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ORIGINAL RESEARCH

Positive Culture Prior to Transperineal Prostate Biopsy Was Not Associated with Post-Biopsy Febrile Urinary Tract Infection Development

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Purpose: To investigate the association between urine culture before transperineal prostate biopsy and post-biopsy febrile urinary tract infection (fUTI).

Patients and Methods: We retrospectively reviewed 307 patients who underwent urine culture before transperineal prostate biopsy between April 2017 and September 2020. Patients with indwelling urinary catheters (n=7) were excluded. Urine culture was performed 1–3 days before the biopsy, and all patients received prophylactic cefazolin regardless of culture results. A urine culture was defined as positive if cell density was more than 1×10^5 colony-forming units per mL. Baseline characteristics and the incidence of post-biopsy fUTI were compared between patients showing positive pre-biopsy culture results and those showing negative findings.

Results: Out of 300, seven patients (2.3%) had positive urine culture results before the biopsy. Age (p=0.077); prostate-specific antigen at diagnosis (p=0.267); prostate volume (p=0.78); number of biopsy cores (p=0.277); percentage of patients testing positive for cancer on biopsy (p=0.71); and percentages of patients with a history of biopsy (p>0.999), diabetes mellitus (p=0.604), and immunosuppressive medication use (p>0.999) were similar between the two groups. No patient in the positive urine culture group had post-biopsy fUTI. However, 1.7% (five patients) of the negative urine culture group had the disease (p>0.999) (four patients with prostatitis and one with pyelonephritis). Among them, two patients were diagnosed by urine culture at the time of post-biopsy fUTI.

Conclusion: In asymptomatic patients, positive pre-biopsy cultures were not associated with the development of post-biopsy fUTI.

Keywords: urinary tract infection, prostate biopsy, transperineal, urine culture

Introduction

Prostate biopsy (PB) is necessary for diagnosing prostate cancer. Although the efficacy to detect malignancy is similar in both transrectal and transperineal approaches,[1] many institutions have adopted the transrectal prostate biopsy (TR-PB) because of its simplicity, particularly concerning anesthesia.[2–4]

However, TR-PB is associated with a higher incidence of infection than a transperineal prostate biopsy (TP-PB).[5] With the increasing antibiotic resistance of the rectal flora,[6] TP-PB should be considered to reduce the risk of infectious complications as it does not involve any passage through the rectum. However, while the frequency of infections in TP-PB is reported to be 0.38–3.82%,[7–9] these infections could sometimes be severe and even life-threatening. Although some

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reports suggest that antibiotic prophylaxis is not necessary for TP-PB,[10] prophylactic therapy is generally recommended to reduce the risk of infection.

Because of the presence of bacteria in feces or urine, consideration of pre-biopsy rectal swab culture is shown to reduce the risk of post-biopsy infection in TR-PB.[11] Although the presence of bacteria on the perineal skin or in urine can also lead to post-biopsy infections in TP-PB, the clinical utility of pre-biopsy urine culture is not well known.

Here, we aimed to investigate the association between urine culture before transperineal PB and post-biopsy febrile urinary tract infection (fUTI).

Materials and Methods

This study was approved by our institutional review board (Admission number: 2020–125). The need for informed consent was waived given the retrospective nature of the study. However, information regarding this study was still disclosed on the website, and opportunities for refusal were guaranteed.

Study Design and Patient Population

We performed a retrospective analysis of 307 patients who underwent urine culture tests before TP-PB between April 2017 and September 2020. Patients were excluded if a urinary catheter was placed.

Protocol

All patients were hospitalized. Urine culture tests were performed 1–3 days before TP-PB. The urine culture was considered positive if the cell density of more than 1×10^5 colony-forming units per mL (CFU/mL) was observed. All patients were treated with prophylactic cefazolin 1 g intravenously before biopsy regardless of the urine culture results. TP-PB was performed under general or subarachnoid anesthesia of the spine. Perineal and perianal sterilization was performed using iodine, but not in the rectum. A urinary catheter was placed after biopsy. Patients who were stable on the first postoperative day had their urinary catheter removed and were discharged.

Data Collection and Statistical Analysis

All data were collected from electronic medical records. In this study, baseline characteristics data (age, prostate-specific antigen (PSA) at diagnosis, prostate volume, number of biopsy cores, number of cancer-positive patients identified upon biopsy, and history of biopsy, diabetes mellitus, and immunosuppressive medication use) were collected retrospectively. According to pre-biopsy urine culture results, patients were divided into two groups: (1) positive urine culture group and (2) negative urine culture group. To compare the baseline characteristics between the two groups, chi-square and Fisher's exact tests were used for categorical variables, while the Mann–Whitney *U*-test was used to evaluate continuous variables.

Among patients with positive urine culture results, the types of bacteria isolated were also examined. The incidence of post-biopsy complications (fUTI, dysuria, macrohematuria, and others) within 30 days after biopsy was compared between the two groups. fUTI was defined as a symptomatic status in the genitourinary tract with fever (temperature >38°C). To diagnose whether or not the patient had pyelonephritis, prostatitis, or epididymitis, we referred to clinical symptoms such as costovertebral angle tenderness, tenderness on rectal examination, and scrotal pain.

Antimicrobial susceptibility was defined according to the Clinical and Laboratory Standards Institute guidelines. A p-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 307 patients who underwent urine culture tests before TP-PB within the study period were initially included. However, patients who had indwelling urethral catheters (n=7) were excluded. Finally, the 300 patients who met the inclusion criteria were selected for this study.

Table 1 shows patient characteristics. Of the 300 patients, positive pre-biopsy urine cultures were identified in seven patients (2.3%). Statistical analysis revealed no significant difference between the positive urine culture group and the negative urine culture group in terms of median age (74 vs 71 years old, p=0.077), median PSA level at diagnosis (8.63 vs 6.72 ng/mL, p=0.267), median prostate volume (30.5 vs 33.2 cc, p=0.78), number of biopsy cores (14 vs 14 cores, p=0.277), percentage of cancer-positive patients identified upon biopsy (57.1% vs 63.4%, p=0.71), and percentages of patients with a history of biopsy (28.5% vs 29.3%, p>0.999), diabetes mellitus (0% vs 16.7%, p=0.604), and immunosuppressive medication use (0% vs 2%, p>0.999).

Figure 1 shows the bacterial characteristics of pre-biopsy urine culture. In 12 out of the 300 patients, bacteria

Table 1 Patients Characteristics of the 300 Patients Who Were Performed Transperineal Prostate Biopsy

Variables	All	Positive Urine Culture	Negative Urine Culture	p-value
Number of patients, n (%)	300	7 (2.3)	293 (97.7)	
Median age, years (IQR)	71 (67–76)	74 (74–78)	71 (67–75)	0.077
Median PSA at biopsy, ng/mL (IQR)	6.81 (5.12–10.32)	8.63 (6.93–11.75)	6.72 (5.12–10.3)	0.267
Median prostate volume, cc (IQR)	33 (25–48)	30.5 (23–59.5)	33.2 (25–48)	0.78
Median number of biopsy cores, n (IQR)	14 (14–16)	14 (12–15)	14 (14–16)	0.277
Positive biopsy, n (%)	190 (63.3)	4 (57.1)	186 (63.4)	0.71
Prior biopsy, n (%)	88 (29.3)	2 (28.5)	86 (29.3)	0.999<
Diabetes mellitus, n (%)	49 (16.3)	0 (0)	49 (16.7)	0.604
Immunosuppression, n (%)	6 (2)	0 (0)	6 (2)	0.999<

Abbreviation: IQR, interquartile range.

were isolated in pre-biopsy urine culture; however, only seven patients had a positive urine culture (ie, $>10^5$ CFU/mL). Among these seven patients, five patients had one type of bacteria isolated, and two patients had two types of bacteria isolated in their urine cultures. One of the patients with two types of bacteria isolated had one bacteria with counts $>10^5$ CFU/mL and one with counts $<10^5$ CFU/mL. The distributions of patients with bacterial species at counts $>10^5$ CFU/mL in pre-biopsy culture are as follows: *Staphylococcus epidermidis* (n=3), *Streptococcus agalactiae* (n=1), *Staphylococcus aureus* (n=1), *Enterococcus faecalis* (n=1), *Staphylococcus caprae* (n=1), and *Raoultella ornithinolytica* (n=1). All other bacteria other than *Enterococcus faecalis and Raoultella ornithinolytica were* susceptible to cefazolin. Table 2 shows the antimicrobial susceptibility of each bacteria (more than 1×10^5 CFU/mL) on pre-biopsy positive urine culture. Out of seven bacteria available for evaluation, six were susceptible to CEZ (85.7%). Out of eight bacteria available for evaluation, five were susceptible to LVFX (62.5%).

Table 3 shows infectious and non-infectious complications following TP-PB, stratified by pre-biopsy urine culture results. There were no cases of post-biopsy fUTI in the positive urine culture group; however, 1.7% (five

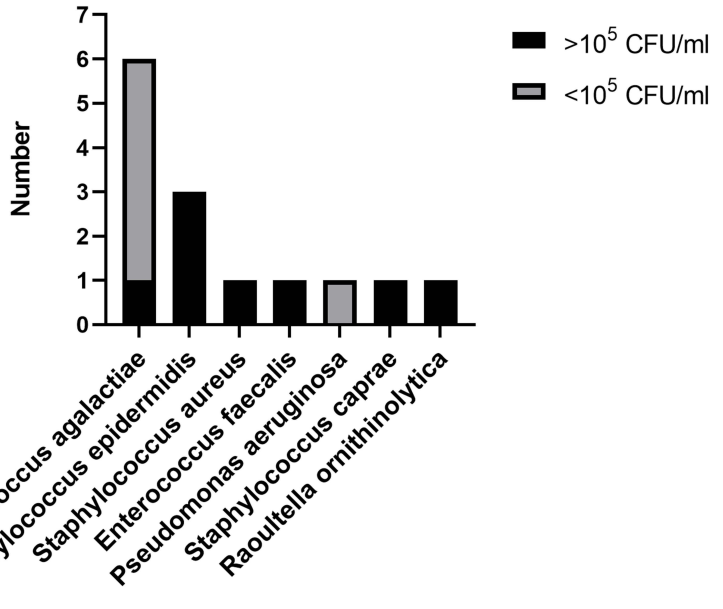

Figure 1 Bacterial characteristics observed in pre-biopsy urine culture.

Table 2 Antimicrobial Susceptibility of Each Bacteria (More Than 1×10^5 Colony-Forming Units per ml) on Pre-Biopsy Urine Culture

Patient Number	Bacterial Characteristics	Antibiotics																
		PCG	TAZ/ PIPC	ABPC	CEZ	CTM	CTX	CFPN-PI	CMZ	CCL	CDTR-PI	FRPM	MEPM	EM	MINO	CPFX	LVFX	STFX
1	Streptococcus agalactiae	S	-	S	S	S	S	S	S	S	S	S	S	R	R	R	S	S
2	Staphylococcus epidermidis	-	-	R	S	S	-	-	S	-	-	-	-	R	S	R	R	R
3	Staphylococcus epidermidis	-	-	S	S	S	-	-	S	-	-	-	-	S	S	R	R	S
4	Staphylococcus epidermidis	-	-	S	S	S	-	-	S	-	-	-	-	S	S	R	R	S
	Enterococcus faecalis	-	-	S	-	-	-	-	R	-	-	-	-	-	I	S	S	S
5	Staphylococcus aureus	-	-	R	S	S	-	-	S	-	-	-	-	R	S	I	S	S
6	Staphylococcus caprae	S	-	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
7	Raoultella ornithinolytica	-	S	-	R	S	S	-	S	-	-	-	S	-	-	-	S	S

Abbreviations: PCG, penicillin G; TAZ/PIPC, tazobactam/piperacillin; ABPC, ampicillin; CEZ, cefazolin; CTM, cefotiam; CTX, cefotaxime; CFPN-PI, cefcapene pivoxil; CMZ, cefmetazole; CCL, cefaclor; CDTR-PI, cefditoren pivoxil; FRPM, faropenem; MEPM, meropenem; EM, erythromycin, minocycline; CPFX, ciprofloxacin; LVFX, levofloxacin; STFX, sitafloxacin hydrate; S, susceptible; I, intermediate; R, resistant.

Table 3 Infectious and Noninfectious Complications Following Transperineal Prostate Biopsy

Variables	Positive Urine Culture	Negative Urine Culture	p-value
Number of patients, n	7	293	
Any complications, n (%)	3 (42.8)	58 (19.8)	0.151
Infection, n (%) Prostatitis, n (%) Pyelonephritis, n (%) Epididymitis, n (%)	0 (0) 0 (0) 0 (0) 0 (0)	5 (1.7) 4 (1.4) 1 (0.3) 0 (0)	0.999<
Voiding symptom, n (%) Urinary retention, n (%)	1 (14.2) 0 (0)	19 (6.5) 9 (3.1)	0.386 0.999<
Macrohematuria, n (%)	3 (42.9)	39 (13.3)	0.06
Others, n (%)	0 (0)	6 (2)	0.999<

patients) were diagnosed with fUTI in the negative urine culture group (p>0.999). Statistical analysis revealed that non-infectious complications, such as voiding symptoms (14.2% vs 6.5%, p=0.386), urinary retention (0% vs 3.1%, p>0.999), and macrohematuria (42.9% vs 13.3%, p=0.06), were not significantly different between the two groups.

Table 4 shows the association between pre-biopsy urine culture and urine culture upon fUTI diagnosis, considering the time and type of infection, in patients with post-biopsy fUTI. There were four patients with prostatitis and one patient with pyelonephritis. Among these cases, 40% (2 patients) had a positive urine culture at the time of fUTI. All patients with infection were treated with piperacillin-tazobactam with no fatal adverse event.

Discussion

Of the 300 patients selected in the study, only seven patients (2.3%) had a positive urine culture prior to TP-PB. In addition, we observed that post-biopsy fUTI was not identified in patients with positive pre-biopsy urine culture but rather in patients with negative urine culture results. This study can be considered a study of asymptomatic patients because patients with indwelling urinary catheters were excluded. To the best of our knowledge, this is the first study to investigate the clinical efficacy of performing pre-biopsy urine culture in the development of fUTI following TP-PB.

The prevalence of prostate cancer has increased partly due to the increased availability of PSA for diagnosis. PB is still considered the gold standard for the diagnosis of

Table 4 The Association Between Pre-Biopsy Urine Culture and Urine Culture Upon Febrile Urinary Tract Infection in Patients with Infection Following Transperineal Prostate Biopsy

Age	Prostate Volume	Number of Biopsy Cores	Diabetes Mellitus	Immunosuppression	Urine Culture at Prebiopsy	Urine Culture at Infection	Type of Post-Biopsy Infection	Date of Infection Onset (Days After Biopsy)
69	41	14	No	No	No growth	Escherichia coli	Prostatitis	19
69	18	20	No	Yes	No growth	No growth	Prostatitis	1
74	70	15	No	No	No growth	No growth	Prostatitis	1
65	48	14	No	No	No growth	Acinetobacter baumannii / Staphylococcus epidermidis	Prostatitis	7
79	63	14	No	No	No growth	No growth	Pyelonephritis	5

prostate cancer. Although TR-PB is widely performed worldwide, the increasing antibiotic resistance of the rectal flora is associated with the increasing incidence of severe post-biopsy infections.[12,13] Although severe infections could also occur in TP-PB, this approach avoids contact with the rectal flora, thereby decreasing the likelihood of infection. In our study, the incidence of post-biopsy infectious complications was observed to be 1.7% (5 out of 300 patients), which is consistent with previous studies (0.36–3.82%).[7–9] Since PB is a commonly performed procedure, the safety profile of TP-PB must be further investigated to prevent associated infectious complications.

Although several studies have examined the effectiveness of pre-biopsy rectal swab culture,[11,16–18] only a few studies have explored the clinical utility of urine culture before TR-PB.[14,15] Bruyère et al reported that 3.4% (12 of 353 patients who received transrectal needle biopsy) had positive pre-biopsy urine culture (>1×10^5 CFU/mL) 48–72 h before PB, and only 1.1% of patients with negative pre-biopsy urine culture developed infectious complications following PB. In their study, all patients received ofloxacin 200 mg 2–6 h before PB.[14] Qi et al have also shown that 4% (6 of 150 patients who underwent prostate needle biopsy) had evidence of bacteriuria (>1×10^5 CFU/mL) in urine cultures 14 days before PB. Among these, no patient developed infectious complications following PB. In their study, all patients received prophylactic ciprofloxacin 500 mg the night before and the morning of the biopsy.[15] Both studies described above have suggested that routine urine culture before planned PB in asymptomatic patients was unnecessary. Although the cause of infectious complications of TR-PB could be bacteria found in either feces or urine, the results from these studies may be attributed to the more significant influence of the rectal flora on post-biopsy infection than that of urine.

However, infectious complications of TP-PB may be caused by bacteria in the perineal skin or urine. To date, no report has examined the utility of urine culture before TP-PB to assess the likelihood of infectious complications. In our study, the incidence of positive urine culture before TP-PB was only 2.3%. Among these patients, no infectious complication was observed. Furthermore, no significant difference was observed between the positive and negative pre-biopsy urine culture groups for background characteristics, such as age, prostate volume, number of biopsies, as well as a history of biopsy, diabetes mellitus, and use of immunosuppressive drugs. Our results suggest that routine pre-biopsy urine culture is unnecessary for treating post-biopsy fUTI in asymptomatic patients.

Another key finding from this study is that a single 1 g dose of intravenous cefazolin may be sufficient prophylactic antibiotics for fUTI following TP-PB. Some reports have indicated that quinolone-based antibiotics are effective for prophylaxis.[19,20] However, the development of resistance to quinolone-based antibiotics is an alarming issue,[6] and the routine use of broad-spectrum antimicrobials, such as quinolones, for prophylaxis remains debatable. However, further prospective randomized controlled trials are necessary to assess the efficacy of cefazolin for prophylaxis.

Several limitations of this study must be acknowledged before interpreting our findings. First, this study was based on a limited population at a single institution; the lack of statistical significance in the analysis may be attributed to a low statistical power due to the small sample size. Furthermore, multivariate analysis for the adjustment for potential confounders was challenging because of the extremely low incidence of post-biopsy infectious complications. Second, the retrospective descriptive design was not ideal for attaining study goals. The optimal study design for investigating the benefit of pre-biopsy urine culture would be a randomized controlled trial that compares patients with and without pre-biopsy urine culture. However, because of the low incidence of positive pre-biopsy urine culture and post-biopsy infection, achieving the large sample size required may not be feasible. In addition, the indwelling urethral catheter after biopsy in the current protocol may be a potential confounding factor of post-biopsy fUTI.

Third, due to the retrospective study, the result of urine analysis before the biopsy was lacking. Also, voiding conditions before biopsy, such as post voiding residual or International Prostate Symptom Score, were lacking. These factors may also be potential confounding factors in considering post-biopsy fUTI. Fourth, the urine culture was considered positive if a bacterial density of more than 1×10^5 CFU/mL was observed in accordance with previous studies and guidelines.[14,15,21] Microbiological criteria for the diagnosis of asymptomatic bacteriuria in men have not been adequately validated. This cutoff needs to be validated to see if it is optimal in the current study setting.

Despite these limitations, this study has demonstrated the association between urine culture before TP-PB and post-biopsy fUTI. Our findings indicated that pre-biopsy urine culture was not helpful for the treatment of post-biopsy infection in TP-PB. The uniqueness of this study is a considerable strength.

Conclusion

We examined the results of urine culture before TP-PB. In asymptomatic patients, the incidence of positive urine culture was observed to be very low. Positive pre-biopsy cultures were not associated with the development of post-biopsy fUTI.

Abbreviations

fUTI, febrile urinary tract infection; PB, prostate biopsy; TR-PB, transrectal prostate biopsy; TP-PB, transperineal prostate biopsy; CFU, colony-forming units; PSA, prostate-specific antigen.

Ethics Approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. The study was approved by the Institutional Review Board of Kagawa University (permission number: 2020–125). The need for informed consent was waived given the retrospective nature of the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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