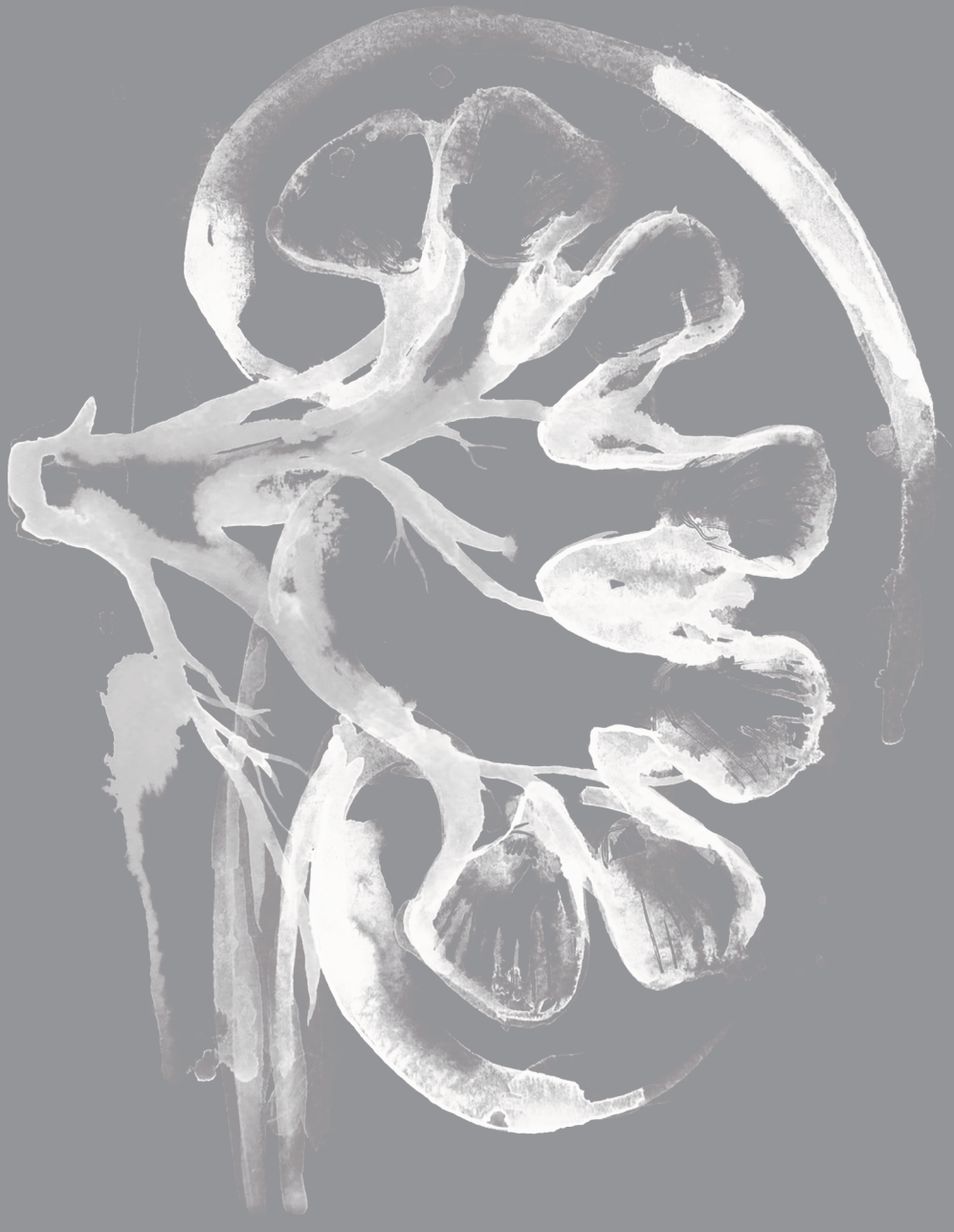

Chapter 1

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

Willize E. van der Starre[*], Cees van Nieuwkoop[*], Sunita Paltansing, Jan W. van 't Wout, Geert H. Groeneveld, Martin J. Becker, Ted Koster, G. Hanke Wattel-Louis, Nathalie M. Delfos, Hans C. Ablij, Eliane M.S. Leyten, Jeanet W. Blom, Jaap T. van Dissel
[*]Both authors contributed equally

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Abstract

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 health care centres or emergency departments during January 2004 through December 2009. Resistance was defined using EUCAST criteria (MIC ciprofloxacin > 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 (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 six 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 ESBL-positive compared to <1% in fluoroquinolone-susceptible isolates.

Conclusions

Recent hospitalization, urinary catheter and fluoroquinolone use in the past six 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.

Introduction

Fluoroquinolones and trimethoprim/sulfamethoxazole are the preferred agents for oral treatment of febrile UTI. Fluoroquinolones are recommended to be the first choice, particularly because there is a relative 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 better select the most appropriate empirical antimicrobial oral treatment.

Previous studies on fluoroquinolone-resistant *E. coli* primarily have focused 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 relation with extended spectrum beta-lactamase (ESBL)-positivity.

Patients and methods

We conducted a nested case-control study from a prospective multicentre cohort study. Participating centres were 35 primary health care centres and emergency departments of 7 hospitals, all clustered into one single area of the Netherlands. From January 2004 till 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 of 18 years or above, 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 leukocyturia as defined by a positive leukocyte esterase dipstick test or the presence of more than 5 leukocytes per high-power field (pyuria) in a centrifuged sediment. Exclusion criteria were current treatment for urolithiasis or hydronephrosis, pregnancy, hemo- 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 upon notification. This was done by qualified research nurses or the clinical investigators (CvN, WEvdS) 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 (oral ciprofloxacin 500 mg 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 ciprofloxacin 500 mg twice daily).
As data on environmental exposures 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 health care facility, ownership and/or contact with pets or livestock and receipt of home health care 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 six 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 analyzed 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 analyzed using local standard microbiological methods. In 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 over 10^3 cfu/mL urine or a bacterial monoculture over 10^2 cfu/mL urine in the presence of pyuria[21]. Urine cultures revealing growth of 2 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 with ciprofloxacin MIC values > 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-disk diffusion test using ceftazidime/ceftazidime clavulanate and cefotaxime/cefotaxime clavulanate or by E-test.

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 Chi-square 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 backward selection method with conditional tests. Interactions between paired variables were tested. A two-tailed P-value <0.05 was considered to indicate statistical significance. All analysis were 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%) and *Enterococcus faecalis* (1.6%) and others (Figure 1). In 199 (25%) patients, the urine culture showed either no significant bacteriuria or mixed flora; 52% of them could be explained by antibiotic pretreatment.

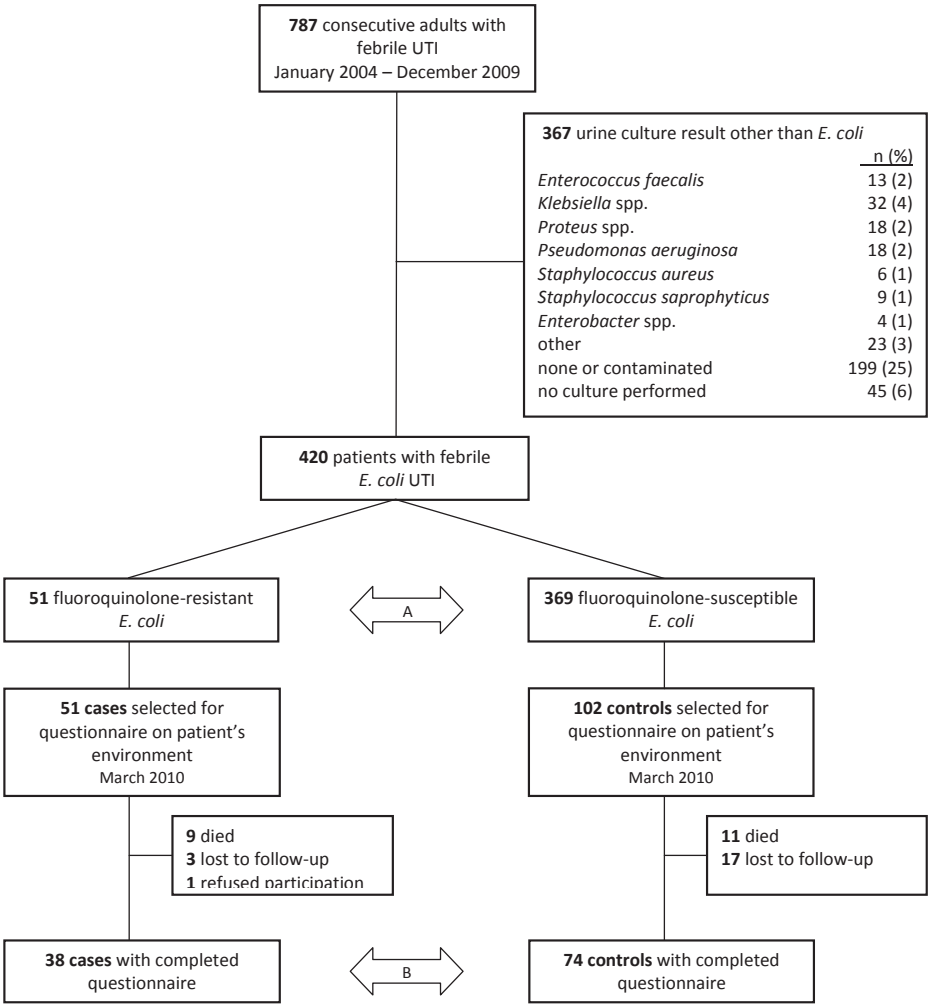

Figure 1. Flowchart of participants in the study
A: analysis of host-related risk factors for fluoroquinolone resistance,
B: analysis of environmental risk factors for fluoroquinolone resistance.

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 [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 that 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 (OR 6.0; 95% 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 past six months (OR 2.3; 95% CI 1.2-4.4) and fluoroquinolone usage past six months (OR 18.6; 95% CI: 6.6-52.4). None of the environmental characteristics were significantly associated with fluoroquinolone resistance, with ORs all around 1.

Independent risk factors for fluoroquinolone-resistant *E. coli* in the multivariate analysis were the presence of an 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 six 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 with a 26.7% risk to have fluoroquinolone-resistant *E. coli* compared to 330 patients with no risk factor who had a 8.2% risk to have 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-

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 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 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/sulfonamide	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.

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 of the 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 8 patients with ESBL-positive *E. coli,* 6 fulfilled the questionnaire; none of them had contact with animals. There were no statistically significant differences in the frequency of fluoroquinolone-resistant *E. coli* in between the years 2004 through 2009 and there was no trend towards a gradual increase (data not shown).

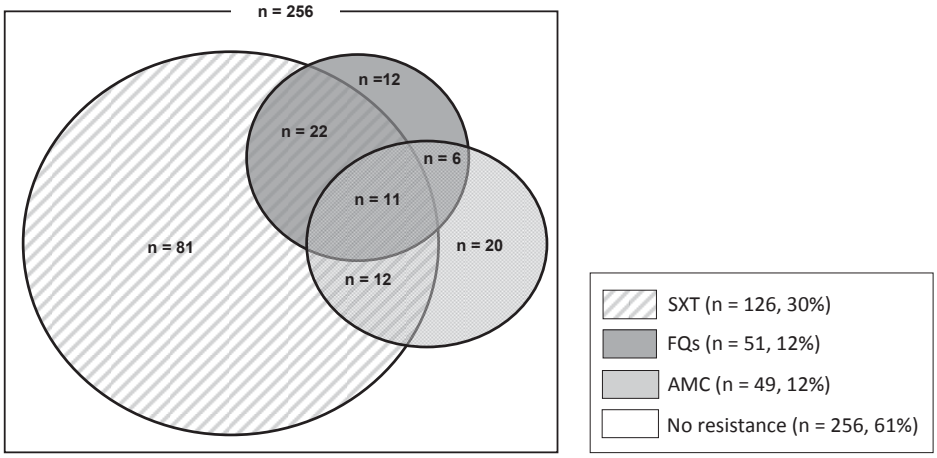

Figure 2. Distribution of resistance to oral antibiotics in 420 patients with febrile *E. coli* UTI. SXT: trimethoprim/sulfamethoxazole, FQs: fluoroquinolones, AMC: amoxicillin/clavulanate.

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 switched in 71% to another antibiotic after a median of 6.5 days [IQR 5.3-8.0] (Table 2).

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

Treatment			Outcome		
Empiric 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), meropenem (n=1)

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 six 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 for 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 health care centres and emergency departments participated.

There are however also some limitations. Our study had a relative 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 microbiological 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 fluroquinolone-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 a 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 to 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 be still 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 of 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 with fluoroquinolone resistance. In addition, other risk factors were discovered like previous invasive procedures[14], recurrent 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 likely 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 to previous studies we used an additional questionnaire to evaluate potential environmental risk factors for fluoroquinolone resistance. This was done retrospectively holding a risk for 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 with 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 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 2-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 relation between animal food supply and fluoroquinolone-resistant *E. coli* in humans revealed conflicting results but at least indicate this is might be a major concern for the community.[23,28,31,32]

In case of the 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 to less than 1% in 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 about 20% in patients with at least one of the three risk factors we identified, but even with no risk factor there was a 8% risk for fluoroquinolone resistance. Further studies are therefore be required in order to better stratify fluoroquinolone resistance risk in patients with febrile UTI.

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