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Antibiotics and observation have a similar impact on asymptomatic patients with a raised PSA

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What's known on the subject? and What does the study add?
As PSA exhibits suboptimal specificity, different strategies have been proposed in order to decrease the number of negative biopsies. An empirical course of antibiotics has been proposed as a cost-saving strategy to differentiate patients with benign cancer as it could potentially avoid unnecessary biopsies.

Despite being limited by its non-randomized open-label design, our data suggest that no specific PSA reduction threshold can accurately discriminate prostate cancer. The empirical use of antibiotics for asymptomatic patients with elevated PSA levels should be discouraged.

OBJECTIVES

- To compare the influence of a 4-week course of empirical antimicrobial therapy or observation on the prostate-specific antigen (PSA) levels of asymptomatic patients with a raised baseline PSA.
- To identify whether a decrease in PSA can predict the risk of prostate cancer (PCa) detection on prostate biopsy.

PATIENTS AND METHODS

- Patients were referred to our ambulatory centre because of a raised PSA level (>2.5 ng/mL) with a normal digital rectal examination. A 12-core prostate biopsy was indicated in these patients and they were offered antibiotic treatment with levofloxacin 500 mg daily for 30 days.
- Patients who did not agree to use antibiotics but who still showed interest in participating underwent simple observation, serving as controls.
- Total and free PSA levels at baseline and after 45 days were measured. Variation in PSA level was calculated.
- All patients underwent a 12-core prostate biopsy 6 weeks after the initial visit.

RESULTS

- In all, 245 men were enrolled, but 43 were lost due to follow-up. A total of 145 patients who used antibiotics and 57 controls were included in the analysis.
- The median baseline PSA levels were 7.6 and 7.7 ng/mL in the antibiotic and control groups, respectively, with median follow-up levels of 6.8 and 7.0 ng/mL. The follow-up PSA level was significantly lower than the initial PSA level ($P = 0.009$).
- Mean absolute and percentage variation in PSA level were similar in both groups ($P = 0.828$ and 0.128, respectively).
- The overall PCa detection rate was 15.8%, and did not differ among the groups ($P = 0.203$). Regarding the percentage variation in PSA level, patients diagnosed with PCa tended to have their PSA level increased (22.4 vs −5.3%; $P = 0.001$). Indeed, a decrease of 20% in PSA was not predictive of a negative prostate biopsy ($P = 0.41$).
- The area under the receiver operating characteristic curve for percentage PSA variation as a predictor of PCa was 0.660.

CONCLUSIONS

- PSA levels tend to fall when repeated after 45 days, regardless of antibiotic use.
- Despite being associated with the chance of PCa, no percentage PSA variation threshold value exhibits satisfactory discriminatory properties.

KEYWORDS

PSA, antibiotics, prostate cancer

INTRODUCTION

Prostate cancer (PCa) remains a major health concern throughout the world. Previous studies have confirmed that the serum PSA level is an important risk factor and its use has had a positive impact on the diagnosis and the clinical management of PCa.

As PSA exhibits sub-optimal specificity, different strategies have been proposed to decrease the number of negative biopsies. Some authors advocate a repeat PSA test as an appropriate initial approach in asymptomatic patients with a raised PSA and a normal DRE [1]. Although more controversial, it has also been suggested that antibiotic treatment could be an

TABLE 1 Baseline patient characteristics

Characteristics	Group		Total	*P* value
	Control	Levofloxacin		
No. (%) of patients	57 (28.2)	145 (71.8)	202	
Mean (SD) age, years	66.3 (7.1)	65.5 (6.9)	65.7 (6.9)	0.456
Median (25th–75th percentiles) baseline PSA, ng/mL	7.6 (4.2–11.2)	7.7 (5.7–11.4)	7.7 (5.2–11.4)	0.204
Mean (SD) baseline free : total PSA ratio, %	16.5 (7.7)	15.8 (5.8)	16.0 (6.3)	0.533
Median (25th–75th percentiles) prostate volume, mL	46 (30.5–70.5)	40 (30–60)	40 (30–65.2)	0.139

appropriate initial regimen in those patients [2]. An empirical course of antibiotics has been proposed as a cost-saving strategy to differentiate patients with benign and malignant conditions as it could potentially avoid unnecessary biopsies [3,4].

Nevertheless, it has been extensively shown that PSA levels physiologically fluctuate and, to date, there are no convincing data to prove that antibiotic treatment actually decreases PSA to a greater extent than observation [5–7]. Also, it is yet to be proven whether it is safe to defer prostate biopsy in those whose PSA level decreases after antibiotic treatment.

PATIENTS AND METHODS

The trial was approved by the institutional review board, and eligible patients signed an informed consent. The patients were aged 45–80 years and were referred to our institution because of a raised PSA level (>2.5 ng/mL) with a normal DRE and without pelvic pain or irritable voiding symptoms. Patients previously subjected to prostate biopsy, urinary tract infections, acute urinary retention and acute prostatitis were excluded. To determine total and free PSA levels, blood samples from the patients with abnormal levels were processed using the chemiluminescent immunometric total and free PSA assay, Immulite® 2000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA).

Patients had the raised PSA confirmed at our laboratory (total and free PSA levels, where measured) and had a 12-core prostate biopsy performed when it was indicated they were participants in the present study. During the waiting period for the prostate biopsy, consisting of 6 weeks at the time of the study, patients were offered levofloxacin 500 mg daily for 30 days. Patients who did not agree to use the antibiotic but who still showed interest in participating in the study underwent simple observation, serving as controls.

A follow-up PSA test was carried out 45 days after the initial visit for all patients. All subjects had a standard TRUS-guided 12-core prostate biopsy performed even if there was a decrease in PSA. The histological analysis of the biopsy specimens was done according to institutional routines irrespective of patient group. While no widely accepted definition exists, clinically intra-individual significant changes ('responders') were defined as having a decrease of 20% or more in total PSA [5].

Age, mean baseline free : total PSA ratio and percentage PSA variation data are presented as means ± SD and analysed using the Student's t-test. The PSA values are presented as median and interquartile interval (P25–P75) and compared by the Mann–Whitney *U*-test or the Wilcoxon signed-rank test. Repeated measures ANOVA was used to compare PSA values in the interval of time and in the groups. The performance of percentage PSA variation and the percentage of free PSA as a prognostic test for PCa was evaluated using receiver operating characteristic (ROC) curve analyses. A level of significance of 5% was adopted. The data were analysed using SPSS 13.0 (SPSS 13 for Windows, rel. 13.0; 2004, SPSS, Inc.).

RESULTS

During a period of 30 months (from March 2005 to August 2007), a total of 245 eligible patients were enrolled. In all, 43 patients were lost to follow-up (34 patients had missing PSA responses and nine patients missed the biopsy day), leaving 202 patients (145 in the antibiotic arm and 57 in the control arm). All baseline demographic and medical data were similar in both groups (age, prostate ultrasonography volume, median total PSA and mean free : total PSA ratio) and are presented in Table 1.

The median follow-up PSA level was not different between the antibiotic and observation groups. The percentage PSA variation was also similar ($P = 0.129$). There was also no significant difference in the number of 'responders' ($P = 0.940$) classified as a decrease of 20% or more in follow-up PSA, a threshold suggested previously [5] (Table 2).

A comparative analysis was performed to evaluate the following: the investigation of PSA variation during this period in each group; the interaction of follow-up and baseline PSA differences; and the correlation of PSA and its relations in the two different moments. To achieve these goals, a repeated measures ANOVA was used. The ANOVA tests showed that there was a significant association in terms of absolute PSA change during the trial interval (time $P = 0.021$). Unlike the control group, where there was no significant change of PSA, a significant change in PSA occurred in response to quinolone use ($P = 0.906$ and $P = 0.015$, respectively; Wilcoxon signed-rank test). However, the interaction effect on PSA variation was not a significant difference between the groups (ΔPSA, $P = 0.383$). Finally, the mean PSA levels in the groups were also similar (group $P = 0.280$). Therefore, although the PSA reduction was influenced by antibiotic use, this PSA variation was found not to be significant in discriminating negative and positive biopsies.

Characteristics of negative and positive biopsies are summarized in Table 3. The overall PCa detection rate was 15.8%. The median baseline PSA level was not statistically significant between patients with positive and

TABLE 2 Clinico-pathological parameters at follow-up

	Group			
	Control	Levofloxacin	Total	*P* value
Median (25th–75th percentiles) follow-up PSA, ng/mL	6.8 (4.2–10.8)	7.0 (5.2–10.5)	6.9 (5.1–10.6)	0.723
Mean (SD) percentage PSA variation	5.9 (47.0)	−3.5 (36.9)	−0.8 (40.1)	0.129
No. (%) of responders*	18 (31.6)	45 (31.0)	63 (31.2)	0.940
No. (%) showing positive biopsy	12 (21.1)	20 (13.8)	32 (15.8)	0.203

**Decrease in follow-up PSA of more than 20%.*

TABLE 3 Characteristics of negative and positive biopsies

	Biopsy assessment			
	Negative	Positive	Total	*P* value
No. (%) of patients	170 (84.2)	32 (15.8)	202	
Median (25th–75th percentiles) baseline PSA, ng/mL	7.6 (5.4–11.1)	8.0 (4.4–14.0)	7.7 (5.2–11.4)	0.890
Mean (SD) baseline free : PSA ratio	16.7 (6.2)	11.8 (5.7)	16.0 (6.3)	<0.001
Mean (SD) percentage PSA variation	−5.3 (34.6)	22.4 (57.0)	−0.8 (40.1)	0.001
No. (%) of responders*	55 (32.4)	8 (25.0)	63 (31.2)	0.410

**Decrease in follow-up PSA of more than 20%.*

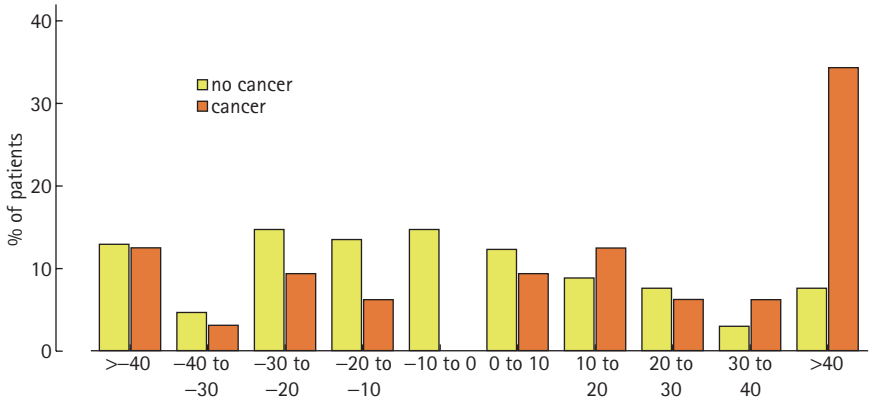
negative prostate biopsies ($P = 0.890$). However, the mean percentage PSA variation and the ratio of free : total PSA were significantly different, ($P = 0.001$ and $P < 0.001$, respectively; Table 3). Using a retrospective power calculation to analyse the percentage PSA variation, the present study has 95.6% power to detect this 27.7% difference between positive and negative biopsies.

Considering the PSA 'normalization', 26 patients who had a baseline PSA level >4 ng/mL (14.2%) had a follow-up PSA < 4 ng/mL; and in nine (4.4%) patients the follow-up PSA level was <2.5 ng/mL. In these groups, two of 26 (7.7%) patients and one of nine (11.1%) patients had a positive biopsy.

Using a single threshold value of 20% PSA reduction, the data showed that eight of 32 (25%) patients with PCa would be missed if they did not proceed to biopsy. Also, a 20% PSA reduction did not predict a negative biopsy ($P = 0.410$). On the other hand, a threshold value of a 20% increase in PSA statistically predicted a positive biopsy (89.1 vs 67.4%; $P = 0.001$).

The percentage PSA variation presented a normal distribution in benign conditions,

FIG. 1. Distribution of percentage PSA variation by percentage of patients and diagnosis.

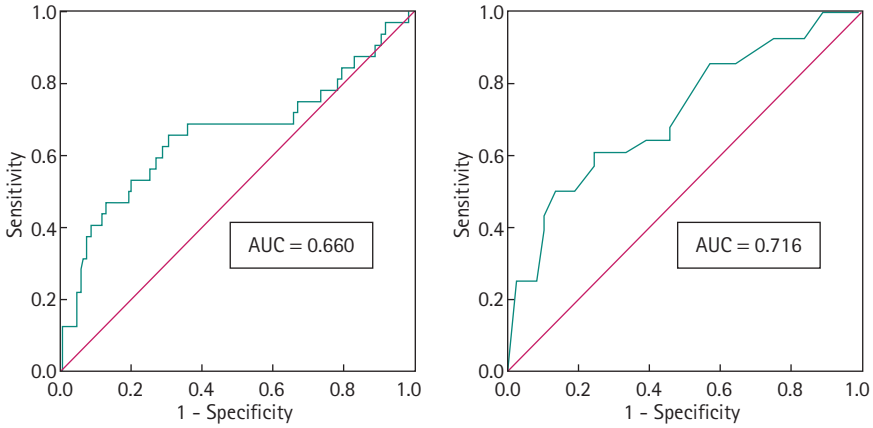


while patients with a positive biopsy had an asymmetrical distribution (Fig. 1).

The use of thresholds for the following percentage PSA variations – 45% decrease, 20% decrease, and 0 and 20% increases – yielded 90, 75, 68 and 47% sensitivities, and respective specificities of 11, 32, 61 and 83%.

Moreover, in a ROC curve, the association between a positive biopsy and baseline total PSA was poor [area under the curve (AUC) = 0.510]. Correspondingly better, but still performing poorly, the percentage PSA variation had an AUC = 0.660 (standard error = 0.062; 95% CI = 0.539–0.782). The best threshold value (7% PSA increase) provided a sensitivity of 65%, a specificity of 69%, a positive predictive value of 28.7%, and a negative predictive value of 91.4% ($P = 0.001$). Figure 2 shows the low accuracy of the percentage PSA variation. The baseline free : total PSA ratio shows a better performance (AUC = 0.716; standard error = 0.055; 95% CI = 0.609–0.824). The threshold of a 20% free : total PSA ratio

FIG. 2. The diagnostic performance of percentage PSA variation and percentage free PSA in positive biopsies assessed by ROC curve analysis. A threshold of a 20% decrease or more in the percentage PSA variation provides 74% sensitivity and 31% specificity. (i.e. almost 30% of the tumours could be missed if this threshold value were adopted).



showed an 89% sensitivity, a 31% specificity, a positive predictive value of 18%, and a negative predictive value of 94.2% (Fig. 2).

DISCUSSION

Previous observations suggested that after an initially raised PSA, a course of antibiotic treatment could lead to a decrease in PSA level and obviate the need for prostate biopsy in such patients [8,9] However, not only is there a lack of appropriate studies documenting that antibiotics lead to a decrease in PSA levels, but there are also no data proving that it is safe to defer biopsy in those patients who exhibit a fall in PSA values.

The present study did not find any difference in PSA variability between levofloxacin and the observation group ($P = 0.383$). We believe that this is due to the low prevalence of infectious processes causing a raised PSA level. Because we included only asymptomatic patients in the present study, the PSA 'normalization' rate was 13%, regardless of the use of levofloxacin. On the other hand, Schaeffer *et al.* [9], studying patients with chronic bacterial prostatitis, reported that 42% of patients have their post-treatment PSA normalized (<4 ng/mL). Similarly, Bozeman *et al.* [10] described a 46% 'normalization' rate in patients with pathologically proven chronic prostatitis after a trial of antibiotics and a non-steroidal anti-inflammatory medication. The mean baseline PSA level was 8.4 ng/mL and the post-treatment PSA level fell to 5.3 ng/mL. The authors affirmed that those patients no longer had an indication for biopsy. However, only 51 of 95 (53%) patients were biopsied, and 13 of 51 were diagnosed with PCa. A decrease in the PSA level of 4.8% was observed in patients with PCa [10]. The results of the present study showed that two patients diagnosed with cancer had a post-test PSA level below the threshold of 4 ng/mL. Furthermore, when we employed a threshold of 2.5 ng/mL, still one patient had a positive biopsy. We conclude that is not safe to defer prostate biopsy based on PSA reduction after antimicrobial treatment.

Chronic inflammation has recently been linked to prostate adenocarcinoma pathogenesis [11]. In asymptomatic populations, the rate of infection is unclear and could be very low. Also, according to the National Institutes of Health (NIH) consensus, only 5–10% of all symptomatic men suffer from a bacterial source and nearly 90% of patients diagnosed with prostatitis are characterized by symptoms in the absence of a detectable infection [12]. Further, it seems clear that certain antibiotics exert immunological and anti-inflammatory effects beyond their intrinsic antibacterial action [13]. Such anti-inflammatory effects could also, in theory, lower PSA values. The potential benefits of empirical antimicrobial courses (they decrease the rate of unnecessary biopsies) must be weighed against the harms of unbound antibiotic use (the risk of toxicity and the development of resistant strains).

The present study showed a tendency for PSA level to fall, but antibiotic treatment does not cause a significant decrease in PSA compared with observation ($P = 0.129$). Moreover, the variations in PSA, regardless of the antibiotic course, were similar to random fluctuations in healthy men [6,7].

Clinically, instead of the presumption that a PSA reduction will defer the need for biopsies, an increase in PSA level seems more meaningful, obviating the need for an invasive test. In the present study, we found that patients with histologically proven PCa have more sustained absolute PSA increases than negative results (22.4% vs −5.3 ng/mL; $P = 0.001$). Recently, Stopiglia *et al.* [14] reported on 98 patients with type IV inflammatory prostatitis who were randomly assigned to either ciprofloxacin or placebo. They found that a decrease in PSA was not associated with a diagnosis of PCa (31 vs 26.7%).

Some authors suggest, as an alternative, evaluating men with a raised PSA according to the white blood cell (WBC) count in expressed prostatic secretions (EPS) or prostatic massage urine (VB3) [15–17]. However, Nadler *et al.* [18] found no correlation between total PSA and WBC count in either EPS or VB3. Nonetheless, prostatitis is a clinical diagnosis and the use of WBC counts in prostatic secretions is debatable. Furthermore, the medical history based on the NIH-Chronic Prostatic Symptom Index is uniformly accepted to differentiate patients with prostatitis from healthy subjects [19].

The strength of the present study lies in the prospective design with a control arm in which all 202 patients underwent biopsy. Also, the cohort characteristics were similar between the groups. All patients were managed by the same follow-up procedures and approaches.

The present study has a few important limitations. First, the lack of randomization could have biased the results. It should be noted that, although patients' characteristics were similar, the groups were distinctive in number. Second, patients were not subjected to urine culture or prostatic secretion testing.

However, the use of WBCs in either EPS or VB3 as a marker for prostatitis is limited [12]. Previous studies found no correlation between the PSA level and the degree of inflammation [18]. Also, it is well known that inflammation is not linked with symptoms or quality of life (NIH type IIIb chronic prostatitis) [20]. In fact, urologists frequently diagnose prostatitis but rarely (less than 4%) perform the Mears–Stamey diagnostic test [16]. Therefore, the selection criteria of the present study, although not able to differentiate between men with and without inflammatory prostatitis, seem to be similar to daily clinical practice, where the routine performance of these tests does not appear to affect antibiotic usage.

Analysing the ROC curves, we confirmed the poor sensitivity and specificity of percentage PSA variation as a discriminative test. Different studies suggest that a significant decrease in PSA level after a course of antibiotics could lower the cancer risk [9,10]. On the other hand, we observed that the best predictive threshold was an increase of 7% in follow-up PSA. Adopting this value, there was a 62% sensitivity, a 68% specificity and a 94% negative predictive value. As a screening test, the use of the 7% PSA increase as a threshold could be considered good . However, it is well known that negative predictive values are biased by prevalence rates. Interestingly, our histologically proven PCa prevalence rate was lower than the current literature for patients with a PSA level ≥2.5 ng/mL [21,22]. Also, we confirmed that the free : total PSA ratio seems to be a more accurate tool to discriminate PCa from benign conditions than percentage PSA variation (AUC = 0.716 and 0.660, respectively).

In conclusion, despite being limited by its non-randomized open-label design, the data from the present study suggest that antibiotics should not be used to prevent patients with a raised PSA level from undergoing a prostate biopsy. PSA variation has a limited predictive performance regarding biopsy results.

Therefore, we found the arbitrary definition of 'clinical responders', with a decrease of 20% or more in follow-up PSA, to be inappropriate.

The mean percentage PSA variation is higher in patients with PCa than those without. However, no specific threshold accurately discriminated between PCa and benign conditions.

Until further randomized controlled trials are conducted, the empirical use of antibiotics for asymptomatic patients with raised PSA levels should be discouraged.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **AUC**, area under the curve; **EPS**, expressed prostatic secretions; **NIH**, National Institutes of Health; **PCa**, prostate cancer; **ROC**, receiver operating characteristic; **VB3**, prostatic massage urine; **WBC**, white blood cells.