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CONCISE ARTICLE

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Incidence and Risk Factors for Nosocomial Infections Caused by Fluoroquinolone-Resistant *Escherichia coli*

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Abstract The aim of the retrospective case-control study presented here was to elucidate the incidence, risk factors, and outcomes of nosocomial infections caused by quinolone-resistant *Escherichia coli* (QREC). During the 3-year period studied, 51 nosocomial QREC infections were found, and the characteristics of these cases were compared with those of 102 control patients with quinolone-susceptible nosocomial infections. In the multivariate analysis, risk factors were identified as prior quinolone therapy (odds ratio [OR], 18.49; 95% confidence interval [CI], 5.53–61.82; *P* value <0.001), urinary tract abnormalities (OR, 6.69; 95% CI, 1.68–26.63; *P*=0.007), and prior therapy with other antimicrobial agents (OR, 3.57; 95% CI, 1.38–9.27; *P*=0.009). No difference in mortality or in length of hospital stay was found. Prudent use of quinolones, especially in patients with urinary tract abnormalities, is probably the best way to avoid an increase in the incidence of QREC infections, but further studies on interventions with restricted use of quinolones are necessary to demonstrate the effectiveness and safety of this strategy.

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Introduction

The growing use of fluoroquinolones has led to the emergence of quinolone-resistant *Escherichia coli* (QREC) [1, 2]. Fluoroquinolone resistance among *Escherichia coli* is already a clinical problem in some European countries, such as Spain [3], where quinolone-resistant strains of *Escherichia coli* are not only a problem in hospitals but also in the community [4]. In earlier studies, risk factors for QREC reportedly included prior exposure to quinolones [2, 4, 5] and other antibiotics [4], urinary tract abnormalities [6], urinary catheter [4], residence in a long-term care facility [7], older age [7], and cancer [8]. Few prior studies of QREC have concentrated solely on nosocomially acquired infections.

In Finland, the incidence of fluoroquinolone resistance among *Escherichia coli* has been minimal thus far. During recent years, however, the use of fluoroquinolones has steadily increased: in 1993 the defined daily dose per 1000 inhabitants was 0.56, in 1997 it was 0.74, and in 2001 it was 1.46. During the same period of time, the percentage of norfloxacin-resistant *Escherichia coli* strains among all *Escherichia coli* strains isolated from urinary samples in the laboratory of Helsinki University Central Hospital steadily increased: 0.1% in 1993, 1.1% in 1994, 2.6% in 1998, and 4.2% in 2001.

Fluoroquinolones are used extensively in clinical practice because of their broad spectrum of activity, good oral absorption, and good tolerability. The emergence of resistance might be avoided by restricting the use of quinolones. The aim of the present study was to characterize the risk factors for QREC among patients at a tertiary-care hospital in whom the use of fluoroquinolones is warranted.

Patients and Methods

This study was performed at Helsinki University Central Hospital, a 1600-bed university hospital located in Helsinki, Finland. The microbiological records from the period January 1997 to December 1999 were reviewed to identify all isolations of *Escherichia coli*

Table 1 Univariate and multivariate analyses of potential risk factors for nosocomial infections caused by quinolone-resistant *Escherichia coli*

Variable	Cases (n=51)	Controls (n=102)	Univariate analysis			Multivariate analysis	
			P value	OR	95% CI	P value	OR
Mean age (range)	62.6 (20–90)	67.1 (21–96)	0.29				
Time from admission to isolation in days	10.0	8.3	0.26				
Female	30 (58.8%)	71 (69.6%)	0.21	0.62	0.31–1.25		
Prior fluoroquinolone therapy	25 (49.0%)	5 (4.9%)	<0.001	17.06	6.17–47.14	<0.001	18.49
Prior therapy with other antimicrobial agent	38 (74.5%)	44 (43.1%)	0.0024	3.74	1.80–7.80	0.009	3.57
Urinary tract abnormalities	10 (19.6%)	6 (5.9%)	0.012	3.76	1.32–10.67	0.007	6.69
Immunosuppression	18 (35.3%)	16 (15.7%)	0.0077	2.90	1.33–6.28		
Surgery	14 (27.5%)	47 (46.1%)	0.034	0.43	0.21–0.91		
Organ transplant	5 (9.8%)	2 (2.0%)	0.041	4.75	1.02–22.07		

resistant to norfloxacin or ciprofloxacin. The medical records of the patients from whom the isolates were obtained were then examined retrospectively.

A case patient was defined as a patient who developed a nosocomial infection caused by QREC in Helsinki University Hospital. The definitions of the Centers for Disease Control, Atlanta, Ga, USA, were used to determine the presence and type of infection [9]. Infection was considered nosocomial if it appeared at least 48 h after admission and there was no evidence suggesting it had been incubating or present at the time of admission. Each patient with nosocomial QREC was included in the study only once. Two controls were selected for each case patient. Control patients had to have the same nosocomial infection as the case patient, classified by anatomic site [9], but their *Escherichia coli* infections had to be susceptible to fluoroquinolones. Same year of diagnosis was preferred but cases and controls were not matched according to any other criteria.

Susceptibility testing of *Escherichia coli* isolates was performed using the disk diffusion method according to the methods of the National Committee for Clinical Microbiology Standards [10]. Susceptibility to norfloxacin was primarily analyzed for all isolates obtained from urine. For isolates from any other sample type and for urine isolates resistant to three or more antimicrobial agents, susceptibility to ciprofloxacin was routinely determined. Zones of inhibition were determined, and isolates showing zone diameters corresponding to MIC values $\geq$4 and $\geq$16 for ciprofloxacin and norfloxacin, respectively, were considered resistant. MIC values were not routinely determined.

Statistical analyses were performed using NCSS 2000 software (NCSS, USA) and conditional logistic regression with Intercooled Stata 7.0 for Windows (Stata, USA). Univariate analysis was performed separately for each variable. P values were calculated using Fisher's exact test for binomial variables and the Mann-Whitney test for continuous variables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for binomial variables. Possible risk factors with P values <0.2 in univariate analysis and possible confounding factors were included in the multivariate analysis. Multivariate analysis was performed as a conditional logistic regression because the year of diagnosis was matched. A P value <0.05 was considered statistically significant.

Results and Discussion

During the 3-year study period, QREC was isolated from 157 patients, but the medical records of one patient were not available for analysis. The isolated QREC strains caused infection in 116 (74%) patients, while the remaining 40 (26%) were classified as colonizing strains. A total of 79 (50%) strains were nosocomially acquired and 77 (50%) were acquired in the community. Fifty-one cases of nosocomially-acquired infection caused by QREC were included in the case-control study: 37 patients with urinary tract infection (including 5 bacteremic cases), 10 with surgical site infection, 3 with skin and soft tissue infection, and 1 with pneumonia. Eight cases of nosocomial QREC were left out of the case-control study for the following reasons: seven infections were acquired in other hospitals and for one case no control was available.

In the univariate analysis (Table 1) no statistically significant risk factors were found for the following variables: age, sex, long-term care, use of urinary or other catheters, neutropenia, malignancy, hepatic cirrhosis, HIV/AIDS, diabetes, ICU stay, or neurological, rheumatic, chronic renal or heart diseases. The mean time from admission to isolation was 10 days for patients in the case group and 8.3 days in the control group (P=0.29, NS). The following factors were included in the multivariate analysis: prior fluoroquinolone therapy (within 30 days), prior therapy with other antimicrobial agents (within 30 days), urinary tract abnormalities, surgery within 30 days, immunosuppression, and other possible confounding factors (ICU stay, use of urinary catheter, and time from admission to isolation).

In the multivariate analysis, the following statistically significant risk factors for nosocomial infection caused by QREC were found: prior fluoroquinolone therapy (OR, 18.49; 95% CI, 5.53–61.82), urinary tract abnormalities (OR, 6.69; 95% CI, 1.68–26.63), and prior therapy with other antimicrobial agents (OR, 3.57; 95% CI, 1.38–9.27) (Table 1). Cases and controls differed remarkably in the number of days fluoroquinolones had been used during the past 30 days, i.e., 6.78 versus 0.15 days, respectively (P<0.05). The main fluoroquinolones used were ciprofloxacin, norfloxacin, and ofloxacin.

Resistance to multiple antibiotics was high among patients with nosocomially acquired QREC compared to patients with quinolone-susceptible *Escherichia coli* (Table 2). Resistance to three or more classes of antimicrobial agents other than fluoroquinolones was found in 21 of the 51 (39%) case strains and in 4 of the 102 (4%) control strains (P<0.05). None of the isolates was resistant to third-generation cephalosporins. No differences between

Table 2 Resistance patterns of nosocomial *Escherichia coli* isolates

Sample type	Antimicrobial agent	Cases (I+R/all tested)	Controls (I+R/all tested)	*P* value
Urine	cephalothin	61.3% (19/31)	25.8% (16/62)	<0.001
	nitrofurantoin	25.8% (8/31)	3.2% (2/62)	<0.001
	trimethoprim/sulfamethoxazole	90.3% (28/31)	16.1% (10/62)	<0.001
Other	ampicillin	88.2% (15/17)	31.6% (12/38)	<0.001
	ceftazidime	0% (0/17)	0% (0/38)	NS
	tobramycin	23.5% (4/17)	2.6% (1/38)	0.055
	trimethoprim/sulfamethoxazole	82.3% (14/17)	15.8% (6/38)	<0.001

I, intermediate; R, resistant; NS, not significant

cases and controls were found in the length of hospital stay (17.7 vs. 18.7 days, *P* NS) or 30-day survival rate (97.6% vs. 94.5%, *P* NS).

Many other studies have demonstrated a correlation between quinolone use and quinolone resistance. During fluoroquinolone treatment or prophylaxis, patients have been shown to be colonized with resistant strains [11, 12]. Several studies comparing quinolone-resistant and quinolone-susceptible *Escherichia coli* infections have indicated the same causality [2, 4, 5, 7]. Urinary tract abnormality has also been identified as a risk factor for QREC [6], but some studies of QREC did not examine this variable [2, 5, 7].

In this and certain other studies [4, 5, 12], the QREC strains were resistant to several unrelated classes of antimicrobial agents. Despite this multiresistance, the clinical course of our case and control patients did not differ. This may be explained by the fact that the isolates were sensitive to second- and third-generation cephalosporins, which are the first-line empiric intravenous antimicrobial agents in our hospital. Current fluoroquinolone-resistant strains also appear to have a lower invasive capacity [13]. Among patients with a healthy urinary tract, QREC is less likely to cause invasive infections. Cheong et al. [5] found slightly higher mortality in patients with QREC bacteremia during hospitalization than in susceptible controls (30% vs. 16%), but the difference was not statistically significant (P=0.08).

Our study had several limitations. First, the study population was rather small. Second, we examined risk factors using a common study design in which control patients had antibiotic-susceptible bacteria. When assessing our results, it should be noted that at least current fluoroquinolone users do not fall within the control group. For this reason, the odds ratio for fluoroquinolones may be higher in this kind of study than in a study in which controls were selected from the base population of all hospitalized patients [14]. However, even in studies that used the latter study design, previous quinolone usage has been a significant risk factor [15]. A study design that incorporates resistant cases and susceptible controls, however, provides the opportunity to gather comparative information on mortality and morbidity for these types of infections.

Awareness of the risk of bacteria selecting for resistance has already led to clinical modifications in the treatment of certain patient groups, i.e., restricting the prophylactic use of fluoroquinolones among neutropenic hematologic and oncologic patients. However, in the treatment of a patient with a urinary tract abnormality, it is often difficult to avoid the use of fluoroquinolones. Urinary tract abnormalities predispose patients to repeated urinary tract infections and treatment with antimicrobial agents. This most probably leads to the selection of resistant strains in fecal *Escherichia coli* and to the development of urinary tract infections, which may be invasive, caused by QREC.

Quinolone-resistant *Escherichia coli* may become an important problem in both the hospital and the community setting. Further studies on interventions with limited use of fluoroquinolones would provide useful information on whether quinolone resistance could be avoided without negative effects using this strategy. Continuous monitoring of regional resistance patterns and the prudent use of quinolones, especially in patients with urinary tract abnormalities, are probably the best currently available means of controlling fluoroquinolone-resistant *Escherichia coli*.

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