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Febrile Urinary Tract Infection After Prostate Biopsy and Quinolone Resistance

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Purpose: Complications after prostate biopsy have increased and various causes have been reported. Growing evidence of increasing quinolone resistance is of particular concern. In the current retrospective study, we evaluated the incidence of infectious complications after prostate biopsy and identified the risk factors.

Materials and Methods: The study population included 1,195 patients who underwent a prostate biopsy between January 2007 and December 2012 at Chung-Ang University Hospital. Cases of febrile UTI that occurred within 7 days were investigated. Clinical information included age, prostate-specific antigen, prostate volume, hypertension, diabetes, body mass index, and biopsy done in the quinolone-resistance era. Patients received quinolone (250 mg intravenously) before and after the procedure, and quinolone (250 mg) was orally administered twice daily for 3 days. We used univariate and multivariate analysis to investigate the predictive factors for febrile UTI.

Results: Febrile UTI developed in 39 cases (3.1%). Core numbers increased from 2007 (8 cores) to 2012 (12 cores) and quinolone-resistant bacteria began to appear in 2010 (quinolone-resistance era). In the univariate analysis, core number ≥ 12 (p=0.024), body mass index (BMI) > 25 kg/m^2 (p=0.004), and biopsy done in the quinolone-resistance era (p=0.014) were significant factors. However, in the multivariate analysis adjusted for core number, the results were not significant, with the exception of BMI > 25 kg/m^2 (p=0.011) and biopsy during the quinolone-resistance era (p=0.035), which were significantly associated with febrile UTI.

Conclusions: Quinolone resistance is the main cause of postbiopsy infections in our center. We suggest that further evaluation is required to validate similar trends. Novel strategies to find alternative prophylactic agents are also necessary.

Keywords: Prostate biopsy, Prostatitis, Quinolone resistance

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INTRODUCTION

Prostate cancer is the most frequently diagnosed tumor in elderly men and is the sixth leading cause of cancer death among men worldwide [1]. With the widespread popularity of prostate-specific antigen (PSA) testing, an ultrasound-guided transrectal prostate biopsy has become one of the most common urological procedures. Many men are now undergoing transrectal biopsy owing to increasing

awareness of prostate cancer. Thus, with the increased incidence of prostate biopsy, there has been a concomitant increase in complications of infection. Clinically significant infectious complications include urinary tract infection (UTI), acute bacterial prostatitis, epididymo-orchitis, and sepsis.

According to the European Association of Urology guideline, oral or intravenous antibiotics are essential before biopsy. Quinolones are the drug of choice, with cipro-

floxacin superior to ofloxacin [2]. Resistance to quinolones is on the rise, however, owing to their increased use. Infectious complications are a continued threat following transrectal ultrasound (TRUS)-guided prostate biopsies. The incidence of serious complications requiring hospital admission ranges from 0.1% to 2.5%, most often secondary to UTI, fever, or sepsis [3]. Recently, quinolone resistance has increased rapidly worldwide and is especially high in Korea. Quinolone resistance of *Escherichia coli* in Korean hospitals had already exceeded 30% in 2004 [4].

Increasing core number during prostate biopsy is a recent trend to achieve a higher detection rate of prostate cancer. In 2007, an average of 8 cores was performed in our hospital; in 2012, however, the number increased to 12 cores for prostate biopsy. These factors may also increase the risk of infection. Since 2010, postbiopsy febrile complications have increased in Chung-Ang University Hospital. Accordingly, we evaluated the incidence of infection after prostate biopsy and additionally identified risk factors retrospectively.

MATERIALS AND METHODS

1. Population and design
The study population included 1,195 patients who underwent a prostate needle biopsy in our hospital between January 2007 and December 2012. All patients were referred for biopsy owing to an abnormal digital rectal examination (DRE) result or a PSA concentration over 4 ng/mL. Patients with bacteriuria or pyuria were excluded from the study.

Oral anticoagulant agents were discontinued 7 days before biopsy. Enemas were not given before biopsy. Patients received levofloxacin or ciprofloxacin (250 mg, intravenous) before and after the procedure, and fluoroquinolone (250 mg, orally) was administered twice daily for 3 days after biopsy. The Institutional Review Board approved this study.

2. Biopsy technique
Biopsies were performed by a well-trained third-year urologic resident using the standardized protocol. TRUS was performed with a multiplanar multifrequency probe attached to the ultrasound scanner. Prostate biopsy specimens were taken with an automated spring-loaded gun. From 2007 to 2010, mainly 8-core biopsy was performed. Tissues were collected from both sides of the base, mid, midlateral, and apex. Average core number was increased to 12 in 2011 and additional samples were collected from the base lateral and apex lateral lobe between 2011 and 2012.

3. Selection of cases and controls
Patients who experienced postbiopsy febrile UTI that occurred within 7 days were investigated. Febrile UTI was defined by the following symptoms: fever ($>38\,℃$), leukocytes in urine sediment, and tenderness of the prostate during DRE. Included patients were hospitalized and treated with third-generation cephalosporin. Urine culture and blood culture were performed before antibiotic therapy.

4. Data collection and analysis
Clinical and laboratory information were collected from each patient's medical record. Clinical information included age, PSA, estimated prostate volume, occurrence of hypertension, occurrence of diabetes, body mass index (BMI), and biopsy done in the quinolone-resistance era. To measure the relevance of these factors and UTI, univariate analysis and multivariate analysis were performed. The retrospective study was appropriately designed and p-values of <0.05 were considered statistically significant. Statistical analyses were performed by using SPSS ver. 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

From 2007 to 2012, 1,195 men underwent TRUS-guided prostate biopsy. The mean age of the patients was 66.3±9.8 years and their mean PSA level was 12.5 ng/mL. The mean prostate volume was 50.6±21.4 mL. All men in the biopsy group were Asian. The most common comorbidity was hypertension (41.9%). Among the 1,195 subjects, 409 (34.2%) were diagnosed with prostate cancer (Table 1).

The incidence of prostate biopsy and the number of cores taken during biopsy gradually increased. Prostate biopsy at our institution increased from 127 cases in 2007 to 253

TABLE 1. Patient characteristics

Characteristic	Value
Age (y)	66.25±9.79
PSA (ng/mL)	12.52±168.80
Free PSA (ng/mL)	6.91±38.84
Prostate volume (mL)	50.58±21.36
Adenocarcinoma	409 (34.2)
Core number	
≤8	556 (46.5)
9–11	204 (17.1)
≥12	435 (36.4)
Gleason score	
≤6	191 (46.7)
7	127 (31.1)
8	65 (15.9)
≥9	26 (6.4)
Hypertension	501 (41.9)
Diabetes	210 (17.6)
Body mass index (kg/m^2)	
<23	417 (34.9)
23–25	337 (28.2)
>25	441 (36.9)
PreQera (2007–2009)	424 (42.4)
Qera (2010–2012)	577 (57.6)

Values are presented as mean±standard deviation or number (%). PSA, prostate-specific antigen; PreQera, before the quinolone-resistance era; Qera, quinolone-resistance era.

TABLE 2. Comparison of the characteristics of normal patients and those with febrile urinary tract infection

Variable	Normal	Febrile UTI	Odds ratio (95% CI)	p-value
No. of patients	1,156 (96.7)	39 (3.3)		
Age (y)				
<60	286 (24.7)	15 (38.5)		0.137
60–70	421 (36.4)	10 (25.6)	0.453 (0.201–1.022)	0.057
>70	449 (38.8)	14 (35.9)	0.595 (0.283–1.250)	0.170
PSA				
<4	239 (20.7)	10 (25.6)		0.652
4–10	615 (53.2)	18 (46.2)	0.700 (0.318–1.537)	0.374
>10	302 (26.1)	11 (28.2)	0.871 (0.364–2.084)	0.756
Size (mL)				
≤25	171 (14.8)	3 (7.7)		
>25	985 (85.2)	36 (92.3)	2.083 (0.634–6.840)	0.226
Diagnosis				
BPH	754 (65.2)	31 (79.5)		
Adenocarcinoma	402 (34.8)	8 (17.9)	0.424 (0.185–0.970)	0.042
Cores				
<12	200 (17.3)	4 (10.3)		
≥12	414 (35.8)	21 (53.8)	2.091 (1.102–3.969)	0.024
Hypertension	482 (41.7)	19 (48.7)	1.328 (0.701–2.516)	0.383
Diabetes	204 (17.6)	6 (15.4)	0.848 (0.351–2.052)	0.715
Body mass index (kg/m^2)				
<23	411 (35.6)	6 (15.4)		0.012
23–25	327 (28.3)	10 (25.6)	2.095 (0.753–5.824)	0.156
>25	418 (36.2)	23 (59.0)	3.770 (1.519–9.352)	0.004
Period				
2007–2009	282 (24.4)	2 (5.1)		
2010–2012	874 (75.6)	37 (94.9)	5.969 (1.430–24.923)	0.014

Values are presented as number (%).
UTI, urinary tract infection; CI, confidence interval; PSA, prostate-specific antigen; BPH, benign prostatic hyperplasia.

TABLE 3. Multivariate analysis to determine the significant predictive factors for postbiopsy febrile urinary tract infection

Variable	Odds ratio (95% CI)	p-value
Diagnosis		
Benign prostatic hyperplasia	-	
Adenocarcinoma	0.481 (0.198–1.169)	0.106
Cores		
<12	-	
≥12	1.369 (0.694–2.703)	0.365
Body mass index		
<23	-	0.026
23–25	1.810 (0.629–5.207)	0.271
>25	3.383 (1.327–8.626)	0.011
Period		
2007–2009	-	
2010–2012	4.902 (1.114–21.563)	0.035

CI, confidence interval.

cases in 2012. An average of 8.43 cores was taken in 2007, and this value increased to 11.74 cores in 2012. Quinolone was widely used before prostate biopsy.

Overall, 39 men (3.1%) were hospitalized within 7 days after biopsy owing to febrile UTI. They were treated by use of third-generation cephalosporin. There were no mortalities.

Table 2 illustrates the univariate analyses conducted to identify potential independent risk factors associated with febrile UTI. There was no significant relationship between the development of febrile UTI and patient age, serum total PSA, prostate volume, hypertension, diabetes, or BMI.

Of the 409 patients who had adenocarcinoma on biopsy, only 7 patients (1.71%) developed febrile UTI. This suggested that prostate cancer was not responsible for the infectious complication.

In the univariate analysis, complications were directly correlated with the number of needle cores in patients who underwent <12 vs. >12 cores (p=0.024). However, the multivariate logistic regression analysis did not show any significant correlations between febrile UTI and the number of cores after adjustment for confounders (p=0.365) (Table 3).

Of 210 patients with a history of diabetes, only 4 patients (1.9%) developed febrile UTI. Patients with BMI >25 kg/m^2 had an increase in frequency of febrile UTI (5.2%). BMI >25 kg/m^2 was a definite risk factor for the development of febrile UTI after prostate biopsy in univariate (p=0.004) and multivariate (p=0.011) analysis.

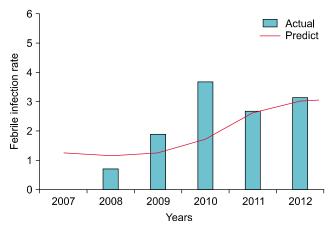The overall incidence of infectious complications was

FIG. 1. Actual and predict incidence rate of postbiopsy urinary tract infection.

TABLE 4. Susceptibility to antibiotics in patients with febrile urinary tract infection

Antibiotic	Drug sensitivity, n (%)
Amikacin	25/25 (100)
Imipenem	25/25 (100)
Piperacillin/tazobactam	20/20 (100)
Cefazolin	21/21 (100)
Tigecycline	17/17 (100)
Aztreonam	18/20 (90.0)
Tobramycin	16/18 (88.9)
Trimethoprim/Sulfa	14/20 (70.0)
Amoxicillin/CA	16/24 (66.7)
Cephalothin	9/21 (42.9)
Fluoroquinolone	6/20 (30.0)
Piperacillin	6/24 (25.0)
Ampicillin	3/21 (14.3)

CA, clavulanic acid.

3.1%. When stratified by year, the incidence of infectious complications was 5 times higher in 2010–2012 than in 2007–2009, with statistical significance in the univariate ($p=0.014$) and multivariate ($p=0.035$) analysis. Fluoroquinolone resistance was more common in the latter period. To predict the probability of infection on the basis of the multivariate analysis result, in 2010, actual infection was higher than expected. This coincided with the quinolone resistance that occurred in our hospital (Fig. 1).

Of the 39 patients with febrile UTI, 25 patients (67.6%) had positive urine or blood cultures. *E. coli* was the most frequent pathogen (n=20, 80%), followed by *Enterococcus faecalis* (n=2) and *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Burkholderia cepacia* (n=1). Quinolone resistance was observed in 70% of patients who developed febrile UTI. Resistance patterns were most commonly seen with ampicillin (85.7%), piperacillin (75%), fluoroquinolone (70%), cephalothin (57.1%), and amoxicillin/clavulanic acid (33.3%). However, 90% or greater susceptibility was demonstrated for amikacin, imipenem, piperacillin/tazobactam, cefazolin, tigecycline, and aztreonam. Table 4 shows a more comprehensive list of susceptibility patterns for bacteria in urine and blood.

DISCUSSION

The efficacy of fluoroquinolone was initially hypothesized to result from its potent activity against a large spectrum of clinically relevant pathogens, especially *E. coli*; additionally, excellent prostatic tissue levels were obtained after oral administration. This assumption was further confirmed by the high rates of success when fluoroquinolone was used prior to biopsy procedures [5,6].

However, the routine prophylactic application of fluoroquinolones has posed a problem. Our results indicated that the incidence of infection was similar to that reported in other studies. Recently, the incidence of quinolone resistance has increased further with an increased ratio of quinolone-resistant *E. coli* as well. This suggests that the increased prevalence of quinolone-resistant *E. coli* is the cause of infection. Many recent reports have shown that fluoroquinolone-resistant infection after prostate biopsy is on the rise [7].

The likely reason for increased quinolone resistance could be increased use. Since the 1980s, the broad-spectrum fluoroquinolone ciprofloxacin has been the antibiotic of choice for the treatment of UTIs, mostly because of its potent activity against a large spectrum of clinically relevant pathogens. Between 2008 and 2012, fluoroquinolone resistance gradually increased from 33% to 85%. This phenomenon has prompted an ongoing search for improved prophylactic antibiotic protocols.

South Korea is a country with especially high quinolone usage, with daily defined doses much higher than in other countries [8]. It would be particularly useful to reduce the use of fluoroquinolone. Any move toward a better antibiotic regimen should be based on comparative prospective randomized studies. Perhaps the use of less common antibiotics should be reserved for prophylaxis and treatment of infection in the context of antibiotic cycling. These practices would decrease the likelihood of introducing resistance mechanisms against them. Furthermore, no study to date, including the present study, has demonstrated that extended dosing as a prophylactic regimen is superior to single dosing.

It may be important to consider the replacement of antibiotics or the use of individual customized antibiotics. The choice of antibiotics is crucial in determining the outcome. Duplessis et al. [9] and Taylor et al. [10] proposed that rectal cultures be obtained before TRUS-guided biopsy to identify fluoroquinolone-resistant flora to facilitate targeted antibiotic prophylaxis and decrease the overall cost of care. This would complicate the adherence to a specific treatment protocol. Resistance profiles could vary among isolates indicating that a single treatment algorithm would not work for all bacteria. Thus, follow-up of culture results and the customization of each patient's treatment regimen

are indicated. Additionally, a regular review of regional and local resistance patterns is also recommended, because these reveal resistance patterns of various bacterial species and could guide the practitioner toward better treatment options.

According to our data, amikacin, imipenem, piperacillin/tazobactam, cefazolin, and tigecycline were useful. Compared with fluoroquinolones, imipenem had demonstrably much lower resistance rates. However, the inclusion of such agents in a routine prebiopsy preparation protocol will involve greater expense and the obligation of injections. Also, imipenem use must be carefully considered to avoid creating resistance to these agents. Carignan et al. [11] recommended the use of amikacin or carbapenem.

An analysis of the resistance demonstrated that penicillins had the highest level of resistance. We observed high levels of ampicillin resistance (85.7%), similar to other reports. Ampicillin should not be considered as a first-line antibiotic for treatment of postbiopsy febrile UTI.

Some studies identified diabetes or increased core number as the cause of postbiopsy febrile UTI [12,13], unlike the current findings. Our study shows obesity as a risk factor for infection, but not diabetes. In our opinion, patients diagnosed with diabetes are getting close to glucose control, whereas patients identified as obese could include those with glucose intolerance or undiagnosed diabetes. In addition, obese patients are known to be vulnerable to infection [14].

In 14 of the 39 cases (32.4%), no bacteria were isolated from either blood or urine. However, antibiotic treatment resulted in the improvement of clinical symptoms and leukocytosis. Negative cultures in the setting emphasized the importance of taking multiple blood cultures from different sites.

Our study had several important limitations. First, the sample size of the groups with infection was limited because of the low incidence of such complications in general. Second, it was a retrospective nonrandomized study using data derived from an Institutional Review Board-approved database and the medical records of the enrolled patients. The impetus to initiate an investigation on febrile UTI was determined solely by the patient's symptoms and not by a standardized collection of urine or blood cultures for all patients after biopsy. Thus, there may have been a risk of missing cases of asymptomatic bacteriuria, although the clinical implications of this would be limited. Third, the initial design of the study did not consider a previous history of quinolone use.

CONCLUSIONS

The increase in UTI was due to quinolone-resistant bacteria. Therefore, alternative prophylactic antibiotics for prostate biopsy must be researched further. The physician is compelled to consider several factors and customize anti-

biotic prophylaxis on an individual basis. Postbiopsy infections after standard fluoroquinolone prophylaxis are suggested to be treated with regimens such as imipenem, piperacillin/tazobactam, or cefazolin until culture findings are available to guide therapy.

CONFILICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol 2012;61:1079-92.
2. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, Mason MD, et al. Guidelines on prostate cancer. Arnhem: European Association of Urology; 2012.
3. Djavan B, Waldert M, Zlotta A, Dobronski P, Seitz C, Remzi M, et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. J Urol 2001;166:856-60.
4. Kim CS. Quinolone resistance in urologic field: present and future. Korean J Urogenit Tract Infect Inflamm 2007;2:40-7.
5. Kim SJ, Kim SI, Ahn HS, Choi JB, Kim YS, Kim SJ. Risk factors for acute prostatitis after transrectal biopsy of the prostate. Korean J Urol 2010;51:426-30.
6. Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. BJU Int 2000;85:682-5.
7. Steensels D, Slabbaert K, De Wever L, Vermeersch P, Van Poppel H, Verhaegen J. Fluoroquinolone-resistant E. coli in intestinal flora of patients undergoing transrectal ultrasound-guided prostate biopsy: should we reassess our practices for antibiotic prophylaxis? Clin Microbiol Infect 2012;18:575-81.
8. OECD. Health policies and data [Internet]. Cedex: OECD; [cited 2014 Jul 10]. Available from: http://www.oecd.org/health/health-systems.
9. Duplessis CA, Bavaro M, Simons MP, Marguet C, Santomauro M, Auge B, et al. Rectal cultures before transrectal ultrasound- guided prostate biopsy reduce post-prostatic biopsy infection rates. Urology 2012;79:556-61.
10. Taylor AK, Zembower TR, Nadler RB, Scheetz MH, Cashy JP, Bowen D, et al. Targeted antimicrobial prophylaxis using rectal swab cultures in men undergoing transrectal ultrasound guided prostate biopsy is associated with reduced incidence of postoperative infectious complications and cost of care. J Urol 2012;187:1275-9.
11. Carignan A, Roussy JF, Lapointe V, Valiquette L, Sabbagh R, Pepin J. Increasing risk of infectious complications after transrectal ultrasound-guided prostate biopsies: time to reassess antimicrobial prophylaxis? Eur Urol 2012;62:453-9.
12. Pepe P, Aragona F. Morbidity after transperineal prostate biopsy in 3000 patients undergoing 12 vs 18 vs more than 24 needle cores. Urology 2013;81:1142-6.
13. Nam RK, Saskin R, Lee Y, Liu Y, Law C, Klotz LH, et al. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. J Urol 2010;183:963-8.
14. Semins MJ, Shore AD, Makary MA, Weiner J, Matlaga BR. The impact of obesity on urinary tract infection risk. Urology 2012;79:266-9.