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Antimicrobial Original Research Paper

The incidence and risk factors of resistant *E. coli* infections after prostate biopsy under fluoroquinolone prophylaxis: a single-centre experience with 2215 patients

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We evaluated the incidence and risk factors of resistant *Escherichia coli* infections after the prostate biopsy under flouroquinolone prophylaxis. From January 2003 to December 2012, we retrospectively evaluated the records of 2215 patients. The risk factors were described for infective complications and resistant *E. coli* in positive cultures was calculated. Of 2215 patients, 153 had positive urine cultures, such as 129 (84.3%) *E. coli*, 8 (5.2%) *Enterococcus* spp., 6 (3.9%) *Enterobacter* spp., 5 (3.2%) *Pseudomonas* spp., 3 (1.9%) MRCNS, and 2 (1.3%) *Klebsiella* spp. Of the positive urine cultures which yielded *E. coli*, 99 (76.7%) were evaluated for fluoroquinolone resistance. Of those, 83 (83.8%) were fluoroquinolone-resistant and composed of 51 (61.4%) extended-spectrum beta-lactamase (ESBL)-positive. Fluoroquinolone-resistant *E. coli* ratios were 73.4 and 95.9% before 2008 and after 2008, respectively (P=0.002). The most sensitive antibiotics for fluoroquinolone-resistant *E. coli* strains were imipenem (100%), amikacin (84%) and cefoperazone (83%). The use of quinolones in the last 6 months and a history of hospitalization in the last 30 days were found to be significant risk factors. We found that resistant *E. coli* strains might be a common microorganism in patients with this kind of complication. The risk factors for development of infection with these resistant strains were history of the use of fluoroquinolones and hospitalization

Keywords: Prostate biopsy, Resistant *E. coli*, Risk factors

Introduction

Transrectal ultrasound (TRUS)-guided prostate biopsy is the most common method utilized in the diagnosis of prostate cancer.[1] Following the biopsy, some complications such as rectal or perineal bleeding, haematuria, fever, and infection can occur.[2] The most serious complications of prostate biopsy are the urinary tract infection and bacterial sepsis. Several studies have reported that bacteremia ratio was 16–73% after prostate biopsy.[3,4] The use of prophylactic antibiotics in the prevention of these complications is very important. Although there is not a guideline for the procedure, the majority of physicians use antibiotic prophylaxis and colon cleansing with rectal enema before biopsy. Regarding the antibiotic prophylaxis before biopsy, although there are different proposals in the literature, a clear regime was undefined. However, most studies admit that fluoroquinolone prophylaxis is helpful in preventing infective complications.[5]

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A committee report, which reviewed 88 urology units' data in 2002, stated that the rate of response to quinolone was 81% and it was still safe in this area.[6] Fluoroquinolones are strong antibiotics providing broad coverage for common colonic flora. They also penetrate well into the normal prostate gland. Coupled with their overall safety and ease of use, they become the agent of choice. On the other hand, their excessive consumption in different areas caused quinolone resistance. Resistance mechanisms of microorganisms such as creating a change to antibiotic target enzyme or secreting enzymes as beta-lactamase, which inactivates antibiotics, can be observed.[7,8]

In the present study, we evaluated the incidence of resistant *Escherichia coli* infections after prostate biopsy under flouroquinolone prophylaxis and risk factors which caused infections with resistant microorganisms.

Material and Methods

From January 2003 to December 2012, we retrospectively evaluated the records of 2215 patients who underwent TRUS-guided prostate biopsy. The institutional ethics

committee approved this study. The indications for prostate biopsy were abnormal digital rectal examination findings and/or elevated serum prostate specific antigen level. All patients received cleansing enema before the biopsy. The participants received 500 mg of oral ciprofloxacin 1 hour before the biopsy and 12 hours after the procedure. An automatic biopsy gun with an 18-gauge 22 cm needle was used to obtain 12-core prostate biopsy (7.5-MHz transrectal probe; Siemens Sonoline, Erlangen, Germany). The patients were admitted to our hospital for one night for the potential complications, including haematuria, fever, urinary retention, and anal bleeding. If no complication was observed, we discharged them from the hospital on the following morning.

Urine culture was performed before prostate biopsy to rule out urinary tract infection and asymptomatic bacteriuria.

The clinical diagnosis of infective symptoms secondary to prostate biopsy was attained by a body temperature $>38^{\circ}C$ with or without chills in association with significant lower urinary tract symptoms, leukocytes in urine sediment, leucocytosis (greater than 10 000 cells/ml), and the absence of other clinically apparent sources of infection. Patients having infective symptoms within seven days after biopsy were enrolled in this study. The symptoms were associated with the biopsy procedure. Any event more than 7 days after prostate biopsy was unlikely to be related to TRUS-guided biopsy. For patients who developed pyuria (10 white blood cells/mm^3), samples of urine cultures were obtained for bacteriology and antibiotic susceptibility. Antibiotic susceptibility of defined bacteria was determined according to CLSI suggestions, using Kirby–Bauer disk diffusion method in Muller–Hinton agar. Antibiotic susceptibility results were reported as susceptible, intermediate, and resistant.

Microorganisms which were produced extended-spectrum beta-lactamase (ESBL), were described by using double disk synergy test method.[9] Potential risk factors for the development of flouroquinolon resistance and ESBL producing, including age, diabetes mellitus, hypertension, prior use of quinolons within six months, history of hospital admission within 30 days, and the first or repeat biopsies, were evaluated. Year by year, antibiotic resistance and frequencies of infection were presented as counts and proportions. The relationship between year grouping and antibiotic resistance and dependency of *E. coli* positivity on year grouping (before 2008 and after 2008) were evaluated. Univariate effects of risk factors including age, diabetes mellitus, hypertension, prior use of quinolons within six months of the biopsy, history of hospital admission within 30 days, and the first or repeat biopsies on *E. coli* positivity and ciprofloxacin sensitivity were evaluated. Chi-square test or Fisher's Exact test were used all these comparisons. Independent *t*-test was used to compare age means between infected and non-infected patients. The level of statistical significance was set at 0.05.

Results

Of the 2215 patients, 2005 underwent first biopsy and 210 repeat biopsies. The average age of the patients included in the study was 66.5 ± 8.6 (37–85). The mean age of patients who had/had not infectious complications was similar. (65.5 versus 66.7).

Clinically and laboratory, none of the patients were suspected of having a urinary tract infection, asymptomatic bacteriuria or acute prostatitis before biopsy. The patients developed infective symptoms at an average 4 days after prostate biopsy. Of 2215 patients, 306 (13.8%) had symptoms of infection, including fever, dysuria, and pyuria leucocytosis. Among these, 153 (50%) had positive urine cultures (Fig. 1). Of the positive urine cultures that yielded *E. coli*, 99 (76.7%) were evaluated for fluoroquinolone (ciprofloxacin) resistance. In these group, 83 (83.8%) were fluoroquinolone-resistant. In addition, 129 *E. coli* strains were examined for ESBL producing and ESBL positivity was found in 67 (51.9%) of these strains.

Antibiotic susceptibility results of all *E. coli* strains and ciprofloxacin-resistant *E. coli* strains is shown on Table 1. Ciprofloxacin and other antibiotic susceptibility results of ESBL-producing *E. coli* strains are shown on Table 2.

It is observed that ESBL-producing strains are resistant to many antibiotics except carbapenems. When quinolon resistance of *E. coli* strains were evaluated according to years' fluoroquinolone-resistant *E. coli* ratios were 73.4 and 95.9% before 2008 and after 2008, respectively ($P=0.002$). In the same way, changes in rates of ESBL-producing *E. coli* are 45.9 and 57.4%, respectively ($P=0.003$). The most sensitive antibiotics for fluoroquinolone-resistant or ESBL-producing *E. coli* strains were imipenem (100 and 100%, respectively), amikacin (84 and 73.8%, respectively), and cefoperazon (82.8 and 72.7%, respectively). When the risk factors regarding the infection caused by ESBL-producing or quinolon-resistant *E. coli* strains were examined, the use of quinolones in the last 6 months and a history of hospitalization in the last 30 days were found to be significant (Table 3).

Discussion

Our study showed that while fluoroquinolone prophylaxis started before TRUS-guided prostate biopsy is still effective in preventing infectious complications that might develop after biopsy, fluoroquinolone-resistant or ESBL-producing *E. coli* strains might be a common microorganism in patients with this kind

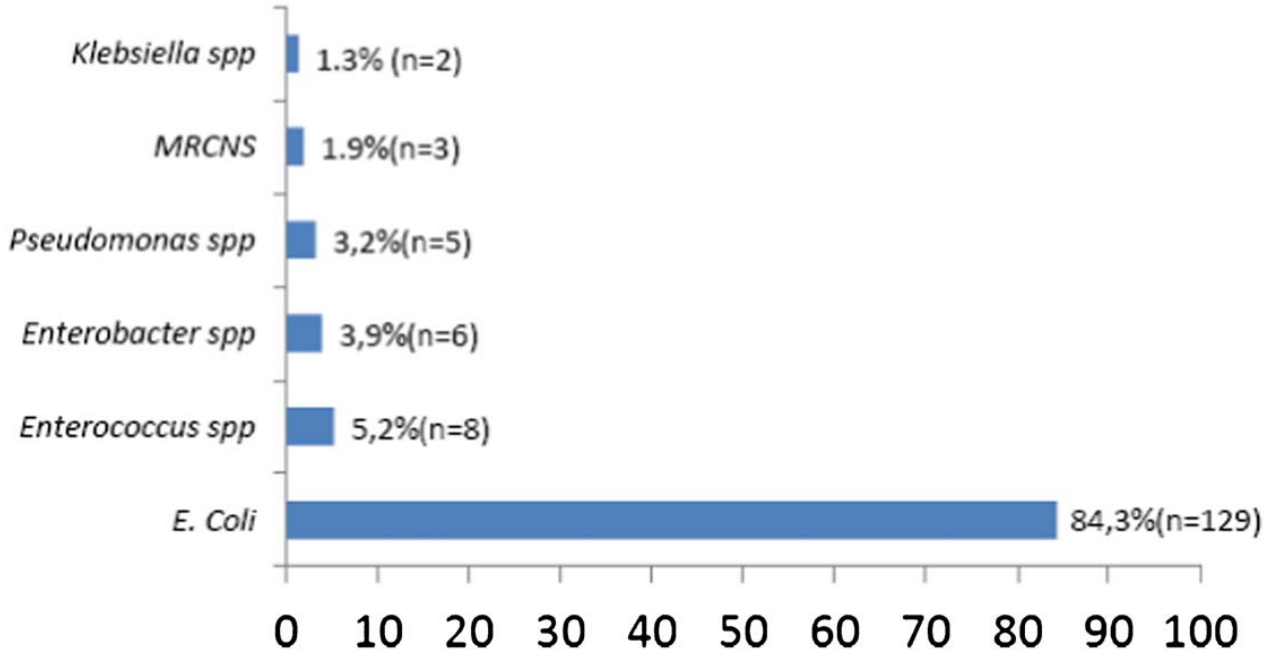

Figure 1 The results of positive urine cultures.

of complication. There are various studies about the antibiotics to be used for prophylaxis in patients scheduled for prostate biopsy.[10,11] Fluoroquinolones are the most accepted antibiotics, due to their broad coverage for the common colonic flora, in particular the coliforms. Fluoroquinolones also have a well penetration in the normal prostate gland.[5,12] In addition, due to their overall safety and ease of use, they become the agent of choice. Complications associated with infection after prostate biopsy are well defined in the literature and the reported rates range from 1.7 to 11.3% despite antibiotic prophylaxis.[13,14] One of the most serious complications among those are urinary tract infections and bacterial sepsis. In the relevant studies, the most frequently isolated microorganism in both blood and urine samples is *E. coli*.[15] In our study, the rate of complications associated with infection after prostate biopsy was 13.8% and the most frequently isolated microorganisms was *E. coli* (84.3%).

Different studies showed that there was a steady increase in hospitalization rates due to infectious complications after prostate biopsy and the most common agent in the relevant cases was fluoroquinolone-resistant *E. coli*.[2,16,17] In our study, the fluoroquinolone resistance rate in samples producing *E. coli* strains was 83.8%. When the time periods before and after 2008 were compared, fluoroquinolone resistance rate in *E. coli* strains significantly increased after 2008 (73.5% against 95.9%, respectively). Ozden *et al.* reported that ESBL-producing *E. coli* was isolated as well as quinolone-resistant *E. coli* in infections that developed after prostate biopsy.[18] They found that 43% of the *E. coli* strains produced ESBL. Similarly, in our study, 51.9% of a total of 129 *E. coli* strains produced ESBL.

We examined various risk factors for the development of infection in both ESBL-producing strains and strains that developed resistance to fluoroquino-

Table 1 Antibiotic susceptibility results of all *E. coli* strains and ciprofloxacin-resistant *E. coli* strains

	All *E. coli* strains (n=153)		Ciprofloxacin-resistant *E. coli* (n=83)	
	Number	Resistant (%)	Number	Resistant (%)
Amikacin	118	19	81	16
Ceftazidime	49	51	34	50
Ampicillin	81	93	48	96
Cefepime	69	64	46	70
Cefoxitin	77	42	52	37
Ceftriaxone	115	66	83	72
Cefuroxime	102	76	71	80
Ciprofloxacin	99	84	83	100
İmipenem	116	0	83	0
Trimethoprim-sulfamethoxazole	109	73	71	70
Piperacillin	26	35	15	60
Gentamicin	105	55	68	59
Cefoperazone	44	14	29	17
Tobramycin	23	74	13	77

Table 2 Antibiotic susceptibility results of ESBL-producing *E coli* strains

Antibiotics	*E. coli* (*n*)	Resistance (%)	*P* value
Amikacin	ESBL+ (65)	26.2	0.020
	ESBL− (53)	9.5	
Ceftazidime	ESBL+ (34)	70.5	<0.001
	ESBL− (15)	6.6	
Ampicillin	ESBL+ (46)	100	0.212
	ESBL− (35)	82.8	
Cefepime	ESBL+ (45)	93.4	<0.001
	ESBL− (24)	8.4	
Cefoxitin	ESBL+ (51)	54.9	0.001
	ESBL− (26)	15.4	
Ceftriaxone	ESBL+ (66)	93.9	<0.001
	ESBL− (49)	28.6	
Cefuroxime	ESBL+ (60)	98.3	<0.001
	ESBL− (42)	45.3	
Ciprofloxacin	ESBL+ (54)	94.5	0.003
	ESBL− (44)	72.7	
Imipenem	ESBL+ (67)	0	…
	ESBL− (49)	0	
Piperacillin	ESBL+ (10)	60	0.046
	ESBL− (16)	18.7	
Trimethoprim-sulfamethoxazole	ESBL+ (61)	75.5	0.665
	ESBL− (48)	70.9	
Gentamicin	ESBL+ (56)	71.5	<0.001
	ESBL− (49)	36.8	
Cefoperazone	ESBL+ (22)	27.3	0.021
	ESBL− (22)	0	
Tobramycin	ESBL+ (13)	77	1.000
	ESBL− (10)	70	

lones. A history of the use of fluoroquinolones in the last 6 months and hospitalization in the last 30 days were found to be significant. It was reported that a history of the use of third-generation cephalosporin and quinolone was described as an independent risk factor for the development of infection in quinolone-resistant or ESBL-producing microorganisms.[1,19–21] Finally, our results were in accordance with the literature in this regard.

The main reason why we observed infection by ESBL-producing microorganisms especially in patients with a history of hospitalization in the last month might be the wide use of broad-spectrum antibiotics in our hospital. Unnecessary or improper use of antibiotics produce resistant strains and colonization over time initially and then infection in appropriate circumstances.

The other risk factors (e.g. diabetes mellitus, hypertension, age, number of biopsies) showed no significance in terms of the development of infection with resistant strains. These findings are comparable with the results of previous studies.[1,22] The reason why we had no significance between development of infection with resistant microorganisms and recurrent biopsies was the fact that the time elapsed between the biopsies was probably more than a year.

The study found that the most effective antibiotic in infections caused by both quinolone-resistant and ESBL-producing *E. coli* strains was carbapenems, including imipenem, followed by amikacin and cefoperazone. Of course, we do not suggest that these antibiotics should definitely be used in empiric treatment in infectious complications developing after prostate biopsy. This result only reflects the situation in our centre. In this regard, every centre needs to select empiric antibiotics on the basis of local distribution of pathogens and antibiotic susceptibility data.

Table 3 Risk factors for infections caused by resistant *E. coli* strains

Risk factors		ESBL+ (%)	ESBL− (%)	*P* value	Ciprofloxacin resistance (%)	Ciprofloxacin susceptible (%)	*P* value
Age (mean)		66.4	65.7	0.271	65.4	66.0	0.741
DM	Yes	43.5	56.5	0.491	85	15	1.000
	No	53.8	46.2		84.6	15.4	
HT	Yes	59.6	40.4	0.156	88.9	11.1	0.400
	No	45.8	54.2		81.1	18.9	
History of hospital admission within 30 days	Yes	88.9	11.1	**0.034**	85.7	14.3	**0.041**
	No	49.2	50.8		44.6	55.4	
Prior use of quinolons within 6 months of the biopsy	Yes	100	0	**0.000**	87.5	12.5	**0.021**
	No	47	53		34.4	65.6	
Biopsy	First	52.3	47.7	1.000	84.3	15.7	1.000
	Repeat	50	50		86.7	13.3	

As for the answer to the question of whether we should change our antibiotic prophylaxis in patients undergoing prostate biopsy or not, quinolone prophylaxis still seems to work considering the fact that the microorganisms can be isolated in 153 (6.9%) of a total of 2215 patient's urine samples. Nevertheless, alternative regimens of prophylaxis can be considered particularly in patients with a history of the use of quinolone or recent hospitalization.

The current study has some limitations as it is a retrospective study and the number of samples that can be evaluated is relatively small, although it is currently the largest series reported from a single centre. On the other hand, this study could be considered significant as it suggested that the agent might be the resistant microorganisms and the determined risk factors in patients with infectious complications developing after prostate biopsy. It is clear that more extensive studies are required to investigate the prospective and possible risk factors related to this subject.

In conclusion, quinolone-resistant or ESBL-producing *E. coli* strains were found to be the common microorganisms in infections occurring after TRUS-guided prostate biopsy under quinolone prophylaxis. The most important risk factors for the development of urinary tract infection caused by these microorganisms were a history of the use of quinolones and hospitalization.

Disclaimer Statements

Contributors Özlem Kandemir: conception and design of study, interpretation, drafting of manuscript, approval of final version of manuscript; Murat Bozlu: data analysis and interpretation, approval of final version of manuscript; Ozan Efesoy: acquisition of data, approval of final version of manuscript; Onur Gültekin: acquisition of data, approval of final version of manuscript; Mesut Tek: acquisition of data, approval of final version of manuscript; Erdem Akbay: data analysis, approval of final version of manuscript.

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Ethics approval The institutional ethics committee approved this study.

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