Do antibiotics decrease prostate-specific antigen levels and reduce the need for prostate biopsy in type IV prostatitis? A systematic literature review

Karel Tim Buddingh[1]; Marlies G.F. Maatje[2]; Hein Putter[1]; Rene Kropman[2]; Rob C.M. Pelge[1]
[1]Leiden University Medical Centre, Department of Urology; [2]HagaZiekenhuis, The Hague Department of Urology; Netherlands

Cite as: *Can Urol Assoc J* 2017 Dec. 1; Epub ahead of print**.**
http://dx.doi.org/10.5489/cuaj.4515

Published online December 1, 2017

****

Abstract

Introduction: Inflammation of the prostate can be a cause of elevated prostate-specific antigen (PSA) in men referred for suspected prostate cancer. This systematic review assesses the evidence for antibiotic therapy in patients with type IV (asymptomatic) prostatitis with regard to reduction of PSA levels and discrimination between prostate cancer and inflammation.
Methods: MEDLINE, EMBASE, and the Cochrane registry were searched for papers reporting on cohorts of men with elevated PSA and type IV prostatitis that were treated with antibiotics.
Results: The search yielded 160 papers, of which 11 met the inclusion criteria: two randomized trials and nine cohort studies. In total, the studies reported on 1011 patients with type IV prostatitis, of whom 926 were treated with antibiotics. PSA normalization was seen after antibiotic treatment in 33.2% of patients (95% confidence interval [CI] 24.9–42.8). Meta-analysis of the randomized trials did not demonstrate a higher likelihood of PSA normalization in the antibiotics arm as compared to the control arm (odds ratio [OR] 1.27; 95% CI 0.58–2.76; p=0.553). Four studies performed prostate biopsies in all patients. Although three of these studies demonstrated lower prevalence of prostate cancer in patients in whom PSA had normalized, meta-analysis failed to show a statistically significant difference (OR 0.39; 95% CI 0.06–2.49; p=0.319).
Conclusions: The available evidence does not support antibiotic therapy for differentiation between benign and malignant cause of elevated PSA in men with type IV prostatitis.

Introduction

Inflammation of the prostate can be a cause of an elevated prostate specific antigen (PSA) in men referred for suspected prostate cancer. In the presence of symptoms of acute bacterial prostatitis or recurrent urinary tract infections, antibiotic therapy is clearly indicated. There is, however, a group of patients with inflammation of the prostate without symptoms or urinary tract infections: NIH Type IV prostatitis.[1] The European Association of Urology (EAU) Guidelines for Urological Infections present antibiotics as an effective method to lower PSA in men with type IV prostatitis,[2] citing a single paper.[3] It remains unclear whether other studies support this practice.

Several randomized trials have allocated *all* asymptomatic men with an elevated PSA to a course of antimicrobial therapy. These trials were summarized by Yang et al in 2015.[4] Their meta-analysis demonstrated that there was no difference in the proportion of patients with responsive PSA. Furthermore, patients with responsive PSA in the antibiotics group were not less likely to have prostate cancer than those with spontaneously decreased PSA in the control group.

Abovementioned studies, by design, included a large number of men without prostatitis. Therefore, a positive effect of antibiotics in men with type IV prostatitis may have been obscured. A number of investigators have assessed the effect of antibiotics specifically in patients with leucocytosis in expressed prostate secretion (EPS), post prostate massage voided urine (VB3) or histologically proven asymptomatic prostatitis.

The aim of this study was to systematically review the evidence for antibiotic therapy in patients with type IV prostatitis with regard to reduction of PSA levels and discrimination between prostate cancer and inflammation only.

Methods

Search strategy

A systematic literature search was conducted of the Medline, EMBASE and Cochrane Clinical Trials database up to 20-04-2016. Results were limited to English language papers. Medline and EMBASE were searched using the following query:

- Prostatitis OR prostate inflammation
- AND prostate specific antigen OR PSA
- AND antibiotic OR antibiotics OR anti-microbial

Subsequently, the reference lists of the included papers were searched for any further relevant articles.

As part of the publication bias analysis, the International Clinical Trials Registry Platform (ICTRP) was searched for any relevant trials.

Inclusion criteria

Articles were identified that reported on a cohort of men with NIH type IV prostatitis (confirmed either by laboratory results or histopathology results) that was treated with any form of antibiotics. Papers were included if they reported follow-up PSA levels and/or outcome of prostate biopsy after treatment with antibiotics.

Outcome parameters

1. Decrease in PSA in patients who were or were not treated with antibiotics
2. Outcome of prostate biopsy in patients who had or had not exhibited a decline in PSA level

Data extraction and statistical analysis

Data were extracted from the selected studies by two of the authors independently (KTB and MM). When necessary, differences in interpretation were resolved by a third author (RP).

Statistical analysis was performed in R[5]. Meta-analysis was performed. Calculation of effect sizes with 95% confidence intervals was accomplished by using inverse variance weighting. Between-study heterogeneity was assessed with the χ^2 test for heterogeneity. Data with significant heterogeneity (<5%) were pooled using a random-effects model, data without significant heterogeneity were pooled using a fixed effects model.[6] Forest plots were generated for graphical presentation of the outcomes. Funnel plots to assess for study bias were not deemed useful as the number of studies in each analysis was too small.[7]

Quality of studies was assessed using the NHLBI tool for Quality Assessment of Observational Cohort and Cross-sectional Studies and Quality Assessment of Controlled Intervention Studies where applicable.[8]

Results

Search

The primary search yielded 160 papers. After examining titles and abstracts 130 papers could be excluded (for inclusion flow-chart see Supplementary Figure 1). Full texts of the remaining 30 papers were examined. A further 19 were excluded for not meeting the inclusion criteria (17 papers) or because only abstracts were published of the studies (two papers). Examination of the reference lists of the eleven included papers[3,9-18] did not yield further studies that met the inclusion criteria.

The search of the International Clinical Trials Registry Platform did not reveal any studies that met the inclusion criteria.

Study characteristics

Study characteristics are shown in Table 1. Two studies were randomized controlled trials that assessed the effect of antibiotics versus placebo or no treatment in men with type IV prostatitis.[16,18] The rest were prospective or retrospective cohort studies without a control group. Most studies diagnosed type IV prostatitis by white blood cell (WBC) count in EPS or VB3; one investigated patients with histologically proven type IV prostatitis upon biopsy.[9] Fluoroquinolones were given in all but one study;[15] duration of treatment ranged between 2 to 8 weeks. In total, the studies reported on 1011 patients with type IV prostatitis of whom 926 were treated with antibiotics.

Quality of studies

Quality of studies was assessed using aforementioned NHLBI tools. Most cohort studies were rated 'Good Quality';[9-15] two were rated 'Fair Quality'.[3,17] The two randomized controlled trials were rated as 'Good Quality'[16] and 'Fair Quality'.[18]

Decrease in PSA

Initial and final PSA levels were reported in seven studies (see Table 2). In the antibiotics group, the mean PSA decreased in all studies, with mean decrease ranging from 1.2 to 3.6ng/mL. The only study to report on PSA levels in the control group found a decrease in PSA from 5.2 to 4.0 ng/mL in the antibiotics group (levofloxacin 500mg once daily for 4 weeks) and no decrease in the control group (p = <0.001).[18]

The proportion of patients with normalisation of PSA levels was reported by all but one study. The pooled average percentage of patients with normalised PSA after antibiotic treatment was 33.2% (95%-CI 24.9-42.8%).

A pooled analysis of the two randomized trials[16,18] yielded an OR for normalisation of PSA of 1.27 (95%-CI 0.58 – 2.76, p = 0.553) (see Figure 1a).

Result of prostate biopsies

Outcome of prostate biopsies in all patients was reported in four studies (see Supplemmentary Table 1). Three of these studies reported a lower incidence of prostate cancer in patients in whom PSA had normalized compared to patients in whom PSA had not normalized. However, in meta-analysis, this effect did not reach statistical significance (OR 0.39; 95%-CI 0.06 – 2.49, p = 0.319) (see Figure 1b).

Discussion

This is the first systematic review to assess the effect of antibiotics specifically in men with type IV prostatitis. In all the included studies men treated with antibiotics exhibited a decrease in PSA. However, lack of control groups in most studies makes it impossible to conclude that this decrease in PSA can be attributed to antibiotics. Meta-analysis of the available randomised trials did not demonstrate superiority of antibiotic treatment above no treatment for normalisation of PSA.

Previous meta-analysis focused upon antibiotic treatment of *all* men with elevated PSA[4]. No significant difference could be demonstrated between the antibiotic group and the control group in terms of normalisation of PSA. The current systematic review addresses the same question in men with biochemically or histologically proven inflammation of the prostate.

This review focuses solely on men with asymptomatic (type IV) prostatitis. However, none of the included studies administered a standardized questionnaire (such as the NIH-chronic prostatitis symptom index) to rule out a type III prostatitis. In most papers, clinical assessment including DRE was used to qualify patients as asymptomatic. As such the patient group may have been confounded by men with unrecognized chronic prostatitis type III.

As most studies in this systematic review did not include a control group, it is possible that other factors than the antibiotic therapy may have played a role in the decrease in PSA. One such factor could be natural fluctuation.[19] Theoretically, men who are referred for evaluation when their PSA is at a high point in their natural fluctuation will show regression to the mean in course of time.

In order for antibiotics to have an effect on prostate inflammation, bacterial micro-organisms have to play an active role in the inflammation. Most studies in this systematic review do not report routine cultures of EPS or VB3 urine. Karazanashvili et al report 15% positive culture rate. Kaygisiz et al found 20% positive cultures.[11] Potts et al report 36% positive cultures.[15] It could be hypothesized that any effect of antibiotics would be limited to the subgroup of patients with positive cultures. However, Potts et al found that positive culture was not a predictor of response to antibiotics.

Different types of histological prostatic inflammation have been described and a consensus classification was published in 2001.[20] The system grades inflammation by anatomical location (glandular, periglandular or stromal), extent (focal, multifocal or diffuse) and grade (mild, moderate or severe). It remains to be seen whether the proposed classification corresponds with outcome in terms of symptoms or PSA. Correlation between positive EPS and histological prostatitis is reported to be fair to poor.[11,13] Whether data of EPS-proven prostatic inflammation and biopsy-proven prostatitis should be combined may therefore be subject of debate. Inflammation upon first biopsy reduces the odds of prostate cancer in repeat biopsies,[21] presumably reflecting an elevated PSA as a result of inflammation. Only one of the included studies included men based upon biopsy results; therefore the outcome of this review mainly reflects findings in men with EPS-proven prostatitis.

Any systematic review is limited by the quality of the available studies. The most important limitation is that most studies were retrospective and did not include a control group (i.e. men with type IV prostatitis that were treated with placebo or no treatment). Two of the papers found in the initial search were excluded as they were published as conference abstracts only. The quality of abstracts cannot be assessed in the same way as that of full publications. Many abstracts do not progress to full publications; in the studies that are published there may /be substantial abstract-to-publication discordance in data.[22]

Publication bias, if present in this review, is likely to favour studies that show a positive effect of antibiotics on PSA. This could be the reason why most cohort studies report substantially higher rates of PSA normalisation than the randomized trials. A search of the International Clinical Trials Registry Platform revealed no non-published studies that met the inclusion criteria and thus no further evidence of publication bias. A formal assessment by means of funnel plot was deemed inappropriate because of too few studies[7].

Any beneficial effect of antibiotics, or lack thereof, should be weighed against the possible side effects of prolonged therapy with quinolones. Although they are generally well tolerated, side effects range from frequent and mild such as diarrhoea and vomiting, to rare but severe such as tendon ruptures and arrhythmia[23]. Furthermore, resistance to oral antibiotics, especially fluoroquinolones is an important factor leading to post prostate biopsy sepsis.[24]

The European Association of Urology Guidelines on Urological Infections[2] recommend the use of antibiotics in patients with evidence of prostatic inflammation, referring to the paper by Bozeman et al.[3] It is apparent from this review that this may be an oversimplification of the clinical problem and that this recommendation may need to be nuanced.

Conclusion

This systematic review demonstrates that patients with type IV prostatitis treated with antibiotics exhibit a decrease in PSA. Due to a paucity of controlled studies, however, there is no evidence that the reduction of PSA is causally related to the antibiotic regimen. More importantly, meta-analysis of the two available randomized trials did not reveal any difference in in PSA levels treated with or without antibiotics. Therefore, the available evidence does not support antibiotic therapy for differentiation between patients with and without prostate cancer. Physicians should be aware of the limited evidence when considering antibiotic therapy in patients with type IV prostatitis.

References

1 Nickel, J. C. Prostatitis. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada* **5**, 306-315, doi:10.5489/cuaj.11211 (2011).

2 Grabe, M. B. R. B. J. T. E. C. T., Cek, M.; Koves B.; Naber K.G.; Pickard R.S.; Tenke P.; Wagenlehner F.; Wullt, B. . EAU Guidelines on Urological Infections. (2015).

3 Bozeman, C. B., Carver, B. S., Eastham, J. A. & Venable, D. D. Treatment of chronic prostatitis lowers serum prostate specific antigen. *The Journal of urology* **167**, 1723-1726 (2002).

4 Yang, L. *et al.* Antibiotics may not decrease prostate-specific antigen levels or prevent unnecessary prostate biopsy in patients with moderately increased prostate-specific antigen levels: A meta-analysis. *Urologic oncology* **33**, 201 e217-224, doi:10.1016/j.urolonc.2015.02.001 (2015).

5 Team, R. D. C. R: A language and environment for statistical computing. *Vienna, Austria: R Foundation for Statistical Computing. Retrieved from http://www.R-project.org* (2010).

6 Riley, R. D., Higgins, J. P. & Deeks, J. J. Interpretation of random effects meta-analyses. *Bmj* **342**, d549, doi:10.1136/bmj.d549 (2011).

7 Song, F., Khan, K. S., Dinnes, J. & Sutton, A. J. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. *International journal of epidemiology* **31**, 88-95 (2002).

8 Tools for Quality Assessment. *Retrieved from www.nhlbi.nih.gov October 1st 2016*.

9 Guercio, S. *et al.* PSA decrease after levofloxacin therapy in patients with histological prostatitis. *Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica / Associazione ricerche in urologia* **76**, 154-158 (2004).

10 Karazanashvili, G. & Managadze, L. Prostate-specific antigen (PSA) value change after antibacterial therapy of prostate inflammation, as a diagnostic method for prostate cancer screening in cases of PSA value within 4-10 ng/ml and nonsuspicious results of digital rectal examination. *European urology* **39**, 538-543, doi:52500 (2001).

11 Kaygisiz, O. *et al.* Effects of antibacterial therapy on PSA change in the presence and absence of prostatic inflammation in patients with PSA levels between 4 and 10 ng/ml. *Prostate cancer and prostatic diseases* **9**, 235-238, doi:10.1038/sj.pcan.4500885 (2006).

12 Kim, Y. J. *et al.* Prostate Cancer Can Be Detected Even in Patients with Decreased PSA Less than 2.5 ng/ml after Treatment of Chronic Prostatitis. *Korean journal of urology* **52**, 457-460, doi:10.4111/kju.2011.52.7.457 (2011).

13 Kobayashi, M., Nukui, A. & Morita, T. Serum PSA and percent free PSA value changes after antibiotic treatment. A diagnostic method in prostate cancer suspects with asymptomatic prostatitis. *Urologia internationalis* **80**, 186-192, doi:10.1159/000112612 (2008).

14 Lee, A. G., Choi, Y. H., Cho, S. Y. & Cho, I. R. A prospective study of reducing unnecessary prostate biopsy in patients with high serum prostate-specific antigen with consideration of prostatic inflammation. *Korean journal of urology* **53**, 50-53, doi:10.4111/kju.2012.53.1.50 (2012).

15 Potts, J. M. Prospective identification of National Institutes of Health category IV prostatitis in men with elevated prostate specific antigen. *The Journal of urology* **164**, 1550-1553 (2000).

16 Stopiglia, R. M. *et al.* Prostate specific antigen decrease and prostate cancer diagnosis: antibiotic versus placebo prospective randomized clinical trial. *The Journal of urology* **183**, 940-944, doi:10.1016/j.juro.2009.11.044 (2010).

17 Tang, P., Xie, K. J., Wang, B., Deng, X. R. & Ou, R. B. Antibacterial therapy improves the effectiveness of prostate cancer detection using prostate-specific antigen in patients with asymptomatic prostatitis. *International urology and nephrology* **42**, 13-18, doi:10.1007/s11255-009-9598-x (2010).

18 Ugurlu, O. *et al.* Impacts of antibiotic and anti-inflammatory therapies on serum prostate-specific antigen levels in the presence of prostatic inflammation: a prospective randomized controlled trial. *Urologia internationalis* **84**, 185-190, doi:10.1159/000277596 (2010).

19 Komatsu, K., Wehner, N., Prestigiacomo, A. F., Chen, Z. & Stamey, T. A. Physiologic (intraindividual) variation of serum prostate-specific antigen in 814 men from a screening population. *Urology* **47**, 343-346 (1996).

20 Nickel, J. C. *et al.* Consensus development of a histopathological classification system for chronic prostatic inflammation. *BJU international* **87**, 797-805 (2001).

21 Moreira, D. M. *et al.* Baseline prostate inflammation is associated with a reduced risk of prostate cancer in men undergoing repeat prostate biopsy: results from the REDUCE study. *Cancer* **120**, 190-196, doi:10.1002/cncr.28349 (2014).

22 Scherer, R. W., Langenberg, P. & von Elm, E. Full publication of results initially presented in abstracts. *The Cochrane database of systematic reviews*, MR000005, doi:10.1002/14651858.MR000005.pub3 (2007).

23 Owens, R. C., Jr. & Ambrose, P. G. Antimicrobial safety: focus on fluoroquinolones. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **41 Suppl 2**, S144-157, doi:10.1086/428055 (2005).

24 Van der Wielen, G. V. R.-A. F., O.E.; Bellaar Spruyt, J.A.; Froeling, F.M.J.A. [Antibiotic treatment of infectious complications and urosepsis after transrectal prostate biopsy or gold marker implantation]. *Tijdschrift voor Urologie* (2014).

Figures and Tables

Fig. 1A. Meta-analysis of two randomized trials. Odds ratio (OR) of normalization of prostate-specific antigen. Left favours control group; right favours antibiotics. CI: confidence interval.

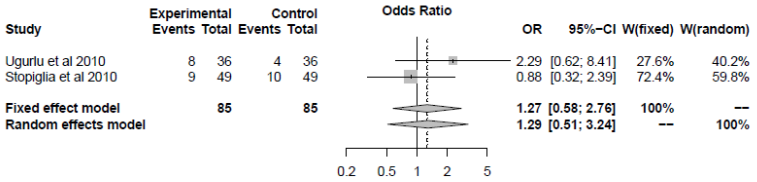


Fig. 1B. Meta-analysis of four cohort studies. Odds ratio (OR) of finding prostate cancer in patients in whom prostate-specific antigen (PSA) normalized after antibiotic treatment vs. those with persistent elevated PSA. Left favours lower risk in patients with normalized PSA. Right favours higher risk in patients with normalized PSA. CI: confidence interval.

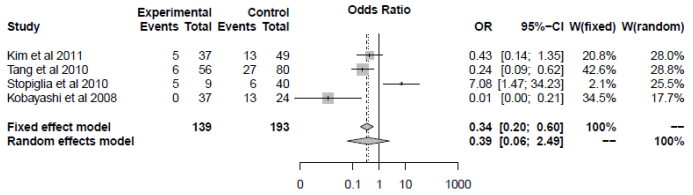


Table 1. Study characteristics

Study	N	Type of study	Inclusion criteria	Method for diagnosing inflammation	Antibiotic regimen
Lee et al 2012	215	Prospective cohort study	- PSA 4–10 - Normal DRE	- WBC>10 in EPS or VB3	Levofloxacine 100 mg 3x/day for 8 weeks
Kim et al 2011	86	Prospective cohort study	- PSA 4–10 - Normal DRE	- WBC>10 in EPS	Ciprofloxacin 500 mg/day for 4 weeks
Tang et al 2010	136	Retrospective cohort study	- PSA 4–50 - Normal DRE	- WBC>10 in EPS	Levofloxacine 500 mg 1x/day for 2 weeks
Ugurlu et al 2010	72	Randomized controlled trial	- PSA 2.5–10 - Normal DRE	- WBC>10 in EPS	Levofloxacin 500 mg 1x/day for 4 weeks
Stopiglia et al 2010	98	Randomized controlled trial	- PSA 2.5–10 - Normal DRE	- WBC>20 in EPS OR>10 in VB3	Ciprofloxacin 500 mg 2x/day for 4 weeks
Kobayashi et al 2008	51	Retrospective cohort study	- PSA >4 rising and falling - Normal DRE	- WBC>10 in VB3	Levoflocacin 300 mg 1x/day
Kaygisiz et al 2006	25	Prospective cohort study	- PSA 4–10 - Normal DRE	- WBC>10 in EPS	Ofloxacin 400mg 1x/day for 3 weeks
Guercio et al 2004	26	Retrospective cohort study	- PSA>4	- Inflammation upon first biopsy	Levofloxacin 500 mg 1x/day for 3 weeks
Bozeman et al 2002	95	Retrospective cohort study	- PSA 4–25 - Normal DRE	- WBC>10 in EPS	Quinolone, trimethoprim-sulfamethoxazole or doxycycline for 4 weeks
Karazanashvili et al 2001	61	Retrospective cohort study	- PSA 4–10 - Normal DRE	- WBC>10 in EPS	Ofloxacin 400 mg 2x/day for 2 weeks
Potts 2000	51	Retrospective cohort study	- PSA>4	- WBC>10 in EPS or>20 in VB3	Trimethoprim sulfa-methoxazole for 4 weeks

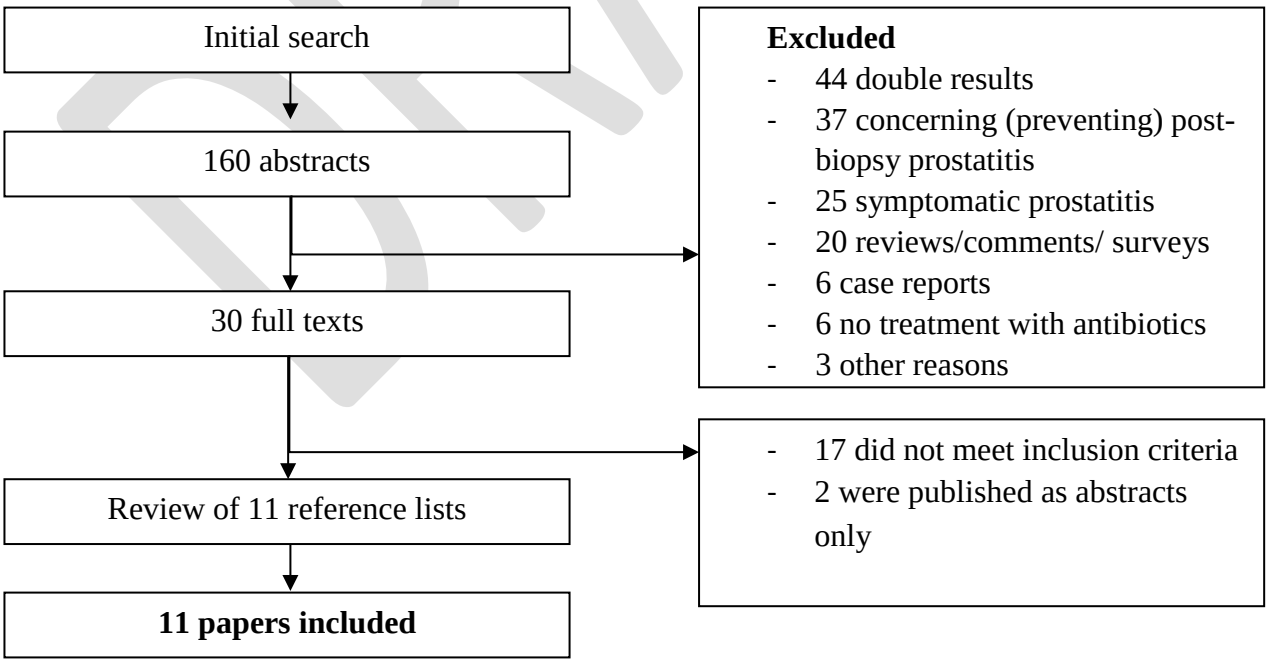
EPS: expressed prostatic secretion; DRE: digital rectal exam; PSA: prostate-specific antigen; VB3: voided bladder urine; WBC: white blood cell count.

Table 2. Reduction in PSA in antibiotics group and control group

Study	N	Mean initial PSA	Mean final PSA	PSA normalized
Lee et al 2012	215	6.3±1.7	NR	53 (24.7%)
Kim et al 2011	86	8.1 (4.6–24.8)	5.4 (1.4–12.9)	37 (43.0%)
Tang et al 2010	136	14.0±7.8	10.4±7.7	56 (41.2%)
Ugurlu et al 2010				
Antibiotics	36	5.2 (4.3–6.4)	4.0 (3.1–4.9)	8 (22.2%)
Control	36	5.0 (3.6–6.5)	5.1 (3.3–6.5)	4 (11.1%)
Stopiglia et al 2010				
Antibiotics	49	5.0	NR	9 (18.4%)
Control	49	5.7	NR	10 (20.4%)
Kobayashi et al 2008	51	11.5±8.8	10.2±8.0	5 (9.8%)
Kaygisiz et al 2006	25	6.8±2.1	5.1±2.1	NR
Guercio et al 2004	26	7.1 (4.1–15)	5.8 (2–15)	7 (26.9%)
Bozeman et al 2002	95	8.5±4.7	5.4±3.8	44 (46.3%)
Karazanashvilli 2001	61	NR	NR	37 (60.6%)
Potts et al 2000	51	NR	2.9	22 (43.1%)

NR: not reported; PSA: prostate-specific antigen.

Supplementary Fig. 1. Search flow chart.



Supplementary Table 1. Outcome of prostate biopsy in patients with and without normalization of PSA

Study	Biopsy protocol	Prostate cancer detection in patients with normalized PSA	Prostate cancer in patients with persistent elevated PSA
Kim et al 2011	All patients	5/37 (13.5%)	13/49 (26.5%)
Tang et al 2010	All patients	6/56 (10.7%)	27/80 (33.8%)
Stopiglia et al 2010 Antibiotics Control	All patients	 5/9 (55.6%) 3/10 (30%)	 6/40 (15%) 14/39 (35.9%)
Karazanashvilli et al 2001	All patients	0/37 (0%)	13/24 (54.2%)

NR: not reported; PSA: prostate-specific antigen.