

# Evaluation of influence of the UPOINT-guided multimodal therapy in men with chronic prostatitis/chronic pelvic pain syndrome on dynamic values NIH-CPSI: a prospective, controlled, comparative study

Denis V. Krakhotkin , Volodymyr A. Chernylovskiy, Evgeny E. Bakurov and Johann Sperl

## Abstract

**Background:** The aim of this work was to evaluate the influence of UPOINT-guided (Urinary, Psychosocial, Organ-specific, Infection, Neurologic/systemic, Tenderness of skeletal muscles) multimodal therapy in patients with chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS) on the dynamic values of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score.

**Patients and methods:** In our study we investigated 110 patients aged 26–68 years with CP/CPPS. We performed digital rectal examination (DRE), pre- and post-massage test (PPMT) urine culture, urine analysis, transrectal ultrasound investigation of prostate, antibiotic susceptibility testing. We divided the patients into the intervention group and the control group which was followed up without any therapy. For the intervention group we offered multimodal therapy based on each predominated positive phenotype. For the urinary phenotype, patients in intervention group received 10 mg alfuzosin. For organ-specific and tenderness domains, the patients of the intervention group received 63 mg Cernilton and 1 g Quercetin. For infection control, the patients of the intervention group received antimicrobial agents according to the results of the post-massage urine culture, antibiotic susceptibility testing and a high level of contamination  $>10^5$  colony-forming units (CFU)/ml. Microbiological assessment of PPMT urine culture was conducted with aerobic and anaerobic methods of cultivation

**Results:** The 110 patients had an average age of  $43.9 \pm 11.1$  years and a median duration of symptoms of  $6.21 \pm 1.8$  months. Of these, 11 patients did not complete the trial and therefore in quantitative terms, the distribution of patients was as follows: 54 in the intervention group and 45 in the control group. The average total NIH-CPSI score before treatment was  $29.8 \pm 6.1$  in both groups. The mean NIH-CPSI of the pain, urinary, and quality of life (QOL) subscores before treatment was  $15.1 \pm 3.0$ ,  $7.4 \pm 1.4$  and  $8.1 \pm 2.1$ , respectively in both groups. After 6 weeks the PPMT urine culture of patients of the intervention group showed the absence or low-level contamination of microorganisms. After conducting the treatment, the mean total NIH-CPSI score in the intervention and control groups was  $13.9 \pm 2.8$  ( $p = 0.025$ ) and  $29.8 \pm 5.8$  ( $p = 0.18$ ), respectively. The average NIH-CPSI pain subscore in the intervention and control group after treatment was  $6.7 \pm 1.4$  ( $p = 0.018$ ) and  $15.1 \pm 2.8$  ( $p = 0.21$ ), respectively. The mean NIH-CPSI urinary subscore after treatment in the intervention and control group was  $3.22 \pm 1.07$  ( $p = 0.045$ ) and  $7.4 \pm 1.2$  ( $p = 0.15$ ), respectively. The average NIH-CPSI QOL subscore after treatment in the intervention and control group was  $3.87 \pm 1.28$  ( $p = 0.015$ ) and  $8.1 \pm 1.9$  ( $p = 0.35$ ). After multimodal therapy, the prevalence of different UPOINT-positive domains in the patients of both intervention groups did not exceed 14%.

Ther Adv Urol

2019, Vol. 11: 1–9

DOI: 10.1177/  
1756287219857271

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Correspondence to:  
**Denis V. Krakhotkin**  
Central District Hospital,  
Outpatient Clinic,  
Sadovaya Lane 23,  
Kamenolomni, 346480,  
Rostov Region, Russia  
[den\\_surgeon@mail.ru](mailto:den_surgeon@mail.ru)

**Volodymyr A. Chernylovskiy**  
Department of Urology 1,  
City Clinical Hospital № 4,  
Dnipro, Ukraine

**Evgeny E. Bakurov**  
Rostov Regional Hospital  
ROKB 1, Department of  
Surgery №1, Rostov-  
on-Don, Russia

**Johann Sperl**  
Private Dermatology  
Practice, Berlin, Germany

**Conclusions:** The UPOINT clinical phenotypes significantly changed after multimodal treatment, including antibiotics, phytotherapy and  $\alpha$ -blockers in patients with CP/CPPS. This combination of treatment showed a decreasing total NIH-CPSI score and an elevation of QOL in patients.

**Keywords:** chronic prostatitis/chronic pelvic pain syndrome, UPOINT, multimodal therapy

Received: 8 July 2018; revised manuscript accepted: 26 May 2019.

## Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common condition that causes severe symptoms of distress and has a significant influence on the quality of life (QOL) in 8.2% of men. The treatment of patients with a diagnosis of CP/CPPS has always been an intractable task in clinical practice. Many clinical trials failed to identify an effective monotherapy due to its heterogeneous etiology. The incidence of CP/CPPS ranges between 2.2 and 13.8% depending of specific populations and countries. CP/CPPS is characterized by a plurality of symptoms, including pain in the pelvic region, irritative or obstructive voiding symptoms, other pelvic disturbances, sexual dysfunction and psychological disorders.<sup>1,2</sup> CP/CPPS remains a challenging condition for diagnosis and treatment. The more focused approach of therapy of this syndrome is based on the classification of the National Institutes of Health (NIH) without assuming etiology. CP/CPPS is defined when pelvic pain is present for at least three preceding months and no other identifiable causes have been detected.<sup>3,4</sup> To date, CP/CPPS has been treated using  $\alpha$ -blockers, anti-inflammatory drugs, antibacterial agents, and phytotherapy with different results.<sup>5</sup> Management of CP/CPPS also includes nonpharmacological approaches such as: local thermotherapy, extracorporeal shockwave therapy, acupuncture and electroacupuncture, biofeedback, myofascial trigger point release, physical activity, lifestyle interventions and psychological support. These treatments can be used alone or in combination. Recently a *Cochrane Review* found that acupuncture and extracorporeal shockwave treatment are the most effective nonpharmacological interventions for decreasing prostatic symptoms measured by the NIH Chronic Prostatitis Symptom Index (CPSI) score.<sup>6</sup> In the majority of cases, chronic pelvic pain may have pelvic floor tenderness which reproduces the patient's pain on palpation; this occurs in approximately 85% of men.<sup>7</sup> The role of infection in the development of CP/CPPS is controversial. Bacterial infections have been hypothesized to have a role in the

pathogenesis of CPPS but there have been limited studies demonstrating a cause–effect relationship that supports this hypothesis. Rudick and colleagues showed that the strain CP1 from the family of uropathogenic *Escherichia coli* (UPEC) was implicated as an etiological agent in men with CP/CPPS and confirmed its role in an animal model. In another study, Shoskes and colleagues demonstrated the higher prevalence of anaerobic bacteria as representatives of the urinary microbiome in men with CP/CPPS. The prostate gland of men with CP/CPPS may be colonized both by traditional uropathogens (such as *E.coli*, *Klebsiella spp.* and other Enterobacteriaceae) and bacteria causing disease in other adjacent or distant organs (Streptococci, coagulase-negative Staphylococci, *Chlamydia trachomatis* and *Mycoplasma spp.*) that are still not classified as prostatic pathogens.<sup>8–10</sup> In 2009, Shoskes and colleagues developed a six-point clinical phenotyping system called UPOINT (Urinary, Psychosocial, Organ-specific, Infection, Neurologic/systemic, Tenderness of skeletal muscles) to classify patients with CPPS and interstitial cystitis and subsequently direct appropriate therapy. The clinical domains are urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurological/systemic, and tenderness of muscles. This algorithm of clinical phenotyping of the patients with CP/CPPS may also include the sexual dysfunction domain in the UPOINT(S) system.<sup>2,11</sup> The additional sexual dysfunction domain did not change the correlation with NIH-CPSI scores.<sup>12</sup> The first UPOINT retrospective study showed the strong correlation between the NIH-CPSI total score and the number of UPOINT-positive domains in each patient. Nowadays the UPOINT-guided multimodal therapy has been shown to significantly improve symptoms.<sup>13</sup> Monotherapy is mainly not effective for alleviating symptoms, because it is not targeted to the individual pathophysiologies for heterogeneous population of patients with CP/CPPS. UPOINT is used to classify individuals with CP/CPPS to define their unique clinical phenotype, which can then be used

to guide therapy. The number of positive UPOINT domains correlates strongly with the severity and duration of prostatitis symptoms, as measured with the NIH-CPSI. In a prospective study of patients with CP/CPPS treated with directed multimodal therapy, as guided by their UPOINT phenotypes, 84% had a significant improvement in symptoms and QOL.<sup>16</sup> The general purpose of UPOINT was to guide therapy for patients with CP/CPPS and to gain insight into the pathophysiology of CP/CPPS by examining the incidence and treatment response of different phenotype combinations.<sup>14</sup> Despite emerging alternatives with multimodality treatment, dissemination of current guidelines is slow and monotherapy, typically with antibiotics, is common. Because of this, outcomes, both in clinical practice and clinical trials, remain poor.<sup>15</sup> The recent data replicate previous findings that there is a relationship between the NIH-CPSI total score and the number of positive UPOINT domains.<sup>12,16</sup> There is no gold standard for a definitive diagnosis of CP/CPPS, which is typically based on patient history, symptoms and exclusion of other causes.<sup>17</sup> Our prospective study will be dedicated to evaluation of influence UPOINT-guided multimodal therapy on the dynamic of NIH-CPSI scores and the prevalence of positive UPOINT domains after treatment.

### Patients and methods

In our study 110 patients aged 26–68 years with a diagnosis of CP/CPPS were enrolled from January 2018 to June 2018. We performed digital rectal examination, the two-glass pre-massage and post-massage test (PPMT) with urine culture and antibiotic susceptibility testing, urinalysis, and a transrectal ultrasound investigation of the prostate. The symptom severity for each patient was assessed by the NIH-CPSI, which was reported as subscores for pain (0 to 21), urinary (0 to 10) and QOL (0 to 12) as well as the total score (0 to 43). We collected and analyzed the data of NIH-CPSI with its subscores before and through 5 months of treatment. We adopted the criteria described by Shoskes and colleagues<sup>16</sup> for the determination of which UPOINT domains were positive in each patient. In brief, the urinary domain was positive if the patient presented with high postvoid residual urine volume, urgency, frequency and nocturia. The psychosocial domain was positive if the patient had clinical depression, feeling of helplessness, hopelessness. The organ-specific domain was considered positive if there was specific prostate tenderness on digital rectal

examination, leukocytosis in the prostatic fluid or post-prostatic massage urine, hematospermia, or an extensive prostatic calcification. The infection domain was positive if any aerobic or anaerobic microorganism was localized in the post-massage urine with a level of contamination  $\geq 10^3$  colony-forming units (CFU)/ml or the patient had a well response on the antibiotic treatment. The neurological/systemic domain was positive if the patient felt pain beyond the abdomen and the pelvis, or had a current diagnosis of irritable bowel disease, fibromyalgia or chronic fatigue syndrome. The tenderness domain was considered as positive if there were palpable spasms or trigger points in the abdomen or pelvic floor. Criteria for inclusion in the trial were digital rectal examination without suspicion of urological cancers, absence of history of urological operations and biopsy of prostate, full completion of information by NIH-CPSI and UPOINT clinical phenotype. We divided patients into the intervention and the control group (men without any therapy) for comparative purposes. We offered therapy based on the predominated positive phenotype for the intervention group. For the urinary UPOINT-positive domain, the patients of the intervention group received 10 mg alfuzosin. For the infection domain, the patients of the intervention group received antimicrobial agents according to the results of the post-massage urine culture, antibiotic susceptibility testing and a high titer of isolated microorganisms  $>10^5$  CFU/ml. The intervention group received 63 mg Cernilton four times daily and the 1 g Quercetin three times daily for the organ-specific and tenderness UPOINT-positive domains. The patients with neurologic/systemic UPOINT-positive domain in the intervention group were referred to a neurologist and physiotherapist for the treatment of fibromyalgia. For the psychosocial domain, the patients of the intervention group were referred to a psychologist or psychiatrist for the management of severe depression in 10% cases from the total number of patients with CP/CPPS. The psychiatric and psychological aid included the following: (1) cognitive-behavioral methods, focused on changing of behavior and thoughts, since learning specific coping skills were required for dealing with negative emotions; (2) relaxation techniques, were any process or activity that helped patients to relax and achieve a state of calmness, including stress management; and (3) social/family support: promoting communication with patients and their families; understanding, encouraging and comforting patients. The total duration of UPOINT-guided

treatment, including all types of interventions for patients with CP/CPPS was 5 months. Microbiological assessment of post-massage urine culture was conducted by aerobic and anaerobic methods of cultivation using extended set nutrient media. They included the following: Endo, HighChrome selective agar for *Candida* fungi, yolk salt agar, HighChrome selective agar for Enterococci, blood agar, prepared on the basis of Müller–Hinton agar with the addition of sheep erythrocytes. For non-Clostridial bacteria the following were used: the Müller–Hinton environment with the addition of sheep erythrocytes, Blaurokka media and agar Schaedler. The crops were incubated in aerobic and anaerobic (10% CO<sub>2</sub>, 10% H<sub>2</sub>, 80% N<sub>2</sub>) cultivation conditions at 37°C. All patients signed the written informed consent for participating in the study. The principles of the 1964 Declaration of Helsinki were used in planning and implementing the study. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki. Each patient provided informed consent for participation in this study. For descriptive statistics all data presented are mean ± standard deviation with a 95% confidence interval. Parametric Student's *t* tests, nonparametric Mann–Whitney U tests and Chi-squared tests were performed for the differences in the mean age, duration of disease, total NIH-CPSI score, NIH-CPSI pain subscore, NIH-CPSI urinary subscore, and NIH-CPSI QOL subscore before and after treatment. All analyses were performed using SPSS software version 16.0.

## Results

The 110 patients with CP/CPPS had a mean age 43.9 ± 11.1 years (range 26–68 years) and median duration of symptoms was 6.21 ± 1.8 months (range 3–12 months). Of these, 11 patients did not complete the trial (did not meet the inclusion criteria) and therefore in quantitative terms, the distribution of patients was as follows: 54 in the intervention group and 45 in the control group. The average total NIH-CPSI score before treatment was 29.8 ± 6.1 in both groups. The mean NIH-CPSI of pain, urinary, QOL subscores before treatment was 15.1 ± 3.0, 7.4 ± 1.4 and 8.1 ± 2.1, respectively in both groups. The taxonomic structure of pre-massage and post-massage urine culture presented mixed aerobic–anaerobic microflora. The etiological structure and the

mean level contamination of microorganisms in PPMT urine culture in both groups is shown in Table 1. In our study the highest susceptibility observed for fluoroquinolones and cephalosporins was 92% and 85% cases, respectively. In the intervention group a positive infection domain was observed in 95% of cases (51 patients) and the mean level of contamination in post-massage urine culture was >10<sup>5</sup> CFU/ml. Therefore, the patients in the intervention group with a positive infection domain received the combined antibiotic treatment; this included the following regimens: 500 mg levofloxacin orally once a day for 6 weeks and 400 mg Cefixime orally once a day for 2–3 weeks. The urinary UPOINT-positive domain was observed for the intervention and control groups in 72% (39 patients) and 69% (31 patients) cases, respectively. The patients of the intervention group received 10 mg alfuzosin once a day for 5 months. The organ-specific UPOINT-positive domain was observed in 82% (44 patients) and 80% (36 patients) of cases for the intervention and control groups, respectively. The tenderness UPOINT-positive domain occurred in 62% (34 patients) and 74% (33 patients) of cases for the intervention and control groups, respectively. For these domains the patients of both intervention groups received 63 mg Cernilton four times daily and 1 g Quercetin in tablet form for 5 months. After 6 weeks we repeated the PPMT urine culture and in the majority of cases there were no bacteria and results showed the absence or low-level contamination of microorganisms <10<sup>2</sup> CFU/ml in the intervention group. The mean total number of positive UPOINT domains before treatment was 3.9 ± 0.9 (range 0–6) in both groups. After conducting treatment, the mean total NIH-CPSI score in the intervention and control groups was 13.9 ± 2.8 (*p* = 0.025) and 29.8 ± 5.8 (*p* = 0.18), respectively. The average NIH-CPSI pain subscore in the intervention and control group after treatment was 6.7 ± 1.4 (*p* = 0.018) and 15.1 ± 2.8 (*p* = 0.21), respectively. The mean NIH-CPSI urinary subscore after treatment in the intervention and control group was 3.22 ± 1.07 (*p* = 0.05) and 7.4 ± 1.2 (*p* = 0.15), respectively. The average NIH-CPSI QOL subscore after treatment in the intervention and control group was 3.87 ± 1.28 (*p* = 0.015) and 8.1 ± 1.9 (*p* = 0.35), respectively. The psychosocial UPOINT-positive domain was observed in 60% (32 patients) and 44% (20 patients) of cases for the intervention and control groups, respectively. In our study the consultation of a psychologist or

**Table 1.** Etiological structure and level contamination of isolated microorganisms in PPMT urine culture in men with CP/CPPS in both groups.

Intervention group (54 patients)				Control group (45 patients)			
Isolated microorganism in pre-message urine culture	Decimal logarithm of mean level contamination (CFU/ml)	Isolated microorganism in post-message urine culture	Decimal logarithm of mean level contamination (CFU/ml)	Isolated microorganism in pre-message urine culture	Decimal logarithm of mean level contamination (CFU/ml)	Isolated microorganism in post-message urine culture	Decimal logarithm of mean level contamination (CFU/ml)
Staphylococcus haemolyticus	2.0	Corynebacterium spp.	5.5	Peptostreptococcus spp.	2.0	Corynebacterium spp.	1.9
Peptostreptococcus spp.	2.5	Enterococcus spp.	5.6	Staphylococcus warneri	1.5	Enterococcus spp.	1.6
Staphylococcus warneri	2.2	Staphylococcus epidermidis	5.2	Veillonella spp.	1.2	Escherichia coli	1.2
Veillonella spp.	1.5	Escherichia coli	7.0	Mobiluncus spp.	1.5	Veillonella spp.	1.4
Staphylococcus lentus	1.4	Veillonella spp.	5.4	Staphylococcus epidermidis	1.1	Eubacterium spp.	1.3
Mobiluncus spp.	1.7	Eubacterium spp.	6.2	Prevotella spp.	1.2	Peptococcus spp.	2.5
Staphylococcus epidermidis	2.1	Peptococcus spp.	6.8	Corynebacterium spp.	1.8	Propionibacterium spp.	1.1
Prevotella spp.	2.3	Propionibacterium spp.	5.1	Staphylococcus caprae	1.3	Prevotella spp.	1.8
Staphylococcus xylosum	1.9	Prevotella spp.	4.8	Fusobacterium spp.	1.1	Staphylococcus aureus	1.4
Corynebacterium spp.	2.4	Staphylococcus warneri	5.8	Staphylococcus equorum	1.4	Klebsiella spp.	1.5
Staphylococcus caprae	2.2	Staphylococcus aureus	6.0	Peptococcus spp.	1.2	Staphylococcus lentus	1.3
Fusobacterium spp.	2.5	Klebsiella spp.	7.1	Propionibacterium spp.	2.0	Bacteroides spp.	2.1
Staphylococcus equorum	1.4	Staphylococcus lentus	5.0	Bacteroides spp.	1.4	Staphylococcus haemolyticus	1.2
Peptococcus spp.	1.6	Bacteroides spp.	6.0	Proteus spp.	1.6	Proteus spp.	1.7
Propionibacterium spp.	2.2	Staphylococcus haemolyticus	5.2	Peptostreptococcus spp.	1.9	Peptostreptococcus spp.	1.9
Eubacterium spp.	2.3	Pseudomonas aeruginosa	5.5	Staphylococcus saprophyticus	1.3	Staphylococcus saprophyticus	1.3
Bacteroides spp.	2.4	Proteus spp.	5.7	Streptococcus spp.	1.5	Streptococcus spp.	1.5
Morganella morganii	2.0	Peptostreptococcus spp.	5.9	Fusobacterium spp.	1.8	Fusobacterium spp.	1.8
		Staphylococcus saprophyticus	6.3	Mobiluncus spp.	1.2	Mobiluncus spp.	1.2
		Streptococcus spp.	5.5				
		Fusobacterium spp.	6.9				
		Morganella morganii	6.3				
		Mobiluncus spp.	5.2				

CFU, colony-forming units; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; PPMT, pre-message and post-message.



**Table 2.** The dynamic of changes NIH-CPSI total score and the pain, urinary and QOL subscores in both groups.

Scores	Intervention group (n = 56)			Control group (n = 45)		
	Pre-treatment	Post-treatment	p value	Pre-treatment	Post-treatment	p value
NIH-CPSI (total)	29.8 ± 6.1	13.9 ± 2.8	0.025	29.8 ± 6.1	29.8 ± 5.8	0.18
Pain subscore	15.1 ± 3.0	6.7 ± 1.4	0.018	15.1 ± 3.0	15.1 ± 2.8	0.21
Urinary subscore	7.4 ± 1.4	3.22 ± 1.07	0.05	7.4 ± 1.4	7.4 ± 1.2	0.15
QOL subscore	8.1 ± 2.1	3.87 ± 1.28	0.015	8.1 ± 2.1	8.1 ± 1.9	0.35

Data are presented as median (±standard deviation).  
NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; QOL, quality of life

**Table 3.** The prevalence of UPOINT-positive domains before and after treatment in the intervention group.

Intervention group (n = 54)		
UPOINT-positive domain	Before treatment	After treatment
Urinary domain	72% (38)	12% (6)
Psychosocial domain	50% (27)	9% (5)
Organ-specific domain	82% (44)	8% (4)
Infection domain	95% (51)	11% (6)
Neurologic/systemic domain	15% (8)	2% (1)
Tenderness domain	62% (33)	7% (4)

psychiatrist was needed in 10% cases from all men with CP/CPSP due to severe depression (five patients in the intervention group). In the remaining cases, psychological problems were resolved by diminishing the pain syndrome and urinary symptoms. The average total number of positive UPOINT domains after treatment were  $1.75 \pm 0.74$  ( $p = 0.022$ ) and  $3.9 \pm 0.8$  ( $p = 0.124$ ; range 0–6) in the intervention and the control group, respectively. The dynamics of the changes of the NIH-CPSI total score and the pain, urinary and QOL subscores for both groups are shown in Table 2. The prevalence of UPOINT-positive domains before and after treatment in the intervention group is shown in Table 3. The significant decrease of the UPOINT psychosocial domain was associated with an improvement of clinical symptoms in the majority men with CP/CPSP. The amelioration of UPOINT organ-specific and tenderness domains was related with a decreasing inflammatory process within the prostate while taking the Cernilton

and Quercetin. After UPOINT-guided multimodal therapy, the prevalence of different UPOINT-positive domains in patients of the intervention group did not exceed 14%.

### Discussion

The etiology of CP/CPSP is still not clearly defined although there are a lot of published articles and randomized controlled studies about various modality treatments. There have been many attempts to explain the possible cause of this condition in the literature for the last 10–15 years. The NIH classification divides the CP/CPSP into IIIA (inflammatory) and IIIB (noninflammatory) categories but each does not indicate the exact etiology of the pathological process, to allow the determination of the absence or presence of the inflammatory process inside prostatic tissue. Shoskes and colleagues reported that urinary microbiomes from patients with CP/CPSP have higher  $\alpha$ (phylogenetic) diversity and higher

counts of *Clostridia spp.* compared with controls.<sup>10</sup> These uropathogens are not determined with routine urine culture methods and the extended set of nutritive media or 16S-rDNA sequencing for aerobic–anaerobic associations should be used.<sup>18</sup> Thus, the categories IIIA and IIIB of CP/ CPPS can be considered as different stages of disease. Perhaps, these are related to the anaerobic environment, which is maintained within prostatic tissue as biofilms or pods. Therefore, bacterial infection plays an important role in the initiation, neurologic and organ-specific manifestations CP/ CPPS due to the reactions of cell immunity, activation of mast cells and peripheral neurons.<sup>19,20</sup> Our study showed that the prevalence of the UPOINT infection clinical phenotype was no more than 14% of cases after conducting multimodal UPOINT-guided therapy and was mainly related to the presence of resistant strains of microorganisms. The UPOINT infection domain before treatment was observed in 95% and 40% cases for the I and II groups, respectively. Antibiotic treatment was received only in group I due to higher levels of contamination in the post-massage urine culture ( $>10^5$  CFU/ml). The improvement for UPOINT organ-specific and tenderness domains was related to a decrease in the inflammatory process within the prostate on the background of therapy with Cernilton and Quercetin. The prevalence of these domains after treatment did not exceed 8% and 11%, respectively. The decline of the incidence of the UPOINT infection domain in group II was also observed on the background of therapy by Cernilton and Quercetin. Wagenlehner and colleagues demonstrated that men who received a pollen extract (Cernilton) experienced an improvement in NIH-CPSI of at least 25% compared with 50% in the placebo arm.<sup>21</sup> Antibiotics have anti-inflammatory properties which reduce potent reactive oxygen species generated by neutrophils at the sites of inflammation and inhibition of production tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, IL-1, and Prostaglandin E (PGE). In our case, they were used only in group I due to the high levels of contamination of isolated bacteria.<sup>22</sup> The majority of the isolated microorganisms in pre and post-massage urine culture are found in asymptomatic patients as representatives of the urine microbiome.<sup>23,24</sup> The decline of the amount of positive UPOINT domains for each patient is temporary due to the improvement of clinical symptoms and depression due to pain syndrome. Nevertheless, the

UPOINT-guided multimodal strategy treatment provides better results than monotherapy. The temporary character of positive changes of clinical symptoms of CP/ CPPS during long-term follow up is associated with an uncompleted action of therapy which is not covered by all possible branches of pathogenesis of the disease. A limitation of our study was a lack of good evidence for each modality treatment proposed for patients with CP/ CPPS. There are data on the presence of microRNAs herpes simplex virus (HSV) I and II types that may implicate both with the possible pathogenesis of prostate cancer and chronic inflammation of surrounding noncancerous tissues.<sup>25,26</sup> Patients with benign prostate hyperplasia may have a Cytomegalovirus (CMV) infection, HSV I and II types, or human papillomavirus (HPV) 11, 16, 18, 31, 33 types which can also be implicated in the possible pathogenesis of CP/ CPPS.<sup>27</sup> Therefore, the success of multimodal therapy will depend on the knowledge of the exact etiology and the stages of pathogenesis of CP/ CPPS which are still not fully elucidated. It is also necessary to conduct as many randomized controlled studies as possible for each type of treatment proposed for CP/ CPPS in the European Association of Urology guidelines

### Conclusions

Our study showed that UPOINT clinical phenotypes significantly changed after multimodal treatment, including antibiotics, phytotherapy and  $\alpha$ -blockers in patients with CP/ CPPS. The combination of these modalities of treatment showed a decreasing total NIH-CPSI score and an improvement in patient QOL. In patients with CP/ CPPS it was necessary to use the UPOINT-guided multimodal therapy ([www.upointmd.com](http://www.upointmd.com)). Such an approach should consider the prevalence of the most dominant UPOINT clinical phenotypes in each population of men and accordingly, conduct more targeted therapy. The effectiveness of this strategy in the management of CP/ CPPS will depend on the knowledge of the precise pathophysiological pathways and etiology of the disease which could provide more targeted treatment with long-term remission and better clinical outcomes.

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

### Conflict of interest statement

The authors declare that there is no conflict of interest.

### ORCID iD

Denis V. Krakhotkin  <https://orcid.org/0000-0003-1540-6647>

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