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ARTICLE

Prevalence and risk factors for quinolone resistance among *Escherichia coli* strains isolated from males with community febrile urinary tract infection

A. Smithson · C. Chico · J. Ramos · C. Netto · M. Sanchez · J. Ruiz · R. Porron · M. T. Bastida

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Abstract The purpose of this study was to evaluate the prevalence and clinical risk factors for quinolone resistance (QR) in *E. coli* strains from males with febrile urinary tract infection (FUTI). An ambispective cross-sectional study was performed in which we evaluated 153 males with a community FUTI caused by *E. coli*. Among the 153 FUTI episodes, 101 (66%) were due to quinolone susceptible *E. coli* strains while 52 (34%) were caused by QR *E. coli* strains. In the univariate analysis QR was associated with older age, higher Charlson scores, dementia, past UTI, urinary tract abnormalities, previous antibiotic use, particularly with fluoroquinolones (FQ), a healthcare-associated (HA)-UTI (HA-UTI) and to four of the components included in the definition of HA-UTI: hospital admission, nursing home residence, indwelling urethral catheter and invasive urinary instrumentation. In the multivariate analysis, HA-UTI (OR 3.82, 95% CI 1.3–11.24; *P* 0.015) and use of antimicrobials in the previous month (OR 5.82, 95% CI 2.3–14.88; *P*< 0.001) mainly with FQ (OR 13.97, 95% CI 2.73–71.53; *P* 0.002) were associated with QR. To have a HA-UTI and a previous use of FQ in the preceding month were strong risk factors for QR *E. coli*, and thus empirical antimicrobial treatment with quinolones should be avoided in these patients.

A. Smithson (✉) · C. Netto
Emergency Department, Fundació Hospital de l´Esperit Sant,
C/Avinguda Mossen Pons i Rabadà s/n,
08923 Santa Coloma Gramenet, Barcelona, Spain
e-mail: asa30412@hotmail.com

C. Chico · J. Ramos · M. Sanchez · J. Ruiz · R. Porron
Internal Medicine Department,
Fundació Hospital de l'Esperit Sant,
Santa Coloma de Gramenet, Barcelona, Spain

M. T. Bastida
Microbiology Laboratory, Fundació Hospital de l'Esperit Sant,
Santa Coloma de Gramenet, Barcelona, Spain

Introduction

Escherichia coli is responsible for the vast majority of febrile urinary tract infections (FUTI) in men [1]. Although the clinical diagnosis of FUTI in males is relatively easy it is often difficult to establish the exact topographic location of the infection in the urinary tract. It has been demonstrated, with different diagnostic methods such as the measurement of serum prostate-specific antigen (PSA) [1] and the use of transrectal ultrasonography [2] and leukocyte scintography [3], that the prostate is the organ most frequently involved in males with FUTI. Thus, it is considered that most of these infections are in fact acute bacterial prostatitis (ABP) which correspond to the type I prostatitis in the NIH classification [4].

Quinolones, mainly fluoroquinolones (FQ), reach high concentrations in the prostatic tissue and in the seminal fluid and, therefore, are considered to be the first therapeutic choice in males with FUTI, except when resistance to these agents is confirmed or strongly suspected [5]. The widespread use of FQ in veterinary medicine and in the treatment of several human infectious diseases, mainly urinary tract infections (UTI), has led to an increasing resistance to these agents among *E. coli* isolates [6]. According to the European Antimicrobial Resistance Surveillance Network (EARS-Net) quinolone resistance (QR) has constantly been rising in Europe and this tendency is particularly relevant in Spain in which, as stated in their 2009 surveillance report, 30% of all invasive *E. coli* isolates are resistant to FQ, which limits empirical treatment with these antimicrobials [7].

Several studies have globally evaluated, both in women and males, risk factors for QR in *E. coli* strains isolated from patients with community acquired [8–10] or nosocomial UTI [11] but, to our knowledge, none has specifically

evaluated this issue in male patients with FUTI. In the setting of ABP, Etienne et al. found that 15% of the *E. coli* strains isolated from community acquired ABP and 36% of those strains isolated from patients with nosocomial ABP were resistant to FQ, although risk factors for QR were not assessed [12]. As quinolones are the optimal treatment of FUTI in men, identification of risk factors for QR would improve the selection of which males with FUTI could receive quinolones as empirical treatment. Recently, the importance of healthcare-associated (HA)-UTI has been recognised when classifying community infections. In a study by Khawcharoenporn et al. performed among patients with UTI diagnosed in an emergency department (ED) that included both women and males with either cystitis, pyelonephritis or urosepsis, the authors reported that those with HA-UTI had higher rates of levofloxacin resistance than patients with community-acquired (CA)-UTI [13]. The importance of HA-UTI as a risk factor for QR among *E. coli* strains isolated from males with FUTI has not been, to our knowledge, evaluated.

The objective of our study was to evaluate the prevalence and the clinical factors associated with QR among *E. coli* strains isolated from males with FUTI.

Materials and methods

This was an ambispective (retrospective and prospective) cross-sectional study in which we collected data from all male patients aged≥18 years with a community FUTI caused by *E. coli* that attended the ED of our 165-bed primary care hospital from January 2008 to January 2011. Data were recorded retrospectively from January 2008 to October 2009 and prospectively from October 2009 to January 2011. FUTI was defined as an armpit temperature≥38°C and one or more symptoms of UTI (urinary urgency, frequency and/or dysuria), in absence of other sources of infection. Patients with nosocomial infections, defined as infections that were noted 48 h after admission, were excluded from the study. The study was conducted with the approval of the hospital Ethics Committee.

Based on the previous accepted definitions of healthcare-associated bloodstream infections [14], HA-UTI was defined as those UTI affecting patients that fulfilled any of the following criteria: hospitalization in an acute care hospital for 2 or more days in the previous 90 days; residence in a nursing home or in a long-term care facility; received intravenous therapy at home or in a day hospital, hemodialysis treatment, intravenous chemotherapy, 30 days before the infection; received wound care or specialized nursing care in the preceding 30 days. We also included as HA-UTI those FUTI that occurred in patients with long-term indwelling urethral catheters or who had gone through an invasive urinary tract procedure in the previous 30 days. Patients who did not fit the criteria for HA-UTI were considered to have a CA-UTI.

A structured questionnaire including demographic and clinical data was completed for each patient. Clinical variables recorded were: age, dementia, HA-UTI, diabetes mellitus, chronic kidney failure (creatinine concentration> 1.2 mg/dl), cirrhosis, active neoplastic disease (solid tumor or hematologic malignancy diagnosed or treated in the past 5 years), chronic obstructive lung disease, chronic heart failure, use of any immunosuppressive agent including corticosteroids within 30 days of the FUTI, the Charlson comorbidity index [15] and antibiotic treatment prior to presentation of the UTI in the previous 30 days. We also recorded whether the patient had urinary tract abnormalities or previous UTI. Urinary tract abnormalities included: prostate benign hypertrophy or cancer, bladder diverticuli, urethral strictures, congenital abnormalities, renal lithiasis and cysts, neurological bladder and vesicoureteral reflux.

Urine samples were obtained from clean-catch midstream urine or from urinary catheters and cultured on MacConkey agar. Positive urine cultures were defined by bacterial growth$\geq 10^3$ colony forming units/mL [16]. Identification of *E. coli* was performed by means of standard methods. Patients with polymicrobial urine cultures were excluded from the study. Susceptibilities to amoxicillin, amoxicillin-clavulanic acid, cefuroxime, gentamicin, pipemidic acid, ciprofloxacin, trimethoprim-sulfamethoxazole (co-trimoxazole) and fosfomycin were tested by agar disk diffusion method according to the Clinical Laboratory Standards Institute criteria (CLSI) [17]. Intermediate and resistant *E. coli* strains to either of the antimicrobials tested were grouped together for data analysis. *E. coli* were catalogued as an extended-spectrum β lactamase (ESBL) producing strains in case of resistance to ceftriaxone, ceftazidime and/or to aztreonam, susceptibility to cefoxitin and evidence of synergism between amoxicillin-clavulanic acid and third generation cephalosporins, as recommended by the CLSI [17]. PSA levels were measured by monoclonal fluoro-immunoassay (normal PSA level, ≤ 4 ng/ml) in a subgroup of patients. This subgroup of patients did not include those with known active prostatic cancer.

Statistical analysis

Qualitative data are expressed as percentages. Quantitative data are expressed as mean (± standard deviations). Continuous variables are compared by the Student *t* test or the Mann-Whitney U test when the distribution departed from normality. Categorical data were compared

by using the chi-square or the Fisher exact test as appropriate. Any risk factor for QR with a borderline significant P value in the univariate analysis ($P \leq 0.1$) was included in a binary logistic regression analysis with QR as the dependent variable. Statistical significance was defined as a two-tailed P value of ≤ 0.05. Statistical analysis was carried out by the program SPSS (version 15.0; SPSS, Inc., Chicago, IL).

Results

During the study period, 153 patients with a community FUTI due to *E. coli* were attended in our ED. One hundred forty one (92.1%) of the *E. coli* strains were isolated from midstream urine and 12 (7.9%) from urinary catheters. Table 1 shows the clinical characteristics of the patients included in the study. One hundred twenty (78.5%) patients had a CA-UTI and 33 (21.5%) a HA-UTI. Sixty-six patients (43.1%) were elderly (≥ 65 years) and 68 (44.4%) had one or more associated long-term medical conditions. Among the patients with known urinary abnormalities, prostate benign hypertrophy was the most common and was present in 60 (39.2%) patients. Regarding physical examination, flank pain was present in 35/145 (24.1%) and prostate tenderness in 34/80 (42.5%) of the patients in which either lumbar or rectal examination were evaluated. Additionally, in 79 patients on whom both exploratory maneuvers were performed, flank pain and prostatic tenderness were simultaneously present in 5 (6.3%) cases and absent in 35 (44.3%) patients.

Table 1 Characteristics of the patients included in the study and univariate analysis of risk factors associated with community febrile urinary tract infection caused by quinolone resistant *E. coli* strains

Characteristic[a]	All patients (N=153)	QS *E. coli* (n=101)	QR *E. coli* (n=52)	P value[e]
Age (y)	60.7±17.1	58±16.9	66±16.6	0.006
HA-UTI	33 (21.5)	10 (9.9)	23 (44.2)	< 0.001
Hospital admission	18 (11.7)	4 (3.9)	14 (26.9)	< 0.001
Nursing home residence	6 (3.9)	1 (0.9)	5 (9.6)	0.018
IV home-day hospital treatment	1 (0.6)	1 (0.9)	0	1
Chronic hemodialysis	0	0	0	
Specialized nursing care	1 (0.6)	0	1 (1.9)	0.340
Indwelling urethral catheter	12 (7.8)	2 (2)	10 (19.2)	< 0.001
Invasive urinary instrumentation	19 (12.4)	4 (4)	15 (28.8)	< 0.001
Dementia	8 (5.2)	2 (2)	6 (11.5)	0.019
Diabetes mellitus	33 (21.5)	19 (18.8)	14 (26.9)	0.248
Chronic kidney failure	21 (13.7)	16 (15.8)	5 (9.6)	0.289
Cirrhosis	0	0	0	
Neoplasia	10 (6.5)	5 (5)	5 (9.6)	0.309
Heart failure	1 (0.6)	0	1 (1.9)	0.34
Chronic obstructive lung disease	20 (13)	12 (11.9)	8 (15.4)	0.543
Immunosuppressive or corticosteroid treatment	6 (3.9)	3 (3)	3 (5.8)	0.409
Charlson score	2.9±2.7	2.5±2.8	3.6±2.3	0.024
Previous urinary infection	61 (39.8)	29 (28.7)	32 (61.5)	< 0.001
Urinary abnormality	84 (54.9)	46 (45.5)	38 (73)	0.001
Previous antibiotic treatment[b]	36 (23.5)	10 (9.9)	26 (50)	< 0.001
Fluoroquinolones	19 (12.4)	2 (2)	17 (32.7)	< 0.001
Aminopenicillins	11 (7.1)	6 (5.9)	5 (9.6)	0.511
Cephalosporins[c]	3 (1.9)	2 (2)	1 (1.9)	1
Other antitibiotics[d]	2 (1.3)	0	2 (3.8)	0.11

HA-UTI healthcare-associated urinary tract infection, *QS* quinolone susceptible, *QR* quinolone resistant

[a] Data presented as mean±SD or numbers of patients (percentages)

[b] Information about the specific type of antimicrobial was absent in one patient who received an antibiotic course regarding an ITU

[c] Including second and third generation cephalosporins

[d] Corresponded to one patient taking spiramycin and another one taking metronidazole

[e] Univariate analysis of QS *E. coli* compared to QR *E. coli*

The resistance rates of the *E. coli* strains included in the study are shown in Table 2. Among the 153 *E. coli* isolates, 18 (11.7%) were resistant to pipemidic acid and 34 (22.2%) were also resistant to ciprofloxacin. Thus, 101 (66%) of the *E. coli* strains were catalogued as quinolone susceptible (QS) and 52 (34%) as QR. Table 2 also shows the univariate analysis of the antimicrobial resistance rate differences between QS *E. coli* and QR *E. coli* strains. QR *E. coli* strains were more frequently resistant to other antibiotics including amoxicillin-clavulanic acid, cefuroxime, gentamicin and co-trimoxazole. A higher frequency of ESBL was also observed in the QR *E. coli* strains.

Bacteremia was found in 23/103 (22.3%) patients from whom blood cultures were drawn. Among these 103 patients, bacteremia was present in 11/64 (17.2%) of the FUTI caused by QS *E. coli* strains and in 12/39 (30.8%) of the episodes caused by QR *E. coli* strains (P=0.1). Total PSA values were evaluated in 47 (30.7%) of the patients, with a mean value 18.92±29.86 ng/ml, and were elevated (≥ 4 ng/ml) in 31 (65.9%). Although FUTI episodes caused by QS *E. coli* strains had a higher degree of prostatic involvement (PSA levels 24.7±39.4 ng/ml) compared to those caused by QR *E. coli* strains (PSA levels 14.2±18.6 ng/ml), these differences were not statistically significant (P=0.23).

In the univariate analysis (Table 1) males with FUTI caused by QR *E. coli* strains were more likely to be older, to have a HA-UTI, dementia and higher Charlson scores. They also had a higher frequency of previous UTI, urinary tract abnormalities and antibiotic use in the previous month compared to their *E. coli* QS counterparts. We performed three multivariate models, as similarly done by others [18]. In each model we included those variables with a P value≤0.1 in the univariate analysis (Table 3). In the first (general) model we included HA-UTI and previous antibiotic use but not their individual components, such as the different forms of health care contacts or specific antimicrobials. The independent risk factors for a QR *E. coli* FUTI selected in this model were to have a HA-UTI and a previous antimicrobial use. In the second model we introduced the different components included in the HA-UTI definition with a P value≤0.1 in the univariate analysis, as shown in Table 1 (hospital admission, nursing home residence, indwelling urethral catheter, invasive urinary instrumentation), instead of HA-UTI, and the same variables as in the first (general) model. In this model, none of the variables included in the definition of HA-UTI that resulted as significant in the univariate analysis reached statistical significance in the multivariate model. In the third model we introduced FQ use, as this was the only antimicrobial with a P value≤0.1 in the univariate analysis, and the same variables as in the first (general) model. In this final model, prior treatment with FQ was associated with QR *E. coli* FUTI.

Regarding the antimicrobial empirical treatment, 77 (50.3%) patients were treated with cephalosporins, which represented the most common therapeutic option, followed by FQ in 46 (30%) patients and amoxicillin-clavulanic acid in 21 (13.7%). Only 7 (15.2%) out of the 46 patients that were treated with FQ received an inadequate treatment as the FUTI was caused by a QR *E. coli* strain. The mean duration of the treatment in the 153 patients included in the study was 16.7±6.8 days, without significant differences

Table 2 Resistance rates found in the *E. coli* strains included in the study and existing differences between quinolone susceptible and quinolone resistant *E. coli* strains

Antimicrobial agent[a]	All patients (N=153)	QS *E. coli* (n=101)	QR *E. coli* (n=52)	P value[f]
Pipemidic acid	18 (11.7)			
Fluoroquinolones	34 (22.2)			
Amoxicillin[b]	93 (61.1)	46 (45.5)	47 (92.1)	< 0.001
Amoxicillin-clavulanic acid	19 (12.4)	9 (8.9)	10 (19.2)	0.067
Cefuroxime sodium	8 (5.2)	2 (2)	6 (11.5)	0.019
Ceftriaxone[c]	5 (3.2)	1 (1)	4 (7.7)	0.046
Gentamicin[d]	9 (5.9)	0	9 (17.6)	< 0.001
Co-trimoxazole	41 (26.7)	15 (14.8)	26 (50)	< 0.001
Fosfomycin[e]	4 (2.6)	1 (1)	3 (5.8)	0.11

HA-UTI healthcare-associated urinary tract infection, *QS* quinolone susceptible, *QR* quinolone resistant

[a] Data presented as numbers of resistant isolates (percentages)

[b] Data referred to 152 *E. coli* strains (101 QS and 51 QR)

[c] Corresponded to extended-spectrum β-lactamase producing strains

[d] Data referred to 152 *E. coli* strains (101 QS and 51 QR)

[e] Data referred to 150 *E. coli* strains (99 QS and 51 QR)

[f] Univariate analysis of QS *E. coli* compared to QR *E. coli*

Table 3 Multivariate analysis of risk factors for community febrile urinary tract infections in males caused by quinolone resistant *E. coli* strains

Model[a]	OR (95% CI)	*P* value
General model		
Age, years		NS
HA-UTI	3.82 (1.3-11.24)	0.015
Dementia		NS
Charlson-score		NS
Previous urinary infection		NS
Urinary abnormality		NS
Previous antibiotic treatment	5.85 (2.3-14.88)	< 0.001
Model with specific types of health care contact[b]		
Hospital admission		NS
Nursing home residence		NS
Indwelling urethral catheter		NS
Invasive urinary instrumentation		NS
Model with specific antimicrobials[b]		
Fluoroquinolones	13.97 (2.73-71.53)	0.002

HA-UTI healthcare-associated urinary tract infection, *CI* confidence interval, *OR* odds ratio, *NS* not statistically significant

[a] Three models are presented. In the general model, "exposure to antimicrobial use" and "healthcare-associated infection" were analyzed as dichotomous variables. In the other two models, these two variables were substituted by the different types of "healthcare contact" and "exposure to antimicrobials" that had a *P* value≤0.1 in the univariate analysis

[b] The remaining variables that resulted as significant in the general model are not shown because the ORs and the *P* values were very similar

between FUTI episodes caused by QS or QR *E. coli* strains (data not shown).

When analyzing the destination of the patients, 57 (37.2%) were discharged from the ED, 32 (20.9%) were admitted to the observation unit (OU) of the ED, 62 (40.5%) were admitted to hospital, either to the internal medicine or the urology department and 2 (1.3%) were transferred to a tertiary care hospital. The mean hospital stay was 0.6±0.7 days for patients admitted to the OU and 4.6±2.7 days for those admitted to hospital. Those FUTI caused by QS *E. coli* strains required less days of hospitalization (1.6±2.6 days) compared to those episodes related to QR *E. coli* strains (2.7±2.9 days)(P=0.027). Two patients died, both with an QS *E. coli* urinary infection, one directly related to the infection (septic shock) and another one due to progression of a prostate cancer.

Discussion

In our study, 34% of the *E. coli* strains isolated from men with community FUTI were QR, the prevalence of which is significantly higher than previously reported by others in the literature although similar to the frequency of QR seen among invasive *E. coli* isolates reported in the 2009 EARS-Net surveillance report [7]. In Spain, Velasco et al. observed that 10% of *E. coli* strains responsible for community FUTI in males were QR [19] while Alos et al. found that 25% of the *E. coli* isolated from men with community UTI were QR [20]. In a study from patients with ABP, Etienne et al. evidenced that 15% of the *E. coli* strains causing community-ABP and 36% of those isolated from patients with nosocomial ABP were resistant to FQ [12]. On the other hand, Koijjers et al. have recently reported that only 3% of *E. coli* strains from men with UTI were QR, although patients with fever, urological complaints or with urinary catheters were excluded from this study [21].

In the present study, despite several variables were more prevalent in patients with an infection related to a QR *E. coli* strain, in the multivariate analysis, only a healthcare related acquisition of the UTI and the use of FQ in the preceding month remained associated to QR *E. coli*. The relationship between HA-UTI and QR has also been recently evidenced in a study performed by Khawcharoenporn et al. among patients with a community UTI attended in an ED. The authors observed that HA-UTI were more frequently caused by uropathogens resistant to FQ than CA-UTI [13]. In this study 10% of the *E. coli* strains isolated from CA-UTI and 39% of those isolated from patients with a HA-UTI were QR, frequencies which are very similar to the ones observed in our study. At present, one of the main problems when analyzing HA-UTI is that its diagnostic criteria are not properly defined. In 2002, Friedman et al. demonstrated that health associated bloodstream infections in adults were similar to nosocomial infections regarding the frequency of various comorbid conditions, source of infection, pathogens involved and their susceptibility pattern [14]. Since then, the definition of HA-bloodstream infection used by Friedman et al. has been incorporated, sometimes with minor differences, in different infectious settings.

In the field of urinary infections, although different studies have used adaptations of the definition of HA-UTI given by Friedman et al., to our knowledge not a single prospective study has evaluated the usefulness of these diagnostic criteria in UTI, and thus there is not an accepted definition for HA-UTI. The association of HA-UTI with QR suggests that the health care setting serves as a reservoir for QR and that patients acquire these QR *E. coli* resistant strains after establishing contact with it. This is supported by a study of Colodner et al. in which the authors observed a linear increase in the percentage of QR *E. coli* strains isolated from patients with CA-UTI depending on the number of previous hospitalizations [10]. Lautenbach et al. have recently demonstrated that gastrointestinal tract

colonization with *E. coli* showing reduced susceptibility to levofloxacin is common among hospitalized patients, which also supports the concept that a previous hospitalization is a potential source of acquisition of a QR *E. coli* strain [22].

Another interesting observation of our study was that QR *E. coli* strains were more frequently resistant to other antimicrobials, compared to the QS *E. coli* strains, which has previously also been reported by other authors [6]. Resistance to quinolones in *E. coli* most commonly arises in a stepwise manner as a result of an accumulation of chromosomal mutations within the genes encoding the quinolone targets [23]. In Gram-negative bacteria, mutations first affect the *gyrA* gene and tend to be present at certain locations [24]. Additional chromosomal mutations that affect the accumulation of quinolones, including those affecting either the expression of porins or those involved in regulatory genes which affect the activity of a wide range of efflux pumps are also involved in the development of QR in *E. coli* isolates [23]. Mutations that lead to an increased expression of multidrug efflux pumps, particularly of the AcrAB, may explain the higher frequency of resistance to other antimicrobials found in QR *E. coli* strains [25]. In a recent study, 50% of the *E. coli* strains with reduced susceptibility to levofloxacin showed increased drug AcrAB efflux pump expression, higher than previously seen, which suggests that this mechanism of resistance may be becoming widespread over time [25]. Resistance to FQ can also be transmitted through plasmids [26]. Strains that posses the quinolone plasmids encoded resistance are frequently associated with CTX-M enzymes that inactivate third generation cephalosporins, which may partially explain the frequent association, as observed in our study, between QR and ESBL production in Enterobacteriaceae [26].

The other variable that was associated with QR in the multivariate analysis was having received antibiotic treatment, particularly FQ, in the preceding month. The impact of antibiotic prescription on antimicrobial resistance has been evaluated in a meta-analysis by Costelloe et al. in which the authors found that antibiotics prescribed in primary care were associated with subsequent UTI caused by *E. coli* QR strains, particularly when administered in the preceding month [27]. Prior antibiotic use with quinolones has widely been recognised as a factor related to QR in *E. coli* strains causing community UTI [8–10, 13]. It has been demonstrated that prolonged administration of FQ in patients with ABP leads to a substitution in the faeces of the QS *E. coli* strains, isolated before treatment, by genetically distinct QR *E. coli* strains [28]. It has been speculated that these QR *E. coli* strains are not the result of the selective pressure exerted by FQ on intermediate-susceptible *E. coli* strains but rather the consequence of unmasking QR *E. coli* present in low numbers in the gastrointestinal tract before treatment or the acquisition of an exogenous QR *E. coli* strain during treatment [28]. These QR *E. coli* strains, colonizing the gastrointestinal tract, could be the source of the infection in men with FUTI and recent intake of FQ, following a "fecal-urethral" pathway. The "fecal-urethral" pathway, which is the route of infection in women with UTI, is not clearly the way of acquisition of the infection in men according to a study of Johnson et al. in which only a minority of men with FUTI had the same *E. coli* strain in rectal isolates and in urine, suggesting that an alternative infection route or exacerbations of a pre-existing chronic bacterial prostatitis (CBP) could be involved in the pathogenesis of UTI in men [29]. In our study, nearly 40% of the patients referred a history of previous UTI, which rose to 60% in the group of FUTI caused by QR *E. coli* strains.

Recurrent UTI in men are frequently associated with the existence of a subjacent CBP [1]. Mazzoli has demonstrated that *E. coli* strains isolated from patients with CBP are frequently biofilm producers, which in turn, has been recognised as one of the main causes of recurrent infections [30]. Although the data regarding the antibiotic susceptibility profile is not shown in the article by Mazzoli it is suggested that biofilm producer's strains showed high antimicrobial resistance, which could be related to a previous antimicrobial exposure. Patients with CBP usually receive long and recurrent antimicrobial courses, which frequently involve the administration of FQ. One might speculate that the administration of repeated therapeutic courses of FQ could expose *E. coli* strains present in the deep biofilm layers to sub-inhibitory concentrations of FQ, which could lead to the selection of QR strains that could cause subsequent episodes of UTI. In fact in our study a high proportion of patients with a FUTI caused by a QR *E. coli* strain had a previous history of UTI and had received FQ in the past month (data not shown).

The present study has some potential limitations that have to be taken into consideration. First of all, as previously mentioned, we have used a definition of HA-UTI that has not been supported by prospective studies. Second, we included as QR not only those *E. coli* strains resistant to ciprofloxacin but also those that were resistant to pipemidic acid and susceptible to ciprofloxacin while other studies, but not all [20], tend to evaluate only FQ *E. coli* resistant strains. Most *E. coli* isolates with diminished susceptibility to ciprofloxacin are resistant to nalidixic acid and carry a mutation in the *gyrA* gene [24]. *E. coli* strains susceptible to FQ that already carry a mutation in the *gyrA* gene can easily develop a second mechanism of resistance and therefore acquire higher levels of resistance in the presence of quinolones when compared to those not having the mutation [24]. The clinical importance of this eventuality has clearly been demonstrated in typhoid fever caused

by nalidixic resistant and ciprofloxacin susceptible *Salmonella typhi* strains in which the treatment with FQ is associated with a high risk of therapeutic failures [31]. Based on this evidence it has been suggested that invasive infections caused by nalidixic resistant and quinolone susceptible *Enterobacteriacea* strains should not be treated with FQ particularly if there is a high bacterial inoculum or if these agents achieve low concentrations at the location of the infection [32]. The importance of treating with FQ urinary infections caused by *E. coli* strains resistant to nalidixic acid and susceptible to ciprofloxacin has not been properly evaluated although the fact that most quinolones, particularly levofloxacin, have a renal elimination, probably limits the importance of this effect. The third consideration is that we have analyzed an apparent miscellaneous group of patients with FUTI, as we included males with acute pyelonephritis, ABP and those with FUTI without topographic location of the infection. This approach could be questioned but as stated in the Guidelines on Urological Infections from the European Association of Urology, most men with FUTI have a concomitant infection of the prostate and therefore should be considered as an ABP [33].

The importance of this study is that it not only confirms the significance of previously known risk factors for QR in men, mainly the existence of a previous exposure to FQ, but also highlights the relevance of new risk factors such as having had a recent health contact. Although FQ are considered the optimal treatment in males with FUTI, risk factors for QR such as whether the patient has an HA-UTI or whether he has received antibiotic treatment with FQ in the preceding month should be taken into consideration before initiating empirical treatment with these agents, at least until antimicrobial susceptibility tests are available for the clinician.

Conflicts of interest None to declare.

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