# ROLE OF ANTIBIOTIC THERAPY BEFORE PROSTATE BIOPSY IN PATIENTS WITH MARGINALLY ELEVATED PSA-A HOSPITAL BASED STUDY


## Abstract:

### Introduction:

Prostate specific antigen is widely used for screening and early detection of prostate cancer. However, PSA is not a cancer specific tumor marker. We evaluated the effects of antibiotic treatment on serum total prostate specific antigen, free prostate specific antigen and percent free prostate specific antigen in men with prostate specific antigen between 4 and 10 ng/ml and normal digital rectal examination (DRE).

### Materials and Methods:

152 men requiring urological consultation for PSA between 4 and 10 ng/dl, were enrolled. Exclusion criteria were patients with urinary tract infection and documented history of prostatitis. Prostate massage and laboratory-specific analyses to rule out prostatitis were not undertaken. Basal total-PSA (t-PSA) and free-PSA (f-PSA) were determined. Ofloxacin (200mg BID) / Nitrofurantoin (100mg BID) were given orally for 1 week followed by 100mg OD for 3 weeks. t-PSA and f-PSA levels were repeated 4 weeks after therapy. The change in PSA levels to nadir was maximum within 4 weeks. Patients with raised PSA after a course of antibiotics underwent prostate biopsy whereas patients with PSA reductions were followed.

### Results:

We studied a total of 152 patients with mean age of 67 ± 6.7 years. The patients were randomly divided into 2 groups. Mean total PSA was 6.09 ± 1.34 and 3.84 ± 1.25 ng/ml before and after treatment, respectively (mean change -2.25 ± 0.52, $p < 0.001$) in Group A. 50 patients with elevated PSA were followed up with repeat levels for another 4 weeks without antibiotic therapy. 12 patients (24 %) had reduction in PSA levels in that group. 47 out of 102 (46.07%) had a reduction in PSA levels < 4 ng/ml after antibiotic therapy. Out of the remaining 55 patients who underwent prostate biopsy, 30 (54.54%) patients did not harbor malignancy. 19 out of these patients had chronic prostatitis on histological examination. Only percent free prostate specific antigen change after treatment was found to be significantly different between patients with and without prostate cancer.

### Conclusions:

Antibiotic therapy significantly reduces PSA levels in males with elevated PSA. Empirical antibiotic treatment in asymptomatic patients with a PSA level 4-10 ng/ml and a normal DRE may be used to select prostate biopsy candidates. Indian males may have increased incidence of subclinical prostatitis.

**Introduction:**

Disruption of the natural anatomic and physiologic barriers between the prostatic milieu and the bloodstream is an important factor determining increased serum prostate-specific antigen (PSA) levels. Inflammation alters prostatic duct integrity causing PSA leakage from the acini and ductal lumina.

In 1989, Dalton was the first to report total PSA elevation in acute prostatitis. (1) Many experimental and clinical studies suggest a correlation between acute and chronic prostatitis and increased serum PSA levels. (2, 3) Subclinical inflammation of the prostate could elevate serum PSA in asymptomatic patients without clinically detectable prostate cancer.

Gerstenbluth and colleagues reported chronic prostatitis as a common finding in radical prostatectomy specimens. (4) In the majority of cases, prostatitis is an incidental pathological finding that causes no clinical symptoms. These patients are categorized by the National Institutes of Health (NIH) into category IV prostatitis (asymptomatic inflammatory prostatitis). It has been suggested that repeating the measurement of PSA in symptomatic men can help avoid unnecessary prostatic biopsy. (5)

Although prostatitis may cause PSA elevation, asymptomatic patients are not routinely screened for this disease before Transrectal biopsy. PSA is widely used for screening and early detection of prostate cancer. However, PSA is not a cancer specific tumor marker, and other physiological and benign conditions such as benign prostatic enlargement and prostatitis in addition to cancer can increase serum PSA and lead to potentially unnecessary biopsy procedures. Studies revealed that only 20% to 30% of men with PSA between 4 and 10 ng/ml will actually have prostate cancer, meaning that the remaining 70% to 80% will undergo unnecessary biopsies. (6) In these patients Benign Prostatic Hyperplasia (BPH), prostatitis and UTI are often given as the more common benign reasons for a high serum PSA level. A combination of history, a Digital Rectal Examination (DRE) and serum PSA level helps to differentiate many of these conditions, but a significant proportion remain indistinguishable. Such men present urologists with a difficult diagnostic dilemma; who needs a biopsy?

Prostate biopsy can be a painful procedure with potentially significant morbidity. A valid goal in management must therefore be to minimize the rate of negative biopsy. Much effort has been directed at differentiating between benign and malignant causes of an elevated serum PSA. The most important of these approaches include PSA density, PSA velocity, free to total PSA ratio and age-specific reference PSA ranges.

The aim of our study was to investigate the possibility of reducing the number of prostate biopsies in patients showing PSA decrease or normalization after antibiotic therapy. We evaluated the effects of antibiotic treatment on serum total prostate specific antigen, free prostate specific antigen and percent free prostate specific antigen in men with prostate specific antigen between 4 and 10 ng/ml and normal digital rectal examination (DRE).This approach could be

useful in patients for whom it is necessary to postpone biopsy and in patients, with previous negative biopsies, willing to avoid biopsy until further PSA increase.

**Materials and Methods:**

Between May 2014 to April 2016, men requiring urological consultation having PSA values between 4 and 10 ng/dl, were enrolled. The same qualified urologist performed DREs and it was considered normal if there was no palpable induration, nodule or suspicion of malignancy.

Exclusion criteria were patients with urinalysis evidence of acute urinary tract infection (pyuria and bacteriuria), those with a prior diagnosis of prostate cancer and acute prostatitis, an indwelling catheter or previous prostatic surgery of any nature, recent instrumentation of the genitourinary tract (less than 3 months), any form of hormonal manipulation or a history of allergy to Ofloxacin/nitrofurantoin. A total of 152 men were included in the study. Prostate massage and laboratory-specific analyses to rule out prostatitis were not undertaken. Basal total-PSA (t-PSA) and free-PSA (f-PSA) were determined. Percent free PSA was calculated as the ratio of free PSA-to-total PSASamples were assayed in streptavidin coated tubes by using immunometric assay technique (COBAS® INTEGRA 6000, Roche Diagnostics, Switzerland) based on chemiluminescence method. All samples were analysed in the same laboratory to prevent the variations in measurement. A comprehensive internal quality control programme was followed and results were released after calibrating values between mean ±1SD. This internal quality control analysis was performed daily.

Ofloxacin (200mg BID) / Nitrofurantoin (100mg BID) were given orally for 1 week followed by 100mg OD for 3 weeks. t-PSA and f-PSA levels were repeated 4 weeks after therapy. Patients with raised PSA after a course of antibiotics underwent prostate biopsy whereas patients with PSA reductions were followed. Prostatic biopsy was taken with patient in left lateral decubitus position. Under strict aseptic precautions, biopsy gun was introduced per-rectally and 10 – 12 core biopsy was obtained under TRUS guidance. The instrument used for biopsy was BARD® MAX-CORE® Disposable Core Biopsy Instrument (Catalogue Number: MC1820, Gauge size and needle length: 18g (1.2mm) x 20cm (200mm), Length of sample notch: 1.8cm (18mm), Penetration depth: 22mm). Cores obtained from left and right lobes were labelled and sent separately in formalin bottles. Biopsy results were classified as benign or showing cancer

Differences between patients with and without prostate cancer in terms of PSA modifications were analyzed by Student's t test. Comparisons of PSA modifications before and after antibiotic treatment were evaluated by paired t test. ROC curves were used to describe the performance of diagnostics value of PSA modifications. Statistical analysis was done using MedCalc (MedCalc® v 15.4, Belgium) software. A p value less than 0.05 was considered significant.

**Results:**

We studied a total of 152 patients with mean age of 67 ± 6.7 years. The patients were divided into 2 groups. 102 patients were given antibiotics and PSA levels were repeated after 4 weeks. In 50 patients PSA levels were repeated after 4 weeks without antibiotic therapy. 47 out of 102 patients in whom antibiotic therapy was given showed a reduction in repeat PSA levels < 4 ng/ml. (46.07%) In the control group, 12 out of 50 patients had reduction in PSA < 4ng/ml. (24%) ($p<0.001$)

The change in PSA levels in patients with/without antibiotic therapy has been shown in Tables 1, 2.

| **Table 1: Effect on antibiotics on PSA** | | | | |
|---|---|---|---|---|
| n = 102 | | | | |
| | **Pre Antibiotic Therapy** | **Post Antibiotic therapy** | **% Change** | **p value** |
| **t-PSA (ng/ml)** | 6.09 ± 1.34 | 3.84 ± 1.25 | -36.9 | 0.001 |
| **t-PSA (ng/ml)** | 1.82 ± 0.48 | 1.23 ± 0.31 | -32.4 | 0.012 |
| **% f-PSA** | 29.88 | 32.03 | | |

| **Table 2: Change in PSA without antibiotics** | | | | |
|---|---|---|---|---|
| n = 50 | | | | |
| | **Basal levels** | **Repeat Levels after 4 weeks** | **% Change** | **p value** |
| **t-PSA (ng/ml)** | 6.82 ± 1.23 | 5.61 ± 1.36 | -17.7 | 0.124 |
| **f-PSA (ng/ml)** | 1.71 ± 0.36 | 1.54 ± 0.29 | -9.9 | 0.095 |
| **% f-PSA** | 25.07 | 27. 45 | | |

The change in total PSA levels and free PSA in patients on antibiotics was 36.9% and 32.4% respectively. On the other hand the change in patients without antibiotics was only 17.7 and 9.9%.

47 out of 102 (46.07%) had a reduction in PSA levels < 4 ng/ml after antibiotic therapy. Out of the remaining 55 patients who underwent prostate biopsy, 30 (54.54%) patients did not harbor malignancy. 19 out of these patients had chronic prostatitis on histological examination. The comparison of variables pre and post antibiotic therapy in patients undergoing biopsy is depicted in table 3.

| | Table 3: n = 55 | | | | | |
|---|---|---|---|---|---|---|
| | Prostate Cancer (25) | | | Benign (30) | | |
| | Pre Antibiotic Therapy | Post Antibiotic therapy | p value | Pre Antibiotic Therapy | Post Antibiotic therapy | p value |
| t-PSA (ng/ml) | 6.67 ± 1.69 | 5.57 ± 1.62 | 0.14 | 6.12 ± 1.31 | 4.56 ± 1.61 | 0.001 |
| f-PSA (ng/ml) | 1.17 ± 0.43 | 1.04 ± 0.54 | 0.012 | 1.91 ± 0.47 | 1.51 ± 0.47 | 0.092 |
| % f-PSA | 17.54 | 18.6 | | 31.05 | 33 | |

Although mean total PSA (t-PSA) and Free-PSA (f-PSA) decreased after treatment in both groups, this reduction of t-PSA in patients with prostate cancer and f-PSA in patients without prostate cancer were not statistically significant. On the other hand, in patients without prostate cancer mean % f-PSA increased insignificantly after treatment whereas % F – PSA increased in patients with prostate cancer.

Receiver Operating Characteristics (ROC) curve analysis of both parameters (t-PSA and f-PSA) revealed that f-PSA was more sensitive for detection of malignancy (AUC – 0.82 ± 0.15) as compared to t – PSA (AUC – 0.68 ± 0.19)

**Discussion**

PSA has been identified as a gamma-semino protein from the seminal plasma. Wang et al. reported the possibility that PSA might be a tumor marker for prostate cancer and Papsidero et al. applied PSA to the clinical diagnosis of early prostate cancer and the follow- up of prostate cancer patients. (7,8) However, because PSA is a serine protease secreted by prostate epithelial cells as well as primary gastric, mammary gland, and breast cancer tissue, PSA is nonspecific to the prostate. (9) Moreover, the PSA level is increased by prostate cancer as well as by BPH, prostatitis, and other circumstances such as prostate biopsy, DRE, and acute urinary retention. This leads to potentially unnecessary biopsy procedures. Studies have revealed the lack of specificity of PSA measurement as the only biopsy indicator.

Prostate biopsy is generally recommended for men with total PSA greater than 4 ng/ml and palpably normal DRE as the rate of prostatic cancer detection in this population is 20% to 30%. This rate reflects the lack of specificity of PSA and remains a major problem for using PSA to screen for prostate cancer. Prostatic inflammation is thought to be a cause of PSA increase and several studies investigated the relationship between increased serum PSA and asymptomatic prostatic inflammation. (10,11) Some of these studies revealed that subclinical prostatic inflammation contributes to PSA increase in patients without clinically detectable prostate

cancer. In contrast, some others reported no significant influence of prostatic inflammation on serum PSA. (12,13)

Nadler et al. concluded that men with increased PSA and chronic prostatitis should be treated as one would treat any other patient screened for prostate cancer with an increased PSA. (14) Although disagreement exists with respect to the effect of prostatic inflammation on serum PSA, in daily practice antibiotics are often prescribed for men with newly increased PSA on the presumption that the patient has subclinical infectious prostatitis. (15)

Several studies regarding this issue used expressed prostatic secretion (EPS) or first urine following the prostatic massage (VB3) to demonstrate prostatic inflammation. (11) In our study we did not use EPS or VB3, as in daily practice many urologist prescribe antibiotics for men with a newly increased PSA.

In our study, antibiotic treatment resulted in reduction in PSA. This reduction in PSA was 36.9 % in our study and it has been reported as 23.4 to 30 % in other studies. (16) Although this reduction may partly be due to antibacterial therapy of prostate inflammation, one must also remember that a significant degree of biological variation can be observed in PSA in normal men. Komatsu and colleagues observed a physiological fluctuation in PSA from 10% to 20% in a screening population. (17)

Bozeman et al reported that in 44 of their 95 patients (46.3%) with PSA greater than 4 ng/ml, serum PSA decreased to less than 4 ng/ml after antibiotic treatment and these 44 patients were considered to have no clear indication for biopsy. (16) Similarly in our study PSA reduction to less 4 ng/ml was seen in 47/102 patients (46.07%). Karazanashvili and Managadze detected no cancer among their 37 patients in whom PSA concentration decreased to less than the 4 ng/ml level after antibiotic treatment. (18) In the study by Kaygısız et al PSA values decreased to less than 4 ng/ml after antibiotic therapy in 18 of 48 patients (37.5%) and 10 of these 18 patients underwent biopsy.10 None of these 10 patients had prostate cancer on biopsy. (11) In the study by Kobayashi et al the treatment response was a PSA decrease greater than 20% from baseline and 15 patients had such a response. Of these 15 patient, 9 underwent biopsy and had no cancer. The authors reported that watchful observation may be an optional tool for patients showing a significant PSA decrease following antibiotic treatment. (19)

It has been reported that % f-PSA will increase after prostatitis therapy. (20) Kaygısız et al also reported significantly reduced f-PSA and significantly increased % f-PSA after antibiotic therapy. (11) Like mean total PSA, in our study mean f-PSA also decreased after treatment.

Baltaci and colleagues observed that antibiotic therapy will decrease serum total prostate specific antigen, however it will not decrease the risk of prostate cancer even if the prostate specific antigen decreases to less than 4 ng/ml. Therefore, prescribing antibiotics for asymptomatic men with a newly increased prostate specific antigen may not be an appropriate method of management according to their study. (21)

Increasing drug resistance to commonly used antibiotics is an important point to address if one aims to evaluate the benefits of empirical antibiotic treatment. Several papers were published in last years which suggest that fluoroquinolones are not recommended for the first line or empirical therapy because of concerns regarding bacterial drug resistance. Data shows that patients with recent exposure to fluoroquinolones are more likely to develop sepsis caused by fluoroquinolone-resistant E. Coli after TRUS guided prostate biopsy. We did not observe any major biopsy-related complication including sepsis in our patients and we think that the search for the most appropriate antibiotic to be used in prostatitis and prostate biopsy patients should be continued.

**Conclusions:**

Empirical antibiotic therapy significantly reduces PSA levels in males with clinically benign prostate with borderline elevated PSA (Between 4 – 10 ng/ml). A repeated value of PSA after one month course of antibiotics will help to select patients requiring prostate biopsy. Unnecessary prostate biopsies in patients with borderline elevated PSA can thus be avoided. Indian males may have increased incidence of subclinical prostatitis.

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