The Role of Ciprofloxacin Resistance and Extended-spectrum beta-lactamase (ESBL) Positivity in Infective Complications Following Prostate Biopsy

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Purpose: To evaluate ciprofloxacin resistance (CR) and extended-spectrum beta-lactamase (ESBL) positivity in the rectal flora, antibiotic prophylaxis received, and post-biopsy infectious complications in patients undergoing prostate biopsy.

Material & Methods: Rectal swab samples collected from 99 patients suspected of prostate cancer two days before prostate biopsy were tested for microbial susceptibility and ESBL production. All patients were given standard ciprofloxacin and ornidazole prophylaxis. Ten days post-biopsy, the patients were contacted by phone and asked about the presence of fever and/or symptoms of urinary tract infection.

Results: Escherichia coli (*E.coli*) was the most common isolate detected in 82 (75%) of the rectal swab samples. Ciprofloxacin resistance was detected in 33% and ESBL positivity in 22% of the isolated E.coli strains. No microorganisms other than *E.coli* were detected in blood, urine, and rectal swab cultures of patients who developed post-biopsy complications. CR E.coli strains also showed resistance to other antimicrobial agents. The lowest resistance rates were to amikacin (n = 2, 7.4%) and nitrofurantoin (n = 1, 3.7%). Seven patients (7.6%) developed infectious complications. There was no significant difference in probability of hospitalization between patients with CR strains (14.3%) and those with ciprofloxacin-susceptible strains (14.3% vs. 4.7%; $p = 0.194$). However, strains that were both CR and ESBL-positive were associated with significantly higher probability of hospitalization compared to ciprofloxacin-susceptible strains (28.6% vs. 3.8%; $p = 0.009$).

Conclusion: The higher rate of infectious complications with CR and ESBL-positive strains suggests that the agents used for antibiotic prophylaxis should be reevaluated. It is important to consider local resistance data when using extended-spectrum agents to treat patients presenting with post-biopsy infectious complications.

Keywords: ciprofloxacin resistance; ESBL; infective complications; prostate biopsy

INTRODUCTION

Transrectal ultrasound-guided biopsy (TRUS-bx) is the standard diagnostic method for prostate cancer (PCa).[1] Although TRUS-bx is a safe procedure, the incidence of infective complications has risen in recent years.[2] In multicenter studies, reported rates of infectious complications vary between 0.1% and 7% depending on the antibiotic prophylaxis administered.[2] The pathogenesis of post-biopsy infectious complications is complicated. Risk factors such as diabetes mellitus (DM), prostatitis, immunosuppression, and repeated prostate biopsies have been identified; however, increasing quinolone resistance (QR) and the presence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae have been mostly emphasized.[3,4,5,6]

Rising prevalence of fecal carriage of ESBL-positive pathogens in healthy populations is accompanied by a rapid increase in the rate of infections caused by ESBL-producing gram-negative bacteria.[7] ESBL-positive bacterial colonization may also cause urosepsis after TRUS-bx.[8] E.coli and K.pneumonia are the two most prevalent bacteria that synthesize ESBL and cause morbidity. Gram-negative bacteria that produce one of the ESBL enzymes are generally resistant to all extended-spectrum cephalosporins and aztreonam.[9]

The frequency of QR together with ESBL positivity in E.coli ranges from 50% to 100%.[10] Co-resistance to extended-spectrum beta-lactams and quinolone may be attributed to the wide use of quinolones like beta-lactam agents, as well as to multi-resistant gene transfer between patients via plasmids carrying ESBL-encoding genes.[11] It is believed that there is a strong correlation between ESBL-positive and ciprofloxacin-resistant bacteria and infectious complications after prostate bi-

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Table 1. Patients characteristics.

Number of patients	92
Age, year; mean ± SD	63.6 ± 7.2
Variables	n (%)
Smoking Status	22 (23.9)
Antibiotic use in the last 6 months	59 (64.8)
Ciprofloxacin use in the 6 months	43 (46.7)
Clinical History	
Urogenital infection	9 (9.8)
Catheterization history	8 (8.7)
Previous biopsy history	32 (34.8)
Number of prior biopsies	
1	26 (81.3)
2	5 (15.6)
3	1 (3.1)
Comorbidities	
COPD	7 (7.6)
DM	20(21.7)
HT	32 (34.8)
Hemorrhoids	13 (14.1)
BPH	41 (44.6)
Biopsy Results a (n=86)	
BPH	4 (4.7)
Adenocarcinoma	19 (22.1)
Benign prostate tissue	39 (45.3)
Chronic active inflammation	26 (28.3)
Stool Culture Pathogen b(n=102)	
E. coli	76 (74.5)
Klebsiella	10 (9.8)
Enterobacter	6 (5.9)
Proteus	4 (3.9)
Pantoea	3 (2.9)
Citrobacter	2 (2.0)
Hafnia	1 (1.0)
Post-biopsy Complications	
Hospital admission	7 (7.6)

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; DM, Diabetes Mellitus; HT, Hypertension; BPH, Benign Prostatic Hyperplasia;
a Biopsy results were available for 86 patients.
b Numbers and percentages are based on total agents isolated.

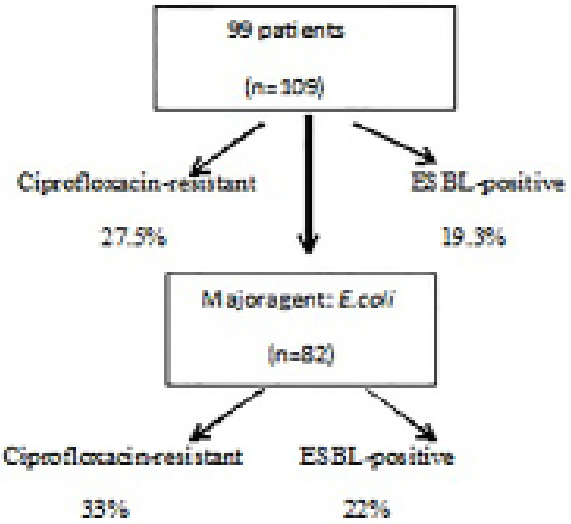

Figure 1. Ciprofloxacin resistance and ESBL positivity detected in 99 patients.

opsy.[12]

Due to increasing rates of complications after prostate biopsy in our hospital, we conducted this study to determine antibiotic resistance profiles of the rectal flora and the frequency of ESBL production among patients undergoing prostate biopsy, and evaluate the relationship between post-biopsy infectious complications and floral resistance profiles, comorbidities, and other factors.

MATERIALS AND METHODS

Study population

This prospective study was conducted at Ankara Dışkapı Training and Research Hospital, which has a patient capacity of 850. Ninety-nine patients were scheduled for TRUS-bx between October 2015 and October 2016 for suspected prostate cancer (suspicious digital rectal examination and/or prostate specific antigen [PSA] over 2.5 ng/mL). Patients and their relatives were questioned about antibiotic use on the day the rectal swab culture was taken. Patients taking antibiotics were not included in the study. Presence / absence of post-biopsy infective complications were the main analyzed outcome (primary outcome) of this study.

Study design

Ethics committee approval was obtained from Ankara Dışkapı Training and Research Hospital (decision number 36/10) and informed consent was obtained from all patients included in the study. Rectal swab samples were obtained two days before prostate biopsy. The patients were questioned regarding risk factors, including age, smoking, use of ciprofloxacin in the last six months, catheterization history, urogenital infection, previous biopsy history, and comorbidities such as DM, chronic obstructive pulmonary disease (COPD), cancer, hypertension (HT), hemorrhoids, immunosuppression, history of heart valve replacement, benign prostatic hyperplasia (BPH).

After culture incubation, isolates found to be gram-negative and oxidase negative were identified using citrate agar, Triple Sugar Iron (TSI) agar, and Motility-Indole-Lysine(MIL) agar broths. API 20E kit was used for bacteria that could not be identified by those methods.

Antibiotic susceptibility tests were done using Kirby-Bauer disc diffusion method as per the recommendations of the European Committee on Antimicrobial Susceptibility Testing. ESBL production was detected using modified disc (combined disc) diffusion test (EUCAST V. 6.0, 2018). Antibiotic susceptibility was determined using ciprofloxacin (CIP, 5µg), levofloxacin (LEV, 5µg), ampicillin (AMP, 10µg), amoxicillin/clavulanic acid (AMC, 20/10µg), cefepime (FEP, 30µg), cefuroxime (CXM, 30µg), gentamicin (GM, 10µg), amikacin (AK, 30µg), TMP-SXT (1.25/23.75µg), cefoxitin (FOX, 30µg), cefotaxime (CTX, 5µg), ceftriaxone (CRO, 30µg), and ceftazidime (CAZ, 10µg) discs.

Biopsy technique and patient follow-up

Patients were prescribed 500 mg ciprofloxacin and 500 mg ornidazole every 12 hours for 5 days (taken the day before the procedure, in the morning of the procedure, and for 3 days post-biopsy)[1,13,14]. All patients underwent bowel cleansing about 2-4 hours prior to biopsy. Transrectal ultrasound-guided 12-core systematic biopsy using an 18-gauge biopsy needle was done as an outpatient procedure in an examination room in the urology ward. The patients were contacted by phone 10 days after biopsy and questioned about symptoms of fever, urinary incontinence, rectal blinding, bloody voiding, frequent urination, and flank pain. Sympto-

Table 2. Resistance Rates to Other Antimicrobial Agents in Ciprofloxacin-susceptible and resistant E. coli Isolates

Antibiotic resistance levels and ESBL positivity	Ciprofloxacin-resistant *E. coli* n=27		Ciprofloxacin-sensitive *E. coli* n=55		*P*	OR (95% CI)
	n	%	n	%		
Ampicillin	21	77.8	23	41.8	.002	4.8 (1.7-14.8)
AMC	18	66.7	15	27.3	.001	5.2 (1.9-14.7)
Cefuroxime	11	40.7	6	10.9	.002	5.5 (1.7-18.4)
Cefoxitin	8	29.6	2	3.6	.001	10.8 (2.3-80.0)
Ceftriaxone	10	37.0	6	10.9	.005	4.7 (1.5-15.9)
Cefotaxime	12	44.4	6	10.9	.001	6.4 (2.1-21.3)
Ceftazidime	11	40.7	6	10.9	.002	5.5 (1.8-18.4)
Cefepime	9	33.3	4	7.3	.002	6.2 (1.7-25.8)
Amikacin	2	7.4	-	-	.187	6.8 (0.4-261.0)
Gentamicin	8	29.6	1	1.8	< .001	21.8 (3.2-516.5)
Nitrofurantoin	1	3.7	-	-	.220	4.1 (0.3-124.3)
SXT	17	63.0	14	25.5	.001	4.9 (1.8-13.6)
ESBL	12	44.4	6	10.9	.001	6.4 (2.1-21.3)

Abbreviations: AMC, Amoxicillin-clavulanate; SXT, Trimethoprim-sulfamethoxazole; ESBL, Extended-spectrum beta-lactamases

matic patients were advised to seek medical attention immediately.

Patients who presented to the emergency department with fever ≥38°C and/or urinary symptoms, and met the systematic inflammatory response syndrome (SIRS) criteria for sepsis were admitted. Hospitalized patients had blood and urine cultures and were evaluated for infection-related complications based on three criteria: symptomatic urinary system infection, acute prostatitis, and sepsis.

Statistical Analysis

Descriptive and advanced analyses were performed using SPSS, Open Epi, and Excel programs. Potential risk factors were evaluated using estimated odds ratio (OR), 95% confidence interval (CI), and 5% margin of error. *P* value < 0.05 was considered statistically significant. Chi square test and Fischer's exact test swere used to test relationships between categorical variables. Resistance levels to other antibiotics tested in the study were evaluated in ciprofloxacin-resistant isolates. A logistic regression model was used to predict the risk factors for ciprofloxacin resistance. The model included the following variables: history of catheter use, history of repeat biopsy, history of urogenital infections, and ciprofloxacin use in the last 6 months. The Wald test (enter method) was used in the model.

RESULTS

The rectal swab samples of 99 patients were analyzed for ESBL positivity, ciprofloxacin resistance, and related risk factors. On the day of biopsy, seven patients objected to the procedure for various reasons. Therefore, post-biopsy complications were assessed in 92 patients. Evaluation of the study group is presented in **Table 1**.

E.coli was the predominant agent isolated from rectal swab samples. E.coli was also the only agent isolated in blood and urine cultures and rectal swab samples of patients who had complications; no other microorganisms were detected.

The prevalence of ciprofloxacin resistance was 27.5% and rate of ESBL positivity was 19.3% in the fecal flora of the 109 agents isolated from 99 patients (**Figure 1**).

Most of the ciprofloxacin-resistant *E.coli* strains also exhibited resistance to other antimicrobial agents. Resistance was lowest to amikacin (n = 2, 7.4%) and nitrofurantoin (n = 1, 3.7%). Ciprofloxacin-resistant E.coli strains were significantly resistant to all antibiotics tested (**Table 2**).

Ciprofloxacin use in the previous six months was identified as a significant risk factor for ciprofloxacin resistance (p = .008). CR was not associated with the presence of DM, HT, BPH, history of repeated biopsies, or the use of antibiotics other than quinolone. After controlling for other factors, the logistic regression model indicated that catheter use increased the risk of developing ciprofloxacin resistance by 7.4 fold, urogenital infection history by 5.4 fold, and ciprofloxacin use in the last 6 months by 2.9 fold (**Table 3**).

Post-biopsy infectious complications were evaluated in 92 patients. The infectious complications and features of the bacteria isolated in 7 (7.6%) patients who were hospitalized are summarized in **Figure 2**. Two of the 7 patients were treated in the intensive care unit. There were no mortalities.

In terms of comorbidities, when compared as inpatients and outpatients, the estimated relative risk of DM was 1.5 times higher among inpatients than outpatients, but the difference was not statistically significant (95% CI: 0.3-8.3) (p = .643).

There was no significant difference in probability of hospitalization between patients with ciprofloxacin-resistant strains and those with ciprofloxacin-susceptible strains (p = .194). However, the probability of hospitalization was significantly greater in patients showing rectal flora colonization with ciprofloxacin-resistant

Table 3. Logistic Regression Analysis of Ciprofloxacin Resistance and Related Risk Factors.

Risk factors	*p*	OR_{adj}	95% CI
Catheter history (Yes/No)	0.030	7.4	1.2-45.6
Repeated biopsy (Yes/No)	0.249	1.9	0.6-5.5
Urogenital infection history (Yes/No)	0.057	5.4	1.0-30.9
Ciprofloxacin use in the last 6 months (Yes/No)	0.037	2.9	1.1-8.2
Constant	0.244	-	-

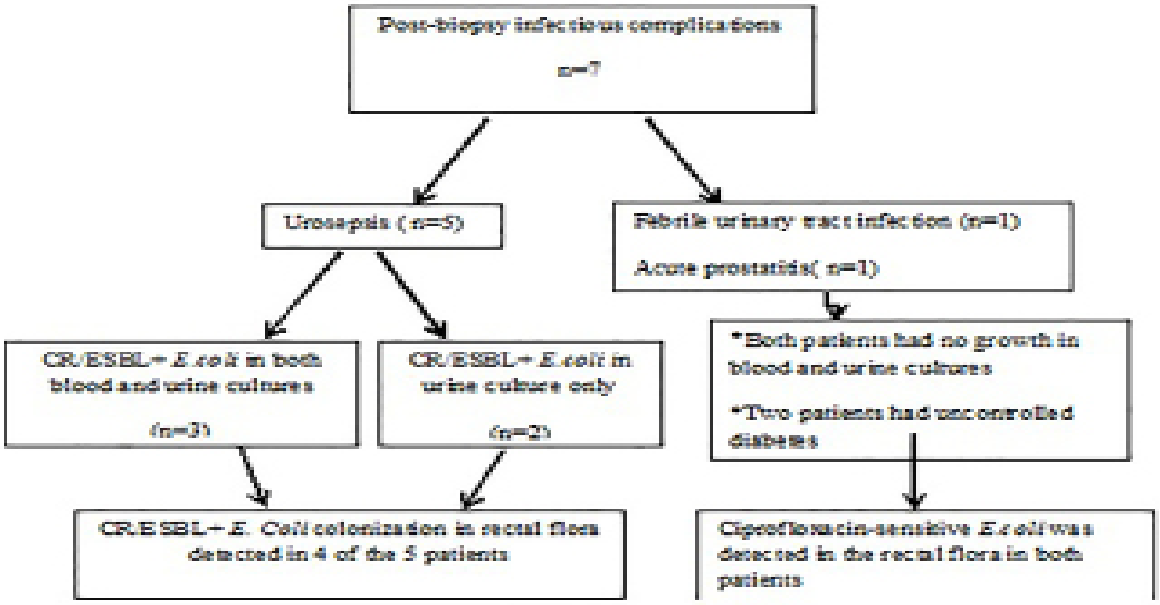

Figure 2. Outcome of the patients hospitalized post-biopsy due to infectious complications.

and ESBL-positive strains compared to those with susceptible strains (p = .009).

DISCUSSION

Increasing rates of quinolone resistance and ESBL-producing bacteria pose the greatest concern regarding post-biopsy infectious complications.[4,6] The prevalence of fluoroquinolone resistance in rectal flora was reported as 10.6% by Batura et al. in 2010, compared to 25% in a study by Liss et al. in 2015.[15,16]) In our study, quinolone resistance was calculated as 27% overall and 33% in the predominant agent, *E. coli*. In another study conducted in our region in 2014, fluoroquinolone resistance was reported at a similar rate (32.7%).[17] Tigen et al., who also analyzed patient data in our region, reported the prevalence of ESBL in rectal samples as 18%.[18] In our study, the prevalence of ESBL positivity in the rectal swab samples of 99 patients was 19.3% for all agents and 22% for *E. coli*.

Although it is known that the use of quinolone antibiotics increases the prevalence of resistant bacteria in fecal flora, Yağcı et al. pointed out that there is a paucity of data regarding how long the flora maintains such resistance after antibiotics are discontinued.[19] In line with previous studies, our analysis of CR and related risk factors showed that the use of ciprofloxacin in the previous six months was a statistically significant risk factor.

E.coli may also develop resistance to other antibiotics by means of efflux pumps, enzymatic target modification and reduced membrane permeability.[20] Minamida et al. compared quinolone-resistant and susceptible *E.coli* isolates with regard to their resistance to other antimicrobials and reported that resistant strains developed stronger resistance to other antibiotics compared to the quinolone-susceptible strains.[21] In this study, amikacin and phosphomycin resistance were not detected in quinolone-resistant isolates. Similarly, Hasanzadeh et al. showed that antibiotics with the least resistance in quinolone-resistant strains were amikacin (10.6%), phosphomycin (5.3%), and nitrofurantoin. When we performed a similar comparison between the two groups in our study, we observed higher resistance to antibiotics other than amikacin and nitrofurantoin.[22] Although resistance to nitrofurantoin was low, this antibiotic does not have good tissue penetration and hence is not suitable for the treatment of infectious complications of the kidney parenchyma or prostate tissue.[23] Phosphomycin resistance was not detected. The findings suggest that multidrug-resistant bacteria are becoming a major concern and are restricting the already limited treatment options.

In multicenter studies, rates of post-biopsy infectious complications vary between 0.1% and 7% and sepsis rates between 0% and 3.6% depending on the antibiotic prophylaxis used.[2] In our study, 7 of the 92 patients (7.6%) were hospitalized and urosepsis was diagnosed in 5 patients (5.4%). Our high rate of infectious complications may be related to the higher resistance rates. In hospitalized patients, the predicted relative risk of ciprofloxacin resistance and ESBL positivity in the case of rectal swabs is 10.0 fold (95% CI: 2.0-51.3). Among the 5 patients diagnosed with urosepsis, 4 had strains that were both ESBL-positive and ciprofloxacin-resistant. Previous studies have demonstrated that agents with both ESBL positivity and ciprofloxacin resistance are strongly associated with post-biopsy infections.[12]

Of the 7 patients who were hospitalized in this study, 2 patients who had negative rectal swabs for ciprofloxacin-resistant, ESBL-positive bacteria had a history of uncontrolled DM. DM has been shown to be an important risk factor for the development of infectious complications.[24,25] Post-biopsy infectious complications developed in 10% of our diabetic patients. Diabetes was also associated with a 1.5-fold higher risk of hospitalization, but this relationship was not statistically significant.

Due to increasing rates of ESBL and quinolone resistance, a combination of quinolones with aminoglycosides is suggested in studies.[26,27] Lorber et al. reported

an 83% reduction in urosepsis cases with the administration of intramuscular gentamicin and ciprofloxacin prophylaxis.[27] On the other hand, Miyazaki et al. compared patients given only levofloxacin prophylaxis and patients given combined amikacin and levofloxacin, and found no significant difference between the groups in terms of post-biopsy pyretic urinary tract infection. The authors attributed this to the effectiveness of the route of administration on the prostatic tissue and underlined the need for further investigation.[28]

The present study has some limitations. Although information regarding antibiotic use was obtained verbally from patients and confirmed using the hospital records system, there remains the possibility that some drugs were taken without a prescription or the patient did not recall taking them. Resistance rates can also vary depending on the culture methods. Moreover, if ESBL-producing strains carry an additional enzyme not inhibiting byclavulanic acid (e.g. metallo-beta-lactamase or AmpC enzyme), the sensitivity of the test decreases significantly. This can be avoided by using chromogenic agar, using agar containing cloxacillin, supplementing with EDTA to inactivate metallo-beta-lactamases, and using cefepime, which is a weak substrate for most AmpC enzymes. Despite the fact that most automated systems have these capabilities, the diagnostic sensitivity of these methods is lower than that of classical methods.[29]

CONCLUSIONS

Quinolone-resistant strains can develop co-resistance to multiple agents. In particular, there appears to be a steady rise in ESBL production among quinolone-resistant strains. This suggests that ESBL data should be considered as well as quinolone resistance when planning antibiotic prophylaxis. Another important finding of this study is the higher rate of post-biopsy infection associated with strains that are both ciprofloxacin-resistant and ESBL-positive. Therefore, broad-spectrum antibiotics must be considered in the selection of empirical antibiotics.

CONFLICT OF INTEREST

The authors report no conflict of interest.

REFERENCES

1. Heidenreich, A., et al., EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent—update 2013.Eur Urol, 2014,65: 124-137
2. Loeb, S., et al., Systematic review of complications of prostate biopsy.Eur Urol, 2013.64: 876-92.
3. Liss, M.A., et al., The Prevention and Treatment of The More Common Complications Related to Prostate Biopsy Update. 2016.
4. Taylor, S., et al., Ciprofloxacin resistance in the faecal carriage of patients undergoing transrectal ultrasound guided prostate biopsy. BJU int, 2013.111: 946-53.
5. Zowawi, H.M., et al., The emerging threat of multidrug-resistant Gram-negative bacteria in urology. Nat Rev Urol, 2015.12: 570-84.
6. Song, W., et al., Incidence and management of extended-spectrum beta-lactamase and quinolone-resistant escherichia coli infections after prostate biopsy.Urology, 2014.84: 1001-7.
7. Woerther, Paul-Louis, et al. "Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-M." Clinical microbiology reviews 26.4 (2013): 744-758.
8. Hadway, P., et al., Urosepsis and bacteraemia caused by antibiotic-resistant organisms after transrectal ultrasonography-guided prostate biopsy.BJU int, 2009.104: 1556-8.
9. Bennett, J.E., R. Dolin, and M.J. Blaser, Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 2014: Elsevier Health Sciences.
10. Pitout, J.D., Infections with extended-spectrum β-lactamase-producing Enterobacteriaceae. Drugs, 2010.70: 313-3.
11. Lautenbach, E., et al., Risk factors for fluoroquinolone resistance in nosocomial Escherichia coli and Klebsiella pneumoniae infections.Archives of Internal Medicine, 2002.162:2469-77.
12. Williamson, D.A., et al., Infectious complications following transrectal ultrasound–guided prostate biopsy: new challenges in the era of multidrug-resistant Escherichia coli. Clinical infectious diseases, 2013. 57: 267-74.
13. American Urological association. Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis. Available at:http://www.auanet.org/education/guidelines/antimicrobial- prophylaxis.cfm
14. Brewster, S., et al., Fatal anaerobic infection following transrectal biopsy of a rare prostatic tumour.B J Urol, 1993.72: 977-8.
15. Steensels, D., et al., Fluoroquinolone-resistant E. coli in intestinal flora of patients undergoing transrectal ultrasound-guided prostate biopsy—should we reassess our practices for antibiotic prophylaxis? Clin Microbiol Inf, 2012;18: 575-81.
16. Liss, M.A., et al., Comparative effectiveness of targeted vs empirical antibiotic prophylaxis to prevent sepsis from transrectal prostate biopsy: a retrospective analysis.J Urol, 2015.194: 397-402
17. Tigen, E.T., et al., Outcomes of Fecal Carriage of Extended-spectrum β-Lactamase After Transrectal Ultrasound–guided Biopsy of the Prostate.Urology, 2014.84: 1008-15
18. Kisa, Erdem, et al. "Fosfomycin: a good alternative drug for prostate biopsy prophylaxis the results of a prospective, randomized trial with respect to risk factors." Intl Braz J Urol 2017; 43: 1068-74.
19. Yagci, D., et al., Prevalence and risk factors for selection of quinolone-resistant Escherichia

coli strains in fecal flora of patients receiving quinolone therapy.Antimicrobial agents and chemotherapy, 2009.53: 1287-9

20. Sieczkowski, M., et al., Fluoroquinolone-based antimicrobial prophylaxis in patients undergoing transrectal ultrasound-guided prostate biopsy.European J Clin Microbiol & Inf Dis, 2015.34: 1815-21
21. Minamida, S., et al., Prevalence of fluoroquinolone-resistant Escherichia coli before and incidence of acute bacterial prostatitis after prostate biopsy.Urology, 2011.78: 1235-9.
22. Hasanzadeh, Amir, et al. "Prevalence and significance of fluoroquinolone-resistant bacteria carriage in patients undergoing transrectal ultrasound prostate biopsy." Urol J 2017; 14: 3085-90.
23. Lipsky, B.A., I. Byren, and C.T. Hoey, Treatment of bacterial prostatitis.Clinical Infectious Diseases, 2010;50: 1641-52.
24. Tsu, J.H.-L., et al., Prevalence and Predictive Factors of Harboring Fluoroquinolone-resistant and Extended-spectrum β-Lactamase–producing Rectal Flora in Hong Kong Chinese Men Undergoing Transrectal Ultrasound-guided Prostate Biopsy.Urology, 2015;85: 15-22.
25. Kehinde, E.O., et al., Combined ciprofloxacin and amikacin prophylaxis in the prevention of septicemia after transrectal ultrasound guided biopsy of the prostate.J Urol, 2013;189: 911-5.
26. Womble, P.R., et al., A statewide intervention to reduce hospitalizations after prostate biopsy.The J Urol, 2015;194: 403-9.
27. Lorber, G., et al., A single dose of 240 mg gentamicin during transrectal prostate biopsy significantly reduces septic complications. Urology, 2013;82: 998-1003.
28. Miyazaki, Yu, et al. "A Prospective Randomized Trial Comparing a Combined Regimen of Amikacin and Levofloxacin to Levofloxacin Alone as Prophylaxis in Transrectal Prostate Needle Biopsy." Urol J 2016; 13: 2533-40.
29. Akova M., GenişlemişSpektrumlu Beta-LaktamazlarveKlinikÖnemi In: Gram-NegatifBakteriİnfeksiyonları Ed: S. Ulusoy, H. Leblebici, D. Arman, Bilimsel Tıp Yayınevi, 2012 :79-90