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Treatment of chronic prostatitis

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Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common but poorly understood condition. Previously known as 'nonbacterial' prostatitis, CP/CPPS is the most common clinical prostatitis syndrome. Despite this, it is defined only by symptoms—objective tests have failed to clearly define a subset of patients so that etiology can be determined, natural history predicted, and therapy targeted. Current opinions about the cause of CP/CPPS are plagued by assumptions that have been accepted simply because more compelling explanations have not emerged. But new insights arising from recent studies are challenging these long-held beliefs.

CP/CPPS is principally defined as pain in a man's pelvic region that persists for at least 3 months. This primary symptom is often accompanied by voiding difficulties and effects on sexual function, usually pain related to ejaculation.[1] As might be expected in light of this broad and vague definition, CP/CPPS is a commonly diagnosed problem—estimates from outpatient surveys indicate that 2 million men seek treatment for CP/CPPS each year in the US.[2] Symptoms tend to be episodic, relapsing and intermittent, which further complicates the efficacy of therapeutic interventions.

Despite its name, it is by no means certain that CP/CPPS is associated with inflammation of the prostate or is even a disease of the prostate. The use of common CP/CPPS treatments is based on empiric observations; few objective data are available to guide clinicians. The widespread use of antimicrobials—the most commonly prescribed drugs for CP/CPPS[3]—is based on the decades-old assumption that infection is the cause of this syndrome.

The current classification scheme for the clinical prostatitis syndromes is also based on the assumption that infection has a causative role.[4] Men with acute symptoms whose midstream urine is positive for uropathogens (*Enterobacteraciae*, *Enterococcus*) are categorized as having type I or acute bacterial prostatitis, whereas those with chronic symptoms and a positive urine culture are diagnosed with type II (chronic or recurrent bacterial prostatitis). Type III is defined by negative midstream urine culture and chronic symptoms. Previously known as 'nonbacterial' prostatitis and now dubbed CP/CPPS, type III is the most common of the clinical prostatitis syndromes. It is subcategorized according to the presence (TYPE IIIA) or absence (TYPE IIIB) of leukocytes in prostatic fluid expressed in response to prostate massage. If the prostatic fluid of men categorized as type III has a tenfold higher count of uropathogens than the first 10 ml of voided urine, then they are considered to have chronic bacterial prostatitis. This definition— based on quantitative culture of urine fractions as described by Meares *et al.*[5] more than 30 years ago and known as the four-glass test—is still used by the US FDA to identify patients with chronic bacterial prostatitis for the purpose of determining if an antimicrobial drug is a safe and effective treatment.

The problem with this classification scheme is that it has never been validated. Recent large clinical trials performed by the Chronic Prostatitis Collaborative Research Network (CPCRN) have identified serious shortcomings in this framework. The CPCRN comprises 11 clinical centers in North America funded by the National Institutes of Health. All 11 centers are based on urology practices at tertiary care medical centers. Here, I present the results of selected studies conducted by the CPCRN in its 7 years of operation.

The CPCRN created a validated measure for CP/CPPS symptoms called the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI).[6] A baseline study of 488 men with CP/CPPS recruited prospectively to a central database showed no correlation between symptoms and the presence of leukocytes in prostatic fluid or uropathogenic bacteria in the prostate (i.e. a positive four-glass test.)[3] These findings challenge the notion that inflammation and infection are significant factors in the etiology of CP/CPPS.

A case-control study comparing results of the four-glass test in the 488 patients with CP/CPPS with those of 121 simultaneously-recruited,

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age-matched, asymptomatic men[7] failed to detect a difference between the two groups. Localization of *Escherichia coli* and other *Enterobacteraciae* did not differ in symptomatic and asymptomatic men. In addition, commensural skin organisms, such as *Staphylococcus* and *Streptococcus*, were detected in the prostates of the same proportion of men in each group (70%). This indicates that these bacteria alone do not cause CP/CPPS.

The enumeration of leukocytes in prostatic fluid by brightfield microscopy distinguishes type IIIa (inflammatory) from type IIIb (non-inflammatory) prostatitis. Leukocyte number is significantly higher in patients with CP/CPPS compared to asymptomatic controls.[7] For example, the prostatic fluid of 32% of men with CP/CPPS contained more than 10 leukocytes per high-power field compared to 20% of age-matched, asymptomatic men. While this difference is unlikely to be due to random chance alone, the degree of overlap indicates that subcategorization of type III prostatitis on the basis of leukocyte status is not clinically meaningful and does not contribute to improving patient management.

The CPCRN tested the *a priori* standard oral therapies for men with CP/CPPS in a randomized, prospective, placebo-controlled trial. The antibiotic ciprofloxacin, the ALPHA BLOCKER tamsulosin and the two drugs in combination were tested in men with long-standing, refractory CP/CPPS, according to a 2 × 2 FACTORIAL DESIGN.[8] The study showed no difference in NIH-CPSI scores or response rate after 6 weeks of treatment.[9] This indicates that ciprofloxacin and tamsulosin do not substantially relieve symptoms in men with long-standing, refractory CP/CPPS.

The main limitation of these studies is generalization of their findings to patients in the community setting. It is possible that men with long-standing and refractory symptoms are more likely to be referred to tertiary medical centers, and therefore enrolled in clinical trials. Indeed, many CPCRN studies enroll patients in this category.[8] These study participants may be end-stage prostatitis patients who failed treatment with the study drugs, which are commonly prescribed in the community setting. Men with less severe symptoms that are cured by medical therapy may in fact be more representative of the CP/CPPS population as a whole, but this is not known. The proportions of these subpopulations referred to urologists, compared to primary care providers or internists, could also differ significantly.

Two recent studies conducted outside North America indicate that longer treatment with the alpha blockers terazosin[10] and alfuzosin[11] in men not previously treated with alpha blockers was efficacious. Until treatment patterns for CP/CPPS change, it will be difficult to test antimicrobials in naïve men with symptoms of more than 3 months duration. In the meantime, an empiric trial of antimicrobials in men with newly-detected symptoms consistent with prostatitis is a reasonable alternative—but ongoing empiric administration of antimicrobials to men with long-standing CP/CPPS should be abandoned.

In conclusion, data from recent studies do not support the tenets upon which the diagnosis and treatment of prostatitis have been based for the past three decades. The four-glass test and repeated use of antimicrobial drugs for persistent CP/CPPS should be abandoned. It is time for urologists to accept the findings of careful clinical trials rather than outdated, untested dogma when deciding how best to help their patients with long-standing CP/CPPS manage this common and distressing problem.

GLOSSARY

CP/CPPS TYPE IIIA
Negative midstream urine culture with leukocytes present in prostatic fluid (expressed prostatic secretions or post-prostate massage urine)

CP/CPPS TYPE IIIB
Negative midstream urine culture with leukocytes absent from prostatic fluid (expressed prostatic secretions or post-prostate massage urine)

ALPHA BLOCKERS
These drugs—prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin—relax smooth muscle of the prostate and at the base of the bladder

2 × 2 FACTORIAL DESIGN
A clinical trial that tests two different treatments individually and together, and makes overlapping comparisons to determine outcomes

Competing interests
The author declared he has no competing interests.

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