



## Original Article

## Efficacy of two-time prophylactic intravenous administration of tazobactam/piperacillin for transrectal ultrasound-guided needle biopsy of the prostate

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## ARTICLE INFO

## Article history:

Received 22 January 2015

Accepted 6 June 2015

Available online 17 July 2015

## Keywords:

Acute bacterial prostatitis

Piperacillin/tazobactam

Prostate biopsy

Rectal disinfection

## ABSTRACT

**Background:** Prevalence of fluoroquinolone (FQ)-resistant *Escherichia coli* has been recently increasing worldwide. We analyzed the incidence and characteristics of acute bacterial prostatitis after transrectal ultrasound-guided needle prostate biopsy (TRUSP-Bx) with prophylactic tazobactam/piperacillin (TAZ/PIPC) treatment as an alternative regimen.

**Methods:** A total of 391 patients who underwent TRUSP-Bx were included in the study. All patients received intravenous TAZ/PIPC (4.5 g) 30 minutes before and 6 hours after TRUSP-Bx.

**Results:** Acute bacterial prostatitis developed in six patients (1.5%); the frequency of its occurrence was significantly higher in patients in whom rectal disinfection was not performed ( $P < 0.05$ ). These six patients developed clinical symptoms of acute bacterial prostatitis a median of 24 hours after the biopsy. *Escherichia coli* was isolated in urine or blood bacterial cultures in four cases, and *Klebsiella pneumoniae* in two cases. All of the isolated organisms showed excellent sensitivity to TAZ/PIPC.

**Conclusions:** The incidence rate of acute prostatitis with prophylactic TAZ/PIPC was consistent with those reported previously with FQ-based regimens, despite the favorable sensitivity of isolated organisms. Two-time regimen of TAZ/PIPC may not always prevent the post-TRUSP-Bx infection, possibly due to the pharmacokinetic characteristics of TAZ/PIPC. However, if each case was considered individually to select the best setting and frequency of dosage of TAZ/PIPC, this can be an optimal prophylaxis in the era of widespread FQ-resistant microorganisms.

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## Introduction

Transrectal ultrasound-guided needle prostate biopsy (TRUSP-Bx) is generally accepted as a standard procedure for the diagnosis of prostate cancer. Bacterial infection is one of the most serious complications associated with TRUSP-Bx. The incidence of bacterial complications, such as acute prostatitis, ranges from 1% to 5% [1–3]. Therefore, pre-procedure antibiotic prophylaxis is usually performed to reduce the risk of bacterial infection. Because fluoroquinolones (FQs) have a broad spectrum of activity against a

majority of Gram-negative bacteria and exhibit excellent prostatic tissue bioavailability [4–6], they are widely used as antibiotic prophylaxis with TRUSP-Bx.

However, prevalence of FQ-resistant *Escherichia coli* has been recently increasing worldwide [7–10], and a trend of increasing resistance to FQs has also been observed in Japan [7,8]. Actually, some previous reports have demonstrated emergence of FQ-resistant *E. coli* infections following TRUSP-Bx after prophylactic use of FQs [11,12]. Therefore, other prophylactic antibiotic regimens need to be considered to decrease the risk of infectious complications of TRUSP-Bx in the era of widespread FQ-resistant microorganisms.

In the present study, we evaluated the prophylactic efficacy of intravenous tazobactam/piperacillin (TAZ/PIPC) for use with TRUSP-Bx. We analyzed the incidence rate, clinical characteristics,

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and bacterial cultures of acute bacterial prostatitis occurring after TRUSP-Bx with prophylactic TAZ/PIPC administration.

## Materials and methods

A total of 391 patients who underwent TRUSP-Bx at Ishikawa Prefectural Central Hospital, Kanazawa, Japan between January 2010 and August 2012 were included in our study. The indications for TRUSP-Bx were as follows: elevation of serum prostate-specific antigen levels or aberrant findings on digital rectal examination (DRE) based on the criteria of a mass prostate-specific antigen examination in Kanazawa City as described previously [13]. Before the prostate biopsy, all patients underwent urinalysis, DRE, and transrectal ultrasound to confirm the absence of signs of urinary tract infections. All biopsies were TRUSP-Bx, and an automatic biopsy gun with an 18-gauge needle was used to obtain 8-core biopsies. None of the patients received an enema before the biopsy. Disinfection of the rectum by using an iodine swab was at the discretion of the attending physician. All patients were administered intravenous TAZ/PIPC (4.5 g) twice: 30 minutes before the biopsy and 6 hours after it. All patients were hospitalized at our institution for one night to observe any possible complications, such as hematuria, fever, urinary retention, and anal bleeding. Patients without signs of these complications were discharged the following morning.

Acute bacterial prostatitis caused by TRUSP-Bx was diagnosed using these criteria: core body temperature  $> 38^{\circ}\text{C}$ , the presence of leukocytes in the urine sediment, the isolation of any microorganisms from urine or bladder cultures, and tenderness of the prostate found on DRE within 7 days of the biopsy. Before the initiation of antibiotic treatment, all microorganisms isolated from urine or blood cultures were tested for antibiotic susceptibility. The minimum inhibitory concentration (MIC) was measured using the broth microdilution method, based on the criteria of the Clinical and Laboratory Standards Institute (CLSI). Drug susceptibility was determined based on the breakpoint MIC established by the CLSI.

We recorded the clinical characteristics and results of bacterial cultures in patients diagnosed with acute bacterial prostatitis. In addition, all patients were divided into two groups as follows: patients with acute bacterial prostatitis after TRUSP-Bx (Group 1) and patients without bacterial complications after TRUSP-Bx (Group 2).

We then analyzed the risk factors for acute bacterial prostatitis after TRUSP-Bx.

The Chi-square test was used to compare patients' background characteristics between the two groups. The Mann-Whitney *U* test was used for comparison of the age distribution between the two groups. In all analyses, which were performed using the SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA),  $P < 0.05$  was considered statistically significant.

## Results

A total of 391 patients, 333 undergoing a first biopsy and 58 undergoing a second biopsy, were enrolled in this study. None of the patients had any definite clinical signs of a urinary tract infection before the biopsy based on urinary analysis. The patients' background characteristics in Group 1 and Group 2 are shown in Table 1. Acute bacterial prostatitis after TRUSP-Bx occurred in six patients (1.5%). There was no significant difference between Group 1 and Group 2 in patients' background characteristics regarding median age, median prostate volume, prevalence of diabetes mellitus, and the median International Prostate Symptom Score, and past histories of TRUSP-Bx. Enforcement of rectal disinfection was significantly lower in Group 1 than in Group 2 ( $P < 0.05$ ).

Table 2 summarizes the data from the six patients who developed acute bacterial prostatitis after TRUSP-Bx. The median age of the patients was 66 years (range, 54–74 years). These patients developed clinical symptoms of acute bacterial prostatitis a median of 24 hours after the biopsy (range, 6–168 hours). *E. coli* was isolated in four cases, and *Klebsiella pneumoniae* in two cases from their bacterial cultures. For the treatment of the infections, cephalosporins were used in four patients, carbapenems in one patient, and FQs in one patient. All patients received immediate antibiotic administration, and the median duration of treatment was 7 days. All patients were successfully treated without incidence of septic shock or death.

Drug susceptibility of the bacterial isolates to a wide range of antibiotics was also evaluated (Table 3). One isolate was of an extended-spectrum  $\beta$ -lactamase producing bacteria. All bacteria isolated from blood and/or urine of the patients with acute bacterial prostatitis showed excellent sensitivity to TAZ/PIPC. In addition,

**Table 1**  
Patients' characteristics and comparisons between Group 1 and Group 2.

Categories	Group 1 (n = 6)	Group 2 (n = 385)	P
	Acute prostatitis	No bacterial complications	
Median age (range)	66 (54–74)	68 (51–88)	0.2
Median prostate volume (mL)	21.4	27.9	0.33
Rate of diabetes mellitus (%)	0 (0.0)	70 (18.2)	0.25
Median IPSS score	11.5	13.0	0.33
Rate of rectum sterilization (%)	2 (33.3)	312 (81)	0.0035
No. of re-biopsy	2 (33.3)	55 (14.3)	0.19

IPSS, international prostatic symptoms score.

**Table 2**  
Details of patients with acute bacterial prostatitis after transrectal prostate needle biopsy.

No.	Age (yr)	Biopsy numbers	Interval <sup>a)</sup> (hr)	Therapy		Culture		Isolated organisms
				Antibiotics (g/d) $\times$ d	Urine	Blood		
1	60	1	6	MEPM 1.5 g $\times$ 7	–	+	<i>Escherichia coli</i>	
2	68	2	24	SBT/CPZ 2 g $\times$ 9	+	–	<i>E. coli</i>	
3	74	1	168	CAZ 2 g $\times$ 9	+	+	<i>E. coli</i>	
4	64	1	6	CTM 3 g $\times$ 6	–	+	<i>Klebsiella pneumoniae</i>	
5	68	1	24	LVFX 500 mg $\times$ 7	–	+	<i>E. coli</i>	
6	54	2	72	CTRX 2 g $\times$ 5	–	+	<i>K. pneumoniae</i>	

<sup>a)</sup> Interval from biopsy to appearance of acute bacterial prostatitis.

CAZ, ceftazidime; CTM, cefotiam; CTRX, ceftriaxone; LVFX, levofloxacin; MEPM, meropenem; SBT/CPZ, sulbactam/cefoperazone.

**Table 3**  
Microbiological findings of the patients with acute bacterial prostatitis.

Patient	Bacteria	Drug susceptibility											
		ABPC	PIPC	CEZ	CTM	CAZ	CPR	GM	AMK	MINO	LVFX	IPM	TAZ/PIPC
1	<i>Escherichia coli</i>	S	S	S	S	S	S	S	S	S	S	S	S
2	<i>E. coli</i>	S	S	S	S	S	S	S	S	S	S	S	S
3	<i>E. coli</i>	S	S	S	S	S	S	S	S	S	S	S	S
4	<i>Klebsiella pneumoniae</i>	R	R	R	S	R	S	S	S	R	S	S	S
5	<i>E. coli</i>	R	R	S	S	S	S	S	S	R	S	S	S
6	<i>K. pneumoniae</i>	R	S	S	S	S	S	S	S	S	S	S	S

ABPC, ampicillin; AMK, amikacin; CAZ, ceftazidime; CEZ, cefazolin; CPR, cefpirome; CTM, cefotiam; GM, gentamycin; IPM, imipenem; LVFX, levofloxacin; MINO, minocycline; PIPC, piperacillin; R, resistant; S, sensitive; TAZ, tazobactam.

isolate sensitivity to other drugs, including third- and fourth-generation cephalosporins, carbapenems, aminoglycosides, and FQs, was also excellent.

## Discussion

It is widely accepted that prophylactic antibiotics before TRUSP-Bx are effective in preventing infectious complications. Despite the use of prophylactic antibiotics, bacterial infections causing fever occur in 1–5% of patients [6,14–16]. The most severe complications, such as urosepsis or septic shock, occur in 0–0.6% of patients [11,12,15]. Thus, many researchers have attempted to identify the optimal antibiotic regimen for use with TRUSP-Bx to decrease the risk of bacterial complications.

In particular, FQs have a broad spectrum of action, which is adequate for common urinary and colorectal flora. The bioavailability of FQs in the prostatic tissue is known to be high. Therefore, FQs are the most common prophylactic antibiotics for use with TRUSP-Bx and are recommended by the American Urological Association, European Association of Urology, and Japanese Urological Association (JUA) [17–19]. Indeed, numerous studies have demonstrated a decrease in the incidence of infectious complications to rates < 1–4% with FQs use [6,14,16].

By contrast, some recent reports have reported an increase in the incidence of urinary tract infections after TRUSP-Bx caused by FQ-resistant microorganisms. Alex et al [10] reported that the incidence of urinary tract infections after TRUSP-Bx with prophylactic ciprofloxacin treatment increased from 0.52% during the 2002–2009 period to 2.15% in 2010–2011; they demonstrated that the emerging resistance to FQs is the most likely cause for the increasing risk of infectious complications after TRUSP-Bx. Steensels et al [20] found that seven (3.0%) of 236 patients had infectious complications after TRUSP-Bx with prophylactic treatment with ciprofloxacin or levofloxacin for 3 days; FQ-resistant *E. coli* was isolated in all of their blood cultures. In addition, our previous report showed that acute prostatitis caused by FQ-resistant *E. coli* developed in 1.3% of the patients who received prophylactic oral levofloxacin (400 mg) combined with intravenous isepamicin sulfate (200 mg) [21].

Like FQs, TAZ/PIPC has a wide spectrum of action against common urinary and colorectal flora, and some reports have demonstrated the prophylactic efficacy of TAZ/PIPC for bacterial infections after TRUSP-Bx [22–24]. TAZ/PIPC is a time-dependent antibiotic agent which differs from FQs in that it has a concentration-dependent antibiotic action. Surveillance as described previously in Japan showed that MIC<sub>90</sub> values for TAZ/PIPC against *E. coli* were 8 µg/mL [24]. A static effect of TAZ/PIPC can be achieved when the time above the MIC reached 30% of the dosing interval [25,26]. The MIC of TAZ/PIPC at a dose of 4.5 g twice/d exceeds 30% of the time above the MIC and was 16 µg/mL [27], and TAZ/PIPC dosing of 4.5 g twice/d is likely to achieve the target of MIC<sub>90</sub> of TAZ/PIPC against *E. coli* (30% of the time above

the MIC) [24,27]. Therefore, we administered TAZ/PIPC twice in our prophylactic regimen, which consisted of 4.5-g doses given intravenously 30 minutes before and 6 hours after TRUSP-Bx. There has been limited information regarding an efficacy of prophylactic TAZ/PIPC for prostate biopsy.

We found that acute prostatitis occurred in six patients (1.5%), which seems to be consistent with the complication rates reported previously with other prophylactic regimens. This finding suggests that our prophylactic regimen is not inferior to the existing modalities. However, all microorganisms isolated from bacterial cultures of the patients with acute prostatitis showed excellent sensitivity to TAZ/PIPC. Therefore, prophylactic two-time intravenous administration of 4.5 g of TAZ/PIPC may not offer the most optimum pharmacokinetic benefit to all patients who undergo TRUSP-Bx. In particular, it might not have been the best alternative for six patients with bacterial acute prostatitis. For this reason, TAZ/PIPC has a time-dependent antibiotic effect. A maximum bacterial effect, which is not a static effect of TAX/PIPC, is achieved when the time above the MIC reaches 50% of the dosing interval [25,26]. The MIC of TAZ/PIPC at a dose of 4.5 g twice/d exceeds 50% of the time above the MIC and was 4 µg/mL [24,27]. By contrast, the MIC of TAZ/PIPC at a dose of 4.5 g thrice/d exceeds 50% of the time above the MIC and was 16 µg/mL [24,27]. Therefore, for achievement of a maximum bacterial effect of TAZ/PIPC, two administrations/d cannot achieve the target of MIC<sub>90</sub> of TAZ/PIPC against *E. coli*, and three administrations/d needs to achieve the target of MIC<sub>90</sub> of TAZ/PIPC against *E. coli* (50% of time above MIC) [24,27]. The reported incidence of asymptomatic transient bacteremia after TRUSP-Bx ranges from 16% to 73%, and asymptomatic bacteremia occurs frequently, especially in the patients with various risk factors such as an enlarged prostate or voiding dysfunction [2]. Therefore, when intravenous TAZ/PIPC is used prophylactically with TRUSP-Bx, an increased frequency of dosage should be considered for patients with such risk factors. Indeed, Cormio et al [23] reported that none of the patients who received a prophylactic dose of intramuscular TAZ/PIPC (2,250 mg) twice/d for 2 days developed acute prostatitis. By contrast, Yasuda et al [24] described that an infectious complication after prostate biopsy was detected in 2.5% (4/160 patients) in the patients group who received a single dose of 4.5 g TAZ/PIPC, 30 minutes before the biopsy, and in 0.45% (2/442 patients) in the group who were administered TAZ/PIPC twice: 30 minutes before and 5 hours after the biopsy. It was concluded twice administrations of TAZ/PIPC appear to be effective as preoperative prophylaxis against the occurrence of febrile infectious complication after TRUSP-Bx. In addition, all of the patients with acute prostatitis had some risk factors, such as voiding disturbance, diabetes mellitus, and steroid dosing in this previous report [24]. The difference in incidence of acute bacterial prostatitis is likely to be due to the difference in the ratio of the patients with these risk factors. Therefore, further studies including the setting of dose intensity of TAZ/PIPC according to risk factors can contribute to being a better optional prophylaxis for TRUSP-Bx.

Hence, we tried to identify the risk factors for acute prostatitis after TRUSP-Bx to improve the development of a prophylactic TAZ/PIPC regimen. Rectal disinfection was found to be the only significant factor influencing the risk of bacterial complications after TRUSP-Bx. Panupong et al [28] reported that rectal disinfection before a biopsy significantly reduces the incidence of postoperative bacteremia. In *in vitro* experiments, Park et al [29] counted bacterial colonies that were derived from a rectal swab taken before using povidone-iodine and after the biopsy. They found that the mean number of colony-forming units decreased by 99.9% after rectal povidone-iodine preparation. Pu et al reported in their systematic review and meta-analysis that rectal disinfection with povidone-iodine significantly reduces the incidence of fever, bacteriuria, and bacteremia [30]. Our finding also supports a recommendation of rectal disinfection for patients undergoing TRUSP-Bx. However, further studies, including various human populations and additional rectal bacterial evaluations, are required to reach a more definitive conclusion. By contrast, we could not identify other risk factors, such as voiding disturbance and diabetes mellitus, as reported previously for the development of acute bacterial prostatitis [2,24]. In the present study, a very small number ( $n=6$ ) of the patients were included in Group 1, and further studies including a large number of patients are likely to be required to perform a more precise analysis.

Although the incidence of sepsis after TRUSP-Bx is relatively low, some cases of fatal sepsis with delayed antibiotic treatment have been reported [11,12]. Presently, physicians cannot entirely prevent bacterial complications after TRUSP-Bx, but prophylactic measures can be taken. Therefore, sufficient information regarding the possibility of bacterial complications should be given to the patients who undergo TRUSP-Bx. In the present study, all patients with acute prostatitis were treated immediately with antibiotics, and all were successfully treated without any signs of bacterial sepsis. However, the species and strains of the isolated bacteria were somewhat different from the microorganisms isolated from patients who undergo prophylactic treatment with FQs. In the present study, *E. coli* was isolated in four cases and *K. pneumonia* in two cases, whereas FQ-resistant *E. coli* was detected in most patients with acute prostatitis after TRUSP-Bx in some previous studies [10,20,21]. This discrepancy may be due to differences between TAZ/PIPC and FQs in pharmacokinetics or antibiotic activity in the prostate. Our bacterial findings suggest that FQs may now be the most recommended class of antibiotics for prophylaxis of infections after TRUSP-Bx, and that two-time prophylactic intravenous administration of TAZ/PIPC could not be always effective for all patients who undergo TRUSP-Bx. However, further studies including the better setting of dose intensity of TAZ/PIPC can contribute to being an optional prophylaxis for TRUSP-Bx in the era of widespread FQ-resistant microorganisms.

### Conflicts of interest

The authors declare that they have no conflicts of interest.

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