

# Antibiotic prophylaxis with intravenous ceftriaxone and fluoroquinolone reduces infectious complications after transrectal ultrasound-guided prostatic biopsy

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**Purpose:** To assess the rates of infectious complications before and after the change of prophylactic antibiotic regimens in prostate needle biopsy.

**Materials and Methods:** The records of 5,577 patients who underwent prostate needle biopsy at Asan Medical Center between August 2005 and July 2012 were retrospectively reviewed. Group 1 (n=1,743) included patients treated between 2005 and 2009 with fluoroquinolone for 3 days, group 2 (n=2,723) included those treated between 2009 and 2012 with ceftriaxone once before the biopsy and fluoroquinolone before biopsy and continue therapy for 3 days, and group 3 (n=1,111) received the same treatment for more than 7 days after the biopsy. Univariable and multivariable logistic regression models addressed risk factors associated with infectious complication after prostate needle biopsy.

**Results:** Infectious complication after prostate needle biopsy developed in 18 (group 1), seven (group 2), and two patients (group 3) (p=0.001). In group 1, seven patients with infectious complication had positive blood cultures and harbored fluoroquinolone-resistant *Escherichia coli*, four had ceftriaxone susceptible isolates, and three had extended spectrum beta-lactamase-positive *E. coli*. Two patients in group 1 required intensive care because of septic shock. In multivariable analysis, the patients with combination of fluoroquinolone and ceftriaxone had significantly lower infectious complication rate than the fluoroquinolone alone (p=0.003).

**Conclusions:** Antibiotic prophylaxis with ceftriaxone and fluoroquinolone before prostate needle biopsy decreased the risk of potentially serious infectious complications.

**Keywords:** Antibiotic prophylaxis; Biopsy; Ceftriaxone; Infection; Prostate

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## INTRODUCTION

Transrectal ultrasound-guided prostate needle biopsy (PNB) is the standard procedure for the detection of prostate cancer. Although it is a safe and well-tolerated outpatient procedure, it is associated with various complications including hematuria, rectal bleeding, acute urinary retention, prostatitis, urinary tract infection (UTI), and occasionally sepsis [1,2]. Febrile UTI is the most frequent complication of prostate biopsy. Quinolones are antimicrobial agents characterized by high bioavailability and a broad antimicrobial spectrum, and they are found at high concentrations in prostatic tissues. The beneficial effects of quinolones on decreasing the incidence of infectious complications of prostate biopsy have been reported in several studies [3-5]. Randomized controlled trials have demonstrated their efficacy in decreasing the risk of sepsis after PNB [6,7]. The American Urological Association Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis advocates antibiotic prophylaxis prior to transrectal prostate biopsy [4]. According to the protocol of our institution, patients receive a dose of an oral fluoroquinolone before biopsy and continue therapy for 2 to 3 days. In recent years, however, there has been an alarming increase in fluoroquinolone resistance [8,9]. A high fecal carriage rate of fluoroquinolone-resistant coliforms has been reported in patients undergoing PNB [10,11]. A recent large study described the impact of fluoroquinolone resistance on post-PNB infections, and a 4-fold increase in post-PNB infections from 0.52% in 2002–2009 to 2.15% in 2011 has been reported [12]. A similar increase in the incidence of infectious complications after PNB was observed by our group, which prompted us to review our PNB protocol and antibiotic regimen in patients undergoing PNB. The antibiotic regimen was modified to include ceftriaxone to bypass resistance to fluoroquinolone and because it achieves a high concentration in the prostate tissue [13]. In the present study, we compared infectious complication rates in patients undergoing PNB between those treated with prophylactic fluoroquinolone and those treated with a combination of fluoroquinolone and a single dose of intravenous (IV) ceftriaxone, which was shown to be highly effective against fluoroquinolone-resistant *Escherichia coli* isolates in patients with suspected UTI [14].

## MATERIALS AND METHODS

### 1. Population and design

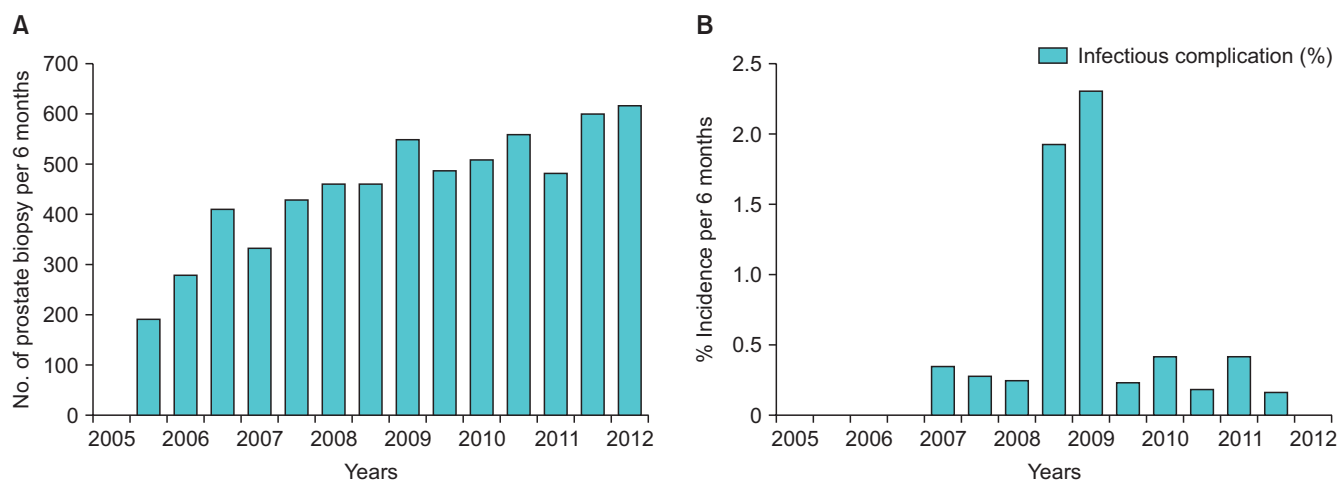
The study was performed with the approval and oversight

of the Institutional Review Board of the Asan Medical Center. We retrospectively evaluated the records of 5,577 patients who underwent PNB at Asan Medical Center between August 2005 and July 2012. Cases were defined as patients experiencing post-PNB bacteremia or febrile UTI. This retrospective study was performed in two phases between 2005 and 2012, and patients were divided into three groups as follows. Patients treated between August 2005 and August 2009 with 500 mg of fluoroquinolone orally twice daily for 3 days beginning 12 hours before the biopsy were included in group 1 (n=1,743), whereas patients treated between September 2010 and July 2012 with 2 g of IV ceftriaxone once just before biopsy and 500 mg of fluoroquinolone orally twice daily beginning 12 hours before the biopsy for 3 days were included in group 2 (n=2,723), and those treated for more than 7 days were in group 3 (n=1,111). Whether fluoroquinolone orally twice daily for 3 days or more 7 days was administered at the discretion of the each physician. Serum prostate-specific antigen (PSA) levels were measured before the prostate biopsy. Patients were advised to self-administer a fleet enema at home on the day before and underwent a fleet enema at hospital on the day. All patients underwent a standard 12-core PNB. Before the biopsy, all patients were informed about possible postprocedural complications and instructed to call or return to the urology clinic or the Emergency Department if they suspected complications, including fever or chills. After the biopsy, an infectious complication was considered if the patient was diagnosed with a body temperature  $>38^{\circ}\text{C}$ , leukocytosis (white blood cell count  $>12,000$  cells per  $\text{mm}^3$ ), a UTI, or acute prostatitis. The urine and blood samples of these patients were sent to a laboratory for microbiological investigations including sensitivity studies and culture. A positive blood culture was required to define sepsis. Our study analyzed the possible predisposing risk factors for infectious complication in the three groups of patients. Patients with infectious complication were initially treated with 2 g IV ceftriaxone once daily until culture findings became available to guide therapy.

We excluded the patients who received other antibiotic prophylaxis and did not visit the emergency room due to febrile illness after PNB.

### 2. Statistical analysis

Categorical variables were presented as frequencies and percentages, and continuous variables as mean with standard deviation or median with interquartile range (IQR). The chi-square test was used to compare categorical variables in the three subgroups. Continuous variables in these three subgroups were compared using the analysis of variance.



**Fig. 1.** (A) Number of prostatic biopsy per 6 months and (B) incidence of infectious complication after prostate needle biopsy of the prostate between 2005 and 2012.

**Table 1.** Characteristics of patients in each group

Characteristic	Group 1 (n=1,743)	Group 2 (n=2,723)	Group 3 (n=1,111)	p-value
Age (y), mean±SD	64.4±9.0	64.0±8.8	63.4±9.7	0.013
Diabetes mellitus	216 (12.4)	313 (11.5)	109 (9.8)	0.107
Cerebro-vascular accidents	102 (5.9)	144 (5.3)	46 (4.1)	0.133
PSA level (ng/mL), median (IQR)	5.9 (4.2–8.8)	4.9 (3.6–7.2)	4.9 (3.6–7.3)	0.426
Prostate volume (mL)	41.6±26.0	43.5±27.3	44.6±25.1	0.001
Prior prostate needle biopsy	142 (8.1)	238 (8.7)	50 (4.5)	0.001
Infectious complication	18 (1.0)	7 (0.3)	2 (0.2)	<0.001
No. of intensive care unit admissions	2 (0.1)	0 (0)	0 (0)	0.133

Values are presented as number (%) unless otherwise indicated.

Group 1, fluoroquinolone for 3 days after the biopsy; group 2, ceftriaxone before the biopsy + fluoroquinolone for 3 days after the biopsy; group 3, ceftriaxone before the biopsy + fluoroquinolone for more than 7 days after the biopsy; SD, standard deviation; PSA, prostate-specific antigen; IQR, interquartile range.

Univariable analysis and multivariable analysis were used with logistic regression models to evaluate the relationship of infectious complication with variables associated with risk factor. Correlations between infectious complications and variables were expressed as odds ratios with 95% confidence interval. All reported p-values were two-sided, and p-values <0.05 were considered statistical significant. All statistical analyses were performed using the IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

## RESULTS

The overall complications and their incidence rates were post-PNB infection in 27 patients (0.48%), bleeding in 23 patients (0.41%), and voiding difficulty in 13 patients (0.23%). We documented 27 cases of infectious complication, resulting in an incidence rate of 0.3% in the 2005–2007 groups, which increased to 2.31% in 2009. Therefore, the antibiotic regimen was modified, which resulted in a decrease in the incidence

of infectious complication to 0.2% in the 2010–2012 period (Fig. 1). The mean age of the patients included in the study was 64.0 years (range, 18–92 years). Infectious complication occurred in a median of 2 days (IQR, 1–5 days) after PNB. The median duration of hospital admission for infectious complication was 2 days (IQR, 1–5 days).

Table 1 summarizes the characteristics of patients in each group. Infectious complication occurred in 18 of 1,743 (1.0%), seven of 2,723 (0.3%), and two of 1,111 patients (0.2%) in groups 1, 2, and 3, respectively (p<0.001).

Table 2 shows the characteristics of bacteria isolated from the urine and blood of patients admitted with infectious complication after PNB. Of the 18 patients with infectious complication in group 1, 11 patients had positive urine cultures, and fluoroquinolone-resistant *E. coli* was responsible for 11 of 18 patients (61%) infectious complication cases. Of these 18 patients in group 1, seven had positive blood cultures including *E. coli* and all seven patients harbored fluoroquinolone-resistant *E. coli*. Two patients (0.1%)

in group 1 were admitted to the intensive care unit (duration: range, 1–2 days). Of the seven patients with infectious complication in group 2, two had positive urine cultures. Two patients had positive blood cultures, including *E. coli*, and isolates showed resistance to fluoroquinolone. None of

the patients in groups 2 and 3 required admission to the intensive care unit. There was no mortality among patients admitted with infectious complication in groups 2 and 3.

Table 3 shows the possible etiological risk factors predisposing to infectious complication after PNB. In multivariable analysis, large prostate volume ( $p=0.024$ ) was statistically significant risk factor for infectious complication. The combination of fluoroquinolone and IV ceftriaxone was significantly lower infectious complication rate than the fluoroquinolone alone ( $p=0.003$ ). But diabetes mellitus ( $p=0.251$ ) was not statistically significant risk factor for infectious complication.

**Table 2.** Characteristics of bacteria isolated from the urine and blood of patients admitted with infectious complication after PNB

Characteristic	Group 1	Group 2	Group 3
Urine culture			
<i>Escherichia coli</i>	11	2	0
Fluoroquinolone resistance	11	2	
ESBL	3	1	
<i>Klebsiella pneumoniae</i>	1	0	0
Blood culture			
<i>E. coli</i>	7	2	0
Fluoroquinolone resistance	7	2	
ESBL	3	0	

Group 1, fluoroquinolone for 3 days after the biopsy; group 2, ceftriaxone before the biopsy + fluoroquinolone for 3 days after the biopsy; group 3, ceftriaxone before the biopsy + fluoroquinolone for more than 7 days after the biopsy; PNB, prostate needle biopsy; ESBL, extended spectrum beta-lactamase.

## DISCUSSION

The use of PNB has increased significantly in recent years with the widespread use of PSA screening for prostate cancer. Although it is a safe and well-tolerated outpatient procedure, it is associated with various complications. UTI, which is the second most frequent complication of prostate biopsy after bleeding complications, can be described as a minor or major complication depending on its severity.

**Table 3.** Univariable and multivariable analysis of possible risk factors predisposing to infectious complication in logistic regression analysis

Variable	Infectious complication (n=27)	No infectious complication (n=5,550)	Odds ratio	95% CI	p-value
Univariable analysis					
Age (y), mean±SD	62.1±8.4	64.0±9.1	0.978	0.940–1.017	0.268
Diabetes mellitus	6 (22.2)	632 (11.4)	2.223	0.894–5.529	0.086
Cerebro-vascular accidents	0 (0)	292 (5.3)	-	-	0.346*
PSA level (ng/mL), median (IQR)	5.2 (3.8–7.9)	4.6 (3.4–9.4)	0.997	0.978–1.016	0.739
Prostate volume (mL)	55.0±75.6	43.0±26.0	1.008	1.001–1.015	0.021
Pre-PNB urine cultures					
No growth	20 (87.0)	2,810 (91.3)	1	-	-
Growth	3 (13.0)	267 (8.7)	1.579	0.466–5.347	0.463
Antibiotic prophylaxis					
Group 1	18 (1.0)	1,725 (99.0)	1	-	-
Group 2	7 (0.3)	2,716 (99.7)	0.247	0.103–0.593	0.002
Group 3	2 (0.2)	1,109 (99.8)	0.173	0.040–0.746	0.019
Prior prostate needle biopsy	3 (11.1)	427 (7.7)	1.500	0.450–5.001	0.510
Multivariable analysis					
Diabetes mellitus	6 (22.2)	632 (11.4)	1.739	0.676–4.473	0.251
Prostate volume (mL)	55.0±75.6	43.0±26.0	1.008	1.001–1.015	0.024
Antibiotic prophylaxis					
Group 1	18 (1.0)	1,725 (99.0)	1	-	-
Group 2	7 (0.3)	2,716 (99.7)	0.268	0.111–0.647	0.003
Group 3	2 (0.2)	1,109 (99.8)	0.193	0.044–0.835	0.028

Values are presented as number (%) unless otherwise indicated.

CI, confidence interval; SD, standard deviation; PSA, prostate-specific antigen; IQR, interquartile range; PNB, prostate needle biopsy; group 1, fluoroquinolone for 3 days after the biopsy; group 2, ceftriaxone before the biopsy + fluoroquinolone for 3 days after the biopsy; group 3, ceftriaxone before the biopsy + fluoroquinolone for more than 7 days after the biopsy.

\*Pearson chi-square test.

Sepsis, one of the most serious clinical sequelae, is diagnosed in 0.1%–2.2% of cases after biopsy [15]. The most common organism responsible for these infectious complications is *E. coli*, and the proposed mechanism of infection is the introduction of bacteria into the bladder and bloodstream from the rectum.

Fluoroquinolones are used widely because of their broad antimicrobial spectrum and high bioavailability in the prostate. However, the widespread use of fluoroquinolones is associated with the emergence of resistant pathogens [16–18]. Several recent reports have described the emergence of quinolone-resistant infections after PNB [2,3,5,14]. The fluoroquinolone resistance rate for *E. coli*-associated UTIs ranges from 10% to 20% in different studies [19,20]. Hospital laboratories in England and Wales noted a statistically significant increase (from 0.5% to 3.7% from 1990 to 1999) in the mean resistance of *E. coli* to fluoroquinolones in blood cultures [21].

The incidence of infectious complication after PNB in the present study increased from 0.3% in 2005 to 2.31% in 2009 ( $p < 0.001$ ) in group 1 despite the use of fluoroquinolone prophylaxis, and the majority of etiological isolates were positive for fluoroquinolone-resistant *E. coli*. However, the organism has remained susceptible to ceftriaxone in our unit. In addition, ceftriaxone is characterized by a long serum half-life and sustained prostate tissue concentrations [13]. Therefore, in the present study, we tested the efficacy of ceftriaxone and fluoroquinolone as new prophylactic antibiotics, and our results showed that the addition of IV ceftriaxone to fluoroquinolone resulted in a significant decrease in the rate of incidence of infectious complication from an average of 1.0% in group 1 to 0.3% in groups 2 and 3 ( $p < 0.001$ ). The low rate of infectious complications after PNB remained relatively unchanged at approximately 0.2% per year for 3 years after the introduction of the combination regimen (Fig. 1). No significant differences in infectious complications were detected between groups 2 and 3. This present study showed that the use of fluoroquinolone for more than 7 days was not necessary.

Several studies have demonstrated a strong association between the incidence of infectious complications and fluoroquinolone-resistant bacteria. Furthermore, these studies analyzed the risk factors of infectious complications. Carignan et al. [9] reported that fluoroquinolone resistance contributed to the increasing incidence of post-PNB infections in their center and identified recent hospitalization, diabetes mellitus, and chronic obstructive pulmonary disease as independent risk factors. Kehinde et al. [22] reported that normal patients with predisposing risk factors to septicemia

(diabetes, acute prostatitis, UTI, chronic renal failure or patients on high dose steroid therapy) had statistically significantly higher septicemia rates ( $p < 0.001$ ). Loeb et al. [23] also recently reported that diabetes mellitus was significantly associated with an increased risk of fever after PNB. But the present study showed that diabetes mellitus ( $p = 0.251$ ) was not statistically significant risk factor for infectious complication after PNB. We had reviewed the data of patients with diabetes mellitus. The most patients with diabetes mellitus were well controlled serum glucose level. We thought that good glyceric control prior to PNB could be employed to reduce the risk of infectious complication [24].

Similar to the present study, many study recently have tried to use novel prophylactic antibiotics. Kehinde et al. [22] reported that the addition of IV amikacin to quinolone prophylaxis significantly reduced the incidence of septicemia after PNB. Lorber et al. [25] reported that Addition of a single dose of gentamicin 240 mg resulted in a significant drop in infection rates after PNB. And Adibi et al. [26] also reported that the addition of gentamicin to current prophylactic regimens significantly reduced the rate of hospitalization for postbiopsy infectious complications and was shown to be cost-effective. But Carignan et al. [9] described the emergence of quinolone-resistant infections after PNB and reported that empirical treatment should include either a third-generation cephalosporin or carbapenem and vancomycin for gram-positive coverage. In our hospital, fluoroquinolone-resistant *E. coli* is more susceptible to ceftriaxone than to gentamicin.

If subgroups of patients at high risk for harboring resistant organisms could be identified, they could be targeted to improve prophylactic coverage. Kim et al. [27] reported that the prevalence of quinolone resistance was 16.8% in rectal swabs performed before PNB and selection of prophylactic antibiotics before the biopsy may be reconsidered. Duplessis et al. [28] reported that the identification of fluoroquinolone-resistant Enterobacteriaceae infections using selective media in rectal cultures obtained before transrectal ultrasound-guided PNB facilitates targeted antibiotic prophylaxis and appears to be highly efficacious in reducing infectious complications. Although the lack of a comparable study, our study showed similar results compared with targeted antimicrobial prophylaxis using rectal cultures. Rectal culture is time-consuming compared with the antibiotic regimen used in the present study. Although antibiotic prophylaxis in our study reduced infectious complications after prostatic biopsy, we consider that broad spectrum antibiotics would induce more resistant bacteria that could not be controlled by conventional treatment. We



need to try to carefully choose the prophylactic regimens by recognizing the low risk group and the high risk group and in order to avoid unnecessary antibiotics for prophylaxis.

The identification of patients at high risk for post-PNB infectious complications such as those with diabetes or a history of urosepsis, bacterial prostatitis, organ transplant, or fluoroquinolone use in the preceding 12 months, who may benefit from targeted prophylaxis, may be a cost-effective strategy. In the future, more extensive research is needed to determine the effect of targeted prophylaxis on patients at high risk for infectious complication development. But we must change the prophylactic antibiotic regimen when we can't control the infectious complication after PNB. The present study provided information about novel approach for antibacterial prophylaxis.

The present study had several limitations. First, the study design was retrospective and nonrandomized. In addition, the initial design of the study did not include the assessment of risk factors for infectious complications, such as a history of urosepsis, bacterial prostatitis, organ transplant and fluoroquinolone use in the preceding 12 months. Therefore, these risk factors could not be included in the analysis. Second, patients living outside the city in which our hospital is located may have presented to local hospitals when developing post-PNB infections, resulting in the underestimation of the true frequency of this complication. Third, further analysis of our data showed that in the 7-year study period, various generic versions of fluoroquinolone were used, which could vary in their pharmacokinetics and bioavailability.

## CONCLUSIONS

Antibiotic prophylaxis with ceftriaxone before PNB decreased the risk of potentially serious infective complications. If we must change the prophylactic antibiotic regimen when we can't control the infectious complication after PNB, the present study provided information about novel approach for antibacterial prophylaxis.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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