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# CHRONIC PROSTATITIS: EPIDEMIOLOGY AND ROLE OF INFECTION

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**ABSTRACT**

We review the epidemiology of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and the role of infectious agents, emphasizing critical data necessary to define current research issues. The epidemiologic literature is limited, but the worldwide prevalence appears to be in the range of 2% to 10%, indicating that CP/CPPS represents an important international health problem. Recent molecular studies have documented bacterial DNA sequences in prostate tissue from CP/CPPS patients. These data suggest that colonization and/or infection occurs in the prostates of many patients with CP/CPPS. Further molecular research is needed to define the role of bacteria in the etiology of CP/CPPS. UROLOGY **60** (Suppl 6A): 8–13, 2002.


In his classic 1980 monograph, Dr. Stamey stated that "50% of adult men" experience symptoms of prostatitis at some point in their lives.[1] Until the past few years, however, there were few hard data available on this subject.[2]

## EPIDEMIOLOGY OF CHRONIC PROSTATITIS

From an epidemiologic standpoint, there are ≥4 critical concepts that are important for evaluation of a study: (1) the study should be population based, not a selected patient series from tertiary care institutions; (2) there should be a clear case definition with some relation to clinical practice; (3) there should be a standard strategy for surveying the population, ideally incorporating a mechanism to verify cases identified in the survey study; and (4) the population studied should be large enough to provide reasonable power for the statistical comparisons. Fortunately, there are a number of recent studies that incorporate some or many of these desirable characteristics.

Published peer-reviewed studies of various populations from the United States are summarized in Table I.[3–6] Overall, the prevalence of prostatitis-like symptoms (defined variously) ranged from 5% among Wisconsin National guardsmen[3] to 16% among health-care professionals.[6]

Published peer-reviewed studies of non-US populations are summarized in Table II.[7,8] In these 2 studies the prevalence of prostatitis-like symptoms was 10% among patients of family practitioners in Canada[7] and 14% among randomly selected Finnish men.[8]

In addition, 4 unpublished studies were presented at the 2001 and 2002 American Urological Association (AUA) Annual Meetings (Table III).[9–12] Although drawing conclusions from unpublished studies is certainly problematic when the methodology is not available for review, the scarcity of good epidemiologic data renders these recent studies worth inclusion. Of the 4 studies, 3 were conducted in Asia and the fourth was from the United States. The prevalence of prostatitis-like symptoms ranged from 2% among community-dwelling men in Minnesota[11] to 9% in a random sample of men in Penang, Malaysia.[9]

### *Conclusions*

Prostatitis-like symptoms represent an important international health problem. The precise prevalence is uncertain but appears to be in the 2% to 10% range. Depending on the definition, this may range as high as 16% (by history).

*Research Issues.* These studies provide an important foundation for a research agenda. Future studies should be population based. The case definition should be clear and have some relation to clinical practice. Clinical evaluation is necessary to verify

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**TABLE I.** ***Published population-based studies of prostatitis (USA)***

| Study | Population | N (age, yr) | Prevalence of Prostatitis-like Symptoms and/or Diagnosis |
|---|---|---|---|
| Moon (1997)[3] | Wisconsin National Guard | 184 men (20–49) | Symptoms: 5% |
| Roberts *et al.,* (1998)[4] | Olmsted County, Minnesota | 2115 men (40–79) | Symptoms: 9% |
| Collins *et al.,* (1998)[5] | National Ambulatory Medical Care Survey | 58,955 visits (>18) | Diagnosis: urology, 8%<br>Primary care: 1% |
| Collins *et al.,* (2002)[6] | Health-care professionals without prostate cancer | 31,681 men (40–75) | Self-reported history: 16% |

**TABLE II.** ***Published population-based studies of prostatitis (non-USA)***

| Study | Population | N (Age, yr) | Prevalence of Prostatitis-like Symptoms |
|---|---|---|---|
| Mehik *et al.*, Finland (2000)[8] | Randomly selected (Oulu and Lapland provinces) | 1832 (20–59) | 14.2%* |
| Nickel *et al.*, Canada (2001)[7] | Patients of family practitioners (Lennox and Addington counties) | 868 (20–74) | 9.7% |

** Lifetime prevalence.*

**TABLE III.** ***Unpublished population-based studies of prostatitis***

| Study | Population | N (Age, yr) | Prevalence |
|---|---|---|---|
| Khiaw-ngiap *et al.*, Singapore (2001)[10] | 75% Chinese, 12% Malay, 9% Indian | 845 (21–70) | 2.5% |
| Roberts *et al.*, USA (2001)[11] | Random sample of community-dwelling men (Olmsted County, Minnesota) | 1,507 (40–79) | 16% GU pain, 2.2% prostatitis |
| Kunishima *et al.*, Japan (2001)[12] | Random sample (Hokkaido) | 502 (20–79) | 5% |
| Cheah *et al.*, Malaysia (2002)[9] | Random sample (Penang) | 3147 (20–50) | 8.7% |

that chronic prostatitis (CP) is responsible for subjects' symptoms. It is also important to limit confounding issues, including treatment bias, selection bias, and referral bias.

## ROLE OF INFECTION IN CHRONIC PROSTATITIS

Estimates are that anywhere from 2 million[4] to 8 million[13] outpatient visits per year in the United States are for prostatitis, with antimicrobial agents prescribed for most patients. The problem is that well-documented infections detected by traditional culture methods are exceedingly uncommon. For example, in our clinic, only about 7% of patients with CP have chronic bacterial prostatitis.[14]

In the National Institutes of Health (NIH) consensus classification, most patients are classified as having chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).[15] There are 2 subgroups. Patients with white blood cells in their prostatic fluid, post–prostate massage urine, or seminal fluid are classified in the inflammatory category. Patients without white blood cells in any of these samples are classified in the noninflammatory category. There are few data supporting rational treatment decisions for either category.

There is empirical support for a potential role of genitourinary tract infection in CP/CPPS. Antimicrobials often provide transient or partial relief of symptoms, and standard practice is to provide multiple courses of antimicrobials.[16] In addition, microbiologic data support a potential role of cryptic microorganisms in CP/CPPS.[17] Organisms suggested as important in the literature include (1) *Chlamydia trachomatis*,[17–19] (2) *Ureaplasma urealyticum*, (3) other genital mycoplasmas,[20,21] and (4) the protozoan pathogen *Trichomonas vaginalis*.[22,23] Other potentially important organisms are (1) *Neisseria gonorrhea*, which was a common cause of prostatitis in the preantibiotic era; (2) genital viruses, particularly herpes simplex type 1, herpes simplex type 2, and cytomegalovirus; (3) fungi; and (4) various other anaerobic and gram-positive

bacteria.[24–26] Drawing on this important work, our laboratory has performed a series of studies to investigate the potential role of uncommon microorganisms in "nonbacterial" CP.

### *Initial studies*

We had limited success in identifying pathogens in noninvasive specimens, such as urine, expressed prostatic secretions (EPS), and urethral swabs.[14,27] This led us to investigate prostate tissue, obtained via a perineal approach and cultured in an anaerobic research laboratory.[28] We evaluated 85 men who met the NIH definition of CP/CPPS. Subjects had urethral swabs, lower tract localization cultures, and cultures of perineal prostate biopsies. Patients with leukocytes in EPS were more likely to have any bacteria of any kind isolated ($P = 0.01$), positive anaerobic bacterial cultures ($P = 0.03$), higher total bacterial counts ($P = 0.02$), and more species isolated ($P = 0.02$). No single species or group of species was associated with prostatic inflammation. These observations led to 2 hypotheses: (1) that colonization/invasion of the prostate may occur more commonly than is appreciated by standard microbiologic techniques, and (2) that such colonization might be associated with CP/CPPS.

### *Comparison of patients with inflammatory and noninflammatory CP/CPPS*

We selected molecular approaches based on a number of observations.[29,30] Culture is challenging because of inhibitory substances in semen, EPS, and prostate tissue. Many patients have had numerous previous courses of antimicrobials that could interfere with cultivation of microorganisms. Finally, many organisms are not cultivable, even under the most refined present conditions. Environmental studies suggest that most microorganisms do not multiply on conventional media.[31] Although a higher proportion of cultivable bacteria are known in humans, this source still contains a significant number of uncharacterized species that grow poorly on conventional media.[29,30]

*Methods.* We used 2 complementary approaches using polymerase chain reaction (PCR) technology. Detection by this technology does not require microorganisms to survive in laboratory conditions. First, we developed specific PCR assays for each pathogen previously implicated, then validated these assays for prostate tissue specimens.[29] The specific PCR probes were directed at *C. trachomatis*, *T. vaginalis*, all of the genital mycoplasmas (*Mycoplasma hominis*, *U. urealyticum*, and *Mycoplasma genitalium*), as well as a general mycoplasma probe and probes for the herpes simplex viruses (type 1 and type 2) and cytomegalovirus. Second, we used broad-spectrum PCR assays to identify bacterial DNA sequences. Primer/probes were directed at 2 targets, including common tetracycline resistance genes and bacterial ribosomal-encoding genes (16S rDNAs). Tetracycline resistance genes are widely distributed among urogenital bacteria.[32,33] The bacterial ribosomal-encoding genes are distinct from the mammalian ribosomal genes, so they are easily distinguished from human DNA. The 475 base pair products are then cloned in an attenuated strain of *Escherichia coli K12* and sequenced. Homology searches compared the identified sequences with the available databanks (both the GenBank [National Center for Technology Information, Bethesda, MD] and the European Molecular Biology Laboratory [EMBL; Heidelberg, Germany] databases). This resulted in many firm identifications as well as classification of all bacteria detected by extensive phylogenetic analyses.

*Results.* Over 5 years, we evaluated 135 men by standard clinical evaluation, including history and physical examination, symptom scores, uroflowmetry, and an ultrasound residual urine determination. Microbiologic studies included (1) studies for fastidious organisms (gonorrhea, *C. trachomatis*, *T. vaginalis*, and genital mycoplasmas), (2) lower urinary tract localization cultures, and (3) chamber counts of EPS leukocytes. These studies included a protocol with >1000 physician visits, including ≥4 visits for each of 260 men evaluated to select the 135 subjects in the study.[29] We excluded patients with bacteriuria, bacterial prostatitis (either acute or chronic), urethritis (based on finding a positive urethral culture or any leukocytes on a thoroughly examined urethral smear), or urethral culture positive for any of the recognized urogenital pathogens. We used a double-needle technique for obtaining the prostate biopsy tissue to limit contamination. In this approach, a short wide-bore needle is introduced in the midline of the perineum after thorough skin preparation. Through the wide-bore needle, a second, skinny needle was used to obtain specimens of prostate and periprostatic tissue. We also obtained multiple controls from the skin and subcutaneous tissues.

Only 10 (7%) of 135 men had any positive specific PCR assays. These 10 positive findings included (1) *M. genitalium* in 4 men, (2) *C. trachomatis* in 3, (3) *T. vaginalis* in 2, and (4) 1 man positive for both *M. genitalium* and *C. trachomatis*. These observations fit with prior studies suggesting that both *C. trachomatis* and *T. vaginalis* may be identified in prostate tissue. This was, to our knowledge, the first demonstration of *M. genitalium* in the prostate.

The great majority of the specific PCR assays were negative. These included 2541 (99.6%) of the

2552 specific assays. This was despite the use of radioactive probes with very high activity, high PCR cycle numbers, and appropriate positive and negative controls. Thus, we used conditions that were highly likely to identify specific, targeted pathogens if they were present in the tissue evaluated. Specifically, we had no positives for the general mycoplasma PCR and probe, the *U. urealyticum* PCR and probe, either herpes virus PCR and probe, or the cytomegalovirus PCR and probe. Molecular detection sensitivities were far beyond what would be needed to detect single molecules.

In contrast to the specific PCRs and probes, the broad-spectrum PCR assays had a substantial proportion of positive results. We concluded that the microorganisms present were diverse enough that no single set of specific tests would be helpful. We needed a general molecular test that then could be used to home in on a specific level of microorganism detection. We found evidence of tetracycline resistance in 25% of patients; 16S rDNA encoding sequences were found in 77% of the subjects. The tetracycline-resistance positives were a subset of the 16S rDNA–positive patients. Although these assays were done in different laboratories by personnel who were blinded to the results of the other assays, the results were very highly and statistically correlated. We also classified patients with inflammation (defined as $\geq$1000 white blood cells per $mm^3$ of the EPS). Of the 69 men who were 16S rDNA positive, 22 (32%) had inflamed EPS by this definition. In contrast, only 1 (4%) of the 26 16S rDNA–negative men had $\geq$1000 EPS white blood cells per $mm^3$ ($P < 0.001$). Thus, by either definition, the patients with 16S rDNA encoding sequences were more likely to have objective evidence of inflammation in their EPS.

We accomplished extensive cloning and sequencing of the positives.[29,34] Briefly, we found that prostate tissue may contain multiple sources of 16S rDNA encoding sequences. Many of these sequences were novel, defined as <95% correlation to known bacterial rDNAs. DNA sequence data suggest that the 16S rDNA encoding sequences were clearly distinguishable from known skin and laboratory contamination. Further, the correlations between the 16S rDNA encoding data and tetracycline resistance data are consistent with the observation that antimicrobial therapy provides transient, if any, relief of symptoms for many patients.

### *Comparison of patients with CP and prostate cancer*

These observations were criticized[35,36] because we had compared patients with and without white blood cells in their EPS but we had no controls. Therefore, we recently concluded a study in which we compared prostate biopsies from patients with CP/CPPS with men undergoing radical prostatectomy for cancer.[37] There were 107 patients with prostate cancer, and 21 (20%) were 16S rDNA positive. In contrast, of the 170 patients with CP/CPPS, 79 (46%) were positive ($P < 0.001$). This difference was even more striking because the patients with CP/CPPS were much more likely to be strongly positive in semiquantitative assays than were those with prostate cancer.

### *Conclusions*

Our findings suggest that many patients with CP/CPPS have a wide variety of bacterial DNA encoding sequences despite extensive negative investigations by more traditional technologies. Our findings also suggest that some patients have *C. trachomatis*, *T. vaginalis*, and *M. genitalium* in their prostates despite having no evidence of urethritis and negative urethral cultures or antigen tests for these pathogens. Other bacteria were documented in many symptomatic patients, including patients who have had negative microbiologic investigations of their urethral secretions and segmented lower urinary tract localization specimens. Carefully controlled molecular methods may reveal a broader spectrum of microorganisms in patients with CP than more traditional microbiologic methods.

*Research Issues.* Bacterial infection clearly has a role in prostatitis. The question is how big is this role? Bacteria cause acute and chronic bacterial prostatitis. The clinical question is whether infection is important in the etiology of CP/CPPS. Molecular evidence suggests that infection may be important in many patients.

Current evidence does not establish that bacteria are the cause of CP/CPPS. Establishing a role for infection will likely involve multiple steps. Detecting bacteria in prostate tissue represents an important step in the complex path toward establishing etiology. Additional sequencing is necessary to define the microbiology of the prostate gland, to determine the role of microorganisms, and to understand the specific microorganisms that may be important in CP. Such studies should include many more patients with CP/CPPS as well as other populations. If infection is indeed important, then we need to define whether the 16S rDNAs that we are identifying represent the residue of previous infections or reflect an ongoing process of active infection, for example, by monitoring molecules synthesized only by living bacteria. We can then better determine the pathogenesis of CP/CPPS, the role for antimicrobials as well as the optimal agents, and the role for other therapies.

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