

Infection/Inflammation

# Efficacy of Combination Use of Beta-Lactamase Inhibitor with Penicillin and Fluoroquinolones for Antibiotic Prophylaxis in Transrectal Prostate Biopsy

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**Purpose:** To investigate the efficacy of tazobactam/piperacillin (TAZ/PIPC) plus levofloxacin (LVFX) as a prophylactic administration in transrectal prostate biopsy (TPBX).

**Materials and Methods:** We investigated 201 consecutive patients who underwent TPBX in one Japanese hospital during the period of 2009-2010. The patients received TAZ/PIPC 4.5 g i.v. once just before and 3 hours after TPBX, plus oral LVFX 300 mg or 500 mg daily for 3 days. We examined the infectious adverse events and laboratory data (serum white blood cell [WBC] count and C-reactive protein [CRP]) before and 1 day after TPBX.

**Results:** Only one patient (0.50%) in 201 cases had febrile complications after TPBX. Serum WBC and CRP did not rise significantly on the day after TPBX compared with before TPBX ( $p > 0.05$ ). There was no significant difference in the rise of serum WBC and CRP before and after TPBX in the comparison of LVFX 500 mg with LVFX 300 mg in the TAZ/PIPC plus LVFX regimen.

**Conclusions:** TAZ/PIPC plus LVFX can be considered as a prophylactic regimen for preventing infectious complications in TPBX.

**Key Words:** Antibiotic prophylaxis; Biopsy; Infection

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**Article History:**

received 20 January, 2011  
accepted 14 March, 2011

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## INTRODUCTION

Infectious adverse events after transrectal prostate biopsy (TPBX) have been increasing, and even septic and fatal cases have been reported [1,2]. Fluoroquinolones have long been used for prophylactic administration owing to their good efficacy and high concentration in the prostate after dosing. However, especially in urinary tract infections (UTIs), fluoroquinolone-resistant *Escherichia coli* (FQRE) has been rapidly increasing. Resistance ratios to levofloxacin (LVFX) have jumped up to 5% to 20% [3]. Because TPBX is increasingly used to detect prostate cancer, adverse events are a growing concern [2]. Intravenous antibiotics should be considered, partly for preventing septic cases as mentioned above. Another resistant strain, extended-spectrum beta-lactamase (ESBL)-producing *E. coli*,

also poses difficulties for treatment. Some kinds of carbapenems are available for this resistant strain, but it has the potential to be an intractable infection. Some authors previously reported a case of prostatitis caused by ESBL-producing *E. coli* and it could be treated by imipenem and tazobactam/piperacillin (TAZ/PIPC) [4].

Beta-lactamase inhibitors have generally been combined with penicillins partly because this combination can bring out the antibiotic activity fully and prevent the emergence of antibiotic-resistant strains [5]. TAZ/PIPC (Zosin<sup>®</sup>) is an intravenous antibiotic agent consisting of 4 g of piperacillin and 0.5 g of tazobactam at an 8:1 ratio and is a modification of Tazosin<sup>®</sup>, which was used before and consisted of 2 g of piperacillin and 0.5 g of tazobactam [5,6]. Penicillins combined with beta-lactamase inhibitors such as TAZ/PIPC are widely used to treat UTIs and show good efficacy for *E.*

*coli*, including FQRE and ESBL-producing *E. coli*, and are recommended for TPBX in the Japanese UTI association guidelines especially in high risk group [7]. In this study, we examined whether TAZ/ PIPC plus LVFX could suppress infectious adverse events after TPBX.

## MATERIALS AND METHODS

### 1. Prostate biopsy

We performed a study of 201 consecutive men scheduled for TPBX because of an elevated prostate-specific antigen (PSA) level, an abnormal digital rectal examination (DRE), or abnormal magnetic resonance imaging (MRI) or transrectal ultrasound (TRUS) findings. TPBXs were performed in Akashi Municipal Hospital from March 2009 to September 2010. All biopsies were performed with an 18-gauge Bard Max Core disposable biopsy instrument biopsy needle (C.R. Bard Inc., Convington, GA, USA) in conjunction with a medical ultrasound console (Aloka SSD-2000, Aloka Co. Ltd., Tokyo, Japan). Acetylsalicylic acid or oral anti-coagulant agents were stopped appropriately before TPBX with the approval of the prescribing physician as a rule. We took 8 (sextant + 2 transitional zone) cores. No preparatory cleansing enemas were used, and the TPBX procedure was performed with only sacral anesthesia with 1% lidocaine and povidone iodine sterilization just before the TPBX.

### 2. Prophylactic antibiotic administration

For prophylactic antibiotic medication, each patient received TAZ/PIPC 4.5 g i.v. and LVFX 100 mg or 500 mg taken orally 30 minutes before TPBX. Patients continued to take 100 mg after every meal or 500 mg LVFX once a day for 3 days with or without stypic or anti-plasmin. The dose of LVFX was changed to 500 mg from 300 mg per day from August 2009 in this study. Another TAZ/PIPC was given 3 hours after TPBX. Patients were examined for infectious adverse events after TPBX and white blood cell (WBC) counts (/mm<sup>3</sup>) and C-reactive protein (CRP) (μg/ml) in plasma were measured before and 1 day after TPBX.

All patients undergoing TPBX were hospitalized on the day of TPBX and were discharged the next day if there were no adverse events requiring further hospitalization. The day after TPBX, patients' laboratory data were checked including WBC and CRP in serum. If a patient had symptoms from infectious complications such as chills or fever greater than 38.0°C after TPBX, he was asked to return to the emergency department. He immediately underwent a urinalysis, urine culture, and blood analysis, and any other complica-

tions were recorded. As a rule, if acute prostatitis was diagnosed, the patient was hospitalized and treated with the third- or fourth-generation cephalosporin or carbapenem i.v., and blood and urine culture tests were performed.

### 3. Statistical analyses

Statistical analysis was performed by use of Student's t-test or Welch's t-test or Fisher's exact test with the JSTAT - Java Virtual Machine Statistics Monitoring Tool (Sun Microsystems, Inc., Santa Clara, CA, USA). Statistical significance was set at p-value < 0.05.

## RESULTS

Patient data are shown in Table 1. One of 201 patients (0.50%) had a febrile complication such as acute prostatitis after TPBX. Our data from laboratory tests done the day after TPBX, including serum WBC count and CRP, did not demonstrate a significant rise in these variables compared with the pre-TPBX data as shown in Table 2 (p > 0.05). The serum WBC count before and after TPBX (day 1) was 6,123 ± 1,655 and 6,427 ± 1,898 (/mm<sup>3</sup>), respectively. Serum CRP before and after TPBX (day 1) was 0.1702 ± 0.4020 and 0.2602 ± 0.4534 (μg/ml), respectively (Table 2). No patients showed obvious side effects from this regimen (TAZ/PIPC plus LVFX).

A case with febrile complication had fever (37.6°C) from the night of TPBX and his serum WBC and CRP rose up (18,100/mm<sup>3</sup> and 4.1 μg/ml, respectively) on the next day. He had dysuria and was diagnosed as having acute prostatitis. He was treated by i.v. doripenem 0.5 g/day and his symptoms and laboratory data reacted very well and improved. His urine culture test on the day after TPBX showed no growth of bacteria. His TPBX pathological result was prostate cancer.

In addition, we compared LVFX 500 mg with LVFX 300 mg in the TAZ/PIPC plus LVFX regimen; however, there were no significant differences between the two groups re-

TABLE 1. Patients

No. of patients	201
Age (yr) (medium)	54-91 (72)
Serum prostate-specific antigen (ng/ml) (medium)	1.5-1,815 (8.21)
Prostate cancer	83/201
Febrile complication	1/201

TABLE 2. Analysis of laboratory data in serum WBC and CRP

	Before TPBX value	After TPBX value (day 1)	p-value
WBC (/mm <sup>3</sup> ) (n=201)	6,123±1,655	6,427±1,898	> 0.05
CRP (μg/ml) (n=198 <sup>a</sup> )	0.1702±0.4020	0.2602±0.4534	> 0.05

WBC: white blood cell, CRP: C-reactive protein, TPBX: transrectal prostate biopsy, <sup>a</sup>: three patients did not have a valuable data regarding serum CRP

**TABLE 3.** Comparison of change of serum WBC and CRP before and after TPBX between LVFX doses (300 mg and 500 mg)

	WBC (/mm <sup>3</sup> ) (after TPBX-before TPBX)	CRP (µg/ml) (after TPBX-before TPBX)
TAZ/PIPC plus LVFX 300 mg (n=61)	172.1±1,690	0.0295±0.6412
	p > 0.05	p > 0.05
TAZ/PIPC plus LVFX 500 mg (n=140)	397.1±1,422	0.0876±0.4057

WBC: white blood cell, CRP: C-reactive protein, TPBX: transrectal prostate biopsy, LVFX: levofloxacin, TAZ/PIPC: tazobactam/piperacillin

garding the febrile complication rate ( $p > 0.05$ ) or change in serum WBC and CRP before and after TPBX (Table 3).

## DISCUSSION

Prostate biopsies can cause infectious adverse events, especially with the transrectal approach [8]. TPBX is a test for the detection of prostate cancer and most patients have cancer-negative results in general [9]; therefore, severe adverse events must be prevented. Recently, the ratio of infectious complications after TPBX has risen and even septic or fatal cases have been reported [1,2]. One of the main reasons for this unfortunate fact is the increase of antibiotic-resistant *Enterobacteriaceae* [10,11]. Naturally, *E. coli* is one of the main targets to suppress in this procedure, and infectious adverse events may be partly caused by antibiotic-resistant bacteria [1,4].

Fluoroquinolones are often used for prophylactic medication in TPBX, partly because they are retained at high concentrations in the prostate as mentioned above [12,13]; however, fluoroquinolone-resistant *E. coli* are spreading, especially in UTI [3]. A guideline for prophylactic antibiotic medication for TPBX in 2006 and 2007 recommends fluoroquinolones in low-risk groups and TAZ/PIPC in high-risk groups [7,14]. However, infectious complications and septic cases after TPBX increased after the publication of this guideline [15]. Our regimen was set for the following reasons: 1) good efficacy of TAZ/PIPC for *E. coli* including beta-lactamase-producing bacteria, 2) good intra-prostate concentrations and permeability of LVFX, 3) the data on TAZ/PIPC alone mentioned below, and 4) the higher resistance ratio of *E. coli* to LVFX in our previous study (data not shown) than before [3], and 5) the higher ratio of ESBL-producing *E. coli* among all *E. coli* isolated recently than before in our institution (data not shown). Guidelines need to be updated to reflect the current antibiotic susceptibilities of emergent bacterial strains [16]. As reported in the literature, the ratios of febrile infectious complications range from 0.51% to 7.27% [2,8,17], which suggests that our method could be one of the recommendations for this purpose. In addition, our previous method [LVFX plus aminoglycoside (isepamicin)] has shown good efficacy for this purpose [8]; however, partly because of the spread of resistant strains, the previous method should be reconsidered and revised by the current data. For instance, Kato et al reported a case of septic shock caused by fluoroquinolone-resistant *E. coli* after TPBX [15], and Carlson et al re-

ported multi-drug-resistant *E. coli* urosepsis cases including a death case following TPBX [18]. In addition, Kim et al reported 923 cases of TPBX and concluded that almost cases of acute prostatitis (2.0%) were caused by fluoroquinolone-resistant *E. coli* [19]. This may suggest that the trend in infection and resistant strains could change and should be monitored and the guidelines revised if necessary.

Regarding antibiotic-resistant *E. coli*, ESBL-producing *E. coli* have been reported as problematic to treat even in UTIs as mentioned above [20,21]. Lee et al reported the prevalence of ESBL-producing uropathogens in UTI patients, and the overall prevalence ratio was 12.6% in their 3-year study [22]. This trend is apparently growing and raises some doubt as to whether we can decrease the dose of TAZ/PIPC or LVFX for future's study. Our laboratory data for serum WBC and CRP demonstrate that our regimen offers good efficacy for suppressing inflammation and infectious adverse events after TPBX. Our ratio of infectious complications after TPBX was 0.50%, indicating its suitability even for high-risk patients. Our next step will, as mentioned above, be to consider reducing the dose of TAZ/PIPC and LVFX to once each on the day of TPBX (just before the procedure) for low-risk patients, while strictly monitoring for resistant strains.

Some authors report the efficacy of oral antibiotics for this purpose, but it might be necessary to combine intravenous antibiotics for suppression of septic cases. Because TPBX detects prostate cancer in only 20% to 30% of cases, and because most of these patients have organ-confined cancer that may not cause early death [8,23], serious complications from the diagnostic procedure itself should be regarded as unacceptable as mentioned above. Our results of only one febrile complication in 201 consecutive cases and no influence on infection-related laboratory data (WBC and CRP) support an updated methodology for prophylactic medication.

Guidelines need to be updated regularly, because long repetition of a single recommendation may lead to widespread emergence of resistant bacterial strains. In general, more than two different regimens should be offered. Our data definitely showed a lower infectious complication ratio after TPBX, even though direct comparison could not be done because of the difference in core number, compared with the regimen of TAZ/PIPC alone (13.5 g per day, once daily) as used in Kobe University Hospital [7/180: 3.89% in 10 (sextant + 2 transitional zone + 2 far lateral periphe-

ral zone) cores; data not shown]. In addition, the data analyzed to observe an effect of LVFX dosing (300 mg or 500 mg per day as shown in Table 3) suggested that our TAZ/PIPC plus LVFX protocol was not affected by LVFX doses.

In addition, the TPBX cases from Kobe University Hospital reported here included low-risk patients because the data were from consecutive TPBX cases. Moreover, our previous regimen and study [8] was performed from 2003 to 2008, and the high prevalence of ESBL-producing *E. coli* was reported from the study done from 2007 to 2009 [22]. Taken together, these data suggest that our current regimen could be considered as one of the recommendations for not only high-risk patients but also non-high-risk patients.

Even though we showed good efficacy, this study may have limitations and further comparison study with the same patient group, study period, and method may be required. This single-arm study was also performed to confirm not only the effect of this regimen but also the safety for patients without any severe side effects.

## CONCLUSIONS

TAZ/PIPC plus fluoroquinolones can be considered a valuable prophylactic regimen for preventing infectious complications in TPBX. TAZ/PIPC plus fluoroquinolones is one of the options for prophylactic antimicrobial administration in TPBX, especially in high-risk groups.

## ACKNOWLEDGEMENTS

We thank Dr. Kunito Yamanaka for taking care of the patients and Gary Mawyer M.F.A. for English editing.

## Conflicts of Interest

The authors have nothing to disclose.

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