Recent developments in diagnosis and therapy of the prostatitis syndromes

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Chronic pelvic pain syndromes, including prostatitis, remain a difficult clinical entity in terms of diagnosis and treatment to both urologists and patients. This review attempts to highlight the most recent developments and advances in the field of chronic pelvic pain syndromes in terms of prevalence, aetiology, pathogenesis, diagnosis, and current approaches to treatment.

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Abbreviations

BPH	benign prostatic hyperplasia
CPPS	chronic pelvic pain syndrome
EPS	expressed prostatic secretion
NIH	National Institutes of Health
PCR	polymerase chain reaction
TNFα	tumour necrosis factor alpha
UTI	urinary tract infection
WBC	white blood cell

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Introduction

Prostatitis syndromes represent a common clinical entity and have been grouped together in one classification as they all encompass symptoms and clinical signs associated with disorders of the prostate gland. Historically, prostatitis has been classified into four clinical entities: acute bacterial, chronic bacterial, non- or abacterial prostatitis and prostatodynia. Common wisdom has accepted that a relevant percentage of cases is caused by a bacterial infection, and if bacteria cannot be isolated such as in cases with abacterial prostatitis, it is either because of inadequate bacterial culture techniques or the presence of cryptic, non-cultivable microorganisms that somehow evade conventional diagnostic techniques. In the past 5 years a renewed interest in prostatitis syndromes has arisen after a consensus conference of the National Institute of Diabetes and Digestive and Kidney Diseases of the United States of America in 1995. Significant progress has been made in terms of increased knowledge about the prevalence, aetiology, pathogenesis and treatment of chronic pelvic pain syndromes (CPPSs) since then.

Epidemiology

Prostatitis almost rivals prostate cancer and benign prostatic hyperplasia (BPH) concerning incidence, prevalence, and actual office visits, with an estimated incidence and prevalence ranging from 5 to 8% in the United States [1••,2,3••]. This impressive number indicates the significant cultural and economical problem that is associated with the disease. The physical domain of the overall quality of life is severely impaired in men with CPPS, whereas the mental health impact is more profound using CPPS patient scores that are worse than those for the most severe subgroups of diabetes mellitus and chronic heart failure, as measured using the Medical Outcomes Short Form 12 (SF-12) and the National Institutes of Health (NIH) Chronic Prostatitis Symptom Index, as has recently been reported by McNaughton-Collins *et al.* [4].

Aetiology

As has been detailed recently by J. Curtis Nickel, many researchers feel that the majority of patients with prostatitis do, in fact, have a microbial aetiology for their disease, but that urologists fail to culture the correct aetiological micro-organisms during their clinical and microbiological evaluation of the patient [5•]. Others believe that the majority of cases of chronic prostatitis, especially those in patients with no objective

signs of inflammation, do not have a microbial aetiology. To complicate things further, many asymptomatic patients in whom a diagnosis of chronic prostatitis has not been made have presented with both inflammation and microorganisms that have been identified in prostate-specific specimens such as expressed prostatic secretions (EPSs). One of the fundamental questions in this case is how long should prostate-specific fluid specimens (EPSs) be cultured to achieve the correct diagnosis? Shoskes and colleagues [6], from the NIH Chronic Prostatitis Collaborative Network, recently reported that by culturing EPSs or semen for 5 days rather than the conventional 2 days, an additional 7.5% of CPPS patients would be found positive for bacteria that actually localize to the prostate gland. Gram-positive bacteria identified by the use of this culturing protocol were associated with increased markers of inflammation in EPSs.

In addition, Shoskes and Shahed [7] found that bacterial signals could predict the response to antibiotic therapy in men with category III CPPS, using a highly sensitive 16S recombinant RNA reverse transcriptase–polymerase chain reaction (PCR) for the detection of bacterial genomic fragments. Men with negative cultures and negative signals might subsequently be able to avoid the expense and side-effects of unnecessary and prolonged courses of antimicrobial agents, and could be subjected to more effective anti-inflammatory or neuromuscular therapies that might offer the better choice in these cases [7].

It is, however, crucial to know what flora are normal to the prostate, if there are any 'normal' flora at all. After the study of Krieger *et al.* [8], Hochreiter and colleagues [9•] analysed 28 tissue samples of the prostate from 18 organ donors from whom prostate tissue could be obtained under surgical conditions at organ withdrawal during radical prostatectomies. These specimens were recovered from 14 sterile surgical prostate specimens derived from seven patients undergoing radical prostatectomy for prostate cancer who previously underwent transrectal biopsy, and six sterile surgical specimens from two men who underwent non-radical, transvesical prostatectomies for the treatment of BPH, including one from a patient with a history of an indwelling transurethral catheter for several weeks. In the study, the authors found that only three of the 28 organ donor prostate samples had histological signs of minimal inflammation and all other samples appeared to be normal without histological evidence of any inflammatory reaction. In the prostate cancer and BPH groups, there was a strong association between evident inflammation and positive PCR findings. Of 11 samples, only three without but all nine with inflammation were PCR positive. The authors concluded that negative PCR reactions in the prostate tissue of apparently healthy men made the presence of normal bacterial flora in the prostate extremely unlikely.

Another interesting study from the Seattle group [10••] systematically examined the degree and nature of inflammation in the prostate in symptomatic patients with CPPS, characterizing prostate histopathology in 368 biopsies from 97 patients with the chronic prostatitis/CPPS. Prostatic inflammation was detected in only 33% of patients. The finding of moderate or severe inflammation in only 5% of 97 patients in the study argues for the need to re-evaluate current concepts of the pathophysiology of chronic prostatitis/CPPS.

In this respect, one of the most promising approaches is the examination of parameters that equal oxidative stress and also investigating the levels of inflammatory cytokines in EPS and prostate-specific secretions. Using parameters of oxidative stress is especially beneficial in cases in which the only isolate is a Gram-positive bacterium, often considered a commensal. Using this approach, Shahed and Shoskes [11] demonstrated that Gram-positive bacteria may be considered pathogens in a subset of men with CPPS, on the basis of the injury response measured in the EPS. Evidence for this includes elevated oxidative stress, induced antioxidant enzymatic activity, the induction of antioxidant enzyme gene expression, the clinical response to antibiotics and a post-treatment reduction in oxidative stress. The promise of this approach lies in the fact that oxidative stress might be a key pathway in CPPS, which may be successfully targeted with antioxidant therapy in patients with negative cultures in the future.

The Chicago group of Nadler and colleagues [12••] studied the presence of IL-1β and tumour necrosis factor alpha (TNFα) in prostatic secretions during the evaluation of men with confirmed chronic prostatitis. IL-1β and TNFα levels in EPSs were usually detectable and appeared to be higher in men with CPPS IIIA than in those with CPPS IIIB and healthy controls, respectively. Overall, there was a clear correlation between IL-1β and TNFα, but no correlation between white blood cells (WBCs) and IL-1β that might conclusively identify cytokines as novel clinical parameters for the identification, characterization, and potential management of men with CPPS, which differs from traditional methods based on WBC counts and microbiological analysis.

The question of whether yeasts are instrumental in CPPS patients has occupied the minds of numerous researchers. It is well known that antifungal agents are sometimes remarkably effective in cases of prostatitis symptoms that are refractory to antimicrobial chemotherapy. Fungi have been implicated in most cases of prostatitis in immunosuppressed patients [13], although

several papers recently suggested that the prevalence of fungal prostatitis might also actually be underestimated in normal immunocompetent individuals [14,15]. Obviously, determining the real prevalence of prostatitis caused by fungal infection requires detailed microbiological studies that will have to be based on specialized cultures on both Sabouraud culture media and DNA analysis.

Diagnosis according to the new classification

Thirty years of work with the previous classification of prostatitis syndromes did not yield much success; subsequently the new 1997 NIH classification has spurred renewed interest in prostatitis [16••]. The first two categories have not been changed substantially, but the remainder has. Categories I and II are acute and chronic bacterial prostatitis according to the new classification. However, these forms represent the least common forms of the disease. The former type is an acute urinary infection; bacteria are present in midstream urine and the same organisms that cause urinary tract infections (UTIs), Gram-negative pathogens, can be predominantly found and isolated. Chronic bacterial prostatitis elicits recurrent infections caused by the same organisms. Between these episodes, careful culturing reveals the prostate as the source of recurrent infection. Category III includes chronic abacterial prostatitis and the non-inflammatory chronic pelvic pain syndrome (NIH IIIb). There has been much debate over what to call the third category, the most common form of this disease. The previous two terms, non-bacterial prostatitis and prostatodynia, to speak with the words of John Krieger, carried emotional baggage for patients, physicians and investigators. Many healthcare professionals believed only patients who presented with high levels of WBCs had something wrong with them. Unfortunately, in most cases urologists were unable to pinpoint the problem, that is, bacteria. After much discussion, a consensus was finally achieved to call this type of prostatitis 'chronic abacterial prostatitis/chronic pelvic pain syndrome', allowing for the possibility that something other than the prostate may also cause problems, namely, urogenital and perianal pain complaints. Most clinicians now accept the philosophy that chronic pelvic pain is a defining factor in this syndrome. Two subcategories can be subsidized under this third category; an inflammatory group (subcategory IIIa) and a non-inflammatory group (subcategory IIIb).

Previously, inflammation was thought to occur in prostatic secretions only in cases with prostatitis. It is now well recognized that inflammation occurs in post-voiding urine, post-massage urine, and seminal fluid, which broadens this concept to include patients who would previously have been categorized just as inflammatory by increased leukocyte counts in the semen. The significance of leukocyte counts in the infectiological investigation of different specimens from the lower urinary tract is still under debate. A recent survey [17] indicated that most urologists never employ the 'four-glass test' during lower urinary tract evaluation for prostatitis. However, current 'state of the art' diagnostic protocols for CPPS are based on the evaluation of urethral smears, first urine, midstream urine, EPS and post-massage urine. Krieger *et al.* [18] underscored that examinations of first urine and midstream urine in patients with chronic prostatitis have low sensitivity for the detection of urethral inflammation, whereas the combination of EPS and post-massage urine succeeded in identifying prostatic inflammation. In addition, it has been shown that the determination of leukocytes in post-massage urine is a feasible and reliable method when compared with the analysis of EPS, which is sometimes difficult to recover. However, an analysis of post-massage urine can be taken into consideration as an indicator in the diagnosis of prostatic inflammation, even though the evidence for the usefulness of the method in patients in whom EPS cannot be obtained is correlative so far [19•].

Category NIH IV, asymptomatic inflammatory prostatitis, is seen quite frequently when prostate biopsies are performed in men who present with an elevated level of prostate-specific antigen. Typically, these men are free of symptoms, and their biopsies reveal no cancerous transformation. In every study that is available regarding this benign category, prostatitis is the most common diagnosis, based on the presence of inflammation in the biopsy specimen. Another patient population that needs to be included are men who frequent infertility clinics in urology practices. These men really do not have symptoms other than infertility, yet they present with numerous white cells in the semen (leukospermia). This group of male patients might also be included in the asymptomatic category (subcategory IV).

Treatment

Antibiotics currently form the mainstay of clinical practice in North America as far as patients presenting with chronic prostatitis are concerned. This practice continues despite the fact that almost all standard localization cultures are negative (in most cases cultures are never formally performed, as recently shown by McNaughton-Collins *et al.* [17]). The reason for this therapeutic paradox must be that the average practising clinician feels that any antimicrobial therapy provides benefit for many patients with prostatitis. In fact, clinical trials tend to confirm that as many patients with demonstrable infection (i.e. chronic bacterial prostatitis) as without respond to antibiotics. The

successful culture of micro-organisms in prostate-specific specimens is complicated by the presence of inhibitory substances known to exist in prostate secretions and by the history in most patients of multiple previous courses of antibiotics. Then there is the almost insurmountable problem of interpreting the microbiological findings of EPS and semen in the presence of the contaminating, indigenous flora of the urethra. The prostate-specific specimen, EPS, ejaculate, and post-prostatic-massage urine must be cultured after passage through the potentially contaminated urethra. As recently demonstrated by the Giessen group in the largest study to date examining the effect of ciprofloxacin in chronic prostatitis [20••], eradication of the pathogen in EPS was achieved in 92% of patients 3 months after therapy and in approximately 70–80% of patients evaluated 12 and 24 months after treatment, respectively. However, eradication of the pathogen was unpredictable and was not possible in every case. Similar results have been obtained by Naber *et al.* [21•], who investigated the safety and efficiacy of the treatment of bacterial prostatitis with ciprofloxacin. Using ciprofloxacin a clinical response rate of 98.1% could be achieved.

Repetitive prostate massage, the traditional and standard therapy for prostatitis for decades (abandoned after 1968), has become repopularized [22,23]. This is partly because of the failure of traditional medical therapy to improve the symptoms of most patients with prostatitis, but also because of the belief that chronic bacterial infection exists in the prostate gland in blocked ducts or microabscesses. In fact, more bacteria are identified in specimens of prostatic fluid expressed after repetitive prostate massage than are identified in an initial single localization study. In a recent study [22], 46% of the 22 evaluable patients had a greater than 60% decrease (significant improvement) in the severity of symptoms, whereas 27% had a similar significant improvement in the frequency of symptoms when assessed last. Thirty-three per cent reported marked subjective improvement at the last evaluation. The combination of prostatic massage and antibiotics for treating difficult refractory cases of prostatitis may be promising, but its ultimate value needs to be confirmed.

Non-traditional dietary supplements are gaining popularity in the treatment of CPPS. Some patients report improvement with quercetin, which has recently been marketed under the name of Prosta-Q. In the first of its kind double-blind placebo trial [24••], comparing the effects of quercetin versus placebo, 67% of patients who were taking the bioflavonoid had an improvement in symptoms of at least 25%. Among the 17 patients who received Prosta-Q in the open-label study, 82% had at least a 25% improvement in symptom scores.

Another interesting option appears to be finasteride. Although the mechanism of its effect is still unclear, finasteride was shown to provide relief in a double-blind placebo-controlled trial [25]. The prostatitis symptom severity index and prostatism scores dropped significantly in patients in the finasteride group, and there were significant differences in the changes of prostate volume and in serum prostate-specific antigen concentrations between the finasteride and placebo groups.

Conclusion

Despite the significant progress that has been made in recent years, especially as a result of molecular techniques that help to identify microorganisms more easily than do conventional techniques, more research is needed to elucidate the aetiology, pathogenesis and pathophysiology of prostatitis and subsequently to improve the diagnosis and treatment of prostatitis.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 •• Litwin MS, McNaughton-Collins M, Fowler FJ Jr, *et al.* The National Institutes of Health Chronic Prostatitis Symptom Index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol 1999; 162:369–375.

A breakthrough collaborative work laying new foundations for the study of prostatitis in terms of diagnosis, evaluation and follow-up.

2 Collins MM, Stafford RS, O'Leary MP, Barry MJ. Distinguishing chronic prostatitis and benign prostatic hyperplasia: results of a national survey of physician visits. Urology 1999; 53:921–925.

3 •• Nickel JC, Nyberg LM, Hennenfent M. Research guidelines for chronic prostatitis: consensus report from the first National Institutes of Health International Prostatitis Collaborative Network. Urology 1999; 54:229–233.

A summary of the 1997 Guidelines for the new NIH prostatitis classification.

4 McNaughton-Collins M, O'Leary MP, Litwin MS, *et al.* Quality of life is impaired in men with chronic prostatitis: results from the NIH Cohort Study [Abstract 98]. J Urol 2000; 163 (Suppl.):23.

5 • Nickel JC. Chronic prostatitis: an infectious disease? Infect Urol 2000; 13:31–38.

A recent article by a world-known prostatitis expert summarizing the queries and conundrums in the field.

6 Shoskes DA, Mazurick C, Landis R, *et al.* Bacterial cultures of urine, prostatic fluid and semen of men with chronic pelvic pain syndrome: role of culture for 2 vs 5 days [Abstract 102]. J Urol 2000; 163 (Suppl.):24.

7 Shoskes DA, Shahed A. Presence of bacterial signal in expressed prostatic secretions predicts response to antibiotic therapy in men with chronic pelvic pain syndrome [Abstract 99]. J Urol 2000; 163 (Suppl.):23.

8 Krieger JN, Riley DE, Roberts MC, *et al.* Prokaryotic DNA sequences in patients with chronic prostatitis. J Clin Microbiol 1996; 34:3120–3128.

9 • Hochreiter WW, Duncan JL, Schaeffer AJ. Evaluation of the bacterial flora of the prostate using a 16S rRNA gene based polymerase chain reaction. J Urol 2000; 163:127–130.

An important investigation into normal prostatic flora.

10 •• True LD, Berger RE, Rothman I, *et al.* Prostate histopathology and the chronic prostatitis/chronic pelvic pain syndrome: a prospective biopsy study. J Urol 1999; 162:2014–2018.

A breakthrough study that correlates histopathology with leukocyte counts in men with CPPS.

11 Shahed A, Shoskes DA. Oxidative stress in prostatic fluid of men with chronic pelvic pain syndrome: correlation with bacterial growth and treatment response [Abstract 103]. J Urol 2000; 163 (Suppl.):24.

12 Nadler RB, Koch AE, Calhoun EA, *et al.* IL-1 beta and TNF-alpha in prostatic secretions are indicators in the evaluation of men with chronic prostatitis. J Urol 2000; 164:214–218.
•• An interesting study examining the importance of parameters of inflammation.

13 Elert A, von Knobloch R, Nusser R, *et al.* Isolated candidal prostatitis. J Urol 2000; 163:244.

14 Lawrence MA, Ginsberg D, Stein JP, *et al.* Coccidioidomycosis prostatitis associated with prostate cancer. Br J Urol Int 1999; 84:372–373.

15 Caballes RL, Caballes RA Jr. Primary cryptococcal prostatitis in an apparently uncompromised host. Prostate 1999; 39:119–122.

16 Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA 1999; 282:236–237.
•• A contemporary definition of prostatitis syndromes.

17 McNaughton-Collins M, Fowler FJ Jr, Elliott DB, *et al.* Diagnosing and treating prostatitis: do urologists use the four-glass test? Urology 2000; 55:403–407.

18 Krieger JN, Jacobs J, Ross SO. Detecting urethral and prostatic inflammation in patients with chronic prostatitis. Urology 2000; 55:186–192.

19 Ludwig M, Schroeder-Printzen I, Ludecke G, Weidner W. Comparison of expressed prostatic secretions with urine after prostatic massage a means to diagnose chronic prostatitis/inflammatory chronic pelvic pain syndrome. Urology 2000; 55:175–177.
• An important study concerning the usefulness of diagnostic tools in CPPS, particularly the investigations of lower urinary tract samples, outlines current standards of diagnostic protocols.

20 Weidner W, Ludwig M, Brahler E, Schiefer HG. Outcome of antibiotic therapy with ciprofloxacin in chronic bacterial prostatitis. Drugs 1999; 58 (Suppl. 2):103–106.
•• The largest therapeutic study to date evaluating the importance of the fluoroquinolone ciprofloxacin in the treatment of chronic bacterial prostatitis.

21 Naber KG, Busch W, Focht J. Ciprofloxacin in the treatment of chronic bacterial prostatitis: a prospective, non-comparative multicenter clinical trial with long-term follow-up. The German Prostatitis Study Group. Int J Antimicrob agents 2000; 14: 143–149.
• The most recent study on the efficacy of the treatment of bacterial prostatitis with fluoroquinolones.

22 Nickel JC, Downey J, Feliciano AE Jr, Hennenfent B. Repetitive prostatic massage therapy for chronic refractory prostatitis: the Philippine experience. Tech Urol 1999; 5:146–151.

23 Nickel JC, Alexander R, Anderson R, *et al.* Prostatitis unplugged? Prostatic massage revisited. Tech Urol 1999; 5:1–7.

24 Shoskes DA, Zeitlin SI, Shahed A, Rajfer J. Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. Urology 1999; 54:960–963.
•• The first ever double-blind study on the effects of bioflavonoids in prostatitis.

25 Leskinen M, Lukkarinen O, Marttila T. Effects of finasteride in patients with inflammatory chronic pelvic pain syndrome: a double-blind, placebo-controlled, pilot study. Urology 1999; 53:502–505.