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# PSA Levels of 4.0 – 10 ng/ml and Negative Digital Rectal Examination. Antibiotic Therapy versus Immediate Prostate Biopsy

**Avraham Shtricker, Shai Shefi, Avi Ringel, Gabriel Gillon**

*Department of Urology, Tel Aviv Central Consulting Clinic, Clalit Healthcare Services, Tel Aviv, Israel*

**ABSTRACT**

*Purpose:* The management of mildly elevated (4.0-10.0 ng/ml) prostate specific antigen (PSA) is uncertain. Immediate prostate biopsy, antibiotic treatment, or short term monitoring PSA level for 1-3 months is still in controversy.
*Materials and Methods:* We conducted a retrospective chart review of patients in a large community practice (2003 - 2007) who had PSA levels between 4.0-10 ng/mL without any further evidence of infection. Data was gathered regarding patient's age, whether standard antibiotic therapy (10-14 days of ofloxacin or ciprofloxacin) had been administered before the second PSA measurement, results of a second PSA test performed at 1- to 2-month intervals, whether a prostate biopsy was performed and its result.
*Results:* One-hundred and thirty-five men met the study inclusion criteria with 65 (48.1%) having received antibiotics (group 1); the PSA levels decreased in 39 (60%) of which, sixteen underwent a biopsy which demonstrated prostate cancer in 4 (25%). Twenty-six (40%) patients of group 1 exhibited no decrease in PSA levels; seventeen of them underwent a biopsy that demonstrated cancer in 2 (12%). The other 70 (51.9%) patients were not treated with antibiotics (group 2); the PSA levels decreased in 42 (60%) of which, thirteen underwent a biopsy which demonstrated prostate cancer in 4 (31%). In the other 28 (40%) patients of group 2 there was no demonstrated decrease in PSA, nineteen of these subjects underwent a biopsy that demonstrated cancer in 8 (42%).
*Conclusions:* There appears to be no advantage for administration of antibacterial therapy with initial PSA levels between 4-10 ng/mL without overt evidence of inflammation.

***Key words:*** *PSA; digital rectal examination; antibiotics; biopsy*
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## INTRODUCTION

The prostate-specific antigen (PSA) level is considered one of the most prevalent cancer markers in current clinical practice. Its high sensitivity but low specificity have led to controversy in regards to the recommended management of patients with mild PSA elevation whose digital rectal examination (DRE) is negative (1-7). Seventy percent of patients with abnormal PSA are found not to have cancer on prostate biopsy, itself a potentially morbid procedure (1). The three common ways of dealing with elevated PSA are (1) the use of empiric antibiotic treatment followed by a repeat PSA, (2) repeated PSA measurement after 1-2 months, and (3) immediate prostate biopsy (1,2,4-7). Of the three, the use of antibiotics would appear to

be the most sound, given that unproven sub clinical prostatitis, and not malignancy, leads to the majority of cases of spurious PSA elevation (1-7).

In an effort to achieve a more effective indication for dealing with PSA elevation in the community, we conducted a retrospective study for evaluating the effect of antibiotics on PSA levels in patients who have a negative DRE yet possess an initially mild PSA elevation (4.0-10 ng/mL) and negative clinical and laboratory signs of prostate or urinary infection. Moreover, can the antibiotic therapy contribute to obviate unnecessary prostate biopsy.

## MATERIALS AND METHODS

We conducted a retrospective electronic chart review of all the patients seen in our service between 2003-2007 who had PSA levels between 4.0-10 ng/mL, a negative digital rectal examination (DRE) and no clinical or laboratory signs of urinary infections (negative urine culture and negative urine sediment). The data collected included the patient's age, whether standard antibiotic therapy (10-14 days of ofloxacin or ciprofloxacin) had been given before the second PSA measurement, based on the urologist's own decision, the results of the second PSA test that was done after a 1- to 2-month interval, whether a TRUS (transrectal ultrasound) guided prostate biopsy was eventually performed (mostly when a PSA decrease was less than 10%) and, if so, the result. The 10-core biopsy was performed based on the urologist's decision relying on his or her own PSA judgment requiring PSA adjustment (age related, race related, density, velocity, etc.). Cases that involved events that might falsely elevate the PSA result (e.g., urinary tract infection, urinary retention) were excluded from the study. All the specimens were analyzed in authorized laboratories within our catchments' area (using Immulite 2000 analyzer third generation PSA).

Analysis of data [age, PSA changes, antibiotics therapy, biopsy result (presence of cancer)] was carried out using SPSS 10.0 statistical analysis software (SPSS Inc., Chicago, IL, USA). Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov test (cutoff at $p < 0.01$). Continuous variables were described using mean ± standard deviation. Categorical variables were described using frequency distributions and were presented as frequency (%). The Student's-t-test for independent samples was used to compare PSA elevation prior to and following antibiotic therapy. Change from baseline antibiotic therapy was also compared by antibiotic therapy. Multivariate logistic regression analysis was used to model detected prostate cancer. All tests were two-sided and considered significant at $p < 0.05$.

## RESULTS

A total of 135 men met the study inclusion criteria within the study period. Their average age was 66.48 ± 8.32 years, the average initial PSA level was 6.28 ± 1.59 ng/mL, the average second PSA level was 5.68 ± 1.77 ng/mL, and the average difference between the two tests was 0.60 ± 1.71 ng/mL. Sixty-five of these patients (48.1%) underwent prostate biopsy: the pathologic findings were prostate cancer in 18 (28%), chronic inflammation (based on massive lymphocyte infiltration or giant cell granuloma) in 13 (20%), and benign prostatic hyperplasia (BPH) in the remaining 32 (52%).

Sixty-five of the 135 patients (48.1%) were treated with antibiotics (group 1): the PSA levels decreased in 39 (60%) of them, sixteen underwent a biopsy, which demonstrated prostate cancer in 4 (25%), and BPH in the rest. In 26 (40%) patients of group 1 no decrease in PSA levels were exhibited, seventeen of them underwent biopsies which demonstrated cancer in 2 (12%), chronic inflammation in 8 (47%) and BPH in the rest .The other 70 (51.9%) patients were not treated with antibiotics (group 2): the PSA levels decreased in 42 (60%) of them, thirteen underwent a biopsy which demonstrated prostate cancer in 4 (31%),chronic inflammation in 2(15.4%) and BPH in the rest. In 28 (40%) patients of group 2 there was no decrease in PSA, nineteen of them underwent a biopsy which demonstrated cancer in 8 (42%), chronic inflammation in 3(15.7%) and BPH in the rest (p value for each parameter between the groups revealed a level > 0.05).

The average initial PSA level in group 1 was 6.3, the average second PSA level was 5.41, an aver-

age decrease of 14.1%, the average initial PSA level in group 2 was 6.26, the average second PSA level was 5.95, an average decrease of 4.95% (p = 0.08).

Multivariate analysis (described in the methods ) of age, PSA changes, antibiotics therapy and biopsy results (presence of cancer) revealed no significant difference between the study groups (P Value > 0.05 in all categories). Table-1 shows the distribution of diagnoses and performance of biopsies for each subgroup.

## COMMENTS

The results of this chart review failed to show any advantage for Random quinolone antibiotic treatment while dealing with initial PSA levels between 4-10 ng/mL with no signs or symptoms of infection. A decrease in PSA after antibiotic therapy does not rule out prostate cancer and conversely, a lack of decrease does not exclude it. Therefore, the antibiotics therapy does not contribute to obviate unnecessary prostate biopsy.

The use of antibiotics is prevalent among some of the urologists who intended to reduce PSA elevation presumably caused by an inflammatory process.

It has previously been suggested that all patients should receive empiric antibiotic therapy for prostatitis or inflammation after their first elevated PSA result and before recommending a biopsy (1,2,4,6-8). There is, however, a mean variation of approximately 15% in the measurements of total, free and percent free PSA that does not appear to be significantly affected by age and total PSA level (9). Okada et al. (8) assessed high PSA readings due to inflammation and, based on histological findings, concluded that acute inflammation within the prostate is a significant contributor to elevated serum PSA levels, especially in patients with small prostates. Statesman et al. (10) studied the inflammation in prostate biopsies in which there was no cancer and found inflammation in virtually every one of them, even in the ones without any signs of clinical prostatitis. These authors concluded that sub clinical inflammation could cause PSA elevation, emphasizing that nearly half of all clinically asymptomatic men with an elevated PSA level have laboratory signs of prostatitis. They suggested that two weeks of ciprofloxacin administration would result in a drop in the elevated PSA levels of almost 50% of patients with lower urinary tract symptoms (LUTS) and normal DRE results, thus avoiding prostate biopsy. This approach, however, requires careful follow-up, especially for patients whose PSA levels fail to decrease to normal levels (1). In Kaygisiz et al. study (6), all 48 of their patients were administered antibiotics and underwent biopsies. The PSA levels decreased below 4 ng/mL in 18 (37%) of them and the biopsies of these men were negative for malignancy. The findings for the other 30 men were prostate cancer in 10.8%. These authors suggested that antibiotic therapy should be administered for 3 weeks, regardless of inflammation findings, when PSA levels are mildly high (i.e.,

***Table 1 –*** *Results of PSA changes and prostate biopsies in 135 patients.*

| | **Group 1** (N = 65) **No Antibiotic** | | | | **Group 2** (N = 70) **Antibiotic** | | | |
|---|---|---|---|---|---|---|---|---|
| Significant decrease in PSA (> 10%) | (N = 39) + | | (N = 26) - | | (N = 42) + | | (N = 28) - | |
| Prostate biopsy | + | - | + | - | + | - | + | - |
| Number of patients | 16 | 23 | 17 | 9 | 13 | 29 | 19 | 9 |
| Prostate cancer | 4 | N/A | 2 | N/A | 4 | N/A | 8 | N/A |
| Chronic inflammation | - | N/A | 8 | N/A | 2 | N/A | 3 | N/A |
| BPH only | 12 | N/A | 7 | N/A | 7 | N/A | 8 | N/A |

*+: affirmative, -: negative; BPH: benign prostatic hyperplasia PSA: prostate-specific antigen*

4-10 ng/mL), subsequently followed by the decision of whether or not to carry out a biopsy. Bozeman et al. reported that when serum PSA had normalized with treatment there was no longer an indication for transrectal ultrasound-guided biopsy in almost half of their 95 patients diagnosed with elevated PSA and chronic inflammation, suggesting that chronic prostatitis is an important cause of elevated PSA and that when identified, treatment can decrease the percent of negative biopsies (7). On the other hand, Habermacher et al. (11) noted that almost all cases of asymptomatic prostatitis are not caused by bacteria, thus eliminating the need for antibacterial therapy. We had far fewer cases with histologic evidence for chronic prostatitis in our study (20%) than had been reported by other authors (7,11). This may explain why prompt administration of antibacterial therapy was not helpful in our series. Any elevation of PSA, be it spurious or true, should be an indication for repeat PSA testing, but we advocate withholding antibiotics until a bacterial cause has been identified.

The influence of inflammatory foci on total and free PSA concentrations remains a controversial issue (2). Ozen et al. (3) claim that benign prostatic hyperplasia (BPH) and BPH with prostatitis appear to be more frequent causes of PSA elevation. A recent editorial by Scardino criticized the unjustified use of antibiotics in a group of patients similar to ours and emphasized the various inherent disadvantages associated with this approach, such as cost, toxicity, and the promotion of resistant bacterial species development that exposed the patient to more resistant and aggressive sepsis should a biopsy eventually be done. Screening PSA management was not influenced by antibacterial therapy, thereby preventing 35% of what would have been unnecessary biopsies (5).

There appears to be no advantage for antibacterial therapy for decreasing initial PSA levels between 4-10 ng/mL.

Our study is limited by being retrospective, relatively small and dealing with heterogeneous co-morbidities in both groups with only about half undergoing a biopsy, yet the number of participants enrolled from one clinic using a sole laboratory improves its significance that enables us to shed another light on the above-mentioned debate.

## CONFLICT OF INTEREST

None declared.

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**Correspondence address:**
Dr. Avraham Shtricker
10 Rav Ashi Street
Tel Aviv, 69395 Israel
Fax: + 972 3 5260218
E-mail: shtrickeravi@hotmail.com

## EDITORIAL COMMENT

The diagnostic efficacy of the PSA test is a matter of general concern, especially in men both with indolent disease and PSA levels less than 10 ng/ml. Also, randomized controlled trials regarding the prognostic utility of this value are currently underway (1, 2). As the authors stated, prostate biopsy is a procedure that brings about potential morbidity and occasionally septic complications to patients (3). Yet, the false positive rates are high in the mentioned PSA range, and in these cases are thus managed with various approaches (1,2). In the current study, the authors evaluated the efficacy and outcome of an approach, antimicrobial intervention followed by a reassessment of PSA. Although this approach is not strongly recommended in current clinical practice (4), it has been introduced in the previously reported literature.

The authors retrospectively examined the influence of antimicrobials on serum PSA levels in 145 patients with negative DRE and PSA between 4.0 and 10.0 ng/ml. Sixty-five patients (45%) were treated with antimicrobials, and PSA levels thereafter decreased in 39 (60%). Thirty-three men (50%) underwent biopsy, and 6 (9%) and 8 (12%) were histologically diagnosed with prostate cancer and chronic prostatitis, respectively. The remaining 80 patients were managed without antibiotics. The PSA level decreased in 42 (52%) of them one month after the first measurement. Thirty-two of these untreated men (40%) received biopsy, and 12 (15%) and 5 (6%) patients were diagnosed as having prostate cancer and chronic prostatitis, respectively. Multivariate analyses showed the absence of non-specific age-dependent factors regarding the diagnostic results. Antimicrobial treatment did not have an influence on the PSA level and biopsy indication. Thus, the authors concluded no advantage of antimicrobial therapy for men with the initial PSA levels between 4 and 10 ng/ml, and recommended the recalculation of the serum PSA level one month after the first measurement.

Although the present results may not be surprising, they are thought to be feasible and reliable (4). I think that the present study has an impact; it potentially suggests possibly questioning why the serum PSA concentration elevates in benign prostatic disorders. The current one as well as several previous studies showed the fraction of patients with bacterial prostatitis among those having grey-zone PSA levels is small (5). The majority of patients histologically diagnosed with prostatitis under this type of situation are thought

to have non-bacterial prostatitis, and it is undeniable that this is relevant to the elevated PSA level. Further studies on precise histopathological findings such as the presence of bacterial or non-bacterial inflammation are warranted as well as feasible interval for the PSA reassessment.

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***Dr. Noboru Hara***
*Division of Urology*
*Dept. of Regenerative & Transplant Medicine*
*Niigata University*
*Niigata, Japan*
*E-mail: harasho@med.niigata-u.ac.jp*

## EDITORIAL COMMENT

Prostate cancer detection is difficult due to the limited specificity of PSA test. PSA elevation can be due to prostate cancer, benign prostate enlargement, asymptomatic prostatitis or a combination of factors. A common practice is to prescribe an empiric course of antibiotics and then recheck a PSA level with the belief that a lower PSA is reassuring.

Shtricker et al. performed a retrospective review of men with PSA 4-10 ng/mL and no clinical indication of prostatitis. A ten to fourteen day course of fluroquinolone antibiotic was prescribed in some patients. Some patients had a prostate biopsy performed. The authors concluded that antibiotic treatment was not useful based on their analysis of biopsy results. The conclusions, which can be drawn from this retrospective non-randomized comparison of potentially heterogeneous groups, are limited by methodological flaws. Of the study population, only 48% received antibiotic treatment and only 48% were ultimately biopsied. The criteria for which patients received antibiotic treatment and prostate biopsy were not described. Others might find fault with a 2-week course of antibiotic treatment, as traditionally 3 to 4 weeks is prescribed for prostatitis due to limited antibiotic penetration into the prostate.

Growing evidence does seem to suggest that the traditional practice of antibiotic treatment for moderate PSA elevation (4 to 10 ng/mL) is not justified. A recent report found that in men whose PSA normalized to less than 4.0 ng/mL after antibiotic (a group often given the option of avoiding biopsy) there was still a 29% prevalence of prostate cancer (1). The necessity

of prostate biopsy should be based on repeating PSA to confirm PSA elevation, risk stratification using PSA data (PSA velocity, age normal PSA, free PSA), and the implications of finding prostate cancer in the individual patient involved.

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***Dr. Kenneth G. Nepple &***
***Dr. Terry L. Wahls***
*Department of Urology*
*University of Iowa*
*Iowa City, Iowa, USA*
*E-mail: terry.wahls@va.gov*

## EDITORIAL COMMENT

In a retrospective cohort study the authors evaluated whether or not to perform, an immediate prostate biopsy or to treat patients with initial PSA levels between 4-10 ng/mL with antibiotics and monitor the PSA level for 1-3 months. This represents an important and controversial topic with not enough recent data to make clear recommendations. While prostatic inflammation has been associated with increased PSA levels, antibiotics have no effect on nonbacterial prostatitis. PSA levels vary spontaneously, rising and falling at an average of 15% from week to week. A rise of < 20-46% from one year to the next is more likely to be the result of biological variation than cancer (ref 9 in the article).

Is PSA elevation produced by asymptomatic bacterial prostatitis, which is an uncommon condition? There is no evidence to support it. As there have been no randomized trials to show that antibiotics are more likely to lower PSA levels than a placebo, the study by Shtricker et al. included a control group, which strengthens their conclusion that antibiotic therapy does not contribute to obviate unnecessary prostate biopsies. This conclusion should be followed in routine practice.

***Dr. Arnauld Villers***
*Service d'Urologie*
*Hôpital Claude-Huriez*
*Lille, France*
*E-mail: arnauld.villers@wanadoo.fr*

## EDITORIAL COMMENT

PSA variability continues to plague prostate cancer screening. Eastham et al. previously examined this issue using blood samples from the Polyp Prevention Trial (1). In men with a PSA level > 2.5 or > 4.0 ng/mL on one test, the PSA "normalized" below these thresholds at the next measurement in 26% and 30%, respectively. This led the authors to recommend repeat PSA measurements to further evaluate an abnormal result before proceeding to more invasive testing (i.e. prostate biopsy).

An alternate strategy to reduce confounding from PSA variability is a trial of empiric antibiotics,

given the prevalence of subclinical prostatitis. Indeed, Simardi et al. (2) showed a direct relationship between mean PSA levels and the percentage of inflammation on prostate biopsy ($p = 0.02$). Nevertheless, this practice is controversial due to the potential side effects of antibiotics.

Several prospective studies have evaluated the utility of empiric antibiotics with conflicting results (3-5). One positive study was reported by Serretta et al. (5) including 99 men with a PSA > 4 ng/mL and normal DRE, all of whom underwent repeat PSA measurement and prostate biopsy after a course of antibiotics. The prostate cancer detection rate was 20% in men whose PSA decreased with antibiotics, compared to 40% in those whose PSA did not decrease ($p = 0.02$) (4). Furthermore, no prostate cancers were identified among men with an initial PSA less than 10 ng/mL which decreased by > 50%, nor in any participant whose PSA decreased by > 70% with antibiotics regardless of the initial PSA level.

Despite the retrospective, non-randomized nature of the current study by Shtricker and colleagues, it adds to the growing literature showing that PSA may spontaneously decrease over time without antibiotics. It also demonstrates that a reduction in PSA by more than 10% following antibiotics does not rule out prostate cancer.

Nevertheless, it remains possible that empiric antibiotics may help improve the specificity of PSA testing in specific patient subgroups. Prospective randomized studies are underway which should help to shed additional light on this issue. In the meantime, patients presenting with an elevated PSA should be evaluated for signs or symptoms of prostatitis. If empiric antibiotics are given and the PSA does not decrease to baseline, it may be beneficial to wait several weeks before performing prostate biopsy to allow time for the intestinal flora to normalize. At the time of biopsy, patients who received prior antibiotics should be counseled about the risk of infection and instructed to seek prompt medical attention if fever or other symptoms develop.

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***Dr. Stacy Loeb***
*Department of Urology*
*Johns Hopkins Medical Institutions*
*Baltimore, Maryland, USA*
*E-mail: stacyloeb@gmail.com*