ELSEVIER

OVERVIEW SUMMARY STATEMENT

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ABSTRACT

Members of the Chronic Prostatitis Collaborative Research Network (CPCRN) met in a 1-day symposium to review recent findings and to debate unanswered issues in the diagnosis and management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The meeting was focused on producing an overview summary statement that would, as nearly as possible, represent the consensus views of the attendees. As discussed below, the participants agreed that a history, physical examination, and urinalysis/urine culture are mandatory for the evaluation of all patients presenting with CP/CPPS, with other assessments categorized as recommended or optional, depending on the history and physical findings. Observations and suggestions regarding first- and second-line therapies are also offered, with the recognition that randomized, placebo-controlled trials to guide selection of therapies for chronic nonbacterial prostatitis are currently lacking. UROLOGY **60** (Suppl 6A): 1–4, 2002. © 2002, Elsevier Science Inc.

The Chronic Prostatitis Collaborative Research Network (CPCRN) was formed in 1997 by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) to conduct research in chronic prostatitis (CP). The Network launched a prospective longitudinal Chronic Prostatitis Cohort Study,[1] which is collecting data on the natural treated history of the disorder, as well as outcomes of investigational treatments. The Network also developed the first validated instrument for assessing symptom severity in CP, the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI).[2]

Members of the CPCRN met in a 1-day symposium held in Chantilly, Virginia, March 26, 2002, to present and discuss updated information from ongoing trials, including the Chronic Prostatitis Cohort Study, as well as results of recent pilot studies examining a number of pharmacologic and nonpharmacologic therapies. The symposium format combined brief presentations with extended periods of open discussion, which are included in abridged form in this supplement to *Urology*.

In the discussions, symposium participants focused on applying the presented findings to the development of a working consensus on the diagnosis and appropriate management of chronic nonbacterial prostatitis, and to identifying unresolved issues that should be the focus of future investigations. Although much has been learned in the 5 years since the CPCRN was formed, symposium participants emphasized that the information available does not allow the development of evidence-based guidelines or recommendations. This summary report is instead offered as a clinically useful update on diagnosis and management of chronic nonbacterial prostatitis.

DIAGNOSTIC CRITERIA

In a 1995 NIDDK-sponsored workshop on CP, the decision was made to characterize chronic non-

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bacterial prostatitis as a chronic pelvic pain syndrome (CPPS), in recognition that pelvic pain complaints were the most characteristic symptoms and that the role of the prostate in producing symptoms is in fact still unknown. This entity, chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS), or category III prostatitis, was further categorized as having 2 subclasses, inflammatory and noninflammatory, based on the presence or absence of leukocytes in the expressed prostatic secretions, post–prostate massage urine, and semen.[3]

Given the limited data on etiology and mechanisms of category III prostatitis, CP/CPPS cannot be rigidly defined. Differing criteria can be applied to make the diagnostic category more or less inclusive. Symposium participants suggested that CP/CPPS could be broadly defined as the presence of characteristic symptoms of discomfort or pain in the pelvic region for a period $\geq$3 months within the past 6 months. The NIH Chronic Prostatitis Symptom Index (NIH-CPSI) is an excellent tool for qualifying the severity of the patient's symptoms. CP/CPPS is primarily a diagnosis of exclusion, with diagnostic assessment focused on detecting any underlying abnormalities or primary disorders that may be producing the pelvic pain and associated symptoms.

Ongoing research is directed at identifying laboratory markers that might serve to corroborate the patient's complaint and to differentiate any subgroups that might differ in disease mechanisms and treatment response. Although some preliminary studies have identified inflammatory markers of potential importance, there are as yet no objective measures that can be applied for diagnosis or monitoring. In fact, as discussed below, recent data now available from the Chronic Prostatitis Cohort Study[4] suggest that the leukocyte counts used to distinguish subcategories of CP/CPPS may have limited clinical utility.

DIAGNOSTIC ASSESSMENT

Recommendations for the evaluation of patients presenting with CP are presented in the summary by Nickel contained in these proceedings. Briefly, symposium participants considered that a history, physical examination, and urinalysis/urine culture are mandatory for the evaluation of all patients presenting with CP/CPPS.

Participants felt that the NIH-CPSI (reproduced as Table I in the summary by Litwin) has value for the diagnosis and follow-up treatment of patients with CP, although it was developed primarily as a research instrument and its clinical utility has not been fully evaluated. Nonetheless, it has been used for this purpose by practicing urologists. Lower urinary tract localization studies have long been considered by researchers, if not by clinicians, to be necessary for the work-up of all patients presenting with CP. In the Chronic Prostatitis Cohort study, 8% of the patients had positive localization studies for established urinary pathogens, and >60% had localizing cultures for any type of bacteria, suggesting a possible bacterial cause for their pain and the potential for benefit from antimicrobial therapy. Symposium participants felt that there was little evidence that the results provided useful guidance to the management of CP/CPPS, and therefore, localization studies were considered recommended, rather than mandatory, in the initial assessment of patients presenting with CP/CPPS. However, such studies may prove very helpful for patients with a history of urinary tract infection (bacteriuria, possible category II), where results may guide therapeutic decisions.

There is insufficient evidence to recommend urine cytology for all patients presenting with CP/CPPS. However, urine cytology is mandatory for patients with microscopic hematuria. It is recommended for the evaluation of patients with irritative voiding symptoms (ie, suprapubic pain or dysuria). Cystoscopy can identify potentially important and treatable lower urinary tract abnormalities. Indications for cystoscopy in patients include hematuria, suspicious cytology, abnormal urodynamics, and irritative or obstructive voiding symptoms.

SIGNIFICANCE OF LEUKOCYTES AND THE ROLE OF INFLAMMATION IN CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

The role of inflammation in the onset and perpetuation of CP/CPPS is at the present time unknown. Some patients may have inflammation as the cause of their symptoms. However, white blood cells in the fluids (semen, post–prostate massage urine or expressed prostatic secretions) do not appear to be the optimal marker of inflammation, and the current categorization of CP/CPPS as inflammatory or noninflammatory based on leukocyte counts appears to offer little clinically useful information. As the Cohort Study has shown,[4] leukocyte counts do not correlate with symptom severity, nor do they appear to have great value in selecting treatment or predicting treatment response. However, there is preliminary evidence suggesting that other inflammatory markers, in particular, interleukin-1β and tumor necrosis factor-α, may be predictive. Several studies that have looked at markers of oxidative stress and cytokine levels have found a correlation with symptoms and/or response to treatment.[5–8] Further investigation in this area may lead to the development of

clinically useful assays as well as provide insights into the mechanisms underlying CP/CPPS.

SIGNIFICANCE OF BACTERIAL PRESENCE AND THE ROLE OF INFECTION IN CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

Current evidence does not establish that bacteria are the cause of CP/CPPS. However, recent findings indicate that many patients with CP/CPPS have molecular markers indicative of past or present colonization or infection, despite repeated negative cultures.[9] These organisms may be pathogens that cannot be isolated from the fluids available for testing or that cannot be cultured on conventional media. Another hypothesis is that bacterial presence may be the stimulus for an immune response that results in inflammation and pain.

The symposium participants concluded that inflammation and bacterial presence may be important in the etiology of CP/CPPS but cannot be adequately assessed with current clinically available methods.

TREATMENT OF CHRONIC PROSTATITIS

Antimicrobial therapy must be considered an unproven therapy for the treatment of CP/CPPS, because to date, there are no published randomized placebo-controlled trials to establish its efficacy. Nonetheless, both clinical experience and a recent open-label study indicate that antimicrobial therapy often provides some degree of symptom relief in CP, regardless of disease category.[10]

The observed benefit may ultimately prove to be a placebo effect, but it is also possible that antimicrobial agents are effective against organisms that cannot be isolated or cultured by currently available clinical microbiology techniques. It is also possible that the anti-inflammatory effects of the antimicrobials may account for part or all of the symptom relief reported by patients. Given the absence of proven therapies in CP/CPPS, it is reasonable to offer patients a single 4- to 6-week trial of antimicrobial therapy. If the agent does not provide at least temporary symptom relief, this approach should not be repeated.

α-Blockers, such as terazosin and alfuzosin, are commonly used to treat CP/CPPS, although, again, there are few well-designed studies to evaluate their efficacy. A number of observations of the physiology and pathophysiology of the lower urinary tract have been adduced to support the choice of α-blockers for the management of CP/CPPS, as summarized by Datta later in this supplement. For now, α-blockers are a reasonable option for second-line therapy, particularly if flow rate and residual urine determinations or urodynamic studies suggest lower urinary tract dysfunction.

Anti-inflammatory agents have potential, although as-yet unproven efficacy. The only randomized placebo-controlled trial of this class of medication found a statistically significant response for 50 mg/day rofecoxib, a cyclooxygenase-2 inhibitor, on some but not all endpoints evaluated.[11] At the present time, a short course of a nonsteroidal anti-inflammatory agent is considered to be a reasonable treatment option, given the favorable adverse-effect profile, the promising results seen in small preliminary studies, and the increasing evidence that anti-inflammatory markers are elevated in CP/CPPS.

There are 2 other agents that may be exerting anti-inflammatory effects and that have shown efficacy in small placebo-controlled trials: pentosan polysulfate and finasteride.[12,13] These therapies mentioned above all merit further investigation in larger and longer duration trials.

Cernilton and quercetin are 2 herbal therapies that have shown benefit in small preliminary studies. Cernilton, a pollen extract, has been evaluated in an open-label study in selected patients.[14] Quercetin, a bioflavonoid found in red wine, onions, and other foods, was found effective in a small but well-designed placebo-controlled trial as well as a preliminary open-label study.[15,16] Other popular "prostatic health" supplements, including saw palmetto, stinging nettle, *Pygeum africanum*, and zinc, do not appear to be effective for CP/CPPS. Quercetin and Cernilton produce few if any adverse effects and may offer meaningful benefit to a substantial proportion of CP/CPPS patients.

Nonpharmacologic therapies for CP/CPPS include biofeedback and a number of heat modalities. Biofeedback has been studied only in a very small number of patients. However, approximately 33% of patients in a treatment-resistant population had meaningful improvement after an 11-week program of biofeedback-based pelvic floor training.[17] Where available, biofeedback can be considered for treatment-resistant patients in whom flow rate and residual urine determination and/or urodynamic studies suggest voiding dysfunction.

A number of thermal therapies for CP/CPPS have been tried, but differences in patient selection, modality, delivery, achieved temperatures, and outcome measures render it difficult or impossible to compare reports to evaluate the overall success of this approach. Because of the significant morbidity associated with these therapies, they should probably be reserved for treatment-resistant patients whose quality of life is severely affected by the disorder.

FUTURE CLINICAL TRIALS

The uncertainty about the etiology, mechanisms, and treatment of CP/CPPS can be discouraging to both patients and clinicians. Nonetheless, significant progress has been made in the last few years in the understanding and management of this disorder. The many small preliminary studies summarized throughout these proceedings suggest—if they cannot demonstrate—that there are a number of promising therapies that can be tried, most with quite tolerable adverse-effect profiles.

Importantly, well-designed studies are now in various stages of planning, recruitment, and data analysis. Already the Chronic Prostatitis Cohort Study is providing abundant demographic and epidemiologic data[1] that may aid in diagnosis and prognosis, as well as provide useful leads for investigations into the etiology of CP/CPPS. Continued follow-up investigation will likely yield information for use in planning clinical trials, perhaps helping to identify subgroups of patients with higher response rates to particular therapies.

The symposium closed with a discussion of what new trials should be instituted. Among the areas identified as deserving further investigation were (1) larger placebo-controlled studies of anti-inflammatory agents; (2) larger-scale phytotherapeutic trials; (3) a well-designed trial of prostatic massage; (4) development and study of a more cost-effective approach for biofeedback training; and (5) a multicenter thermal therapy trial, using a standardized approach, validated outcome instruments, and a sham therapy control group.

CP/CPPS is now achieving greater recognition as a significant disorder. As basic and clinical investigations into the pathophysiology and treatment of CP/CPPS continue, patients and clinicians can confidently expect more efficacious and more evidenced-based options for the management of this common and distressing disorder.

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