$) or cefepime (HR, 1.05 [95% CI, 1.00–1.10]; $P = .048$) during hospitalization increased the risk of new FQREC colonization.

CONCLUSIONS—The acquisition of FQREC in the hospital setting is complex, and antimicrobial stewardship programs should take into account patterns of antibiotic use in implementing strategies to reduce the development of new FQREC colonization. Future studies are needed to identify risk factors for infection in hospitalized patients newly colonized with FQREC.

Since the introduction of ciprofloxacin in 1987, fluoroquinolones have rapidly become one of the most commonly prescribed classes of antibiotics.[1] However, along with increases in fluoroquinolone (FQ) use, the prevalence of FQ-resistant organisms, particularly *Escherichia coli*, has significantly increased in both the healthcare and community setting.[2] Infections due to FQ-resistant *E. coli* (FQREC) have been associated with poor clinical outcomes, including greater mortality,[3,4] and represent a major public health threat.

The emergence of FQ resistance in *E. coli* occurs as a multistep process, with increasing numbers of target gene mutations leading to progressively higher FQ minimum inhibitory concentrations (MICs).[5–7] Studies have demonstrated that gastrointestinal tract colonization with FQREC may develop in response to antibiotic exposure,[8,9] such that *E. coli* isolates causing clinical infections are most often derived from colonizing organisms. Despite this, the majority of studies evaluating risk factors for acquisition of FQREC have focused on clinical isolates causing infection.[10–19] A smaller number of studies[9,20–24] have evaluated risk factors for gastrointestinal tract colonization with FQREC in hospitalized patients. However, only a few of these studies[9,22,24] have focused on risk factors for the acquisition of FQREC in patients initially colonized with FQ-susceptible *E. coli* (FQSEC), despite the fact that risk factors for baseline FQREC colonization near the time of admission are likely to differ from those for nosocomial acquisition. These studies were limited by small sample sizes,[9,22,24] lack of multivariable analysis,[24] and evaluation of acquisition of any FQ-resistant gram-negative organism,[9,22] with *Pseudomonas aeruginosa* predominating among the colonizing FQ-resistant isolates. Furthermore, although exposure to antibiotics is one of the most readily modifiable risk factors for the acquisition of FQREC in the hospital setting, earlier studies have focused on the dichotomous administration of antibiotics[9,20,21] or formulary changes[22] rather than the more complex patterns of use that occur in the hospital setting.

Evaluating risk factors for the acquisition of FQREC in patients initially colonized with FQSEC is critical for informing potential interventions to limit the emergence of FQREC in the hospital setting. Furthermore, elucidation of the selection pressure exerted by the time-varying use of antibiotics will be critical in the development of effective antimicrobial stewardship strategies. Therefore, we conducted this study to identify risk factors for the development of FQREC gastrointestinal tract colonization in hospitalized patients, including the impact of patterns of antibiotic prescription during hospitalization.

PATIENTS AND METHODS

Study Design and Setting

A prospective cohort study was conducted at 2 hospitals in the University of Pennsylvania Health System (UPHS) in Philadelphia: hospital 1, a 725-bed academic tertiary care medical center, and hospital 2, a 344-bed urban community hospital. Three hospital-wide annual fecal surveillance surveys were conducted at hospital 1 and hospital 2, as previously described,[20,25] during the years 2002, 2003, and 2004. For this study, target units were selected on the basis of high prevalence rates of FQREC as previously determined by the annual surveys (4 units at hospital 1 and 2 units at hospital 2).

Target units were surveyed over a 3-month period, with all patients admitted to the unit eligible for inclusion in our study cohort. On the first day of a unit survey, all patients hospitalized on the unit by 8:00 am were identified and approached for informed consent. For patients unable to provide informed consent, a legal decision maker (eg, family member) was approached for informed consent. Fecal samples were obtained from patients who provided informed consent and submitted to the Hospital of the University of Pennsylvania Clinical Microbiology Laboratory for processing. Study patients were followed up longitudinally and continued to have fecal samples submitted every 48–72 hours until the time of hospital discharge or death. New patients admitted to the unit during the survey period were also eligible to be enrolled in the study. At the end of the 3-month enrollment period, all patients currently undergoing surveillance continued to be followed up until the time of hospital discharge or death. However, no new patients were enrolled during the third month of the survey to allow for complete follow-up of all patients already enrolled. Each patient was included as a subject only once, with only the first episode of eligibility included. The study was approved by the institutional review board of the University of Pennsylvania.

Study Population

The source population for the present study consisted of all patients who were determined to be colonized with FQ-susceptible *E. coli* on the initial surveillance culture. These patients were subsequently followed up with serial fecal samples obtained every 48–72 hours as described until recovery of FQREC or discharge or death.

Microbiological Methods

Detection of *E. coli* with reduced FQ susceptibility from fecal samples was performed as previously described,[20,25] with levofloxacin used as a marker for susceptibility to FQs. Isolates with MICs in the susceptible but elevated range (ie, reduced FQ susceptibility) may harbor mutations in FQ target genes and, given the multistep nature of development of FQ resistance, are critical in explaining the emergence of FQ resistance.[5–7,26] Therefore, for the present study, FQ resistance was defined as a levofloxacin MIC greater than or equal to 0.25 μg/mL.[25]

Data Collection

Data were abstracted from the Pennsylvania Integrated Clinical and Administrative Research Database,[27,28] which includes demographic, laboratory, pharmacy, and billing information. The following data were collected for all patients: demographic characteristics, surveillance year, hospital of admission, transfer from another institution or nursing home, admissions to UPHS in the 30 days before sampling, service location at the time of sampling (ie, medicine vs surgery), and hospital length of stay before the initial surveillance culture. Data on comorbid conditions were also ascertained at the time of the sampling, including diabetes mellitus, malignancy, renal insufficiency (creatinine level ≥2.0 mg/dL or receiving dialysis), hepatic dysfunction (eg, cirrhosis), human immunodeficiency virus infection, solid organ or hematopoietic stem cell transplant, neutropenia (absolute neutrophil count, <500 neutrophils/mm^3), significant cardiovascular disease (eg, severe congestive heart failure), significant respiratory disease (eg, severe chronic obstructive pulmonary disease and chronic bronchitis), and any surgical procedure performed in the 30 days before sampling. Data on the presence of a urinary catheter, central venous catheter, or diarrhea before the initial surveillance culture were collected for all patients. Furthermore, data on the receipt of corticosteroids or other immunosuppressive agents in the 30 days before fecal sampling were documented.

Assessment of Antibiotic Exposures

Data were obtained on all antibiotics administered from the initial surveillance culture to new FQREC colonization or discharge or death (ie, the time at risk). For the purposes of analysis, antibiotics were categorized by class or by specific agent, if only one agent of a given class was used, as follows: levofloxacin, cefepime, vancomycin, aminoglycosides (ie, gentamicin and tobramycin), piperacillin-tazobactam, nafcillin, other penicillins (ie, amoxicillin-clavulanate and ampicillin-sulbactam), first-generation cephalosporins (ie, cephalexin and cefazolin), trimethoprim-sulfamethoxazole, doxycycline, metronidazole, imipenem, and clindamycin. Antibiotics were subsequently assessed as time-varying covariates (exposed vs nonexposed on a given day).

Statistical Analysis

Standard methods of survival analysis were used to determine the association between potential risk factors and time to development of colonization with FQREC. Time zero for all patients was defined as the day of the initial surveillance culture. Bivariable analyses were performed to evaluate risk factors for development of new FQREC colonization during hospitalization using Kaplan-Meier product-limit survival curve estimates and the log rank statistic for the comparison of multiple survival curves. Multivariable analyses were subsequently performed using Cox proportional hazards regression analyses with antibiotic exposure modeled as time-varying covariates to account for different timing and durations of therapy. A stepwise selection procedure was used, with variables with *P* values less than .20 on bivariable analyses considered as candidate variables and maintained in the final model if their inclusion was statistically significant on likelihood ratio testing.[29] Hospital length of stay before the initial sample was retained a priori in the model regardless of its

significance on bivariable analyses given its clinical importance. A hazard ratio (HR) and 95% confidence interval (CI) were calculated to evaluate the strength of any association.

For all calculations, a 2-tailed *P* value less than .05 was considered to be significant. All statistical calculations were performed using commercially available software (Stata, ver 11.0; StataCorp).

RESULTS

Study Population

During the 3-year study period, a total of 522 (44.0%) of 1,186 patients who were approached for enrollment provided informed consent. There were no significant differences with regard to mean age, race and ethnicity, year of enrollment, and hospital of admission when comparing patients who did and did not enroll in the study. A total of 516 patients had initial fecal cultures positive for *E. coli*, of which 451 (87.4%) were FQ-susceptible (levofloxacin MIC, <0.25 μg/mL). Of these 451 patients who were colonized with FQSEC, 395 underwent subsequent serial sampling during hospitalization (ie, had at least 1 sample following the initial surveillance culture) and represented the primary study cohort. The mean age (± standard deviation [SD]) of patients was 62 ± 15.6 years, and 216 (54.7%) were male. Of the 395 patients, 239 (60.5%) were white, 131 (33.2%) were Black, 4 (1.0%) were Asian, 2 (0.5%) were Hispanic, and the remainder were self-identified as “other.” A total of 320 patients (81.0%) were hospitalized at hospital 1, whereas 75 (19.0%) were hospitalized at hospital 2. Finally, of the 395 patients, a total of 284 (71.9%) received at least 1 day of an antibiotic during the sampling period. The most commonly prescribed antibiotics after the initial surveillance culture were vancomycin (*n* = 92; 23.3%), cefepime (*n* = 86; 21.8%), metronidazole (*n* = 86; 21.8%), levofloxacin (*n* = 81; 20.5%), and a first-generation cephalosporin (*n* = 59; 14.9%).

Microbiological Results

Of the 395 patients initially colonized with FQSEC who underwent serial sampling, 73 (18.5%) patients developed colonization with FQREC during hospitalization. Of these, 36 patients had an isolate with high-level FQ resistance (levofloxacin MIC, ≥8 μg/mL), and 37 patients had an isolate with low-level FQ resistance (levofloxacin MIC, ≥0.25 μg/mL but <8.0 μg/mL). The mechanisms of resistance of these isolates have been previously described.[30] Finally, there was no evidence of clonal relatedness of the 73 unique FQREC isolates based on molecular typing by pulsed-field gel electrophoresis (PFGE).

Risk Factors for the Development of FQREC Colonization

A total of 73 patients (18.5%) had a subsequent culture positive for FQREC. The median time to the isolation of FQREC among these patients was 7 days (interquartile range [IQR], 4–16). In bivariable analyses, several variables were noted to be significantly associated with acquisition of FQREC colonization (Table 1). For example, patients who developed FQREC colonization, compared with those who remained colonized with FQSEC, were more likely to have been hospitalized at hospital 2 (23.3% vs 18.0%; $P < .001$), been admitted from a nursing home (6.9% vs 5.0%; $P = .02$), and had a central venous catheter

present before sampling (23.3% vs 18.0%; $P = .02$). In addition, patients who developed new FQREC colonization, compared with those who remained colonized with FQSEC during the sampling period, had greater exposure to cefepime (median, 7 days [IQR, 5–10] vs 4.5 days [IQR, 2–8.5]) and a first-generation cephalosporin (median, 5 days [IQR, 2–8] vs 3 days [IQR, 2–5]).

On multivariable analysis using Cox proportional hazards regression (Table 2), risk factors for acquisition of FQREC included duration of hospitalization before the initial sample (HR, 1.02 [95% CI, 1.01–1.03]; $P = .003$) and admission to hospital 2 (HR, 2.05 [95% CI, 1.12–3.74]; $P = .02$). Malignancy was protective against the development of FQREC colonization (HR, 0.37 [95% CI, 0.21–0.67]; $P = .001$). Finally, after controlling for confounders, the receipt of cefepime (HR, 1.05 [95% CI, 1.00–1.11]; $P = .048$) or a first-generation cephalosporin (HR, 1.19 [95% CI, 1.10–1.29]; $P < .001$) during hospitalization was associated with an increased risk of acquisition of FQREC. The receipt of FQ was not significant in the final model (HR, 0.99 [95% CI, 0.94–1.06]; $P = .86$).

DISCUSSION

In this 3-year prospective cohort study, we found that a total of 73 patients (18.5%) became newly colonized with FQREC during hospitalization. Risk factors for the acquisition of FQREC in patients initially colonized with FQSEC included duration of hospitalization and admission to 1 of 2 study hospitals. Furthermore, the receipt of cefepime or a first-generation cephalosporin during hospitalization, measured as time-varying exposures, increased the risk of FQREC acquisition.

Numerous studies evaluating risk factors for FQ resistance in *E. coli* clinical isolates have implicated previous FQ use,[10–19] both as prophylaxis and as treatment. However, the emergence of FQ resistance in *E. coli* is likely to occur at the level of gastrointestinal tract colonization, and risk factors for FQREC, including antibiotic selection pressure, may differ depending on assessment of colonizing *E. coli* versus clinical isolates. Indeed, in our study and others,[9,21,22,24] previous FQ use was not identified as a risk factor for FQREC colonization in hospitalized patients. In particular, it is possible that, rather than driving the emergence of FQREC through de novo mutations in existing colonizing FQSEC, antibiotic exposures during hospitalization may select for FQREC isolates that were present at low numbers in patients colonized with multiple strains. The results of our study are further strengthened by the large sample size, evaluation solely of *E. coli* versus multiple gram-negative organisms (ie, for which different risk factors for resistance may exist), and evaluation of antibiotics received in the hospital setting as time-varying covariates versus dichotomous variables.

A novel finding of our study was that acquisition of FQREC colonization was associated with prescription of cefepime and first-generation cephalosporins after initial colonization with FQSEC. An earlier study[22] evaluating the effect of a hospital-wide formulary change from ciprofloxacin to levofloxacin identified exposure to aminoglycosides and ceftazidime as risk factors for the development of colonization with FQ-resistant gram-negative organisms (eg, *P. aeruginosa* and *E. coli*). However, antibiotic exposures in this study were

evaluated as dichotomous variables (ie, exposure was evaluated as yes vs no). The use of different methods of describing previous antibiotic exposure (ie, dichotomous vs continuous) has been shown to substantially impact the identification of risk factors for antibiotic-resistant organisms,[31] and we sought to more fully characterize the complex patterns of exposure that occur after hospital admission by modeling antibiotic use as time-varying covariates.

The mechanism as to why the prescription of cephalosporins (no patients received ceftriaxone or ceftazidime in this study) was associated with isolation of FQREC is unclear, but it is possible that the use of antibiotics that are frequently active against the susceptible but not the resistant form of the organism (in particular, the first-generation cephalosporins) may have selected for emergence of colonizing FQREC isolates. Earlier studies have demonstrated high rates of co-resistance to other antibiotics in FQREC,[25,32–34] particularly in isolates with efflux pump overexpression as the predominant mechanism of resistance. Indeed, in a study evaluating risk factors for efflux pump overexpression in FQREC,[35] the receipt of a first-generation cephalosporin was identified as a significant risk factor on multivariable analysis. In a case-case-control study evaluating the association between FQ use and isolation of FQ-resistant *E. coli* and *Klebsiella pneumoniae*,[36] previous exposure to any cephalosporin (eg, narrow spectrum or extended spectrum) was protective against isolation of FQ-susceptible organisms. Therefore, while the exact mechanisms leading to this association need to be further elucidated, consideration of this finding will be important in the implementation of antibiotic stewardship measures, particularly in institutions with high rates of cephalosporin use.

The results of our study also demonstrated a protective effect of malignancy on acquisition of FQREC, possibly due to the majority of oncology patients being hospitalized at hospital 1 versus hospital 2. Along these lines, hospitalization at hospital 2 was associated with a significantly increased risk of FQREC acquisition on multivariable analysis. It is possible that this association may reflect differences in the local resistance profiles for the specific catchment areas of the 2 hospitals. Furthermore, although the results of PFGE testing did not demonstrate any clonal relatedness that would suggest an outbreak of a specific strain (ie, confined to a single hospital), it is possible that increased patient-to-patient or health-care-worker-to-patient spread in a smaller hospital may have been a mediator of this association.

There are several potential limitations of this study. Selection bias is a potential concern, because only ~45% of eligible subjects were enrolled. However, participants and nonparticipants were similar in regard to demographic characteristics, year of enrollment, and hospital of admission. In addition, sampling variability may have limited the detection of colonizing FQREC isolates from a single patient, particularly those present in low numbers. Finally, this study was conducted in a single healthcare system, and these results may not be generalizable to other institutions with differing characteristics.

In conclusion, our study demonstrated a relatively high incidence of nearly 20% for new colonization with FQREC in the hospital setting. We found that the use of cefepime or a first-generation cephalosporin conferred an increased risk of colonization with FQREC in hospitalized patients initially colonized with FQSEC. The results of our study also highlight

the importance of assessing risk factors for the development of colonization and infection with FQREC independently. The development of FQ resistance in *E. coli* is complex, and future studies will need to focus on the evaluation of strategies to limit the spread of these increasingly prevalent organisms as well as risk factors for subsequent infection in patients with acquisition of FQREC in the hospital setting.

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TABLE 1

Characteristics Associated with the Development of Fluoroquinolone-Resistant *Escherichia coli* Colonization in Hospitalized Patients

Variable	FQREC negative (*n* = 322)	FQREC positive (*n* = 73)	*P*
Mean age (±SD), years	61.3 ± 15.1	63.2 ± 17.6	.31
Female sex	142 (44.1)	37 (50.7)	.26
Nonwhite race	124 (38.5)	32 (43.8)	.05
Surgical service	72 (22.4)	12 (16.4)	.02
LOS before the initial sample, days, median (IQR)	2 (1–5)	5 (1–12)	<.001
Hospital 2	58 (18.0)	17 (23.3)	<.001
Year of culture			
2002 (reference)	97 (30.1)	32 (43.8)	
2003	225 (69.9)	41 (56.2)	.02
Admitted from nursing home	16 (5.0)	5 (6.9)	.02
Transferred from another hospital	43 (13.4)	14 (19.2)	.77
UPHS admission in previous 30 days	99 (30.8)	27 (37.0)	.98
Urinary catheter	132 (41.0)	37 (50.7)	.25
Mechanical ventilation	45 (14.0)	18 (24.7)	.63
Central venous catheter	153 (47.5)	41 (56.2)	.02
Diarrhea present	11 (3.4)	8 (11.0)	.53
Diabetes mellitus	77 (23.9)	16 (21.9)	.61
Neutropenia	9 (3.1)	0 (0.0)	.13
Hepatic dysfunction	11 (3.4)	4 (5.5)	.66
Severe cardiovascular disease	44 (13.7)	8 (11.0)	.90
Severe respiratory disease	40 (12.4)	7 (9.6)	.36
HIV infection	6 (1.9)	2 (2.7)	.02
Malignancy	147 (45.4)	18 (24.7)	<.001
Receipt of transplant	19 (6.1)	6 (8.7)	.69
Renal insufficiency	46 (14.3)	13 (17.8)	.59
Surgical procedure in previous 30 days	56 (17.4)	21 (28.8)	.20
Receipt of corticosteroids in previous 30 days	43 (13.4)	10 (13.7)	.78

NOTE. Data are no. (%) of patients, unless otherwise indicated. FQREC, fluoroquinolone-resistant *E. coli*; HIV, human immunodeficiency virus; IQR, interquartile range; LOS, length of stay; SD, standard deviation; UPHS, University of Pennsylvania Health System.

TABLE 2

Multivariable Cox Proportional Hazards Regression Model of Risk Factors Associated with Fluoroquinolone-Resistant *Escherichia coli* Colonization in Hospitalized Patients

Variable	HR (95% CI)	*P*
LOS before the initial sample	1.02 (1.01–1.03)	.003
Admission to hospital 2	2.05 (1.12–3.74)	.02
Central venous catheter	0.67 (0.40–1.13)	.13
Malignancy	0.37 (0.21–0.67)	.001
Receipt of cefepime[a]	1.05 (1.00–1.10)	.048
Receipt of a first-generation cephalosporin[a,b]	1.19 (1.10–1.29)	<.001

NOTE. CI, confidence interval; HR, hazard ratio; LOS, length of stay.

[a]Modeled as a time-varying covariate.

[b]Cefazolin and cephalexin.