Special Report on Prostatitis: State of the Art

Highlights of the Third Annual International Prostatitis Collaborative Network Meeting
October 23-25, 2000, Washington, DC

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The initial two meetings of the International Prostatitis Collaborative Network (IPCN), held in 1998 and 1999, accomplished the four original objectives of the collaborative group:

1. To review the recommendations of the NIH Prostatitis Steering Committee in regard to the new definition and classification system for the prostatitis syndrome.
2. To review the use of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) as a valid outcome measure in clinical research in prostatitis.
3. To develop International Consensus Guidelines for future research in the prostatitis syndromes.
4. To provide an international forum for the presentation of original research in prostatitis.

The new definition and classification of the chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is now accepted by this international prostatitis research group as the standard system to be used in clinical trials. The NIH-CPSI is accepted by researchers, journal editors, and regulatory bodies as a valid outcome measure in prostatitis trials. The IPCN is promoting the translation and validation of the NIH-CPSI in languages other than English. Consensus guidelines for research in CP/CPPS have been developed and published[1] and are now being employed in standardized prostatitis clinical treatment protocols. The largest collection of original research studies in prostatitis was presented at the second annual meeting of the IPCN in 1999.[2]

The third annual IPCN meeting convened in Washington in October 2000. Its objectives were:

1. To continue to provide an international forum for presentation of prostatitis research.
2. To begin the process of developing guidelines for the diagnosis and treatment of prostatitis.
3. To provide "State of the Art" updates in relevant fields in prostatitis research.

Reviewed by J. Curtis Nickel, MD, FRCSC, Queen's University, Kingston, Canada, for participants of the Third Annual International Prostatitis Collaborative Network Meeting

References

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2. Nickel JC, for participants of the Second Annual International Prostatitis Collaborative Network Meeting. Special report on prostatitis initiatives and future research. Highlights of the Second Annual International Prostatitis Collaborative Network Meeting; November 3-5, 1999; Bethesda, Md. *Rev Urol.* 2000;2:158-166.

Diagnosis and Treatment of Chronic Prostatitis

Reviewed by J. Curtis Nickel, MD

A panel of international experts in the diagnosis and treatment of prostatitis discussed standard and accepted diagnostic and therapeutic plans. Following consensus discussion with members of the IPCN, suggestions regarding diagnosis and treatment were developed (Table 1). These suggestions will be developed into guidelines as more information and data become available and as discussion continues at future annual meetings of the IPCN.

Pathologic Findings Associated with Chronic Prostatitis

Reviewed by Lawrence D. True, MD

The nature and extent of inflammatory cell infiltrates in prostate parenchyma of patients with CP/CPPS has not heretofore been systematically analyzed. We evaluated the nature and extent of prostate inflammation in biopsies from 97 patients who presented clinically with CP/CPPS and who satisfied NIH criteria for Category III Chronic Abacterial Prostatitis.[1] In all patients the inflammatory infiltrate was exclusively mononuclear, consisting predominantly of lymphocytes. There was a virtual absence of neutrophils, eosinophils, and basophils or mast cells. Furthermore, no patients had granulomatous inflammation. We developed an instrument to evaluate the distribution and intensity of inflammation that was designed to be readily applied by other institutions with, we hoped, high reproducibility. This instrument evaluated inflammation by distribution (glandular, periglandular, and/or stromal), extent (focal, multifocal, or diffuse) and intensity or grade (mild = fewer than 10 lymphocytes/high power field (hpf); moderate = 10 to 200 lymphocytes/hpf; severe = more than 200 lymphocytes/hpf).

Only 33% of patients had prostate inflammation. When present, inflammation was predominantly stromal. In fewer than 5% of patients was inflammation periglandular or glandular. In 28% it was mild. Only 5% of patients had moderate or severe inflammation. The number of inflammatory cells in expressed prostatic secretions did not correlate with the degree of tissue inflammation.

We concluded that CP/CPPS patients do not have significant prostate inflammation and that animal models with prostate inflammation are not representative models of CP/CPPS.

Table 1
Suggestions for Guidelines on Diagnosis and Treatment of Prostatitis

DIAGNOSIS
Mandatory
1. History
2. Physical examination, including digital rectal examination
3. Lower urinary tract localization test (4-glass or 2-glass test)

Recommended
1. Symptom inventory or index
2. Flow rate
3. Residual urine determination (by ultrasound)

Optional
1. Semen analysis and culture
2. Urethral swab for culture
3. Pressure flow studies
4. Video urodynamics (including flow–EMG studies)
5. Transrectal ultrasound of the prostate
6. Prostate-specific antigen (PSA)

TREATMENT
First-Line Therapy
1. Antibiotics
2. Alpha-blockers
3. Anti-inflammatory agents

Second-Line Therapy
1. Physical therapy
2. Microwave heat therapy
3. Phytotherapy (including bioflavanoids)

Third-Line Therapy
1. Finasteride
2. Pentosan polysulfate

Other
1. Surgery

Reference
1. 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.

Immunology and Prostatitis

Reviewed by Richard Alexander, MD

There is a growing body of evidence that some kind of immune response is occurring in the prostate whose cause, significance, and implications are completely unknown. Our work is based on the hypothesis that autoimmunity may contribute to the symptoms of CP/CPPS in some men.

Autoimmune diseases, such as rheumatoid arthritis, tend to be chronic, episodic, and relapsing and are commonly accompanied by pain and inflammation. In rheumatoid arthritis the joints are easily examined and the pain, deformity, and limitation of movement caused by the disease are readily apparent. If the same thing were occurring in the prostate, however, it would be much more difficult to determine, because the gland is not as readily examined and the innervation of the pelvis does not give rise to distinct localizing and specific symptoms.

An important clue to understanding prostatic autoimmunity is the common finding of inflammatory infiltrates in the prostate. Asymptomatic inflammatory prostatitis is very common when prostatic tissue is removed from a patient for any reason and examined histologically. Most men who have prostatic tissue sampled, as after transurethral resection of the prostate (TURP) or for a prostate biopsy for cancer, do not have the symptoms of CP/CPPS; hence the correlation between inflammatory infiltrates in the prostate and the clinical syndrome of CP/CPPS is poor. However, it is clear that inflammation always occurs for a reason, and there are many different types of inflammatory responses. It is my belief that understanding the

process of inflammation in the prostate will give us many important insights into the diseases of the gland, including autoimmune prostatitis.

We have found evidence of autoimmunity in some patients with CP/CPPS. Our work has concentrated on T lymphocytes, because these cells are responsible for recognizing antigens and generating an immune response. We found that men with CP/CPPS had a proliferative T-cell response to seminal plasma that was not found in normal men and that the antigen recognized derived from the prostate.[1] Further characterization of the antigen recognized in the seminal plasma demonstrated that prostate-specific antigen (PSA) is recognized by T lymphocytes from some men with CP/CPPS but not those from normal men.[2] We are presently characterizing a number of T-cell lines and clones to determine the precise antigen derived from PSA and the major histocompatibility complex (MHC) restriction element in patients with CP/CPPS and granulomatous prostatitis.

Further evidence supporting the autoimmune hypothesis in chronic prostatitis comes from the examination of semen for cytokines. Cytokines are small proteins secreted by cells of the immune system that are responsible for controlling the immune response. Since these cytokines are soluble and secreted locally at the site of an immune response, we reasoned that they may be detectable in the prostatic secretions and therefore in the semen. We found the pro-inflammatory cytokines TNFα and IL-1β in the semen of some men with CP/CPPS but not in that of normal men.[3] Other investigators have made similar observations.[4] These cytokines are also present in the joint fluid of patients with rheumatoid arthritis and appear to be a critical early mediator of joint inflammation. The presence of these cytokines in the semen of prostatitis patients is particularly interesting because pharmacologic agents aimed at blocking these inflammatory cytokines, particularly TNFα, have been found clearly to be effective therapies for other autoimmune diseases, such as rheumatoid arthritis. One such drug, Enbrel (etanercept) has been approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis and has demonstrated significant efficacy in clinical use. We have initiated a randomized, placebo-controlled clinical trial of Enbrel for CP/CPPS, and the trial remains open to recruitment at 2 centers in the US at present.

References

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3. Alexander RB, Ponniah S, Hasday J, Hebel JR. Elevated levels of pro-inflammatory cytokines in the semen of patients with chronic prostatitis/chronic pelvic pain syndrome. *Urology*. 1998;52:744-749.
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Infertility and Chronic Prostatitis

Reviewed by Wolfgang Weidner, MD

Infections of the male genitourinary tract contribute to male infertility to a variable extent, depending on the evidence of proven inflammation. Especially in CPPS, the exact identification of the infective agent contributes to its impact on alterations in the ejaculate. It appears to be proven that inflammation does not exert an objective negative effect on sperm density, motility, or even conventional morphology. In chronic bacterial prostatitis (NIH Cat II), changes in motility and morphology depend on the species of bacteria involved (eg, significant influence in the case of *E. coli*), the bacteria-sperm ratio, and the time of potential bacterial growth.[1] Concerning morphology, only analysis according to strict criteria (Tygerberg) provides evidence for a decreased number of morphologically altered sperm; especially, acrosomal defects appear to be increased in patients with type IIIa or IIIb prostatitis. Inflammatory obstruction is insignificant in prostatitis patients, meaning that obstructive azoospermia does not play a clinical role in the daily work-up. This is associated with decreased secretory function that is evident from prostatic (gamma-GT, zinc), vesicular (fructose), and epididymal (alpha-glucosidase) secretory parameters.

Although leukocytospermia is generally associated with bacterial ejaculate infection, it needs to be proven that leukocytospermia is increased significantly in type II and IIIa CPPS over levels seen in type IIIb and in controls. It is not proven whether this leukocytospermia is always associated with evidence of reactive oxygen species (oxidative stress). Elevated cytokines may also be correlated with an inflammatory leukocyte response in prostatic secretions. These cytokines may play a role in decreased sperm function and sperm-egg interaction that has been widely neglected so far. This is also apparent for the detection of seminal plasma sperm antibodies, which occur in very low titers in types of prostatitis.

In conclusion, the impact of different types of CPSS on semen morphology and infertility is only partially understood. The therapeutic implications are often unclear; further basic and clinical research is needed in this specialized field.

Reference

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Phytotherapy in Chronic Prostatitis

Reviewed by Daniel Shoskes, MD

The rush of consumers toward phytotherapy and other alternative/complementary therapies is well documented. It should not be surprising, therefore, that patients with chronic prostatitis, a chronic disease with a very poor record of cure or control using conventional medications, very frequently turn to phytotherapy. Indeed, preliminary clinical evidence suggests that phytotherapy might be the initial treatment of choice in nonbacterial prostatitis (category III CP/CPPS prostatitis/chronic pelvic pain syndrome).

There are several potential advantages to phytotherapy. It has a high degree of patient acceptance; it is often less expensive than pharmaceuticals; and it may have unique actions not duplicated by other drugs. There are, however, several potential disadvantages. Foremost among them is the lack of FDA oversight and quality control, at least in the United States. Several consumer watchdog groups have documented the highly variable content of phytochemical products. In some cases fewer than 30% of the products bought actually had the active agents in them. Furthermore, no side effect or drug interaction databases are maintained, and serious complications can potentially occur when phytochemicals are taken with other drugs. Finally, while extravagant claims of efficacy are common, there have been few well-designed clinical trials to back them up.

In chronic prostatitis, the only placebo-controlled, double-blind trial has been for the bioflavonoid quercetin.[1] Quercetin has documented antiinflammatory and antioxidant properties. In the trial, patients taking placebo had a mean improvement in NIH symptom score from 20.2 to 18.8 (not significant), while those taking the bioflavonoid had a mean improvement from 21.0 to 13.1 (P = .003). Twenty percent of patients taking placebo and 67% of patients taking the bioflavonoid had an improvement of symptoms of at least 25%. Improvement in symptoms was correlated objectively with a reduction in oxidative stress in the prostatic fluid.[2] The bee pollen product cernilton has been studied in open-label nonrandomized fashion in several studies in Europe. Rugendorff et al. found that 78% of patients with nonbacterial prostatitis or prostatodynia had improvement following treatment with 1 g of cernilton 3 times per day, provided that there were no complicating factors such as prostatic calculi or bladder neck sclerosis.[3]

Other agents that have been used for benign prostatic hypertrophy have also been used by patients with prostatitis, although there are no published studies of their efficacy for prostatitis. These agents include zinc, saw palmetto, and pygeum.

In summary, phytotherapy may provide a new avenue for patient therapy in chronic pelvic pain syndrome, although quality control of these agents is currently a major problem. Phytotherapy should be subjected to the same rigorous clinical testing using well-designed trials and validated end points required for other treatments of this disorder.

References

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Diagnosis and Treatment of Chronic Abacterial Prostatitis

Reviewed by Mary McNaughton Collins, MD, MPH

The optimal management of chronic abacterial prostatitis is not known. The wide scope of recommended treatments for chronic prostatitis indicates how little is known about what causes the condition and how to diagnose and treat it. Chronic prostatitis often causes frustration on the part of the physician and confusion and dissatisfaction on the part of the patient. Thresholds for referral vary, and the condition carries the potential for inappropriate antibiotic use. We sought to examine the evidence regarding the effectiveness of therapies for chronic abacterial prostatitis.

We made a systematic review of the literature[1] to answer the question: Are there effective therapies for chronic abacterial prostatitis? Studies were identified by searching MEDLINE (1966-1999), the Cochrane Library, and bibliographies of identified articles and reviews and by contacting an expert. Treatment articles were included if they reported on randomized or controlled trials. No language restrictions were applied. For each article, 2 investigators independently extracted key data on study design, patient characteristics, treatment characteristics, and outcomes.

Fourteen treatment trials met the inclusion criteria: 7 randomized controlled trials and 7 controlled clinical trials. The disparity among studies in design, interventions, and other factors precluded quantitative analysis or pooling of the findings. Treatment trials included 570 men (mean age in various trials ranged from 38 to 45)

and evaluated medications used to treat benign prostatic hyperplasia (finasteride, alfuzosin, phenoxybenzamine), antiinflammatory drugs (pentosan polysulfate sodium, seaprose s), antibiotics (minocycline), thermotherapy (transurethral microwave themotherapy and transrectal microwave hyperthermia), and miscellaneous medications (allopurinol, amino acid preparation). No trial was done in the United States.

The few treatment trials were methodologically weak and involved small sample sizes. Treatment trials are urgently needed, and such trials should report important patient characteristics (ie, ethnicity), details of the study design, assessment measures, and clinical outcomes. Physicians should understand the impact of chronic prostatitis on quality of life and the potential for lost productivity, and they should avoid the routine use of unsubstantiated treatments that may have more adverse events and greater costs than potential benefits. The routine use of antibiotics and alpha blockers to treat chronic abacterial prostatitis is not supported by the existing evidence. ■

Reference

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