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Targeted Antimicrobial Prophylaxis with Cefmetazole Based on Presence of Fluoroquinolone-Resistant Isolates to Prevent Post-Prostate Biopsy Infectious Complications

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Abstract: Fluoroquinolones (FQs) have been traditionally used for prophylaxis against bacterial infection. However, the rapid emergence of FQ-resistant *Escherichia coli* due to overuse and misuse have resulted in an increase in post-biopsy infections. We requested 723 patients undergoing transrectal or transrectal plus transperineal targeted prostate biopsy to provide preprocedure rectal swabs. The rectal swabs were plated onto deoxycholate hydrogen sulfate lactose agar culture and FQ resistance tests were conducted using the disc diffusion method following the guidelines of the Clinical and Laboratory Standards Institute. All patients undergoing biopsy were given a 1.0 g intravenous injection of cefmetazole (CMZ) 30 min before and 12 h after biopsy. Patients with FQ-resistant organisms received an additional 1.0 g intravenous injection of CMZ every 12 h for an additional 1.5 days, while those without FQ-resistant organisms received levofloxacin 500 mg for 4 days. We evaluated infectious symptoms during the 30 days after the biopsy. We also evaluated the incidence of acute prostatitis within 7 days after the biopsy and isolation rates of FQ-resistant strains. A total of 289 patients (40%) had FQ-resistant isolates on rectal swabs. The overall infectious complication rate was 0.69%. Two patients with FQ-resistant isolates and three patients without them experienced infectious episodes. One patient with FQ-resistant isolates and two patients without them suffered acute prostatitis. The difference in the rates of infectious complication and acute prostatitis rates between FQ-resistant and FQ-susceptible carriers were not significant (p = 1.0 and 1.0, respectively). Post-biopsy sepsis was identified in one patient (0.14%) who had FQ-resistant *Escherichia coli*. Targeted antimicrobial prophylaxis with cefmetazole based on presence of FQ-resistant isolates on rectal swabs may prevent post-prostate biopsy infectious complications, especially in geographic lesions with a high incidence of FQ-resistant strains in rectal flora.

Keywords: fluoroquinolones; prostate biopsy; infectious complications; antimicrobial prophylaxis; rectal swab

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1. Introduction

Although the mortality of prostate cancer (PCa) has been slightly decreasing recently, it is still the main malignancy in Japan and in Western countries [1]. Transrectal and transperineal prostate biopsies are mandatory for histological confirmation of the diagnosis. In practice, transrectal prostate biopsy is easy to perform in an outpatient setting with or without local anesthesia. However, transrectal biopsies can cause severe infections such as sepsis, prostatitis, and urinary tract infections in comparison to transperineal prostate biopsies [2,3].

Fluoroquinolones (FQs) have been traditionally used for prophylaxis against bacterial infection after transrectal prostate biopsy because of their coverage against common causative bacteria and favorable prostatic penetration [2]. However, the rapid emergence of FQ-resistant *Escherichia coli* (*E. coli*) due to overuse and misuse of FQs has increased

post-biopsy infections [2,4,5]. The European Commission have prohibited the use of FQs and recommended the use of fosfomycin trometamol, cephalosporins, and aminoglycosides for antimicrobial prophylaxis [6]. On the other hand, the American Urological Association recommends applying FQs or cephalosporins (most commonly, ceftriaxone) together with an aminoglycoside [7]. The prevalence of FQ-resistant bacteria in the rectum of patients undergoing a transrectal biopsy has been reported to be approximately 20%, and the frequency of FQ-resistant bacteria in Asia is greater than that reported in Western countries [8–11]. Therefore, knowledge of geographical differences in antibiotic resistance would be required to select appropriate prophylactic antibiotics for reducing post-biopsy infectious complications [12].

To overcome this complication related to FQ-resistant Enterobacteriaceae, a candidate approach is rectal culture-based antibiotic prophylaxis. This strategy may reduce the use of therapeutic antibiotics after prostate biopsies and will prevent the development of drug-resistant strains. Taylor first reported that targeted antimicrobial prophylaxis using rectal swab cultures was associated with a notable decrease in the incidence of infectious complications after transrectal prostate biopsy caused by FQ-resistant bacteria [13]. Among the 112 men who underwent rectal swabs before transrectal biopsy, 22% harbored FQ-resistant organisms and all these men followed the targeted antimicrobial prophylaxis approach [13]. As a result, none had an infectious complication [13]. In contrast, 9 (2.6%) of the 335 men undergoing empirical prophylaxis had an infectious complication [13]. It is noteworthy that seven of these infections were due to FQ-resistant strains [13]. Although targeted antimicrobial prophylaxis is a theoretical approach for preventing post-prostate biopsy infections, there are conflicting reports regarding the impact of rectal culture-based targeted antimicrobial prophylaxis for reducing infectious complications and/or cost of care [13–16].

Augmented prophylaxis is another strategy to prevent infectious complications after prostate biopsy under the high prevalence of FQ-resistant strains. The idea is to use two or more different classes of antibiotics, broadening the antimicrobial spectrum to cover possible resistance to a single antibiotic [6]. Most randomized control studies compared augmented prophylaxis including FQ with another antibiotic and empirical monoprophylaxis [6]. However, no recommendation can be derived from the previous randomized control studies at present.

The European Association of Urology recommends selecting the transperineal approach for prostate biopsy, which is the least contaminating method, according to several meta-analyses and a systematic review [6]. Transperineal prostate biopsies were associated with significantly fewer infectious complications compared with transrectal prostate biopsies (risk ratio 0.55) [3].

We have started rectal swab cultures before transrectal prostate biopsies and isolated FQ-resistant organisms since 2013 in our institution. According to the high positivity of FQ-resistant rectal flora, we started a targeted antibiotic prophylaxis to reduce post-prostate biopsy infectious complications. In this study, we retrospectively evaluated the incidence of infectious complications after prostate biopsies and validated our antimicrobial prophylaxis approach in its ability to reduce the rate of complications.

2. Materials and Methods

2.1. Study Population, Rectal Swab Method, and Endpoints

From March 2013 to December 2019, we requested 723 patients undergoing transrectal or transrectal plus transperineal targeted prostate biopsies to provide preprocedure rectal swabs. Transrectal biopsy was performed after rectal povidone–iodine preparation without anesthesia and the transrectal plus transperineal targeted prostate biopsy was also performed after rectal povidone–iodine preparation with spinal or general anesthesia. We obtained demographic data on all patients and their history of antibiotic use within the preceding 12 months. This clinical study was approved by the Mie University Institutional Review Board (#H2020-017). Indications for performing a prostate biopsy were suspicious

characteristics on a digital rectal examination or elevated prostate-specific antigen levels. In addition, systematic plus targeted prostate biopsies were recommended for patients with a Prostate Imaging-Reporting and Data System (PI-RADS) score of 3 or higher on multiparametric or biparametric magnetic resonance imaging (MRI). Patients who had prior complications with cephalosporins or fluoroquinolones were excluded.

Rectal swabs were plated onto deoxycholate hydrogen sulfate lactose (DHL) agar (Kyokuto Pharmaceutical Industrial Co., Ltd., Tokyo, Japan) and incubated overnight at 35 °C in ambient air. FQ resistance tests were conducting using the disc diffusion method following the guidelines of the Clinical and Laboratory Standards Institute using commercially available antibiotic discs.

The primary endpoint of this study was to retrospectively analyze the infectious complication rates during the 30 days following the biopsy using electronic medical records. The secondary endpoints were to examine the prevalence of FQ-resistant organisms by rectal swab tests preceding prostate biopsies at our institution and the incidence rate of acute prostatitis rates within 7 days following a prostate biopsy [15,17]. Blood culture and urine culture were carried out to diagnose an acute prostatitis.

2.2. Antibiotic Prophylaxis before and after Prostate Biopsy

All patients undergoing biopsy were given a 1.0 g intravenous injection of cefmetazole (CMZ) 30 min before and 12 h after the biopsy. After disinfection of the rectum with povidone–iodine, 12 cores of prostate tissue were collected in most cases by transrectal ultrasonography-guided biopsy with or without additional transperineal targeted biopsy. If the DHL agar with an antibiotic disc had no colonies, we used levofloxacin (LVFX) 500 mg for 4 days. If DHL agar with the disc had colonies, we carried out 1.0 g intravenous injection of CMZ every 12 h for an additional 1.5 days (Figure 1). We evaluated infectious symptoms during the 30 days after the biopsy using electronic medical records.

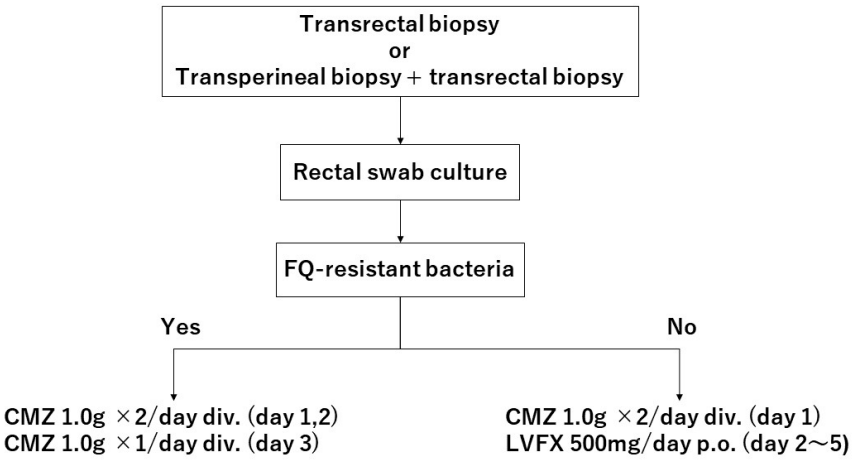

Figure 1. A flow chart of antibiotic prophylaxis in patients undergoing prostate biopsies. FQ, fluoroquinolones; CMZ, cefmetazole; LVFX, levofloxacin.

2.3. Statistical Analysis

Differences in the demographic features between patients with FQ-resistant bacteria and without it were statistically compared using the Mann–Whitney U test or chi-square tests and *p*-values less than 0.05 were considered significant. All analyses were performed using EZR version 1.61 (Jichi Medical University Saitama Medical Center, Saitama, Japan) [18].

3. Results

Among the 723 cases, a total of 289 patients (40%) had FQ-resistant isolates on rectal swabs, while 433 patients did not carry them. The median age, body mass index, serum PSA level, history of prior prostate biopsy, presence or absence of diabetes, and use of

antimicrobial agents within the past year were not significantly different between patients with and without FQ-resistant bacteria, but the prostate volume was significantly smaller in patients with FQ-resistant bacteria ($p = 0.011$) (Table 1). The overall infectious complication rate was 0.69%. Two patients with FQ-resistant isolates and three patients without them experienced infectious episodes, but the difference was not significant ($p = 1.0$). Among the patients with infectious complications, the diagnoses of two patients were not confirmed as a bacterial acute prostatitis, since one was suspected to be a diverticulitis of the colon and the other developed a fever 15 days after the prostate biopsy (Table 2). Therefore, the actual cases with acute prostatitis according to the definition were one patient with FQ-resistant isolates and two patients without them, and the difference was not significant ($p = 1.0$). Post-biopsy sepsis was identified in one patient (0.14%) who had FQ-resistant *E. coli*.

Table 1. Patient's characteristics.

	All (n = 723)	FQ-Resistant Bacteria		*p* Value
		Yes (n = 289)	No (n = 434)	
Median age	69 ± 8.1	69 ± 7.6	68 ± 8.4	$p = 0.116$ *1
Median BMI	23.7 ± 3.0	23.7 ± 3.3	23.6 ± 2.8	$p = 0.961$ *1
PSA (ng/dL)	7.8 ± 630.0	7.8 ± 814.8	7.9 ± 469.2	$p = 0.777$ *1
Prostate volume (mL)	30.9 ± 25.6	29.9 ± 24.2	39.8± 24.8	$p < 0.001$ *1
History of prostate biopsy	166 (23.0 %)	67 (23.2 %)	99 (22.8 %)	$p = 0.907$ *2
Diabetes mellitus	112 (15.5 %)	39 (13.5 %)	73 (16.8 %)	$p = 0.226$ *2
Use of antimicrobial within the last 1 year	155 (26.8 %)	65 (28.4 %)	90 (25.8 %)	$p = 0.491$ *2

BMI, body mass index; FQ, fluoroquinolones; PSA, prostate-specific antigen. *1: Mann-Whitney U test; *2: qui-squared test.

Table 2. Patients' clinical parameters and infectious complications.

Case	Age	BMI	PSA (ng/mL)	Prostate Volume (mL)	History of Prostate Biopsy	Use of Antimicrobial within the Last 1 Year	Diabetes Mellitus	FQ-Resistant Bacteria	Blood Culture	Antimicrobial	Remarks
1	69	25.5	20.63	112.2	No	No	No	No	negative	CMZ	
2	61	25.8	3.42	38	No	Yes (Drug unknown)	Yes	Yes	Escherichia coli (FQ-resistant)	DRPM	
3	50	25.1	5.46	11.9	No	Yes (Drug unknown)	No	Yes	negative	MEPM	Suspicious of diverticulitis
4	76	23.6	17.4	45	Yes	Unknown	Yes	No	negative	MEPM	
5	57	24.7	4.47	45	No	Yes (CAM)	No	No	negative	MEPM → VCM → CTRX	Fever after 15 days

BMI, body mass index; CAM, clarithromycin; CTRX, ceftriaxon, DRPM, doripenem; MEMP, meropenem; PSA, prostate-specific antigen; VCM, vancomycin.

4. Discussion

In the present study, the high prevalence (40%) of FQ-resistant bacteria in the rectal swabs of men undergoing transrectal prostate biopsy was revealed in our institution. The FQ-resistant bacterial rate in rectal cultures before transrectal prostate biopsy was 9.62–48.1% in previous reports [9,11,13,19–21]. The prevalence of FQ-resistant bacteria varies significantly among different geographical areas [22]. A nationwide multi-center survey investigating the incidence of infections following prostate biopsies was conducted [23]. Among patients with positive culture findings, *E. coli* was the most frequently isolated strain. Moreover, among the *E. coli* strains isolated by urine culture, 66.7% of them produced extended-spectrum β-lactamase (ESBL) and 77.8% showed ofloxacin resistance [23]. Similarly, among the *E. coli* strains isolated by blood culture, 66.7% produced ESBL and 100% showed levofloxacin resistance [23]. As the results show, *E. coli* is the most commonly isolated organism from post-biopsy infections, and FQ-resistant and extended-spectrum β-lactamase (ESBL)-producing types were the two important pathogens in post-biopsy

infections [24]. Infections caused by a transrectal biopsy depend upon the bacterial flora harbored in the rectum, which was introduced into the urinary tract or into the bloodstream by perforating the rectal mucosa with the biopsy needle [19,25,26]. Therefore, it is critical to select the appropriate antimicrobial prophylaxis depending on the risk factors for infectious complications after transrectal prostate biopsy which is increasingly linked with FQ-resistant strains.

Several factors associated with FQ-resistant bacteria on rectal swabs in men undergoing transrectal biopsy have been reported. Tan et al. reported that an increasing patient age, use of antimicrobials within the last 6 months, and ethnicity were associated with a higher risk of harboring FQ-resistant bacteria in the rectal vault [27]. The use of fluoroquinolones less than 6 months before biopsy was also reported as a risk factor for fecal carriage of FQ-resistant strains [28]. Kamei et al. showed that diabetes was a risk factor for antimicrobial resistance carriage before biopsy, which included carriers of FQ-resistant and ESBL-producing *E. coli* [29]. We also investigated several factors using our cohorts to detect any association with FQ-resistant strains carriage in the rectal swabs, but only prostate volume was significantly different between FQ-resistant strain carriers and non-carriers. The reason for the difference remains unknown.

Recently, a large randomized trial evaluated rectal culture-based prophylaxis and its effect on infection rates of transrectal prostate biopsies [15]. After rectal swab collection, the patients were randomized 1:1 to receive empirical prophylaxis with oral ciprofloxacin or culture-based prophylaxis. Among the 1288 patients with available data, infection rates within 7 days after biopsy were 4.3% and 2.5%, respectively, with no statistically significant difference. However, the presence of ciprofloxacin-resistant strains in rectal flora resulted in a 6.2-fold higher risk of early post-biopsy infection in the empirical prophylaxis cohort compared to almost identical rates in the culture-based prophylaxis cohort. In this study, ciprofloxacin-resistant bacteria were detected in 15.2% of patients [15], which is relatively low compared to our results. Therefore, the results should be interpreted carefully in geographic regions with higher rates of resistant strains in rectal flora, where the impact of culture-based prophylaxis will likely be more significant.

Although ESBL-producing Enterobacteriaceae have been increasingly identified in post-biopsy infection, we focused on FQ-resistant strains in the rectal swabs before biopsy since the rate of resistance to FQ among ESBL-producing *E. coli* ranges from 50% up to 100% [30,31]. Additionally, the national surveillance of the prevalence of ESBL-producing strains in Enterobacteriaceae was 3.1–6.2% at the time of planning this study [32,33]. On the other hand, our hospital belongs to an academic medical center and thus we received a lot of high-risk candidates for prostate biopsy. Therefore, we selected CMZ as the targeted antimicrobial prophylaxis for the carriers with FQ-resistant strains since the sensitivity of CMZ is also high against ESBL-producing *E. coli* in Japan [34,35]. As for carriers of FQ-susceptible strains, since we could not completely exclude the possibility of non-FQ-resistant, ESBL-producing Enterobacteriaceae, we selected CMZ together with LVFX as targeted antimicrobial prophylaxes according to a report by Shigemura [36].

According to our targeted antimicrobial prophylaxis strategy, the incidence of post-biopsy infectious complications was 0.69%, which was lower compared to that reported by national survey 15 years ago in Japan (1.1%) but was similar to recent reports by Sadahira (0.6%) and Hiyama (0.7%) [10,19,37]. Moreover, the incidence of post-biopsy acute prostatitis was also low (0.41%). Selecting CMZ as the targeted antimicrobial prophylaxis may have contributed to this low incidence.

Our study revealed no difference in the incidence of infectious complications and acute prostatitis between patients with FQ-susceptible strains and FQ-resistant ones. The low incidences may partially contribute to the non-statistical difference in these outcomes between the two groups. Additionally, since patients with FQ-susceptible strains had a much larger prostate than patients with FQ-resistant ones (which is a risk factor for post-biopsy prostatitis), we should also carefully interpret the results because this bias may distort the results. Despite this, our approach may be effective for preventing post-biopsy

prostatitis, even if the FQ-resistant bacterial rate in the rectal culture before transrectal prostate biopsy was high as detected in our cohort or as Sadahira reported in a recent Japanese cohort [19].

While the optimal duration and regimen for reducing the risk of infectious complications for men undergoing prostate biopsy is still not standardized, a single dose of LVFX was recommended for low-risk cases and 1-day intravenous piperacillin and tazobactam was recommended to high-risk patients according to the 2015 guidelines for the prevention of preoperative infections published by the Japanese Urological Association [38]. According to a recent systematic review, a full 1-day prophylaxis antibiotic is recommended [2]. Therefore, our antimicrobial prophylaxis for transrectal prostate biopsy might be overuse and according to the results of the study, we have recently changed our protocol for antimicrobial prophylaxis. A single dose of 500 mg LVFX (before biopsy) for patients with FQ-susceptible strains and 1-day intravenous 1.0 g CMZ (30 min before and 4 h after biopsy) for patients with FQ-resistant strains are currently selected for the prophylaxis at our institution.

The reduction of infectious complications also depends upon nonantibiotics strategies, such as consideration of biopsy route (transperineal biopsy rather than transrectal biopsy), rectal preparation with povidone–iodine, and addition of natural flavonoids to antibiotics [3,39]. In Japan, magnetic resonance imaging–ultrasound fusion-guided biopsy has been covered by government health insurance since April 2022, and therefore, a transperineal approach using this method is currently commonly used at our institution.

The present study has some limitations. First, this study is a retrospective analysis. However, during the study time, most men undergoing transrectal prostate biopsy received a rectal swab examination and followed the regimens of antibiotic prophylaxis as described. Second, we only evaluated the fecal carriage of FQ-insusceptible bacteria at a single point in time and did not evaluate ESBL-producing strains. The optimal culture strategy needs to be established in consideration of local antimicrobial resistance patterns. Third, although most cases received rectal swabs within one month before transrectal prostate biopsy, the timing was not standardized. Liss et al. reported that screening rectal cultures obtained from the office visit before biopsy (approximately 2 weeks before) and the cultures performed at prostate biopsy showed similar results in 93% of the cases [40]. The optimal timing of rectal swab collection should be established. Fourth, we did not evaluate and consider the cost effectiveness of rectal culture-based antibiotic prophylaxis for transrectal prostate biopsy [14].

Despite the limitations, our data suggest that rectal swabs before transrectal prostate biopsy and targeted antibiotic prophylaxis based on the detection of FQ-resistant strains could reduce post-biopsy infectious complications even if the rate of FQ-insusceptible bacteria carriers who received the biopsy was as high as 40%. The optimal antibiotics agents and duration need to be further analyzed.

5. Conclusions

Targeted antimicrobial prophylaxis based on the presence of FQ-resistant isolates on rectal swabs with cefmetazole yields similar infection rates in FQ-resistant strain carriers compared to non-carriers, and was validated in this study, although geographic microbial heterogeneity can limit the generalizability of the results.

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Institutional Review Board Statement: This clinical study was approved by The Clinical Research Ethics Review Committee of Mie University Hospital (#H2020-017). Date of approval: 21 February 2020. This study was performed in accordance with the Declaration of Helsinki.

Informed Consent Statement: As the study design was retrospective and observational, the requirement for obtaining informed consent from the participants was waived.

Data Availability Statement: All data generated or analyzed during this study are included in this published article.

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