



# Male CP/CPPS: where do we stand?

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Received: 20 September 2018 / Accepted: 2 March 2019 / Published online: 12 March 2019  
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## Abstract

**Introduction** Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), commonly encountered in urologic practice, carries with it a stigma of poor understanding, ineffective treatment, and significant financial and quality of life burden.

**Materials and methods** This clinically practical review is based on the authors' personal clinical experience in interpretation and application of currently available evidence.

**Results** Significant progress has been made in terms of classification and evaluation of the disease, leading to encouraging improvements in treatment outcomes. The Chronic Prostatitis Symptom Index (CPSI) is a helpful tool in clinical evaluation and has proven invaluable for research purposes, while UPOINT has demonstrated the heterogeneity of the disease and provides physicians with a uniquely patient-centered approach to treatment. The importance of the microbiome in the evaluation of CP/CPPS patients has yet to be fully appreciated. While personalized, multi-modal therapy appears to be the key to treatment, the addition of pelvic floor physiotherapy (PFPT) with injection of trigger points, and psychosocial therapies to the multi-modal approach armamentarium are promising advances. Innovative interventional approaches are encouraging but require study.

**Conclusions** While encouraging therapies have been added to personalized, multi-modal treatment strategies, newer innovative therapies appear promising for improved treatment of CP/CPPS patients.

**Keywords** Chronic prostatitis · Chronic pelvic pain syndrome · Evaluation · Treatment

## Introduction

Prostatitis-related conditions represent the most common urologic diagnosis amongst men <50 years of age presenting to outpatient urology clinics [1]. Up to 10% of the male population will exhibit symptoms of this chronic syndrome at some point throughout their lifetime [2]. An overview of 24 identified epidemiologic studies estimated the global prevalence of prostatitis to be 7.1% [3]. Not surprisingly, chronic prostatitis carries with it a high cost to society in terms of direct and indirect financial burden and has a significant impact on quality of life (QOL) [4]. Furthermore, although studies have reported conflicting results, a recent

meta-analysis has suggested that patients with CP/CPPS may exhibit inferior semen parameters [5] secondary to the inflammatory milieu from the prostate [6]. This may contribute to increased prevalence of male factor infertility in CP/CPPS patients.

Any discussion of prostatitis as a disease requires attention to the definition of the illness, as “prostatitis” refers to a spectrum of syndromes characterized in varying degrees by bacterial infection of the prostate, genitourinary/pelvic pain (which may or may not include the prostate) and variable lower urinary tract symptoms (LUTS). Drawing on data collected from the Meares–Stamey four-glass test [7], which was pioneered a decade earlier, Drach and colleagues [8] originally described their four categories of prostatitis in 1978: acute and chronic bacterial prostatitis, nonbacterial prostatitis and prostatodynia. This classification system was further improved upon by the current NIH classification [9]. Within it, the authors kept the Category I and II definitions as acute and chronic bacterial prostatitis, respectively, while Category III, a nonbacterial version of prostatitis, characterized by genitourinary pain and LUTS

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in the absence of identifiable bacterial infection, was further described as either IIIA or inflammatory, versus IIIB or non-inflammatory (previously prostatodynia). The distinction between IIIA and IIIB was based on the presence or absence of leukocytes in expressed prostatic secretions, post-prostatic massage urine, or semen specimens. Finally, Category IV was added to the description of syndromes, recognizing a rather common condition where asymptomatic patients exhibit evidence of prostatic inflammation.

Category III chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common form of the symptomatic prostatitis subtypes, comprising up to 90–95% of prostatitis diagnoses [10, 11]. Chronic prostatitis/chronic pelvic pain syndrome will be the focus of this clinically practical review which should not be interpreted as a rigorous comprehensive review of the literature or a defined meta-analysis but rather based on the authors' personal clinical experience in interpretation and application of currently available evidence.

## Evaluation

### History and CPSI symptom index

As in any clinical encounter, a thorough history is an important step in establishing a diagnosis and developing a differential diagnosis of other confusable diseases that must be ruled out in those presenting with symptoms of CP/CPPS. The National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI) is a useful adjunct to the history, as it can quantify a patient's symptom experience and can be administered within a few minutes in an outpatient setting. The same collaboration that led to the current NIH categorization of prostatitis developed and validated the NIH-CPSI questionnaire [12] and the tool has proven useful both in clinical evaluation and monitoring of CP/CPPS patients and in research—it represents the most commonly used outcome measure in clinic trials of CP/CPPS. The questionnaire consists of nine questions, addressing three domains: pain is addressed in four questions, urinary function is covered in two questions, while the final three questions inquire about the impact of the patient's symptoms on QOL. Pain severity categories were recently developed for the pain domain [13] with a score of 0–7 considered as mild, 8–13 moderate, and 14–21 is considered severe pain.

### Physical examination

A focused physical examination, including a pelvic exam and digital rectal exam (DRE), is considered mandatory in the evaluation of any patient with symptoms of CP/CPPS. The authors prefer a careful pelvic exam in lithotomy

position, which allows for inspection of pelvic floor muscle tenderness and spasm and can help identify any trigger point tenderness that may be present. It is important to note that a midstream urine for culture and sensitivity (C&S) should be collected prior to any urinary tract manipulation, including the DRE (see below for discussion regarding urine studies). Furthermore, the pelvic exam should precede the DRE as the authors have found certain patients with significant prostatic tenderness, a common finding in CP/CPPS, may not tolerate the pelvic exam following prostatic palpation.

### Urine studies

The classic four-glass test developed by Meares and Stamey [7] is practically challenging for many clinicians to perform in an outpatient setting [14] but can still prove helpful in difficult cases. The purpose is localization of bacteria and inflammation to the urethra, prostate or bladder. The first specimen—voided bladder 1 (VB1)—is the initial 10 cc of urine from a collection and corresponds to the urethra. The second specimen—VB2 or midstream collection—corresponds to bladder urine. A follow-up prostate massage results in the expressed prostatic secretion (EPS) specimen. Finally, the VB3 or post-prostatic massage specimen is the first 10 cc of urine collected immediately following prostatic massage represents an alternative prostate-specific specimen. The differential findings in microscopy and culture results can describe the inflammatory and bacterial status of each location. First introduced in 1985 [15], a more practical approach is a two-glass screening test, which consists of two urine collections: pre- and post-prostatic massage. It has been shown to be robust in diagnosis compared to the four-glass test, when in a study of 353 patients enrolled in the NIH Chronic Prostatitis Cohort study, it resulted in the same diagnosis as the four-glass test in > 96% of test subjects [16].

### Microbiome

Recent investigations into the microbiome of the lower urinary tract have provided some additional insights into our understanding of the role of bacterial pathogenicity in CP/CPPS. Category III prostatitis is defined as no bacterial infection using traditional culture-based microbiology techniques. The majority of bacteria species are resistant to current culture methods or exist in a “biofilm” mode of growth [17] and we now understand that the lower urinary tract, including the prostate is not sterile. What we still do not know is how many of these culture-resistant bacteria are actual pathogens.

In their analysis of 25 CP/CPPS patients in 2016, Shoskes et al. [18] used the 16S rRNA gene amplification method to detect bacteria in urine specimens of CP/CPPS patients and compared their urinary microbiomes to healthy controls.

They found some differences between the groups, specifically higher phylogenetic diversity and higher counts of Clostridia species in CP/CPPS patients. The same research group later evaluated the gut microbiome using similar methods [19] and showed significantly less microbiome diversity and decreased prevalence of Prevotella species amongst CP/CPPS patients compared to controls. Distinct microbiota in CP/CPPS patients was similarly reported by Nickel et al. [20], specifically higher concentrations of *Burkholderia cenocepacia* in CP/CPPS patients compared to a matched asymptomatic control group. While intriguing, the clinical significance of these findings remains unclear and further research is required.

### Imaging and cystoscopy

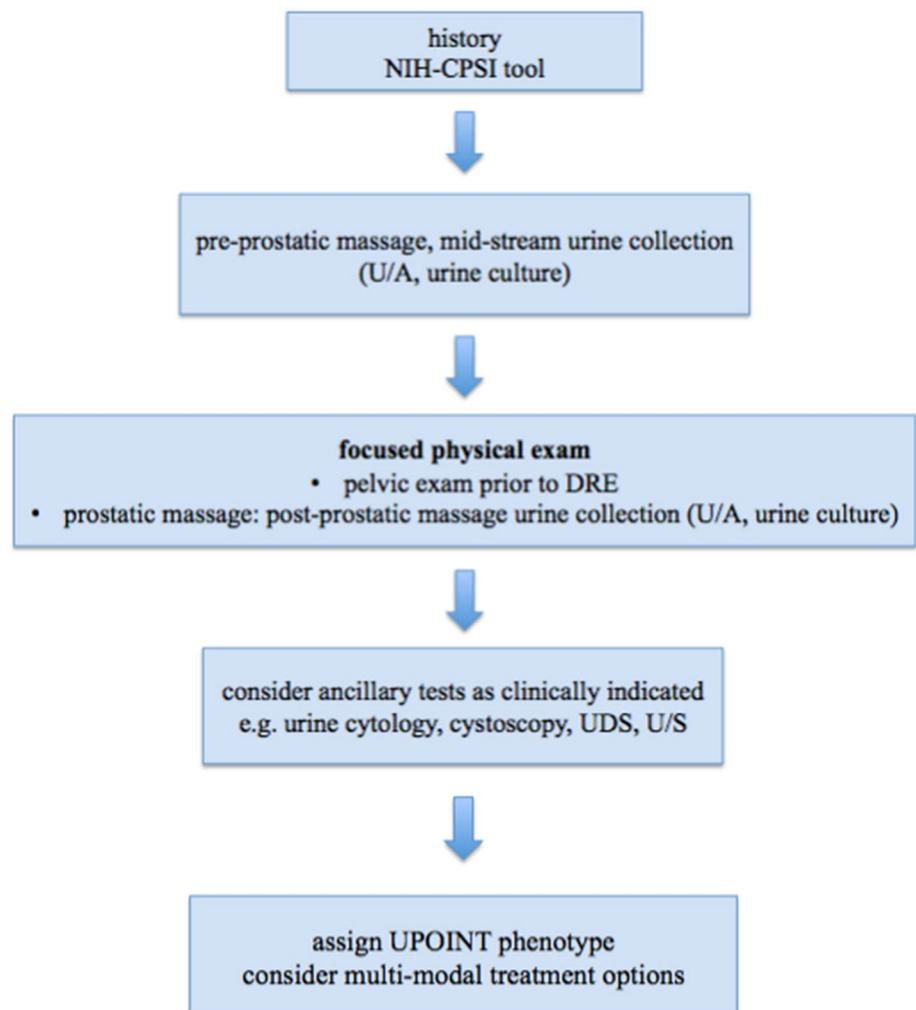
The role of imaging in the diagnosis of CP/CPPS remains a useful tool to rule out confusable diseases and should be used as indicated on a case-by-case basis. Except for specific indications, no imaging study is considered recommended

or mandatory in various clinical practice guidelines in the evaluation of CP/CPPS [21, 22]. Although it remains a useful tool in evaluation of the prostate, ultrasound has little value in establishing diagnosis of CP/CPPS. It can be utilized to determine post-void residual bladder volumes, particularly in men with obstructive voiding symptoms. Confusable diseases such as obstructed seminal vesicles, prostatic abscess, and prostatic calculi may also be diagnosed using transrectal or transabdominal ultrasound of the prostate and should be considered when appropriate. Cystoscopy should be reserved for those patients presenting with microscopic or macroscopic hematuria, treatment refractory storage or voiding symptoms, abnormal urine cytology, or for those in whom malignancy is suspected (Fig. 1).

### UPOINT

First described in 2009 [23, 24], the UPOINT phenotyping tool described a novel approach to pelvic pain patients. Inspired by the dismal results of the tiered monotherapy

**Fig. 1** Suggested evaluation of a patient suspected of CP/CPPS. Adapted with permission from Can Urol Assoc J 2018; 12 (6Suppl3): S152-4. <https://doi.org/10.5489/cuaj.5322>. ©CUA2018



approach, it recognized the heterogeneity of this diverse population. After initial validation trials in female interstitial cystitis/bladder pain syndrome (IC/BPS) patients [24], the UPOINT tool was validated in male CP/CPPS patients [25]. It classified patients' symptoms into six distinct subgroups: urinary, psychosocial, organ-specific, infectious, neurologic and tenderness (pelvic floor tenderness). Patients could be classified into one or in most cases multiple domains. The approach stimulated movement away from traditional rigid disease treatment paradigms, and allowed more emphasis on the importance of a multi-modal approach to treatment of this variable chronic pain condition [26].

## Treatment

Multiple reviews and meta-analyses have been published in recent years regarding the treatment and management of CP/CPPS [27–30]. The goal of the current review was not to recreate these, but to provide insights with respect to more recent studies and novel treatment modalities based on the authors' clinical and research experience.

## Pharmacologic therapy

### Antibiotics

Although the mainstay for treatment of bacterial prostatitis, very few randomized studies have investigated the role of antibiotic therapy in CP/CPPS patients. Those trials that have been completed are either of low quality or were underpowered. Two studies investigating fluoroquinolones [31, 32] showed no statistical difference between the groups in terms of symptoms. Therefore, although there is only weak evidence for antibiotic therapy in this nonbacterial category of prostatitis, the authors feel an initial trial of antibiotic therapy in those who are antibiotic naïve may be reasonable, particularly if the diagnosis is unclear and the investigations reveal CP/CPPS Category IIIA (inflammatory subtype).

### Alpha-blockers

Given the preponderance of pelvic floor dysfunction and voiding dysfunction associated with CP/CPPS, there is a rationale for treatment with alpha-blockers—they have shown overall treatment effect from randomized control trials (RCTs) in terms of symptom improvement in meta-analyses [28, 29]. Two large RCTs that failed to show a benefit of alpha-blocker therapy [32, 33] may have been underpowered to show a benefit in the alpha-blocker monotherapy arm and furthermore, patients were not selected on the basis of symptoms—patients without LUTS may indeed benefit

little from this approach. The authors believe that patients with CP/CPPS presenting with voiding LUTS may derive the most benefit.

### Anti-inflammatories

Several randomized studies have examined the effect of various anti-inflammatories on CP/CPPS patients including corticosteroids [34], COX-2 inhibitors rofecoxib [35] and celecoxib [36], pentosan polyphosphate (PPS) [37], zafirlukast [38], and tanezumab [39]. The COX-2 medications and the PPS trial showed modest benefits in symptom outcomes, albeit with questionable clinical significance, while the other trials failed to show a difference in terms of symptoms. Meta-analyses found a modest overall symptom improvement with anti-inflammatory treatment. While the clinical impact of anti-inflammatory therapy remains unclear, the authors continue to use NSAIDs for symptomatic control of inflammation and pain.

Cernilton [40] and quercetin [41] are nutraceuticals that have been examined for their anti-inflammatory properties in CP/CPPS patients. Although only evaluated in small trials, these phytotherapies have shown benefit with treatment and given their minimal side effect profile, the authors generally regard these agents as reasonable options for CP/CPPS patients with the organ-specific domain.

### Neuromodulators

Although neuromodulatory medication has been effective in treatment of neuropathic pain and in related conditions such as IC/BPS, there remains only one RCT in the CP/CPPS population [42]—it did not show statistically significant overall improvement, but subjects did experience a modest improvement in pain symptoms. The authors have observed this in their clinic and employ this approach, particularly tricyclic antidepressants (the authors tend to use gabapentoids less often), with good results in selected patients, particularly those with more widespread pain and less prostate gland centrality.

### 5-Alpha-reductase inhibitors (5-ARIs)

Three trials have investigated the use of the 5-ARI, finasteride [43–45] in CP/CPPS patients. Results from these small trials showed only modest improvements. The authors do use this approach in some older men with CP/CPPS and a co-existing diagnosis of benign prostatic hyperplasia.

### Intraprostatic botulinum neurotoxin type-A

Owing to its modulation of cellular pain mediators and apparent anti-inflammatory effect [46] in addition to its

known sensory effects, intraprostatic injection of botulinum neurotoxin type-A has been previously proposed [47] and recently evaluated in a randomized pilot study of 60 patients diagnosed with CP/CPPS [48]. The pilot study showed a significant benefit in terms of overall CPSI scores and LUTS but still warrants further investigation evaluating different target injection sites, such as pelvic muscle trigger point injection.

### Trigger point injection

Pelvic floor assessment has become an important evaluation in CP/CPPS patients, and in those patients with pelvic floor trigger point pain, directed injection therapy appears to be helpful. Literature in this domain is limited [49], but one retrospective study [50] did show a significant improvement in overall CPSI scores with the majority of men deriving a significant benefit from the treatment modality. The specific injection or injection cocktail should include some combination of local anesthetic [49]. In the authors' clinic, injection therapy of myofascial trigger points has proved a useful adjunct to PFPT (see below).

## Non-pharmacologic therapy

### Pelvic floor physiotherapy

Pelvic floor physiotherapy has emerged as a useful tool in the treatment armamentarium of CP/CPPS. Anderson et al. [51] first published their PFPT protocol for treatment of men with CP/CPPS in their study of 138 patients where up to 72% were moderately or markedly improved following at least 1 month of treatment protocol. Similar results have been published in subsequent studies and PFPT remains an accepted treatment modality. A physiotherapist experienced in PFPT methods is crucial for success. PFPT has become a pivotal therapy as part of our multi-modal treatment strategy, but we have learned that it is only appropriate for men with clinically defined pelvic floor dysfunction diagnosed on careful clinical evaluation of the pelvic floor.

### Acupuncture

Several trials of acupuncture for CP/CPPS have been reported [52–55], showing modest benefit in treatment arms compared to sham therapies. Most recently, Qin et al. [55] reported their randomized, sham-controlled trial in 68 patients. Significant improvements in CPSI scores were reported and appeared robust over a follow-up period of 56 weeks. We have learned that the success of acupuncture lies in the expertise of the acupuncturist, the actual technique

employed and the patient's belief in the potential benefits of the therapy.

### Extracorporeal shock wave lithotripsy (ESWL)

A recent Cochrane review in non-pharmacologic interventions for CP/CPPS [30] evaluated four trials [56–59] investigating use of ESWL for treatment of CP/CPPS and although of low quality, the trials did show improvement of symptoms in the treatment arms and significantly reduced CPSI scores at 3 months follow-up. These are intriguing results and require further study to determine which phenotype of patient might benefit most.

### Transrectal thermotherapy

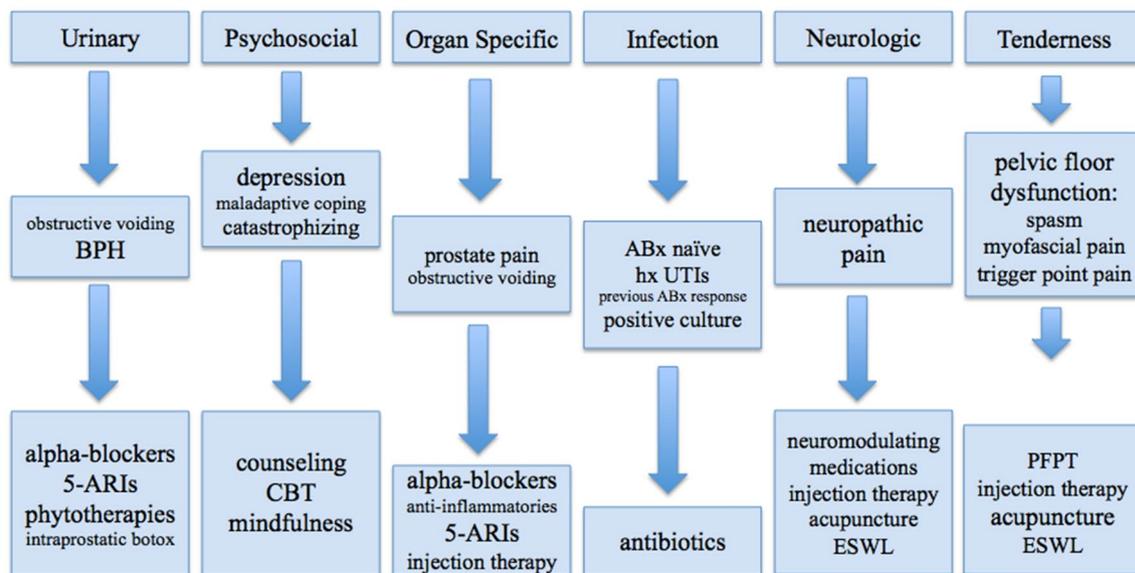
Transrectal thermotherapy and other minimally invasive thermotherapy approaches have been employed in the past [60, 61] to ameliorate symptoms. However, in current practice these therapies have largely been abandoned for simple, conservative local heat therapy such as heating pads with similar benefits.

### Psychological interventions

Psychiatric factors are important in CP/CPPS and significantly affect QOL in these patients [62]. Although UPOINT phenotyping made strides to highlight the psychosocial aspect of this chronic disease, a recent systemic review evaluating psychological factors and comorbidities in CP/CPPS suggested it may not be enough [63]. There is a paucity of literature in psychological interventions for this patient group. A CBT program specific to CP/CPPS has been introduced [64] and its clinical impact appears to be favorable for men with treatment refractory CP/CPPS [65]. The authors' continued experience with CBT in men with CP/CPPS is not as favorable in terms of benefit as seen in women with urological chronic pelvic pain, but should be considered with the best success in educated and committed patients who exhibit a positive attitude for health and well-being.

### Phenotype directed multi-modal therapy approach

The authors' personal and published [24–26] experience is that determining a CP/CPPS "clinical picture" by identifying each individual's many clinical phenotypes (the authors use UPOINT to accomplish that) allows one to plan a personalized multi-modal therapeutic strategy. The authors have found that with explanation of why we are using the various treatments, there is improved patient buy-in to the program and they become a partner in improving their own condition. A spouse or partner participating at this stage has been proven to be very



**Fig. 2** Multi-modal therapy options for CP/CPSP patients, classified by UPOINT phenotype. Adapted with permission from Can Urol Assoc J 2018; 12 (6Suppl3): S161-3. <https://doi.org/10.5489/cuaj.5325>. ©CUA2018

helpful as well. It is important to establish realistic goals, not necessarily cure. Patients should realize that goals of treatment include, of course, amelioration of symptoms, but also improving coping skills and lessening the impact of this chronic condition on their quality of life and day-to-day activities (Fig. 2).

## Conclusions

The evaluation and treatment of chronic prostatitis/chronic pelvic pain syndrome has changed over the past several decades, with slow progress being made. The UPOINT method of phenotyping patients continues to show promise in better delineating patients' personal "clinical picture" and identifying phenotype-specific pathogenesis and phenotype-specific therapies. Although initial results have identified a uniqueness of the microbiome in CP/CPSP patients, further work is needed to understand the clinical relevance and how it may be exploited to further our understanding and treatment of CP/CPSP.

The realm of pharmacologic therapy as treatment has failed to reveal any universal cure and that will likely remain the case for some time to come. Encouraging therapies added to our armamentarium include personalized multi-modal therapy strategies, pelvic floor physiotherapy—including injection of trigger points—and psychosocial interventions, while newer innovative therapies may represent the most encouraging hope for improved treatment in the field.

**Acknowledgements** Dr. Nickel's CP/CPSP research is funded by the Canada Research Chair Program.

## Compliance with ethical standards

**Conflict of interest** All the authors contributed significantly to the production of the manuscript in all aspects. The authors have no conflicts of interest to declare.

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