



Research Article

Comparison of a combined regimen of fosfomycin and ciprofloxacin with ciprofloxacin alone as antimicrobial prophylaxis for transrectal prostate biopsy in the era of high fluoroquinolone-resistant rectal flora

Do Gyeong Lim^a, Seung Il Jung^{a,*}, Myung Soo Kim^a, Ho Seok Chung^a, Eu Chang Hwang^a, Dong Deuk Kwon^a

^a Department of Urology, Chonnam National University Medical School, Gwangju, 501-757, Korea

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ABSTRACT

Background: To assess the prophylactic effect of fosfomycin (FM) and ciprofloxacin combinations for infectious complications of transrectal ultrasound-guided prostate biopsy (TRUSPB) compared to that of ciprofloxacin alone.

Methods: In total, 1,578 patients were enrolled and were divided into two groups according to the prophylactic antibiotics. Group 1 (n = 1234) received ciprofloxacin on the day of the biopsy and for an additional 1–2 days, whereas Group 2 (n = 334) was given FM in addition to ciprofloxacin in the same manner as Group 1. The primary outcome was overall infectious complications within 1 month of TRUSPB. The secondary outcome was the risk factors of infectious complications after TRUSPB.

Results: Infectious complications occurred in 31 patients (2.5%) and 1 patient (0.3%) in Groups 1 and 2, respectively. Our results indicated that fluoroquinolone (FQ) and FM significantly reduced the risk of infectious complications compared to FQ (relative risk: 0.12; 95% confidence interval 0.02–0.87, $P = 0.015$). Based on the multivariate analysis, previous antibiotic exposure (odds ratio [OR] = 3.59, $P = 0.026$), and the addition of FM (OR = 0.12, $P = 0.038$) were associated with infectious complications. Based on the rectal swab, FQ resistance was 28.0% (n = 294) in total. FQ resistance in the FQ and FM group was higher than that in the FQ group (n = 178, 54.9% vs. n = 116, 16.0%, $P < 0.001$).

Conclusion: The combination of ciprofloxacin and FM exhibited reduced infectious complications after TRUSPB compared with ciprofloxacin monotherapy and may be applicable in the era of the high abundance of FQ-resistant rectal flora.

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1. Introduction

Prostate cancer is one of the most frequently diagnosed cancers in men and is the fifth leading cause of death worldwide.¹ To confirm prostate cancer histologically, a transrectal ultrasound-guided prostate biopsy (TRUSPB) is most frequently conducted worldwide.

In general, TRUSPB is regarded as a safe procedure; its complications include hematospermia, hematuria, rectal bleeding, acute urinary retention, and infection.^{2,3} Most of these complications are

prone to be self-limiting, but several infectious complications such as urinary tract infection (UTI), prostatitis, epididymo-orchitis, and sepsis, in particular, can lead to a life-threatening condition.^{3–5}

To reduce the incidence of these infectious complications, the use of prophylactic antibiotics is recommended. Fluoroquinolones (FQs) are the most commonly recommended prophylactic antibiotics for TRUSPB.^{2,6} However, with increasing FQ-resistant uropathogens, the investigation of alternatives to FQ as prophylactic antibiotics for TRUSPB is necessary.⁷

An alternative approach is to use rectal swab cultures to assess rectal flora before prostate biopsy.^{8,9} According to several studies, the use of targeted prophylactic antibiotics based on rectal swab cultures may be effective in reducing the rates of infectious complications.^{10,11} However, the effectiveness of targeted prophylactic antibiotics based on rectal flora is inconclusive because of limited data.^{5,12}

* Corresponding author. Department of Urology, Chonnam National University Hwasun Hospital, 322 Seoyang-ro, Hwasun-eup, Hwasun-gun, Jeonnam, 58128, Korea.

E-mail address: drjsi@yahoo.co.kr (S.I. Jung).

Although few newly developed antibiotics are in the pipeline, old-fashioned antibiotics, such as aminoglycosides and fosfomycin (FM), have recently emerged as alternatives to quinolone-based prophylactic antibiotics for TRUSPB.⁵ Whether combination therapy with amikacin and FQ is effective in reducing the incidence of infectious complications after TRUSPB is under debate.^{13–15}

With its suitable penetration into prostatic tissue and the lower resistance rate comparable to FQ, FM has caught the attention of physicians as an alternative to quinolones.¹⁶ Although most clinical studies have indicated that FM is associated with a reduced incidence of infectious complications after TRUSPB compared to ciprofloxacin, there is no consensus regarding a single regimen that is superior.¹⁷

In this study, we investigated whether the addition of FM to ciprofloxacin-based antimicrobial prophylaxis reduces infectious complications after TRUSPB in the era of high FQ-resistant rectal flora.

2. Materials and methods

2.1. Data collection

This retrospective study was performed between January 2011 and June 2019 at Chonnam National University Hwasun Hospital, Republic of Korea. In total, 1,578 patients were enrolled in this study and were divided into two groups according to the prophylactic antibiotics. The 1,234 patients in Group 1 (FQ group) were given only ciprofloxacin for 1–2 days after the day of the biopsy (400 mg, intravenous [IV], twice daily). In addition to FQ administration, in the same manner, a single 3 g oral dose of FM was administered to the 334 patients in Group 2 (FQ and FM group) the night before the procedure. The primary outcome was the efficacy of the extended antibiotic prophylaxis in patients undergoing TRUSPB. The secondary outcome was risk factors for infectious complications after TRUSPB.

All biopsy procedures were conducted using an LOGIQ E9 TRUS device (General Electric, Milwaukee, WI, USA). An ACECUT automatic biopsy gun (CIVCO Medical Solutions, Kalona, IA, USA) with an 18-gauge needle was used to obtain standard 8–12 core biopsies, using the same protocol.

Most of the patients underwent rectal swab before TRUSPB, except for the patients who refuse rectal swab or some patients in the early days of this study when the rectal swab was not routine examination. All patients who underwent TRUSPB were administered an enema (COLCLEAN-S ENEMA® 133 mL; dibasic sodium phosphate, monobasic sodium phosphate) on the day of the biopsy. Rectal cleansing with povidone–iodine (povidone–iodine 10% solution) was performed immediately before the biopsy.

All patient characteristics were assessed, including age, serum prostate-specific antigen, prostate volume, diabetes, surgical history, prostatitis, UTI, and antibiotic exposure (FQ or others) within 6 months, as well as previous prostate biopsy history (within 1 year or more than 1 year prior) before TRUSPB. Perioperative data were also obtained for all patients, such as the number of biopsy cores, prophylactic antibiotic type, duration of antibiotic use, local anesthesia, infectious complications after TRUSPB, and pathological results.

We conducted an inquiry into several specified complications after TRUSPB, which included infectious complications, history of acute urinary retention, and hematuria. To discriminate biopsy-related events, the period for the assessment of infectious complications was limited to 30 days after the procedure. Infectious complications included hospital admission because of infection, fever, symptomatic UTI, acute prostatitis, bacteremia, sepsis, and systemic inflammatory response syndrome (SIRS). In case of

admission because of infectious complications, an examination of blood and urine samples was conducted to confirm the pathogens and their antibiotic sensitivity.

This study protocol was reviewed and approved by the institutional review board of the Chonnam National University Hwasun Hospital (IRB no. CNUHH-2017-040). The study was conducted following the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies.

2.2. Statistical methods

Statistical analyses were performed using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). Median values and the interquartile range are reported for continuous variables, and categorical variables are reported as frequencies (%). Chi-square tests were conducted to assess associations between covariate distributions and infectious complications. Multivariate logistic regression (stepwise backward procedure) was performed to determine factors influencing infectious complications. Statistical significance was set at $P < 0.05$ for all analyses.

3. Results

In the present study, a total of 1,578 patients undergoing transrectal ultrasound-guided prostate needle biopsy were retrospectively evaluated: the focus of the study was the efficacy of FM and FQ combined prophylactic antibiotics for TRUSPB. Based on the antibiotics used, the patients were assigned to two groups, the FQ group (Group 1, $n = 1,234$) and the FM and FQ group (Group 2, $n = 334$). Both Groups 1 and 2 were given FQ in the same manner for 1 or 2 days, including the day of the biopsy. In addition to FQ, the patients in Group 2 took 3 g FM powder orally the night before the biopsy.

In the total study population, 51 patients experienced complications; among these patients, 32 (2.0%) had infectious complications. 83.5% ($n = 1317$) of the total study population underwent rectal swab culture. The patients with bacterial growth of rectal swab were 1,048 in which FQ resistance was 28.0% ($n = 294$).

Total infectious complications occurred in 31 patients (2.5%) and 1 patient (0.3%) in the FQ group and the FQ and FM group, respectively, which was statistically significant ($P = 0.015$). Based on the relative risk formula, the risk ratio was calculated as 0.12 (95% confidence interval 0.02–0.87). The FQ resistance in the FQ and FM group was higher than that in the FQ group ($n = 178$, 54.9% vs. $n = 116$, 16.0%, $P < 0.001$).

As seen in Table 1, at the time of biopsy, there was no significant difference in characteristics between the two groups, except for prostate volume ($P < 0.001$). They were not different with regard to prior history of prostatitis, UTI, and FQ exposure within 6 months. In the univariate analysis, it was revealed that age (OR = 0.965, $P = 0.046$), antibiotic exposure within 6 months (OR = 4.134, $P = 0.011$), and the addition of FM (OR = 0.113, $P = 0.032$) were associated with infectious complications. However, prostate volume (OR = 1.004, $P = 0.585$) was not associated with infectious complications. In the multivariate analysis to assess variables related to infectious complications, antibiotic exposure within 6 months (OR = 3.589, $P = 0.026$) and the addition of FM (OR = 0.120, $P = 0.038$) were associated with infectious complications (Table 2).

Table 3 shows the information on the results of cultures for patients with infectious complications, which include the type of infectious complications, the result of urine culture and blood culture, FQ resistance, and extended-spectrum beta-lactamase (ESBL) positivity. Among 32 patients with infectious complications, 31 patients in Group 1 (FQ group) had infectious complications

Table 1
Patient clinical and laboratory characteristics at the time of the prostate biopsy.FQ versus FQ and FM.

Variable		FQ	FQ and FM	P value
No. of patients	1,578	1,234	344	
Age (IQR, y)	70.0 (64.0–75.0)	70 (64.0–75.0)	70.0 (65.0–76.0)	0.116
PSA (ng/mL)	6.99 (4.43–14.97)	7.0 (4.67–14.96)	6.80 (4.26–15.67)	0.685
Prostate volume (cc)	33.0 (24.3–48.0)	32.8 (24.0–47.0)	36.1 (26.9–53.72)	<0.001
Prior UTI within 6 mo	19 (1.2)	18 (1.5)	1 (0.3)	0.094
Prior prostatitis history within 6 mo	31 (2.0)	27 (2.2)	4 (1.2)	0.214
Prior prostate biopsy within 1 y	40 (2.6)	29 (2.4)	11 (3.2)	0.401
Prior operation history within 6 mo	78 (5.0)	60 (4.9)	18 (5.2)	0.828
Healthcare worker related	20 (3.1)	9 (2.9)	11 (3.2)	0.833
Overseas travel history within 4 wk	6 (0.9)	5 (1.6)	1 (0.3)	0.104
Antibiotics (FQ) exposure within 6 mo	58 (3.8)	44 (3.7)	14 (4.1)	0.748
FQ resistance from rectal swab	294 (28.0)	116 (16.0)	178 (54.9)	<0.001
Prophylactic antibiotic duration (d)	3.0 (1.5–3.0)	3.0 (2.0–3.0)	1.5 (1.5–1.5)	<0.001
Histological results				
BPH	833 (52.8)	664 (53.8)	169 (49.1)	0.006
Carcinoma	713 (45.2)	539 (43.7)	174 (50.6)	
Other	31 (2.0)	30 (2.4)	1 (0.3)	
Complications within 4 wk	51 (3.2)	49 (4.0)	2 (0.6)	0.001
Infection	32 (2.0)	31 (2.5)	1 (0.3)	0.015
Hematuria	11 (0.7)	11 (0.9)	0	0.135
Acute urinary retention	9 (0.6)	8 (0.6)	1 (0.3)	0.693
Admission due to complication	31 (2.0)	29 (2.4)	2 (0.6)	0.045

FM, fosfomycin; FQ, fluoroquinolone; IQR, interquartile range; PSA, prostate-specific antigen; UTI, urinary tract infection; BPH, benign prostatic hyperplasia.

Table 2
Results of univariate and multivariate analyses affecting infectious complications within 4 weeks of prostate biopsy

Parameters	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.965 (0.931–0.999)	0.046	0.973 (0.938–1.009)	0.139
PSA	0.974 (0.939–1.010)	0.153		
Prostate volume	1.004 (0.991–1.017)	0.585		
Antibiotic (FQ) exposure within 6 mo	4.134 (1.394–12.260)	0.011	3.589 (1.162–11.090)	0.026
FQ resistance from rectal swab	1.103 (0.420–2.897)	0.843		
Histological prostate cancer detection	1.835 (0.863–3.900)	1.835		
Adding fosfomycin (FQ & FM)	0.113 (0.015–0.832)	0.032	0.120 (0.016–0.887)	0.038

FM, fosfomycin; FQ, fluoroquinolone; PSA, prostate-specific antigen; UTI, urinary tract infection; OR, odds ratio; CI, confidence interval.

such as fever, acute prostatitis, bacteremia, SIRS, and sepsis and one patient in Group 2 (FM & FQ) had a fever.

4. Discussion

The present study compared the effect of FM and FQ combination therapy with that of FQ alone as prophylaxis for infectious complications after TRUSPB. As per our results, 51 of 1,578 (3.2%) experienced complications; among these, 32 patients suffered infectious complications. The infectious complication rates for the groups were 2.5% ($n = 31$) and 0.3% ($n = 1$) in the FQ group and the FM and FQ group, respectively, which was statistically significant ($P = 0.015$). Concerning FQ resistance based on the rectal swab, the resistance of the total population was 28.0% ($n = 294$), of which 16% ($n = 116$) and 54.9% ($n = 178$) were in the FQ group and the FM and FQ group, respectively. Although FQ resistance was higher in the FM and FQ group compared to that in the FQ group, the occurrence of infectious complications was higher in the FQ group than in the FM and FQ group ($P < 0.001$). In the univariate and multivariate analyses, antibiotic (FQ) exposure within 6 months and the addition of FM were related to infectious complications.

From the perspective of statistics, the absolute risk reduction (ARR) works out as 2.2 and the relative risk as 0.12. At first glance, this figure may seem to be trivial. However, if you calculate the number needed to treat (NNT), it equals to 50, which means that when a urologist does transrectal ultrasound guided prostate needle biopsy with fosfomycin and ciprofloxacin combined

prophylactic antibiotics for 50 patients, it may prevent at least 1 patient from experiencing infectious complications such as urosepsis compared to fluoroquinolone only in statistic view. Furthermore, given the relative risk, the relative risk reduction is calculated as 0.88, which means that taking fosfomycin and ciprofloxacin combined prophylactic antibiotics for TRUSPB may reduce the infectious complication rate by approximately 88 percentage compared with taking ciprofloxacin only.

Therefore, the comprehensive view indicated that using FM and ciprofloxacin combined prophylaxis before TRUSPB may be beneficial in lowering infectious complications, especially where ciprofloxacin-resistant infection after TRUSPB has been increasing.^{2,18–21}

To reduce infectious complications after TRUSPB, several measures have been proposed in diverse fields. One strategy is to reduce the incidence of unnecessary prostate biopsies for prostate cancers, especially in the gray zone.

Despite several endeavors to minimize unnecessary prostate biopsies, if prostate cancer is suspected, TRUSPB is necessary for its diagnosis and to obtain a histopathologic result according to NCCN guidelines. Although TRUSPB is known as a safe procedure, it still carries the possibility of infectious complications, such that it is crucial to use appropriate antibiotics before TRUSPB. To the best of our knowledge, there is no exact method to obtain an infectious-complication-free procedure, but reducing the rate of infectious complications could be possible by selecting the appropriate antibiotics, which could be done using rectal swab culture before the biopsy. In a study comparing targeted

Table 3
Results of cultures for patients with infectious complications

Case	Group	Type of infectious complication	Urine culture	Blood culture	FQ resistance	ESBL positivity
1	FQ	Sepsis	<i>Escherichia coli</i>	<i>Escherichia coli</i>	Yes	No
2	FQ	AP, Bacteremia	<i>Escherichia coli</i>	No growth	Yes	Yes
3	FQ	AP, Bacteremia	No growth	<i>Escherichia coli</i>	Yes	No
4	FQ	AP	<i>Escherichia coli</i>	<i>Escherichia coli</i>	Yes	No
5	FQ	AP, SIRS	NR	NR	NR	NR
6	FQ	AP	<i>Escherichia coli</i>	No growth	Yes	No
7	FQ	AP, Sepsis	No growth	<i>Escherichia coli</i>	Yes	Yes
8	FQ	Fever	NR	NR	NR	NR
9	FQ	AP	NR	NR	NR	NR
10	FQ	Fever	NR	NR	NR	NR
11	FQ	AP	NR	NR	NR	NR
12	FQ	AP, Bacteremia	<i>Escherichia coli</i>	No growth	Yes	No
13	FQ	Fever	NR	NR	NR	NR
14	FQ	AP, Sepsis	<i>Escherichia coli</i>	<i>Escherichia coli</i>	Yes	No
15	FQ	AP, Bacteremia	<i>Klebsiella pneumoniae</i>	<i>Klebsiella pneumoniae</i>	Yes	Yes
16	FQ	AP, Sepsis	<i>Escherichia coli</i>	<i>Escherichia coli</i>	Yes	No
17	FQ	AP, Sepsis	<i>Escherichia coli</i>	<i>Escherichia coli</i>	Yes	No
18	FQ	AP	NR	NR	NR	NR
19	FQ	AP, Sepsis	<i>Escherichia coli</i>	<i>Escherichia coli</i>	Yes	Yes
20	FQ	Fever	NR	NR	NR	NR
21	FQ	Sepsis	No growth	<i>Escherichia coli</i>	Yes	Yes
22	FQ	Fever	NR	NR	NR	NR
23	FQ	AP, Sepsis	No growth	<i>Escherichia coli</i>	No	No
24	FQ	AP, Sepsis	No growth	<i>Escherichia coli</i>	No	No
25	FQ	AP, Sepsis	No growth	<i>Escherichia coli</i>	No	No
26	FQ	Bacteremia	No growth	<i>Escherichia coli</i>	Yes	No
27	FQ	Fever	NR	NR	NR	NR
28	FQ	AP	NR	NR	NR	NR
29	FQ	Bacteremia	No growth	<i>Escherichia coli</i>	No	No
30	FQ	Bacteremia	No growth	<i>Escherichia coli</i>	No	No
31	FQ	Fever	<i>Enterococcus spp.</i>	No growth	NR	NR
32	FQ & FM	Fever	<i>Escherichia coli</i>	No growth	Yes	No

FQ, fluoroquinolone; FM, fosfomycin; ESBL, extended-spectrum beta-lactamase; NR, not reported; AP, acute prostatitis; SIRS, systemic inflammatory response syndrome.

antibiotic prophylaxis based on a rectal swab culture before the biopsy to obtain empirically derived antibiotic prophylaxis, it was revealed that targeted antibiotic use was associated with decreases in the incidence of infectious complications after the procedure and the cost of care.⁸ However, in a Canadian study, it was observed that only 9% of the total group with ciprofloxacin resistance suffered an infectious complication, despite a significant correlation between postinfectious complications and the identification of ciprofloxacin resistance.²² In summary, it was shown that there was no consent for routine rectal culture, but prebiopsy rectal culture may be recommended for high-risk groups for TRUSPB.⁵

To mitigate infectious complications, FQ has been routinely used as a first-line prophylactic antibiotic because of its high penetration into the prostate gland and its safety.^{23,24} However, recent studies reported that antibiotic resistance and infectious complications after TRUSPB are rising globally, which is considered a result of the increase in FQ-resistant *E. coli*.^{18–20,25,26} Regarding this, many physicians, including urologists, not only questioned the effectiveness of FQ as prophylaxis for TRUSPB but also suggested alternatives. Currently, the most clinically significant resistant pathogens following TRUSPB are FQ resistant and/or ESBL-producing, for which a combination or targeted antibiotic prophylaxis, such as FQ and aminoglycosides, is recommended.¹⁶ Although a UK study investigating FQ and amikacin combination therapy versus FQ showed a reduction in post-TRUSPB bacteremia from 2.5% to 0.3%¹³, a Korean study showed no statistically significant difference between these two treatments despite amikacin sensitivity in infectious complications.¹⁵ Thus, the effectiveness of FQ and amikacin combination therapy before TRUSPB should be evaluated further.

In addition to aminoglycosides, FM, an old-fashioned antibiotic that is known for having good potential against both gram-positive

and gram-negative uropathogens, particularly *E. coli*, *Citrobacter*, *Enterobacter*, *Klebsiella*, and *Enterococcus spp.*, has emerged as an alternative to FQ because of its reasonable penetration into the prostate and lower resistance rate compared to FQ.¹⁶ In a pharmacokinetic study, Gardiner et al. assessed FM concentrations in urine, plasma, and prostatic tissues and reported that FM was potentially therapeutic and effective against some urinary pathogens in the prostate for up to 17 h after oral dosing.²⁷ When the breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were used as a reference, *E. coli* isolates with FM MICs of ≤ 32 $\mu\text{g/ml}$ were categorized as susceptible. In terms of minimal inhibitory concentration (MIC), a high proportion of uropathogens are known to have a very low MIC, for example, half of the *E. coli* isolates with FM MICs ≤ 4 $\mu\text{g/mL}$.²⁷ In terms of effectiveness as prophylaxis for TRUSPB, it was demonstrated that FM is associated with a reduction in the incidence of febrile or afebrile UTIs compared to FQ in several studies, including a meta-analysis of clinical studies comparing FM and ciprofloxacin as prophylaxis before TRUSPB.^{28,29} In addition, FM is considered to have a good clinical response to UTIs, including multiple drug resistance (MDR) and ESBL-*E. coli* infections based on a systematic review of MDR Enterobacteriaceae and two clinical studies on oral FM for ESBL-*E. coli* infections.^{30,31} However, there is still concern that some strains might be resistant to the drug concentrations achievable in the prostate.²⁷

This is the reason combination therapy with FM and FQ was chosen as an alternative to the previous standard of FQ prophylaxis for TRUSPB. With its reasonable penetration into the prostate, FM is anticipated to be active against FQ-resistant uropathogens in the prostate and FQ may cover the possible residual resistant uropathogens in the bloodstream. In addition, this combination

therapy would be beneficial because FM is not expensive and can be easily taken orally with few adverse effects.

The present study had several limitations. Owing to the characteristics of the retrospective design, the distribution of the patients in the groups was not balanced and consisted of 1,234 and 334 in the FQ group and the FM and FQ group, respectively. As the concept of targeted antibiotics was not established in the early days of this study, some patients with FQ resistance were administered FQ. However, as targeted prophylaxis has developed, other patients with FQ resistance were treated with targeted antibiotics such as amikacin, tazobactam, as determined by the rectal swab culture, which was excluded in the study. This could be a reason for the imbalance of group data. In addition, although severe infectious complications were reported, mild infections might have been missed. Therefore, a prospective randomized trial is necessary to solve these problems. Furthermore, there is no absolute study to examine the exact timing for the use of FM. Thus, if possible, a study to compare the effectiveness of FM according to the time of administration, such as the night before the procedure and the morning on the day of the biopsy, should be performed.

Regarding the administration of FQ, either oral or IV form of ciprofloxacin could be applied according to clinical situations. Owing to the excellent bioavailability of oral FQ, serum drug concentration of it is equivalent to IV form. In this study, the patients who were scheduled to take TRUSPB should be hospitalized and maintain IV line in case of emergent situations such as sepsis. Therefore, we chose to use IV form of ciprofloxacin at the day of the biopsy.

To the best of our knowledge, there is only one study that investigated combination therapy with FM and ciprofloxacin versus ciprofloxacin monotherapy for TRUSPB in addition to this study. It was conducted in Canada during our documentation period.³² Although the Canadian study focused on the incidence of sepsis within 1 month after TRUSPB, our study dealt with the overall incidence of infectious complications, including sepsis, for the same period. Because of this difference, it is anticipated that our study may be applied to a much broader clinical spectrum. In general, the results of both studies were similar, but the form of expression was slightly different. For example, the Canadian study provided the relative risk as adjusted by propensity, but this study used the naïve figure. In terms of statistics, by using the NNT (number needed to treat), this study helps readers understand more easily, such that it might be more intuitive than the Canadian study. Because both studies were conducted retrospectively, prospective randomized studies should be conducted in the future.³²

Korea is an area with highly increasing antimicrobial resistance, including FQ resistance, and this study should be more meaningful in the era of high FQ resistance because it dealt with infectious complications after TRUSPB compared to sepsis only.³³ Although FQ resistance was higher in the FM and FQ group than in the FQ group, the rate of infectious complications was less in the FM and FQ group than in the FQ group; thus, the combination prophylaxis of FM and FQ might be applied regardless of rectal swab cultures.

Conflicts of interest

All authors have no conflict of interest to declare.

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