



UPOINT System: A Diagnostic/Therapeutic Algorithm for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common condition that significantly affects the quality of life. On the other hand, urologists find it challenging to treat this disorder effectively. To date, the Urinary, Psychosocial, Organ-Specific, Infection, Neurological/Systemic, and Tenderness (UPOINT) system is the only classification tool that can improve the treatment outcomes significantly compared to monotherapy. This review focused on the most recent advances in the diagnosis and treatment of CP/CPPS.

Keywords: Chronic prostatitis with chronic pelvic pain syndrome; Phenotype; Therapeutics

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INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common urological condition that has a significant negative impact on the quality of life and poses a financial burden similar to other chronic illnesses, such as diabetes mellitus, Crohn's disease, and myocardial infarction [1]. The characterization and treatment of prostatitis have been challenging for urologists, and there has been no validated classification system for this condition for decades. In 1999, the National Institutes of Health (NIH) developed a classification system based on the clinical syndromes to define this disease better (Table 1). This system can classify prostatitis into the following four categories: acute bacterial prostatitis, chronic bacterial prostatitis, CP/CPPS, and asymptomatic prostatitis [2].

Accounting for more than 90% of all urological outpatients, CP/CPPS is among the most common urologic disorders in men younger than 50 years. Moreover, the condition is often poorly understood, and its management is challenging [3].

This may be correlated with the heterogeneity of CP/CPPS. Owing to the clinical diversity of patients with this disease, each patient should be classified according to the unique clinical phenotype. The Urinary, Psychosocial, Organ-Specific, Infection, Neurological/Systemic, and Tenderness (UPOINT) system is a diagnostic/therapeutic algorithm developed in 2009 [4]. This review article presents the development of the UPOINT phenotyping system and the latest treatment methods for CP/CPPS based on this system.

DEVELOPMENT OF THE UPOINT

The UPOINT system is used to clinically classify a patient's symptoms into six broad categories to facilitate individualized and multimodal therapy. Each domain is treated differently, thereby allowing for a multimodal approach. This system was found to be effective in assessing the symptom severity in chronic pelvic pain. That is, patients with more positive domains have a longer duration of symptoms and a higher National Institutes of Health Chronic Prostatitis

Table 1. National Institute of Health (NIH) chronic prostatitis/chronic pelvic pain syndrome classification system

| Traditional classification | NIH classification | Description |
|-------------------------------|--|---|
| Acute bacterial prostatitis | Category I | Acute infection of the prostate |
| Chronic bacterial prostatitis | Category II | Chronic infection of the prostate |
| Nonbacterial prostatitis | Category IIIA (inflammatory CP/CPPS) | Significant number of leukocytes in expressed prostatic fluid or semen |
| Prostodynia | Category IIIB (noninflammatory CP/CPPS) | Insignificant number of leukocytes in expressed prostatic fluid or semen |
| | Category IV (asymptomatic inflammatory CP) | Leukocytes and/or bacteria in expressed prostatic fluid or semen without the presence of pelvic pain/urinary symptoms |

CP/CPPS: chronic prostatitis/chronic pelvic pain syndrome.

Symptom Index (NIH-CPSI) score [4]. Magri et al. [5] evaluated the UPOINT phenotyping system. The results showed that 77.5% of 914 patients experienced a significant decrease in the CPSI score at 18 months. Moreover, a Swedish study validated the correlation between the number of positive domains and the NIH-CPSI score [6]. Although further validation studies will be needed, the UPOINT clinical phenotyping system provides a useful and clinically relevant framework for multimodal therapy for the management of CP/CPPS.

NOVEL TREATMENTS

1. Urinary

The efficacy of several alpha-blockers used in monotherapy has been assessed, but the results varied. Nickel et al. [7] conducted a randomized controlled trial (RCT) and reported that tamsulosin 0.4 mg daily significantly improved the NIH-CPSI scores across multiple domains compared to the placebo. In another study, silodosin 4 mg reduced the NIH-CPSI scores compared to the placebo [8]. Alpha-blockers may be beneficial when used in multimodal therapy. Owing to the heterogeneity of previous studies, however, the authors of a recent study could not recommend alpha-blockers as first-line monotherapy [9].

Some studies reported that phosphodiesterase-5 inhibitors could improve the lower urinary tract symptoms (LUTS) by inhibiting nitric oxide synthase. Kong et al. [10] reported that the use of mirodenafil in combination with levofloxacin versus levofloxacin alone improved the NIH-CPSI score by -7.2 and -3.2 ($p < 0.05$), respectively.

2. Psychosocial

Cannabis has been used in other chronic pain syndromes for symptom relief. Tripp et al. [11] performed a study on

men with CP/CPPS who visited clinics and shared their experience with cannabis online. In total, 342 participants responded to questions regarding the baseline NIH-CPSI scores, symptom improvement with cannabis usage, and side effects. The results showed that 57% of clinics and 63% of online participants believed that cannabis was effective to some extent in treating CP/CPPS symptoms. Moreover, it may play a role in the management of CP/CPPS. On the other hand, multiple studies revealed an association between regular cannabis use and low sperm concentration and total sperm count as well as decreased sperm function [12,13]. CP/CPPS is a disease common in men younger than 50 years old. Thus, male fertility and the desire for future offspring should be considered before initiating therapy with cannabis [5].

3. Organ-Specific

Phytotherapies, such as quercetin, saw palmetto, and cernilton, have been used owing to their success in improving the symptoms of patients with CP/CPPS [14]. In another study on the effects of pollen extract, compared to patients ($n=10$) in the placebo group, patients in the experimental group experienced an improvement in pain and LUTS based on a symptom questionnaire survey [15].

OM-89 is a novel oral immunostimulatory agent developed from lysed pathogenic *Escherichia coli* bacteria. Wagenlehner et al. [16] conducted a randomized, double-blind placebo-controlled study on 185 patients who received either OM-89 or a placebo. The results showed that the NIH-CPSI score decreased by 40.5% and 44.0% in the treatment and placebo groups, respectively. Moreover, the positive response rates were 67% and 64.3%, respectively. On the other hand, the results did not differ significantly.

Increasing evidence suggests that low-intensity pulsed ultrasound (LIPUS) can inhibit inflammation and pain by

regulating the cyclooxygenase pathway. Li et al. [17] performed a randomized study on 96 CP/CPPS patients who either received treatment with transperineal ultrasonography daily for two weeks or underwent a sham treatment. The results showed that the two groups differed significantly in terms of the total NIH-CPSI and pain and urinary symptom scores after the LIPUS treatment.

4. Infection

Antibiotics are often used for patients with CP/CPPS. On the other hand, the use of antibiotics has been controversial in the absence of infection. Zhou et al. [18] reported that the mean NIH-CPSI score decreased by 18.5 points in the tetracycline group. Nevertheless, two other RCTs compared the efficacy of ciprofloxacin or levofloxacin for six weeks versus placebo in the treatment of CP/CPPS. The results did not reveal any significant difference in the changes in NIH-CPSI scores [14]. Hence, there is no sufficient evidence supporting the efficacy of antibiotics in the primary treatment of CP/CPPS [1,9].

Anti-inflammatory medications have been a therapeutic option for CPPS. On the other hand, the outcomes have varied. A previous study showed that celecoxib improves the condition of patients. On the other hand, deterioration was observed two weeks after therapy [19]. In another RCT on pentosan polysulfate sodium, there was no significant improvement in the Clinical Global Improvement and total NIH-CPSI scores [15].

New second-generation drugs, including beclomethasone dipropionate, are aimed to decrease the systemic activity while maintaining local efficacy. Hence, they have attracted increasing interest. Bozzini et al. [20] performed a study on 180 men with CP/CPPS, who received beclomethasone dipropionate suppositories. Of these patients, 136 received a *Serenoa repens* extract. The results showed that the men in the steroid group and those in the steroid and *S. repens*-combined group experienced significant decreases in voiding frequency (-3.55 vs. -3.68 voids per day, respectively) and increases in uroflowmetry (3.26 vs. 5.61 ml/s, respectively). Moreover, both groups experienced an improvement in perineal pain based on the visual analog scale. Therefore, beclomethasone dipropionate suppositories were considered safe and were associated with improvement in LUTS and pain.

Kotb et al. [21] examined the efficacy of antifungals and

urinary alkalization with potassium citrate in 1,000 men who did not respond to four weeks of treatment with antibiotics and alpha-blockers [31]. Of 1,000 men, 803 experienced at least 80% improvement in their urinary and pain symptoms. A low initial prostate-specific antigen level and age were associated with a better response to antifungals.

5. Neurological/Systemic

Neuromodulatory techniques have shown promising results in the treatment of CP/CPPS. In a randomized, placebo-controlled, double-blind trial, Kessler et al. [22] examined the effects of sono-electromagnetic (SEM) therapy in the treatment of refractory CP/CPPS. The patients had received other therapies, including antibiotics, nonsteroidal anti-inflammatory drugs, and alpha-blockers, for at least six weeks. At home, the device was placed over the perineum twice a day for 10 minutes using a portable device provided by the manufacturer. After 12 weeks, there was no significant difference in the NIH-CPSI scores between the SEM and placebo groups. On the other hand, subgroup analysis showed that the benefit of SEM was more evident than that of the placebo in patients with a symptom duration of <12 months.

Although the precise mechanism of action is not completely understood, acupuncture has been used as a complementary therapeutic option in the management of refractory CP/CPPS in Eastern countries. Several studies have reported that acupuncture may increase the endogenous release of opioids and modulate the sympathetic tone and pain pathways [14,23]. Qin et al. [24] conducted a recent systematic review of acupuncture for the treatment of CP/CPPS. They reported that it was effective in managing CP/CPPS.

6. Tenderness

The targeting of key modulators in the pain pathway and nerve growth factor (NGF) inhibition has attracted increasing interest. Both modulators have been found to reduce pain in animal models. Tanezumab, a monoclonal antibody against NGF, is an effective agent. Nickel et al. [25] performed a pooled analysis in patients with chronic pelvic pain, including women with interstitial cystitis and men with CP/CPPS. Pooled analysis showed that tanezumab improved the pain scores. On the other hand, the results were not significant in the male population with CP/CPPS. Therefore,

tanezumab is considered a promising therapy. Nevertheless, further studies, particularly in the CP/CPPS population, will be needed.

Botulinum neurotoxin-A (BoNT-A) is a toxin familiar to several urologists and is used in different urologic conditions, including neurogenic detrusor overactivity. Falahatkar et al. [26] performed a randomized, double-blind study. They reported statistically significant continuous and stable improvement in the total and subscale scores of the NIH-CPSI during the final six-month evaluation in 60 patients with CP/CPPS who received a transurethral intraprostatic injection of BoNT-A or normal saline. Similar results were obtained using other instruments, such as the American Urologic Association (AUA) symptom score, visual analog scale, and quality of life scores. No significant adverse events were recorded except in two patients who developed transient gross hematuria, which was managed conservatively.

EVOLUTION OF PHENOTYPE MAPPING

With the initial success of including the phenotype domains in the UPOINT system to better classify and treat CP/CPPS, the classification systems for CP/CPPS have been developed. Table 2 lists the diagnostic criteria and possible treatments for the UPOINT phenotypes [15]. Magri et al. [27] evaluated the inclusion of a sexual dysfunction domain to the UPOINT clinical phenotyping system. In this study, 937 European patients with CPPS were classified retrospectively using the modified UPOINTS system (S, sexual

dysfunction domain). The UPOINTS scores correlated with the NIH-CPSI scores in this cohort. Similarly, another study found that the addition of a sexual dysfunction domain improved the quality of life [28]. On the other hand, Samplaski et al. [29] reported that erectile dysfunction did not independently affect the severity of CP/CPPS symptoms or the quality of life.

The UPOINT system focuses on categorizing and individualizing therapy for CP/CPPS via symptom phenotype mapping. The Dimitrakoff, Allsop, Bhair, Brook, Erstad, and Cohen (DABBEC) system is a mechanistically predictive phenotyping system. The two main domains of CP/CPPS in the DABBEC phenotyping system (DPS) are the hypothalamic-pituitary-adrenal domain and the CYP21A2 domain (adrenocortical function). Significant correlations between the specific biomarkers and CP/CPPS have not been elucidated. Unlike the UPOINT system, however, the DPS mechanistic phenotyping system is used to categorize CP/CPPS within these domains, which might provide more insight into the pathophysiology of CP/CPPS and new targeted therapies [30].

Cluster analysis is performed to assess the similarities among the apparent heterogeneous phenotypes [29]. This analysis was performed on the UPOINT domains. The results showed two main clusters with homogenous profiles (urinary, organ-specific, and tenderness domains as one cluster, and neurologic, infection, and psychosocial domains as the other). The two homogeneous clusters suggest that the patient groups may differ in terms of their pathophysiology and treatment response [31]. Davis et al. [32] performed a

Table 2. Diagnostic criteria and treatments for UPOINT phenotypes

| Domain | Diagnostic criteria | Possible treatment |
|---------------------|---|---|
| Urinary | Bothersome irritative or obstructive urinary symptoms High postvoid residual | Alpha-blockers Antimuscarinics 5-ARI |
| Psychosocial | Clinical depression Catastrophizing (verbalized helplessness and hopelessness) | Psychologic or psychiatric counseling Cognitive-behavioral therapy |
| Organ-specific | Prostate tenderness Symptom relief with voiding | Quercetin Pollen extract |
| Infection | Positive cultures of prostatic fluid in the absence of UTI Urethritis | Antibiotics |
| Neurologic/systemic | Pain outside pelvis Neuropathic pain | Neuromodulating medications Acupuncture |
| Tenderness | Pelvic floor dysfunction: spasm Muscle trigger points in pelvis/abdomen | Pelvic physical therapy Myofascial release Injection therapy |

UPOINT: Urinary, Psychosocial, Organ-Specific, Infection, Neurological/Systemic, and Tenderness, UTI: urinary tract infection, 5-ARI: 5-alpha reductase inhibitor.

subtype-based cluster analysis using validated questionnaires and urologic examinations on patients with urologic pelvic pain. The results revealed seven distinct homogeneous clusters (ejaculatory pain/sexual dysfunction, new pain, low pain symptom/distress, prostate disease, testicular pain, long-term genitopelvic pain, and whole-body pain). Interestingly, whole body pain was a separate cluster that is similar to the second cluster based on the UPOINT domains in the Samplaski group (neurologic, infection, and psychosocial). Therefore, there may be a subtype of urologic pelvic pain with a central/systemic pathophysiology.

CONCLUSIONS

CP/CPPS is a condition that can be challenging to treat, and a multimodal approach is commonly required. UPOINT-directed therapy is an approach that simplifies treatment in patients with CPPS. The efficacy of the UPOINT clinical phenotyping system as a diagnostic and treatment tool has been validated in patients with CP/CPPS. The UPOINT system itself may require improvement, and the criteria for each domain have not been fully validated. Nevertheless, this system is considered to be an effective diagnostic and treatment algorithm.

CONFLICT OF INTEREST

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

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