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Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection

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Objectives: To assess risk factors for fluoroquinolone resistance in community-onset febrile *Escherichia coli* urinary tract infection (UTI).

Methods: A nested case–control study within a cohort of consecutive adults with febrile UTI presenting at primary healthcare centres or emergency departments during January 2004 through December 2009. Resistance was defined using EUCAST criteria (ciprofloxacin MIC >1.0 mg/L). Cases were subjects with fluoroquinolone-resistant *E. coli*, and controls those with fluoroquinolone-susceptible isolates. Multivariable logistic regression analysis was used to identify potential risk factors for fluoroquinolone resistance.

Results: Of 787 consecutive patients, 420 had *E. coli*-positive urine cultures. Of these, 51 (12%) were fluoroquinolone resistant. Independent risk factors for fluoroquinolone resistance were urinary catheter [odds ratio (OR) 3.1; 95% confidence interval (CI) 0.9–11.6], recent hospitalization (OR 2.0; 95% CI 1.0–4.3) and fluoroquinolone use in the past 6 months (OR 17.5; 95% CI 6.0–50.7). Environmental factors (e.g. contact with animals or hospitalized household members) were not associated with fluoroquinolone resistance. Of fluoroquinolone-resistant strains, 33% were resistant to amoxicillin/clavulanate and 65% to trimethoprim/sulfamethoxazole; 14% were extended-spectrum β-lactamase (ESBL) positive compared with <1% of fluoroquinolone-susceptible isolates.

Conclusions: Recent hospitalization, urinary catheter and fluoroquinolone use in the past 6 months were independent risk factors for fluoroquinolone resistance in community-onset febrile *E. coli* UTI. Contact with animals or hospitalized household members was not associated with fluoroquinolone resistance. Fluoroquinolone resistance may be a marker of broader resistance, including ESBL positivity.

Keywords: antibiotic resistance, ESBLs, pyelonephritis, ciprofloxacin

Introduction

Fluoroquinolones and trimethoprim/sulfamethoxazole are the preferred agents for oral treatment of febrile urinary tract infection (UTI). Fluoroquinolones are recommended to be the first choice, particularly, because there is a relatively low rate of antimicrobial resistance.[1–4] However, the emergence of fluoroquinolone-resistant *Escherichia coli* in the community may limit oral treatment options.[5] Reported rates of *E. coli* resistance to ciprofloxacin in UTI vary widely over the years and between countries, ranging from <1% to 38%.[6,7] In the Netherlands, a country known for its restrictive usage of antimicrobials and overall low rates of antimicrobial resistance, *E. coli* resistance to ciprofloxacin increased from 3% in 2001 to 11%

in 2008 with even higher rates in patients at urology services.[8,9] Moreover, fluoroquinolone resistance in *E. coli* isolates is frequently associated with resistance to other classes of antibiotics.[10] Therefore, there is a need for knowledge of risk factors for fluoroquinolone-resistant *E. coli* in patients presenting with febrile UTI in order to select the most appropriate empirical antimicrobial oral treatment.

Previous studies on fluoroquinolone-resistant *E. coli* have focused primarily on host-related risk factors such as older age, prior fluoroquinolone usage, urinary tract disorders and hospitalization.[7,11–16] Others have studied the emergence of *E. coli* resistance in the environment and found household members, pets and livestock colonized with resistant *E. coli* strains to be possible sources of human infection.[17–20] To our knowledge, these potential environmental risk factors for fluoroquinolone resistance have not been assessed in a general population presenting with community-onset febrile UTI or acute pyelonephritis.

We therefore conducted a multicentre nested case–control study to identify host-related and environmental risk factors for fluoroquinolone resistance in adults presenting with community-onset febrile UTI. In addition, the relationship with extended-spectrum β-lactamase (ESBL) positivity was investigated.

Patients and methods

We conducted a nested case–control study from a prospective multicentre cohort study. Participating centres were 35 primary healthcare centres and emergency departments of 7 hospitals, all clustered in one area of the Netherlands. From January 2004 until December 2009, consecutive patients who presented with febrile UTI were considered for enrolment in the study. The local ethics committees approved the study and all participants provided written informed consent.

Inclusion criteria were age ≥18 years, fever (≥38.0°C) and/or a history of fever and chills within 24 h before presentation, at least one symptom of UTI (dysuria, frequency, urgency, perineal pain, flank pain or costovertebral tenderness) and a positive nitrite dipstick test or leucocyturia as defined by a positive leucocyte esterase dipstick test or the presence of more than five leucocytes per high-power field (pyuria) in a centrifuged sediment. Exclusion criteria were current treatment for urolithiasis or hydronephrosis, pregnancy, haemo- or peritoneal dialysis, a history of kidney transplantation or known presence of polycystic kidney disease. Patients were only included once in the study.

Cases were eligible patients with urine culture-confirmed febrile UTI caused by fluoroquinolone-resistant *E. coli*. Patients with febrile UTI due to fluoroquinolone-susceptible *E. coli* served as controls.

Procedures

Demographic, clinical and microbiological data were collected within 24–48 h of notification. This was done by qualified research nurses or the clinical investigators (C. v. N. and W. E. v. d. S.) by reviewing the medical record completed with an interview by telephone or in person using a standardized questionnaire including host-related variables. All patients were empirically treated with antibiotics according to local policy (500 mg of oral ciprofloxacin twice daily for outpatients and for inpatients cefuroxime ± gentamicin intravenously). Based on the culture results, hospitalized patients were subsequently switched to oral antibiotic treatment (first choice 500 mg of ciprofloxacin twice daily).

As data on environmental exposure were initially not collected, we contacted patients for a second time in March 2010. All cases were selected for additional interview and for each case, two controls were selected matched by centre and date of inclusion. A standardized questionnaire was used containing the following dichotomous items present within 3 months before initial inclusion: household member with UTI; recent hospitalization; working in healthcare facility; ownership and/or contact with pets or livestock; and receipt of home healthcare support. The interviewer was blinded to the antimicrobial susceptibility outcome of the isolated *E. coli* strains.

Definitions

Recurrent UTI was defined as two or more episodes in the last 6 months or three or more episodes of UTI in the last year. A urinary tract disorder was defined as the presence of any functional or anatomical abnormality of the urinary tract excluding the presence of a urinary catheter or history of nephrolithiasis. These two latter variables were analysed separately. Data regarding recurrent UTI and antibiotic use in the past 6 months were missing in 5 and 13 patients, respectively. Missing values of these categorical variables were considered to indicate the absence of that characteristic.

Microbiological analysis

Clean midstream-catch urine cultures were obtained before starting antimicrobial therapy and were analysed using local standard microbiological methods. In the case of a urinary catheter the urine sample was collected from the port of the catheter. A positive urine culture was defined as bacterial growth of $>10^3$ cfu/mL urine or a bacterial monoculture of $>10^2$ cfu/mL urine in the presence of pyuria.[21] Urine cultures revealing growth of two or more different bacterial species reflecting mixed skin or gut flora, were considered to indicate contamination.[21] Susceptibility tests were done from the selective media using the Vitek2 system (bioMerieux). MIC breakpoints for resistance were based on EUCAST criteria (www.eucast.org). *E. coli* isolates for which ciprofloxacin MICs were >1 mg/L were considered to be fluoroquinolone resistant. In 16 *E. coli* isolates ciprofloxacin susceptibility was not specifically tested. Fifteen of these were norfloxacin susceptible and thus considered fluoroquinolone susceptible; one was resistant to norfloxacin and considered fluoroquinolone resistant.

ESBL production was phenotypically detected by double-disc diffusion test using ceftazidime/ceftazidime clavulanate and cefotaxime/cefotaxime clavulanate or by Etest.

Statistical analysis

Descriptive analysis included means or percentages with 95% confidence intervals (CIs) or medians and ranges, as appropriate. Univariate analysis was performed using the Mann–Whitney *U*-test for continuous variables and χ^2 tests for categorical variables. All variables associated with ciprofloxacin resistance in univariate analysis with $P<0.2$ were included in a multiple logistic regression model using a backward selection method with conditional tests. Interactions between paired variables were tested. A two-tailed *P* value of <0.05 was considered to indicate statistical significance. All analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 787 patients with febrile UTI were enrolled. *E. coli* was the most frequent causal uropathogen, present in 420 (53%) of the patients. Additional causative organisms were *Klebsiella* spp. (4.1%), *Enterococcus faecalis* (1.6%) and others (Figure 1). In 199 (25%) patients, urine culture

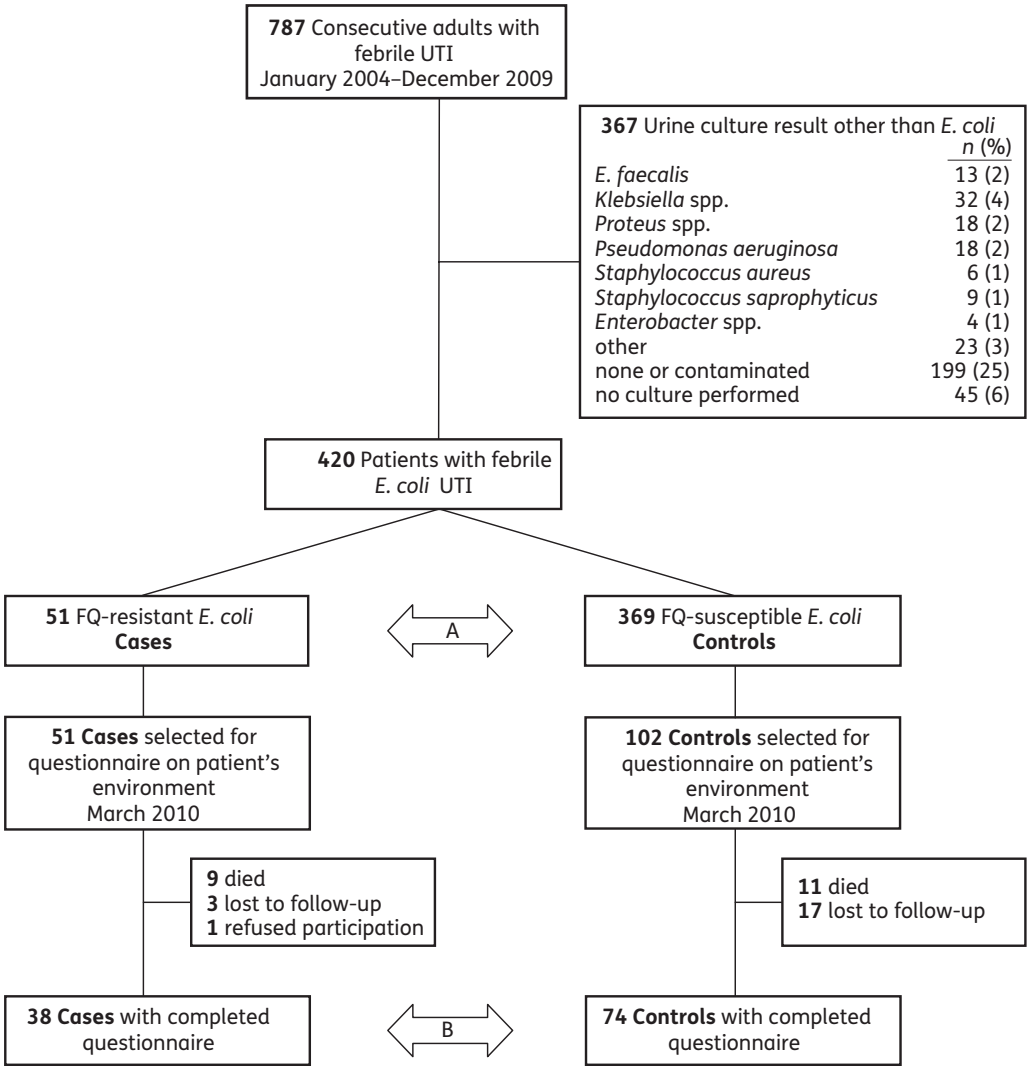

Figure 1. Flow chart of participants in the study. FQ, fluoroquinolone.

showed either no significant bacteriuria or mixed flora; 52% of them could be explained by antibiotic pre-treatment.

Of 420 patients with *E. coli*-positive urine cultures, 51 (12%) had a culture with a fluoroquinolone-resistant isolate (designated as cases) and 369 with a fluoroquinolone-susceptible isolate (designated as controls). The median age was 66 years [interquartile range (IQR) 45–78], 137 (33%) were men and 224 (53%) had co-morbidity. Baseline characteristics of the study population are summarized in Table 1.

Out of the 369 controls, 102 were matched by centre and date of inclusion to the 51 cases for additional interview on environmental issues, but otherwise selected randomly. These 102 selected controls were comparable to the remaining 267 controls with respect to gender, age and comorbidity, except for diabetes mellitus, which was more frequent in the selected controls (19% versus 11%, $P=0.047$). During follow-up till March 2010, 9 cases and 11 controls died. Of the remaining 42 cases and 93 controls, 38 cases (response rate 90%) and 74 controls (response rate 80%) participated (Figure 1).

Risk factors for fluoroquinolone-resistant E. coli

Univariate and multivariate potential risk factors for fluoroquinolone-resistant *E. coli* are listed in Table 1. Significant univariable host-related risk factors were the presence of a urinary catheter [odds ratio (OR) 6.0; 95% confidence interval (CI) 2.0–18.1], underlying urinary tract disorder (OR 2.3; 95% CI 1.2–4.4), recurrent UTI (OR 2.2; 95% CI 1.2–4.1), hospitalization in the past 6 months (OR 2.3; 95% CI 1.2–4.4) and fluoroquinolone usage in the past 6 months (OR 18.6; 95% CI 6.6–52.4). None of the environmental characteristics was significantly associated with fluoroquinolone resistance, with ORs all ~1.

Table 1. Baseline characteristics of 420 patients presenting with febrile UTI due to *E. coli*

Patient characteristics	All, $n=420$	Cases, $n=51$ (12%)	Controls, $n=369$	Univariate OR (95% CI)	P	Multivariate[a] OR (95% CI)
Age, years, median (IQR)	66 (45–78)	71 (54–80)	66 (44–78)		0.115	
≥65 years	216 (51)	30 (59)	186 (50)	1.41 (0.78–2.54)	0.260	
Male sex	137 (33)	18 (35)	119 (32)	1.15 (0.62–2.12)	0.664	
Co-morbidity						
any	224 (53)	33 (65)	191 (52)	1.71 (0.93–3.14)	0.082	
urinary catheter	14 (3)	6 (12)	8 (2)	6.02 (2.00–18.1)	<0.001	3.14 (0.85–11.60)
urinary tract disorder[b]	83 (20)	17 (33)	66 (18)	2.30 (1.21–4.35)	0.009	
history of nephrolithiasis	38 (9)	5 (10)	33 (9)	1.11 (0.41–2.98)	0.841	
diabetes mellitus	59 (14)	11 (22)	48 (13)	1.84 (0.88–3.83)	0.099	
malignancy	34 (8)	6 (12)	28 (8)	1.62 (0.64–4.14)	0.305	
cerebrovascular disease	57 (14)	7 (14)	50 (14)	1.02 (0.43–2.38)	0.973	
COPD	52 (12)	7 (14)	45 (12)	1.15 (0.49–2.70)	0.756	
immunocompromised state	44 (11)	4 (8)	40 (11)	0.70 (0.24–2.05)	0.512	
Recurrent UTI[c]	109 (26)	21 (41)	88 (24)	2.24 (1.22–4.10)	0.008	
Hospitalization in the past 6 months	72 (17)	15 (29)	57 (15)	2.28 (1.17–4.44)	0.013	2.03 (0.96–4.31)
Residence in nursing home	16 (4)	4 (8)	12 (3)	2.53 (0.78–8.17)	0.108	
Antibiotic treatment in the past 6 months	140/407 (34)	23/49 (47)	117/358 (33)	1.82 (1.00–3.33)	0.049	
fluoroquinolones	18 (4)	12 (24)	6 (2)	18.6 (6.62–52.4)	<0.001	17.5 (6.0–50.7)
β-lactams	30 (7)	4 (8)	26 (7)	1.12 (0.38–3.36)	0.836	
trimethoprim/sulphonamide	14 (3)	2 (4)	12 (3)	1.21 (0.26–5.59)	0.803	
nitrofurantoin	16 (4)	2 (4)	14 (4)	1.04 (0.23–4.70)	0.964	
Patient environment characteristics[d]	$n=112$	$n=38$	$n=74$			
household member with UTI	3 (3)	0	3 (4)	—	0.214	
daily contact with pets[e]	28 (25)	10 (26)	18(24)	1.12 (0.45–2.72)	0.818	
daily contact with livestock	1 (1)	1 (3)	0 (0)	—	0.161	
household healthcare employee	9 (8)	3 (8)	6 (8)	0.97 (0.23–4.12)	0.969	
home care medical support	19 (17)	7 (18)	12 (16)	1.17 (0.42–3.26)	0.768	

Data are presented as *n* (%), unless otherwise stated. COPD, chronic obstructive pulmonary disease.
[a]Multivariate OR, adjusted for sex, obtained by backward regression analysis using conditional tests and selecting all variables with $P<0.2$ in univariate analysis as independent covariates.
[b]Defined as the presence of any functional or anatomical abnormality of the urinary tract except urinary catheter and history of nephrolithiasis.
[c]Defined as three or more UTIs in the past 12 months or two or more UTIs in the past 6 months.
[d]Environmental characteristics evaluated in 112 patients completing questionnaire, see Figure 1.
[e]Dogs and/or cats.

Independent risk factors for fluoroquinolone-resistant *E. coli* in the multivariate analysis were the presence of a urinary catheter (OR 3.1; 95% CI 0.9–11.6), recent hospitalization (OR 2.0; 95% CI 1.0–4.3) and fluoroquinolone use in the past 6 months (OR 17.5; 95% CI 6.0–50.7). Potential interactions between variables (e.g. urinary tract disorder and presence of a urinary catheter), were additionally tested, but they did not significantly change the model. In total, 90 (21%) of the patients had at least one of those three risk factors accompanied by a 26.7% risk of having fluoroquinolone-resistant *E. coli* compared with 330 patients with no risk factor who had an 8.2% risk of having fluoroquinolone-resistant *E. coli*.

Microbiological outcome

Among 420 *E. coli* isolates tested, 12% were resistant to ciprofloxacin, 51% to amoxicillin, 11% to amoxicillin/clavulanate, 30% to trimethoprim/sulfamethoxazole, 5% to cefuroxime and 6% to gentamicin. Fluoroquinolone-resistant *E. coli* strains were frequently resistant to other antibiotic classes used for treatment of febrile UTI: 33% to amoxicillin/clavulanate; and 65% to trimethoprim/sulfamethoxazole. The distribution of cross-resistance to oral antibiotics used for febrile UTI is illustrated in Figure 2. The prevalence of ESBL-producing *E. coli* was low (2%), but differed significantly between cases and controls [7 (14%) versus 1 (<1%), respectively ($P<0.001$)]. Of the eight patients with ESBL-positive *E. coli*, six completed the

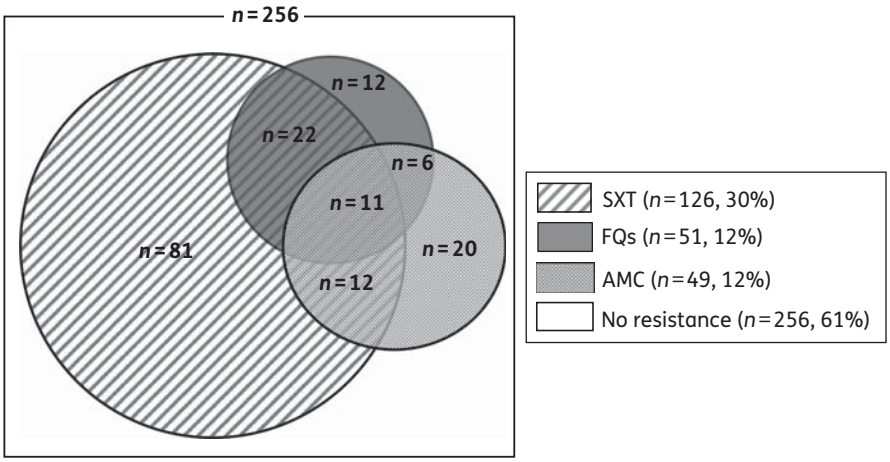

Figure 2. Distribution of resistance to oral antibiotics in 420 patients with febrile *E. coli* UTI. SXT, trimethoprim/sulfamethoxazole; FQs, fluoroquinolones; AMC, amoxicillin/clavulanate.

questionnaire; none of them had contact with animals. There were no statistically significant differences in the frequency of fluoroquinolone-resistant *E. coli* in the years between 2004 and 2009 and there was no trend towards a gradual increase (data not shown).

Clinical outcome

Among the 51 patients with fluoroquinolone-resistant *E. coli* febrile UTI, 16 (31%) were empirically treated with an inappropriate antibiotic, including 10 patients who were treated with ciprofloxacin (Table 2). Median fever duration in patients receiving ciprofloxacin was 2 days (IQR 1–4); 70% of those switched to another antibiotic after a median of 6 days (IQR 2–7). Patients treated with cefuroxime plus gentamicin had slightly longer fever duration [median 3 days (IQR 2–4)] and 71% switched to another antibiotic after a median of 6.5 days (IQR 5.3–8.0) (Table 2).

Discussion

In this study, we evaluated host-related and environmental risk factors for fluoroquinolone resistance in adults with community-onset febrile *E. coli* UTI. We identified recent hospitalization, the presence of a urinary catheter and fluoroquinolone usage in the past 6 months as independent host-related risk factors for resistance. Environmental dynamics, like contact with pets, livestock or hospitalized household members, were not identified as risk factors. To our knowledge, this is the first prospective study evaluating a combination of those risk factors for fluoroquinolone-resistant *E. coli* among adults with community-onset febrile UTI or acute pyelonephritis. These data suggest that development of fluoroquinolone resistance in a general population at risk of febrile UTI is driven by individual fluoroquinolone usage rather than by within-household or animal–human transmission of resistant *E. coli*. However, this study does not exclude the suggested possibility of an animal origin of fluoroquinolone resistance via foodborne transmission.[22,23]

The strengths of this study are its prospective design and the broad population of interest, reflecting daily practice of patients presenting with febrile UTI or acute pyelonephritis, as both primary healthcare centres and emergency departments participated.

There are, however, also some limitations. Our study had a relatively small sample size of cases with fluoroquinolone resistance. However, to our knowledge this study is the largest prospective study on patients with fluoroquinolone-resistant *E. coli* febrile UTI so far, as most previous studies were retrospective chart reviews of microbiology laboratory databases.[7,11–16] Such studies may overestimate the prevalence of resistance among uropathogens from patients with community-onset UTIs. One study at US emergency departments had a similar prospective design including 1271 patients with acute pyelonephritis of which 689 were caused by *E. coli*.[4] Yet the prevalence of fluoroquinolone-resistant *E. coli* in this study was 3%–5% and too low to evaluate risk factors for fluoroquinolone resistance. In our study the prevalence of fluoroquinolone resistance in *E. coli* was remarkably higher (12%), but consistent with a recent survey in the Netherlands.[8]

We used an MIC breakpoint for ciprofloxacin resistance of >1 mg/L according to EUCAST criteria. As, to date, different laboratories over the world use different clinical MIC breakpoints for resistance, it is of interest that we found no differences in outcome of the patients with fluoroquinolone-resistant *E. coli* who were empirically treated with ciprofloxacin compared with those treated with appropriate antibiotics (Table 2). Moreover, the majority of patients recovered on ciprofloxacin as their fever resolved before the outcome of the urine culture became available and antibiotic treatment was subsequently switched. This may indicate that febrile UTI is to some extent a self-limiting disease or possibly ciprofloxacin treatment may still be effective in ranges of MICs >1 mg/L. We could not explore this hypothesis further as we do not have results of the actual MICs for the fluoroquinolone-resistant isolates.

Several studies also found recent hospitalization,[14,15] urinary catheter[11,13] and fluoroquinolone usage[7,11–16] to be related to fluoroquinolone resistance. In addition, other risk factors were discovered, such as previous invasive procedures,[14] recurrent

Table 2. Empirical antimicrobial treatment and outcome of 51 patients with febrile UTI due to fluoroquinolone-resistant *E. coli*

Treatment			Outcome		
empirical antibiotic(s)	*n*	inappropriate[a], *n* (%)	fever duration	no. of patients switched to other antibiotic (%)	days until antibiotic switch
ciprofloxacin	10	10 (100)	2.0 (1.0–4.0)	7 (70)	6.0 (2.0–7.0)
cefuroxime	19	3 (16)	2.0 (1.0–4.0)	17 (90)	5.0 (4.0–6.0)
cefuroxime + gentamicin	14	1 (7)	3.0 (2.0–4.0)	10 (71)	6.5 (5.3–8.0)
amoxicillin/clavulanate	5	2 (40)	2.5 (1.3–3.8)	3 (60)	3.0 (3.0–3.5)
other[b]	3	NA	NA	NA	NA

NA, not applicable.
Data are presented as median (IQR), unless otherwise stated.
[a]Inappropriate empirical antibiotic treatment defined as *E. coli* resistant to the antibiotic given.
[b]Trimethoprim/sulfamethoxazole, $n=1$; ceftazidime, $n=1$; and meropenem, $n=1$.

UTI,[12,14,15] older age,[7,11] presence of complicated UTI,[7] underlying chronic disease[15,16] and urinary tract abnormalities.[11,15] All these risk factors for fluoroquinolone resistance seem biologically plausible and the differences in outcome of these studies probably reflect differences in study population. However, it should be noted that like our study, a recent meta-analysis demonstrated that in a general population individual antibiotic usage is the driving force for resistance of urinary bacteria.[24] Though some studies identified foreign travel to be a risk factor for infections with an antimicrobial-resistant uropathogen, in particular a trimethoprim/sulfamethoxazole-resistant strain, this was not found for infections with fluoroquinolone-resistant *E. coli*.[25–28] We did not systematically collect data on foreign travel to explore this issue in our study.

Compared with previous studies we used an additional questionnaire to evaluate potential environmental risk factors for fluoroquinolone resistance. This was done retrospectively, holding a risk of observer recall and selection bias. Yet several measures were taken to minimize this. First of all, the interviewer was blinded to the data with respect to fluoroquinolone susceptibility making observer bias unlikely. Secondly, when obtaining the questionnaire the patients were not specifically informed whether they had fluoroquinolone-resistant *E. coli*. Furthermore, cases and controls had comparable response rates. Thus recall bias is unlikely. Finally, the selected controls were comparable to the non-selected as they were randomly selected and matched only by centre and date of presentation with febrile UTI.

We did not find environmental risk factors for fluoroquinolone resistance. Thus our findings do not support the concern for an animal or human reservoir of fluoroquinolone resistance. This may contrast with previous findings, but it should be emphasized that the evidence for animal–human and human–human transmission of fluoroquinolone-resistant *E. coli* in UTI is limited to specific strains.[17,18,20,29] As each strain could have its specific mode and likelihood of transmission, our data do not contradict these studies. At least it suggests that to date such clones have not played a major role in a general Dutch community setting of patients at risk for febrile UTI. Further surveillance studies should include the genetic characterization of *E. coli* strains to confirm or refute the hypothesis that fluoroquinolone resistance in the community is driven by the introduction of clonal *E. coli* groups.[30] Furthermore, it must be emphasized that our study does not exclude a possible two-hit mechanism for fluoroquinolone resistance, with an initial input of fluoroquinolone-resistant strains from food supply of colonized animals into the population followed by selection at the individual level by personal fluoroquinolone use. Further studies are urgently warranted to explore this hypothesis, particularly as the relationship between animal food supply and fluoroquinolone-resistant *E. coli* in humans revealed conflicting results, but at least indicate that this might be a major concern for the community.[23,28,31,32]

In cases of isolation of fluoroquinolone-resistant *E. coli*, we found accompanying high rates of resistance to other antibiotics: 33% to amoxicillin/clavulanate; and 65% to trimethoprim/sulfamethoxazole. Similar multidrug resistance rates were found in a large study in North America.[10] Moreover, 14% of fluoroquinolone-resistant *E. coli* isolates in our study were ESBL positive compared with <1% of fluoroquinolone-susceptible isolates. This supports a previous finding that fluoroquinolone susceptibility in *E. coli* makes the presence of ESBL positivity unlikely.[33] In this respect, this highlights the importance of risk factors for fluoroquinolone resistance as these may also be risk factors for ESBL production.

The extent to which antibiotic resistance risk stratification could guide empirical therapy for febrile UTI is unknown. This study demonstrates that the absolute risk of fluoroquinolone resistance increases by ~20% in patients with at least one of the three risk factors we identified, but even with no risk factor there was an 8% risk of fluoroquinolone resistance. Further studies are therefore required in order to better stratify fluoroquinolone resistance risk in patients with febrile UTI.

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Transparency declarations

None to declare.

References

1 Warren JW, Abrutyn E, Hebel JR *et al*. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis* 1999; **29**: 745–58.

2 Wagenlehner FM, Weidner W, Naber KG. Pharmacokinetic characteristics of antimicrobials and optimal treatment of urosepsis. *Clin Pharmacokinet* 2007; **46**: 291–305.

3 Geerlings SE, van den Broek PJ, van Haarst EP *et al*. [Optimisation of the antibiotic policy in the Netherlands. X. The SWAB guideline for antimicrobial treatment of complicated urinary tract infections]. *Ned Tijdschr Geneeskd* 2006; **150**: 2370–6.

4 Talan DA, Krishnadasan A, Abrahamian FM *et al*. Prevalence and risk factor analysis of trimethoprim-sulfamethoxazole- and fluoroquinolone-resistant *Escherichia coli* infection among emergency department patients with pyelonephritis. *Clin Infect Dis* 2008; **9**: 1150–8.

5 Johnson L, Sabel A, Burman WJ *et al*. Emergence of fluoroquinolone resistance in outpatient urinary *Escherichia coli* isolates. *Am J Med* 2008; **121**: 876–84.

6 Talan DA, Stamm WE, Hooton TM *et al*. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. *JAMA* 2000; **283**: 1583–90.

7 Arslan H, Azap OK, Ergonul O *et al*. Risk factors for ciprofloxacin resistance among *Escherichia coli* strains isolated from community-acquired urinary tract infections in Turkey. *J Antimicrob Chemother* 2005; **56**: 914–8.

8 Degener JE, de Neeling AJ. Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands. *Nethmap* 2009. http://www.swab.nl/swab/cms3.nsf/uploads/1D61A8F6E60555F3C125763900414B7B/$FILE/nethmap2009_21_9-2009.pdf (24 November 2010, date last accessed).

9 Nys S, Terporten PH, Hoogkamp-Korstanje JA *et al*. Trends in antimicrobial susceptibility of *Escherichia coli* isolates from urology services in The Netherlands (1998–2005). *J Antimicrob Chemother* 2008; **62**: 126–32.

10 Karlowsky JA, Hoban DJ, Decorby MR *et al*. Fluoroquinolone-resistant urinary isolates of *Escherichia coli* from outpatients are frequently multidrug resistant: results from the North American Urinary Tract Infection Collaborative Alliance-Quinolone Resistance study. *Antimicrob Agents Chemother* 2006; **50**: 2251–4.

11 Ena J, Amador C, Martinez C *et al*. Risk factors for acquisition of urinary tract infections caused by ciprofloxacin resistant *Escherichia coli*. *J Urol* 1995; **153**: 117–20.

12 Killgore KM, March KL, Guglielmo BJ. Risk factors for community-acquired ciprofloxacin-resistant *Escherichia coli* urinary tract infection. *Ann Pharmacother* 2004; **38**: 1148–52.

13 Lin CY, Huang SH, Chen TC *et al*. Risk factors of ciprofloxacin resistance in urinary *Escherichia coli* isolates. *J Microbiol Immunol Infect* 2008; **41**: 325–31.

14 Colodner R, Kometiani I, Chazan B *et al*. Risk factors for community-acquired urinary tract infection due to quinolone-resistant *E. coli*. *Infection* 2008; **36**: 41–5.

15 Vasquez GA, Siu HR, Luna EM *et al*. Risk factors for quinolone-resistant *Escherichia coli* urinary tract infection. *Infect Dis Clin Pract* 2009; **17**: 309–13.

16 Chaniotaki S, Giakouppi P, Tzouvelekis LS *et al*. Quinolone resistance among *Escherichia coli* strains from community-acquired urinary tract infections in Greece. *Clin Microbiol Infect* 2004; **10**: 75–8.

17 Johnson JR, Clabots C. Sharing of virulent *Escherichia coli* clones among household members of a woman with acute cystitis. *Clin Infect Dis* 2006; **43**: e101–8.

18 Johnson JR, Owens K, Gajewski A *et al*. *Escherichia coli* colonization patterns among human household members and pets, with attention to acute urinary tract infection. *J Infect Dis* 2008; **197**: 218–24.

19 Johnson JR, Miller S, Johnston B *et al*. Sharing of *Escherichia coli* sequence type ST131 and other multidrug-resistant and urovirulent *E. coli* strains among dogs and cats within a household. *J Clin Microbiol* 2009; **47**: 3721–5.

20 Thorsteinsdottir TR, Haraldsson G, Fridriksdottir V *et al*. Broiler chickens as source of human fluoroquinolone-resistant *Escherichia coli*, Iceland. *Emerg Infect Dis* 2010; **16**: 133–5.

21 Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. *Clin Infect Dis* 2004; **38**: 1150–8.

22 Hooton TM, Samadpour M. Is acute uncomplicated urinary tract infection a foodborne illness, and are animals the source? *Clin Infect Dis* 2005; **40**: 258–9.

23 Johnson JR, Kuskowski MA, Menard M *et al*. Similarity between human and chicken *Escherichia coli* isolates in relation to ciprofloxacin resistance status. *J Infect Dis* 2006; **194**: 71–8.

24 Costelloe C, Metcalfe C, Lovering A *et al*. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; **340**: c2096.

25 Murray BE, Mathewson JJ, DuPont HL *et al*. Emergence of resistant fecal *Escherichia coli* in travelers not taking prophylactic antimicrobial agents. *Antimicrob Agents Chemother* 1990; **34**: 515–8.

26 Burman WJ, Breese PE, Murray BE *et al*. Conventional and molecular epidemiology of trimethoprim-sulfamethoxazole resistance among urinary *Escherichia coli* isolates. *Am J Med* 2003; **115**: 358–64.

27 Colgan R, Johnson JR, Kuskowski M *et al*. Risk factors for trimethoprim-sulfamethoxazole resistance in patients with acute uncomplicated cystitis. *Antimicrob Agents Chemother* 2008; **52**: 846–51.

28 Sannes MR, Belongia EA, Kieke B *et al*. Predictors of antimicrobial-resistant *Escherichia coli* in the feces of vegetarians and newly hospitalized adults in Minnesota and Wisconsin. *J Infect Dis* 2008; **197**: 430–4.

29 Ramchandani M, Manges AR, Debroy C *et al*. Possible animal origin of human-associated, multidrug-resistant, uropathogenic *Escherichia coli*. *Clin Infect Dis* 2005; **40**: 251–7.

30 Smith SP, Manges AR, Riley LW. Temporal changes in the prevalence of community-acquired antimicrobial-resistant urinary tract infection affected by *Escherichia coli* clonal group composition. *Clin Infect Dis* 2008; **46**: 689–95.

31 Vincent C, Boerlin P, Daignault D *et al*. Food reservoir for *Escherichia coli* causing urinary tract infections. *Emerg Infect Dis* 2010; **16**: 88–95.

32 Graziani C, Luzzi I, Corro M *et al*. Phylogenetic background and virulence genotype of ciprofloxacin-susceptible and ciprofloxacin-resistant *Escherichia coli* strains of human and avian origin. *J Infect Dis* 2009; **199**: 1209–17.

33 Tolun V, Kucukbasmaci O, Torumkuney-Akbulut D *et al*. Relationship between ciprofloxacin resistance and extended-spectrum β-lactamase production in *Escherichia coli* and *Klebsiella pneumoniae* strains. *Clin Microbiol Infect* 2004; **10**: 72–5.