Prostatic calculi influence the antimicrobial efficacy in men with chronic bacterial prostatitis

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We studied the efficacy of culture-specific antibiotic therapy for chronic bacterial prostatitis (CBP) patients with or without prostatic calculi. This study included 101 patients (21–62 years old) who met the consensus criteria for CBP (National Institutes of Health category II). According to the results of transrectal ultrasonography (TRUS), all patients were divided into two groups: Group 1, CBP with prostatic calculi, n=39; Group 2, CBP without prostatic calculi, n=62. All patients received optimal antimicrobial therapy for 4 weeks and followed up for a minimum of 3 months (range: 3–8 months). In addition to expressed prostatic secretions (EPS) and urine culture, all patients were asked to complete the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) and the subjective global assessment (SGA). The microbiological eradication rate at the end of treatment were 32/39 (82.1%) and 54/62 (72.6%) in Group 1 and Group 2, respectively. We observed a decrease in the total NIH-CPSI score median values from 24 to 19 in Group 1 and from 24 to 11 in Group 2. The pain subscore (P<0.01), urinary subscore (P<0.05) and quality of life (QoL; P<0.05) as well as the total NIH-CPSI score (P<0.01) were significantly improved after antimicrobial treatment in Group 2 compared to Group 1. Response, defined as a decrease of the NIH-CPSI total score by at least 50%, was seen in Group 1 versus Group 2 in 38.5% and 58.1% (P<0.01), respectively. Our results showed that prostatic calculi influence the antimicrobial efficacy in men with CBP. There was a noticeable decrease in the cure rate of CBP patients with prostatic calculi due to relapse after antimicrobial therapy.


Keywords: antimicrobial drugs; chronic prostatitis; prostatic calculi

INTRODUCTION

Chronic prostatitis (CP) represents a prevalent clinical condition that affects young and middle-aged men. It is characterized by chronic pelvic pain, urinary symptoms and an impairment in quality of life (QoL).¹ The National Institutes of Health (NIH) classification of prostatitis adopted in 1995 includes several clinical categories, ranging from acute or chronic bacterial infections, chronic pelvic pain syndrome (CPPS) and even asymptomatic inflammation of the prostate.² Category II chronic bacterial prostatitis (CBP) is characterized by recurrent episodes of symptomatic urinary tract infection mainly caused by uropathogens infecting the prostate gland and causing urological pain and/or voiding symptoms.

Stones formed in human prostate have been generally called prostatic calculi or calcareous concretions. Prostatic calculi are presumed to form by the precipitation of prostatic secretions and calcification of the corpora amylacea under inflammatory conditions.³ The second pathomechanism discussed in stone formation is that intraprostatic reflux may cause chemical prostatitis. Some studies showing many constituents of prostatic calculi could be found only in urine, not in prostatic secretions.⁴⁻⁷

Prostatic calculi are very common in prostatitis, and one study indicated that prostatic calculi were found in 59% of the patients and only 1% of the controls (P<0.001), confirming their specific relation to prostate inflammation.⁸ It has been reported that a prostatic calculus is actually a cluster of bacteria and that these calculi may be the cause of prolonged bacteriosis in patients with recurrent urinary tract infections.⁹ However, it is unclear whether prostatic calculi influence the efficiency of antimicrobial therapy in patients with CP.

In the present study, we aimed to examine, through a pilot study, the impact of prostatic calculi on the efficiency of antimicrobial therapy in men with CBP (NIH category II).

MATERIALS AND METHODS

From March 2008 to October 2010, 106 men with a clinical diagnosis of CBP were selected from a population of 1258 patients with suspected CP. Before their inclusion in the study, all patients provided written informed consent.

Men were eligible for the study if their age was at least 18 years, and they reported symptoms of voiding or pain in the pelvic region for at least 3 months during the 6 months before entry. The exclusion criteria were the presence of a history of epididymitis or sexually transmitted disease; treatment with antimicrobial substances penetration into...
prostatic 4 weeks prior to the study entry; residual urine volume
> 50 ml resulting from bladder outlet obstruction; cancer of the geni-
tourinary tract; a history of intravesical chemotherapy; active urethral
stricture; a history of pelvic radiation or systemic chemotherapy;
neurological disease affecting the bladder; prostate or bladder surgery;
inflammatory bowel disease; liver function test values (SGOT/AST,
SGPT/ALT or total bilirubin) twice greater than the upper limit of
normal; and serum creatinine 0.5 mg per 100 ml above the upper limit
of normal or a calculated serum creatinine clearance of less than
30 ml min$^{-1}$.

All patients had a complete history, physical examination and trans-
rectal ultrasonography (TRUS) of the prostate (Figure 1). The bac-
teriological diagnosis was confirmed by the Meares–Stamey four-glass
lower urinary tract localization test$^{12}$ using the following criteria: (i)
if the bacterial colony forming units (CFUs) of the cultured
expressed prostatic secretion (EPS) obtained by rectal digital prostatic
massage or, if sufficient EPS could not be obtained, the CFU of the
cultured voided bladder urine after prostatic massage (VB3) was
$\geq 10^5$ CFU ml$^{-1}$ and the leucocyte was $\geq 10$ per high-power field
(HPF×400) in EPS or VB3, respectively; and (ii) a 10-fold increase
in CFU in EPS and urine after prostate massage (VB3) compared with
first voided urine (VB1) and midstream urine (VB2). All colony
counts were reported for any bacteria isolated and drug sensitivity
tests of bacteria were performed. The bacteriological response was
based on the results of the appropriate cultures taken before, after
therapy and the end of study.

Symptoms were quantified by the National Institute of Health
Chronic Prostatitis Symptom Index (NIH-CPSI).$^{13}$ The NIH-CPSI
consists of nine questions, exploring the three major domains of pros-
tatitis, i.e., pain (scored 0–21), voiding disturbances (scored 0–10) and
QoL impact (scored 0–12); the total NIH-CPSI score is 0–43. All
patients were asked to complete the NIH-CPSI questionnaire before
treatment and the end of study.

To distinguish treatment responders from non-responders, patients
with more than 50% improvement in their total NIH-CPSI score were
classified as responders, and patients with 25%–50% improvement in
their NIH-CPSI total scores were classified as partial responders.
Patients with less than 25% improvement were classified as poor
responders.$^{14,15}$

In addition, a subjective global assessment (SGA) was completed.$^{16–19}$
With SGA, the patient’s improvement was graded as none (<25% improvement), mild (25%–50% improvement), moderate (50%–75% improvement) or marked improvement (>75%). Responders were
predefined as those who indicated that they had a moderate or marked
improvement in their global symptoms.

Patients were divided into two groups according to the results of
TRUS of the prostate: Group 1, CBP with prostatic calculi; Group 2,
CBP without prostatic calculi. Hyperechoic areas without shadowing
and tiny stippled calcifications (less than 3 mm) were not considered
as prostatic calculi for the purpose of this study. The duration of total
therapy in this clinical study was 4 weeks. All patients received optimal
antimicrobial therapy according to the results of their culture and
sensitivity test.

The follow-up schema included clinical examinations and the ques-
tionnaire-based reevaluation of NIH-CPSI and SGA at 1, 3, 5, 8 and
12 months after treatment. Any patient receiving the drug for less
than 28 days or follow-up period less than 1 month was considered as
a dropout. Eradication was defined as causative organisms absent
($<10^5$ CFU ml$^{-1}$) at the end of therapy. Continued eradication was
defined as causative organisms absent ($<10^6$ CFU ml$^{-1}$) after com-
pletion of therapy and during the follow-up period; Relapse was
defined as causative organisms absent ($<10^6$ CFU ml$^{-1}$) after com-
pletion of therapy but recurrence of the same organisms during the
follow-up period at $\geq 10^5$ CFU ml$^{-1}$; Superinfection was defined as
causative organism absent ($<10^5$ CFU ml$^{-1}$) after completion of
therapy but appearance of another infecting organism at the follow-
up period at $\geq 10^6$ CFU ml$^{-1}$.

Statistical analysis was performed using SPSS, version 11.0 (SPSS
Inc., Chicago, IL, USA). Ordinal scale values were compared with the
Mann–Whitney–Wilcoxon test, and categorical variables were
compared with the chi-square test. Spearman’s rank correlation
coefficient was used as a nonparametric test to assess the linear cor-
relation between variables. The parametric variables are reported as
median values (range). The criterion for statistical significance was
$P<0.05$.

RESULTS
The mean age of the 106 CBP patients included in this study is 37.6
years (range: 21–62 years). TRUS showed that 41 (38.7%) of them had
significant calculi within the prostate. Five men failed to complete the
4-week treatment because of drug side effects, including two in
Group 1 and three in Group 2. They were excluded from further
analysis. Patients were followed up for a minimum of 3 months (range:
3–8 months). Follow-up data were obtained on 101 men at the end of
the study (39 in Group 1 and 62 in Group 2).

Patients were assessed for pathogens at the start of treatment (base-
line), at the end of antimicrobial treatment and the end of study. As
shown in Table 1, main bacterial strains include: Gram-negative bac-
teria (Escherichia coli, Pseudomonas aeruginosa, Pseudomonas spp.)
and Gram-positive bacteria (Enterococcus faecalis, Staphylococcus
aureus, Staphylococcus haemolyticus, Staphylococcus epidermidis,
Staphylococcus warneri). Antibiotics chosen on the basis of sensitivities
included fluoroquinolones, Co-Trimoxazole and macrolides. The
therapeutic protocols are shown below: levofloxacin 500 mg daily;
ciprofloxacin 250 mg twice daily; Co-Trimoxazole (80/400 mg) two
tablets twice daily; and roxithromycin 150 mg twice daily. The dura-
tion of total therapy in this clinical study was 28 days.

Table 1 also shows the post-therapy eradication rates, continued
eradication rates, relapse rates and superinfection rates for frequently
isolated pathogens. At the end of treatment (4 weeks) visit, the bac-
teriological response was eradication in 32 of 39 (82.1%) patients in
Group 1; the remaining seven patients (17.9%) had a persistent infec-
tion. The microbiological eradication rate was 87.1% in Group 2. At

![Figure 1](image) Typical TRUS appearance of prostatic calculi of the patients described in this study. TRUS, transrectal ultrasonography.
the end of the study, the bacteriological response was continued eradication in 45 patients (72.6%) in Group 2, while five patients (8.1%) had a recurrence of his original pathogen and four patients (6.5%) had become infected with a new pathogen. However, the response was continued eradication only in 17 of 39 patients (43.6%) in Group 1, while relapse and superinfection were found in 12 (30.8%) and 3 patients (7.7%), respectively. There were statistically significant differences in continued eradication and relapse rate between Group 1 and Group 2.

In our series, the follow-up ranged between 3 and 8 months. As shown in Table 2, at 3–5 months after therapy, one patient in Group 1 and five patients in Group 2 were lost to follow-up. At 6–8 months after therapy, four patients in Group 1 and nine patients in Group 2 were lost to follow-up. We analyze the eradication data on the basis of the time lag between the end of therapy and the end of the follow-up period. There were statistically significant differences in eradication rate between Group 1 and Group 2 at 3–5 months and 6–8 months of follow-up phase, respectively.

There were no significant differences between the two groups with regard to the total NIH-CPSI score and subscore before treatment. As shown in Table 3, at the end of study, there were significant differences in total score (P<0.01), pain subscore (P<0.01), urinary subscore (P<0.05) and QoL subscore (P<0.05) between Group 1 and Group 2. We also analyzed the relationship between eradication of bacteria and symptom improvement. There were significant symptom improvement (via NIH-CPSI score) in the successfully treated patients (microbiological eradication by patient) compared with unsuccessfully treated patients.

As shown in Figure 2, the number of patients rated as responders (more than 50% improvement in their total NIH-CPSI score) was significantly different between Group 1 and Group 2 at the end of the study (38.5% vs. 58.1%, P<0.01). Similarly, a significantly greater percentage of patients in Group 2 demonstrated a 50% improvement in SGA compared to Group 1 (45.2% vs. 28.2%, for a ≥ 50% SGA improvement) at the end of the study. In CBP patients with or without prostatic calculus, no correlation was found between the type of organisms isolated and the response to therapy.

**DISCUSSION**

Prostatic calculi are common in urological practice. They are associated with chronic inflammation, epithelial damage and obstruction of the glandular tissue on histological examination; however, their clinical significance remains unclear. There may be different incidences of prostatic calculi with diverse definition and community.
Prostatic calculi influence antimicrobial efficacy in CBP patients

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In one study of 47 TRUS scans for men with CP/CPPS, prostatic calculus was seen in 47% patients. This prostatic calculus was associated with inflammation, positive bacterial cultures and longer symptom duration but not symptom severity. The investigators concluded that calculus might be a disease marker and potential therapeutic target in men with CPPS.21 In our series, 106 CBP patients were evaluated with TRUS, the incidence of prostatic calculus was 38.7%. However, there was no significant difference in chronic prostatitis symptom scores (total and all subdomains) between patients with CBP with and without prostatic calculus.

Prostatic calculi influence antimicrobial efficacy in CBP patients where a typical pathogen is isolated from the site of infection. Because of suitable pharmacokinetic characteristics, good penetration into the prostate and a wide antibacterial spectrum, sulfonamides, macrolides and fluoroquinolones are the drugs of choice for CBP patients. According to some studies, the cure rate after fluoroquinolone application ranges from 63% to 86%.23,24 Unfortunately, there is no real acceptance as to when therapeutic trials meet the criteria of a sufficient follow-up so as to give proven evidence of microbial eradication. The present study was designed to compare the antimicrobial therapeutic efficacy between CBP with prostatic calculus and without prostatic calculus. After 4 weeks of antimicrobial treatment, 82.1% of the patients with prostatic calculus and 87.1% of the patients without prostatic calculus in the microbiologically assessable population experienced eradication of all pathogens present at study entry. However, at the end of the study visit, the continued eradication rates in patients with calculus and without calculus were 43.6% and 72.6% (P<0.01), respectively. Our results support the hypothesis that prostatic calculus may hamper antibiotic therapy;25 in our series, sonographic evidence of prostate calculus was a predictive parameter for the outcome of antimicrobial therapy.

Figure 2 Clinical response rates after antimicrobial therapy in men with CBP. Group 1: CBP with prostatic calculus; Group 2: CBP without prostatic calculus. NIH-CPSI responders: patients with more than 50% improvement in their total NIH-CPSI score. SGA responders: patients with more than 50% improvement in their SGA. CBP, chronic bacterial prostatitis; NIH-CPSI, National Institute of Health Chronic Prostatitis Symptom Index; SGA, subjective global assessment. **P<0.01, vs. Group 1.

The results of this trial demonstrate that prostatic calculi influence the antimicrobial therapeutic efficacy in men with CBP. After 4 weeks of antimicrobial therapy and follow-up, a greater percentage of organisms were continuously eradicated in patients without prostatic calculus (72.6%) than with prostatic calculus (43.6%; P<0.01). Similarly, patients

Table 3 The results of NIH-CPSI of all patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
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<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>NIH-CPSI</td>
<td>median value (range)</td>
<td>median value (range)</td>
</tr>
<tr>
<td>Total score</td>
<td>24.0 (21.0–32.0)</td>
<td>19.0 (9.0–24.0)</td>
</tr>
<tr>
<td>Pain subscore</td>
<td>12.0 (7.0–18.0)</td>
<td>8.0 (3.0–13.0)</td>
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<tr>
<td>Urinary subscore</td>
<td>6.0 (2.0–8.0)</td>
<td>5.0 (1.0–7.0)</td>
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<tr>
<td>QoL subscore</td>
<td>8.0 (6.0–9.0)</td>
<td>6.0 (4.0–8.0)</td>
</tr>
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</table>

Abbreviations: NIH-CPSI, National Institute of Health Chronic Prostatitis Symptom Index; QoL, quality of life.

Group 1: chronic bacterial prostatitis with prostatic calculus; Group 2: chronic bacterial prostatitis without prostatic calculus.

Data presented as median values (range).

*P<0.05, **P<0.01, vs. Group 1.

CONCLUSIONS

The results of this trial demonstrate that prostatic calculi influence the antimicrobial therapeutic efficacy in men with CBP. After 4 weeks of antimicrobial therapy and follow-up, a greater percentage of organisms were continuously eradicated in patients without prostatic calculus (72.6%) than with prostatic calculus (43.6%; P<0.01). Similarly, patients...
without prostatic calculi resulted in a significantly higher symptom improvement compared to those with prostatic calculi.

AUTHOR CONTRIBUTIONS
The work presented here was carried out under collaboration of all authors. WPZ and PW designed the study, carried out the study, followed up for patients, analyzed the data, interpreted the results and participated in drafting and revising the paper. YTL made substantial contributions to the conception and design of the study and assessment the pathogens and the choice of antimicrobial drugs. JC, ZZG, HJ, DX and SW participated in patient screening and assessment. All authors read and approved the final manuscript.

COMPETING FINANCIAL INTERESTS
The authors declare that they have no competing financial interests.

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