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Infections

Seminal Microflora in Asymptomatic Inflammatory (NIH IV Category) Prostatitis

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Abstract

Objectives: To prove the need for the quantitative full-microflora semen analysis for determining the role of microorganisms in the etiology of asymptomatic inflammatory prostatitis, and to correlate the seminal white blood cell (WBC) counts with interleukin 6 (IL-6) levels.

Methods: Thirty-seven men with asymptomatic inflammatory (National Institutes of Health [NIH] IV category) prostatitis and 32 controls were investigated by using routine semen analysis, IL-6 levels of seminal plasma, and quantitative microbiological analysis of semen.

Results: The IL-6 concentration in seminal plasma was significantly higher in NIH IV category prostatitis patients than in the controls, and was in good correlation with the WBC count in semen ($r = 0.74$, $p < 0.001$). In most of the specimens, the counts of anaerobic microorganisms were equal to or outnumbered the aerobic ones. One to eight different microorganisms could be found in any particular semen sample, and the total concentration of microorganisms ranged from 2.0 to 7.5 \log_{10} CFU/ml. Both parameters were significantly higher in NIH IV category prostatitis patients than in controls (median: 4.8 vs. 3.9 \log_{10} CFU for total concentration, $p < 0.001$; median: 5 vs. 3 for number of different species, $p = 0.004$).

Conclusions: Unlike the controls the NIH IV category prostatitis patients harbour abundant polymicrobial microbiocenosis in their semen, containing anaerobic, microaerophilic and aerobic bacteria. Detection of IL-6 in seminal plasma serves as an additional tool for diagnosing NIH IV category prostatitis.

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1. Introduction

The new prostatitis classification created in 1995 by the National Institutes of Health (NIH) includes

category IV defined as asymptomatic inflammatory prostatitis [1]. This condition is characterized by the presence of inflammatory cells in seminal fluid, expressed prostatic secretions, or

prostate biopsies, and is typically found incidentally.

Leukocytes (white blood cells [WBCs]) are present throughout the male reproductive tract and can be found in low count in almost every human ejaculate. They are believed to play a role in immunosurveillance and phagocytic clearance of abnormal sperm [2]. At the same time, the origin and meaning of increased leukocyte infiltration in semen, termed “leukocytospermia,” that characterizes the NIH IV category prostatitis patients is the subject of controversy. The World Health Organization (WHO) currently defines *leukocytospermia* as the presence of peroxidase-positive leukocytes in concentration of >1 M per ml of semen [3]. However, according to our previous study results [4] as well as the results of some other studies [5–8], this limit probably needs to be lowered. Though asymptomatic, the increased leukocyte count in semen may not be safe for reproductive function, since it has been associated with a significant decrease in sperm motility, increase in oxidative stress levels, and DNA damage [9–12].

While many investigators have studied symptomatic prostatitis, little research has been done with regard to asymptomatic prostatitis. The latter is thought to be associated with subclinical genital tract infection, yet it usually remains unproved. In most of these patients (up to 80%), pathogenic bacteria cannot be cultured from the prostate-specific specimens in significant numbers, and no correlation between these microorganisms and raised leukocytes can be found [13–18]. At the same time, the microbiologic studies in case of leukocytospermia are scarce and have included anaerobic bacteria in only rare cases [8,14]. However, since routine (aerobic) bacteriologic analysis cannot reveal the full complexity of seminal fluid

microbiocenosis, advanced methods should be introduced.

Some previous studies have also indicated the association of proinflammatory cytokines like IL-6 in seminal plasma with seminal leukocytes, as well as with some clinically relevant parameters of semen quality, but not with the results of semen cultures [19,20].

Our aim was to prove the need for the quantitative full-microflora semen analysis to determine the role of microorganisms in the etiology of asymptomatic inflammatory prostatitis. In addition, we aimed to correlate the seminal WBC counts with the IL-6 levels.

2. Material and methods

2.1. Study group

The study was carried out at Tartu University Hospital. The study group included 69 men who participated in the prospective study of the etiopathogenesis of chronic prostatitis. These men consulted a physician because of infertility of the couple or prophylactic purposes. None of the study subjects presented any clinically relevant symptoms of chronic prostatitis/chronic pelvic pain syndrome. Exclusion criteria were stated according to the suggestion of the NIH Workshop on Chronic Prostatitis in Bethesda, MD, USA, 1995 [21]. None of the patients had received antimicrobial therapy within 3 months. All men gave consent for the additional microbiologic studies of their semen.

Of these men, 37 had significant number of leukocytes (>0.2 M per ml) in their semen [4]; therefore, NIH IV category prostatitis (asymptomatic inflammatory prostatitis) was diagnosed in them according to the NIH Classification of the Prostatitis Syndromes [1]. The remaining 32 men had an insignificant number of leukocytes in their semen (<0.2 M per ml); therefore, they served as a control group for this study, as well as for our previous study described elsewhere [22]. The

Table 1 – Clinical and semen parameters of the NIH IV category prostatitis patients and controls

	NIH IV category prostatitis patients (n = 37)	Controls (n = 32)
	Mean ± SE	Mean ± SE
Age (yr)	26.4 ± 1.09	28.7 ± 0.65
Period of abstinence (d)	4.4 ± 0.46	4.2 ± 0.26
Semen volume (ml)	3.8 ± 0.24	3.8 ± 0.28
Sperm concentration (million/ml)	58.9 ± 9.34	48.2 ± 8.97
Total sperm count (million)	217.9 ± 34.1	178.0 ± 30.9
A+B motility (%)	41.8 ± 2.72	42.9 ± 2.65
Morphologically normal sperm (%) [*]	4.4 ± 0.8	4.6 ± 0.7
Leukocytospermia (million/ml)	1.719 ± 0.356 [†]	0.005 ± 0.002 [†]
IL-6 (pg/ml) [†]	127.1 ± 48.1 [†]	11.8 ± 2.6 [†]

IL-6: interleukin 6; NIH: National Institutes of Health.

^{*} Indicated parameters were available for 24 men of prostatitis group.

[†] $p < 0.001$ (Mann-Whitney rank sum test).

subjects' age, basic clinical parameters, and semen parameters are shown in Table 1.

2.2. Samples

Semen samples were collected by patients after they washed the glans penis with soap and water, and urinated. The samples were obtained by masturbation and ejaculated into a sterile collection tube in a private room near the laboratories. After ejaculation, the semen was incubated at 37 °C for 25 to 45 minutes for liquefaction. The samples were transported to the microbiology laboratory (located near the Andrology Centre) immediately and processed within 1 hour.

2.3. Basic semen parameters

The analysis of semen was performed according to WHO guidelines [3]. Semen volume was estimated by weighing the collection tube with the semen sample and subsequently subtracting the predetermined weight of the empty tube (assumption: 1 g = 1 ml). Motility was assessed to report the number of motile spermatozoa (WHO motility classes A+B+C). Sperm concentration was assessed with the use of the improved Neubauer haemocytometers, and finally smears for morphology assessment were made. Morphology of spermatozoa was evaluated according to strict criteria by Menkveld et al. [23] and NAFA suggestions [24], with the lowest limit of normal morphology set at 5% of all spermatozoa. Total sperm count was calculated by multiplying semen volume by sperm concentration.

2.4. Cytologic analysis

Semen smears were made for detecting WBCs. The smears were air dried, Bryan-Leishman stained, and examined with the use of oil immersion microscopy (magnification: $\times 1000$) by an experienced microscopist. The WBC concentration in semen was calculated by using the known sperm concentration (as $10^6/\text{ml}^{-1}$) according to the following formula:

$$[\text{WBCs}] = \frac{\text{number of WBCs counted} \times \text{number of sperm counted}}{\text{semen sperm concentration}}$$

One hundred round cells were counted twice, and their mean value was registered.

2.5. Detection of IL-6

Interleukin-6 levels of seminal plasma were measured with the use of the Immulite automated chemiluminescence immunoassay analyzer (Immulite DPC, Los Angeles, CA, USA) according to manufacturer's instructions.

2.6. Microbiologic analyses

Semen samples were cultured quantitatively to detect anaerobic, microaerophilic, and aerobic bacteria within 1-2 hours from collection. Wilkins-Chalgren agar (Oxoid, Unipath, Basingstoke, UK) supplemented with 5% horse blood,

Schaedler medium (Oxoid) supplemented with 5% horse blood, vancomycin and nalidixic acid, *Gardnerella vaginalis*-selective agar (Oxoid), MRS agar for lactobacilli (Oxoid), freshly prepared blood agar, and chocolate agar were used. Wilkins-Chalgren and Schaedler media were incubated in an anaerobic glove box (Sheldon Manufacturing Inc, with a gas mixture: 5% H₂, 5% CO₂, 90% N₂) for 5-6 days. MRS medium, chocolate agar, and *Gardnerella vaginalis*-selective agar were incubated in a microaerophilic atmosphere (10% CO₂) for 72 hours. Blood agar was incubated aerobically at 37 °C and inspected after 24 and 48 hours.

Colonies with different morphology were Gram stained and examined microscopically. The microorganisms were identified mostly at the genus level. Standard methods were used for identification of enteric and other gram-negative bacteria [25]. A latex test (Oxoid) was employed for differentiation of *Staphylococcus aureus* and coagulase-negative staphylococci. Streptococci and enterococci were identified by the absence of catalase production and differentiated by fermentation of esculin. Group B streptococci were identified with the use of a latex test (Oxoid). *Corynebacterium seminale* was differentiated by testing its beta-glucuronidase activity with the use of MUG medium (Oxoid). *Gardnerella vaginalis* was identified by its ability to grow on selective medium, characteristic morphology, and negative catalase test. The anaerobes were identified by evaluation of their growth on selective media, colony and cellular morphology, Gram stain reaction, and some rapid tests and diagnostic disks. All anaerobic microorganisms were tested for absence of growth under aerobic and microaerophilic conditions.

Absence of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* was confirmed by a polymerase chain reaction (PCR) method with the use of Amplicor C. trachomatis/N. gonorrhoeae Test (Roche, Mannheim, Germany) after the DNA extraction, which was performed with the use of the High Pure PCR Template Preparation Kit (Roche).

2.7. Statistical methods

Statistical analyses were performed with the use of the Sigma Stat (Jandel Scientific) and Excel (Microsoft Corp, Redmond, OR, USA) software programs. The clinical parameters (age, period of abstinence, and basic sperm characteristics, including volume, concentration, total sperm count, motility, and morphology) passed a normality test; therefore, a t test was used for comparison of the two groups. Inflammatory markers (WBC count and IL-6) were analyzed by means of the Mann-Whitney rank sum test. For comparison of the prevalence and counts of different microorganisms between the groups, Fisher exact test, and Mann-Whitney rank sum test were used. The Spearman rank order correlation was used to find the correlation between WBCs and IL-6, and between microbiologic indicators. Statistical significance was assumed at $p < 0.05$ level for all parameters.

2.8. Ethical considerations

Participation in the study was voluntary. Informed consent was obtained from the patients. The study was approved by

Table 2 – Comparison of seminal microorganisms in asymptomatic inflammatory prostatitis patients and the control group

Microorganisms	NIH IV category prostatitis patients (n = 37)		Controls (n = 32)	
	Median (range) (log) [*]	%	Median/range (log) [*]	%
<i>Staphylococcus aureus</i>	<2 (<2–6.0)	27	<2 (<2–4.0)	37
Coagulase-negative staphylococci	2.0 (<2–5.0)	68	2.2 (<2–4.0)	62
β-haemolytic streptococci	<2 (<2–7.0)	16	<2 (<2–4.0)	9
Group B streptococci	<2 (<2–4.0)	3	<2 (<2–3.3)	3
Streptococci (α- or γ- haemolytic)	2.0 (<2–6.7)	51	<2 (<2–4.0)	37
Enterococci	<2 (<2–2.0)	3	<2 (<2–3.3)	9
<i>Corynebacterium seminale</i>	<2 (<2–5.7) [†]	41 [‡]	<2 (<2–3.3) [†]	13 [‡]
Other corynebacteria	2.6 (<2–6.7) [†]	62 [‡]	<2 (<2–4.0) [†]	31 [‡]
<i>Bacillus</i> species	<2	0	<2	0
<i>Gardnerella vaginalis</i>	<2 (<2–6.0)	14	<2 (<2–7.0)	16
Coliforms	<2 (<2–5.0)	16	<2 (<2–4.3)	3
<i>Haemophilus</i> species	<2	0	<2	0
Yeasts	<2	0	<2	0
Actinomyces	<2 (<2–3.0)	14	<2 (<2–3.0)	3
Peptostreptococci	<2 (<2–7.0)	41	<2 (<2–6.0)	37
Gram-negative anaerobic rods [§]	1.7 (<2–7.0)	46	<2 (<2–7.0)	31
Veillonella	<2 (<2–5.7)	3	<2 (<2–4.0)	6
Bifidobacteria	<2 (<2–2.0)	3	<2 (<2–5.0)	6
Propionibacteria	<2 (<2–3.3)	5	<2 (<2–6.0)	16
Sarcina	<2	0	<2 (<2–4.0)	6
Eubacteria	<2 (<2–4.7)	5	<2 (<2–3.3)	3
<i>Mobiluncus</i> species	<2 (<2–7.0)	11	<2	0
Lactobacilli	<2	0	<2	0

NIH: National Institutes of Health.

^{*} Counts in log₁₀ CFU/ml (detection level was 2.0).

[†] $p < 0.05$ (Mann-Whitney rank sum test).

[‡] $p < 0.05$ (Fisher exact test).

[§] In nine patients, the following gram-negative anaerobic rods were identified: NIH IV category prostatitis patients: 3 *Prevotella* species, 1 *Porphyromonas* species, 1 *Bacteroides ureolyticus*; in control group: 2 *Fusobacterium* species, 1 *B. ureolyticus*, 1 *B. ureolyticus* + *Prevotella* species.

the Ethics Review Committee on Human Research of the University of Tartu.

3. Results

3.1. Clinical and semen parameters

No significant differences were observed when the two groups were compared for age, period of abstinence, and basic sperm parameters. The leukocyte count in semen and IL-6 concentration in seminal plasma were significantly higher in NIH IV category prostatitis patients than in the controls (Table 1), and we found high correlation between these two parameters ($r = 0.74$, $p < 0.001$).

3.2. Microflora of semen

None of the 69 seminal fluid specimens was sterile. More than 20 different microorganisms were isolated in both groups (Table 2). High frequency of anaerobic bacteria was found in both groups—they were present in 70% of the samples in NIH IV group

and in 75% of the samples in the control group. In most of the specimens, the counts of anaerobic microorganisms were equal to or outnumbered the aerobic ones (Table 3). Corynebacteria appeared more frequently and in higher counts in leukocytospermic patients than in controls.

One to eight different microorganisms could be found in any particular semen sample, and the total concentration of microorganisms ranged from 2.0 to 7.5 log₁₀ CFU/ml. These parameters (number of different microorganisms and the total concentration of microorganisms) were in good correlation ($r = 0.70$, $p < 0.001$). Unlike the controls, the NIH IV category prostatitis patients had abundant polymicrobial microbiocenosis in their semen, with both of these parameters being significantly higher in them than in controls (Table 3).

4. Discussion

Our study showed that asymptomatic leukocytospermia most probably has an important infectious

Table 3 – Comparison of some quantitative parameters of seminal microflora in different study groups

	NIH IV category prostatitis patients (n = 37)	Controls (n = 32)
Per cent of specimens with:		
Aerobes > anaerobes	46%	34%
Aerobes = anaerobes	38%	28%
Aerobes < anaerobes	16%	38%
Total concentration of microorganisms (log ₁₀ CFU per milliliter of semen (median [range]))	4.8 (2.0–7.5)*	3.9 (2.3–7.3)*
No. of different microorganisms in semen (median [range])	5 (2–8)†	3 (1–7)†

NIH: National Institutes of Health.
* p < 0.001; † p = 0.004 (Mann-Whitney rank sum test).

component. Although we found microorganisms in all semen specimens, the total concentration and number of different microorganisms were much higher in asymptomatic inflammatory prostatitis patients than in the controls. This knowledge may be important in improving the treatment regimens of leukocytospermic patients.

Previous investigators have found that, in most of the patients with leukocytospermia, pathogenic bacteria cannot be cultured from the semen in significant numbers, and no correlation between seminal microbes and raised leukocytes can be found [13–18,26]. At the same time most of these studies have not included suitable methods for a wide spectrum of bacteria including anaerobic ones. In our study, which revealed a significant difference between asymptomatic inflammatory prostatitis patients and controls, we used a quantitative microbiologic analysis that included suitable media and environmental conditions for aerobic, microaerophilic, and anaerobic bacteria. Anaerobic bacteria were present in three quarters of the semen samples, occurring frequently concurrently in high counts in leukocytospermic patients; these findings support the idea of the polymicrobial nature of this syndrome. Formerly, we had seen quite similar microbiologic findings while studying chronic prostatitis/chronic pelvic pain syndrome (NIH IIIA category) patients [22]. This observation led us to the idea that symptomatic (NIH IIIA) and asymptomatic (NIH IV category) inflammatory prostatitis could have similar nature. As for individual microorganisms, no statistically significant differences between the groups were observed, except for corynebacteria. Some other investigators have

indicated a possible role for corynebacteria in prostatitis [27,28], but that suggestion needs further investigations with species detection.

The question regarding the source of microorganisms arises when semen is used as a specimen. Indigenous microflora exists in the urethra [29,30] as well as on genital skin [31], while upper genital tract normally should be sterile, and the presence of normal microflora in the prostate is unlikely [32]. In our study, contamination was minimized by washing the hands and genitals with soap and water before sampling, and urinating. In addition, we have formerly shown significant differences between the first catch urine (that represents microflora of the urethra) and seminal fluid microflora [22], indicating that most of the microorganisms in semen do not originate from the urethra, but reflect an infection of the upper genital tract.

Leukocytospermia that characterizes the NIH IV category prostatitis does not disturb the patient's everyday life, but may have an adverse effect on sperm quality [9–12]. While sperm damage by WBCs can be mediated by proteases and cytokines or enhanced T-helper 1 modulation [13,14], the main role is believed to be played by reactive oxygen species. The origin of WBCs is not easy to determine; however, the prostate and epididymis are thought to be the major contributors of granulocytes in semen [11]. Although we did not find a correlation of leukocytospermia with the basic semen parameters, some of our patients presented with infertility of the couple. Also other investigators have found that leukocytospermia occurs more frequently in infertile (20–44%) than in fertile (10–16%) men [10,13,14,33] and, similar to our finding, Branigan et al. [33] have noted that leukocytospermia may exist in a significant number of males with unexplained infertility but normal semen analyses. However, no clear causal relationship has been shown between leukocytospermia and male infertility.

Previous studies have shown that IL-6 reveals significantly higher values in the patients with leukocytospermia than in those without [34,35]. Our study confirmed this finding, indicating also its relatedness to microbiologic finding. IL-6 is an important mediator of inflammatory processes and a marker of silent genital inflammations in seminal plasma [19,20] where the prostate has appeared to be its main source [36]. Therefore detection of IL-6 can be suggested as an additional diagnostic tool for men with fertility problems to rule out possible inflammatory causes, as well as for men with asymptomatic leukocytospermia to gain additional data regarding the activity of inflammation.

5. Conclusion

Abundant polymicrobial microbiocenosis, containing anaerobic, microaerophilic, and aerobic bacteria, occurs in the semen of NIH IV category prostatitis patients, and is similar to that of NIH IIIA category patients but differs from that of controls. Detection of IL-6 in seminal plasma serves as an additional tool for diagnosing NIH IV category prostatitis.

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Editorial Comment

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Asymptomatic inflammatory prostatitis (NIH IV prostatitis) is a clinical entity of unknown significance characterised by the presence of inflammatory cells in seminal fluid, expressed prostatic secretion (EPS) or prostate biopsy. It is probably because of its asymptomatic behaviour that little efforts have been made to determine aetiology and clinical relevance of this condition, but being asymptomatic does not necessarily mean being not harmful. Therefore, attempts to provide more information on such clinical entity are certainly welcome.

The present study pointed out that both NIH IV prostatitis patients and controls harboured abundant polymicrobial seminal microflora. These findings are in agreement with those of Lee et al. [1] who found that patients with NIH III prostatitis and healthy controls had similar positive prostate biopsy culture rates (38% and 36%, respectively). In the present study, however, quantitative microbiological analysis showed that NIH IV prostatitis patients harboured a greater amount of seminal microflora than controls. The most interesting finding was that Corynebacteria were the only microbial species statistically more frequent in patients than in controls. These findings are in agreement with those by Tanner et al. [2]. Using analysis of 16S rRNA sequences in the prostatic fluid they demonstrated the presence of a wide spectrum of bacterial species in patients with bacterial and “nonbacterial” prostatitis, confirming that microorganisms associated with prostatitis generally occur as complex microbial communities. They also demonstrated that Corynebacteria

were present in higher proportion than other bacterial species, thus suggesting that Corynebacteria could have a role in or be the consequence of the disease. As a matter of fact, the possible aetiological role of anaerobes in chronic prostatitis had already been postulated by studies whereby anaerobic bacteria were identified in cultures of prostate biopsy [3] as well as EPS [4] of patients harbouring such disease. Taking all these data together there are grounds to assume that NIH IV prostatitis can have an infectious aetiology and that, among a heterogeneous and likely commensal microbial flora, the anaerobic Corynebacteria species can be those pathogenic thus responsible for the inflammatory reaction.

Should we care about NIH IV prostatitis, an inflammatory, likely infectious, yet asymptomatic clinical condition? Concerns arise from the fact that leukocytospermia that characterises NIH IV prostatitis is associated with decreased sperm quality, increased oxidative stress levels and DNA damage.

There is enough yet continuously increasing evidence that leukocytospermia may be responsible for many cases of male infertility, particularly the “unexplained” ones [5]. Leukocytospermia is associated with increased reactive oxygen species (ROS) production by human spermatozoa [6] and ROS-mediated peroxidative damage to the sperm plasma membrane seems to account for the defective sperm functions observed in a high proportion of patients with “unexplained” infertility [7]. Since such sperm damage is not overcome even by assisted reproductive techniques [8], it should be a major uro-andrological task to search for new effective treatment strategies for such leukocytospermia-related infertility.

Another, even greater, matter of concern arises from the fact that prostatic inflammation is

associated with increased ROS production with consequent damage of cell membranes and DNA of prostatic epithelial cells [9]. DNA damage may turn into mutations, some of which may provide cells with anti-apoptotic properties. Therefore, long-lasting inflammation may initiate and/or promote carcinogenesis [9]. Indeed, the inflammatory infiltrate typical of NIH IV prostatitis is frequently found in radical prostatectomy specimens [10].

Chronic inflammation may, in the long run, turn into a regenerative lesion called proliferative inflammatory atrophy (PIA) and consisting of prostatic epithelial cells with high proliferative activity and low apoptotic index surrounded by a massive inflammatory infiltrate [11]. Since PIA is frequently found adjacent to or near areas of prostatic adenocarcinoma or high grade prostatic intraepithelial neoplasia (HGPIN) [12], it has been postulated that it may give rise to prostatic carcinoma either directly or indirectly by first developing into HGPIN [11].

It is still unknown whether PIA should be considered a precursor of carcinoma or merely indicates an intraprostatic environment favourable to cancer development [13] but, certainly, available data hint at a link between long-lasting chronic prostatic inflammation and prostate cancer [14]. It is also unknown whether early identification and treatment of NIH IV prostatitis could prevent development of PIA with its possible consequences but, certainly, in the age of prostate cancer chemoprevention, this issue deserves great attention.

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Editorial Comment

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Chronic prostatitis is a known cause of lower urinary tract symptoms and chronic pelvic pain in men and the prevalence of symptomatic chronic prostatitis is reported to range from 4% to 11%.

While many investigators have studied symptomatic prostatitis, few have investigated NIH category IV prostatitis. In a recent study Carver et al. confirmed the prevalence of NIH category IV

prostatitis in 32.2% of the observed men [1]. Thus the presence of micro-organisms in semen of patients affected by asymptomatic prostatitis, as reported in the present article, must be considered a relevant step in clarifying the role of bacteria in the etiology of the disease.

In the last twenty years several unsuccessful studies have been conducted in order to identify different bacteria or viruses responsible for the etiology or the evolution of prostatitis. Bacterial infection could be considered as either the main determining factor in etiology or as a secondary

event in the inflammation process. It is well-recognized that, even if pathogenic bacteria are present in the prostate, as in men with established chronic bacterial prostatitis, they do not cause chronic pelvic pain unless an acute urinary tract infection develops. These data suggest that bacteria do not have a significant role in the development of chronic pelvic pain syndrome but they could simply be related to the evolution of this disease.

Several urologists currently use antibiotics in their clinical approach to prostatitis. The observation that antimicrobial therapy reduces symptomatology in men with chronic pelvic pain syndrome is being tested in a double-blinded NIH controlled study.

Men with NIH category IV prostatitis had a mean serum PSA level significantly higher than those without prostatitis [1]. This fact could help to

identify possible co-morbidities in disease progression both in terms of BPH and prostate cancer, as recently found in the MTOPS study results [2,3].

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