



## Chronic Prostatitis/Chronic Pelvic Pain Syndrome and Male Bladder Pain Syndrome/Interstitial Cystitis: How Are They Related?

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To date, the heterogeneous pathophysiology of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and bladder pain syndrome/interstitial cystitis (BPS/IC) has not been fully elucidated. Thus, it is difficult to make a full comparison between CP/CPPS and male BPS/IC. Controversy and confusion surrounding the terminologies and classifications of CP/CPPS and BPS/IC complicates the issue. CP/CPPS and male BPS/IC are not mutually exclusive conditions, in that they have similarities in their pathogenesis and clinical presentation. Based on the working definitions of these terms, it would be correct to say that male BPS/IC is subsumed by CP/CPPS, and that male BPS/IC can be regarded as CP/CPPS with clear bladder-specific features. Although the term CP/CPPS may be inappropriate, especially since “CP” may be misleading, the perspective that CP/CPPS and male BPS/IC are male urological chronic pain syndromes could enhance the understanding of the relationship between the two. The European Association of Urology classification for chronic pelvic pain is systematic and corresponds well with our knowledge of chronic pain. Therefore, this classification might be the solution to the problems associated with the existing terminologies and taxonomy of CP/CPPS and BPS/IC. In the management of urological chronic pelvic pain in men, clinical phenotyping systems (the UPOINT or UPOINTs system) profile patients and indicate how tailored treatment could be achieved as individualized, multimodal therapeutic regimens. It would be prudent to include bladder-specific features, such as painful filling or painful urgency, in the criteria for the organ-specific domain of the UPOINT(s) system.

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## INTRODUCTION

Traditionally, chronic pelvic pain accompanied by lower urinary tract symptoms in men was believed to arise from an inflammation of the prostate gland [1]. Men with these symptoms are usually diagnosed with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Although bladder pain syndrome/interstitial cystitis (BPS/IC) is also

characterized by pelvic pain associated with lower urinary tract symptoms, such as increased frequency of urination, it was believed to occur primarily in women. Until recently, male BPS/IC has received scant attention. However, contemporary studies suggest that male BPS/IC is much more common than was previously thought [2-5]; there has been increasing interest in male patients exhibiting symptoms and signs suggestive of BPS/IC.

Male BPS/IC is often initially diagnosed as CP/CPPS [6,7]. Evidence suggests that many men diagnosed with CP/CPPS could instead have been diagnosed with BPS/IC [1,7]. While some previous reports highlight the differences between CP/CPPS and male BPS/IC, there is substantial overlap in the clinical presentation and pathogenesis [1,6]. Moreover, the complex, heterogeneous pathophysiology of CP/CPPS and BPS/IC is poorly understood [8,9]. Therefore, it is difficult to compare and contrast CP/CPPS and male BPS/IC. Controversy and confusion surrounding the terms and taxonomy of CP/CPPS and BPS/IC complicates the issue.

CP/CPPS and BPS/IC are now considered as chronic pain syndromes, rather than prostate or bladder diseases [10,11]. Regarding CP/CPPS and BPS/IC as urological chronic pain syndromes could promote better understanding of the relationship between CP/CPPS and male BPS/IC. This article outlines the relationship between CP/CPPS and male BPS/IC, presenting a prudent approach to male chronic pelvic pain. Herein, the definitions of CP/CPPS and BPS/IC are reviewed, and problems with the existing terminologies are discussed. The European Association of Urology (EAU) chronic pelvic pain classification system is suggested as a solution to these problems. Bladder-specific features in BPS/IC are also addressed.

## TERMS AND DEFINITIONS

### 1. CP/CPPS

In the late 1990s, the National Institutes of Health (NIH) established a consensus on the definition and classification system for prostatitis syndromes, which has become the accepted international norm in both clinical practice and research [12]. The NIH classification of prostatitis syndromes includes four categories: (I) acute bacterial prostatitis, (II) chronic bacterial prostatitis, (III) CP/CPPS, and (IV) asymptomatic inflammatory prostatitis. More than 90% of symptomatic patients with prostatitis syndrome fall under the third category, CP/CPPS, which is described as chronic genitourinary pain in the absence of uropathogenic bacteria localized to the prostate gland using standard methodology.

A detailed definition of CP/CPPS is urologic pain or discomfort in the pelvic region, associated with urinary symptoms or sexual dysfunction with a duration of at least 3 of the last 6 months [9]. The differential diagnoses of pelvic pain, such as urinary tract infection, malignancy,

anatomic abnormalities, or neurologic disorders, need to be excluded. CP/CPPS is subclassified into either the inflammatory (NIH category IIIA) type or the non-inflammatory (NIH category IIIB) type, based on the presence of leukocytes in the prostate samples [9,12]. The pain of CP/CPPS is most commonly localized to the perineum, suprapubic area, and penis; however, it can also be present in the testes, groin, or lower back [13]. In many patients, one of the most prominent, important, and bothersome features is pain during or after ejaculation [14].

In many patients diagnosed with CP/CPPS, the evidence of inflammation of the prostate cannot be found. There are no clinically relevant diagnostic or therapeutic consequences arising from differentiating between the inflammatory and non-inflammatory CP/CPPS [15]. It is also likely that the cause of CP/CPPS is multifactorial [16,17]. Organs other than the prostate gland may be more important in the genesis of this syndrome [12]. Even pelvic pain may be independent of the prostate, at least in some patients with CP/CPPS. Therefore, the term “CP/CPPS” appears to be inappropriate, and “chronic prostatitis” (CP) is especially misleading. We also should consider whether it is appropriate to classify CP/CPPS under prostatitis syndromes.

Unlike BPS/IC, the name and working definition of CP/CPPS have remained stable for the past 20 years. It is my humble opinion to replace the name, CP/CPPS, with a more appropriate term, since it not only confuses clinicians but it also seems to hamper the research advancement in this area.

### 2. BPS/IC

The nomenclature and taxonomy of BPS or IC have been evolving for many years and remain controversial [18,19]. IC, originally considered as a bladder disease, is now considered as a chronic pain syndrome [11]. Hanno [20] stated that the term IC did not describe the clinical syndrome or pathology in many cases. Moreover, the term IC seems to be misleading as it directs attention only to the urinary bladder and inflammation [18].

The meetings of the European Society for the Study of Interstitial Cystitis (ESSIC) in 2005 and 2006 arrived at a consensus: the term “bladder pain syndrome” (BPS) better complies with our present knowledge and current nomenclature of other pain syndromes than the terms “interstitial cystitis” (IC) and “painful bladder syndrome”

(PBS). BPS can be diagnosed based on chronic (more than 6 months) pelvic pain, pressure, or discomfort, perceived to be related to the urinary bladder and accompanied by at least one other urinary symptom, such as persistent urge to void or frequency. Other confusable diseases must be excluded as the cause. Further documentation and classification of BPS, according to the findings of cystoscopy with hydrodistention and morphological findings of bladder biopsies, are encouraged. The presence of symptoms in other organs, as well as cognitive, behavioral, emotional, and sexual symptoms should be addressed [18]. The discontinuation of using the term, IC, might cause serious issues for healthcare systems, potentially affecting the reimbursement and the likelihood of patients receiving disability benefits, and so forth. Therefore, to promote a more straightforward change in nomenclature, the ESSIC agreed that the term BPS/IC could be used in parallel with BPS, at least for the time being [18].

Some clinicians preferred minor modifications, as expressed at the meeting held under the auspices of the Society for Urodynamics and Female Urology (SUFU). The SUFU definition was adopted in the guidelines of the American Urological Association, along with the nomenclature of IC/BPS [21].

## RELATIONSHIP BETWEEN CP/CPPS AND MALE BPS/IC

CP/CPPS and male BPS/IC are not mutually exclusive. There is a considerable overlap in the pathogenesis and clinical presentation between CP/CPPS and male BPS/IC [1,4,6,22-24]. CP/CPPS and BPS/IC are now considered as chronic pain syndromes, rather than prostate or bladder diseases [10,11]. Chronic pain that characterizes both CP/CPPS and BPS/IC is thought to be a consequence of neural sensitization [13,19]. Based on the definitions of the terms, it may be correct to say that male BPS/IC is a subset of CP/CPPS, or that male BPS/IC is subsumed by CP/CPPS. “Pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder,” included in the definition of BPS/IC, is covered by “urologic pain or discomfort in the pelvic region,” included in the definition of CP/CPPS. In a detailed description of 488 men with CP/CPPS, the most frequently reported region of pain or discomfort was in perineum, followed by the suprapubic region [25]. Considering male

BPS/IC as CP/CPPS with clear bladder-specific features could clarify the relationship between these two conditions.

It is problematic to postulate that male BPS/IC is subsumed by CP/CPPS, as this contradicts the fact that CP/CPPS is a prostatitis syndrome. If the proposition that male BPS/IC is encompassed under CP/CPPS is true, then the proposition that male BPS/IC is included under prostatitis syndromes should also be true, as CP/CPPS is considered to be a prostatitis syndrome. This apparent contradiction is caused by the misleading term CP/CPPS and the current classification of prostatitis syndrome. To eliminate such a cognitive dissonance and resolve the confusion regarding terminologies and taxonomies, it may be necessary to change the nomenclature of CP/CPPS and establish a new consensus on the classification system for chronic pelvic pain and prostatitis syndromes.

## BLADDER-SPECIFIC FEATURES AND DIAGNOSIS OF BPS/IC

Painful bladder filling and painful urgency (or painful urge to void) are main bladder-specific symptoms in BPS/IC. Painful filling is described as pain that worsens with the degree of bladder filling. The pain may be relieved at least partially by urination [26-28]. Painful urgency is described as the urge to urinate due mainly to pain, pressure, or discomfort, but not to fear of incontinence [26]. Painful urgency in BPS/IC differs from urgency in overactive bladder (OAB). Urgency is the key symptom of OAB and is defined as a sudden compelling desire to pass urine, which is difficult to defer [29]. “Urgency” in OAB is characterized by a sudden-onset fear of leakage, whereas “painful urgency” in BPS/IC has a persistent nature and is associated with fear of intensifying pain, pressure, or discomfort [30]. Severe storage symptoms are also bladder-specific symptoms, such as increased frequency of urination or nocturia. Here, voiding diary might serve as a useful tool. A recent study showed that patients with BPS/IC had a greater urinary frequency, a lower and more constant voided volume, and a narrower range of voided volume compared with patients with OAB [31].

Urinalysis results are usually normal in BPS/IC [32]. Numerous diagnostic biomarkers for BPS/IC have been explored, including antiproliferative factor, urinary and serum nerve growth factors, and urinary and serum

proinflammatory cytokines or chemokines. However, none of these putative biomarkers have been validated [33]. Potassium chloride bladder permeability test is no longer recommended, as it lacks sufficient evidence in its effectiveness [15].

Cystoscopy with hydrodistention, and biopsy under anesthesia, can be performed if indicated. According to the findings (Hunner lesions or glomerulations) of cystoscopy with hydrodistention and morphological findings of bladder biopsies, BPS/IC can further be classified [15,18]. Office cystoscopy is useful in that it can detect or exclude diseases, such as bladder cancer, and reproduce painful bladder filling in patients with BPS/IC. Hunner lesions or mucosal/submucosal bleeding may also be observed during the office cystoscopy, although the bladder cannot be filled as much as in cystoscopy under anesthesia. It is important to examine the bladder mucosa from the early phase of filling, as Hunner lesions might be obscured soon after bladder distention [32]. The lesions are more readily recognized by a narrow-band imaging cystoscopy [34]. A typical Hunner lesion is a circumscribed, reddened mucosal area with small vessels that radiate towards a central scar, with a fibrin deposit or coagulum attached to this area [18,35]. This site ruptures with increasing bladder distention, with petechial oozing of blood occurring from the lesion and the mucosal margins in a waterfall manner. It is important to detect these Hunner lesions because patients with these lesions have specific characteristics, such that this subgroup can be treated successfully [36].

## PRUDENT APPROACH TO CHRONIC PELVIC PAIN IN MALES

Patients with CP/CPPS or BPS/IC are an inhomogeneous group, with diverse etiologies and different responses to therapy. To classify patients with urological chronic pelvic pain (CP/CPPS and BPS/IC) and to direct appropriate therapy, a six-point clinical phenotyping system (the UPOINT system) had been proposed in the late 2000s [17,28,37,38]. The UPOINT system profiles patients and indicates how tailored treatment could be achieved as individualized multimodal therapeutic regimens. The clinical domains of UPOINT are Urinary symptoms, Psychosocial dysfunction, Organ-specific findings, Infection, Neurologic/systemic conditions, and Tenderness of

muscles, providing mnemonic UPOINT. With sexual dysfunction affecting 40-70% of all men with CP/CPPS [39-41], the inclusion of an additional domain for sexual dysfunction was proposed, and a modified UPOINT algorithm (UPOINTs) has been suggested [42-44].

The original organ-specific domain for CP/CPPS is related only to the "prostate," while the organ-specific domain for BPS/IC is related only to the "bladder." For CP/CPPS, the organ-specific domain is considered to be positive if there is a specific prostate tenderness on examination, leukocytes on microscopic examination of the prostatic fluid, hematospermia, or extensive prostatic calcification [38]. In the UPOINT system for BPS/IC, the criteria for organ-specific domain include pain with bladder recycling (typically pain on bladder filling and temporary relief on voiding), pain on bladder filling with low volumes of irrigation fluid, glomerulations or Hunner lesions noted during cystoscopy, and typical inflammation confirmed by a bladder biopsy [28].

Recent studies suggest that the prevalence of BPS/IC in men might be higher than previously thought [2-5]. Men diagnosed with CP/CPPS may also have bladder-specific symptoms. Therefore, it would be more prudent to include bladder-specific features in addition to prostate-specific findings in the criteria for organ-specific domain when performing UPOINT-based evaluations in men suspected of having chronic pelvic pain. Samplaski et al. [27] characterized patients diagnosed with CP/CPPS using UPOINT domains and subdomains, and the organ-specific domain was subdivided into bladder (organ specific-bladder) and prostate (organ specific-prostate). The organ specific-bladder domain was positive in 33% of their patients. A research network study showed that 75% of all men with BPS/IC or CP/CPPS had painful filling or painful urgency [26].

## EAU CLASSIFICATION OF CHRONIC PELVIC PAIN: SHOULD THE TERM CP/CPPS BE REPLACED?

The first EAU guidelines on chronic pelvic pain were published in 2003 [45]. In 10 years, an updated version was accepted for publication in 2012 by the International Association for the Study of Pain Council [15].

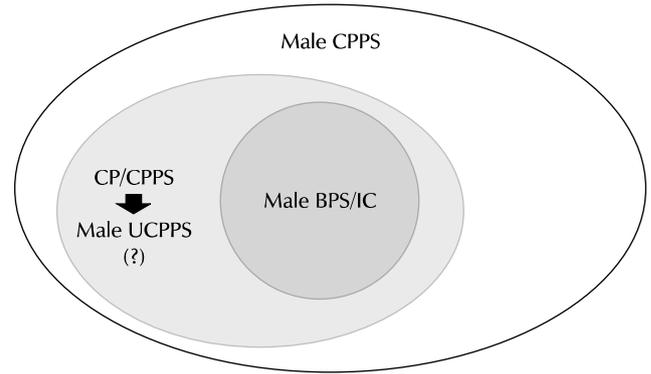
The EAU classification defines chronic pelvic pain as chronic or persistent pain perceived in the structures related

to the pelvis in either men or women. It is often associated with negative cognitive, behavioral, sexual, and emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor, or gynecological dysfunction [15]. Chronic pelvic pain syndrome (CPPS) is a subgroup of chronic pelvic pain. CPPS is defined as the occurrence of chronic pelvic pain with no proven infection or other obvious pathology accounting for pain. In the EAU classification, CPPS is an umbrella term that includes non-urological CPPS, and it should be differentiated from CP/CPPS.

The pain perceived in CPPS may be localized within a single organ, or may be experienced in more than one pelvic organ; moreover, it can even be associated with systemic symptoms, as seen in chronic fatigue syndrome, fibromyalgia, or Sjogren's syndrome. When pain is localized to a single organ, some specialists may wish to consider using an end-organ term, such as bladder pain syndrome (BPS), prostate pain syndrome (PPS), or urethral pain syndrome. When pain is localized to more than one organ, or pain cannot be clearly ascribed to one organ, the term CPPS should be used [15].

The definition and subtypes of BPS in this classification follow the proposal set forth by ESSIC. Consequently, BPS in the EAU classification is on par with BPS/IC (or BPS) in the ESSIC proposal. PPS is defined as the occurrence of persistent or recurrent episodic pain in the region of the prostate during at least 3 of the previous 6 months, which is convincingly reproduced by prostate palpation [15]. CP/CPPS is generally classified as CPPS in the EAU classification, although some cases of CP/CPPS could be classified as PPS.

The EAU classification of chronic pelvic pain is logical and systematic, and it concurs with our knowledge of chronic pain. It could also resolve the problems associated with the current terminologies and taxonomies of CP/CPPS and BPS/IC. Of course, it is difficult to change the terms with a wide currency, and there are many obstacles to changing the existing system. Furthermore, reaching a consensus on new terminologies and classifications is a challenging and time-consuming task. Nevertheless, a change is necessary for the improvement in clinical practice and communication. Whether or not we accept the EAU classification of chronic pelvic pain on an international scale, it seems appropriate to replace the misleading name



**Fig. 1.** Conceptualization of the classification of male chronic pelvic pain syndrome. The Venn diagram shows the relationship between chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), male bladder pain syndrome/interstitial cystitis (BPS/IC), and male chronic pelvic pain syndrome (CPPS). It seems appropriate to replace the misleading term CP/CPPS with male urological CPPS (UCPPS). The “CPPS” in male CPPS is an umbrella term that includes non-urological CPPS and should be differentiated from CP/CPPS.

CP/CPPS with male CPPS or male urological CPPS (Fig. 1).

## CONCLUSIONS

CP/CPPS and male BPS/IC are not mutually exclusive conditions, as they have much in common with respect to their pathogenesis and clinical presentations. Based on the working definitions of these terms, it would be correct to say that male BPS/IC is included under CP/CPPS, and that male BPS/IC may be regarded as CP/CPPS with clear bladder-specific features. Although the term CP/CPPS may be inappropriate and misleading, considering CP/CPPS and male BPS/IC as male urological chronic pain syndromes could help us better understand the relationship between them. The EAU classification of chronic pelvic pain might solve the problems associated with the existing terminology and taxonomy for CP/CPPS and BPS/IC. A multimodal therapeutic approach addressing the clinical phenotypic profile on an individual basis is recommended to manage male cases of chronic pelvic pain. It would be prudent to also include bladder-specific features, such as painful filling or painful urgency in the criteria for organ-specific domain of the UPOINT(s) system.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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