Clinical and Bacterial Risk Factors for Development of Post-Prostate Biopsy Infections

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Purpose: To research on clinical and bacterial risk factors and their relationship with post-prostate biopsy infection (PBI).

Materials and Methods: In this prospective cohort study, rectal swabs were collected from 158 men prior to prostate biopsy and cultured selectively for identify ciprofloxacin-resistant (FQ-R) gram-negative bacteria. The patient characteristics, phylogenetic background, sequence typing and pulsed field gel electrophoresis (PFGE) pattern were compared in two groups of FQ-R *Escherichia coli* rectal and clinical isolates.

Results: In total, PBI was observed in 20 (12.5%) cases; the most of these subjects were FQ-R-colonized. (17/73 [24%] vs 3/85 [3.5%]; $P < 0.001$). FQ-R colonization, diabetes, hospitalization and UTI were independent risk factors (95% CI: 1.1-20.1, OR = 4.73; 95% CI: 1.7-25.3, OR = 6.57; 95% CI: 1.9-27.5, OR = 7.22; and 95% CI: 1.2-14.3, OR = 4.05; respectively), that increased the rate of PBI (All $P < 0.05$). Despite the increase in infections among patients colonized with strains of *E. coli* ST131, its prevalence was near significance between colonized and infected groups ($P = 0.07$). The PFGE patterns and antimicrobial susceptibility profiles of rectal and clinical isolates in 13 patients were similar which is remarkably important and informative.

Conclusion: The most PBIs originate from FQ-R *E. coli* rectal colonization. Rectal culture screening and assessment of clinical risk factors can predict the incidence of PBI in patients.

Keywords: biopsy; drug resistance; Iinfection; prostate

INTRODUCTION

Transrectal ultrasound-guided prostate biopsy (TRUS-Bx) is considered a standard method to diagnose prostate cancer. Therefore, millions of people around the world are evaluated by this approach. Post-prostate biopsy infection (PBI) is an important adverse event that is potentially life threatening for patients[1]. Hence, the American Urological Association and the European Association of Urology (EAU) recommend the preoperative use of fluoroquinolone (FQ) antibiotics before prostate biopsy to prevent infections[2,3]. The most prevalent bacterium responsible for PBI is *Eschericia coli* that most likely originates from the rectum of patients during biopsy[4,5]. In recent years, there have been concerns regarding the expansion of a pandemic clonal group known as *E. coli* sequence type 131 (ST131); most members of this group are resistant to FQ and some of them express the extended-spectrum □-lactamases[6].

E. coli ST131 belongs to phylogenetic group B2, which is associated with greater virulence than other phylogenetic groups and can be colonized in the intestine with high density[7,8]. *E. coli* ST131 is an important cause of extraintestinal infections such as sepsis, meningitis and urinary tract infections that are commonly multidrug resistant (MDR)[9]. Recent studies have shown that *E. coli* ST131 is responsible for more than 40% of bloodstream infections after prostate biopsy, indicating the importance of this type of *E. coli* in rectal colonization [6,7,10,11].

To our knowledge, there are no reports indicating the prevalence of *E. coli* ST131 in patients undergoing prostate biopsy in Iran. In this study, therefore, we have investigated the following: (i) comparison of characteristics in one uninfected and one infected group of patients after prostate biopsy, (ii) determination of the phylogenetic background and the prevalence of ST131 among FQ-R *E. coli* isolates, (iii) co-resistance profile, and, finally, (iv) molecular epidemiology and comparison of PFGE pattern of the FQ-R *E. coli* rectal colonization versus clinical isolates take at the time of PBI.

PATIENTS AND METHODS

Study population and Study design

In total, 185 patients referred to the Urology Research Center, Sina Hospital, Iran, between March 2015 and February 2016, for the purpose of evaluation for prostate cancer using TRUS-Bx. Study design, inclusion and exclusion criteria, method for the isolation of fluoroquinolone resistant bacteria and the antibiotic susceptibility test is clearly explained in our previous work [12].

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Table 1. Clinical characteristics including potential independent risk factors for development of infection after prostate biopsy

Clinical characteristics	No Infection (n = 138)	Infection (n = 20)	*P* Value
Age, y, mean ± sd	64.2 ± .7	65.6 ± 2	.113*
Body mass index, kg/m^2, mean ± sd	25.7 ± 13.3	26.2 ±11.8	.249**
PSA,ng/ml,mean ± sd	16.1 ± 18	23.1 ± 34.7	.158**
Prostate volume, mm3, mean±sd	46.5 ± 16	52.9 ± 26.8	.357*
Hospitalization in past 1 year (%)	15 (10.9)	9 (45)	< .001†
Presence of a catheter (%)	17 (12.3)	4 (20)	.310†
Prostatitis in past 4 months (%)	20 (14.5)	10 (50)	< .001†
UTI in past 4 months (%)	32 (23.2)	14 (70)	< .001†
Previous biopsy (%)	21 (15.2)	5 (25)	.21†
Hypertension (%)	33 (23.9)	8 (40)	.125†
Diabetes (%)	19 (13.8)	11 (55)	< .001†
Pre-biopsy enema (%)	45 (32.6)	6 (30)	.800†
Smoking (%)	22 (15.9)	6 (30)	.128†
Fluoroquinolone-resistant colonization (%)	56 (40.6)	17 (85)	< .001†

Abbreviations: PSA, prostate specific antigen; sd, standard deviation.
*Continuous variables: *t* test.
**Continuous variables: Mann-Whitney.
†Categorical variables: Pearson Chi-Square.

Molecular Typing

In continuation of the previous study, the FQ-R *E. coli* from rectal and clinical isolates was categorized into seven phylogenetic groups using a quadruplex polymerase chain reaction (PCR)-based method (New Clermont method) [13]. For isolates belonging to group B2, the ST131 status was determined by PCR-based detection of SNPs (single-nucleotide polymorphisms) associated with ST131 in mdh and gyrB housekeeping genes. twenty seven randomly selected putative ST131 isolates underwent confirmatory 7-locus multilocus sequence typing (MLST) based on partial sequences for purA, fumC, mdh, icd, gyrB, recA, and adk (http://mlst.ucc.ie/mlst/dbs/*E. coli*); all isolates were confirmed as ST131. The PCR-based detection was applied to identify H30 and H30-Rx ST131 subclones[14,15].

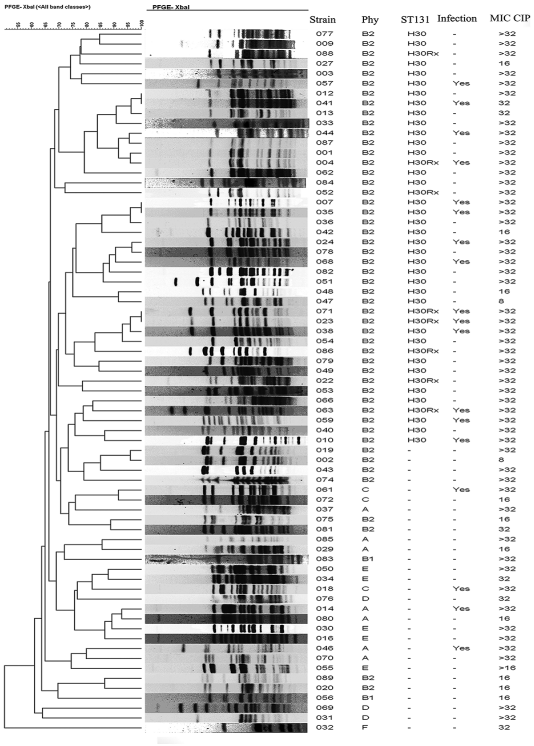

Figure 1. XbaIPulsed-field gel electrophoresis (PFGE) profiles of 71 fluoroquinolone-resistant *Escherichia coli* rectal isolates in patients undergoing transrectal ultrasound prostate biopsy.Data columns, from left to right, show strain Number, *E. coli* phylogenetic group, ST131 status, occurence of infection after prostate biopsy and ciprofloxacin MIC by Etest. Dashes demonstrate negative results.

Pulsed-Field Gel Electrophoresis Analysis

The genetic relationship of the FQ-R *E. coli* in rectal and clinical isolates was assessed by XbaI pulsed field gel electrophoresis (PFGE) analysis according to a standard protocol[16]. The Bionumerics software (Applied Maths, V7.6 Saint-Matins-Latem, Belgium) was employed to gel analysis. The cluster analysis was performed using Dice similarity value ≥ 94% with a band position tolerance 1% based on the Unweighted Pair Group Method with Bionumerics to classify profiles into distinct pulsetypes[16].

The study was designed and performed according to the Helsinki declaration and was approved by the Ethics Committee of the Tehran University of Medical sciences (28848-27-01-94). Informed consent was obtained from all individual participants included in the study.

Statistical Methods

We conducted multiple comparisons to meet the objectives of this study. The normally distributed variables were compared between the infected and non-infected groups using the Student t test. The Mann-Whitney *U* test was also used as non-parametric analogous, when appropriate. Moreover, the categorical variables were compared between aforementioned groups through using the Chi-Squared test; and Fisher Exact test was also applied when the data sparsity was expected. To predict post-prostate biopsy infection, the univariable analyses were initially conducted and those variables with *P*-value < 0.1 were imported into the multivariable model. Finally, it can be said that the strength of associations between predictors of interest and outcome studied were reported as odds ratio (OR) with 95% confidence interval (CI). The IBM SPSS Statistics 21.0 software was used for data analysis.

Table 2. Multivariate logistic regression analysis of independent risk factors for infection after prostate biopsy

Risk factors	Adjusted odds ratio	95% CI	*P* value
Diabetes	6.57	1.7-25.3	.006
Hospitalization in past 1 year	7.22	1.9-27.46	.004
Prostatitis in past 4 months	1.51	.52-4.4	.448
UTI in past 4 months	4.05	1.2- 14.3	.029
Fluoroquinolone-resistant colonizationa	4.73	1.1-20.1	.035

Abbreviation: CI, confidence interval.
Variables with $P < 0.1$ in the univariable analysis were used in the multivariable model.
a indicated by a positive prebiopsy rectal culture.

RESULTS

Risk factor for PBI

Almost all the patients had been infected with FQ-R bacteria. Despite the fact, a patient was coinfected with 2 FQ-R and FQ-sensitive *E. coli* isolates. FQ-R *E. coli* grew in the rectal culture of all but 3 patients with PBI. The rate of PBI was 24% [17/73] in patients with a positive rectal culture versus 3.5% [3/85] in those with a negative rectal culture ($P < 0.001$). **Table 1** shows the relationship between potentially independent risk factors and PBI levels according to the univariable analysis. The most important risk factors associated with an increased PBI included (i) history of hospitalization in the last 1 year ($P < 0.001$), (ii) prostatitis and UTI during the last 4 months ($P < 0.001$), (iii) diabetes ($P < 0.001$) and FQ-R colonization ($P < 0.001$). On multivariable analysis using logistic regression (**Table 2**), FQ-R colonization, and history of hospitalization, UTIs and diabetes remained statistically significant (all P<0.05).

Determination of phylogenetic groups, ST131 status and ST131 subclones

We indicates the compared molecularly the 16 available FQ-R clinical *E. coli* isolates from men who did develop PBI with the 53 available FQ-R rectal *E. coli* isolates from men who did not develop PBI. **Table 3** distribution of phylogenetic groups of FQ-R *E. coli* stratified by presence in rectal culture or in culture taken at the time of PBI ("clinical"). The phylogenetic group B2 was the most dominant phylogroup among rectal and clinical isolates (36/54 [67%] vs. 13/16 [81.2%], respectively ($P = 0.47$). The ST131 status was determined in all isolates belonging to group B2 (42/49 [85.7%]). Despite the increase in infections among patients colonized with strains of *E. coli* ST131, its prevalence was near significance between colonized and infected groups (29/42 [53.7] vs. 13/16 [81.3]: $P = 0.07$). Generally, all *E. coli* ST131 strains belonged to the H30 ST131 subclone, and no difference was found in the prevalence of the H30-RX ST131 subclone between rectal and clinical isolates (4/29 [14%] vs. 4/13 [31%]; respectively; $P = 0.24$).

Genomic Relationships

Of 74 FQ-R gram-negative rectal isolates, 71 (96%) *E. coli* isolates (out of 70 patients) were selected to perform PFGE. PFGE analysis showed that these rectal isolates were genomically diverse. The 42 *E. coli* ST131 strains clustered separately relative to the NonST131 strains. NonST131 strains demonstrated greater genomic heterogeneity than the ST131strains (**Figure 1**). Of 70 patients with rectal FQ-R *E. coli* isolates, PBI was diagnosed in 16 (24%), and 13 (81%) of these cases showed an *E. coli* ST131 isolate. Among the remaining 54 patients, 29 (54%) cases had ST131 isolates. Of 17 patients with diagnosed infections, 13 cases had both clinical and rectal isolates available for genomic comparison. The PFGE pattern between rectal and clinical isolates was indistinguishable in all cases. However, three cases with expanded infection had two different clinical strains. Thus, two patients were infected with two FQ-R *E. coli* strains, with both strains of the first patients (patient A, strains 8 and 11, **Figure 2**) and one of the strains of the second patient matched with the rectal isolates (patient H, strain 6, **Figure 2**). One patient was infected with both an FQ-R and FQ-sensitive strain of *E. coli*, but only the FQ-R isolate matched the rectal strain (patient M, strain 17; **Figure 2**).

DISCUSSION

Table 3. Phylogenetic distribution of FQ-R Escherichia coli isolates

Phylogenetic Group or Sequence Type	70 FQ-R *E. coli* Isolates, No. (%)		*P**
	Pre- TRUS-Bx rectal isolates with not develop PBI (n=54)	Post-TPB infection (clinical isolate) (n=16)	
A	6 (11.1)	1 (6.2)	< 0.001
B1	2 (3.7)	0	< 0.001
B2	36 (66.6)	13 (81.3)	0.473
E	5 (9.2)	0	< 0.001
F	1 (1.9)	0	< 0.001
C	1 (1.9)	2 (12.5)	< 0.001
D	3 (5.5)	0	< 0.001
ST131	29 (53.7)	13 (81.3)	.07

Abbreviation: TRUS-Bx, Transrectal ultrasound-guided prostate biopsy; ST131, Sequence Type 131; CI, confidence interval.
* The P values were calculated using McNemar test.

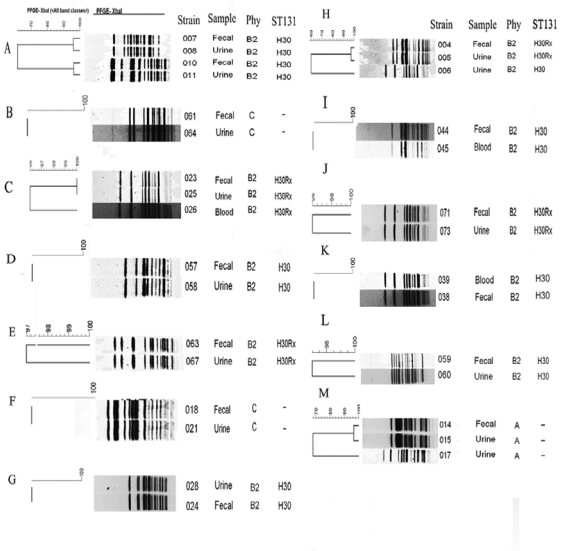

Figure 2. Comparison of XbaI Pulsed-field gel electrophoresis (PFGE) patterns of paired fluoroquinolone-resistant Escherichia coli from rectal and clinical isolates from 13 patients with post–prostate biopsy infection (PBI). Despite two distinct urine isolates explained in the text, clonal similarity for 13 patients with rectal and clinical isolates suggested that most PBIs originate from rectal colonization of FQ-R *E. coli*.

In this study, based on the recommendations of the American Urological Association, a fluoroquinolone was used for antibiotic prophylaxis before TRUS-Bx [(2)]. Pre-TRUS-Bx rectal cultures in ciprofloxacin-enriched selective media revealed FQ-R gram negative bacteria in 46.2% of patients, which is higher than the 10%-36% prevalence reported in developed countries[(4,17,18)], but similar to one report from East Asia[(21)]. It is possible that Asian ethnicity and patterns of antibiotic use in developing countries could influence rectal colonization with FQ-R organisms[(12)].

The risk of PBI in Iranian patients appeared to be increased by a similar proportion compared to the risk described in developed countries. Most previous studies from developed countries have reported the rate of infectious complications after TRUS-Bx to be between 1% and 5% in patients using FQ prophylaxis, although one study reported a rate as high as 10% [(20,21)]. The PBI rate in our study was 12.5%, implying a high rate of infection, but this is not surprising in light of the high rate of rectal colonization with FQ-R bacteria. Of course differences in the definitions of PBI and the methods by which PBI were captured can affect the rates of PBI. Consistent with the rates of colonization with FQ-R bacteria and of PBI, we found that the value of the presence of FQ-R bacteria in rectal culture as a risk factor for subsequent PBI was similar in our population (Odds ratio = 4.7) compared to prior reports in developed countries[(22)].

As expected, FQ-R *E. coli* was by far the most frequent isolate from the rectum and also the most frequent cause of PBI in our study, with 44.3% of patients carrying this bacterium in their rectum. We were able to confirm by PFGE patterns in rectal and clinical isolates that the FQ-R *E. coli* causing the PBI likely originated from the rectum. Prostate biopsy needles can play a role in the transmission of resistant isolates (especially FQ-R *E. coli*) from rectal to bloodstream, urine and prostate. Hence, screening rectal culture seems to be a major step forward in identifying bacteria and their properties, as in our study, rectal culture screening succeed to identify rectal carriage in all men who developed post biopsy infection with FQ-R *E. coli*.

Most information on the prevalence and distribution of pathogenic strains of E.coli is derived from developed countries[(6)]. *E. coli* ST131 is one of the newly emerging pathogens and the majority of its members are FQR and MDR[(6)]. We have therefore studied the distribution of phylogenetic groups as well as the prevalence of ST131, H30 and H30-Rx subclones in rectal and infected isolates in Iran for the first time. In the present study, prevalence *E. coli* ST131 was near significance between colonized and infected groups (53% vs. 81%, $P = .07$). Due to its high prevalence and widespread resistance to several antibiotics in the colonized and infected isolates, measures need to be taken to reduce the risk of infection from FQ-R *E. coli* ST131. At stated before, the screening rectal culture and antibiogram results obtained before TRUS-Bx may be useful in determining an appropriate antibiotic prophylaxis.

The identification of rectal bacteria that can cause PBI is a necessity, but is not sufficient. Most patients with pathogenic FQ-R *E. coli* will still not develop a PBI because PBI results from a balance between multiple host and pathogen factors [(22,23)]. According to the above, we have therefore also considered patient characteristics as risk factors for PBI. In the study of Liss et al., It was observed that the history of hospitalization in last year and colonization with fluoroquinolone-resistant bacteria are two important and independent factors for increasing infections after prostate biopsy. In numerous other studies, going to international travel and the history of using antibiotics and admission before prostate biopsy were introduced as independent risk factors for increasing PBI. Interestingly, in other studies, diabetes and chronic obstructive pulmonary disease as an independent risk factor were introduced. However, according to our findings, diabetes, recent hospitalization and prior UTI were independent risk factors for developing PBI, in addition to FQ-R colonization on rectal culture. Some of these are potentially modifiable factors (e.g. more stringent blood glucose management or delay of PNBx after UTI) and this knowledge can be used to reduce the risk of PBI.

Limitations of this study include the relatively small sample size, and it will be necessary to perform a larger study in our country. Strengths of this study include (i) use of selective media that works better in isolating the rectal FQ-R organisms[(17)] while also saving laboratory costs and time; and, (ii) careful patient follow-up after prostate biopsy.

CONCLUSIONS

The most of post-prostate biopsy infections occur in patients colonized with FQ-R bacteria who have used fluoroquinolone alone as antibiotic prophylaxis. FQ-R *E. coli*, particularly the ST131 group, is the most important pathogen in the context of rectal colonization and PBIs. Therefore, it is necessary to understand better this clonal group. An increase in the FQ-R rectal carriage is associated with elevated post biopsy infection, which rectal culture screening and assessment of clinical risk

factors can predict the incidence of PBI in patients.

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CONFLICT ON INTEREST

The authors report no conflict on interest

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