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Original Article

Infectious complications of transrectal prostate biopsy in patients receiving targeted antibiotic prophylaxis after urethral and rectal swab versus standard prophylaxis: A prospective comparative study

Sotirios Gatsos [a,*], Nikolaos Kalogeras [b], Georgios Dimakopoulos [c], Michael Samarinas [d], Anna Papakonstantinou [b], Efi Petinaki [e], Vassilios Tzortzis [a], Stavros Gravas [f]

[a] Department of Urology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece
[b] Department of Urology, Agios Dimitrios General Hospital, Thessaloniki, Greece
[c] BIOSTATS, Epirus Science and Technology Park, Campus of the University of Ioannina, Ioannina, Greece
[d] Department of Urology, Koutlibanio General Hospital, Larisa, Greece
[e] Department of Microbiology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece
[f] Medical School, University of Cyprus, Nicosia, Cyprus

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ABSTRACT

Background: To evaluate the role of targeted antibiotic prophylaxis (TAP) after rectal and urethral swab cultures compared to empiric antibiotic prophylaxis (EAP) for the prevention of infectious complications after transrectal ultrasound-guided prostate biopsy (TRUS-Bx).

Methods: We conducted a prospective comparative study on 141 patients who underwent TRUS-Bx and were allocated in two groups. The first group (n = 71) received EAP with ciprofloxacin and the second (n = 70) received TAP according to rectal and urethral cultures. Post-biopsy infectious complications rates were compared between the two groups. Fluoroquinolone resistance (FQ-R) in the urethral and rectal swabs was recorded. Baseline characteristics were analyzed to assess their relationship with infectious complications and antibiotic resistance.

Results: A total of 8 infectious complications were observed, 7 of them in the EAP group (9.85%) and 1 in the TAP group (1.4%). There was a statistically significant difference in febrile UTIs between the two groups (6 vs 0, $P = 0.028$). FQ-R rate was 4.3% and 12.9% for rectal and urethral samples, respectively. Recent antibiotic exposure was associated with higher post-biopsy infection rates for EAP group and FQ-R rates for TAP group.

Conclusion: Combination of rectal and urethral swab cultures for TAP was able to detect FQ-R bacteria carriers and was associated with fewer infectious complications compared to EAP.

1. Introduction

Transrectal ultrasound-guided prostate biopsy (TRUS-Bx) is a widely used urological procedure for prostate cancer diagnosis with more than 1 million prostate biopsies being performed each year in Europe and the United States.[1]

Despite its diagnostic value and overall safety, TRUS-Bx is associated with a number of complications. Non-infectious complications have the highest incidence; however, infectious complications, including sepsis, represent the main cause of morbidity and mortality.[2-4] The reported incidence is 5-7%, with a need for hospitalization in 1-3% of the patients and a sepsis rate of 0.8%.[4,5] A surge in these numbers in recent years can be associated with the overuse of antibiotics and in particular fluoroquinolones, that have been the standard antibiotic prophylaxis regimen for the last two decades.[6,7] Data from the SENTRY program, for antibiotic resistance of uropathogens in 18 European countries, reported resistance rates from 21.8% to 40.2% for *Escherichia Coli*, *Klebsiella Pneumoniae*, and *Proteus mirabilis*, according to samples of urinary tract infections (UTI) isolates collected in 2018.[8] Similarly, several studies have provided data for the prevalence of fluoroquinolone-resistant (FQ-R) rectal flora, with its rates varying from 6% to 48.1% for patients undergoing TRUS-Bx.[9,10]

* Corresponding author.
E-mail address: sot.gatsos@gmail.com (S. Gatsos).

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Risk factors for infectious complications, apart from known fluoroquinolone resistance,[11] include prior urinary tract infection, antibiotic use, hospital admission and exposure, travel in FQ-R endemic countries, bacteriuria, and other comorbidities.[12] Targeted antibiotic prophylaxis (TAP) is one of the suggested interventions for these patients. It consists of rectal swab culture prior to biopsy and targeted antibiotics according to the provided results. A recent metanalysis demonstrated infectious complications incidence of 3.4% in empiric antibiotic prophylaxis (EAP) group and 0.8% in TAP group, with its implementation for high-risk patients being recommended by the relevant guidelines.[13,14]

The role of rectal flora in infectious complications is well documented; however, there is a lack of evidence regarding the additional value of culture using urethral swab. We hypothesized that TAP using both swabs could provide an added benefit. The aim of our study was to investigate the role of TAP after rectal and urethral swab cultures compared to EAP for the prevention of infectious complications after TRUS-Bx.

2. Materials and methods

2.1. Study design and population

This non-randomized, prospective comparative study enrolled 141 male patients who were eligible for prostate biopsy. It was conducted with the approval of the local Ethics Committee (ID: 10079/2019) and in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study. Exclusion criteria were the presence of indwelling urinary catheter, inability to receive the proposed antibiotic prophylaxis (i.e., allergies), and patients subjected to saturation biopsy. This study was retrospectively registered in Australian New Zealand Clinical Trials Registry (Trial ID: ACTRN12622000149763). The reporting of the study conforms to the modified CONSORT statement for non-randomized trials.[15]

2.2. Group allocation and intervention

Patients were divided into two groups. The first group received EAP with ciprofloxacin 500 mg twice daily for 5 days starting 1 day prior to biopsy (according to the local protocol) and the second received TAP according to rectal and urethral cultures for a similar duration of 5 days. Antimicrobial sensitivity testing was used to select the antibiotic of choice, according to whichever drug exhibited the lowest minimum inhibitory concentration (MIC) and could be administered orally. Patients with negative cultures or non-FQ-R bacteria received ciprofloxacin similarly to the EAP group. The preferred regimen for those with FQ-R bacteria was augmented prophylaxis as in most cases 2 different antibiotics were needed to cover both isolated bacteria (rectal and urethral).

The allocation to the groups was non-random and it was carried out during the first visit to Urology outpatient clinic. Patients' preference and their ability to schedule additional appointments for sample retrieval and antibiotic prescription based on the results were the main criteria for group allocation. More specifically, patients who were referred by office urologists with a scheduled appointment for biopsy (hence not being subjected to rectal and urethral sampling before their scheduled biopsy) and those not willing to give samples for culture were assigned to EAP group. Non-referred patients who agreed to give rectal and urethral samples were assigned to the TAP group. During their first visit, both groups' patients provided a detailed medical history and a written informed consent. Baseline characteristics including age, diabetes mellitus, prior biopsies, prior UTIs, and recent antibiotic usage were recorded in order to investigate a possible association with infectious complications, as well as FQ-R rates. All these characteristics were also taken into consideration upon patient recruitment, as possible confounding factors, so patient selection was performed in order to match both groups.

Ciprofloxacin was prescribed to EAP group patients. From TAP group at first, rectal swab sample was retrieved, followed by digital rectal examination and prostatic massage. Finally, urethral swab was inserted approximately 2 cm into the urethra to collect expressed prostatic secretions (EPS). Sample was collected after retraction of prepuce and cleaning of urethral meatus with normal saline. The specimens were sent to the microbiology department for culture and patients were contacted with the results and given instructions on the exact antibiotic regimen accordingly. All specimens were collected by a single urologist. No complimentary instructions were given regarding pre-biopsy enema.

Both groups' patients were subjected to twelve core TRUS-Bx with an 18G biopsy needle. The occurrence of infectious complications was investigated and verified at the time of biopsy results announcement by interviewing the patients and assessing their electronic medical record. Three main infectious complications categories were recorded: febrile UTI, afebrile UTI (lower urinary tract symptoms with urinalysis and urine culture findings indicating UTI), and hospitalization for febrile UTI.

2.3. Statistical analysis

Counts and percentages were used to describe all the collected categorical data. Pearson chi-square tests or the Fisher's exact test when assumptions were not met were applied to assess relationships between all variables and post-biopsy infections or resistance in the respective group. Specifically, the Pearson chi-square test was applied in tests where less than 20% of the crosstabulation cells had an expected count of less than five (5) participants and no cell had an expected count of less than one (1) participant. The Fisher's exact test was used when either of these two assumptions were not met. Differences regarding age were examined using the independent samples T test, while normality tests using the Shapiro-Wilk criterion were carried out along with QQ plots to examine normality of the data in each group. Logistic regression models were applied to adjust p-values for all possible effects on the outcomes for each group after checking for all assumptions. After univariate analysis, all findings with a p value lower than 0.2 were entered in a backward elimination method. Interactions of statistically significant variables at a 0.05 significance level were also examined. All formerly non-significant findings were reexamined in the model for any possible changes. The Hosmer Lemeshow test was used to assess goodness of fit. Significance was set at 0.05 in all cases and the analysis was conducted using SPSS v26.0.

3. Results

The study included 141 patients (71 patients in the EAP group and 70 patients in the TAP group) with a mean age of 67.93 ± 6.49 years. The mean age for the EAP group was 68.49 years and for the TAP group was 67.36 years ($P = .300$). Baseline characteristics of the patients included in each group are presented in Table 1. There was no statistical difference between the two groups.

Culture results from rectal swab were negative in 6 patients (8.6%), positive for *E. Coli* in 61 (87.1%), and for *P. Mirabilis* in 3 (4.3%). FQ-R E. Coli was detected in two patients and FQ-R *proteus* in one patient, which resulted in resistance rates of 4.3% for the total group and 4.7% for those with positive rectal cultures. Respectively, culture results from urethral swab were negative for 28 patients (40%) and positive for 42 (60%). The detailed rates of each isolated

Table 1
Characteristics of the patients of the two groups.

		Group				P value
		TAP		EAP		
		N	%	N	%	
Medical history of UTI	No	48	68.6%	53	74.6%	0.424
	Yes	22	31.4%	18	25.4%	
Medical history of prior prostate biopsies	No	57	81.4%	49	69.0%	0.088
	Yes	13	18.6%	22	31.0%	
Medical history of antibiotic usage	No	33	47.1%	29	40.8%	0.451
	Yes	37	52.9%	42	59.2%	
Antibiotic usage in the past 6 months	No	42	60.0%	48	67.6%	0.347
	Yes	28	40.0%	23	32.4%	
Diabetes mellitus	No	55	78.6%	56	78.9%	0.965
	Yes	15	21.4%	15	21.1%	

bacteria and the preferred antibiotic regimen can be seen in Table 2. FQ-R urethral flora was detected in 9 out of 70 patients of TAP group, accounting for a significant resistance rate of 12.9% for the total group and 21.4% (9 out of 42) for those with positive urethral cultures. Two patients presented with FQ-R bacteria in both rectal and urethral swabs. No statistically significant difference was observed in the FQ-R rates of urethral cultures between the patients with FQ-R positive and negative rectal cultures ($P = .156$). Overall, 10 patients had either rectal or urethral FQ-R isolate (14.3%) and received TAP which in most cases consisted of two different antibiotics to cover the isolated bacteria. The remaining 60 non-FQ-R patients received ciprofloxacin monotherapy.

In EAP group, there were totally 7 infectious complications (9.85%), with 1 non-febrile UTI (1.4%), 6 febrile UTIs (8.45%) with 4 of the febrile patients requiring hospitalization (5.6%). In TAP group only 1 patient (1.4%) had non-febrile UTI. A statistically significant difference in febrile UTI rates was found between the two groups (6 vs 0, $P = .028$). There was not a statistically significant difference in total infectious complications ($P = .062$), hospitalization rates (4 vs 0, $P = .119$), and non-febrile UTIs ($P = .992$).

Analysis of baseline characteristics showed that there is a significant association of the use of antibiotics within 6 months before biopsy on post-biopsy infection. The OR of a post-biopsy infection was 12.316 (95% CI: 1.41-107.566, $P = .023$). All other variables did not show a statistically significant association with the development of UTI (Table 3).

The association of the baseline factors with fluoroquinolone resistance, on either rectal or urethral culture are presented in Table 3. The OR of fluoroquinolone resistance was 8.389 for patients with antibiotic exposure in the last 6 months (95% CI: 1.516–46.428, $P = 0.015$). All other variables did not show a significant association with fluoroquinolone resistance.

4. Discussion

To our knowledge, this is the first comparative study investigating the role of combined rectal and urethral swabs in the optimal selection of TAP. Our study demonstrated higher rates of FQ-R bacteria in urethral flora compared to rectal flora in the same cohort of patients (12.9% versus 4.3%). As a result, TAP was altered according to urethral cultures in patients who would otherwise have received the standard fluoroquinolone regimen. This finding supports the role of complimentary urethral swab cultures for more accurate detection of FQ-R carriers.

A statistically significant difference was shown in the rates of febrile UTIs (8.45% in EAP group versus none in TAP). Infection rates were lower for the TAP group compared to EAP patients (9.85% versus 1.4%) resulting in an absolute risk reduction of 8.45%. However, this difference marginally did not reach statistical significance. Hospitalization rates were lower for TAP group (5.6% in EAP group versus none in TAP group), without achieving statistically significant differences. This reduction in infectious complications is in line with published literature and highlights the importance of TAP.[4,5,13]

A recent multicenter study of uropathogens in patients with acute and chronic prostatitis showed a similar bacterial spectrum and susceptibility.[16] In particular, the majority of the samples collected in Greece involved prostatic secretions, with the most frequent isolates being *E. Coli* (35%), *Proteus* spp, *P. Aeruginosa*, and *Klebsiella* ranging from 0 to 8% and over 40% of gram-positive bacteria with FQ-R rates similar to our findings. The importance of detecting and mapping resistant bacterial strains, at patient and population levels, is of paramount importance in an era of ever-growing FQ-R rates, with accumulating evidence supporting the role of prostatic and urethral flora in the pathogenesis of prostatic diseases.[17] Our study found a significant relation between recent, up to 6 preceding months, antibiotic exposure and FQ-R isolates on either rectal or urethral culture, indicating that this subgroup of patients is significantly more likely to develop fluoroquinolone resistance comparing to patients who did not receive antibiotics within 6 months preceding the study.

Recent antibiotic exposure was also significantly correlated to post-biopsy infections in EAP group, by increasing the likelihood of developing an infection compared to patients who did not

Table 2
Bacteria isolated in urethral swabs and antibiotic prophylaxis

Urethral culture	N	Frequency	FQ-R	Antibiotic prophylaxis
Negative	28	40%	–	Ciprofloxacin (n = 28)
Escherichia coli	14	20%	3 (4.3%)	Ciprofloxacin (n = 11), ciprofloxacin plus amikacin (n = 2), cefixime plus amikacin (n = 1)
Staphylococcus coagulase (−)	8	11.4%	2 (2.9%)	Ciprofloxacin (n = 6), ciprofloxacin plus clindamycin (n = 2)
Staphylococcus aureus	3	4.3%	1 (1.4%)	Ciprofloxacin (n = 2), ciprofloxacin plus amikacin (n = 1)
Staphylococcus haemolyticus	3	4.3%	1 (1.4%)	Ciprofloxacin (n = 2), cefaclor plus amikacin (n = 1)
Enterococcus faecalis	2	2.9%	0	Ciprofloxacin (n = 2)
Staphylococcus epidermidis	2	2.9%	1 (1.4%)	Ciprofloxacin (n = 1), ciprofloxacin plus co-amoxiclav (n = 1)
Staphylococcus saprophyticus	2	2.9%	1 (1.4%)	Ciprofloxacin (n = 1), ciprofloxacin plus clindamycin (n = 1)
Proteus spp	2	2.9%	0	Ciprofloxacin (n = 2)
Proteus mirabilis	1	1.4%	0	Ciprofloxacin (n = 1)
Pseudomonas aeruginosa	1	1.4%	0	Ciprofloxacin (n = 1)
Pseudomonas spp	1	1.4%	0	Ciprofloxacin (n = 1)
Morganella morganii	1	1.4%	0	Ciprofloxacin plus amikacin (n = 1)[a]
Staphylococcus hominis	1	1.4%	0	Ciprofloxacin (n = 1)
Staphylococcus lentus	1	1.4%	0	Ciprofloxacin (n = 1)
Total	70	100%	9 (12.9%)	

[a] Patient with non-FQ-R urethral culture bacteria and FQ-R rectal culture bacteria.

Table 3
The association of baseline factors with post-biopsy infections in the control group and fluoroquinolone resistance in the TAP group.

Post-biopsy infections in the control group	*P*-value	OR	95% CI for OR	
			Lower	Upper
Antibiotic exposure in the last 6 months	0.023	12.316	1.41	107.566
Medical history of UTIs	0.664	0.679	0.119	3.886
Medical history of prior prostate biopsies	0.925	1.091	0.179	6.655
Diabetes mellitus	0.866	1.171	0.188	7.304
Age	0.460	1.042	0.934	1.164
Fluoroquinolone resistance in the TAP group	*P*-value	OR	95% CI for OR	
			Lower	Upper
Antibiotic exposure in the last 6 months	0.015	8.389	1.516	46.428
Medical history of UTIs	0.883	1.124	0.238	5.311
Medical history of prior prostate biopsies	0.925	0.907	0.119	6.929
Diabetes mellitus	0.473	1.930	0.320	11.632
Age	0.530	0.961	0.849	1.088

receive antibiotics at the same period. Antibiotic exposure is a factor that has been extensively investigated in accordance with post-biopsy infections, with meta-analysis data supporting its role.[12] Similarly, past antibiotic use has been identified as a risk factor for rectal colonization with FQ-R bacteria in various studies.[18,19] A notable characteristic of the population of our study is the high percentage of recent antibiotic exposure, which accounts for the 36.2% of the patients, with the corresponding published data in other studies ranging from 2.2% to 15.2%.[20,21] This discrepancy can be attributed to a high percentage of patients receiving a course of antibiotics to lower their PSA levels (9.9%, n = 14) and also to higher national antibiotic consumption rates in Greece, with 12 patients (8.5%) having received antibiotics for non-urological indications. Interestingly, respective data for urethral flora are limited to patients with sacral cord injury, subjected to clean intermittent catheterization, linking fluoroquinolone treatment to the development of FQ-R urethral flora.[22] Consequently, to our knowledge this study also represents the first to associate antibiotic exposure to FQ-R EPS cultures, in a cohort of patients subjected to TRUS-Bx.

Regarding preventative methods, the role of various technical aspects of the prostate biopsy has been evaluated.[23] Only rectal cleansing with povidone-iodine was proven to significantly lower the risk of infectious complications and hospitalization in a metanalysis of 12 studies.[24] The duration of antibiotic prophylaxis is still a matter of debate.[23] The use of fluoroquinolones as a prophylactic regimen came under scrutiny during the last years, due to rising safety concerns.[25] A global prevalence study on infections reported that cases requiring post-biopsy antibiotic treatment increased from 6.1 to 9.7%, with the majority of these patients being under prophylaxis with fluoroquinolones.[3] These findings combined with the diminishing bacterial susceptibility to fluoroquinolones led to guidelines revision, with European Association of Urology (EAU) recommending against their use.[26] A metanalysis of randomized controlled trials for alternative antibiotic regimens concluded that EAP was inferior to TAP based on rectal swabs (RR 1.81, $P = 0.0008$) and standard prophylaxis was inferior to augmented prophylaxis (more than one antibiotic) (RR 2.10, $P < 0.0001$).[27] The results of our study are in line with the aforementioned data and recommendations, since FQ-R strains accounted for a significant percentage of the isolates and TAP was superior to EAP (ciprofloxacin). In addition, augmented prophylaxis in our protocol was administered based on the results of both cultures, which could result in a more effective approach.

Furthermore, a paradigm shift has taken place over the past years in the technique of prostate biopsy. Transperineal prostate biopsy (TP-Bx) is associated with fewer infectious complications, as demonstrated by a number of studies, including a metanalysis.[24] Consequently, it has dethroned TRUS-Bx from the relevant guidelines, leaving it as a second choice whenever transperineal approach is not feasible.[26] Despite the substantially lower infection rates, patients undergoing TP-Bx still face a risk of post-biopsy fever of 0.47%–0.69% and post-biopsy sepsis of 0.09%–0.13%.[28] Based on our study, we can speculate that urethral/prostatic flora could also play a role on TP-Bx, giving an option of TAP based on urethral swabs, since one could question the validity of rectal swabs in TP-Bx. Alternatively, in this new era of abandoning TRUS-Bx in favor of TP-Bx, TAP based on both rectal and urethral cultures, alongside the rest of the preventative methods, could increase the safety of TRUS-Bx, for those still opting for it.[29]

Our study suggests a novel way of detecting antibiotic-resistant bacteria carriers and modifying TAP accordingly. It should be underlined that statistical significance does not always imply clinical significance. Therefore, the present study contributes evidence to the pool available for research synthesis on post-biopsy infectious complications and further research is needed to establish its clinical utility. Limitations of the study include the fact that as a comparative, non-RCT, there is no randomization and blinding and the relatively small sample. Strengths of the study are the consistency in sample collection and handling, since samples were collected by a single urologist and analyzed at the same laboratory.

5. Conclusions

TAP using rectal and urethral cultures was associated with fewer infectious complications compared to EAP. Moreover, EPS cultures were able to detect more FQ-R bacteria than rectal swab cultures in the same patient population. The present study introduces a new approach for the optimal selection of TAP in men undergoing prostate biopsy.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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