

## EFFICIENCY OF SHORT AND LONG TERM ANTIMICROBIAL THERAPY IN TRANSRECTAL ULTRASOUND-GUIDED PROSTATE BIOPSIES

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### ABSTRACT

**Objective:** Prostate biopsy is a frequent diagnostic measure to detect prostatic conditions, including primarily prostate cancer. Its performance does not follow a pattern, mainly regarding preparation for the examination through antimicrobial prophylaxis. The aim of this study is to compare the efficiency of short and long term antimicrobial prophylaxis in transrectal ultrasound-guided prostate biopsies.

**Materials and Methods:** A clinical study was conducted with a total of 140 patients submitted to prostate biopsy with transrectal ultrasonographic control. Patients were randomly separated in two groups: Group 1 receiving norfloxacin 400mg single dose before the procedure and Group 2 receiving norfloxacin 400mg initiating before the procedure and then bid up to 6 doses. Efficiency control was determined by the incidence of urinary tract infection (UTI) and complications in both groups after statistical analysis.

**Results:** The incidence of minor complications in our study was 75%, consistent with data found in the literature. Among the patients with diagnosis of simple UTI, 23% belonged to Group 1 and 8% to Group 2 ( $p=0.08$ ). Among the patients with complicated UTI, 37% belonged to Group 1 and none belonged to Group 2 ( $p=0.44$ ).

**Conclusions:** Several advances made transrectal ultrasound-guided prostate biopsies a useful and safe diagnostic tool in the workup of urologic patients. There is no optimal prophylactic preparation to the performance of this procedure. Long term antimicrobial prophylaxis presents a trend toward lower incidence of infectious complications.

**Key words:** prostate; biopsy; needle; ultrasonography; antibiotics

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## INTRODUCTION

Prostatic conditions, including primarily prostate cancer, represent a significant portion of urological practice nowadays. In its diagnostic workup, prostate biopsy may be considered routine in outpatient urologic clinic in cases where patients present alterations in rectal exam and in prostate specific antigen (PSA) serum levels.

Use of transrectal ultrasound to guide prostate biopsy supported improving the sensibility of this

diagnostic procedure standardized as transrectal ultrasound-guided prostate biopsies (TRPB) (1).

Classified as an invasive diagnostic procedure, TRPB may present complications, especially infectious, suggesting the performance of an adequate preparation (2). Based on clinical trials, antimicrobials prescriptions in these preparations became routine. The role of the so-called antimicrobial prophylaxis has been responsible for a significant reduction of infectious complications rates (3).

A standard regimen to prepare for TRPB performance does not exist among urologists (4). Most regi-

mens recommended in the literature advocate antimicrobials use (5-9). The establishment of a rationale for prescribing these agents aims preserving the benefits associated to its therapeutic efficiency, for its indiscriminate use determines selection of resistant bacterial strains (10,11).

In this context, the concept of short term antimicrobial prophylaxis has been presenting increasing scientific evidence, constituting a clinical practice extremely effective, showing good efficacy in diagnostic and therapeutic procedures (12,13), and demonstrating an economic impact reducing costs (7). Its superior efficiency compared to conventional therapeutic regimens used is yet to be proven.

The aim of this study is to compare the efficiency of short and long term antimicrobial prophylaxis in transrectal ultrasound-guided prostate biopsies.

## MATERIALS AND METHODS

### Selection of Patients and Study's Profile

One hundred and forty patients from outpatient general urology clinic presenting indication to TRPB for outpatient workup of prostatic conditions were selected. This indication was primarily based on anomalies at rectal exam or at PSA levels.

A clinical trial, simple-blind, controlled, was designed. The study involved 140 patients randomly separated in two groups of 70 patients: the short term antimicrobial prophylaxis group (Group 1) and the long term antimicrobial prophylaxis group (Group 2). Short term antimicrobial use was defined as a single dose of an antimicrobial agent 1 hour before the TRPB procedure, and long term antimicrobial use an initial antimicrobial dose 1 hour before TRPB procedure and maintenance doses during 72 hours.

Norfloxacin was determined as antimicrobial prophylaxis regimen, in therapeutic maintenance dose of 400mg PO, as single dose or bid regimen. Factors as microbiologic efficiency, experience in the use of the drug, and administration convenience of fluoroquinolones were evaluated for its selection (5,6,13). The safety of short term antimicrobial prophylaxis was established in a pilot study performed for the design of this study.

Patients allergic to norfloxacin, using long term indwelling catheter, with chronic or within less than 30 days of antibiotic use, leucopenia with granulocytes count of less than 1,000/mL, with valvular cardiac conditions or valvular prosthesis, or still those that did not wish voluntarily to participate in the study were all excluded. After reassessing the number of patients according to the selection and adequateness criteria to controls previously established, an analysis of the 105 total patients that could participate in the study was performed, with 51 patients in Group 1 and 54 patients on Group 2.

### Method and Evaluation Criteria

Before TRPB, patients were orally and by written informed consent oriented about potentials risks and complications of the method to be used, and this was approved by the Ethics Committee of the Urologic Department of our hospital.

TRPB was performed through a needle puncture biopsy guided by ultrasound control. Material used was: 18 Gauge x 20cm Biopsy Cut (Core biopsy) – MD Tech ACN™ needle associated to a biopsy gun mechanism – Bard Biopty Gun and AI 5200 S Envision™ - Dornier ultrasound with 11mm 6.5 MHz Dornier end fire transducer. Following the department's routine, 12 prostate biopsies were performed, independently of PSA values and prostate volume evidenced by rectal examination or ultrasound findings.

All patients underwent a short bowel preparation through diet and enema (sodium phosphate and di-sodium phosphate) – Fleet™ enema type – Whitehall performed approximately 4 to 6 hours before the procedure.

For results control, patients underwent medical and laboratorial control, still keeping secret about the groups. Two exams were standardized involving complete blood count and urine culture with resistance testing. The first drawing was performed seven days before the procedure (previous to TRPB) and the second drawing was performed between days 14 and 21 after the procedure (post-TRPB), except for those patients who received emergency care.

Patients came to the revision visit on day 28 after the biopsy. In this visit the patients were inter-

viewed according to the review protocol including their symptoms and signs and requirements for emergency care, and the laboratorial result were reviewed as well. All patients presenting requiring urgent management were assessed in the emergency room of a referenced hospital, and this management was appropriately documented in the medical records.

Factors of interest assessed by the protocol were whether symptoms and signs associated to TRPB were detected or not, from minor complications (dysuria, hematuria, hematospermia) to major complications (bacteremia, urinary retention, sepsis, death) considering the patients' medical management, as well as the occasional requirement of hospitalization or initiating antimicrobials. In addition to the medical history, patients underwent laboratorial control in order to objectively document all cases of urinary tract infection (UTI), which constituted the main interest. With this purpose we defined an UTI case according to the criteria established by Carey & Korman (14), that attribute simple UTI cases to patients presenting positive urinary culture, regardless of the presence of urinary symptoms and, as complicated UTI cases patients presenting positive urinary culture, systemic symptoms and alterations in blood studies (complete blood count and/or blood culture). A positive urinary culture is defined as presence of  $\geq 100,000$  colony forming units (CFU) per milliliter of urine.

We analyzed still the presence of factors that could potentially interfere in the analysis' results as

detecting patients presenting diseases or conditions potentially immunosuppressive (diabetes, neoplasia, AIDS or chronic corticosteroids use), and these were defined as co-morbidities.

**Statistical Analysis**

In determining the efficiency of the treatments proposed we highlighted mean comparisons and proportions of final events between both groups.

Factors of interest aiming to compare the therapeutic efficiency between the groups were statistically analyzed with Student's t test to compare means in continuous variables. c-square, Yates' or Fisher's tests were used to compare proportions in categorical variables.

All tests were two-tailed and were considered significant values attributed to  $p \leq 0.05$ .

**RESULTS**

Results were compared to 105 among 140 patients. Among these, 51 patients received short term antimicrobial prophylaxis (Group 1) and 54 long term antimicrobial prophylaxis (Group 2).

The population of patients valid for efficiency analysis was similar in both groups regarding demographic aspects and basal health profile (age, hematocrit, hemoglobin, total WBC and bands percentage,

**Table 1** – Patients' characteristics in the short (Group 1) and long (Group 2) term antimicrobial prophylaxis groups.

	Group 1	Group 2	p
Number of patients	51	54	0.512
Age (years)	65±7 (54-90)	64±8 (40-81)	0.513
Hematocrit	42.5±3.9%	43.4±4.3%	0.291
Hemoglobin	13.84±1.40g/dl	14.09±1.42g/dl	0.374
WBC count	7.440±1.950/mm <sup>3</sup>	7.860±2.300/mm <sup>3</sup>	0.322
Band percentage	0–2%	0–2%	0.524
Co-morbidity	9 patients	9 patients	1
Positive urine culture	7 patients	9 patients	0.917
Previous TRPB	21 patients	20 patients	0.815

TRPB = transrectal prostate biopsy

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**Table 2** – Difference in proportions of categorical end-points post - transrectal prostate biopsy. TRPB among patients of short (Group 1) and long (Group 2) term antimicrobial prophylaxis groups.

	<b>Group 1</b>	<b>Group 2</b>	<b>p</b>
Minor Complications	40/51 (78%)	40/54 (74%)	0.768
Fever	8/51 (15%)	1/54 (1%)	0.029
Positive Urine Cultures	15/50 (30%)	4/54 (7%)	0.006
Emergency Care	5/51 (9%)	2/54 (3%)	0.389
Empiric Antibiotics	7/51 (13%)	2/54 (3%)	0.138
Hospitalization Rate	2/51 (3%)	0/54 (0%)	0.450

presence of co-morbidities, and positive urine cultures). The number of patients previously submitted to biopsy was also statistically similar when compared between both groups (Table-1).

The incidence of minor complications was statistically similar when both groups were compared (Group 1=78%, and Group 2=74%), with a total of 75% for both groups.

Assessing the end-points for continuous variables as hematocrit, hemoglobin, total WBC, and bands percentage, no statistical difference was evidenced between the groups.

In the positive urine culture group determining potential UTI we may observe that bacteriological analysis of the sample detected a greater number of infections by Gram-negative bacteria (81%) compared to Gram-positive (19%), and no infection by anaerobes was evidenced.

When assessing the end-points of categorical events such as fever, urine culture, requirement of emergency management, prescription of empirical antimicrobials and hospitalization post-biopsy, patients in the group of short term antimicrobial prophylaxis (Group 1) presented a trend towards major

complications compared to the group receiving long term antimicrobial prophylaxis (Group 2). For this the rates of fever (Group 1=15% and Group 2=2%) (p=0.014), and urine cultures (Group 1=29% and Group 2=7%) (p=0.006) statistically significant (Table-2).

By performing a selective analysis of patients for the end-point positive urine culture post-TRPB, limited to patients presenting negative urine culture previous to TRPB, evidence was that Group 1 patients remained with a trend towards higher incidence, but this values were not statistically significant (Group 1=23% and Group 2=8%) (p=0.08). However, for patients presenting positive urine culture previous to TRPB it was carefully determined the highest proportion of positive cultures on Group 1 (Group 1=71% and Group 2=0%) (p=0.005) (Table-3).

Patients with identification of complicated UTI, whether followed by urgent management or hospitalization or not, were analyzed. A total of 10 patients were seen according to urgency criteria or presenting systemic symptoms. Among these patients, 8 belonged to Group 1 and 2 belonged to Group 2. Among the 8 patients belonging to Group 1, 3 pre-

**Table 3** – Difference in positive urine cultures incidence post-TRPB in short (Group 1) and long (Group 2) term antimicrobial prophylaxis groups, urine cultures before – transrectal prostate biopsy (TRPB).

	<b>Group 1</b>	<b>Group 2</b>	<b>p</b>
Negative Urine Cultures before - TRPB	10/42 (23%)	4/45 (8.8%)	0.081
Positive Urine Cultures before - TRPB	2/7 (28%)	0/9 (0%)	0.005

sented complicated UTI documented by urine culture, and among the 2 patients belonging to Group 2 none presented laboratorial documented UTI. For this situation, Group 1 patients presented a trend to higher incidence of complicated UTI (Group 1=37% and Group 2=0%), but this difference was not statistically represented ( $p=0.44$ ).

No complications such as sepsis of urinary origin or deaths associated to the procedure were detected in both groups. Two patients required hospitalization after the biopsy to undergo intravenous antibiotic use, both from Group 1. In one case, treatment was initiated empirically, regardless the result of the urine culture, that came to be negative; the other case presented a positive urine culture previous to the procedure with a multiresistant germ, so management was done based on this previous result.

Based on patients' selection as co-morbidities, we pointed out that both groups presented a statistically similar proportion of patients as co-morbidities present (Group 1=17% and Group 2=16%) ( $p=1$ ). Presence of co-morbidities did not influence the incidence of infectious complications (Group 1=14% and Group 2=23%) ( $p=0.427$ ). When a specific selection of antimicrobial prophylaxis is done for these patients, despite the small number of patients according to these criteria (6 patients in Group 1 e 7 patients in Group 2), we have evidenced a trend towards a higher incidence of infectious complications in Group 1 (Group 1=50% and Group 2=0%) ( $p=0.07$ ).

## DISCUSSION

The diagnosis of prostatic conditions collaborates to a great part of urological practice today. Among these conditions, prostate cancer involves a significant percentage, since it is the most commonly diagnosed neoplasia, and the second greatest cause of death among cancers in American men, with an approximate incidence of 185,000 cases/year (15).

The development of screening involving rectal exam and PSA analysis, associated to the refinement of diagnostic methods, promote early detection

of this disease, offering conditions for a treatment with the best results concerning survival. Regarding the diagnosis, we must emphasize the role of prostate biopsy that provides an objective substrate through histopathologic study for further staging and treatment for the patients.

Prostate biopsy presented several improvement stages. These went from perineal prostate fine-needle aspiration to transurethral prostate biopsies, consolidating as prostate biopsies with core-biopsy-like needles.

Historically, needle biopsy was performed with higher gauge needles (14 gauge) compared to the ones used today (18-20 gauge), without firing mechanism, implying to patients in greater discomfort and infectious complications (16). Associated to the improvement of biopsy mechanisms and to confirmation of transrectal route, the use of transrectal ultrasound as a guide in the biopsy region has helped to an increase in efficiency of the conventional diagnostic method standardized as transrectal ultrasound-guided prostate biopsies (TRPB).

According to Rodriguez Terris (2) and Carey & Korman (14), TRPB presents a frequency of approximately 60 to 70% of minor complications and 0.4 to 4.3% of major complications.

Nowadays, preparation methods to perform TRPB aiming to minimize risks are advocated, but these, as well as the technique of the exam itself, are not properly standardized (4).

Many papers try to settle an optimal framework to prepare to perform TRPB, however few have a prospective design or present control groups. The optimal prophylactic regimen and preparation should be one of easy assimilation to the patient, cost-effective, efficacious in preventing the infectious complications associated to the method, and not inducing bacterial strains' selection.

With this purpose, authors as Carey & Korman (14) and Lindert et al. (17) assessed the efficacy of bowel preparation with enema before TRPB, which did not show any difference in the rates of complications associated to the procedure.

Studies to assess the efficiency of antimicrobial prophylaxis in TRPB preparation were proposed. To determine the drug to be used it is important to

bear in mind some factors. The bacterial flora involved in TRPB complications are Gram-negatives bacteria, primarily represented by *Escherichia coli*, followed by *Enterococcus*, *Klebsiella*, *Proteus* and *Pseudomonas*; but anaerobes should be evidenced such as *Bacteroides fragilis* and *Clostridium sp.*, which accounts for deaths in some series, despite an adequate antibiotic coverage (2). Tissue penetration, bioavailability and clearance pattern should help defining the drug of choice (10).

Several prophylactic regimens using sulfas, penicillins, cephalosporins, aminoglycosides, and anaerobicides, given separately or in combinations, in single or multiple doses, by oral or parenteral route, are proposed in the literature (6-11,16,18,19). In this context, the quinolone group (norfloxacin, ciprofloxacin, and ofloxacin) deserves emphasis due to its wide spectrum antimicrobial activity, high and rapid bioavailability by oral route and capacity of high urinary and prostate tissue concentrations (8,16).

From authors as Schein et al. (13), through studies performed in urgent abdominal surgeries, the concept of short term antimicrobial prophylaxis has been propagated. This practice aims to rationalize the use of antibiotics, since its indiscriminate administration may influence bacterial strains selection, risking the therapeutic efficiency of these drugs and initiating a possible ecologic impact in the patients' symbiotic flora. Strain selection was also evidence in patients submitted to TRPB by authors such as Gilad et al. (11). We may estimated that the use of short term therapies promotes better therapeutic efficiency due to dosing convenience and its ability to reduce in approximately 60% patients' direct costs (7). Nevertheless, in this analysis we should assume that the proposed prophylaxis shall present an adequate efficiency in order that the initial savings do not become diluted in further personal or social costs with treatments or hospital stays (8).

Based on results obtained in our study, we observed that minor complications rate was 75%, consistent with data reported in the literature (14,17).

In positive urine culture rates we could find that bacteriologic analysis of the samples has detected

a higher number of infections by Gram-negative bacteria (81%) compared to Gram-positive (19%), and this data is consistent with the flora usually associated to UTIs. No anaerobe infection was observed in our study.

Our study could document that patients submitted to short time antimicrobial prophylaxis (Group 1) presented a higher statistical rate of simple UTI documented by urine culture positive after biopsies, nevertheless this data may be assumed as a trend since when a control was performed to patients with incidental simple UTI figures did not show statistical significance ( $p=0.08$ ). Yet it was established that for patients presenting urine culture documented UTI before TRPB, prophylactic long term therapy is superior in efficiency ( $p=0.005$ ).

According to the analysis of complications incidence values considered as complicated UTI, it was not statistically different in the groups analyzed. The difference in documented complicated UTI in higher incidence in Group 1 may be deduced as a trend. Also, hospitalizations observed did not imply in direct interference of TRPB performance. Maybe further major studies performance should be necessary in order to attain a more definitive conclusion.

Factors such as biopsies numbers, PSA values, grade of obstructive symptoms, prostate volume, and cancer detection were not directly correlated to the incidence of UTI after TRPB (17). According to Griffith et al. (9), immunosuppressive conditions, such as diabetes mellitus and recent corticosteroid use may be determined as potential risk factors for this, suggesting the use of long term antimicrobial prophylaxis regimens. This data corroborates our study's results for the incidence of infectious complications in patients presenting co-morbidities.

## CONCLUSIONS

The long term antimicrobial prophylaxis established by our study – six doses of norfloxacin 400mg, bid, initial dose one hour before the exam – seems to determine a lower simple and complicated UTI incidence.

It is important, however, to perform further studies aiming at testing new prophylactic regimens, in order to determine an optimal preparation regimen for the performance of transrectal ultrasound-guided prostate biopsies.

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