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NEW PROSPECTS FOR CHRONIC PROSTATITIS

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SUMMARY – Nowadays we may be overlooking an ever more common and most likely infectious disease of uncertain etiology - prostatitis. The field of chronic prostatitis was stagnant for some three decades, however, the state of affairs has changed dramatically over the last few years. Prostatitis is the most common prostate disease in the younger population, which results in more physician visits than either benign prostatic hyperplasia or prostate cancer. Despite its high prevalence, chronic prostatitis as a disease and its etiology have been understudied. This article is concentrated on the entity of chronic prostatitis, which is the most controversial, diagnostically most imprecise, and most frustrating diagnosis in medicine in general. Also, it is the most common ailment in men worldwide. The knowledge about the disease is now progressing at a higher pace, especially concerning its etiology and pathogenesis. Along with a review of the latest findings, an update is provided of the classification, diagnosis, treatment and epidemiology of chronic prostatitis. It is emphasized that the disease should be recognized more often, or at least, epidemiologically speaking, it should be paid more attention.

Key words: *Prostatitis - etiology; Prostatitis - therapy; Chronic diseases - epidemiology*

Introduction

The field of prostatitis, especially chronic, was stagnant for three decades, however, the state of affairs has changed dramatically over the last two years. Prostatitis is the most common prostate disease, resulting in more physician visits than either benign prostatic hyperplasia or prostate cancer, according to the National Institutes of Health, Bethesda, United States[1]. Despite its high prevalence, prostatitis as a disease and its epidemiology, especially its etiology, have been understudied[2]. Our understanding of the pathogenesis, etiology, diagnosis, and treatment of chronic prostatitis has not advanced along with that of other prostatic diseases. Recent articles and scientific papers are focused on the entity and etiology of chronic (idiopathic, abacterial) prostatitis. In this review, we present the latest findings and guidelines on the epidemiology, etiology (microbiology), pathogenesis, classification and therapy of prostatitis, especially chronic, idiopathic prostatitis. The article is primarily based on the research published over the last ten years.

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Epidemiology

The state of the art on prostatitis suffers from many gaps, beginning with the basic epidemiology of the disease. To discuss the epidemiology of prostatitis effectively, an operational definition of prostatitis is essential. However, the task of defining prostatitis is difficult.

Prostatitis is the most common urologic diagnosis in men under 50 years of age, and the third most common in older men[3]. From 10% to 30% of men will have had a diagnosis of prostatitis by 79 years of age[4]. The incidence and prevalence are estimated to range between 5% and 8%. The quality of health is similar to that in patients with unstable angina, recent myocardial infarction, or active Crohn's disease. Thirty-five percent of men have symp-

toms that could be diagnosed as prostatitis over a year. For 8%, it implies at least a minor problem[3]. According to McNeal, a pathologist, the prostate gland is the internal organ of the human body that is most commonly affected by a disease[5]. The varying definitions of prostatitis reflect in the broad range of estimates of epidemiological parameters reported in the literature. The histopathologic prevalence of prostatitis ranges from 35% to 98%, as summarized by Bennett *et al.*, or from 6% to 44%, according to Roberts *et al.*[4]. Using data from the Olmsted County Study of Urinary Symptoms and Health Status among Men, they found the overall prevalence of the physician's diagnosis of prostatitis to be 11%. Only 4% of the nearly 2 million visits for prostatitis *per* year were recorded as 'acute prostatitis', suggesting that chronic prostatitis is quite common[4].

According to Stamey[6], up to 50% of all men experience symptoms of prostatitis during the lifetime. A prostatitis lesion was found in 40 (44%) of 91 men at random autopsy[7]. In another study of 100 consecutive autopsies in men killed in car accidents or died from other causes, the prevalence of histologic signs of prostatitis increased with age and was highest when benign prostatic hyperplasia was also present. Prostatitis was present in 22% and 60% of men under and over 40 years of age, respectively[8].

Chronic Prostatitis and Benign Prostatic Hyperplasia

The line between benign prostatic hyperplasia (BPH) and prostatitis is blurred. Prostatitis as a histologic lesion was found in 98% of patients with benign prostatic hypertrophy[9]. Microbiological tests for BPH revealed high rates of infectivity[9]. In another study, more than 70% of transurethral resection of the prostate specimens showed clinical or laboratory signs of infection[10]. BPH and prostatitis cannot be distinguished according to symptoms, and some believe that they may be the same disease. Many publications have established the most common symptoms reported by men at visits for chronic prostatitis, comparing them with the results of visits for BPH. Pain was more common than voiding complaints, and much more common than sexual dysfunction among those visiting physician for chronic prostatitis. In contrast, pain symptoms were a very infrequent reason for BPH visits. Moreover, the single most common reason for chronic prostatitis visits was painful urination, which was an uncommon reason for BPH visits. These results suggested that pain rather than urinary symptoms might discriminate chronic prostatitis visits from BPH visits. This study also showed that visits for chronic prostatitis were almost equally divided between younger (aged 18 - 49 years) and older (aged ≥50 years) men. Finally, the investigators demonstrated that chronic prostatitis not uncommonly coexisted with the diagnosis of BPH; 9% of chronic prostatitis visits were associated with both chronic prostatitis and BPH diagnoses[11]. A limitation of these three studies, however, is the potential unreliability of the physician's diagnosis of prostatitis.

National Institutes of Health Classification of Prostatitis[12,13]

In 1995, the National Institutes of Health (NIH) workshop on chronic prostatitis recognized the limited understanding of the etiology for most patients previously diagnosed as chronic prostatitis, and the possibility that some organs other than the prostate gland may be important in the pathogenesis of the syndrome. This meeting developed by consensus a new classification system for chronic prostatitis that addressed the concerns raised by the participants and intended for use in clinical practice and research studies. The NIH classifies prostatitis into categories shown in Table 1. The new definition recognizes that pain is the main symptom (with variable voiding and sexual dysfunction symptoms) and optimal criterion to differentiate prostatitis patients from control patients or patients experiencing other genitourinary problems such as BPH. The definition of the chronic prostatitis/chronic pelvic pain syndrome proposed by the 1995 NIH workshop on chronic prostatitis is based on "the presence of genitourinary pain and the absence of uropathogenic bacteria detected by standard microbiological methodology". This syndrome is further categorized into inflammatory (based on the presence of leukocytes in expressed prostatic secretion, postprostatic massage urine or semen), and noninflammatory (no significant presence of leukocytes in similar specimens). Categories I and II are similar to the traditional classification of acute and chronic bacterial prostatitis, respectively. The new categories of chronic pelvic pain syndrome, inflammatory and noninflammatory (category III), and asymptomatic and inflammatory prostatitis (category IV) address the major problems and omissions of the traditional and historical classification system. The adoption of a standard definition and classification system should

Table 1. National Institutes of Health Classification of Prostatitis

Category I	Acute bacterial prostatitis	Acute infection of the prostate gland
Category II	Chronic bacterial prostatitis	Recurrent urinary tract infection
Category III	Chronic abacterial prostatitis/ Chronic pelvic pain syndrome (CPPS)	Chronic infection of the prostate Discomfort or pain in the pelvic region (for at least three months)/variable voiding and sexual symptoms No demonstrable infection
Category IIIA	Inflammatory chronic pelvic pain syndrome	Significant white cells in semen/EPS/VB3
Category IIIB	Noninflammatory chronic pelvic pain syndrome	Nonsignificant white cells in semen/EPS/VB3
Category IV	Asymptomatic inflammatory prostatitis (AIP)	Evidence of inflammation in biopsy/semen/EPS/VB3 No symptoms

EPS=expressed prostatic secretion; VB3=third voided urine specimen

stimulate new and improved therapeutic initiatives in chronic prostatitis research.

Etiology, Pathogenesis and Symptoms

Chronic prostatitis/chronic pelvic pain syndrome

- Dysfunctional high pressure voiding.
- *Chronic bacterial prostatitis* - recurrent urinary tract infections associated with chronic infection of the prostate gland. The condition usually responds (to some extent) to antibiotics but tends to recur.
- *Chronic prostatitis/chronic pelvic pain syndrome*. Discomfort or pain localized to the pelvis (genitourinary discomfort or pain) for at least three months. There is no associated bacterial infection and the condition usually does not respond to antibiotics. The condition is associated with variable irritative and obstructive voiding symptoms.
- Intraprostatic ductal reflux.
- A microorganism based etiology.
- Acknowledged prostate pathogens - gram-negative uropathogens (i.e. *Enterobacteriaceae* such as *Escherichia (E.) coli, Klebsiella* sp., *Pseudomonas* sp., etc.).
- Probable prostate pathogens - gram-positive *Enterococcus* sp. (and *Staphylococcus aureus*).
- Possible prostate pathogens - coagulase negative *Staphylococcus, Chlamydia, Ureaplasma,* anaerobes.
- Acknowledged prostate nonpathogens - *Diphtheroids, Lactobacilli* sp., *Corynebacterium* sp.
- Cryptic nonculturable organism - 'biofilm bacteria', viruses, cell wall deficiency, etc.
- Autoimmune.
- Chemical - urine and its metabolites (i.e. uric acid).
- Neuromuscular.
- Interstitial cystitis.

Most urinary pathogens also are causative agents of acute and chronic prostatitis. *E. coli* predominates as the cause of culturable prostatitis. Other members of *Enterobacteriaceae,* such as *Klebsiella, Enterobacteria, Proteus* and *Serratia*, can be isolated from patients with acute and chronic prostatitis, as also can be *Pseudomonas* and less commonly gram-negative bacteria. Obligate anaerobes have rarely been implicated as the cause of prostatitis. Gram-positive bacteria, particularly cocci, remain controversial as the possible etiologic agents. *E. coli* is implicated in 80% of infections[6,14]. *Pseudomonas aeruginosa, Serratia, Klebsiella* and *Proteus* account for 10% - 15%, and enterococci for 5% - 10% of cases[15,16].

In their study Brunner *et al.* report that of 600 men attending a special prostatitis clinic in Germany, 5% had bacterial prostatitis, 64% had nonbacterial prostatitis, and 31% had prostatodynia[17].

In the study of Lowentritt *et al.*, coagulase-negative staphylococci were the most common isolates (68%) in chronic idiopathic prostatitis[18]. The role of *Staphylococcus epidermidis*, the most commonly isolated organism, in the etiology of chronic idiopathic bacterial prostatitis has also been implicated by Nickel and Costerton[19] and Wedren

et al.[20]. Another coagulase-negative staphylococcus species isolated in this study, *Staphylococcus haemolyticus*, has been reported by Gunn and Davis[21] and Sanchis-Bayarri *et al.*[22] to cause urinary tract infection in men.

A large study including 597 prostatitis patients showed prostatodynia to be diagnosed in nearly one third of them, which is a significant portion of the urologic population[17]. Recent literature data suggest that the condition referred to as chronic idiopathic (nonbacterial) prostatitis may actually have an infectious etiology[18,19,23-26]. Some patients relate the onset of their symptoms to sexual activity[27], sometimes associated with acute urethritis, while others have indicated no relationship with sexual activity. An underlying anatomical or functional condition usually complicates urinary tract infections in men, however, noncomplicated infections, often related to sexual activity do occur as well[14,27].

The role of mycoplasmal, ureaplasmal and chlamydial species in the etiology of the disease is centered on the chronic pelvic pain syndromes[28]. A number of organisms have been reported to possibly cause the syndrome, e.g., *Trichomonas vaginalis*[29-32], *Chlamydia trachomatis*[9,33-36], genital mycoplasmas[17,37], staphylococci[19,34,38], coryneforms[23,39], and genital viruses[40,41]. Researchers from Japan suggest that *Chlamydia trachomatis* often is the causative organism in chronic idiopathic prostatitis[42].

Although *Ureaplasma urealyticum* has long been implicated as sometimes causing nongonococcal urethritis, its role as an etiologic agent of prostatitis is controversial. Common pathogens and unconventional, fastidious bacteria, viruses, parasites and fungi are causative agents in male urethroadnexitis. Uropathogens and sexually transmitted organisms must be considered[43]. Bowie *et al.* report that the most important causes of urinary tract infection in younger men are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, while the most important causes of prostatitis and epididymitis in older men or men with urethral structural abnormalities are classical urinary tract pathogens rather than sexually transmitted pathogens[27]. The ascending spread of urethral pathogens may be the mechanism of infection of the prostate and epididymis. Brunner *et al.* found *Ureaplasma urealyticum* to be positive in high numbers of expressed prostatic secretions and urine voided after prostatic massage in 82 (13.7%) of 597 patients with chronic prostatitis[17]. As the number of ureaplasmas in first-voided urine and midstream urine was significantly lower, the source of the organisms in these patients was assumed to be the prostate. These data and results of tetracycline treatment provide sufficient evidence for the etiologic importance of ureaplasmas in chronic prostatitis. Sexually transmitted organisms are the most common cause of epididymitis in young men, and evidence is accumulating suggesting that sexually transmitted organisms may cause prostatitis[44]. It has been definitely demonstrated that *Ureaplasma urealyticum* is an etiologic agent of nongonococcal urethritis, a sexually transmitted disease. For this reason, it seemed possible that the organism might cause ascending inflammatory reactions of the prostate. In addition to the well known urinogenic enterobacteriae and enterococci, and the sexually transmitted gonococci and trichomonas, *Chlamydia trachomatis* and *Ureaplasma urealyticum* should now be considered particularly important etiologic agents that also are sexually transmitted[37,45].

Many studies suggest that either an agent as yet unidentified or multiple agents may be involved in the etiology of nonbacterial prostatitis[46]. According to some authors, acute prostatitis results from ascending urethral infection[6,47], and from reflux of infected urine into prostatic ducts[16,48].

Diagnosis and Therapy

The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), available online at http://www.QLMed.org/nih-cpsi/, accurately measures the three major domains of the chronic prostatitis syndrome: pain, voiding dysfunction, and impact/quality of life. The NIH-CPSI provides a valid outcome measure for men with chronic prostatitis. It is as useful in research as in clinical practice to follow up patients with chronic prostatitis/chronic pain syndrome. We have concluded that the symptom index is not very suitable when working with our outpatients. Culture diagnosis of acute bacterial prostatitis is straightforward and easily accomplished in the laboratory. On the other hand, the microbiological diagnosis of chronic prostatitis and chronic idiopathic (nonbacterial) prostatitis (more commonly referred to as prostatodynia) is a major challenge. Chronic idiopathic prostatitis, when diagnosed clinically, has a poor record of treatment success. The major difficulty in interpreting microbiological findings is the presence of contaminating, indigenous microbiota. Specimens such as voided urine, urethral swabs, and expressed prostatic secretions used to evaluate a patient with suggestive symptoms become contaminated with the organisms colonizing the distally contaminated urethra. Although an ideal specimen would be un-

contaminated prostatic tissue, there are few such reports in the literature. The microbiological workup of these specimens is further complicated by the presence of inhibitory substances known to exist in the prostatic secretions, and the history of multiple previous courses of antibiotics.

The quantitative bacteriological cultures confirm the diagnosis of bacterial prostatitis when the infectious agent(s) is localized to the prostate gland (i.e. segmented cultures). The technique of obtaining segmented cultures of the male lower urinary tract was first described in 1968 by Meares and Stamey[16] (Table 2). This method, although rarely used today in clinical practice, is still by many consider the 'gold standard' for localizing the prostate gland infection. The sampling conditions require a sufficiently full bladder, and the samples must be collected by using rigorous aseptic technique. The first step of the examination must not be preceded by urethral swabbing. Prostatic secretions are obtained by systematic massage of each lobe of the prostate gland. Bacterial prostatitis is confirmed by the presence of bacteria in the prostatic secretions and in the VB3 (voided bladder) postprostatic massage urine sample in numbers greatly exceeding the bacterial counts of the VB1 and VB2 urine specimens. The traditional criterion for diagnosing chronic bacterial prostatitis is a 10-fold increase in the concentration of culturable microorganisms, when the bacterial count of the postmassage urine sample or expressed prostatic secretion sample is compared with that of the first void (VB1) urine sample[16].

The segmented culture technique is not widely used in primary care settings, the more so, most urologists appear to have abandoned the procedure because of its labor intensity and overall costs. In 1999, Nickel[49] proposed a simple and cost-effective screen for prostatitis, which includes culture and microscopic examination of urine before and after prostatic massage (see Table 2). This pre- and postmassage test (PPMT) was used in a series of 53 patients and in 59 patients whose segmented culture results were available from the literature. In these selected populations, the PPMT alone led to the same diagnosis in 102 (91.1%) patients. Within the expected limitations of this retrospective review, the calculated sensitivity and specificity of PPMT were 91% each. It is important that physicians might be ready to adopt the simpler diagnostic plan for prostatitis because it is by far more efficient in terms of diagnosing the disease than doing no workup for infection localization.

Table 2. Interpretation of four- and two-glass tests (lower urinary tract localization studies)

Test		Four-glass test (Meares and Stamey, 1968)				pre- and postmassage test (PPMT; Nickel, 1999)	
Specimen		VB1	VB2	EPS	VB3	Pre-M	Post-M
Category II	WBC	-	+/-*	+	+	+/-*	+
	Culture	-	+/-*	+	+	+/-*	+
Category IIIA	WBC	-	-	+	+	-	+
	Culture	-	-	-	-	-	-
Category IIIB	WBC	-	-	-	-	-	-
	Culture	-	-	-	-	-	-

Category=National Institutes of Health Classification Category (Table 1); WBC=white blood cells; VB1=first voided urine specimen; VB2=second voided urine specimen or midstream specimen; EPS=expressed prostatic secretion; VB3=third voided urine specimen; Pre-M=urine specimen before prostate massage; Post-M=urine specimen after prostate massage.

The men with the symptoms of prostatitis must be evaluated by both urine and prostatic secretions to document the infection and inflammation. A majority of men with such symptoms do not have an infection that can be documented. These men respond poorly to medication. The men with documented chronic bacterial prostatitis require long courses of antimicrobials for effective cure. In some cases, however, the disease is intractable, and chronic suppression with antimicrobials may be necessary. Chronic prostatitis causes considerable morbidity for many men. Specific therapy leads to cure and improvement for patients with infectious causes. However, the treatment is frequently empirical and unsatisfactory, because we have limited understanding of the causes and pathophysiology of these neglected disease syndromes.

Table 3. Treatment of prostatitis syndromes

Category I	Category II	Category IIIA	Category IIIB	Category IV
I.v. antibiotics +/- catheterization *Follow-up:* oral antibiotics	Antibiotics +/- prostate massage *Follow-up:* antibiotics (suppressive, prophylactic) surgery?	Antibiotic trial +/- prostate massage +/- alpha blockers +/- finasteride +/- phytotherapy + lifestyle changes	Triple therapy: alpha blockers muscle relaxants analgesics +/- tricyclic antidepressants +/- biofeedback + lifestyle changes	No treatment indicated (unless elevated PSA or infertile)

Cryptic microorganisms may be important in some cases. Defining the precise role for such organisms will require better diagnostic algorithms and methods to elucidate the microbiology of the prostate in health and disease. Table 3 shows the treatment of prostatitis syndromes for categories I through IV.

NIH category I (acute bacterial prostatitis): The prostate should not be massaged. Pain killers and stool softeners are prescribed along with adequate hydration of the patient. Suprapubic catheter is inserted if the patient develops urinary retention. If the patient is admitted, he is treated with parenteral antibiotics (aminoglycoside + ampicillin/third generation cephalosporin), whereas sulfamethoxazole + trimethoprim or fluoroquinolone (cipro/levaquin) are used when the treatment is advised on outpatient basis. Antibiotic therapy is given for 2-4 weeks. A poor response to this treatment may be due to the development of prostatic abscess (can be demonstrated on US/CT scan), which, if documented, can be drained by transurethral/transperineal route.

NIH category II (chronic bacterial prostatitis): It is treated by sulfamethoxazole + trimethoprim (for 10 weeks; 30% cure rate) or fluoroquinolones (norfloxacin/ciprofloxacin for 4-6 weeks; 75% cure rate) or a low dose suppressive therapy (TMP-SMX/nitrofurantoin/tetracycline/cephalothin). Some patients with this condition (those not responding to antibiotic therapy) may require surgical debridement (removal of all infective foci/stones by radical transurethral resection of the prostate).

NIH category IIIA (chronic abacterial prostatitis): It is treated by pain killers and a 1-month trial of TMP-SMX or ofloxacin or tetracycline. However, the condition is commonly treated by prostatic massage. Alpha blockers (terazosin) are useful in relieving pain and voiding symptoms often seen in these patients. Newer forms of therapy such as finasteride (in old patients with boggy prostate), pentosan polysulfate (in those with suprapubic pain and irritative voiding symptoms), phytotherapy (saw palmetto extract) and transurethral thermotherapy are currently being studied in these patients.

NIH category IIIB (prostatodynia): These patients are treated with pain killers and anti-inflammatory agents. Alpha blockers are used to relieve pain and improve voiding symptoms. Muscle relaxants such as diazepam are also helpful. These patients also benefit from supportive therapy such as perineal massage, relaxation therapy, perineal support and perineal heat fomentation.

NIH category IV (asymptomatic inflammatory prostatitis): No specific treatment is required in these patients except when there is elevation of PSA or infertility.

Conclusions

Prostatitis (more often chronic, idiopathic) is a common urologic condition that many clinicians find difficult to diagnose, and especially to treat effectively. Culture diagnosis of acute bacterial prostatitis is straightforward and easily accomplished in the laboratory, and nowadays does not represent a problem in practice anymore. On the other hand, the microbiological and clinical diagnosis of chronic prostatitis and especially chronic (nonbacterial) prostatitis (more commonly referred to as chronic pelvic pain syndrome in men) represents considerable challenge. Chronic prostatitis is the most controversial, most impre-

cise, and most frustrating diagnosis in medicine in general. It is also the most common ailment in men worldwide. The mode of transmission has been linked to urinary tract infection and more recently as being sexually acquired. Urinary tract infection has been taken for granted and its mode of transmission ignored. Many recent studies suggest that sexually transmitted organisms, e.g., Chlamydia, Ureaplasma, etc. (as mentioned above in the article), may cause prostatitis. We think it should be, at least epidemiologically and therapeutically, paid more attention. Ever more evidence and studies have been accumulating suggesting that nonculturable organisms may cause prostatitis. In this article, we do not bring any definite conclusions, but have tried to provide and update on prostatitis (especially chronic, idiopathic) as a rising problem in urology considering its prevalence, epidemiology, probable causative agents involved, and treatment outcome.

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SAŽETAK

NOVI IZGLEDI ZA KRONIČNI PROSTATITIS

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Danas možda previđamo prostatitis, sve češću i najvjerojatnije zaraznu bolest neutvrđene etiologije. Područje kroničnog prostatitisa stagniralo je kroz nekoliko desetljeća, da bi se stanje dramatično promijenilo posljednjih nekoliko godina. Prostatitis je najčešća bolest prostate u mlađoj populaciji, koja rezultira većim brojem liječničkih pregleda nego benigna hiperplazija prostate ili rak prostate. Usprkos učestalosti kroničnog prostatitisa, premalo je istraživanja kroničnog prostatitisa kao bolesti, kao i njegove etiologije. Ovaj je članak usredotočen na entitet kroničnog prostatitisa, koji predstavlja najkontroverzniju, najnepreciznu i najviše zbunjujuću dijagnozu u čitavoj medicini. To je također najčešća bolest u muškaraca širom svijeta. Danas se sve brže poboljšavaju saznanja o ovoj bolesti, poglavito o njezinoj etiologiji i patogenezi. Prikazan je pregled najnovijih nalaza i saznanja o klasifikaciji, dijagnostici, liječenju i epidemiologiji kroničnog prostatitisa. Isto tako, smatramo kako bi ovu bolest trebalo više uvažavati ili joj barem s epidemiološkog stajališta poklanjati više pozornosti.

Ključne riječi: *Prostatitis, etiologija; Prostatitis, terapija; Kronične bolesti, epidemiologija*