Opposing Views

Chronic Prostatitis/Chronic Pelvic Pain: The Syndrome

For decades we have used a disease orientated approach to manage prostatitis based on the traditional concept that the condition was an infectious and/or inflammatory disease of the prostate gland. However, the recent literature is littered with well intentioned, well designed but essentially negative clinical trials evaluating antibiotics, anti-inflammatories and prostate centric therapies (α-blockers and 5α-reductase inhibitors).\(^1\) We have recently proposed a different approach to chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) based on the concept that these conditions represent a syndrome with variable but identifiable clinical phenotypes.

To be truly classified as a disease, we must determine a unified mechanism that causes the specific signs and symptoms associated with CP/CPPS. The various hypotheses include infection (cryptic or otherwise), genetic, anatomical, physiological, neuropathic, neuromuscular, endocrine, immune (including autoimmune) and psychological mechanisms. Each of these “theories” has not proven to cause all or even the majority of cases of CP/CPPS, but each has a solid theoretical basis, usually confirmation from animal model studies and at least some scientific or clinical validation in selected patients. I believe that although patients appear to have a similar end stage “syndrome” (or “disease” as suggested by Pontari in his view), we must accept that there is no 1 unifying mechanism that will explain all signs and symptoms. Rather patients in whom this condition develops likely have a genetic or anatomical abnormality that potentiates an initial triggering event (for example infection or trauma), and further mechanisms (including neurological mechanisms as proposed by Pontari) allow maintenance and/or promote progression of the condition into its chronic syndrome.

It is worth looking at those important “negative” randomized, placebo controlled, clinical trials (RCTs) again to determine if reinterpretation of the results can explain why some “disease specific” treatments that are not effective in clinical trials appear to benefit many patients suffering from the “syndrome” in clinical practice.\(^2\) For example, while antibiotics proved to be no better than placebo in multicontr RCTs, examination of the less chronic and/or heavily pre-treated patients has shown that 50% to 75% have significant short and long-term symptomatic improvement.

The National Institutes of Health (NIH) sponsored RCTs evaluating α-blockers in heavily pre-treated patients with CP/CPPS of long duration and in recently diagnosed patients with α-blocker naïve CP/CPPS showed no benefit with the active drug compared to placebo. Yet 4 RCTs with less stringent inclusion criteria clearly demonstrated improvement in men with CP/CPPS treated with various α-blockers compared to placebo. While trials assessing anti-inflammatories, pentosanpolysulfate, finasteride and pregablin were considered negative according to the primary end point, each of these therapies showed significant (or approaching significance) improvement according to validated secondary end points. These reevaluations of our presumed “negative” trials would suggest that some patients with a chronic prostatitis “syndrome” do respond favorably to these specific “disease” targeted therapies. Furthermore, it would be interesting to reflect on the results of these therapies in the many patients who were screened but not entered into these studies (more than 90% of screened patients with CP/CPPS patients were not enrolled in the 3 major NIH trials).

So what do these alternate interpretations of etiological mechanisms and treatment trial results mean to our CP/CPPS patients? I believe that not only do we have to accept that there is no 1 etiological mechanism that defines a specific disease process, but that our patients are a heterogeneous population of unique individuals with different triggers, maintenance mechanisms, symptom complexes and progression trajectories. In other words, each patient with this syndrome has a unique clinical phenotype, a hypothesis we call the “Snow Flake Hypothesis” (first coined by Pontari at the June 2008 meeting of the NIH sponsored Urologic Chronic Pelvic Pain Workshop). We recently described the 6-point (much like the 6 points of a snowflake) UPOINT (U for Urinary, P for Psychosocial, O for Organ specific, I for Infection, N for Neurologic/
systemic and T for Tenderness of muscles) Clinical Phenotype classification system.³

The UPOINT system refers to 6 distinct, clinically relevant and identifiable domains, each of which is associated with potentially effective therapies. A description of these 6 domains and suggested associated therapies has been published previously, including an article in this issue of The Journal of Urology®.²–⁵ Subsequently we have validated the concept in patients being evaluated at chronic prostatitis³ and interstitial cystitis⁵ clinics. The percentage of CP/CPPS patients identified for each domain was 52%, 34%, 61%, 16%, 37% and 53%, respectively. Of the patients 22% were positive for only 1 domain while the others were positive for 2 to 6 domains. Duration of symptoms but not age was associated with the number of domains, while the number of domains was associated with symptom severity (phenotypic progression over time?). The domains outside the prostate (T) and particularly those outside the pelvis (P and N) were associated with the most impact on quality of life.

Our international multicenter research group is presently completing deep phenotyping studies in the psychosocial, infection and neurologic/systemic domains and case control studies to evaluate associated medical conditions, as well as developing a urologist friendly UPOINT phenotyping patient questionnaire. We are anticipating that the enormous resources that NIH has funded the MAPP (Multidisciplinary Approach to the study of chronic Pelvic Pain) program ($37.5 million) will result in a new understanding of mechanisms and development of specific biomarkers that will further allow subcategorization of the UPOINT domains. We have just initiated 2 UPOINT phenotypically directed real-life clinical practice treatment trials.

In conclusion, I believe that CP/CPPS is a syndrome diagnosed by recognizable signs and symptoms that are not due to any single known disease process. The CP/CPP syndrome is further characterized by clearly identifiable and distinct clinical phenotypes that can occur singly or more often together to define a heterogeneous population of truly unique individuals. This new awareness of the benefits of a phenotypic approach to pelvic pain will enhance our understanding of the syndrome, encourage incorporation of new basic science and biomarker discoveries, and lead to a better individualized management strategy for CP/CPPS.

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REFERENCES


Chronic Prostatitis/Chronic Pelvic Pain: The Disease

Chronic prostatitis was a disease 40 years ago. Bacterial infection in the prostate produced symptoms of urinary frequency, urgency and pelvic pain. Many men responded to antibiotics and those who did not were considered to have a persistent bacterial source in the prostate causing problems, and so were given more antibiotics. Since then we have gone through 2 classifications of prostatitis and have separated chronic bacterial prostatitis (category II) from chronic prostatitis/chronic pelvic pain syndrome (category III). We found that the bacterial localization studies for men with CP/CPPS were no different than those for age matched asymptomatic controls, and that most of the patients do not have inflammation on prostate biopsy. So the constellation of symptoms of pain in the perineum, testes, penis, suprapubic area, dysuria and with ejaculation went from being a disease to being a syndrome because we did not know the etiology.

CP/CPPS is now on its way back to being a disease. Given that the cardinal symptom of this condition is pain, it was logical to think that there are alterations in the central and/or peripheral nervous system causing the problem. Evidence from the last decade has begun to confirm what was once suspected. Animal studies have indicated that peripheral inflammation and injury from 1 site in the pelvis or perineum could result in central nervous system inflammation in the spinal cord, and an expanded field of pain and inflammation beyond the