

## Prevalence and Significance of Fluoroquinolone-resistant Bacteria Carriage in Patients Undergoing Transrectal Ultrasound Prostate Biopsy

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**Purpose:** To determine the prevalence of fluoroquinolone-resistant (FQR) bacteria carriage in patients undergoing transrectal ultrasound prostate biopsy (TRUS-Bx), and the relationship between the risk factors and FQR carriers as well as infections after prostate biopsy.

**Materials and Methods:** Rectal swabs were obtained from 158 patients undergoing TRUS-Bx. The FQR organisms were isolated using selective media, and the antibiotic susceptibility pattern was determined. Moreover, after prostate biopsy, blood and urine samples were collected from patients with post-biopsy infection (PBI) during 30 days of follow up.

**Results:** In total, 73 (46.2%) patients were positive for ciprofloxacin-resistant bacteria in rectal cultures. The most dominant isolates were *Escherichia coli* (95.9%). The antibiotic susceptibility patterns for the FQR rectal and clinical isolates showed high levels of resistance to ampicillin (94%) and trimethoprim-sulfamethoxazole (89.5%), while the resistance to amikacin, fosfomycin and imipenem remained very low. The multivariate analysis showed that previous use of FQs (OR, 2.54; 95% CI, 1.17-5.49;  $P = .019$ ) and history of hospitalization (OR, 7.85; 95% CI, 2.075-29.744;  $P = .002$ ) were significantly risk factors for the FQR carriage. On the other hand, the risk of PBI was higher among intestinal carriers of fluoroquinolone resistant bacteria compared with noncarriers, that this difference was statistically significant (24% versus 3.5%,  $P < .001$ ). The rates of PBI and hospitalization after TRUS-Bx were 12.5%, and 4.43%, respectively.

**Conclusion:** An increase in the rectal FQR bacteria carriage is associated with elevated PBI, which strongly recommends the need for an appropriate prophylaxis to reduce infections in patients undergoing TRUS-Bx.

**Keywords:** Biopsy; Drug resistance; Prostate; Risk factors.

### INTRODUCTION

Prostate cancer is one of the most commonly diagnosed cancers among men and represents a significant health problem. Worldwide, more than 1.1 million men are diagnosed with prostate cancer every year with the estimated number of deaths being 313,000 in 2013<sup>(1)</sup>. Transrectal ultrasound prostate biopsy (TRUS-Bx) is considered the essential and gold standard procedure for the histological diagnosis of prostate adenocarcinoma. The risks and complications of TRUS-Bx have been reported in the literature; Some of these complications are minor, such as pain, bleeding, and hemospermia, but some complications are clinically important, including fever, chills, orchiepididymitis, acute bacterial prostatitis, urinary tract infection (UTI), and sepsis<sup>(2,3)</sup>. The frequency of infection varies across studies, with most studies reported the rates of infection and hospitalization to be 1.7–11.3% and 0–6.3%, respectively<sup>(4,5)</sup>. Most often, the organism diagnosed in infectious complications after TRUS-Bx are *Escherichia coli* (*E. coli*), with these strains most likely originating from the patient's rectum at the time of prostate biopsy<sup>(6,7)</sup>.

According to The American Urological Association and European Association of Urology (EAU) guidelines, the use of fluoroquinolone (FQ) prophylaxis is generally considered before TRUS-Bx because it has shown to decrease the rates of infection-related complications<sup>(8,9)</sup>. In recent studies, the rate of fluoroquinolone-resistant (FQR) *E. coli* isolated from UTIs have shown to increase by 4.4 folds<sup>(10)</sup>. Moreover, a recent case series mentioning post-biopsy infections (PBIs) suggests that in this setting, FQR *E. coli* in rectal flora is a risk factor for infectious complications after TRUS-Bx<sup>(11-13)</sup>.

To the best of our knowledge, there are no reports that demonstrate the prevalence of antimicrobial resistance in intestinal flora of patients undergoing TRUS-Bx in Iran. Our first aim of the current study was to determine the prevalence of antibiotic resistance in bacteria isolated from rectal swabs in Iranian patients undergoing TRUS-Bx. Second, we evaluated potential predisposing risk factors and their correlation with the incidence of antibiotic resistance in related patients. Third, we determined the incidence of infection complications after TRUS-Bx. Based on our findings, some recommenda-

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Table 1. Patients' demographic and clinical characteristics

	Total		Ciprofloxacin -susceptible		Ciprofloxacin - resistant		P value
	Total (%)	Mean ± SD	NO. (%)	Mean±SD	NO. (%)	Mean±SD	
Age	158	64.37 ± 8.71	85	62.47 ± 8.23	73	66.60 ± 8.78	.006*
BMI	158	25.92 ± 12.6	85	25.67 ± 13.28	73	26.21 ± 11.8	.252*
PSA	158	9.5 ± 12.7	85	9.1 ± 6.81	73	10.2 ± 8.21	.167*
Prostate volume	158	49.46 ± 22.02	85	46.46 ± 16.43	73	52.94 ± 26.8	.357*
Hospitalization in past 1 months	24 (15.2)		3 (3.5)		21 (28.8)		<.001†
Ciprofloxacin use in past 6 months	55 (34.8)		19 (22.4)		36 (49.3)		<.001†
Diabetes mellitus	25 (15.8)		11 (12.9)		14 (19.2)		.284†
Prostatitis in past 4 months	28 (17.7)		8 (9.4)		20 (27.4)		.003†
UTI in past 4 months	46 (29.1)		19 (22.4)		27 (37)		.044†
Previous biopsy	30 (19)		9 (10.6)		21 (28.8)		.003†
Hypertension	41 (25.9)		22 (25.9)		19 (26)		.983†
Presence of a catheter	21 (13.3)		9 (10.6)		12 (16.4)		.280†
Enema	51 (32.3)		27 (31.8)		24 (32.9)		.834†
Frequent urination	95 (60.1)		50 (58.8)		45 (61.6)		.718†
Smoking	28 (17.7)		15 (17.6)		13 (17.8)		.979†

\*Mann-Whitney Test

† Pearson Chi-Square

tions were provided in the context of prophylaxis and treatment of these patients.

## MATERIAL AND METHODS

### Patients and Study Design

In total, 185 patients suspicious for prostate cancer were referred to the Urology Research Center of Tehran University of Medical Sciences, Iran, for biopsy using TRUS-Bx between March 2015 and February 2016. Demographic information, history of using FQs (6 months prior to biopsy), history of hospitalization (1 year ago), history of infectious diseases (UTI and prostatitis in the last 4 months), underlying diseases (diabetes mellitus and hypertension), history of prostate

biopsy, frequent urination, and smoking was asked and recorded. The level of Prostate-Specific Antigen (PSA) and prostate volume were extracted from patients' medical records. An enema (Fleet®) was administered in some patients for bowel preparation the night before and two hours before biopsy. Oral FQ was administered as the prophylactic antibiotic (500 mg, 2 hours before the biopsy up to 4 days after biopsy twice daily). The rectal swabs were collected from the patients immediately before prostate biopsy and were sent to microbiology laboratory for processing as described below. Exclusion criteria were failure to complete the form, failure to follow-up after TRUS-Bx and the use of other antibiotics alongside FQ.

Post prostate biopsy, all the patients were followed for

**Table 2.** Multivariate logistic regression analysis examining independent patient risk factors for harboring ciprofloxacin-resistant rectal carriage.

Risk factors	Adjusted odds ratio	95% CI	P value
Age	1.043	.998-1.090	.062
Hospitalization in past 1 year	7.856	2.075-29.744	.002
Ciprofloxacin use in past 6 months	2.533	1.169-5.490	.019
Prostatitis in past 4 months	1.515	.519-4.423	.448
UTI in past 4 months	1.351	.583-3.129	.483
Previous biopsy	1.644	.607-4.449	.328

CI, confidence interval

**Table 3.** Sensitivities of *E. coli* and *Citrobacter* spp. to antibiotics in 17 samples (14 urine, 3 blood)

Antibiotic	Susceptible (%)
Ampicillin	0
Levofloxacin	5.9
Cotrimoxazole <sup>a</sup>	17.64
Amoxicillin-clavulanate	23.52
Cefazolin	41.17
Ceftazidime	52.94
Cefepime	64.70
Gentamicin	64.70
Piperacillin-tazobactam	82.35
Nitrofurantoin	88.23
Amikacin	100
Fosfomycin	100
Imipenem	100

<sup>a</sup>Trimethoprim/sulfamethoxazole.

30 days via telephone interview to record the probable presence of infection. The patients were asked a number of questions, including fever over 38°C, chills, dizziness, pain in the bladder and dysuria, and then were guided to visit the Urology Center for sampling. The bacteria isolated from blood and urine samples were evaluated for identification and antibiotic susceptibility.

#### Detection FQ-R *E. coli* and antimicrobial susceptibility testing

The samples collected using rectal swabs (cotton-tipped) before the TRUS-Bx were transferred into 5 ml of brain heart infusion broth (Merck, Germany) containing 10 µg/ml ciprofloxacin. After incubating at 35°C, 0.1 mL of the broth was cultured in MacConkey agar (Merck, Germany) with 10 µg/mL of ciprofloxacin, then plates were incubated overnight at 35°C. The plates with positive cultures were investigated to identify the isolates. An ciprofloxacin minimum inhibitory concentration (MIC) was performed on the strains resistant to cipro-

floxacin using the Etest method (bioMérieux) according to the manufacturer's directions and antimicrobial susceptibility of fluoroquinolone-resistant *E. coli* clinical and rectal isolates was determined with reference to the minimal inhibitory concentration breakpoint recommended by the Clinical and Laboratory Standards Institute<sup>(14)</sup>.

#### Statistical analysis

Normal distribution of the data was evaluated using Lilliefors and Shapiro-Wilk test. Demographic characteristics and risk factors in patients of the two groups who are susceptible and resistant to FQs before and after prostate biopsy were described using mean and 95% confidence interval for quantitative variables and frequency, and percent for count data in Table 1. IBM SPSS Statistics 21.0 software and R version 3.0.1 were used to analyze the obtained results. The differences of the nonparametric variables were analyzed by Mann-Whitney U test. Chi-square test was used to evaluate the association between categorical variables. Simple and Multivariate logistic regression was used to estimate the effects of risk factors on fluoroquinolone resistance. The type of statistical modeling was confirmatory so the enter method was used as a model selection method. The criterion for statistical significance was  $P < .05$ .

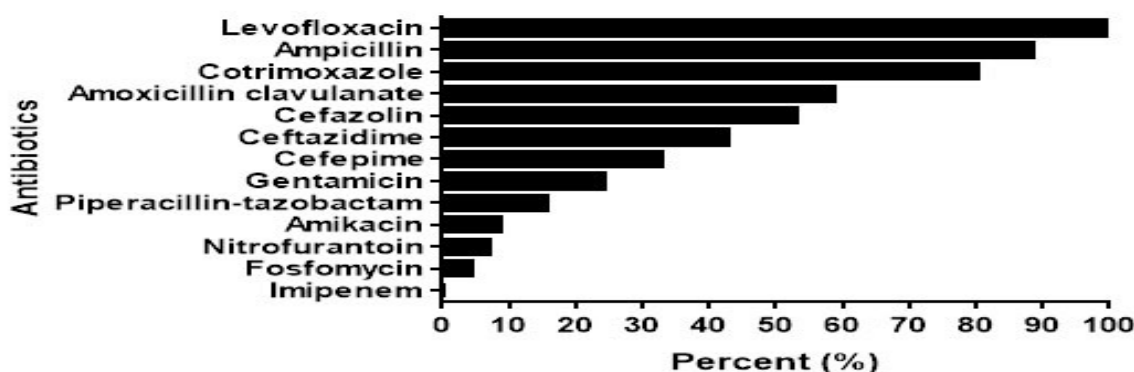
## RESULTS

### Patient Characteristics

Out of the 185 patients referred for biopsy, 27 patients were excluded from the study based on the aforementioned criteria. The remaining 158 patients in this study had an average age of 64.37 years (ranging between 44 and 83). The mean PSA was 10.2 ng/mL, and the mean prostate volume was 49.46 mL (Table 1).

### Microbiological Characteristics

Out of 158 patients, 73 patients (46.2%) had positive culture. Gram-negative isolates resistant to ciprofloxacin were *E. coli* (95.9%,  $n = 70$ ), *Citrobacter* spp. (2.7%,  $n = 2$ ) and *Pseudomonas* spp. (1.6%,  $n = 1$ ). The antibiotic resistance patterns for *E. coli* and *Citrobacter* strains resistant to ciprofloxacin is shown in Figure 1. Very high levels of resistance to the current antibiotics ampicillin (94%) and trimethoprim-sulfamethoxazole (89.5%) were observed. High resistance to cephalosporin generations (36.8% to 52.6%) was significantly different. However, resistance to fosfomycin and imipe-

**Figure 1.** Resistance pattern for fluoroquinolone resistant bacteria

nem had remained very low (5.3% and 0%, respectively). On the other hand, despite the high-level resistance to gentamicin and amoxicillin/clavulanic acid (63.2% and 36.8%, respectively), piperacillin-tazobactam and amikacin resistance remained low (10.5%).

#### Risk Factors for FQ-Resistant Rectal Carriage

Table 1 shows the relationship between potential independent risk factors and FQR rectal carriage bacteria according to the univariate analysis. Patient characteristics that conferred an increased risk of FQR rectal carriage on univariate regression included: (I) a history of hospitalization in the last year (OR, 11.03; 95% CI, 3.13-38.86;  $P < .001$ ), (II) the use of FQ in the last 6 months (OR, 3.38; 95% CI, 1.7-6.71;  $P < .001$ ), (III) a history of UTI (OR, 2.03; 95% CI, 1.01-4.09;  $P = .044$ ) and prostatitis (OR, 11.03; 95% CI, 1.49-8.85;  $P = .003$ ) in the last 4 months, (2) previous biopsy (OR, 3.47; 95% CI, 1.47-8.19;  $P = .003$ ), and (V) aging (OR, 1.052; 95% CI, 1.002-1.102;  $P = .014$ ). The multivariate analysis using logistic regression (the enter method) was used to confirm and predict the independent effects of these variables on carrying of bacteria resistant to FQ (Table 2). In this analysis, the use of FQs in the last 6 months (OR, 2.54; 95% CI, 1.17-5.49;  $P = .019$ ), and a history of hospitalization in the last year (OR, 7.85; 95% CI, 2.075-29.744;  $P = .002$ ) could predict the FQR carriage. Aging, as a potential independent factor in the univariate analysis, increased the FQR carriage, but it was not statistically significant according to the multivariate analysis (OR, 1.043; 95% CI, .998-1.090;  $P = .062$ ). On the other hand, in the univariate analysis, no association was found among the other risk factors such as PSA, prostate volume, blood pressure, diabetes mellitus, enema, frequent urination, and smoking with increased FQR carriage.

**Outcome of Patients with Post-Biopsy Infection (PBI):** Post-biopsy infection (PBI) was observed in 12.5% ( $n = 20$ ) of our study population. Of these 20 patients, 14 (70%) had a positive culture (14 urine and 3 blood samples), that *E.coli* was identified in 13 (93%) patients and *Citrobacter* in 1 (7%). Almost all the patients had been infected with FQ-R bacteria. However, a patient was coinfecting with both a fluoroquinolone-resistant and an FQ-sensitive *E. coli* isolates. Of 20 patients with PBI, 17 (85%) had pre-biopsy rectal cultures and the remaining 3 (15%) did not. So, the risk of PBI was higher among intestinal carriers of fluoroquinolone resistant bacteria compared with noncarriers; The difference was statistically significant (17/73 [24%] versus 3/85 [3.5%];  $P < .001$ ). At the end, seven patients (4.43%) of the study population were admitted to hospital with severe PBI.

The antibiotic susceptibility patterns of bacteria isolated from patients with PBI are presented in Table 3. According to the obtained results, despite the high resistance of clinical isolates to ampicillin, levofloxacin, and trimethoprim-sulfamethoxazole, resistance to imipenem, amikacin, and fosfomycin was not found. According to the univariate and multivariate analyses, the risk of infection was high in patients with positive cultures resistant to FQs before biopsy (OR, 4.73; 95% CI, 1.115-20.061;  $P = .03$ ).

## DISCUSSION

Prostate biopsy is considered as a standard method in the diagnosis of prostate cancer. Thus, millions of

people around the world are evaluated annually by this method<sup>(3)</sup>. The AUA and EAU recommend the use of a FQ as an antimicrobial prophylaxis before the TRUS-Bx procedure<sup>(8,9)</sup>. However, some risks such as infections after the procedure threaten the health of relevant patients. Initially, PBI was reported less than 1%, but several studies in recent years have confirmed increased PBI frequency after the TRUS-Bx procedure<sup>(10,15)</sup>.

Carigan et al. reported that the rate of PBI has increased from 0.52% between 2002 and 2009 to 2.15% between 2010 and 2011<sup>(16)</sup>. Previous studies have shown that FQ resistance in the rectal carriage and the presence of risk factors in the patients are the main reasons for the increased rate of PBI<sup>(17,18)</sup>. The present study that was conducted for the first time in Iran investigated the prevalence of FQR bacteria carriage in the patients undergoing TRUS-Bx and the rates of PBI along with the assessment of the presence of risk factors. Numerous studies have been reported an increasing rate of FQR bacteria in the rectal carriage, ranging from 10% to 32.6%<sup>(12,19-21)</sup>. In our study, the rate of FQR rectal gram-negative bacteria was 46.2%, which was higher than those in previous studies. Nevertheless, other similar studies from East Asia confirmed our findings<sup>(22)</sup>. It seems that the Asian race, taking antibiotics without prescription, particularly the Middle East countries, as well as other risk factors in patients undergoing biopsy are the main reasons for the presence of FQR bacteria in the rectum.

Several studies have been conducted to investigate the relationship between the risk factors and the FQR bacteria in rectum<sup>(23,24)</sup>. In the studies of Sternest et al. and Liss et al., the previous use of the FQ has been identified as an important risk factor<sup>(12,19)</sup>. Using multivariate statistical analysis, Taylor et al., showed that there is independent correlation between the previous use of the FQ and occurrence of UTI in the last 3 months and the FQR bacteria carriage<sup>(21)</sup>. However, in our results, in addition to the previous use of the FQ, it was found that the histories of patients' hospitalization also played an important role in this independent relationship, which can predict the FQR bacteria carriage in the rectum. On the other hand, Duplesis et al. showed aging as a predictor of the FQR bacteria carriage in intestinal normal flora<sup>(25)</sup>, whereas our findings have shown this correlation as a trend close to significance ( $P = .062$ ). It seems that aging and hospitalization raise the chance of encountering of the patients with antibiotics and the FQR bacteria carriage.

The use of selective media containing ciprofloxacin to isolate FQR bacteria was the highlight of this study, which has also been mentioned in the study of Liss et al.<sup>(12)</sup>. We propose to use the enrichment media containing ciprofloxacin to isolate the FQR bacteria for saving the time and costs of testing with regard to the role of the FQR bacteria in PBI development. In general, the FQ resistance in bacteria isolated from patients with PBI was 52% to 100% in previous studies that confirm our findings with 94.1% resistance to the FQ after PBI<sup>(10,16,26)</sup>. Several studies have reported rates of PBI to range from 1% to 4% and even 9.3% in a study conducted by Ashraf et al.<sup>(11,15)</sup>, whereas the overall rate of PBI was 12.5% in our study, indicating a high rate of infection.

Previous studies have shown that the rates of infectious complications in patients with FQR positive rectal cul-

tures, who had used the FQ as prophylaxis, were between 3.3% and 14.9%; whereas in the present study, the rate was 27.4%, which similar to the result obtained by Minimida et al.<sup>(11)</sup> In a large-scale study involving Canadian patients, NAM et al. showed that the rate of postoperative hospitalization following TRUS-Bx procedure increased from 1% in 1996 to 4.4% in 2005, which is consistent with our results (4.43%)<sup>(27)</sup>.

Considering previous reports and our findings, increased FQR bacteria carriage and resulting infections in patients undergoing prostate biopsy is an undeniable fact; therefore, major measures should be considered to improve antibiotic prophylaxis. In our research, the FQR bacteria isolated from the rectum showed high-level resistance to ampicillin, cotrimoxazole, and amoxicillin/clavulanic acid, and this finding is in line with those of previous studies<sup>(12)</sup>. However, the resistance to amikacin, nitrofurantoin, imipenem, and phosphomycin was at very low level, whereas the *E. coli* isolated from urine and blood samples were quite susceptible to imipenem, amikacin, and phosphomycin. In a study by Volkan et al., phosphomycin was used as antibiotic prophylaxis before the TRUS-Bx. According to their results, the rate of PBI had fallen sharply<sup>(28)</sup>. This work confirms our findings with regard to the high sensitivity of FQR *E. coli* to phosphomycin.

Given the increasing rate of resistant *E. coli* isolates carried in the rectum and increased rate of PBI, we suggest that the empirical usage of FQs is associated with an inappropriate antibiotic prophylaxis. Based on the present findings, we suggest to reduce the PBI as follows: the use of prophylactic strengthening in which another antibiotic such as amikacin should be used in addition to FQ; phosphomycin usage as monotherapy and also the use of targeted prophylaxis in which resistant bacteria carried by the rectal swab culture of patients should be achieved one or more weeks prior to prostate biopsy, and appropriate prophylaxis could be selected for this purpose according to the antibiotic sensitivity pattern. This suggestions have other advantages, including saving medical expenses, reducing side effects of antibiotics used experimentally with the possibility of treatment failure, particularly in patients with prostate cancer. There were limitations in our study, such as the relatively small sample size as well as the unavailability of patient records in private clinics. Therefore, a study with a larger sample size needs to be conducted in Iran and the establishment of a shared information bank is required in the country.

## CONCLUSIONS

Owing to the increased prevalence of the rectal fluoroquinolone-resistant bacteria carriage in patients undergoing TRUS-Bx and increasing rates of PBI, an appropriate prophylaxis is necessary to reduce the infections in patients undergoing the biopsy. Evaluation of risk factors can predict the presence of antibiotic-resistant bacteria carried. Identification of antibiotic-resistant bacteria in the rectum along with their antibiotic susceptibility patterns is one of the strategies that could be useful factors in the determination of appropriate antibiotic therapy and targeted prophylaxis.

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## CONFLICT OF INTEREST

The authors report no conflict on interest.

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