MAJOR ARTICLE

# Risk Factors for the Development of Gastrointestinal Colonization With Fluoroquinolone-Resistant *Escherichia coli* in Residents of Long-Term Care Facilities

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***Background.*** The objective of this study was to assess risk factors for the development of fluoroquinolone (FQ)–resistant *Escherichia coli* gastrointestinal tract colonization in long-term care facility (LTCF) residents.

***Methods.*** A prospective cohort study was conducted from 2006 to 2008 at 3 LTCFs. Residents initially colonized with FQ-susceptible *E. coli* were followed by means of serial fecal sampling for new FQ-resistant *E. coli* colonization for up to 12 months or until discharge or death. A Cox proportional hazards regression model was developed to identify risk factors for new FQ-resistant *E. coli* colonization, with antibiotic and device exposures modeled as time-varying covariates.

***Results.*** Fifty-seven (47.5%) of 120 residents became newly colonized with FQ-resistant *E. coli*, with a median time to colonization of 57 days. Fecal incontinence (hazard ratio [HR], 1.78; 95% confidence interval [CI], 1.04–3.06; $P = .04$) was significantly associated with FQ-resistant *E. coli* acquisition. Receipt of amoxicillin-clavulanate (HR, 6.48; 95% CI, 1.43–29.4; $P = .02$) and the presence of a urinary catheter (HR, 3.81; 95% CI, 1.06–13.8; $P = .04$) during LTCF stay increased the risk of new FQ-resistant *E. coli* colonization.

***Conclusions.*** Acquisition of FQ-resistant *E. coli* was common, with nearly half of LTCF residents developing new FQ-resistant *E. coli* colonization. Further studies are needed on interventions to limit the emergence of FQ-resistant *E. coli* in LTCFs.

***Keywords.*** *Escherichia coli*; fluoroquinolones; resistance; long-term care; risk factors.

Given the marked increase in the number of older individuals, long-term care facilities (LTCFs) represent an increasingly important setting for healthcare delivery in the United States [1]. Infection or colonization with antibiotic-resistant organisms is common among LTCF residents and of particular concern, given the presence of immune senescence, chronic comorbidities, and functional impairment among the predominantly elderly residents of LTFCs [2, 3]. Fluoroquinolone (FQ)–resistant *Escherichia coli* is one such antibiotic-resistant organism that has been increasing in LTCFs [4–6], and it accounts for a significant proportion of healthcare-associated infections in this population.

In the clinical setting, the emergence of FQ resistance in *E. coli* occurs at the level of gastrointestinal tract colonization [7, 8], and FQ-resistant *E. coli* isolates causing clinical infections are most often derived from colonizing organisms. However, despite the increasing burden of FQ-resistant *E. coli* in LTCFs, there are few studies evaluating risk factors for FQ-resistant *E. coli* colonization specifically in LTFCs [9–11]. The majority of these studies have been cross-sectional or have

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examined acquisition of resistance among multiple gram-negative organisms (eg, *E. coli* and *Proteus* species) [10, 11], although risk factors for FQ resistance may differ depending on the specific organism.

Identification of risk factors for FQ-resistant *E. coli* acquisition is critical for the development of effective infection control strategies in a setting that is often more resource limited, compared with acute care hospitals, and characterized by extended periods of stay, thus increasing the opportunity for patient-to-patient contact. Furthermore, given that rates of antibiotic use, much of it inappropriate, are high in LTCFs, antibiotic exposure may represent one of the most readily modifiable risk factors for the development of FQ-resistant *E. coli* colonization [12, 13]. However, previous studies have focused on the dichotomous administration of antibiotics [9, 10, 14], rather than on evaluation of the more complex and time-varying nature of prescription that occurs in healthcare settings and that may better inform antibiotic stewardship interventions. Therefore, we conducted this study to identify risk factors for the development of FQ-resistant *E. coli* gastrointestinal tract colonization in LTCF patients, including the role of antibiotic use during LTCF residence.

## SUBJECTS AND METHODS

### Study Design and Setting

A prospective cohort study was conducted at 3 LTCFs within the Academic Long-Term Care Network (ALTCN) of the University of Pennsylvania: LTCF 1, a 124-bed facility; LTCF 2, a 240-bed facility; and LTCF 3, a 200-bed facility. All 3 LTCFs provide skilled nursing care for residents. Universal precautions, including hand washing after patient contact and use of gowns and gloves when caring for open wounds, are used. Furthermore, none of the study LTCFs performed active screening of patients for the presence of antibiotic-resistant organisms or routinely instituted contact precautions for residents colonized with resistant pathogens during the study period. The source population was composed of all patients who were residents of one of the study LTCFs.

Eligible LTCF patients were approached for informed consent during surveys of all units over the study period, from 8 March 2006 to 2 October 2008. For patients who were unable to provide consent (eg, those with cognitive dysfunction), a family member, or the person with power of attorney, was contacted to obtain consent. Fecal samples were obtained via rectal swabbing from patients who provided informed consent and were submitted to the study laboratory at the Philadelphia Veterans Affairs Medical Center for processing. Study patients were followed longitudinally and continued to have fecal samples submitted every 14 days for up to 12 months or until discharge or death. 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 by collection of serial fecal samples approximately every 14 days as described above until recovery of FQ-resistant *E. coli* or for up to 12 months or discharge or death.

### Microbiological Methods

Identification of *E. coli* with reduced FQ susceptibility from fecal samples was performed as previously described [15, 16], with levofloxacin used as a marker for susceptibility to FQs. *E. coli* isolates with minimum inhibitory concentrations (MICs) in the susceptible but elevated range may possess mutations in FQ target genes. Given the multistep nature of the development of FQ resistance, these isolates with reduced FQ susceptibility are critical in assessing the emergence of FQ resistance [17–20]. Therefore, for the present study, FQ resistance was defined as a levofloxacin MIC of $\geq$0.25 μg/mL.

### Data Collection

Data on baseline demographic and clinical characteristics were collected from the LTCF medical record at the time of enrollment, using a standardized data abstraction form. Data were obtained on age, sex, race/ethnicity, LTCF of residence, floor location, length of stay before the surveillance culture, site of admission to the LTCF (eg, acute care hospital or home), and recent hospitalization. The presence of the following in the 30 days before enrollment were also documented: urinary catheter, tracheostomy, enteral feeding tube, diarrhea, fecal incontinence, and confinement to bed or wheelchair. Cognitive status and functional status were derived from assessments of the minimal data set performed routinely for all LTCF residents by the facility staff on a quarterly basis. The presence of comorbid conditions was assessed, including malignancy, diabetes mellitus, hepatic dysfunction (eg, cirrhosis), renal insufficiency (including requirement of hemodialysis or peritoneal dialysis), chronic pulmonary disease, significant cardiovascular disease (eg, severe congestive heart failure), peripheral vascular disease, human immunodeficiency virus infection, and solid organ or hematopoietic stem cell transplant. All antimicrobial therapy received in the 30 days before study enrollment was documented, categorized by agent and class. Finally, data on the receipt of corticosteroids or other immunosuppressive agents in the 30 days before fecal sampling were collected.

### Assessment of Prospective Time-Varying Exposures

Data were obtained on all antibiotics administered from the time of the initial surveillance culture to detection of new

FQ-resistant *E. coli* colonization or up to 12 months or discharge or death (ie, the time at risk). Antibiotics were categorized by specific agent, as well as by class, as follows: FQs, aminoglycosides, carbapenems, extended-spectrum cephalosporins (cefepime, ceftriaxone, and ceftazidime), and antianaerobic (clindamycin, moxifloxacin, metronidazole, ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam, imipenem, and meropenem). Data were also obtained on urinary catheter or central venous catheter use, as well as new bed-bound status or confinement to a wheelchair. All of these exposures were subsequently assessed as time-varying covariates (exposed/nonexposed on a given day of follow-up).

### Statistical Analysis

Standard methods of survival analysis were used to determine the association between potential risk factors and the time to development of colonization with FQ-resistant *E. coli*. Time zero for all patients was defined as the date of the initial surveillance culture. Bivariable analyses were performed to evaluate risk factors for development of new FQ-resistant *E. coli* colonization during LTCF residence, using Kaplan-Meier product-limit survival curve estimates and the log-rank statistic for comparison of multiple survival curves. Multivariable analyses were then performed using Cox proportional hazards regression analyses with antibiotic exposure modeled as time-varying covariates to account for different timing and durations of therapy. Indwelling device exposure (eg, urinary catheter use) and new bed-bound status or wheelchair confinement were also modeled as time-varying covariates. A stepwise selection procedure was used to determine inclusion of candidate variables in the final model, with variables with $P$ values of $< .15$ on bivariable analyses considered as candidate variables and maintained in the final model if their inclusion was statistically significant on likelihood ratio testing [21]. Past FQ use was retained a priori in the model regardless of its statistical significance on bivariable analyses, given its hypothesized role as an important risk factor for development of FQ-resistant *E. coli* colonization. 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 of $< .05$ was considered to be significant. All statistical calculations were performed using commercially available software (SAS v.9.3; SAS Institute, Cary, NC).

## RESULTS

### Baseline Study Population Characteristics

During the nearly 3-year study period, 307 (39.7%) of 774 patients who were approached for enrollment provided informed consent. A total of 234 patients had initial surveillance cultures positive for *E. coli*, of which 140 (59.8%) were FQ susceptible (levofloxacin MIC, $< 0.25$ μg/mL). Of these 140 patients who were colonized with FQ-susceptible *E. coli*, 120 patients underwent subsequent serial sampling during LTCF residence (ie, they had at least 1 sample cultured after the initial surveillance culture) and represented the primary study cohort.

The median age of patients was 76 years (interquartile range [IQR], 64–83.5 years), and 98 (81.7%) were men. Of the 120 patients, 57 (47.5%) were categorized as "white" in regard to racial classification. A total of 32 patients (26.7%) were enrolled from LCTF 1, 75 (62.5%) from LTCF 2, and 13 (10.8%) from LTCF 3. The majority of patients (69.8%) had been transferred to the LTCF of residence from an acute care hospital. The median LTCF length of stay before the initial surveillance culture was 46 days (IQR, 21–296 days). Notably, there was a high prevalence of certain major comorbidities present in the study cohort at the time of enrollment, including diabetes mellitus (37%), severe respiratory disease (23.5%), and malignancy (40.3%).

### Antibiotic Use Characteristics

Thirty-one patients (25.8%) had received at least 1 antibiotic in the 30 days before study enrollment. In regard to antibiotic use following the initial surveillance culture, 48 patients (40.0%) received at least 1 antibiotic. The most commonly prescribed antibiotics in the postenrollment period were FQs (17.5%), antianaerobic agents (18.3%), extended-spectrum cephalosporins (10.0%), cephalexin (10.8%), vancomycin (9.2%), and trimethoprim-sulfamethoxazole (9.2%).

### Risk Factors for the Development of FQ-Resistant *E. coli* Colonization

A total of 57 patients (47.5%) had a subsequent culture positive for FQ-resistant *E. coli*. The median time to isolation of FQ-resistant *E. coli* among these patients was 57 days (IQR, 28–155 days). In bivariable analyses (Table 1), patients who acquired FQ-resistant *E. coli* versus those who remained colonized with FQ-susceptible *E. coli* were more likely to have fecal incontinence (unadjusted HR, 1.80; 95% CI, 1.06–3.04; $P = .03$) and have received amoxicillin-clavulanate following study enrollment (HR, 7.63; 95% CI, 1.75–33.3; $P = .007$).

On multivariable analysis using Cox proportional hazards regression (Table 2), fecal incontinence was a risk factor for acquisition of FQ-resistant *E. coli* (HR, 1.78; 95% CI, 1.04–3.06; $P = .04$). In addition, receipt of amoxicillin-clavulanate (HR, 6.48; 95% CI, 1.43–29.4; $P = .02$) and presence of a urinary catheter (HR, 3.81; 95% CI, 1.06–13.8; $P = .04$) during LTCF stay increased the risk of new FQ-resistant *E. coli* colonization. However, previous FQ use was not significantly associated with FQ-resistant *E. coli* acquisition (HR, 2.04; 95% CI, .27–15.6; $P = .49$).

## DISCUSSION

In this multisite prospective cohort study, we found that nearly half of LTCF residents initially colonized with FQ-susceptible

**Table 1. Unadjusted Hazard Ratios (HRs) for the Development of Fluoroquinolone (FQ)–Resistant *Escherichia coli* Colonization, by Baseline and Time-Varying Characteristics**

| Variable | Value (n = 57) | HR (95% CI) | *P* |
|---|---|---|---|
| Age, y, mean ± SD | 76.6 ± 12.3 | 1.02 (.99–1.04) | .16 |
| Female sex | 15 (26.3) | 1.43 (.79–2.60) | .24 |
| Nonwhite race | 29 (50.9) | 1.14 (.67–1.95) | .63 |
| Site | | | |
| LTCF 1 | 20 (35.1) | Reference | |
| LTCF 2 | 33 (57.9) | 0.86 (.49–1.50) | .59 |
| LTCF 3 | 4 (7.0) | 0.68 (.23–2.00) | .48 |
| Hospitalization in past year | 43 (75.4) | 1.22 (.66–2.24) | .52 |
| Comorbidity or medication[a] | | | |
| Severe cardiovascular disease | 10 (17.8) | 1.57 (.78–3.14) | .21 |
| Fecal incontinence | 27 (47.4) | 1.80 (1.06–3.04) | .03 |
| FQ receipt in past 30 d | 1 (1.8) | 2.32 (.31–17.3) | .41 |
| Time-varying characteristic after enrollment | | | |
| Amoxicillin-clavulanate[b] | 9 (15.6) | 7.63 (1.75–33.3) | .007 |
| Any antibiotic | 25 (43.9) | 0.63 (.15–2.64) | .53 |
| Bed-bound status | 1 (1.8) | 2.02 (.49–8.43) | .33 |
| Wheelchair dependent | 24 (42.9) | 1.46 (.85–2.51) | .17 |
| Urinary catheter | 6 (10.5) | 3.03 (.89–10.3) | .08 |

Data are presented as no. (%) of patients who developed FQ-resistant *E. coli* colonization, unless otherwise indicated.

Abbreviations: CI, confidence interval; LTCF, long-term care facility.

[a] Only baseline characteristics with $P < .30$, except FQ use, are shown.

[b] All other antibiotics had a *P* value of $> .30$.

*E. coli* developed new colonization with FQ-resistant *E. coli* during their LTCF stay. Risk factors for the acquisition of FQ-resistant *E. coli* included fecal incontinence, as well as receipt of amoxicillin-clavulanate and urinary catheter use during LTCF residence, measured as time-varying exposures.

The results of our study are notable for a high rate of FQ-resistant *E. coli* acquisition in the study population, with nearly half of LTCF residents developing new colonization with FQ-resistant *E. coli* during LTCF stay. LTCFs care for a predominantly elderly, vulnerable population with prolonged durations of stay (eg, with increased opportunities for patient-to-patient contact) and are often significantly resource limited as compared to acute care hospitals. This finding emphasizes the importance of evaluating optimal infection control and antibiotic stewardship strategies for limiting FQ-resistant *E. coli* acquisition specifically in LTCFs. Furthermore, given frequent patient transfers between acute and long-term care settings, knowledge of high rates of colonization with antibiotic-resistant organisms in a given patient population may be particularly important from a regional infection control perspective.

**Table 2. Multivariable Cox Proportional Hazards Regression Model of Risk Factors Associated With Fluoroquinolone (FQ)–Resistant *Escherichia coli* Colonization Among Residents of Long-Term Care Facilities**

| Variable | HR (95% CI) | *P* |
|---|---|---|
| Age | 1.02 (.99–1.04) | .22 |
| Fecal incontinence | 1.78 (1.04–3.06) | .04 |
| FQ receipt in past 30 days | 2.04 (.27–15.6) | .49 |
| Amoxicillin-clavulanate receipt after enrollment[a] | 6.48 (1.43–29.4) | .02 |
| Urinary catheter use[a] | 3.81 (1.06–13.8) | .04 |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Modeled as a time-varying covariate.

A novel finding of our study was that FQ-resistant *E. coli* acquisition was associated with receipt of amoxicillin-clavulanate following initial colonization with FQ-susceptible *E. coli*. Given that rates of antibiotic use, much of it inappropriate, are markedly high in LTCFs [12, 13, 22], antibiotic stewardship strategies are critical for curtailing the emergence of resistant organisms, including FQ-resistant *E. coli*. Previous studies focused on FQ-resistant *E. coli* colonization in LTCFs have implicated past FQ use as a risk factor for acquisition of FQ-resistant *E. coli* [9–11]. However, these studies were limited in that they included a number of gram-negative organisms, compared with *E. coli* specifically [10, 11], and evaluated antibiotic exposures as dichotomous variables (ie, exposure or no exposure). In contrast, our study evaluated antibiotic use as prospective, time-varying covariates to more fully characterize the complex patterns of antibiotic use that occur during LTCF residence. Furthermore, the focus of our study was on incident versus baseline colonization with FQ-resistant *E. coli* and on identifying potentially modifiable exposures that occur during the prolonged durations of stay characteristic of the long-term care setting.

The mechanism as to why the receipt of amoxicillin-clavulanate was associated with isolation of FQ-resistant *E. coli* is unclear. However, given its oral bioavailability and spectrum of antibacterial activity, amoxicillin-clavulanate is commonly prescribed and exerts a broad selection pressure. In individual patients, selective pressure exerted by the receipt of amoxicillin-clavulanate may have facilitated the emergence of preexisting subpopulations of *E. coli* with reduced FQ susceptibility. This novel association emphasizes that risk factors for baseline versus new FQ-resistant *E. coli* colonization, including antibiotic exposures, may significantly differ and should be taken into consideration in the development of appropriate antibiotic stewardship measures in the long-term care setting.

Our study also demonstrated a significant association between urinary catheter use and FQ-resistant *E. coli* acquisition during LTCF stay. This finding is particularly concerning because of reported high rates of use of indwelling devices, including urinary catheters, in the long-term care patient population and the subsequent increased risk of colonization with multidrug-resistant organisms [23, 24]. It is clear that

interventions for the optimal use of urinary catheters are urgently needed in LTCFs, including strict indications for use and timely removal to prevent acquisition of FQ-resistant *E. coli* in a vulnerable patient group.

Finally, the presence of fecal incontinence was found to be a risk factor for new development of FQ-resistant *E. coli* colonization in our study. This association suggests a potential role for person-to-person spread (ie, patient-to-patient and healthcare worker-to-patient) of FQ-resistant *E. coli* in LTCFs. Because colonized residents represent a potentially large and often unrecognized reservoir of FQ-resistant *E. coli*, this finding has important implications for infection control strategies in LTCFs. For example, emphasis on strict adherence to hand hygiene is critical for limiting person-to-person spread in a setting characterized by patients who often require a high level of care (eg, care during activities of daily living) and increased opportunity for healthcare worker and patient contact. Furthermore, the role of intensified isolation precautions in patients at high risk of transmission of FQ-resistant *E. coli* (eg, gown/glove use during care of residents with fecal incontinence) should be further explored.

There are potential limitations of the present study. Selection bias is a potential limitation because only approximately 40% of eligible subjects were enrolled. However, there was no significant difference in regard to sites of enrollment for participants and nonparticipants. Sampling variability may have limited the detection of colonizing FQ-resistant *E. coli* isolates from a single patient, particularly isolates present in low numbers. Finally, the present study was conducted in LTCFs that were part of a single healthcare system, and these results may not be generalizable to other LTCFs with differing characteristics.

In conclusion, our study demonstrated a significant rate of new colonization with FQ-resistant *E. coli* in LTCFs. We found that fecal incontinence, as well as prospective exposure to amoxicillin-clavulanate and urinary catheter use, increased the risk of development of FQ-resistant *E. coli* colonization. Given the projected increase in the number of older individuals and the limited resources in LTCFs, compared with acute care hospitals, further research is needed on optimal infection control and antibiotic stewardship strategies to limit the emergence of FQ-resistant *E. coli* specifically in LTCFs.

## Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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