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Research article

Favoring Factors for Urinary Tract Infections due to Fluoroquinolone-Resistant *Escherichia Coli* in A Tertiary Care Department – Single Center Experience

Velma Rebic[1], Mufida Aljicevic[1], Amela Dzubur[1], Edna Supur[1] and Damir Rebic[2]*

[1]*Faculty of Medicine, University of Sarajevo, Bosnia and Herzegovina, Europe*

[2]*Clinic for nephrology, Clinical Center University of Sarajevo, Bosnia and Herzegovina, Europe*

***Corresponding author:** Damir Rebic, Clinic for nephrology, Clinical Center University of Sarajevo, Bosnia and Herzegovina, Europe

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Abstract

Background: Monitoring of antimicrobial resistance is a key component of antibiotic stewardship programs. Cross sectional studies from of a tertiary care center that have investigated favoring factors for fluoroquinolone-resistant *Escherichia coli* in man with urinary tract infection (UTI).

Methods: We performed a cross sectional study including 175 patients of the Department of Nephrology in whom E. coli was isolated from urine or blood cultures in a two-year period. Clinical data were collected from patients' records using a structured questionnaire. Multivariable analysis was performed for the detection of risk factors.

Results: Fluoroquinolone -resistant *E. coli* was detected in 22% of patients. Risk factors for ciprofloxacin-resistant *E. coli* included prior use of fluoroquinolones ($p<0.03$), prior urinary tract catheterization ($p<0.05$) and recurrent UTIs ($p<0.03$). 60.8% of all prescriptions in urinary tract infections were for fluoroquinolones, and this antibiotic class was the empiric antibiotic regimen of choice in 72.5% of all acute, uncomplicated, urinary tract infections.

Conclusions: The increasing prevalence of fluoroquinolone-resistant *E. coli* makes empiric therapy in UTIs with this agent questionable, especially in patients with one or several of the above-mentioned risk factors. Due to the increasing resistance rate, continuous surveillance and susceptibility testing in individual patients, particularly with complicated UTIs, is indispensable for adequate therapy.

Keywords: Fluoroquinolone; resistance; urinary tract infection; *escherichia coli*

Abbreviations: UTI - Urinary Tract Infection; FQ s- Fluoroqinolone; *E. coli - Escherichia coli*; CLSI - Clinical and Laboratory Standards Institute

Introduction

Urinary tract infection (UTI) remains one of the most common clinical entities necessitating antimicrobial therapy. The emergence and spread of drug-resistant uropathogens, particularly *Escherichia coli*, even among community-acquired UTI, has limited treatment choices [1,2]. This is of particular concern in developing countries where the capacity for resistance surveillance and access to healthcare are limited and over-the-counter drug purchase is rampant in the community. Prevalence and risk factors for trimethoprim–sulfamethoxazole-resistant *Escherichia coli* among women with acute uncomplicated urinary tract infection in a developing country [3,4]. The degree to which these rates reflect prevalence in the community is unknown. Additionally, reported risk factors for resistance among truly community-acquired uropathogens are limited to settings in the developed world [5,6]. The dearth of such information is alarming in light of the emergence of highly drug-resistant com-

munity-associated strains in the region [7]. Across Europe, levels of antibiotic consumption show great variations, with the use of fluoroquinolones being highest in Portugal and Spain.

As the emergence of resistance is associated with high antibiotic consumption [8], it is not surprising that resistance to ciprofloxacin in *E. coli* shows great geographical variations, too, reaching high levels in southern Europe and low levels in northern European countries [9]. In addition to attentive monitoring of resistance patterns, the identification of risk factors for infections with resistant strains may contribute to improved empirical treatment. Factors associated with resistance to ciprofloxacin in *E. coli* reported in previous studies are urinary tract abnormalities, older age, previous antimicrobial therapy (especially quinolone therapy), urinary catheterization, recurrent UTIs, male gender and presence of complicated UTI [10]. Resistance rates of in- and outpatients at our hospital ranged from 0 to 40% in 2008 [unpublished internal report]. The aims of this study were to determine resistance rates in patients with UTIs, to assess prescribers' choices for empirical antibiotic therapy, and to identify favoring factors for infections due to fluoroquinolone -resistant *E. coli* in patients at the Department of Nephrology, Sarajevo, Bosnia, and Herzegovina.

Methods

We performed a cross sectional study at the Department of Nephrology. All adult patients were included in whom *E. coli* was isolated from clinical urinary samples or blood cultures (in case of clinical symptoms suggestive of urinary tract infection but negative urinary culture) in the study period. Most of the patients presenting with complicated urinary tract infections are treated at the Department of Nephrology, including kidney transplant recipients. All specimens were tested in a central clinical microbiology laboratory in the Clinical Center. Bacteria were isolated from urine and blood cultures according to standard methods [11]. Antimicrobial susceptibility testing and screening for extended spectrum beta-lactamase (ESBL) was performed according to the Clinical and Laboratory Standards Institute (CLSI) [Clinical and Laboratory Standards Institute. 2008. Performance Standards for Antimicrobial Susceptibility Testing; Eigtheenth Informational Supplement 100-S18. Clinical and Laboratory Standards Instiute, Wayne, PA, USA.]. In the disk diffusion test, ciprofloxacin zone diameters of <15 mm and of >21 mm were considered resistant and susceptible, respectively; zones of 16–20 mm were considered as intermediately susceptible but were categorized as non-susceptible.

Some strains were tested by a commercial microdilution test, minimal inhibitory concentrations (MIC) of ciprofloxacin of <1 mg/L and of >4 mg/L were considered susceptible and resistant, respectively; an MIC of 2 mg/L was intermediately susceptible but was categorized as non-susceptible. The screening test for ESBL was an inhibition zone of <22 mm against ceftazidime or of <27 mm against cefotaxime. Any synergy between amoxicillin/clavulanic acid and ceftazidime or cefepime (double disk method), or between piperacillin/tazobactam and cefotaxime in the disk diffusion test was also an indication for a confirmation test by Etest according to the prescription of the manufacturer (Biodisk, Sweden); a greater than twofold concentration decrease in an MIC for ceftazidime or cefepime, or for cefotaxime tested in combination with clavulanic acid versus its MIC when tested alone was confirmatory for ESBL. In accordance with the CLSI guidelines, all ESBL-producing E. coli strains were classified as resistant to all penicillin's, cephalosporins and aztreonam regardless of the MICs determined for these drugs. Demographic and clinical information of both in- and outpatients was collected from each patient by chart review using a structured questionnaire.

Statistical analysis

Data were analysed using Stata Statistical Software, version 12.0 (StataCorp., College Station, TX, USA). Descriptive statistics were used to summarize patient characteristics and the prevalence of antimicrobial resistance. Univariate and multivariate analyses for putative risk factors for FQs-resistant *E. coli* were conducted. Logistic regression analysis was performed to identify risk factors for acquisition of fluoroquinolone-resistant *E. coli*. The level of significance was set at $p < 0.05$, using two-sided comparisons. The study was approved by the local Ethics committee.

Results

Of 229 patients with growth on culture, six had mixed pathogens. The most common organisms isolated were *E. coli* (76.2%), *Staphylococcus saprophyticus* (8.9%), and *Klebsiella pneumoniae* (3.4%) (Table 1). Four samples (2%) with ≥10 000 CFU/ml of coagulase-negative staphylococci as pure growth (n = 3) or mixed with *S. saprophyticus* (n = 1), with significant pyuria (>5/high-power field), were considered to have true pathogens. Patients' characteristics, clinical presentation and microbiological findings are summarized in Table 2. The median age was 56.8 (51.9–60.4) years. The most common diagnosis was acute UTI (29%). FQs-resistant *E. coli* was isolated in 61 patients. 60.8% of initial antibiotic prescriptions were for fluoroquinolones, and 7% were for sulfamethoxazole-trimethoprim. Fluoroquinolones were the empiric antibiotic therapy of choice in 72.5% of all acute. The characteristics of patients with ciprofloxacin-resistant strains were compared with those of patients with a ciprofloxacin-susceptible strain (Table 3).

Table 1: Pathogens in urinary tract infections.

	Number (n = 235)	%
Escherichia coli	179	76.2
Klebsiella pneumoniae	8	3.4
Enterobacter aerogenes	4	1.7
Citrobacter	3	1.3
Proteus mirabilis	3	1.3

Gram-positive		
Staphylococcus saprophyticus	21	8.9
Staphylococcus aureus	7	3.0
Streptococcus agalactiae	3	1.3
Staphylococcus hominis	2	0.9
Enterococcus faecalis	2	0.9
Staphylococcus haemolyticus	1	0.4

Table 2: Patients characteristics.

	FQs susceptible *E.coli* (174pts)- %	FQs resistant *E.coli* (61pts) - %	
Age, median (95% CI)	55.5 (49.2–58.1)	63.8 (54.0–70.0)	0.062
Female	57	50	0.312
Male	43	51	0.312
Asymptomatic bacteriuria	19	20	1.000
Asymptomatic bacteriuria with urinary catheter	8	15	0.148
Uncomplicated UTI	35	10	<0.001
Acute pyelonephritis	7	2	0.132
Complicated UTI	24	46	0.002
Bacteremia	0	2	0.222
Other/unclear diagnosis	6	7	1.000

Table 3: Favoring factors for UTI with FQs-resistant *E. coli*.

Number of patients	174pts- %	61 pts - %				
Male	43	51	1.34 (0.76–2.38)	0.309	1.57 (0.77-3.17)	0.212
Age >60 years	36	48	1.58 (0.89–2.81)	0.119	1.00 (0.50-2.01)	0.995
In-hospital treatment	29	57	3.30 (1.83–5.94)	<0.001	1.98 (0.95-4.12)	0.069
Diabetes mellitus	7	5	0.69 (0.19–2.45)	0.562		
Malignoma	10	18	0.88 (0.10–7.98)	0.906		
Nosocomial infection	2	2	0.88 (0.10–7.98)	0.906		
Recurrent urinary tract infection	34	54	2.28 (1.28–4.05)	0.005	2.26 (1.07–4.78)	0.032
Urologic surgery in last 12 months	19	44	3.35 (1.82–6.16)	<0.001		
Foreign material in upper urinary tract in last year	6	20	3.79 (1.63–8.81)	0.002		
Urinary catheter in last year	18	54	5.29 (2.87–9.75)	<0.001	2.41 (1.02–5.67)	0.044
FQs in last year	23	59	4.85 (2.66–8.85)	<0.001	2.24 (1.08–4.62)	0.030
Any antibiotics in last year	26	51	2.92 (1.62–5.25)	<0.001	1.59 (0.79–3.20)	0.195
Hospitalisation in last year	10	38	5.28 (2.68–10.43)	<0.001	1.28 (0.50–3.26)	0.607
Kidney disease	2	5	2.72 (0.59–12.48)	0.199	1.97 (0.32–12.06)	0.464
Kidney transplant	5	7	3.55 (0.22–57.60)	0.373		

Significant predictors of ciprofloxacin-resistant *E. coli* in univariable analysis were hospital status, recurrent UTIs, urolithiasis, urinary catheter, prior use of fluoroquinolones, prior use of any antibiotics and prior treatment in the Department of Nephrology. To identify independent risk factors, a multivariable analysis was performed. Thereby, fluoroquinolone use in the preceding year (odds ratio [OR] (95% confidence intervals [CI]): 2.24 (1.08–4.62), p= 0.03), urinary tract catheterisation in the preceding year (OR: 2.41 (1.02–5.67), p= 0.04) and recurrent urinary tract infections (OR: 2.26 (1.07–4.78), p= 0.02) were found to be independently associated with infection or colonisation with a FQs-resistant strain. A further analysis of prior antibiotic use is depicted in Table 4. Only one cycle of fluoroquinolone treatment in the preceding year significantly increased the odds of being infected or colonised with a FQs-resistant *E. coli* strain, whereas one cycle of any antibiotic in last year did not. However, the odds were significantly increased when multiple antibiotic cycles were recorded, regardless of the antibiotic class used. The cumulative antibiograms of FQs-resistant and FQs-susceptible *E. coli* strains are shown in Table 4 too.

Table 4: Antibiotic treatmen in last year and cumulative antibiogram of *E.coli* isolates.

	Susceptible *E.coli*	Resistant *E.coli*	
Number of patients	174 pts- %	61 pts - %	
No prior treatment	61	23	<0.01
Fluoroquinolones	23	59	0.032
All antibiotics	39	77	<0.001
Cumulative antibiograms of *E. coli* isolates (No)			
Ciprofloxacin	174	**61**	
Amoxicillin-clavulanate	6	17	<0.001
Ampicillin	71	83	<0.001
1st generation *Cephalosporins*	9	27	<0.001
Gentamicin	3	39	<0.001
Piperacillin-tazobactam	5	4	0.262
Sulfamethoxazole and trimethoprim	39	57	<0.001
Ceftazidime	3	12	<0.001
Ceftriaxone	1	12	<0.001
Meropenem	5	0	0.329

Discussion

This study provides the prevalence and risk factors for antimicrobial resistance of uropathogens among inpatients with UTI. Two other prospective studies from developing countries enrolled adult outpatients with community-acquired UTI but included both men and women with uncomplicated and complicated infections [12,13]. Thus, their findings, which as expected showed much higher rates of antimicrobial resistance, may not be comparable to ours. The aim of this study was to identify risk factors for colonization or infection with FQs-resistant *E. coli* in patients treated at the Department of Nephrology. Recurrent urinary tract infections, urinary catheterization within the last year and use of fluoroquinolones in the last year turned out to be independently associated with FQs-resistant strains. Those resistant strains were often also resistant to other antibiotics, mostly against ampicillin. Fluoroquinolones turned out to be the most frequently prescribed antibiotics for treatment of acute UTI, and pyelonephritis.

Our study documents risk factors for UTIs caused by FQs-resistant *E. coli* in patients at a tertiary care center. The population studied is exceptional in respect to the high prevalence of diseases that facilitate urinary tract infections, for example urinary tract obstructions, or foreign material in the upper and lower urinary tract. The study has several limitations. Charts of outpatients are usually not as detailed as those of inpatients, probably accounting for systematic deviations in the availability of information. In outpatients, antibiotic therapy for UTI is usually started empirically and cultures are only performed if the patient fails to respond to treatment, has recurrent episodes of UTI or has complicated UTI [14,15]. Thus, data on resistance rates based on laboratory surveillance may overestimate the true levels of antibiotic resistance in the community, accounting for selection bias. Among the potential risk factors assessed for FQs resistance, only the number of UTI episodes in the previous year was shown to be a significant predictor. Prior antimicrobial use (which has classically been linked to resistance), regardless of class and time elapsed before the incident episode, did not predict resistance.

This lack of association was unexpected and difficult to reconcile with the finding of the number of past UTI episodes (which would likely trigger antimicrobial intake) as a risk factor. Failure to find an association could be due to a type II error, i.e., the association could be in a range below what our study was able to detect. Data on time elapsed were not available for 19% of those who had claimed past antimicrobial exposure, thus decreasing the sample available for risk assessment. Moreover, we had to rely on individual recall of antimicrobial usage and could not quantify the degree of exposure in terms of regimen duration and dosage. Thus, we could have missed identifying any possible link between individual antimicrobial exposure and resistance. In a systematic review of the effect of antimicrobial prescribing in primary care on drug resistance in individual patients, a dose–response relationship, particularly for trimethoprim and amoxicillin, was observed [16]. Prior to this meta-analysis, several studies that attempted to assess the relationship between antimicrobial consumption and *E. coli* resistance showed conflicting results.

Risk factors for FQs-resistant *E. coli* in UTIs have been presented by other authors [17,18]. The results of our study are in agreement with risk factors previously reported, with prior exposure to fluoroquinolones being the most commonly described factor to increase risk. Whereas other authors tried to find an association with the presence of a urinary catheter at the time of detection of the ciprofloxacin-resistant strain [19], we included prior urinary tract catheterization within one year as a possible risk factor. However, multivariable analysis did not reveal prior urinary tract catheterization as an independent risk factor. Others have been able to show a correlation between age and fluoroquinolone resistance [20], whereas we could not. Differences between studies may have arisen due to different settings, different populations under study, and, to some extent, disregard of collinearity and co-causality in multivariable analyses.

During the study period, FQs was only recommended as a first-line agent in the treatment of uncomplicated acute pyelonephritis. The results of our study show that those recommendations were not followed properly, as FQs turned out to be the most frequently prescribed antibiotic for treatment of acute, uncomplicated UTIs. The fact that FQs are often given inappropriately is alarming. Some authors demonstrated that most participants underestimated fluoroquinolone use in the management of acute, uncomplicated lower UTI and that they considered the high level of usage to be inappropriate and creates risk of increased resistance [21]. This suggests that part of decreasing the usage of fluoroquinolones is to inform clinicians about their high prescription rate as they tend to underestimate their use and are sometimes not aware of the high selection pressure. How generalizable are our findings? In increasingly urbanized developing countries with rising incomes and ready access to healthcare, comparable antimicrobial resistance patterns may be observed in community pathogens causing acute uncomplicated UTI.

Unfortunately, this remains conjectural because similar prospective studies from other developing countries have yet to be reported. Several other factors such as non-human antimicrobial usage, the availability of substandard drugs, a lack of antimicrobial stewardship, and other environmental influences would need to be considered to determine the applicability of our findings to developing countries in the region.

Conclusion

In summary, our findings support the recommendation for the use of FQs, and not TMP–SMX, as the first-line empiric treatment for acute uncomplicated UTI. Based on the low resistance profile, oral first- and second-generation cephalosporins appear to be acceptable. Unfortunately, such antimicrobial choices are more costly than TMP–SMX. Nonetheless, resistance of *E. coli* is not only selected using fluoroquinolones, but also using unrelated antimicrobial classes including ampicillin, amoxicillin, trimethoprim, or sulfamethoxazole alone, and trimethoprim-sulfamethoxazole [22,23]. Therefore, to decrease selection pressure to those 'classic' antibiotics, more frequent use of other antibiotics, for example nitrofurantoin and Fosfomycin, may be considered. In complicated UTIs, microbiological testing is essential to ensure adequate therapy because of high resistance rates. Our findings need to be confirmed by larger studies in more diverse settings and replicated in other developing countries.

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