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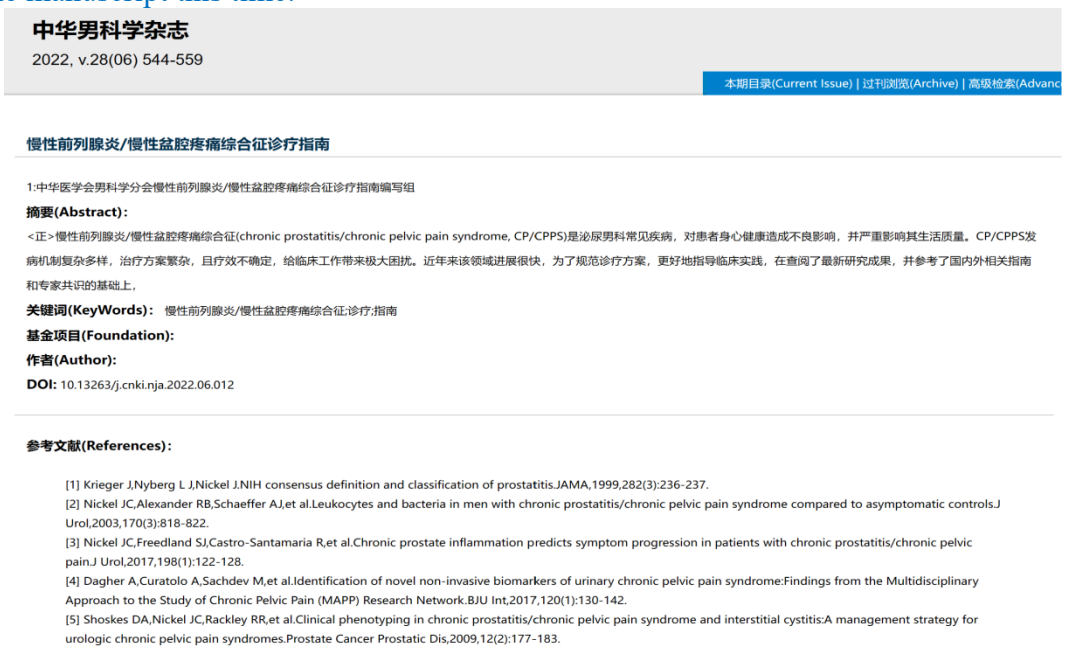
Reviewer A

The authors provided exciting evidence regarding a new TCM method for refractory CP/CPPS. However, the manuscript would greatly benefit from some clarifications:

Lines 124-126: which guidelines are you referring to? Please, cite. Moreover, at least in the EAU guidelines, only acupuncture is mentioned, but there is no broader referral to TCM.

Reply: Thank you so much for your kind and careful remind. We referred to the guidelines for the diagnosis and treatment of chronic prostatitis/chronic pelvic pain syndrome of the Andrology Branch of the Chinese Medical Association. The full text website link is as follows:
http://www.nkxb.cbpt.cnki.net/WKB2/WebPublication/paperDigest.aspx?paperID=186826fe-43a9-471d-a5e6-51183199709e
DOI: 10.13263/j.cnki.nja.2022.06.012
We also upload the full text as the attached file when submitting our revised version of the manuscript this time.



中华男科学杂志
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慢性前列腺炎/慢性盆腔疼痛综合征诊疗指南

1:中华医学会男科学分会慢性前列腺炎/慢性盆腔疼痛综合征诊疗指南编写组

摘要(Abstract):

<正>慢性前列腺炎/慢性盆腔疼痛综合征(chronic prostatitis/chronic pelvic pain syndrome, CP/CPPS)是泌尿男科常见疾病，对患者身心健康造成不良影响，并严重影响其生活质量。CP/CPPS发病机制复杂多样，治疗方案繁杂，且疗效不确定，给临床工作带来极大困扰。近年来该领域进展很快，为了规范诊疗方案，更好地指导临床实践，在查阅了最新研究成果，并参考了国内外相关指南和专家共识的基础上，

关键词(KeyWords): 慢性前列腺炎/慢性盆腔疼痛综合征;诊疗;指南

基金项目(Foundation):

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参考文献(References):

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[5] Shoskes DA,Nickel JC,Rackley RR,et al.Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis:A management strategy for urologic chronic pelvic pain syndromes.Prostate Cancer Prostatic Dis,2009,12(2):177-183.

We added the new reference [4] (Thematic Columns: Guidelines for the diagnosis and treatment of chronic prostatitis/chronic pelvic pain syndrome (Standardization & Guideline section). Authors: Expert team of the Andrology Branch of the Chinese Medical Association for Chronic prostatitis/chronic pelvic pain syndrome diagnosis and treatment guideline. 中华男科学杂志 National Journal of Andrology/Zhonghua Nan Ke Xue Za Zhi 2022, 28(6):544-559.) in the revised version of our manuscript.

In this reference, in addition to acupuncture, rectal administration[126], oral Chinese

medicine[127], and acupressure[128] are all recommended in the treatment of CP/CPPS. We added these relevant references accordingly.

[126] 郭俊, 晏斌, 高庆和, 等.前列安栓治疗慢性前列腺炎有效性与安全性的Meta分析.中医学报，2021,36(8):1789-1794.
[127] Liu BP,Wang YT,Chen SD. Effect of acupuncture on clinical symptoms and laboratory indicators for chronic prostatitis/chronic pelvic pain syndrome:A systematic review and meta-analysis.Int Urol Nephrol,2016,48(12):1977-1991.
[128] 刘绍明，息金波，陈小均，等.芎柏前列散穴位贴敷治疗III型前列腺炎综合征临床观察.中国针灸，2012,32(3):201-204.
We added the new reference [4] (Thematic Columns: Guidelines for the diagnosis and treatment of chronic prostatitis/chronic pelvic pain syndrome (Standardization & Guideline section). Authors: Expert team of the Andrology Branch of the Chinese Medical Association for Chronic prostatitis/chronic pelvic pain syndrome diagnosis and treatment guideline. 中华男科学杂志 National Journal of Andrology/Zhonghua Nan Ke Xue Za Zhi 2022, 28(6):544-559.) in the revised version of our manuscript.
Changes in the text: **Page 4, Line 124.**

Lines 160-161: please provide the full name, including latin name, of all the herbs included.

Reply: There are 8 herbs including Taraxacum mongolicum Hand.-Mazz(蒲公英), Salvia miltiorrhiza Bunge(丹参), Coptis chinensis Franch(黄连), Phellodendron chinense Schneid(黄柏), Eriobotrya japonica Thunb(枇杷叶), Sinapis alba L.(白芥), Sparganium stoloni erum, Buch.-Ham.(三棱), Corydalis yanhusuo (延胡索).

You can see the relevant changes in the text: **Page 5, Line 160-163.**

Lines 191-192 Were the patients allowed to ejaculate eventually before the 20 minutes?
Reply: Actually, ejaculation was allowed before 20minutes. However, all of the acupoints should be massaged at least one time. If the procedure was not finished, we would stop the procedure temporarily and wait a while for the dissipation of the ejaculation impulse.
Changes in the text: **Page 6, Line 195-198.**

Line 195. How many times did the patients have to repeat the treatment session? It is not clear if it's a single treatment or several sessions.
General characteristics could be resumed in a sociodemographic table, which includes also the number/type of treatments previously tried.
Reply: The treatment session would be given once a day, for one week continuously.
Changes in the text: **Page 6, Line 197-198.**
The sociodemographic table has been added in the manuscript in **Table 1**. According to the editor's requirements, we have unified the patient's basic information and medical

history of previous treatment methods into **Table 1**, which is attached to the text. At the same time, during the process of creating the table, we have further standardized the accuracy of wording and replaced **Line 237** radiofrequency ablation with extracorporeal radiofrequency hyperthermia because all patients previously received mainly extracorporeal radiofrequency hyperthermia instead of invasive invasion treatment. We also corrected a numerical error by changing the number from three patients in **Line 243** to four patients tried five methods. Due to the intuitive presentation of the table, we also deleted the repeated descriptions in **Lines 237-240** of the previous version of the original submitted manuscript.

Line 224. Please specify which kind of TCM remedy was included: acupuncture/moxibustion/herbal medicine?
Reply: There were only herbal medicines in our TCM remedy, and the mode of administration was retention enema. The formula was presented previously. **Page 5, Lines 159-163.**

Table 1-2-3 can be combined into a single table. Perhaps you can consider including only patients who reported pain (mVAS) and LUTS (mIPSS), since the score is not applicable to the others.
Reply: We have combined Table1-2-3 into a single table as your suggestion.
Changes in the text: **Table 2.**

Line 252. What do you mean by slight?
Reply: We apologize for not clearly defining the standards for in the original text.
To the degree of improvement, the score increased <60% was defined as slight, and ≥60% was significant. If there is no improvement, the degree of improvement is 0.
Changes in the text: **Page 6, Line 213-214.**
In **Page 7, Line 268-270** we also added the relevant details: Only two patients felt slight improvement of the symptoms (10% and 30% improvement respectively) and one patient felt no improvement.

Lines 257-259 Please provide more objectifiable data regards these findings (numbers, images) otherwise the data cannot be reliably employed as proof of treatment efficacy.
Reply: These data were observed in our hospital. Firstly, according to clinical routine ultrasound examinations, there were no objective images left, only textual descriptions. In addition, for relatively objective data indicators, PSA and urine flow rate, due to the small sample size, there was no significant difference in comparison before and after treatment. Given that the data cannot be reliably employed as proof of treatment effectiveness, to prevent ambiguity, we have deleted this part in the revised manuscript.
Changes in the text: **Page 6, Line 215 and Line 271.**

Lines 260-262 What is the role of lecithin in the prostatic fluid and what are the reference values? Please provide more objectifiable data, otherwise they cannot be employed.
Reply: Generally speaking, if there is inflammation in the prostatic fluid, the lecithin under the microscope would be enveloped and manifested as 'disappeared or decreased'. However, there are still no definite evidence to prove the relationship between the

lecithin in the prostatic fluid and prostatitis. To prevent ambiguity, we have deleted this part also **Page 7, Line 271** in revised version of the manuscript.

Lines 315-321 Please elucidate more clearly the molecular mechanisms through which the Chinese herbs employed have been proven to be effective as anti-inflammatory/draining.

Reply: There are 8 herbs including Taraxacum mongolicum Hand.-Mazz(蒲公英), Salvia miltiorrhiza Bunge(丹参), Coptis chinensis Franch(黄连), Phellodendron chinense Schneid(黄柏), Eriobotrya japonica Thunb(枇杷叶), Sinapis alba L.(白芥), Sparganium stoloni erum, Buch.-Ham.(三棱), Corydalis yanhusuo (延胡索).

Moreover, Coptis chinensis Franch (黄连) possesses a cytokine storm-calming property due to its isoquinoline alkaloids [18]. Phellodendron chinense Schneid (黄柏) contains a new isoquinoline alkaloid glycoside with anti-inflammatory activity [19]. Eriobotrya japonica Thunb (枇杷叶) acts on the mitogen-activated protein kinase (MAPK) pathway, transforming growth factor (TGF)-beta pathway, focal adhesion, tight junctions, and the cytoskeleton to exert anti-inflammatory effects [20]. Sinapis alba L. (白芥) suppresses the mRNA expression of various inflammatory mediators, including TNF-α, IL-6, and IL-1β [21]. Sparganium stoloniferum Buch.-Ham. (三棱), along with Corydalis yanhusuo (延胡索), both exhibit extensive pharmacological effects in terms of anti-inflammatory properties. Their potential mechanism involves suppressing the NF-κB signaling pathway and promoting the resolution of inflammation [22]. Furthermore, both Sparganium stoloniferum Buch.-Ham. (三棱) [23-24] and Corydalis yanhusuo (延胡索) [25] possess analgesic properties.

Changes in the text: **Page 9, Line 338-341, Line 347-358.**

Added references:

18. Lan Y, Wang H, Wu J, Meng X. Cytokine storm-calming property of the isoquinoline alkaloids in Coptis chinensis Franch. Front Pharmacol 2022; 13: 973587

19.Si Y, Li X, Guo T, Wei W, Zhang J, Jia A, Wang Y, Zhao A, Chang J, Feng S. Isolation and characterization of phellodendronoside A, a new isoquinoline alkaloid glycoside with anti-inflammatory activity from Phellodendron chinense Schneid. Fitoterapia 2021; 154:105021.

20.Tao J, Hou Y, Ma X, Liu D, Tong Y, Zhou H, Gao J, Bai G. An integrated global chemomics and system biology approach to analyze the mechanisms of the traditional Chinese medicinal preparation Eriobotrya japonica-Fritillaria usuriensis dropping pills for pulmonary diseases. BMC Complement Altern Med 2016; 16: 4.

21.Xian YF, Hu Z, Ip SP, Chen JN, Su ZR, Lai XP, Lin ZX. Comparison of the anti-inflammatory effects of Sinapis alba and Brassica juncea in mouse models of inflammation. Phytomedicine 2018; 50: 196-204.

22.Zou W, Gong LN, Zhou FH, Long Y, Li Z, Xiao ZQ, OY B, Liu MH. Anti-inflammatory effect of traditional Chinese medicine preparation Penyanling on pelvic inflammatory disease. J Ethnopharmacol 2021; 266: 113405.

23.Jia J, Li X, Ren X, Liu X, Wang Y, Dong Y, Wang X, Sun S, Xu X, Li X, Song R, Ma J, Yu A, Fan Q, Wei J, Yan X, Wang X, She G. Sparganii Rhizoma: A review of traditional clinical application, processing, phytochemistry, pharmacology, and toxicity. J Ethnopharmacol 2021;268: 113571.

24. Lin L, Zhou X, Gao T, Zhu Z, Qing Y, Liao W, Lin W. Herb pairs containing

Curcumae Rhizoma (Ezhu): A review of bio-active constituents, compatibility effects and t-copula function analysis. J Ethnopharmacol. 2023; 319: 117199.
25.Alhassen L, Dabbous T, Ha A, Dang LHL, Olivier Civelli O. The Analgesic Properties of Corydalis yanhusuo. Molecules 2021;26: 7498.

Minor issues:

There seems to be a mistake in the short title (CP/CPPS?).

Line 203: improvement.

Reply: We are very sorry for our negligence of the mistake and we have made correction according to your remind.

We correct the spelling mistake from the previous "Short title: Traditional Chinese Method Treated CP/COPS Promisingly" into present "Short title: Traditional Chinese Method Treated CP/CPPS Promisingly".

Changes in the text**: Page 1, Line 18.**

Besides, we revised the word "improvement" in revised version of the manuscript.

Changes in the text: **Page 6, Line 209.**

Line 311: remove stasis medical herbs? Not clear.

Reply: We deleted the previous description-"remove stasis medical herbs" and we put the new contents as follows: Some components of traditional Chinese medicine have effects and functions to promote blood circulation and reduce blood stasis, and may be helpful to drain the gland fluid **[15]**.

You can see the relevant changes in the text: **Page 9, Line 334-336.**

Reviewer B

The authors reported the clinical utility of THERM therapy for refractory CP/CPPS patients. Even though limited number of patients and single arm study, they showed clinical utility of THERM therapy.

Some modification would be good for understandings of the readers of TAU.

1. in addition to table, figures of VAS and IPSS would be good for the readers.

Reply: Thanks a lot for your kind remind. We have added the figures of both VAS and IPSS as your suggestion.

Changes in the text: You can directly see the revised version of the **Figures. 3-7.**

2. Longitudinal follow up data of IPSS or VAS, if available, would be helpful for the comprehensive understandings of THERM therapy.

Reply: Our research started in October 2022 and completed all post treatment follow-up work by May 2023. We collected corresponding data and submitted an article. According to the suggestion of the editor, we conducted telephone follow-up for these patients recently. And we successfully contacted 13 out of 20 patients, 10 among in theses 13 patients had maintained treatment effectiveness, and 2 patients had varying degrees of recurrence. Another one patient, who received early treatment and improved slightly by 30%, is still seeking appropriate treatment in various hospitals, and his effect is not satisfactory. A longer follow-up clinical research with larger-size patient is supposed to be performed in future.

According to relevant references, regardless of the treatment method used, chronic prostatitis is prone to recurrence after treatment, which is also one of the reasons why CP/CPPS is difficult to treat. For these relapsed patients, further investigation is needed to determine the long-term effects of using our therapy for treatment. Therefore, a longer follow-up clinical research with larger-size patient is supposed to be performed in future.

We are grateful to your advice. In order to more rigorously and objectively indicate our research, we check and revise our manuscript accordingly throughout the whole manuscript. Please see the relevant changes in the text: **Page 3, Line 87-88; Page 10, Line 392, 398-405, 409.**

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3. The authors should mention the use of other Western medicines, if used concomitantly with THERM therapy.

Reply: Generally speaking, in the THERM procedures, we do not normally use Western medicines. However, if the patient had erectile dysfunction, we would give him 50mg sildenafil 1 hour before the treatment, to make sure the procedures could be completed. We added the relevant information in the revised version of the manuscript.

Changes in the text: **Page 5, Line 186-187.**
