Antibiotics Are Not Beneficial in the Management of Category III Prostatitis: A Meta-Analysis

Yongtong Zhu,[1] Chunyan Wang,[2] Xiang Pang,[1] Fei Li,[1] Wei Chen,[1] Wanlong Tan[1]

[1] Department of Urology, Nanfang Hospital, Southern Medical University, Guangzhou, China.
[2] Section 5 Department of Internal Medicine, Guilin TCM Hospital of China, Guilin, China.

Corresponding Author:

Wan-long Tan, MD
Department of Urology, Nanfang Hospital Affiliated to Southern Medical University, Guangzhou 510515, China.

Tel: +86 020 61641762
E-mail: tanwanlong@gmail.com

Received October 2012
Accepted March 2013

Purpose: To determine whether antibiotics are beneficial in the management of category III prostatitis.

Materials and Methods: The PubMed, Medline and Embase databases were searched for all published documents from January 1, 1965 to September 1, 2012 without language restriction. The randomized controlled trials that mentioned comparable groups of antibiotics treatment versus placebo or other control group for patients with category III prostatitis were included based on specific criteria. The quality of studies was assessed by the modified Jadad scale, and Revman 5.0 software was used for data syntheses and analysis.

Results: Seven studies which met the selection criteria were included in this review. All of them were high quality according to the modified Jadad scale. A random effect model was applied because of the high heterogeneity. The meta-analysis showed that summary association between category III prostatitis and antibiotics were not statistically significant.

Conclusion: Our meta-analysis reveals that antibiotics are not beneficial in the management of category III prostatitis. Therefore, we may reduce the usage of antibiotics in such a population.

Keywords: prostatitis; drug therapy; treatment failure; classification; treatment outcome; meta-analysis.

INTRODUCTION

Antibiotics are one of the most common treatments employed by urologists for patients presenting with prostatitis, regardless of culture results. More than 90% of prostatitis cases are category III prostatitis which is not associated with a significant bacteriuria. Whereas, it is a condition referred to chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).[1,2] Subgroups of CPPS are inflammatory CPPS (IIIA) where leukocytes are found in the expressed prostatic secretions, and non-inflammatory CPPS (IIIB).[3] According to the summary of National Institutes of Health (NIH), patients with category III prostatitis are advised to take antimicrobial agents for 3-6 weeks as the first-line treatment,[3,4] which response to the anti-infective therapy. One systematic review published by Thakkinstian and colleagues[5] suggested that antibiotics appeared to be beneficial for patients with CP/CPPS and most appropriate for therapy of CP/CPPS.

Nevertheless, as the diagnosis of category III prostatitis demands the exclusion of infection, the reason for the response associated with antibiotics is not immediately clear.[6] Some people suggested that there was a poor benefit after antibiotic therapy,[7] Nickel and colleagues[8] found that the levofloxacin therapeutic effect in men diagnosed with CP was not significantly different from placebo. Then DeRose and colleagues[9] and Kim and colleagues[10] also demonstrated that antibiotics did not markedly reduce the symptoms in men with CPPS.

Since the diagnostic criteria and treatment were not unified, many early cases led to CP, and the overuse of antibiotics caused bacterial resistance.[11] In order to strictly control the clinical applying indications for fluoroquinolone and strengthen management, our country executed the Clinical Use of Antibiotics Guiding Principle in 2004 and the Clinical Use of Antibiotics Management Approach in August 1, 2012. Therefore, the purpose of this study is to assess whether antibiotics are effective in treating category III prostatitis by synthesizing the data from all related available randomized controlled trials (RCTs).

There are several systematic reviews discuss the relationship between therapeutic intervention and CP/CPPS. Two studies[5,6] only included three RCTs to discuss the relationship between antibiotics and CP/CPPS, one others[12] included two RCTs. Regarding our emphasis and the inconsistent findings on the relationship between antibiotics and category III prostatitis, we conducted an updated meta-analysis of RCTs on this subject. Our goal was to determine whether antibiotics are associated with the management of category III prostatitis.

MATERIALS AND METHODS

Literature Search

We conducted a systematic literature search in the PubMed, Medline and Embase databases to identify the eligible studies before September 1, 2012. The following terms were used in the primary search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]) AND (prostatitis) AND (antibiotics OR *xacin OR antibacterial OR antimicro*). The search was focused on human studies, without language restriction. In addition, we checked the relevant review articles and their references to identify all available literature that may not have been included in the database results. The search following chat is presented in Figure 1.

Inclusion and Exclusion Criteria

The study was included if it met the following criteria: (1) it was an original RCT; (2) the disease has been clearly defined as category III prostatitis or CP/CPPS; (3) the paper had a conclusion about the association between antibiotics and category III prostatitis and (4) the study had provided enough information to estimate the effect sizes. The exclusion criteria were: (1) duplicate study; (2) review paper; (3) systematic review; (4) abstract/title only; (5) non category III prostatitis study; (6) other interventions; (7) non comparative study and (8) non interest outcome.

Data Extraction

Two reviewers independently extracted the information from the eligible studies according to the inclusion and

Table 1. The modified Jadad scale.

Eight items	Yes	No	Not Described
Was the research described as randomized?	1	0	-----
Was the approach of randomization appropriate?*	1	-1	0
Was the research described as blinding?	1	0	-----
Was the approach of blinding appropriate?	1	-1	0
Was there a presentation of withdrawals and dropouts?	1	0	-----
Was there a presentation of the inclusion/exclusion criteria?	1	0	-----
Was the approach used to assess adverse effects described?	1	0	-----
Was the approach of statistical analysis described?	1	0	-----

* Double-blind got 1 score, single-blind got 0.5 score.

exclusion criteria. Disagreement was resolved through discussion. The collected data included first author, publication year, study design, duration of therapy, age, intervention, sample size and the outcome data.

Outcome Measures

The following variables were examined: chronic prostatitis symptom index (CPSI) score, which include pain score, voiding score, quality of life (QoL) score and total score, at the baseline, at the end of study and the change from the baseline to the end.

Study Quality Evaluation

Two reviewers graded each study independently using the modified Jadad scale[13] (Table 1). The score for each article can range from 0 (lowest quality) to 8 (highest quality). Scores of 4-8 represent good to excellent (high quality), whereas, 0 to 3 represent poor or low quality.

Statistical Analysis

All analyses were performed in Review Manager 5 statistical software. The continuous data were summarized as the weighted mean differences (WMD) with the standard deviations (SD).

If the study only reported the median, the range of continuous data and the size of the trial, we used previous formula[14] to translate these data to WMD and SD. When it was desirable to combine two reported subgroup into a single group, we used the formula reported in Table 7.7.a of the Cochrane Hand book 5.0.2 to combine them. If there was a lack of WMD and SD of the changes from baseline, while the baseline and final WMD and SD were known, we imputed SD for the changes from baseline using the formula reported in 16.1.3.2 of the Cochrane Handbook 5.0.2. When considering the sensitivity analysis, the value of Corr was imputed as 0.5. We used the I2 statistic to assess the statistical heterogeneity between the trials. If a heterogeneity of ($I2 > 50\%$) existed we used the random effect model to perform the meta-analysis. Otherwise, the fixed effect model was used. The significance of the overall effect was tested with Fisher's z-test, $P < .05$ was considered as a significant level. All results representing the effect size were stated with 95% confidence intervals (CI). The sensitivity analysis was performed by excluding low quality studies to assess if the results were significant. If the score of trials were more than 5, the publication bias of the study was assessed by a funnel plot.

RESULTS

Study Selection, Characteristics and Quality

Table 2. Characteristics and quality of studies.

Study	Patient	Intervention	No. of Subjects Withdrawn	Duration of Therapy	Age	Modified Jadad Scale
Nickel et al., 2003[8]	CP/CPPS	Levofloxacin	45	12 weeks	56.0 (39-77)	8
		Placebo	35		56.2 (36-78)	
DeRose et al., 2004[10]	CP/CPPS	Mepartricin	15	60 days	34.75 ± 6.69	5
		Placebo	15		36.5 ± 7.54	
Alexander et al., 2004[17]	CP/CPPS	Placebo	45 (4)	6 weeks	42.6 ± 12.0	8
		Ciprofloxacin	42 (7)		45.9 ± 11.7	
		Tamsulosin	45 (4)		45.3 ± 9.7	
		Ciprofloxacin + Tamsulosin	42 (7)		44.5 ± 11.4	
Jeong et al., 2008[16]	CP/CPPS	Doxazosin	26	6 weeks	41.5 (23-56)	4
		Levofloxacin + Doxazosin	29		41.1 (27-60)	
Ye et al., 2008[15]	IIIA	Tamsulosin	**21**	45 days	No mentioned	5
		Tamsulosin + Levofloxacin	21			
	IIIB	Tamsulosin	**21**			
		Tamsulosin + Levofloxacin	21			
Zhou et al., 2008[18]	CPPS	Tetracycline	**24**	12 weeks	29-50 (all)	4
		Placebo	24			
Kim et al., 2011[9]	CP/CPPS	Tamsulosin	40	12 weeks	45.7	5
		Tamsulosin + Ciprofloxacin	28		46.1	

Keys: CP, chronic prostatitis; CPPS, chronic pelvic pain syndrome.

The study selection flow is described in Figure 1. A total of seven RCTs with 539 men[8-10,15-18] were included in our analysis. Of study subjects 267 were randomized to an experimental group and the remaining 272 men were assigned to a controlled group. One trial[15] enrolled patients classified IIIA and IIIB, the remaining studies enrolled patients with CPPS, all of them were belong to category III prostatitis. The mean age ranged from 17 to 78 years while this information was not provided in one trial.[15] The mean duration of treatment ranged from 6 weeks to 12 weeks. The intervention in the trials included levofloxacin,[8,15,16] mepartricin,[10] ciprofloxacin[9,17] and tetracycline.[18] The management of control groups were broadly classified into two methods: placebo[8,10,17,18] and others.[9,15-17] Two articles[15,17] had two sets of data, we calculated them with divided and combined data, respectively. All included studies had the high quality score of the modified Jadad scale. The characteristics and the quality of all included studies are presented in Table 2.

Meta-Analysis for the Change of Total Score of CPSI

All the trials evaluated the effect of interventions on total score of CPSI. Among these RCTs, three trials[8,10,18] compared placebo with antibiotics, three trials[9,15,16] compared α-blocker with α-blocker plus antibiotics, and the

Table 3. Subgrouping based on the treatment duration.

Variables	No. of Studies	Antibiotics/Control	WMD	95% CI	*P*	I^2
< 12 weeks						
Antibiotics vs. placebo						
	2	57/60	-4.18	-6.55 -1.81	.00	81%
Antibiotics + α-blocker vs. α-blocker						
	2	84/87	-5.34	-7.06 -3.62	.00	97%
>12 weeks						
Antibiotics vs. placebo						
	1	45/35	-2.50	-6.48 -1.48	.22	NA
Antibiotics + α-blocker vs. α-blocker						
	1	28/40	-0.07	-2.47 -2.33	.95	NA

Keys: CI, confidence interval; NA, not applicable; WMD, weighted mean differences.

other one study[17] included all the management methods. One trial[17] got the change from the baseline directly; the remaining trials reported the mean scores at follow-up and got the change via the formula.

Our quantitative accumulation analysis with the random-effect model (I2 > 75%) revealed that patients using antibiotics had a greater reduce in total score from baseline when compared with the control group (*P* = .01; Figure 2A). However, the subgroup analysis showed that this difference was not statistically significant both in the antibiotics group versus the placebo group (*P* = .05) and in the α-blocker group versus the α-blocker plus antibiotics group (*P* = .13). The sensitivity analysis was not done necessarily because of the median or the high quality of all the seven studies. There was a potential publication bias in our analysis according to the funnel plot presented in Figure 3.

Considering a longer treatment interval may have a more positive role in the effect of the symptom scores improving, we conducted a subgroup analysis (Table 3) based on the treatment duration by 12 weeks, which was chosen as the dividing line. The analysis result based on the eligibility data showed that antibiotics were not beneficial in the management of category III prostatitis when the treatment duration was more than 12 weeks.

Meta-Analysis for the Change of Pain Score, Voiding Score and QoL Score of CPSI

Excluded the study by Zhou, 2008 as the data were incomplete, there were six trials[8-10,15-17] (491 men) which had evaluated the effect of the interventions on pain score, voiding score and QoL score of CPSI.

With a random-effect model (I2 > 50%), the pooled analysis revealed that patients using antibiotics had a greater reduce in pain score when compared to the control group (*P* = .02; Figure 2B). The subgroup analyses showed the same difference when comparing placebo to antibiotics (*P* = .04), however, the difference between α-blocker and α-blocker plus antibiotics was not statistically significant (*P* = .16).

We used a random-effect model to estimate the voiding score because of the huge heterogeneity between the studies (I2 > 75%). A quantitative accumulation revealed

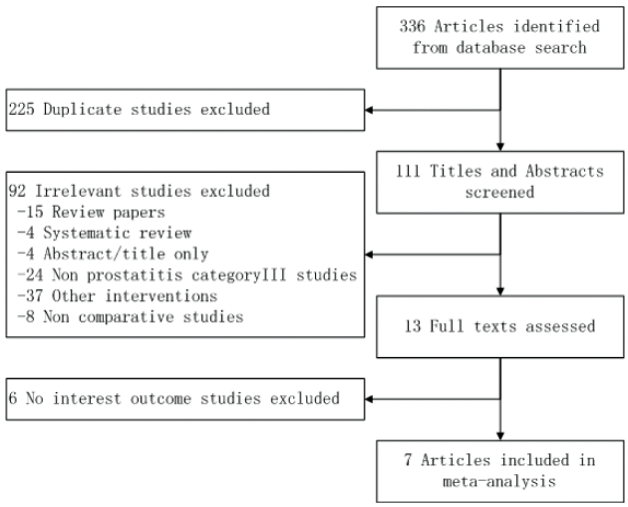

Figure 1. Study selection strategy.

that patients using antibiotics had no significantly greater reduce in voiding score when compared to the control group (P = .10; Figure 2C). The results of the subgroup analyses were the same both in placebo versus antibiotics (P = .08) and in α-blocker versus α-blocker plus antibiotics (P = .21).

With a potential heterogeneity (I2 > 50%), the random-effect model analysis revealed that patients using antibiotics had a significantly greater reduce in QoL score when compared to the control group (Figure 2D). The subgroup analyses showed that the difference was also exist when comparing α-blocker to α-blocker plus antibiotics (P = .04), whereas there was no significant difference in the subgroup of placebo versus antibiotics (P = .10).

DISCUSSION

Category III prostatitis is the most common urologic diseases. The medicine treatment contains antibiotics, α-blockers, anti-inflammatory analgesics, and so on. In our study, there were four interventions in the treatment of category III prostatitis: placebo, antibiotics, α-blockers and α-blockers plus antibiotics. In the same baseline level of CPSI, the difference of the score reduction in the α-blockers group and the α-blockers plus antibiotics group reflected the role of antibiotics in the treatment, although α-blockers also play a role. So these four interventions were divided into two subgroups in our meta-analysis.

In this meta-analysis, the quantitative accumulation results showed that antibiotics had a significantly greater role in the reduction in total score, pain score and QoL score, were same with the former recommendation that antibiotics are useful in category III prostatitis.[8] However, the analysis of the subgroup showed the opposite result; that summary association between category III prostatitis and antibiotics were not statistically significant, especially in total score and voiding score. Our findings revealed that antibiotics are not beneficial in the management of category III prostatitis. In part of the sub-score analysis, antibiotics had a significantly greater reduce in pain and QoL score, but not in voiding score. Such result met the point of view that the antibiotics had anti-inflammatory and analgesic properties.[19] Antibiotics, especially the fluoroquinolones, had been proven to influence the cytokine activity. For example, levofloxacin had an immunomodulatory function on the cytokine production not relying on the antimicrobial activity;[20] cotrimoxazole was prescribed for the anti-inflammatory or immunosuppressive effects on the noninfectious illness,[21] and so on. The subgroup analysis based on the treatment duration showed that antibiotics were not beneficial in the management of category III prostatitis when the treatment duration was more than 12 weeks, even where beneficial when less than 12 weeks. The short-term curative effect is actually the analgesic effect of antibiotics, which caused by patients' subjective feeling. In fact, the long-term curative effect showed that the anti-inflammatory effects of antibiotics were not obvious in prostate category III, which was the reason that antibiotics could not improve category III prostatitis.

In our data, several issues warrant further discussion. The etiology for category III prostatitis has not been fully elucidated and the criteria used for classifying the treatment response were varied, so we did not analyze the treatment responsiveness. Compared with the systematic reviews published by Thakkinstian and colleagues and Cohen and colleagues,[5,12] we included the latest seven randomized

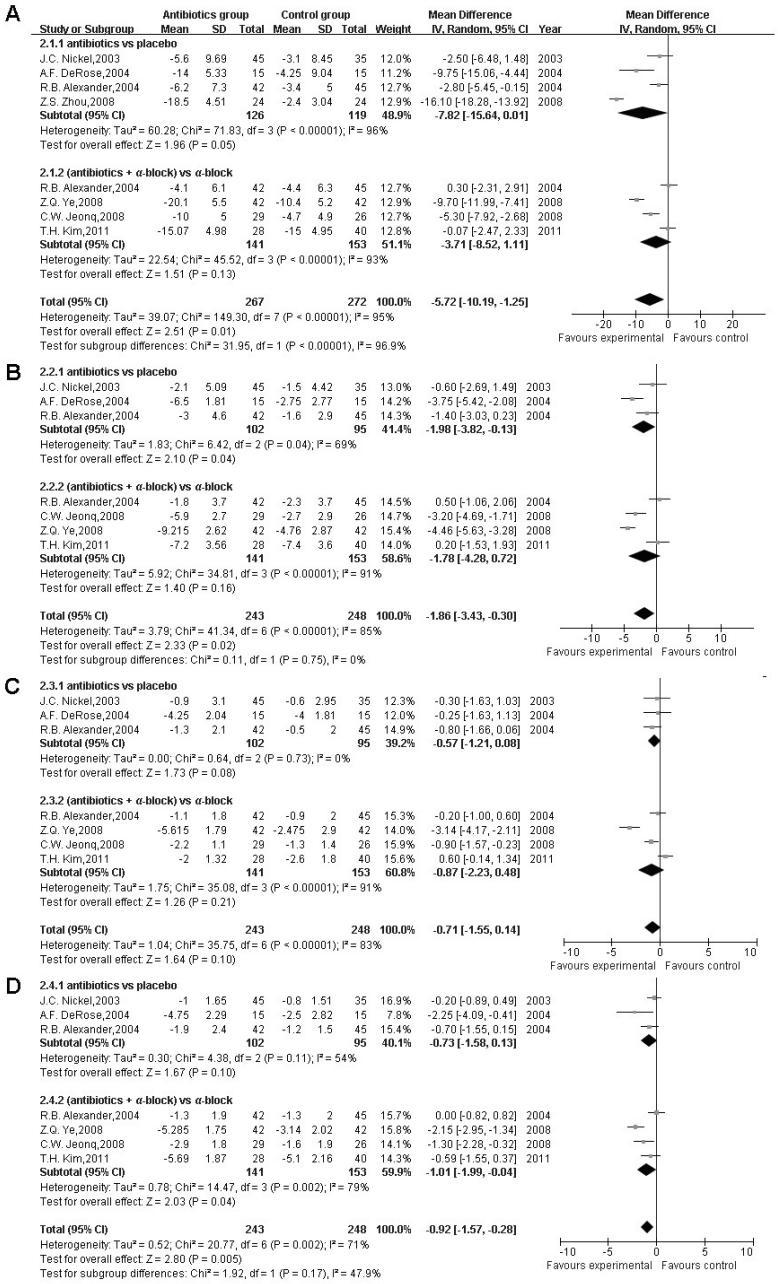

Figure 2. Forest plot of change in (A) total score, (B) pain score, (C) voiding score and (D) Qol score of National Institutes of Health Chronic Prostatitis Symptom Index.

controlled trials, which have the highest quality in published literature. Although the search strategy was without restriction on language, some literature may be omitted because of the limitation of the internet. Meanwhile, as we know, the grey literature was difficult to obtain.

In addition, we included the trials representing the opposite results, so a high heterogeneity was detected in the studies and forced us to apply the random effect model reducing the credibility and increasing the imprecision of the results. As we know, it was questionable that pooled the data by a meta-analysis when the heterogeneity was too high (I2 > 75%), and its effect would not be overcome by the random effect model. However, according to some authoritative literatures,[22,23] we also used this method to

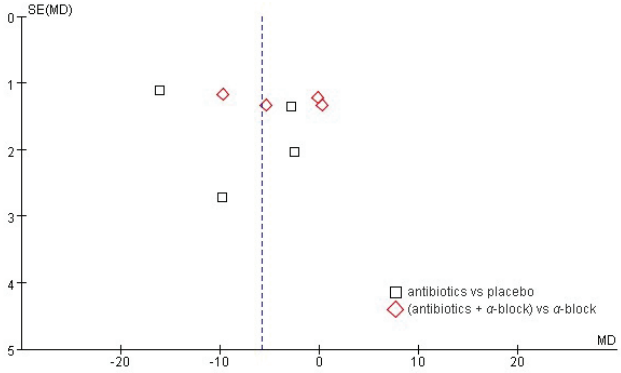

Figure 3. Funnel plot of change in total score of National Institutes of Health Chronic Prostatitis Symptom Index.

evaluate the results, even though it could not avoid the huge heterogeneity. Considering a high heterogeneity and a publication bias existed, we found several sources in these RCTs. First, the patients chosen to study were different. The men with refractory long-standing symptoms represented a small subpopulation of the overall group with CP/CPPS. Second, the agents might be more effective in men who had received less previous treatment. The ideal study should involve patients who were naïve to the antimicrobial therapy. Third, the duration of treatment was different. Some studies did not test the use of drugs for longer than 6 weeks but longer treatment may be warranted. Fourth, the combination therapy was different from the mono-therapy. Fifth, the antibiotic therapy for category IIIA was justified, but not for category IIIB in some trials; others found no significant differences between categories II, IIIA, or IIIB to the antibiotic treatment. Sixth, the dose of antibiotics was change from 100 mg twice daily to 500 mg daily in different countries. Seventh, the revisiting time for treatment ranged from 3 months to 1 year follow-up period. Lastly, some patients were wrongly diagnosed. Although the combining estimates were greatly heterogeneous, the mixed model with random intercept gave consideration to variations at the study level. What's more, the measurement that we used was the score reduced difference instead of the score of CPSI directly, which may reflect the role of antibiotics better than the direct CPSI score.

There were some limitations that needed to be taken into account. The number of patients enrolled was small and the total sample sizes were relatively small, so the credibility of the conclusion was not strong enough and the representative required considering. The sample sizes of the studies were so different that the weight was not the same, which led to a high heterogeneity after the data combination. The incorporative results were often heterogeneous and the origin of this difference was not obvious. Category III prostatitis remains a disputed condition with little consensus regarding the best treatment option. [1] The treatment benefits were modest for some therapies and nonexistent for others, which probably reflected the individual differences.

CONCLUSION

Although it is commonly known that there is a great benefit from antibiotics for category III prostatitis, we found no significant associations between them when analyzing the published studies by meta-analysis. Our meta-analysis reveals that antibiotics are not beneficial in the management of category III prostatitis. Future research to confirm these findings is warranted, and we may reduce the usage of antibiotics in such a population.

ACKNOWLEDGMENT

Yongtong Zhu, Chunyan Wang and Xiang Pang contributed equally to this work.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Lee KS, Choi JD. Chronic prostatitis: approaches for best management. Korean J Urol. 2012;53:69-77.
2. Guo YL, Li HJ. Prostatitis. Beijing, China, People's Military Medical Press; 2007. p. 63-8.
3. Schaeffer AJ. Classification (traditional and National Institutes of Health) and demographics of prostatitis. Urology. 2002;60:5-6.
4. Kim SH, Ha US, Sohn DW, et al. Preventive effect of ginsenoid on chronic bacterial prostatitis. J Infect Chemother. 2012;18:709-14.

5. Thakkinstian A, Attia J, Anothaisintawee T, Nickel JC. alpha-blockers, antibiotics and anti-inflammatories have a role in the management of chronic prostatitis/chronic pelvic pain syndrome. BJU Int. 2012;110:1014-22.
6. Anothaisintawee T, Attia J, Nickel JC, et al. Management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and network meta-analysis. JAMA. 2011;305:78-86.
7. Lombardo F, Fiducia M, Lunghi R, et al. Effects of a dietary supplement on chronic pelvic pain syndrome (Category IIIA), leucocytospermia and semen parameters. Andro. 2012;44 Suppl 1:672-8.
8. Nickel JC, Downey J, Clark J, et al. Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: a randomized placebo-controlled multicenter trial. Urology. 2003;62:614-7.
9. Kim TH, Lee KS, Kim JH, et al. Tamsulosin Monotherapy versus Combination Therapy with Antibiotics or Anti-Inflammatory Agents in the Treatment of Chronic Pelvic Pain Syndrome. Int Neurourol J. 2011;15:92-6.
10. De Rose AF, Gallo F, Giglio M, Carmignani G. Role of mepartricin in category III chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized prospective placebo-controlled trial. Urology. 2004;63:13-6.
11. Wang WF, Dong DX, Cen S, et al. Preliminary Study of Incurable Causes of Chronic Prostatitis. Nat J Andro. 2001;7:233-6.
12. Cohen JM, Fagin AP, Hariton E, et al. Therapeutic Intervention for Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS): A Systematic Review and Meta-Analysis. PLoS One. 2012;7:e41941.
13. Dong J, Su SY, Wang MY, Zhan Z. Shenqi fuzheng, an injection concocted from Chinese medicinal herbs, combined with platinum-based chemotherapy for advanced non-small cell lung cancer: a systematic review. J Exp Clin Cancer Res. 2010;29:137.
14. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.
15. Ye ZQ, Lan RZ, Yang WM, Yao LF, Yu X. Tamsulosin treatment of chronic non-bacterial prostatitis. J Int Med Res. 2008;36:244-52.
16. Jeong CW, Lim DJ, Son H, Lee SE, Jeong H. Treatment for chronic prostatitis/chronic pelvic pain syndrome: levofloxacin, doxazosin and their combination. Urol Int. 2008;80:157-61.
17. Alexander RB, Propert KJ, Schaeffer AJ, et al. Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. Ann Intern Med. 2004;141:581-9.
18. Zhou Z, Hong L, Shen X, et al. Detection of nanobacteria infection in type III prostatitis. Urology. 2008;71:1091-5.
19. Nickel JC, Downey J, Johnston B, Clark J. Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: a prospective multicenter clinical trial. J Urol. 2001;165:1539-44.
20. Yoshimura T, Kurita C, Usami E, et al. Immunomodulatory action of levofloxacin on cytokine production by human peripheral blood mononuclear cells. Chemotherapy. 1996;42:459-64.
21. Roblot P, Becq-Giraudon B. [Non-antibiotic effects of antibiotics: from side effects to therapeutic uses]. Pathol Biol (Paris). 1997;45:751-7.
22. Aboumarzouk OM, Stein RJ, Eyraud R, et al. Robotic versus laparoscopic partial nephrectomy: a systematic review and meta-analysis. Eur Urol. 2012;62:1023-33.
23. Wu LM, Hu J, Gu HY, Hua J, Xu JR. Can diffusion-weighted magnetic resonance imaging (DW-MRI) alone be used as a reliable sequence for the preoperative detection and characterisation of hepatic metastases? A meta-analysis. Eur J Cancer. 2013;49:572-84.