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# Pattern of Bacterial Isolates and Antimicrobial Susceptibility of Urine Culture in Men with Chronic Bacterial Prostatitis and Levels PSA Before and After Treatment

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## Abstract

**Objective:** To study the influence of combined antibiotic therapy on levels PSA in "grey zone" for patients with chronic bacterial prostatitis without signs prostate cancer.

**Patients and Methods:** In our study was presented 125 patients in aged 30-83 years with diagnosis of chronic bacterial prostatitis. We performed digital rectal examination, urine culture, transrectal ultrasound investigation of prostate, PSA analysis before and after antibiotic treatment and antimicrobial susceptibility testing. Criteria for inclusion in the trial were digital rectal examination without suspicion of urological cancers, absence of history of intravesical instrumentation and biopsy of prostate , values PSA in range from 4,0 to 11 ng/ml, symptoms of chronic bacterial prostatitis, absence of abnormalities both upper and lower urinary tracts. For evaluation changes PSA before and after treatment we divided all patients on five groups with different regimen antimicrobial agents in according to results antibiotic susceptibility test.

**Results:** A total of 125 patients with chronic bacterial prostatitis and high level of PSA were estimated by culture of urine for determination spectrum of isolated microorganisms and pattern susceptibility to antimicrobial agents. The average (mean ± standard deviation) age of all men in this study was 59.6 ± 12.7 years. The non-clostridial, non-spore forming anaerobic microorganisms, the taxonomic structure of chronic bacterial prostatitis were more often represented by Peptococcus spp (37,8%), Propionibacterium spp (36%), Eubacterium spp (47,2%), Veillonella spp (24,4%) with average level of bacteriuria Log 1,5 CFU/ml , Log 2,6 CFU/ml, Log 3,2 CFU/ml, Log 1,9 CFU/ml, respectively. In the group of cougulase-negative staphylococci predominated S.epidermidis (29,5%), S.haemalyticus (20,8%), S.aureus (12%) with mean level of bacteriuria Log 1,5 CFU/ml , Log 1,9 CFU/ml, Log 1,8 CFU/ml , respectively. In five groups patients which divided in depending from chosen regimen of combined antibiotic treatment in according results susceptibility testing to antimicrobial agents, the changes of level PSA were following : in I group (25 patients) 7,34 ± 2,6 , 95% CI [6.27 - 8.41] before and 2.26 ± 1.02 , 95% CI [1.84 - 2.68] after treatment, administration ; in II group (22 patients) 7.20 ± 1.76 ,95% CI (6.42 - 7.98) before and 1.8 ± 0.84 , 95% CI (1.43 - 2.17) after; in III groups (26 patients) 7.05 ± 1.35, 95% CI (6.5 - 7.6) before and 1.57 ± 0.89 , 95% CI (1.21 - 1.93) after treatment ; in IV group (24 patients) 7.51 ± 1.39 ,95% CI (6.92 - 8.1) before and 1.45 ± 0.93 , 95% CI (1.29 - 1.61) after treatment ; in V group (28 patients) 7.11 ± 1.16, 95% CI (6.66 - 7.56) before and 1.48 ± 0.86 95% CI (1.15 - 1.81) after treatment . After 3 and 6 months we performed the repeat measurement of level PSA and there was no any elevation higher than > 4 ng/ ml.

**Conclusions:** In patients with baseline level PSA in range 4-10 ng/ml provided that possibility of PCa is excluded by digital rectal examination and transrectal ultrasound investigation, administration of combined antibacterial therapy with fluoroquinolones in account of pattern of isolated microorganisms and results susceptibility to antibiotic can lead to significant decrease level PSA and microbiological eradication pathogens and to avoid unnecessary biopsies of prostate.

**Key words:** Chronic Bacterial Prostatitis; PSA; Antibiotic Treatment; Biopsy of Prostate

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## Abbreviations

CBP-Chronic Bacterial Prostatitis; PCA- Prostate Cancer; PSA- Prostate Specific Antigen; TRUS-Transrectal Ultrasound Investigation; DRE- Digital Rectal Examination

## Introduction

Chronic bacterial prostatitis is a troublesome disease showing an overall clinical 28 and microbiological response to fluoroquinolones, the antibiotics of choice, of only 60% [1]. Prostatitis exhibits a bimodal peak of incidence, with men between 20 and 40 years of age or older than 60 years afflicted most commonly [2]. Despite progress in the management of chronic bacterial prostatitis, many cases are undertreated and a significant number relapse .The reasons are practically unknown and include host, bacterial, and treatment related factors. While patients at increased risk for CBP recurrence and local (organ-specific) conditions have been clearly specified, bacterial- and treatment-related factors remain relatively unclarified [3]. In terms of prevalence of chronic prostatitis is in line with such diseases as diabetes and ischemic disease heart, and has a tremendous impact on the quality of life of the patient. Thus, the fact that chronic prostatitis is one of the most pressing problems of urology all over the world, not is in doubt [4]. The prevalence of CBP is very low, with only 5–10% of all prostatitis cases suffering from this condition. One of the characteristics of this prostatitis is that it is often accompanied by urogenital infection. The pathogens responsible for this syndrome includes gram-positive and gram-negative bacteria, of which, gram-positive often occur transiently, and pathogens that result in complex urogenital tract infections [5]. The major cause for inducing acute bacterial prostatitis is Escherichia coli, which is accompanied by different kinds of other microorganisms such as Pseudomonas aeruginosa, Enterococcus, Proteus, Klebsiella, Enterobacter, and Serratia species [6]. Approximately 10% of men suffering an episode of acute bacterial prostatitis continue to suffer chronic bacterial prostatitis and a further 10% progress to chronic prostatitis/chronic pelvic pain syndrome [7]. Several factors have been associated with chronic prostatitis, including smoking, high caloric diet with low consumption of fruit and vegetables, and slow digestion, although the pathogenesis and aetiopathogenic mechanisms of this disease have yet to be fully elucidated. Clearly, by definition both acute and chronic bacterial prostatitis are caused by prostatic infection, but proper and effective treatment of both conditions requires accurate diagnosis. There is still debate, however, over the pathogenic causes of Category III and IV prostatitis syndromes, the aetiology of which may be immunological, neurological, psychosomatic or anatomical in nature [8]. The pathogens associated with chronic bacterial prostatitis are essentially the common uropathogens, including Escherichia coli and Klebsiella spp [9]. Konstantinos Stamatiou and Drosos E. Karageorgopoulos in one study showed that Enterococcus faecalis and Proteus were susceptible to all antimicrobials in about half of the isolates (54.5 and 50%, respectively), raises questions about the judicious use of antimicrobials, while the relatively high proportion of Gram-positive bacteria (35.7%) in positive cultures [9]. Habits and sexual behaviors suggested to predispose to chronic prostatitis were documented in less than half of the cases in this study indicating thus that other factors than those traditionally associated with chronic prostatitis may predispose to its development [10]. The question of the role of gram-positive bacteria, as well as non-clostridial anaerobes has been debated for several decades and still remains open [11]. A comparison of the clinical details in a series of acute bacterial prostatitis after transrectal prostate biopsy described a higher incidence of sepsis and antibiotic-resistant bacteria in the post biopsy prostatitis group [12]. The low detection rate of prostate biopsy is determined by the lack of specificity of PSA that causes challenging diagnostic problems for urologists, additional morbidity and anxiety for patients and higher costs for health systems. Histological inflammation of the prostate is a very common finding in biopsy specimens of patients with an elevated PSA and no clinical evidence of prostatitis. Inflammation of the prostate is a recognized cause of PSA elevation in absence of PCa. Prostatic inflammation lead to a deterioration of the natural anatomic and physiologic barriers between the prostatic milieu and the bloodstream determining increased PSA levels [13]. Elevated values of serum PSA are not pathognomonic for prostate cancer but they can be found in various clinical conditions, including inflammation and infection. In men with an increasing PSA without clinical evidence of infection, a common clinical approach is to empirically prescribe antibiotics and subsequently re-dose the PSA. Until today, several researchers have examined the impact of empiric antibiotics therapy in patients with an increased PSA, in order to find a balanced costs/effective therapy to avoid unnecessary prostate biopsies and to decrease patient discomfort and morbidity from biopsy [14]. Prostate cancer is determined in only 34% of biopsies performed on the basis of PSA elevation and in 20-30% in patients with normal DRE and PSA values of between 4 and 10ng/mL. Therefore, there is a high level of unnecessary biopsies, particularly in this group [15]. However, increased PSA is also associated with conditions other than cancer, such as prostate inflammation, and prostatitis treatment has been shown to decrease PSA in a significant percent of such patients. Treatment of prostatitis with an antimicrobial and/or anti-inflammatory medication may provide a cost-effective approach to decrease the number of negative biopsies [16,17]. Our study will be dedicated for retrospective analysis of bacterial isolates in urine culture in patients with chronic bacterial prostatitis and levels PSA before and after antimicrobial treatment indicating on the important role investigation of pattern microorganisms in urine culture and levels PSA before antibiotic therapy in preventing unnecessary biopsy prostate in case of elevation in the range 4-10 ng/ml.

## Materials and Methods

### Study participants and criteria inclusion

In our study was presented 125 patients in aged 30-83 years with diagnosis of chronic bacterial prostatitis. We performed digital rectal examination, urine culture, transrectal ultrasound investigation of prostate, PSA analysis before and after antibiotic treatment and antimicrobial susceptibility testing. Criteria for inclusion in the trial were digital rectal examination without suspicion of urological cancers, absence of history of intravesical

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instrumentation and biopsy of prostate , values PSA in range from 4,0 to 11 ng/ml, symptoms of chronic bacterial prostatitis, absence of abnormalities both upper and lower urinary tracts .

## Microbiological assessment and PSA analysis

We collected midstream of urine from patients with chronic bacterial prostatitis for culture investigation. It was used for determination of taxonomic structure and quantity of isolated bacterial uropathogens. In order that to determine the quantity and type bacteria from each breeding produced seed (0.1 ml each) on nutrient media: Endo, High Hrom selective agar for Candida fungi, High Hrom selective agar for enterococci, youlk soult agar , blood agar, prepared on the basis of Müller-Hinton agar with the addition of sheep erythrocytes. For non-clostridial bacteria were used: the Müller-Hinton environment with the addition of sheep erythrocytes, Blaurocca, agar and Shedler. The crops were incubated in aerobic and anaerobic (10% CO2, 10% H2, 80% N2) conditions cultivation in temperature 37°C. Identification of microorganisms carried out by morphological, tinctorial, cultural and biochemical traits. Midstream urine was obtained for urinalysis and culture using methods to isolate pathogens at ≥ 50 cfu/mL. The antibiotic susceptibility testing was performed by the Kirby—Bauer's Disk Diffusion method in accordance with the CLSI guidelines. Susceptibility of isolated microorganisms determined to 35 antibiotics of different groups in aerobic and anaerobic conditions of cultivation. In our study PSA analysis was used for determination baseline level, excluding patients with values more than 11 ng/ml with suspicion on prostate cancer and also as a control of effectiveness of antibiotic treatment. For evaluation changes PSA before and after treatment we divided all patients on five groups with different regimen antimicrobial agents in according to results antibiotic susceptibility test.

## Digital rectal examination and transrectal ultrasound investigation

All patients with chronic bacterial prostatitis underwent TRUS investigation with 10-MHz biconvex transducer in regimen grey scale and colour Doppler for evaluation the condition of parenchyma prostate and excluding the patients with findings of prostate cancer such as massive calcification of parenchyma of prostate and disorganization of the vascular pattern with additional thickened and crimped vessels, presence of hypoechogenic tumor nodes in different parts of parenchyma prostate. Digital rectal examination of prostate was performed for all patients with chronic bacterial prostatitis with aim to rule out patients with any nodes which are suspicious for prostate cancer.

## Statistic analysis

All data are expressed as mean± standard deviation (SD) with 95% confidence interval. Parametric Student's t test and non-parametric Mann-Whitney U test and $\chi 2$ test were performed for the differences in the mean ages, serum PSA level, prevalence

**Table 1:** The prevalence and average level bacteriuria of isolated microorganisms in study population of men

| Isolated microorganism | Decimal logarithm of average level bacteriuria of isolated microorganism | Percentage bacteria from total number of patients (%) |
|---|---|---|
| *Corynebacterium spp* | 1,8 | 44,8 |
| *Enterococcus spp* | 3,5 | 40,8 |
| *Staphylococcus epidermidis* | 1,5 | 29,5 |
| *Escherichia coli* | 4,0 | 44 |
| *Veilonella spp* | 1,9 | 24,4 |
| *Eubacterium spp* | 3,2 | 47,2 |
| *Peptococcus spp* | 1,5 | 37,6 |
| *Propionibacterium spp* | 2,6 | 36 |
| *Prevotella spp* | 1,5 | 3,2 |
| *Staphylococcus warneri* | 1,0 | 2,4 |
| *Staphylococcus aureus* | 1,8 | 12 |
| *Klebsiella spp* | 3,2 | 12,8 |
| *Staphylococcus lentus* | 1,5 | 7,2 |
| *Bacteroides spp* | 2,7 | 5,6 |
| *Bacillus spp* | 1,0 | 1,6 |
| *Megaspherae spp* | 1,7 | 4,8 |
| *Staphylococcus haemalyticus* | 1,9 | 20,8 |
| *Pseudomonas aeruginosa* | 3,3 | 2,4 |
| *Proteus spp* | 2,0 | 3,2 |
| *Peptostreptococcus spp* | 2,1 | 10,4 |
| *Staphylococcus saprophyticus* | 1,2 | 6,4 |
| *Streptococcus spp* | 2,0 | 2,4 |
| *Fusobacterium spp* | 2,2 | 4,8 |
| *Aeromonas hydrophila* | 2,3 | 2,4 |
| *Morganella morganii* | 2,5 | 1,6 |
| *Burkholderia sepacia* | 1,2 | 3,2 |
| *Mobiluncus spp* | 2,2 | 4 |

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each kind of bacteria in urine culture between the patients. Two-sided null hypotheses of no difference were rejected if p values were less than 0.05. All analyses were performed using the SPSS software version 12.0.

## Results

### Microbiological results

A total of 125 patients with chronic bacterial prostatitis and high level of PSA were estimated by culture of urine for determination spectrum of isolated microorganisms and pattern susceptibility to antimicrobial agents. The average (mean± standard deviation) age of all men in this study was 59.6 ± 12.7 years. Table 1 shows the prevalence types of the isolated microorganisms and mean level of bacteriuria for each uropathogen. In all patients the urine had the mixed bacterial infection and amongst of them predominated non-clostridial anaerobes and coagulase-negative staphylococci.

The non-clostridial, non-spore forming anaerobic microorganisms, the taxonomic structure of chronic bacterial prostatitis were more often represented by Peptococcus spp (37,8%), Propionibacterium spp (36%), Eubacterium spp (47,2%), Veillonella spp (24,4%) with average level of bacteriuria Log 1,5 CFU/ml , Log 2,6 CFU/ml, Log 3,2 CFU/ml, Log 1,9 CFU/ml, respectively. In the group of cougulase-negative staphylococci predominated S.epidermidis (29,5%), S.haemalyticus (20,8%), S.aureus (12%) with mean level of bacteriuria Log 1,5 CFU/ml , Log 1,9 CFU/ml, Log 1,8 CFU/ml , respectively. The family Enterobacteriaceae was presented by E.coli (44%) and Enterococcus spp (44,8%) with mean level bacteriuria Log 4,0 CFU/ml and Log 3,5 CFU/ ml, respectively. Figure 1 shows the prevalence of isolated bacteria from urine in patients with chronic bacterial prostatitis .

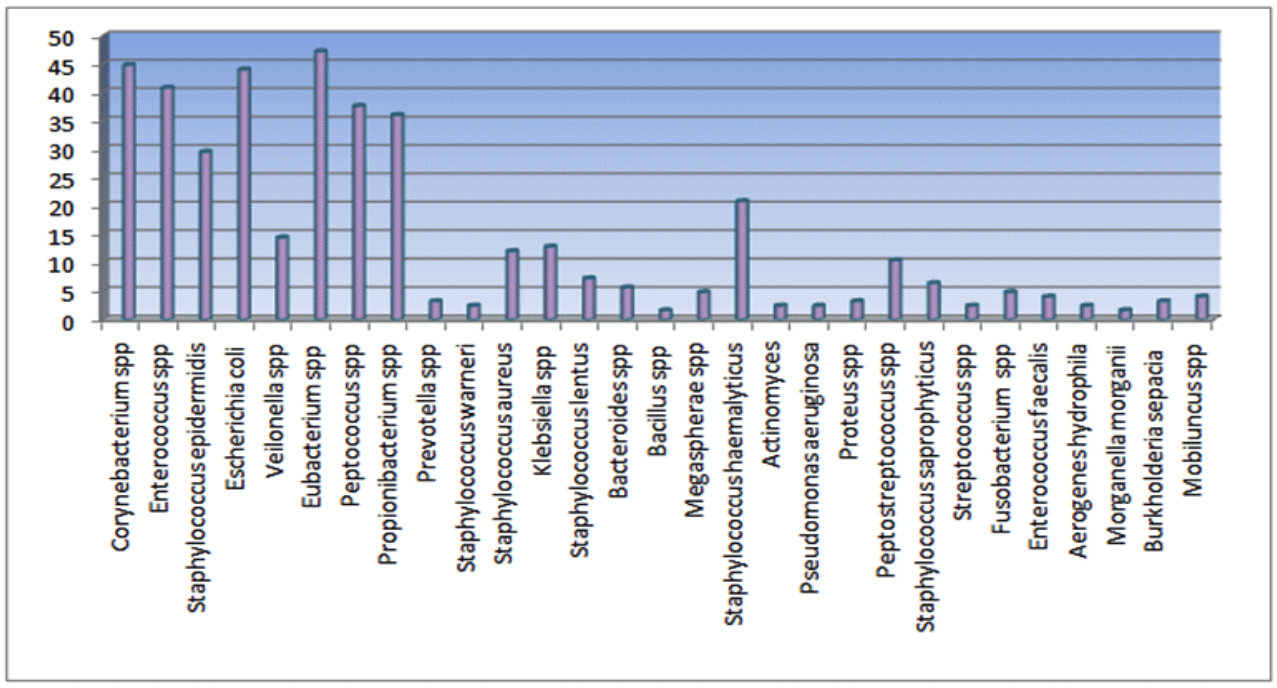


**Figure 1:**Prevalence of isolated bacteria from urine in patients with chronic bacterial prostatitis (%)

A purely nonclostridial anaerobic infection without the participation of aerobic bacteria is rare. More often associations of 2-3 species of anaerobes with various representatives of aerobes are revealed. The most frequent combination of non-clostridial anaerobes was observed with coagulase-negative staphylococci or Corynebacterium spp. The etiological structure of isolated microorganisms were also presented by different gram-negative rods such as Klebsiella spp(12,8%), Bacteroides spp(5,6%),Mobiluncus spp (4%), Burkholderia sepacia(3.2%), Prevotella spp (3,2%), Aeromonas hydrophila(2,4%), Morganella morganii(1.6%) with mean level bacteriuria Log 3,2 CFU/ml, Log 2,7 CFU/ml, Log 2,2 CFU/ml, Log 1,2 CFU/ml, Log 1,5 CFU/ml, Log 2,3 CFU/ml, Log 2,5 CFU/ml , respectively.

### Results of antibiotic susceptibility testing

A tIn our study susceptibility noted for following groups antibiotics: carbapenems, fluoroquinolones, aminoglycosids, cephalosporins, nitrofurans ,macrolids and protected penicillins . Amongst of them most active against bacterial pathogens isolated from urine in patients with chronic bacterial prostatitis were carbapenems, fluoroquinolones and cephalosporins in 90%, 84% and 78% cases, respectively. The lowest sensitivity was in nitrofurans and macrolids in 32% and 45% cases, respectively. Above mentioned results are shown in Figure 2.

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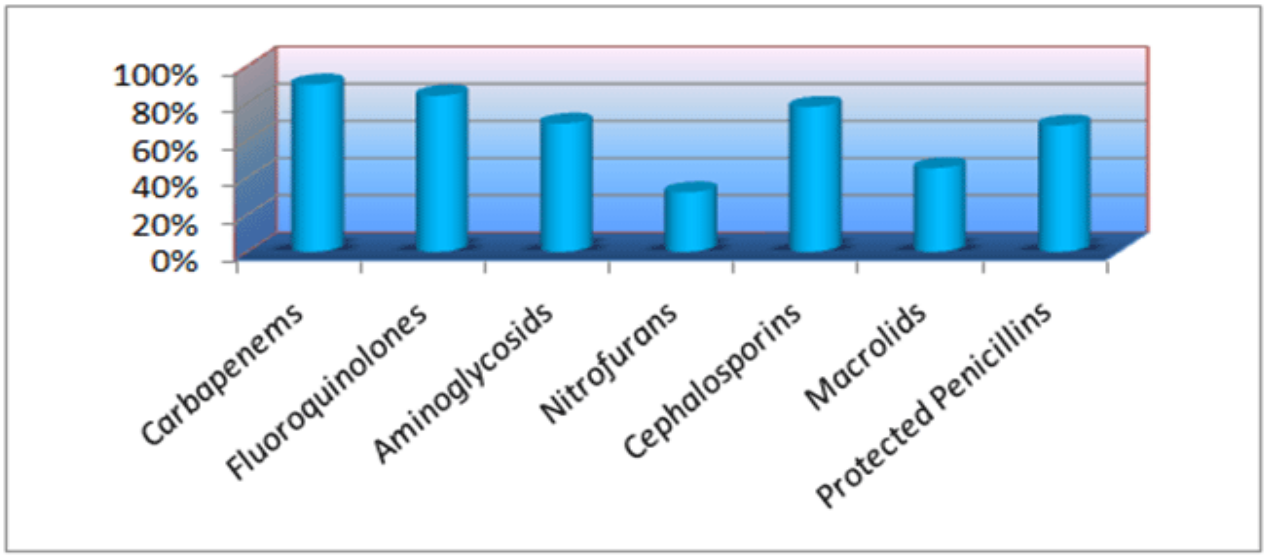


**Figure 2:** Susceptibility of isolated microorganisms to antimicrobial agents

## PSA values after treatment in depending of chosen regimen combined antibiotic therapy and TRUS findings

In five groups patients which divided in depending from chosen regimen of combined antibiotic treatment in according results susceptibility testing to antimicrobial agents, the changes of level PSA were following : in I group (25 patients) 7,34± 2,6 , 95% CI [6.27-8.41] before and 2.26± 1.02 , 95% CI [1.84-2.68] after administration Imipenem 500 mg IM bid for 7 days + Ciprofloxacin 500 mg per os bid for 10 days ; in II group (22 patients) 7.20±1.76 ,95% CI (6.42-7.98) before and 1.8± 0.84 , 95% CI (1.43-2.17) after administration Levofloxacin 500 mg per os once a day 14 days + Cefixime 400 mg per os once a day 5 days ; in III groups (26 patients) 7.05±1.35, 95% CI (6.5-7.6) before and 1.57± 0.89 , 95% CI (1.21-1.93) after administration Amikacin 500 mg IM bid 7 days + Cefixime 400 mg per os once a day 5 days ; in IV group (24 patients) 7.51± 1.39 ,95% CI (6.92-8.1) before and 1.45±0.93 , 95% CI (1.29-1.61) after administration Amoxicillin/clavulanic acid 500 mg bid 7 days + Levofloxacin

**Table 2:** Levels of PSA before and after treatment and regimens of used antimicrobial agents

| Group of patients | Regimen of antibiotic treatment | Level of PSA before treatment Mean± SD, 95% CI | Level of PSA after treatment Mean ± SD, 95% | P value |
|---|---|---|---|---|
| **I (25)** | Imipenem 500 mg IM bid 7 days + Ciprofloxacin 500 mg per os bid 10 days | 7,34± 2,6<br>95% CI (6.27-8.41) | 2.26± 1.02<br>95% CI (1.84-2.68) | *< 0.05* |
| **II (22)** | Levofloxacin 500 mg per os once a day 14 days + Cefixime 400 mg per os once a day 5 days | 7.20±1.76<br>95% CI (6.42-7.98) | 1.8± 0.84<br>95% CI (1.43-2.17) | *< 0.05* |
| **III ( 26)** | Amikacin 500 mg IM bid 7 days + Cefixime 400 mg per os once a day 5 days | 7.05± 1.35<br>95% CI (6.5-7.6) | 1.57± 0.89<br>95% Cl (1.21-1.93) | *< 0.05* |
| **IV (24)** | Amoxicillin/clavulanic acid 500 mg bid 7 days + Levofloxacin 500 mg once a day per os 14 days | 7.51± 1.39<br>95% CI (6.92-8.1) | 1.45 ±0.93<br>95% Cl (1.29-1.61) | *< 0.05* |
| **V (28)** | Imipenem 500 mg IM bid 7 days + Cefixime 400 mg per os once a day 5 days | 7.11 ±1.16<br>95% CI (6.65-7.56) | 1.48± 0.86<br>95% CI (1.15-1.81) | *< 0.05* |

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500 mg once a day per os 14 days; in V group (28 patients) 7.11 ±1.16, 95% CI (6.66-7.56) before and 1.48± 0.86 95% CI (1.15-1.81) after administration Imipenem 500 mg IM bid 7 days + Cefixime 400 mg per os once a day 5 days. Above mentioned results of changes PSA level before and after antibiotic treatment are shown in Table 2.

After treatment repeat urine culture did not show any uropathogens indicating on microbiological eradication in all 5 groups patients with different regimen of treatment. In all patients with chronic bacterial prostatitis and urine culture positive for bacterial mixed infection transrectal ultrasound investigation of prostate with colour Doppler showed typical changes such as diffuse or local enforcement of blood flow in the branches of prostatic arteries (urethral and capsular), diffuse or local decrease of echogenecity of parenchyma of prostate, sites of fibrosis with impoverishment of vascular pattern (figure 3). After 3 and 6 months we performed the repeat measurement of level PSA and there was no any elevation higher than > 4 ng/ ml .

In our study the patients with level PSA > 11 ng/ml which did not change after treatment and suspicious data on prostate cancer during transrectal ultrasound investigation and digital rectal examination were excluded.

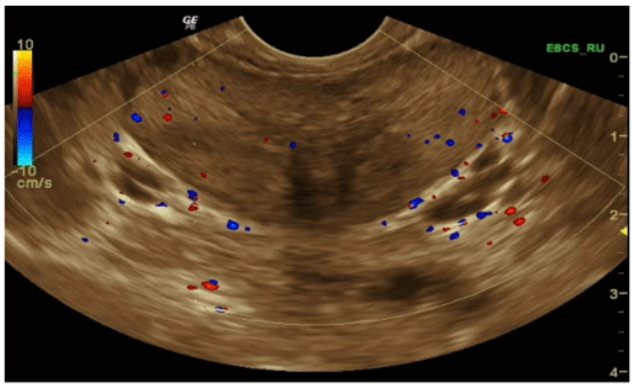


**Figure 3:** Data of transrectal ultrasound investigation of prostate in patient with chronic bacterial prostatitis

## Discussion

This study demonstrated that administration of antibiotic therapy can lead to subsequent decrease level PSA for all examined regimens of antibiotics in according to results of test for susceptibility to antibiotic. There was significant decrease of level PSA after administration of antimicrobial agents in all 5 groups with different regimen of antimicrobial treatment. Schaeffer et al in one study demonstrated decrease the level PSA to normal range after administration fluoroquinolones and microbiological eradication. In according to our results more preferably to describe combined therapy with fluoroquinolones due to their known pharmacokinetic characteristic. In concerning to results of urine culture the etiological structure of isolated microorganisms in urine was presented by mixed bacterial infection and amongst of them predominated non-clostridial anaerobes and coagulase-negative staphylococci. The representatives of Enterobacteriaceae and Corynebacterium were also the most common uropathogens in study population of men with chronic bacterial prostatitis with prevalence for E.coli (44%), Enterococcus spp(40,8%) and Corynebacterium spp (44,8%), respectively. With PSA routine screening, the number of patients diagnosed with PSA in the ''gray zone'' has been increasing rapidly. However, due to conditions such as cancer, inflammation and benign hyperplasia with overlapping low PSA levels, the positive rate hovered around approximately 20% [18]. Agnihotri et al, had higher cancer detection rate overall (57.5%) and also for serum PSA ranges of (4-10) and (10-20) ng/ml, which was 43.35% and 36.57% respectively, irrespective of DRE findings. They had suggested raising the serum PSA cut off in symptomatic men with negative DRE for TRUS biopsy in India to 5.4 ng/ml to avoid 10% unnecessary biopsies [19].

Our results showed that administration combined antibiotic therapy decreased the value PSA up to normal range in all study groups. The most pronounced decline was noted in IV and V groups. In literature there are a lot of studies about of screening prostate cancer in patients who have the values of level PSA in the ''gray zone'' and some of them reported that PCa detection rate was 25-35% but in clinical practice there are situation when biopsy of prostate is described based on value PSA in range 4-10 ng/ml and after that results of biopsy showed in all specimens chronic inflammation without signs of prostate cancer thereby aggravating the inflammatory process without antibiotic prophylaxis before the procedure.

In our study we emphasized about of necessity to examine etiological structure of isolated pathogens in urine culture with subsequent susceptibility antibiotic testing and periodical measurement level PSA and using other urinary biomarkers such as Prostate Index Health, prostate cancer antigen 3, TMPRESS (transmembrane protease, serine 2) during follow-up in order that to avoid unnecessary biopsy and not to miss risk of development of PCa in further.

## Conclusions

In patients with baseline level PSA in range 4-10 ng/ml provided that possibility of prostate cancer is excluded by digital rectal examination and transrectal ultrasound investigation, administration of combined antibacterial therapy with fluoroquinolones in account of pattern of isolated microorganisms and results susceptibility to antibiotic can lead to significant decrease level PSA and microbiological eradication pathogens and to avoid unnecessary biopsies of prostate .

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