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Antibiotic therapy effectiveness as an outcome predictor of complex treatment in chronic prostatitis/chronic pelvic pain syndrome

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Introduction We hypothesized that the history of antibiotic efficacy was related to the outcome of the treatment of patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and evaluated this as a phenotyping factor for such patients.
Material and methods This prospective study included 74 patients with CP/CPPS aged 18–45 years old, who had at least 10 points on the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) scale and did not receive treatment for CP/CPPS for the last 3 months. There were 5 visits. Group 1 (n = 37) included patients with past successful antibiotic therapy. Group 2 (n = 37) included patients without antibiotic effect. All patients orally received: diclofenac sodium (100 mg/day, 2 weeks), modified release tamsulosin (0.4 mg/day, 1 month), and alcohol extract of Serenoa repens (320 mg/day, 6 months). Patients were monitored for symptoms of chronic prostatitis, depression, anxiety, and correlates of inflammation.
Results After the treatment, NIH-CPSI scores significantly decreased (6 points or more) in Groups 1 and 2. The depression and anxiety symptoms significantly decreased only in Group 2. In Group 1, the efficacy of treatment was in 59.5% and 51.4% of patients, and in Group 2 – 83.8% and 78.4% at visits V2 and V4, respectively. The efficacy was significantly (p <0.05) lower in Group 1. The history of antibiotic efficacy and the outcome of this study treatment were significantly related (p <0.05).
Conclusions For CP/CPPS, the history of antibiotic efficacy determines the prognosis of current treatment. The latent bacterial factor is assumed in 24.3–27% of cases of CP/CPPS.

INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common pathology that has no clear association with a bacterial infection and combines signs of prostate inflammation and chronic pain disorder. This form accounts for 90-95% of cases of prostatitis [1]. The disease significantly worsens the physical and mental domains of quality of life [2] and consumes significant resources of the healthcare system [3]. To improve treatment results, along

with the search for new painkillers [4], a multimodal approach is widely used, which takes into account the phenotype domains of specific patients as predictors of the successful outcome [5].
According to the Cochrane report, the most effective remedies to reduce the symptoms in CP/CPPS are: (i) phytotherapy, (ii) α-blockers, (iii) anti-inflammatory drugs and (iv) antibiotics [6]. Antibiotics prescribed for CP/CPPS are strongly recommended, especially to patients who have not received any treatment before [7]. Along with this, however, there

are data indicating the absence of a difference between the efficacy of antibiotics and placebo in the ratio of responders and non-responders [8]. As such, these data prompted us to use antibiotics in the clinic only under strict indications (evidence in favor of the infectious onset of CP/CPPS).

We also prescribed treatment regardless of the severity of pain and dysuric symptoms. The reason for this, we believe, is an extremely weak link between the intensity of symptoms and the activity of the inflammatory process in CP/CPPS [9, 10]. Besides, when choosing a treatment for CP/CPPS, the division into inflammatory and non-inflammatory forms is considered irrational [11].

Objective: To evaluate the efficacy and safety of the combination of diclofenac, tamsulosin, and Serenoa repens extract in CP/CPPS, depending on the efficacy of the previous antibacterial treatment, and to evaluate the clinical significance of the history of antibiotic efficacy as a factor of the CP/CPPS phenotype.

MATERIAL AND METHODS

The treatment was carried out according to the guidelines of the Helsinki Declaration; the study protocol was approved by the local Ethics Committee. It was a prospective study, which included 74 patients with mild-to-severe CP/CPPS according to the criteria of the National Institutes of Health [12].

The criteria for inclusion of patients in the study were:

1) men with CP/CPPS; 2) 18–45 years old; 3) given informed consent to participate; 4) minimum 10 points on the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) scale; 5) no received treatment for CP/CPPS for the last 3 months; 6) history of antibiotic treatment for CP/CPPS.

Symptoms of prostatitis were assessed with NIH-CPSI [13]. Symptoms of depression were assessed on a Patient Health Questionnaire-9 (PHQ-9) scale [14]. Anxiety symptoms were assessed on a Generalized Anxiety Disorder-7 (GAD-7) scale [15]. Clinical examination of patients revealed no signs of neuropathy and disorders of the pelvic floor muscles. Uroflowmetry and ultrasonography of the pelvic organs were also rated.

Sexually transmitted infections were excluded by polymerase chain reaction. No pathogenic microflora (including Candida spp. [16]) was found in the ejaculate, and the conditionally pathogenic microflora did not exceed the level of 1×10^4 CFU/ml.

We did not assess the expressed prostate secretion, as there are cases of its difficult production, which would be a serious obstacle to the assessment of inflammation using the dynamics of ejaculate cytokines. We diagnosed the inflammatory form of chronic prostatitis based on the detection of an increased leukocyte count in the semen ($\geq 10^6$/ml).

The concentration of testosterone, dihydrotestosterone (DHT), estradiol, prostate-specific antigen (PSA) in the blood, and that of interleukin-1β (IL-1β), and interleukin-10 (IL-10) in ejaculate were determined using an enzyme-linked immunosorbent assay.

The assessment was carried out during 5 visits (V0, V1, V2, V3, V4). At visit V0 (1–7 days before V1), the initial acquaintance with the patient was made and informed consent was signed. Visit V1 (1st day) included the examination of patients, diagnosis, and initiation of treatment. Visits V2 (V1+2 weeks), V3 (V1+3 months), V4 (V1+6 months) included control of treatment adherence and evaluation of treatment results.

Patient stratification was carried out based on the documented efficacy of past antibiotic therapy, in the form of a significant reduction in prostatitis symptoms noted by the patient and his doctor. Patients were divided into two comparison groups based on a history of antibiotic efficacy. In the past, patients received CP / CPPS treatment 1 to 6 times using fluoroquinolones, aminoglycosides, tetracyclines, cephalosporins, macrolides, and their combinations for 4-8 weeks. The last antibiotic therapy was completed at least 3 months prior to commencement of this study. Group 1 (n = 37) consisted of patients who had previously clear treatment effect of antibiotics but preferred to avoid using them due to possible side effects. Group 2 (n = 37) included patients who had previously received antibacterial treatment for CP/CPPS without clinical effect. The data from both groups were combined into Group 1 + 2 to assess the overall effect and increase statistical power. All patients received treatment complex regardless of the severity of pain and dysuria, which included diclofenac sodium (100 mg/day, orally after meals, 2 weeks), modified release tamsulosin (0.4 mg/day, oral, 1 month), and alcohol extract of Serenoa repens (320 mg/day, oral, 6 months).

A decrease in the rating of symptoms of prostatitis of 6 or more points on the NIH-CPSI scale was considered clinically significant. A reduction of the NIH-CPSI of less than 6 points was considered as insufficient treatment efficacy. Relapse was considered as an increase of the NIH-CPSI to the initial level after a decrease of 6 or more points.

Statistical analysis was carried out using Student's and Wilcoxon's, Fisher's exact, chi-square tests, Pearson's and Spearman's correlation coefficients, general linear model. Data are represented by mean (M) and standard deviation (SD) or median (Me) and interquartile range (Q25; Q75) depending on the distribu-
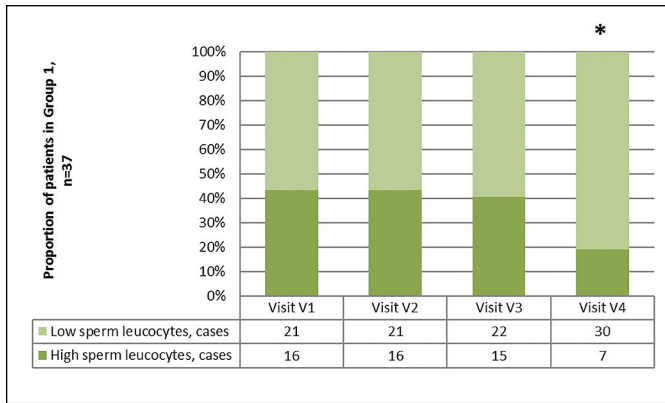
Figure 1. *Dynamics of the ratio of patients with high (≥10⁶/ml) and low (<10⁶/ml) sperm leucocytes in Group 1.*

Note: * – the statistically significant (Fisher's exact test, p <0.05) difference in proportions of patients at this visit and visit V1

Figure 2. *Dynamics of the ratio of patients with high (≥10⁶/ml) and low (<10⁶/ml) sperm leucocytes in Group 2.*

Note: * – the statistically significant (Fisher's exact test, p <0.05) difference in proportions of patients at this visit and visit V1
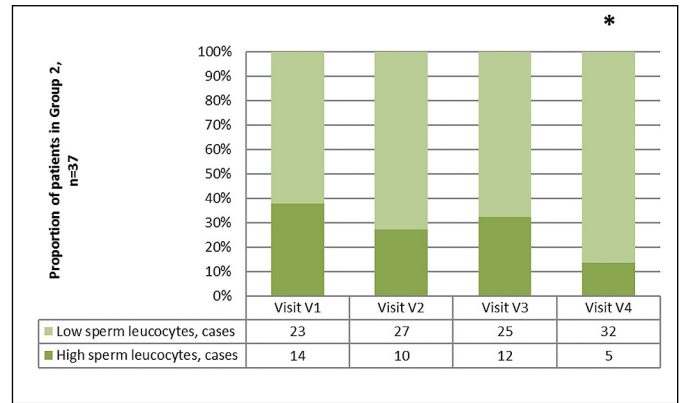
Table 1. *The dynamics of the symptoms of prostatitis in patients with chronic prostatitis/chronic pelvic pain syndrome*

Indicator	Group 1 (n = 37) Mean ±SD				Group 2 (n = 37) Mean ±SD			
	V1	V2	V3	V4	V1	V2	V3	V4
NIH-CPSI, points	16.7 ±4.4	9.0 ±4.8	8.4 ±5.0	10.4 ±6.0	17.8 ±4.1	8.9 ±5.1	7.0 ±5.0	7.8 ±6.6
Mean difference with V1 (95% CI)	–	-7.7 * (-9.2– -6.2)	-8.3* (-10.0–6.6)	-6.3* (-8.3– -4.3)	–	-9.0* (-10.4– -7.6)	-10.8* (-12.7– -9.0)	-10.0* (-12.2– -7.8)*
Mean difference with V2 (95% CI)	7.7* (6.2– 9.2)	–	-0.6 (-1.6–0.3)	1.4 (-0.2– 3.0)	9.0* (7.6–10.4)	–	-1.9* (-3.2– -0.6)	-1.1 (-2.9– 0.8)
Mean difference with V3 (95% CI)	8.3* (6.6– 10.0)	0.6 (-0.3– -1.6)	–	2.0* (0.3–3.7)	10.8* (9.0–12.7)	1.9* (0.6– 3.2)	–	0.8 (-0.7– 2.3)
Mean difference with V4 (95% CI)	6.3* (4.3–8.3)	-1.4 (-3.0– 0.2)	-2.0* (-3.7– -0.3)	–	10.1* (7.8–12.5)	1.1 (-0.8– 2.9)	-0.8 (-2.3– 0.7)	–

SD – standard deviation; * – the indicator denotes statistical significance (p <0.05). NIH-CPSI – National Institutes of Health-Chronic Prostatitis Symptom Index. Study visits: V1 (1st day), V2 (V1+2 weeks), V3 (V1+3 months), V4 (V1+6 months)

tion of the data. The efficacy and safety of treatment were assessed using a relative risk (RR) assessment, the efficacy of antibiotic therapy in history and, accordingly, the data of Group 1 was taken as a risk factor. Statistical analysis was carried out using SPSS, v. 13.0, the level of significance was taken as p <0.05.

RESULTS

Before the treatment, the patients had moderate to severe symptoms of prostatitis (Table 1). Some patients had signs of depression (21.6% in Group 1 and 10.8% in Group 2 had minimum 10 points) and anxiety (21.6% in Group 1 and 18.9% in Group 2 had minimum 10 points) (Table 2).

Table 2. *Dynamics of indicators of depression and anxiety in patients with chronic prostatitis/chronic pelvic pain syndrome*

Indicator	Group 1 (n = 37) Me (Q25;Q75)		Group 2 (n = 37) Me (Q25;Q75)		Group 1+2 (n = 74) Me (Q25;Q75)	
	V1	V4	V1	V4	V1	V4
PHQ-9, points	5.0 (0.0; 8.0)	3.0 (0.0; 6.0)	6.0 (3.5; 8.0)	1.0* (0.0; 5.0)	5.0 (1.0; 8.0)	3.0* (0.0; 6.0)
GAD-7, points	4.0 (2.0; 8.0)	4.0 (2.0; 9.0)	4.0 (2.5; 8.0)	3.0* (0.0; 5.0)	4.0 (2.0; 8.0)	3.0 (1.0; 5.0)

* – the indicator denotes statistical significance (p <0.05). PHQ-9 – Patient Health Questionnaire-9. GAD-7 – Generalized Anxiety Disorder-7. Study visits: V1 (1st day), V4 (V1+6 months).

After the treatment, a significant decrease in NIH-CPSI was observed in both comparison groups. These changes were observed after 2 weeks of treatment and persisted throughout the observation period. The decrease in Group 2 occurred somewhat earlier. Depression and anxiety symptoms significantly decreased (V1 vs V4) only in Group 2. In Group 1 + 2, the indicator of depression affected significant changes (Table 2).

In Group 1 + 2, a significant (p <0.01) direct correlation was observed between NIH-CPSI and PHQ-9 both before (Spearmen's r = 0.320) and after treatment (Spearmen's r = 0.541). In Group 2, there was also a significant relationship between these indicators: before treatment - Spearmen's r = 0.363, p = 0.027; after treatment - Spearmen's r = 0.690, p <0.001. In Group 1, such a relationship was not found.

The inflammatory form of CP/CPPS was diagnosed in Group 1 in 43.2% of cases before treatment and 18.9% after treatment; in Group 2, such diagnosis was made in 37.8% and 13.5% of cases, respectively. A significant decrease in the number of leukocytes in ejaculate was observed (V1 versus V4, p <0.05) in both groups (Figure 1 and Figure 2), and there was no intergroup difference, both before and after treatment.

The maximum urination rate (Table 3) increased significantly in both groups while taking tamsulosin (V2) and also significantly decreased after its discontinuation (V4). There were no significant differences between groups at visits V1, V2, and V4.

All patients showed comparable changes in the echo structure of the prostate gland: fibrosis areas and echo-dense inclusions. An ultrasonographic analysis did not reveal abnormalities in the parameters of the volume of the prostate gland and residual urine both before and after treatment.

No significant difference (V1 vs V4) was revealed between the groups in blood levels of testosterone, DHT, and PSA (Table 4) at each visit. Testosterone significantly increased in Group 2, as well as in Group 1 + 2. The levels of DHT and total PSA decreased significantly during treatment in Groups 1, 2, and 1 + 2. No significant changes were observed in the blood estradiol level.

The clinical significance of the observed changes is complemented by the revealed correlation with other indicators. In Group 1, before treatment, a positive relationship was found between blood estradiol and the depression index on the PHQ-9 (Spearmen's

Table 3. Dynamics of the maximum urine flow rate in patients with chronic prostatitis/chronic pelvic pain syndrome

Indicator	Group 1 (n = 37) Mean ±SD			Group 2 (n = 37) Mean ±SD		
	V1	V2	V4	V1	V2	V4
Q max, mL/sec	19.6 ±5.4	25.9 ±6.5	20.7 ±6.2	21.1 ±6.0	23.9 ±5.0	21.4 ±4.4
Mean difference with V1 (95% CI)	–	6.3* (4.8–7.8)	1.0 (-0.4–2.5)	–	2.8* (1.7–3.9)	0.3 (-0.7–1.2)
Mean difference with V2 (95% CI)	-6.3* (-7.8–-4.8)	–	-5.3* (-6.8–-3.8)	-2.8* (-3.9–-1.7)	–	-2.6* (-3.5–-1.6)
Mean difference with V4 (95% CI)	-1.0 (-2.5–0.4)	5.3* (3.8–6.8)	–	-0.3 (-1.2–0.7)	2.6* (1.6–3.5)	–

SD – standard deviation; CI – confidence interval; * – the indicator denotes statistical significance (p<0.05). Qmax – maximum flow rate. Study visits: V1 (1st day), V4 (V1+6 months)

Table 4. Dynamics of the concentrations of testosterone, estradiol, dihydrotestosterone and prostate-specific antigen in blood and the concentrations of interleukin-1β and interleukin-10 in ejaculate of patients with chronic prostatitis/chronic pelvic pain syndrome

Indicator	Group 1 (n = 37)		Group 2 (n = 37)		Group 1+2 (n = 74)	
	V1, M ±SD	V4, M ±SD	V1, M ±SD	V4, M ±SD	V1, M ±SD	V4, M ±SD
Testosterone ng/mL	5.7 ±1.8	6.1 ±2.0*	5.7 ±2.3	6.1 ±2.4*	5.7 ±2.0	6.1 ±2.2*
Estradiol, pg/mL	20.4 ±12.0	20.4 ±10.9	23.6 ±13.5	24.9 ±12.6	22.0 ±12.8	22.7 ±11.9
DGT, pg/mL	556.9 ±196.9	480.3 ±199.1*	563.3 ±184.6	474.4 ±159.0*	560.1 ±189.5	477.3 ±178.9*
PSA total, ng/mL	2.2 ±0.8	1.8 ±0.8*	2.1 ±0.8	1.6 ±0.8*	2.2 ±0.8	1.7 ±0.8*
IL-1β, pg/mL	168.0 ±46.0	136.2 ±52.7*	161.2 ±56.3	113.5 ±46.0*	163.5 ±50.0	124.8 ±50.4*
IL-10, pg/mL	170.5 ±35.6	211.9 ±40.9*	177.0 ±31.1	221.2 ±34.4*	178.6 ±27.4	219.4 ±37.3*

SD – standard deviation; M – mean; * – the difference before and after treatment is statistically significant (p<0.05); DGT – dihydrotestosterone; IL – interleukin; PSA – prostate-specific antigen. Study visits: V1 (1st day), V4 (V1+6 months).

r = 0.381, p = 0.020), which persisted after treatment (Spearmen's r = 0.374, p = 0.023). In Group 2, only before treatment, there was a negative relationship between blood testosterone level and anxiety score on the GAD-7 (Spearmen's r = -0.361, p = 0.028), as well as between PSA level and depression index on the PHQ-9 (Spearmen's r = -0.390, p = 0.017). In Group 1 + 2, a negative relationship between blood estradiol and IL-10 (Pearson's r = -0.341, p = 0.003) was observed before treatment and estradiol and PSA concentrations (Pearson's r = -0.230, p = 0.048) after treatment.

Assessment of the treatment's effect on cytokine dynamics in the ejaculate of patients of both groups demonstrated a significant decrease in the levels of the pro-inflammatory cytokine IL-1β and a significant increase in the levels of the anti-inflammatory cytokine IL-10 (Table 4). These changes reflect a decrease in inflammation of the prostate gland.

In both groups after treatment, a significant direct correlation was found between the NIH-CPSI and IL-1β in the ejaculate (Group 1 Pearson's r = 0.353, p = 0.032; Group 2 Pearson's r = 0.385, p = 0.001; Group 1 + 2 Pearson's r = 0.364, p = 0.027), as well as the inverse correlation between NIH-CPSI and IL-10 in the ejaculate (Group 1 Pearson's r =- 0.504, p = 0.001; Group 2 Pearson's r = -0.388, p = 0.018; Group 1 + 2 Pearson's r =- 0.439, p <0.001).

Assessment of the effectiveness of pharmacotherapy was based on changes in NIH-CPSI at visits V2 and V4 (Table 5). In Group 1, a significant decrease in the intensity of symptoms was observed in 59.5% and 51.4% of patients at the second and fourth visits. In Group 2, an improvement was noted in 83.8% and 78.4%, respectively, at the second and fourth visits. In terms of the ratio of responders to non-responders, the effectiveness of treatment was significantly lower in the group of 'effective antibiotic therapy' (Group 1) at 2 weeks of treatment, which continued at 6 months of treatment. The relative risk (RR) of improvement of 6 or more points in NIH-CPSI in Group 1 patients was 0.71 (95% CI 0.53–0.96, p <0.05) at 2 weeks and 0.66 (95% CI 0.46–0.94) at 6 months of the study. There were no significant correlations between treatment outcome and leukocytes in ejaculate.

Insufficient efficacy was observed in 27.0% of patients in Group 1 and in 13.7% – in Group 2. Relapses of the disease, observed at visit V4, were in 21.6% of patients in Group 1 and in 8.1% – in Group 2. There was a significant relationship between the efficacy of past antibiotic therapy and the outcome of the treatment, namely, between the effectiveness, treatment failure, and the development of relapses ($\chi^2 = 6.023$, critical $\chi^2 = 5.991$, p <0.05).

Good tolerability of treatment was observed in both groups. All patients completed the full course of treatment. At the same time, non-serious adverse reactions were observed; but no significant difference was revealed between the groups. The most common adverse reactions noted were ejaculation disorders, found in 75.7% of patients in Group 1 and in 73% – in Group 2 (RR 1.04 (95% CI 0.80–1.36, p>0.05). Of these, retrograde ejaculation was in 46.0% and 40.5%, RR 1.13 (95% CI 0.67–1.91, p >0.05); prolonged sexual intercourse, weakening orgasm and decreased ejaculate volume in 29.7% and 32.4%, respectively, RR 0.92 (95% CI 0.47–1.81, p >0.05). Ejaculation disorders stopped within 1 week after completion of the tamsulosin administration.

Table 5. *Evaluation of the treatment efficacy of patients at visits V2 and V4*

Efficacy indicator	Group 1 (n = 37)	Group 2 (n = 37)
% (V2)	59.5 %	83.8 %
R/NR (V2)	22/15	31/6*
%, (V4)	51.4 %	78.4 %
R/NR (V4)	19/18	29/8*

* – the difference between Groups 1 and 2 is statistically significant (p <0.05); R – responders, NR – non-responders; n – number. Study visits: V2 (V1+2 weeks), V4 (V1+6 months)

Table 6. *Comparison of treatment outcomes in our and other studies*

Author, year	Treatment	R	NR	RR vs Group 1, V2 95% CI	RR vs Group 2, V2 95% CI	RR vs Group 1, V4 95% CI	RR vs Group 2, V4 95% CI
Shoskes et al., 2010 [20]	Multimodal therapy	84	16	0.71 0.54–0.94	1.0 0.85–1.18	0.61* 0.44–0.85	0.93 0.80–1.13
Magri et al., 2015 [21]	Multimodal therapy	708	206	0.77 0.59–1.00	1.08 0.94–1.25	0.66* 0.48–0.91	1.01 0.85–1.20
Wagenlehner et al., 2014 [22]	Placebo	57	28	0.89 0.65–1.20	1.25* 1.02–1.54	0.77 0.54–1.08	0.17 0.93–1.46

* – the indicator denotes statistical significance (p <0.05); R – responders; NR – non-responders; RR – relative risk. Study visits: V2 (V1+2 weeks), V4 (V1+6 months)

Ejaculation disorders observed significantly exceeded their expected occurrence provided by the official manufacturer information ($\geq$1/100 <1/10). Perhaps, this is due to the relatively young age of our participants compared with patients who receive tamsulosin as a recommended treatment for benign prostatic hyperplasia.

Orthostatic hypotension also occurred in 8.1% and 5.4% of cases, RR 1.50 (95% CI 0.27–8.47, p >0.05). It stopped after taking tamsulosin. Additionally, 13.5% of patients in Group 1 and 16.2% in Group 2 had epigastric pain or discomfort starting from day 7 of treatment, RR 0.83 (95% CI 0.28–2.50, p >0.05). The pain was mild to moderate in intensity and stopped within 1 week after diclofenac was discontinued. Due to the short-term administration of diclofenac, no patient needed either premature discontinuation of the drug or the appointment of proton pump inhibitors.

DISCUSSION

Many patients in our specialized clinic develop one or more exacerbations of chronic prostatitis per year. According to Mehik et al., there are 27% of such patients, 16% of patients have permanent symptoms of prostatitis [17]. These patients usually received multiple antibiotics in the past with varying efficacy and with the development of known complications of antibiotic therapy. As a result of taking antibiotics, some of the patients did not improve their condition, while others did improve, but remission was usually short-lived. The above mentioned formed a negative attitude in our patients toward regular use of antibiotics. Here we tried to offer an alternative complex of pharmacological agents that does not include an antibiotic and to assess the influence of the efficacy of previous antibiotic therapy on this treatment outcome.

The results of the meta-analysis that predetermined our study are of great interest. An analysis of nineteen randomized placebo-controlled trials (n = 1669) showed that α-blockers, antibiotics, and anti-inflammatory/immunomodulating drugs significantly improved symptoms of CP/CPPS. However, this study also revealed some contradictions. Along with the fact that the use of antibiotics led to a decrease in the NIH-CPSI by an average of 9.7 (95% CI -14.2 to -5.3; p <0.001), the RR in the responder/non-responder ratio was not statistically different from placebo and was 1.2 (95% CI 0.7–1.9; p = 0.527). Moreover, it was shown that the combination of α-blocker and antibiotics also did not exceed the placebo in the ratio of responders/non-responders of RR 0.92 (95% CI 0.3–2.8; p = 0.894). Based on these data, we concluded that antibiotics significantly improved the condi-

tion, although only in a small number of patients with CP/CPPS [9]. Also, the effect of antibiotics may be due to their non-antibacterial properties [18, 19]. The efficacy of our treatment was compared with results of other studies that also used complex treatment, similar criteria for successful treatment (decrease by 6 points according to NIH-CPSI), and the duration of treatment for at least 6 months (Table 6). When calculating RR as a risk factor, the data of Groups 1 and 2 were introduced.

In our study, the efficacy of treatment (V4) in Group 1 was significantly lower in comparison with multimodal therapy [20, 21], and also did not significantly differ from the result of placebo [22]. The positive outcome in Group 2 (V2 only) was significantly greater than with placebo [22] and did not differ from the efficacy of multimodal therapy (V2, V4) [20, 21].

Turning to the value of the latent bacterial factor in CP/CPPS (that cannot be ruled out, even in the absence of identifiable infectious agent(s) through standard diagnostic procedures), some assumptions have to be made. If we assume that inefficacy (insufficient efficacy and relapses) in Group 1 is associated with both bacterial and abacterial factors, and in Group 2, for the most part, only with abacterial factors, then the intergroup difference of inefficacy will be associated mainly with bacterial causes. Thus, according to our results, a clinically significant latent bacterial factor in CP/CPPS can occur in 24.3–27% of cases in which antibiotics may be useful. With that, the question for future studies is whether such patients would further benefit from combining antibiotics and a therapeutic complex tested in this study.

Psychological factors and their relationship with the somatic state of patients are an important aspect of chronic prostatitis [23, 24]. The changes in the psychological state of patients that we discovered confirm this position. In all groups, there were patients with signs of anxiety and depression, and a significant improvement in the psychological state of patients was observed in Groups 2 and 1 + 2. This can be explained by the greater effectiveness of reducing the symptoms of prostatitis in these groups relative to Group 1, which is confirmed by the revealed correlation between the NIH-CPSI and PHQ-9.

The significant improvement in the maximum rate of urination during treatment revealed by our study is consistent with the data from Magri et al., which additionally showed significant differences in the uroflowmetric pattern between the inflammatory and non-inflammatory forms of CP/CPPS [21].

As previously shown, low testosterone levels (<3.5 ng/mL) are also significantly associated with symptoms of CP/CPPS [25]. In our study, such low levels of testosterone were found only in 3 cases

(3.1–3.5 ng/mL) and such a relationship was not detected. The observed correlations between testosterone, estradiol, PSA and estimates of anxiety and depression, and ambiguity of these phenomena suggest complex relationships among these indicators and heterogeneity of patients with CP/CPPS.

In our opinion, the dynamics of blood DHT that were noted reflects the inhibitory effect of the Serenoa repens extract on the activity of 5α-reductase. It is known that taking Serenoa repens extract does not change the concentration of PSA [26]; therefore, we associate the decrease in the concentration of PSA during treatment with a decrease in the activity of inflammation in the prostate gland. It can be assumed that the PSA values before treatment were relatively increased as a result of the exacerbation of prostatitis.

Identified immunological changes are of particular interest; namely, a decrease in the level of pro-inflammatory cytokine IL-1β as a result of treatment, an increase in the level of anti-inflammatory IL-10, and their correlation with the NIH-CPSI index. Similar changes in cytokines during the treatment of patients with CP/CPPS were previously observed [27]. They reflect the significance and dynamics of inflammatory changes in the glands that produce ejaculate in the development of symptoms included in the study patients.

The main limitations of our work are largely common with limitations of many other studies [6]: 1) the risk of bias associated with the inability to fully exclude the placebo effect; 2) only some of the results of our study were obtained using the recommended minimum sample size (Group 1 + 2, n = 74) for the primary outcome of 'prostatitis symptoms'; 3) the duration of patients' observation was only 6 months; 4) the results of the treatment of patients with neurological, muscle-tonic and infectious components of the CP/CPPS phenotype may differ from those obtained.

CONCLUSIONS

The complex of diclofenac, tamsulosin, and Serenoa repens extract positively affects the profile of sex hormones and prostate-specific antigen (PSA) in blood, as well as cytokines in ejaculate in patients with Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), which is significantly associated with a decrease in prostatitis symptoms, depression, and anxiety. The history of antibiotic therapy for CP/CPPS determines the prognosis of current treatment.

Lower efficacy of this treatment and higher rates of relapse in CP/CPPS patients with a history of antibiotic efficacy would suggest that such patients may have a latent bacterial factor. A priori, it is assumed in 24.3–27% of cases of CP/CPPS; these could benefit from inclusion of antibiotics in the therapeutic complex for a better and long-term treatment outcome.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Bartoletti R, Cai T, Mondaini N, et al. Prevalence, incidence estimation, risk factors and characterization of chronic prostatitis/chronic pelvic pain syndrome in urological hospital outpatients in Italy: results of a multicenter case-control observational study. J Urol. 2007; 178: 2411-2415.

2. Schaeffer AJ, Landis JR, Knauss JS, et al. Demographic and clinical characteristics of men with chronic prostatitis: the national institutes of health chronic prostatitis cohort study. J Urol. 2002; 168: 593-598.

3. Collins MM, Stafford RS, O'Leary MP, Barry MJ. How common is prostatitis? A national survey of physician visits. J Urol. 1998; 159: 1224-1228.

4. Dybowski B. Antifungal azoles- new antidote for chronic pelvic pain? Cent European J Urol. 2013; 66: 200-201.

5. Nickel JC. Chronic prostatitis/chronic pelvic pain syndrome: it is time to change our management and research strategy. BJU Int. 2020; 125: 479-480.

6. Franco JVA, Turk T, Jung JH, et al. Pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome: a Cochrane systematic review. BJU Int. 2020; 125: 490-496.

7. EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2021. ISBN 978-94-92671-13-4.

8. Thakkinstian A, Attia J, Anothaisintawee T, Nickel JC. α-blockers, antibiotics and anti-inflammatories have a role in the management of chronic prostatitis/chronic pelvic pain syndrome. BJU Int. 2012; 110: 1014-1022.

9. Nickel JC, Roehrborn CG, O'Leary MP, Bostwick DG, Somerville MC, Rittmaster RS. The relationship between prostate inflammation and lower urinary tract symptoms: examination of baseline data from the reduce trial. Eur Urol. 2008; 54: 1379-1384.

10. Schaeffer AJ, Knauss JS, Landis JR, et al. Chronic Prostatitis Collaborative Research Network Study Group. Leukocyte and bacterial counts do not correlate with severity of symptoms in men with chronic prostatitis: the national institutes of health chronic prostatitis cohort study. J Urol. 2002; 168: 1048-1053.

11. Zhang J, Liang C, Shang X, Li H. Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Disease or Symptom? Current Perspectives on Diagnosis, Treatment, and Prognosis. Am J Mens Health. 2020; 14: 1557988320903200.

12. Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA. 1999; 282: 236-237.

13. Litwin MS, McNaughton-Collins M, Flowler FJ, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol. 1999; 162: 369-375.

14. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16: 606-613.

15. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder. Arch Intern Med. 2006; 166: 1092-1097.

16. Gajdács M, Dóczi I, Ábrók M, Lázár A, Burián K. Epidemiology of candiduria and Candida urinary tract infections in inpatients and outpatients: results from a 10-year retrospective survey. Cent European J Urol. 2019; 72: 209-214.

17. Mehik A, Hellstrom P, Lukkarinen O, Sarpola A, Jarvelin M. Epidemiology of prostatitis in Finnish men: a population-based cross-sectional study. BJU Int. 2000; 86: 443-448.

18. Ochoa-Aguilar A, Ventura-Martinez R, Sotomayor-Sobrino MA, Gómez C, Morales-Espinoza MR. Review of Antibiotic and Non-Antibiotic Properties of Beta-lactam Molecules. Antiinflamm Antiallergy Agents Med Chem. 2016; 15: 3-14.

19. Perret LJ, Tait CP. Non-antibiotic properties of tetracyclines and their clinical application in dermatology. Australas J Dermatol. 2014; 55: 111-118.

20. Shoskes DA, Nickel JC, Kattan MW. Phenotypically directed multimodal therapy for chronic prostatitis/chronic pelvic pain syndrome: a prospective study using UPOINT. Urology. 2010; 75: 1249-1253.

21. Magri V, Marras E, Restelli A, Wagenlehner FM, Perletti G. Multimodal therapy for category III chronic prostatitis/chronic pelvic pain syndrome in UPOINTS phenotyped patients. Exp Ther Med. 2015; 9: 658-666.

22. Wagenlehner FM, Ballarini S, Naber KG. Immunostimulation in chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): a one-year prospective, double-blind, placebo-controlled study. World J Urol. 2014; 32: 1595-1603.

23. Huang X, Qin Z, Cui H, Chen J, Liu T, Zhu Y, Yuan S. Psychological factors and pain catastrophizing in men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): a meta-analysis. Transl Androl Urol. 2020; 9: 485-493.

24. Banyra O, Ivanenko O, Nikitin O, Shulyak A. Mental status in patients with chronic bacterial prostatitis. Cent European J Urol. 2013; 66: 93-100.

25. Lee JH, Lee SW. Testosterone and Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Propensity Score-Matched Analysis. J Sex Med. 2016; 13: 1047-1055.

26. Marcoccia D, Georgiev MI, Alipieva KI, Lorenzetti S. Inhibition of the DHT-induced PSA secretion by Verbascum xanthophoeniceum and Serenoa repens extracts in human LNCaP prostate epithelial cells. J. Ethnopharmacol. 2014; 155: 616-625.

27. Shulyak A, Gorpynchenko I, Drannik G, Poroshina T, Savchenko V, Nurimanov K. The effectiveness of the combination of rectal electrostimulation and an antidepressant in the treatment of chronic abacterial prostatitis. Cent European J Urol. 2019; 72: 66-70.