Treatment of chronic bacterial prostatitis

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Abstract

Bacterial infection of the prostate can be demonstrated by the Meares & Stamey 4-glass or the pre and post prostate massage (PPM) 2-glass test in only about 10% of men with symptoms of chronic prostatitis. NIH-category II chronic bacterial prostatitis (CBP) is mainly caused by Gram-negative uropathogens, whereas the role of certain Gram-positive and sexually-transmitted pathogens is still discussed. For treatment, fluoroquinolones are considered the drugs of choice because of their favorable pharmacokinetic properties and their broad antimicrobial spectrum, with the best evidence supporting ciprofloxacin and levofloxacin. The optimal duration of treatment and follow-up is at least 28 days and 6 months, respectively. Relapse and reinfection due to antimicrobial resistant pathogens are major problems in chronic bacterial prostatitis, and the increasing resistance of *E. coli* against fluoroquinolones in many countries is of great concern. In patients with pathogens resistant to fluoroquinolones, currently no evidence-based recommendation can be given, though antibacterial therapy may be attempted, based on the results of antibiograms. A three month course of treatment with trimethoprim-sulfamethoxazole may be be tentatively administered, though eradication rates with these agents are relatively low, and strong and modern evidence-based foundations for this recommendation are missing. Quality randomized trials are urgently needed to validate the usage of a number of non-fluoroquinolone antibacterial agents whose efficacy in chronic bacterial prostatitis has been reported in the frame of noncomparative single-cohort studies or case series.

Keywords: prostatitis, chronic bacterial prostatitis, antibiotic treatment, antibacterial treatment, antimicrobial resistance

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Summary of recommendations

1. The fluoroquinolone drug class is the first choice systemic treatment for chronic bacterial prostatitis, with the best evidence supporting the use of ciprofloxacin and levofloxacin (Grade of Recommendation [GoR] A).
2. Other fluoroquinolones with evidence of efficacy include lomefloxacin (GoR A), prulifloxacin (GoR A), gatifloxacin (discontinued in the US, GoR B), and moxifloxacin (only case reports available, GoR C).
3. The optimal duration of therapy is at least 28 days, with some studies supporting treatment for up to eight weeks (GoR B).
4. The optimal length of clinical follow-up is at least six months (GoR A).
5. The main unresolved issue is the increasing rate of antimicrobial resistance and lack of oral alternatives to the fluoroquinolones. In patients with pathogens resistant to fluoroquinolones, no high-graded recommendation can be currently given. Quality clinical trials (double-blinded, randomized-controlled setting) with non-fluoroquinolone antibacterial agents are urgently needed in patient populations with fluoroquinolone-resistant CBP. In refractory or fluoroquinolone-resistant chronic bacterial prostatitis, repeated courses of treatment, or long-term antimicrobial treatment is recommended using antimicrobials to which the pathogen is susceptible, based on careful analysis of the antibiogram. As aminopenicillins derivatives and several cephalosporins do not distribute efficiently to the prostatic sites of infection, preference may be given to agents that were reported to be effective on CBP patients as the result of cohort studies, published case series, or small randomized trials (e.g., co-trimoxazole, tetracyclines, macrolides, fosfomycin, aminoglycosides) (GoR C).
6. Prostate surgery is only recommended in patients with chronic bacterial prostatitis who have proven bladder outflow obstruction, with prostatitis likely complicating a concomitant condition of benign hyperplasia (GoR C).
7. Therapy of prostatitis may include agents aimed at reducing pain and inflammation (paracetamol, NSAIDS, or neuropatic pain medications in selected cases) and at facilitating urinary flow in case of pronounced voiding symptoms (alpha-adrenergic blockers) (GoR C).
8. There are insufficient data on alternative and complementary medicine approaches for patients with chronic bacterial prostatitis (GoR D).
9. Non-systemic delivery of antibacterial drugs is not recommended (GoR D).

1 Introduction

Approximately 10% of men with symptoms of chronic prostatitis have bacteriuria with pathogens that can be proven to originate from infection of the prostate using the Meares and Stamey four-glass or the pre and post-prostate massage two-glass test. These patients meet the criteria for NIH category II chronic bacterial prostatitis (CBP) and represent the focus of this chapter. Most cases of chronic bacterial prostatitis are caused by Gram-negative uropathogens, mainly belonging to the Enterobacteriaceae family, though infection by *Pseudomonas spp*. is occasionally diagnosed. Gram-positive pathogens include *Enterococcus* as the most frequently detected genus. The role of certain Gram-positive or sexually-transmitted bacteria is still debated. The purpose of this guideline is to evaluate the evidence supporting current treatment options for patients with chronic bacterial prostatitis, including treatment-refractory cases.

1.1 Prostatitis syndromes

Prostatitis syndromes are among the most common conditions encountered in urologic practice. Classification of prostatitis syndromes is based on the clinical presentation of the patient, the presence or absence of pathogenic bacteria and/or white blood cells in expressed prostatic secretions (EPS) or post-massage urine [1]. Prostatitis is described as chronic when symptoms are present for at least three months. Symptoms mainly include (i) pain, localized at the perineum, scrotum, testes, penis, lower back, groin, pubic area, (ii) voiding symptoms, both irritative (frequency, urgency, etc.) and obstructive (hesitancy, intermittency, weak stream, incomplete emptying), and in some cases (iii) sexual dysfunction (erectile, ejaculatory, etc.).

1.2 Classification

The internationally-accepted classification of prostatitis syndromes follows the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)/National Institutes of Health (NIH) recommendations (Table 1) [2], and recognizes four main categories of prostatitis.

Table 1: National Institutes of Health Prostatitis Syndrome Classification [2]

I	Acute Bacterial prostatitis	
II	Chronic Bacterial Prostatitis	
III	Chronic Prostatitis/Chronic Pelvic Pain Syndrome	
	a)	Inflammatory
	b)	Non-Inflammatory
IV	Asymptomatic Inflammatory Prostatitis	

Acute bacterial prostatitis (NIH category I) is defined as an acute bacterial infection of the prostate, associated with severe prostatitis symptoms, signs and symptoms of systemic infection like fever, chills and malaise, and acute bacterial urinary tract infection [3].

Chronic bacterial prostatitis (NIH category II) is defined as a chronic (>3 months) bacterial infection of the prostate demonstrated by adequate microbiological tests, with documented relapsing bacteriuria caused by the same bacterial strain. Only about 10% of men with chronic prostatitis symptoms have chronic bacterial infection of the prostate that can be demonstrated by the four-glass test [4].

Other categories of prostatitis include chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) (NIH category III), which is diagnosed in patients with chronic prostatitis symptoms, but is not associated with prostatic infection proven by standard microbiological methods.

Prostatitis diagnosed in the absence of symptoms the disease is termed asymptomatic inflammatory prostatitis (NIH category IV).

1.3 Epidemiology

The incidence of bacterial prostatitis may be higher than previously reported. A study performed in year 2005 evaluated new physician-diagnosed prostatitis cases in a managed care population over a two-year interval [5]. The incidence of acute or chronic bacterial prostatitis was 1.26 cases per 1,000 men per year.

2 Methods

We defined one major research question: “What is the optimal treatment for patients with chronic bacterial prostatitis?” This main question was then divided into five issues:

1. What is the first-choice antimicrobial drug category and which drugs have the best evidence for clinical efficacy?
2. Which agents can be administered to treat pain and voiding symptoms in patients with CBP?
3. What is the optimal duration of therapy?
4. What is the desired length of follow-up?
5. What is the major outstanding issue for treatment?

2.1 Review of the literature

We searched the major databases covering the years 1999–2016 (e.g., PubMed/Medline, Embase, Cochrane Library, Biosis, Science Citation Index) using the search term *bacterial prostatitis* in binary combinations with the terms: *chronic, treatment, outcome, complications, antibiotic, antibacterial, antimicrobial*. Similar searches were also conducted using the search term *bacterial prostatitis* in binary combinations with the terms: *trimethoprim, refractory, antibiotic resistance, surgery, TURP, prostatectomy*. To identify papers not yet indexed in the major databases, we reviewed the tables of contents of the most recent issues of the major journals of urology, andrology, or other relevant journals. Papers published in non-peer-reviewed journal supplements were not included. The microbiological rationale supporting restriction of the literature search to the years 1999–2016, is based on the fact that in most countries a minimal inhibitory concentration (MIC) shift has taken place in the late ‘90s in the pathogens causing chronic bacterial prostatitis. Single case reports were excluded, while case series were included in the review process.

The studies were rated according to the levels of evidence (LoE) and the grades of recommendation (GoR) defined by the International Consultation on Urological Diseases (ICUD) standards [6].

2.1.1 Results

These searches identified a total of 2,067 articles, including 1,425 articles published from 1999–2016. Review of the titles and abstracts of the 1,425 identified articles, identified a total of 111 articles that met the criteria for detailed analysis and rating. These 111 articles were reviewed in detail for design, quality and conduct of the study, using a standard checklist adopted from the CONSORT statement (available at www.consort-statement.org).

2.2 Rating of the literature

Of the 111 articles reviewed in detail, in total 82 papers met the criteria for rating (Table 2).

Extracted Table: Table 2

According to the hierarchy of study types these papers included: one systematic review and meta-analysis, 9 randomized clinical trials, 11 non-randomized cohort studies, 2 case-control studies, 8 case series, 32 articles incorporating expert opinion, 2 cost-effectiveness studies, and 17 *in vitro*, laboratory or animal model studies (Table 2).

2.2.1 Search results

Results of database search, and a general outline of included articles and trials are shown in table 2.

One level 1 (LoE 1a) Cochrane systematic review and meta-analysis including total 2,196 patients was identified [7].

Nine level 1 randomized clinical studies (LoE 1b) were identified [8], [9], [10], [11], [12], [13], [14], [15], [16]. These studies included a total of 1,894 participants (Table 2).

The committee identified 14 Level 2 items (2 studies with LoE 2a, 12 studies with LoE 2b): 10 non-randomized cohort studies [17], [18], [19], [20], [21], [22], [23], [24], [25], [26] and 4 case series [27], [28], [29], [30]. These studies included a total of 1,290 participants (Table 2).

The committee identified 31 level three items including: one non-randomized cohort study [31], two case-control studies [32], [33], four case series [34], [35], [36], [37], 20 expert opinion reviews [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], one cost-effectiveness study [58] and and 3 in vitro, laboratory, or animal model studies [59], [60], [61]. These studies included a total of 652 patients with chronic prostatitis, 12 healthy volunteers and 39 TURP patients (Table 2).

The committee identified 27 Level 4 studies including: 12 articles based on expert opinion [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73], one cost-effectiveness study [74], and 14 *in vitro*, laboratory, animal model, or pharmacokinetic studies [75], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88] (Table 2).

3 Clinical presentation and recommended evaluation of patients with chronic bacterial prostatitis

3.1 Diagnosis

Chronic bacterial prostatitis is characteristically associated with recurrent urinary tract infections caused by the same bacterial strain. It represents the most frequent cause of recurrent urinary tract infections in young and middle aged men. If not treated adequately from its early onset, CBP can be a devastating disease, characterized by relapsing episodes that may occasionally involve systemic symptoms, like fever and malaise. Potential complications of this condition include: prostatic abscess, urosepsis, and acute urinary retention.

Accurate diagnosis of chronic bacterial prostatitis (NIH category II) is based on quantitative cultures and microscopy of specimens obtained from lower urinary tract segmented tests. The four-glass procedure, first described by Meares and Stamey, allows culture and pathogen detection in first-void, midstream, post-massage urine and expressed prostatic secretions (EPS) [89]. This test is considered the gold standard for diagnosis of CBP, though no modern controlled study has yet been performed to support this recommendation. Nickel et al validated a simpler test to assess inflammation/infection as a screening test in primary care patient populations [90]. This “two-glass” test, based on the culture of pre- and post-massage urine samples, is a reasonable alternative when EPS cannot be obtained or when direct microbiological assistance is not available, as EPS should be examined immediately after sampling.

3.2 Microbiology

A bacterial strain is considered to be the causative pathogen of a specific case of CBP if its colony forming unit (CFU) value in EPS or post-massage voided urine is at least 10 times higher than the load found in midstream or first-voided urine. When a specific pathogen is detected by non-culture techniques (PCR, etc.), such ratio is impossible to assess. Hence, the diagnosis of CBP becomes more cumbersome, and should be based on different and multiple parameters to achieve good specificity.

The bacterial spectrum of chronic bacterial prostatitis has been investigated in patients from tertiary care institutions in 1989 [4], [91]. Similar to the experience with acute prostatitis, these series reported that facultative Gram-negative bacilli (especially *E. coli*) were responsible for the great majority of cases. Though one study questions the consistency of cultures of Gram-positive bacteria in chronic prostatitis patients [92], recent reports have shown a preponderance of Gram-positive cocci in clinical trials or case series [9], [23], [93]. The continuous evolution of pathogen populations worldwide and nationwide makes it impossible to draw a conclusive picture on the spectrum of pathogens in CBP. It can be stated, though, that most trial reports indicate that the bacterial spectrum of CBP causative agents resembles that of complicated urinary tract infections, with a preponderance of Enterobacteriaceae like *E. coli, Proteus spp.*, *Klebsiella spp.*, and others. *P. aeruginosa* and Enterococci are also isolated, but are more difficult to treat. Concerning the pathogenic role of Gram-positive bacteria, Naber and coworkers have demonstrated that the concordance between microbiological eradication and clinical symptom remission is high when stringent criteria (10,000 CFU/mL in VB3 or EPS specimens, compared to 1,000 CFU/mL for Enterobacteriaceae) are applied in the diagnosis of Gram-positive prostatitis [18].

3.3 Other issues related to clinical assessment

3.3.1 Semen culture

A comprehensive study of 40 men with *E. coli* chronic bacterial prostatitis evaluated the role of semen analysis and cultures. Bacteriospermia (>10^3 CFU/ml) was documented in 21 (53%) of the 40 men prior to treatment [27]. Therefore, semen culture alone is not sufficient to diagnose chronic bacterial prostatitis [14]. A retrospective analysis of a cohort of 696 patients showed that addition of cultures of total ejaculates collected after emission of the post-massage urine (in the frame of a 4-glass test) may increase the rate of pathogen detection [94]. Randomized controlled studies are warranted to draw any conclusion in this regard.

3.3.2 Imaging studies and urodynamics

The role of transrectal prostate ultrasound and urodynamic investigations was evaluated in a prospective study of 164 men. This study showed that these procedures cannot differentiate between chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome [95]. Nevertheless, ultrasound and urodynamic evaluations, together with uroflowmetry, are pivotal to assess the severity of prostatitis syndromes.

A recent study report shows that prostatitis can be differentiated from prostate cancer using Prostate Imaging-Reporting and Data System (PI-RADS) [96]. This study enrolled 68 patients with cancer suspicious lesions. T2w imaging, diffusion weighted imaging, dynamic contrast enhancement, and MR-Spectroscopy were acquired. Furthermore, T2-morphology, ADC-value, perfusion type, citrate/choline-level, and lesion localization were evaluated. Although differentiation between prostatitis and cancer was possible, significant overlap between prostatitis and other benign findings was evidenced. The authors concluded that PI-RADS is only suitable to a limited extent for the primary assessment of prostatitis [96].

In another study, tecnetium-99m scintigraphy imaging was performed in 19 patients with chronic

bacterial prostatitis, compared to controls and patients with CP/CPPS [97]. Hot uptake was found in 68% of chronic bacterial prostatitis patients and 70% of patients with chronic pelvic pain syndrome. Based on the results of these studies it is not possible to draw a final conclusion concerning the benefit of imaging procedures in diagnosing chronic bacterial prostatitis with high specificity.

3.3.3 National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)

The NIH-CPSI provides a standardized assessment of chronic prostatitis symptoms [98]. The NIH-CPSI was designed as a tool for monitoring treatment response in clinical trials of chronic prostatitis/chronic pelvic pain syndrome rather than as a diagnostic tool. Though – due to the overlapping symptoms between CBP and CPPS – the CPSI test has been used for symptom evaluation in some CBP clinical studies, validation of this instrument in assessing the clinical response to therapy and symptom severity in patients with category II chronic bacterial prostatitis has not yet been conducted.

4 Principles of therapy

4.1 Antimicrobial treatment

Appropriate antimicrobial therapy represents the cornerstone of successful treatment of patients with bacterial prostatitis. For effective antimicrobial therapy the pathogens at the site of infection must be exposed to a drug concentration sufficient to kill the bacteria or inhibit their growth, ultimately eradicating the causative pathogens from that site. Evidence suggests that bacteria in prostatic tissue may survive in a milieu protected by biofilms, and that patients affected by biofilm disease may show more severe prostatitis symptoms [99], [100], [101]. Although the efficacy of antimicrobial agents against biofilm-associated bacteria is markedly decreased, fluoroquinolones and macrolides are more active against biofilms than other drugs, e.g. beta-lactams or aminoglycosides [72], [102], [103].

The available evidence derived from pharmacokinetic studies of antimicrobial agents and their penetration into the prostate has been comprehensively reviewed by Charalabopoulos et al. [48] and by Goto et al. [104].

Antibacterial agents achieving concentrations sufficiently high to treat chronic infections in the prostate are fluoroquinolones, macrolides, trimethoprim and aminoglycosides. Other agents whose concentrations have been tested in prostatic tissues include imipenem, aztreonam, clindamycin, and few cephalosporins (reviewed in [48], [53], [104]).

Because of their excellent pharmacokinetic and pharmacodynamic characteristics, fluoroquinolones are considered the drugs of choice for antimicrobial treatment of chronic bacterial prostatitis. The fluoroquinolones ciprofloxacin, levofloxacin, ofloxacin, lomefloxacin and prulifloxacin have been tested in the frame of randomized-controlled trials [8], [9], [10], [11], [13], [14].

Since clinical experience suggests that relapse and reinfection are commonly observed in patients with chronic bacterial prostatitis, only the results of clinical studies with a follow-up of at least six months are characterized by higher levels of evidence [105]. Overall, it appears that 60–80% of patients with *E. coli* and other Enterobacteriaceae can be cured with a four-week course of fluoroquinolone therapy (Table 2). However, clinical experience suggests that prostatitis due to *P. aeruginosa* or *Enterococcus* is more difficult to eradicate. Ciprofloxacin remains one of the best antipseudomonal fluoroquinolones for prostatic infections. In some cases, fluoroquinolones like levofloxacin or off-label moxifloxacin, showing improved activity against Gram-positive pathogens, might be a better option in case of enterococcal infections.

Levofloxacin was investigated in three recent clinical studies. The studies by Bundrick et al. [9] and Zhang et al. [14] were randomized double-blind multicenter trials comparing levofloxacin 500 mg once daily to ciprofloxacin 500 mg twice daily and found that levofloxacin was equivalent [9] or superior [14] to ciprofloxacin, respectively. In the Bundrick study, the microbiological eradication rate by patient at

four weeks was 75% in the levofloxacin group and 77% in the ciprofloxacin group. In the Zhang study, 86% and 60% were the eradication rates os levofloxacin and ciprofloxacin, respectively. One study by Naber et al. was a nonrandomized patient cohort study investigating levofloxacin 500 mg once daily [18]. The study also used different classification schemes for the diagnosis of chronic bacterial prostatitis. The total eradication rate at four weeks was 79%, and at six months 92%. The specific eradication rates of *E. faecalis* and of *P. aeruginosa,* assessed in a classification scheme comparable to the Bundrick study [9] were 56% (10/18) and 100% (3/3), respectively. Other studies have been published, confirming the efficacy of levofloxacin in the treatment of CBP (e.g. [25]).

In general, metanalysis of data from randomized studies showed no differences in efficacy between different fluoroquinolones [7]. In particular, pooled analysis of two RCTs comparing ciprofloxacin vs. levofloxacin [9], [14] showed that pathogen eradication was higher for levofloxacin, when data were analyzed using a fixed effect model (risk-ratio for eradication for levofloxacin vs. ciprofloxacin: 1.22; 95% CI: 1.11 to 1.34, P<0.001). However, significance was lost if a random-effects model was applied (risk-ratio: 1.18; 95% CI: 0.81 to 1.71, P=0.38). This meta-analysis was characterized by considerable heterogeneity (94%).

When CBP is caused by atypical/intracellular bacteria (*Chlamydia spp.,* Mycoplasmata, etc.), a number of therapeutic options are available. Fluoroquinolones, tetracyclines and macrolides have been tested in the frame of controlled trials [13], [106], [107], [108], [109]. In general, azithromycin and doxycycline are potent and equally active against chlamydial infections [108], and azithromycin achieves higher rates of eradication, compared to ciprofloxacin [109].

4.2 Duration of antibiotic treatment and clinical follow-up

We identified a single randomized clinical study comparing different durations of fluoroquinolone treatment. Paglia and coworkers compared administration of levofloxacin 750 mg daily for 21 days with 500 mg daily for 28 days. Clinical success rates for high-dose subjects (64.9%) were noninferior to the group taking 500 mg for 28 days (69.3%) [12]. However, at 3 and 6 months post-therapy clinical success rates were higher for the 500 mg group, suggesting that longer durations of treatment may prolong the relapse-free intervals, even with lower doses of levofloxacin.

Almost all examined studies used a four week treatment regimen (e.g. [8], [9], [10], [17], [18]). In one noncomparative study, treatment with gatifloxacin was four to eight weeks [31]. A cost-effectiveness study comparing different antibiotics and duration concluded that ciprofloxacin 500 mg twice daily for 28 days was the most cost-effective treatment [58]. Based upon these results, we conclude that an oral fluoroquinolone should be given for at least four weeks after the initial diagnosis of chronic bacterial prostatitis.

The off-therapy follow up in most clinical studies was at least 6 months (e.g. [8], [9], [10], [17], [18]); such period or longer is also desirable in the clinical routine.

4.3 Various procedures

One study investigated amikacin 400 mg daily administered for 10 days via submucosal injection [32]. This study reported inferior results, compared with known oral eradication rates. Thus, non-systemic delivery of antibiotics cannot be recommended (GoR D).

No published study in the last 17 years evaluated the effect of prostate surgery on chronic bacterial prostatitis. Expert opinion only recommends interventions in patients with chronic bacterial prostatitis who have proven severe bladder outflow obstruction, often worsening a concomitant benign hyperplasia. Such recommendation has not been validated by clinical studies.

4.4 Refractory disease

There are limited data available on treatment outcomes for patients who fail initial therapy for chronic bacterial prostatitis. One study investigated 36 patients with refractory chronic bacterial prostatitis and documented susceptibility of the same persisting pathogen to fluoroquinolones and macrolides [28]. Of these 36 patients, 27 (75%) were cured by a second cycle of combination pharmacological therapy with the same antibacterial agents used in the first cycle (ciprofloxacin, azithromycin). No other study evaluated patients with recurrent disease. As more studies of this important issue are warranted, currently no recommendation can be given for refractory patients.

4.5 Resistant disease

In case of fluoroquinolone resistance ascertained at diagnosis, or in case of resistance acquired during a first course fluoroquinolone therapy, the therapeutic options are limited and usually not based on robust evidence.

In general, when fluoroquinolones can't be administered because of chemoresistance of causative pathogens, but also when intolerance issues complicate or impede fluoroquinolone therapy (e.g., a history of tendonitis), antibacterial therapy may be attempted with antibacterial agents against which the causative pathogens are susceptible, based on careful analysis of the antibiogram. Intuitively, the choice of the therapeutic agent should be directed towards drugs that have shown some activity in specific CBP cases, as documented by cohort studies, case-control studies, or case series (see paragraph 4.1, above) (GoR C). Among these agents, macrolides, aminoglycosides, fosfomycin, and aminoglycosides may be considered.

Trimethoprim, alone combined with sulphamethoxazole, has been used for decades for treatment of CBP, being the best available treatment option in the pre-fluoroquinolone era. With this agent pathogen eradication is achieved in approximately 30–60% of cases (reviewed in [110]).

Orally administered trimethoprim distributes efficiently to prostatic fluids (3.3 mcg/ml), achieving a twofold concentration compared to plasma [111]. Limited evidence from randomized studies is available supporting the use of co-trimoxazole or trimethoprim in CBP. In 1979, Smith and colleagues reported the results of a double-blind study performed on 27 per-protocol patients, randomized to receive twice-daily oral co-trimoxazole (880–400 mg) for 10 days or 12 weeks [112]. Pathogen eradication (Enterobacteriaceae in all cases) was assessed in 20% of the former group and 60% of the latter group. In general, eradication rates with co-trimoxazole are lower, compared to fluoroquinolones. Co-trimoxazole may be considered a second-choice agent, used in the frame of a long-term therapy (at least three months).

In recent years, a growing number of studies focused on the natural antibiotic fosfomycin [30], [113], [114], [115]. The interest has been fostered by the fact that the resistance rates of uropathogens against fosfomycin remains relatively low in the era of multidrug resistance. For the moment only case series or small cohort studies have been published. Though the studies published so far appear to be moderately biased, the results seem to be promising, as satisfactory eradication rates (55%) upon exposure to relatively low doses of the drug (3 grams every 48–72 hours) have been achieved [30].

A recent nonrandomized, single-cohort study has shown that aminoglycosides show eradication rates of 78% (ranging between 56% [*Enterococcus faecalis*] and 85% [*Escherichia coli*]) [26]. Additional randomized-controlled trials are warranted to further validate these data.

4.6 Management of pain and voiding symptoms

Chronic bacterial prostatitis is characterized by pain and voiding disturbances, but published literature on the treatment of these symptoms is scarce, and so far no randomized controlled trial has addressed these issues. Nevertheless, in the daily practice symptomatic therapy is administered to CBP patients, also on the basis of evidence demonstrating the efficacy of analgesics or alpha-blockers in attenuating the symptoms of CP/CPPS.

In 2015 the Prostatitis Expert Reference Group (PERG), an *ad hoc* panel of experts from UK, generated a series of recommendations concerning pain and voiding symptom management in patients with CBP and CP/CPPS [57]. The bases for these recommendations included the NICE guidelines on the pharmacological management of neuropathic pain and various other guidelines and sources. According to a Delphi panel approach-generated consensus within the PERG, (i) in patients with early-stage disease who present with pain symptoms, regular paracetamol may be offered; (ii) NSAIDS should be offered only for short-term treatment (4–6 weeks) of pain to patients with early-stage CBP whose symptoms are suspected to be due to an inflammatory process; (iii) in patients with early-stage CBP use of opioids for pain management should be avoided; and (iv) if pain is considered to be neuropathic, treatment with a gabapentinoid, a tricyclic antidepressant or a selective serotonin reuptake inhibitor is suggested [57], [116].

Concerning voiding symptoms, a Delphi panel process generated several consensus-based recommendations. For CBP, (i) treatment with alpha-adrenergic antagonists should be considered in patients who present with significant voiding LUTS, but (ii) if no relief from LUTS or other CBP symptom is reached within 4–6 weeks, treatment should be stopped and different pharmacological therapies should be considered. Moreover, (iii) preference may be given to uroselective alpha-blockers llike alfuzosin, tamsulosin and silodosin [57].

4.7 Alternative and complementary medicine approaches

Two animal studies investigated catechin, a green tea extract, and ginseng, in combination with ciprofloxacin in the treatment of chronic bacterial prostatitis [81], [88]. These experiments point to statistically significant decreases in bacterial growth and improvements in prostatic inflammation compared with ciprofloxacin only groups.

A randomized clinical trial showed that *Serenoa repens* plus *Urtica dioica,* curcumin and quercitin extracts, associated with prulifloxacin are able to improve symptoms and quality of life of CBP patients, compared to fluoroquinolone monotherapy [11]. Additional studies are necessary to confirm the microbiological efficacy of these approaches.

5 Discussion and conclusions

Antimicrobial resistance to fluoroquinolones is increasing world-wide. The impact of fluoroquinolone resistance on the treatment of chronic bacterial prostatitis has not been evaluated systematically. However, an increasing number of countries no longer recommend common first-line agents for treatment of chronic bacterial prostatitis [117]. From a pharmacological viewpoint, treatment failure with increasing pathogen MICs has been observed anecdotally in our patients with chronic bacterial prostatitis, as we have seen in the case of upper and lower urinary tract infections and other urogenital infections, such as gonorrhea (for which fluoroquinolones are no longer recommended in the USA).

In patients with pathogens still susceptible to trimethoprim-sulfamethoxazole and resistant to fluoroquinolones, expert opinion recommends a three-month course of treatment with trimethoprim-sulfamethoxazole. In patients with pathogens resistant to fluoroquinolones and trimethoprim-

sulfamethoxazole, currently no high-graded recommendation can be given, though off-label administration of agents that were shown to be effective in case series or observational cohort studies may be attempted, if “salvage” antibacterial therapy is deemed necessary in severe and complicated clinical cases.

6 Future research

The microbiological success of treatment of chronic bacterial prostatitis mainly depends upon the pharmacological properties of antimicrobial agents in the prostate and the susceptibility of the pathogens to such agents.

The mounting worldwide resistance rates against fluoroquinolones require swift responses, and clinical trials with new antibiotics, or studies assessing the efficacy of old antibacterial agents in CBP are urgently needed. As drugs like aminoglycosides, carbapenems, tigecycline, fosfomycin, and others have been recovered in prostatic tissues (surgical specimens in most cases) or have been tested in single patients or healthy volunteers [115], [117], [118], [119], new studies are warranted to confirm the distribution of these agents to prostatic ducts, their concentrations in prostatic secretions, and, ultimately, their efficacy against chronic bacterial prostatitis in a randomized setting.

Future research should also be directed to the activity of agents active in biofilms, to evaluate possible synergism for the treatment of chronic bacterial prostatitis.

Studies validating the effect of alpha-blocker, analgesic and anti-inflammatory therapies in CBP patients are also urgently needed.

References

1. Schaeffer AJ. Prostatitis: US perspective. Int J Antimicrob Agents. 1999;11(3–4):205–11; discussion 213–6. DOI: 10.1016/S0924-8579(99)00046-1
2. Krieger JN, Nyberg L, Jr., Nickel JC. NIH consensus definition and classification of prostatitis. Jama. 1999. 282(3):236–7.
3. Brede CM, Shoskes DA. The etiology and management of acute prostatitis. Nat Rev Urol. 2011 Apr;8(4):207-12. DOI: 10.1038/nrurol.2011.22
4. Weidner W, Schiefer HG, Krauss H, Jantos C, Friedrich HJ, Altmannsberger M. Chronic prostatitis: a thorough search for etiologically involved microorganisms in 1,461 patients. Infection. 1991. 19 Suppl 3:119–25. DOI: 10.1007/BF01643680
5. Clemens JQ MR, O'Keeffe-Rosetti M, Gao SY, Calhoun EA. Incidence and clinical characteristics of NIH type III prostatitis in a managed care population. American Urological Association Annual Meeting. 2005. San Antonio: J Urol.
6. US Department of Health and Human Services PHS, Agency for Health Care Policy and Research. 1992;115–27
7. Abrams P, Khoury S, Grant A. Evidence–based medicine overview of the main steps for developing and grading guideline recommendations. Prog Urol, 2007. 17(3): 681–4. DOI: 10.1016/S1166-7087(07)92383-0
8. Perletti G, Marras E, Wagenlehner FM, Magri V. Antimicrobial therapy for chronic bacterial prostatitis. Cochrane Database Syst Rev. 2013 Aug 12;8:CD009071. DOI: 10.1002/14651858.CD009071.pub2
9. Naber KG. Lomefloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis. Int J Antimicrob Agents. 2002;20(1):18–27. DOI: 10.1016/S0924-8579(02)00067-5
10. Bundrick W, Heron SP, Ray P, Schiff WM, Tennenberg AM, Wiesinger BA, Wright PA, Wu SC, Zadeikis N, Kahn JB. Levofloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis: a randomized double-blind multicenter study. Urology. 2003;62(3):537–41. DOI: 10.1016/S0090-4295(03)00565-X
11. Giannarini G, Mogorovich A, Valent F, Morelli G, De Maria M, Manassero F, Barbone F, Selli C. Prulifloxacin versus levofloxacin in the treatment of chronic bacterial prostatitis: a prospective, randomized, double-blind trial. J Chemother. 2007;19(3): 304–8. DOI: 10.1179/joc.2007.19.3.304
12. Cai T, Mazzoli S, Bechi A, Addonisio P, Mondaini N, Pagliai RC, Bartoletti R. Serenoa repens

associated with Urtica dioica (ProstaMEV) and curcumin and quercitin (FlogMEV) extracts are able to improve the efficacy of prulifloxacin in bacterial prostatitis patients: results from a prospective randomised study. Int J Antimicrob Agents. 2009 Jun;33(6):549-53. DOI: 10.1016/j.ijantimicag.2008.11.012

13. Paglia M, Peterson J, Fisher AC, Qin Z, Nicholson SC, Kahn JB. Safety and efficacy of levofloxacin 750 mg for 2 weeks or 3 weeks compared with levofloxacin 500 mg for 4 weeks in treating chronic bacterial prostatitis. Curr Med Res Opin. 2010 Jun;26(6):1433-41. DOI: 10.1185/03007991003795030
14. Cai T, Mazzoli S, Addonisio P, Boddi V, Geppetti P, Bartoletti R. Clinical and microbiological efficacy of prulifloxacin for the treatment of chronic bacterial prostatitis due to Chlamydia trachomatis infection: results from a prospective, randomized and open-label study. Methods Find Exp Clin Pharmacol. 2010 Jan-Feb;32(1):39-45. DOI: 10.1358/mf.2010.32.1.1423885
15. Zhang ZC, Jin FS, Liu DM, Shen ZJ, Sun YH, Guo YL. Safety and efficacy of levofloxacin versus ciprofloxacin for the treatment of chronic bacterial prostatitis in Chinese patients. Asian J Androl. 2012 Nov;14(6):870-4. DOI: 10.1038/aja.2012.48
16. Stamatiou KN, Moschouris H. A prospective interventional study in chronic prostatitis with emphasis to clinical features. Urol J. 2014 Sep 6;11(4):1829-33. DOI: 10.22037/uj.v11i4.2170
17. Busetto GM, Giovannone R, Ferro M, Tricarico S, Del Giudice F, Matei DV, De Cobelli O, Gentile V, De Berardinis E. Chronic bacterial prostatitis: efficacy of short-lasting antibiotic therapy with prulifloxacin (Unidrox®) in association with saw palmetto extract, lactobacillus sporogens and arbutin (Lactorepens®). BMC Urol. 2014 Jul 19;14:53. DOI: 10.1186/1471-2490-14-53
18. Naber KG, Busch W, Focht J; the German Prostatitis Study Group. Ciprofloxacin in the treatment of chronic bacterial prostatitis: a prospective, noncomparative multicentre clinical trial with long-term follow-up. Int J Antimicrob Agents. 2000;14(2):143–9. DOI: 10.1016/S0924-8579(99)00142-9
19. Naber KG, Roscher K, Botto H, Schaefer V. Oral levofloxacin 500 mg once daily in the treatment of chronic bacterial prostatitis. Int J Antimicrob Agents. 2008;32(2):145–53. DOI: 10.1016/j.ijantimicag.2008.03.014
20. Panagopoulos P, Antoniadou A, Kanellakopoulou K, Tsiodras S, Katsarolis I, Papadopoulos A, Galani L, Giamarellou H. Fluoroquinolone treatment of chronic bacterial prostatitis: a prospective cohort study. J Chemother. 2009 Jun;21(3):317-21. DOI: 10.1179/joc.2009.21.3.317
21. Skerk V, Roglić S, Cajić V, Markotić A, Radonić A, Skerk V, Granić J, Zidovec-Lepej S, Parazajder J, Begovac J. Comparison of clinical symptoms scored according to the National Institutes of Health chronic prostatitis symptoms index and assessment of antimicrobial treatment in patients with chronic prostatitis syndrome. J Chemother. 2009 Apr;21(2):181-7. DOI: 10.1179/joc.2009.21.2.181
22. Magri V, Marras E, Skerk V, Markotić A, Restelli A, Garlaschi MC, Perletti G. Eradication of Chlamydia trachomatis parallels symptom regression in chronic bacterial prostatitis patients treated with a fluoroquinolone-macrolide combination. Andrologia. 2010 Dec;42(6):366-75. DOI: 10.1111/j.1439-0272.2009.01033.x
23. Kolumbić Lakos A, Skerk V, Maleković G, Dujnić Spoljarević T, Kovacic D, Pasini M, Markotić A, Magri V, Perletti G. A switch therapy protocol with intravenous azithromycin and ciprofloxacin combination for severe, relapsing chronic bacterial prostatitis: a prospective non-comparative pilot study. J Chemother. 2011 Dec;23(6):350-3. DOI: 10.1179/joc.2011.23.6.350
24. Magri V, Montanari E, Škerk V, Markotić A, Marras E, Restelli A, Naber KG, Perletti G. Fluoroquinolone-macrolide combination therapy for chronic bacterial prostatitis: retrospective analysis of pathogen eradication rates, inflammatory findings and sexual dysfunction. Asian J Androl. 2011 Nov;13(6):819-27. DOI: 10.1038/aja.2011.36
25. Zhao WP, Li YT, Chen J, Zhang ZG, Jiang H, Xia D, Wang S, Wang P. Prostatic calculi influence the antimicrobial efficacy in men with chronic bacterial prostatitis. Asian J Androl. 2012 Sep;14(5):715-9. DOI: 10.1038/aja.2012.40
26. El Meliegy AI, Torky M. An observational study to monitor the efficacy and tolerability of levofloxacin 500 mg once daily for treatment of chronic bacterial prostatitis in Saudi Arabia. Urol Ann. 2015 Jan-Mar;7(1):71-3. DOI: 10.4103/0974-7796.148623
27. Magri V, Montanari E, Marras E, Perletti G. Aminoglycoside antibiotics for NIH category II chronic bacterial prostatitis: a cohort study with one year follow-up. Exp Ther Med. 2016 Aug;12(4):2585-93.

28. Weidner W, Ludwig M, Brahler E, Schiefer HG. Outcome of antibiotic therapy with ciprofloxacin in chronic bacterial prostatitis. Drugs 1999;58 Suppl 2:103–6. DOI: 10.2165/00003495-199958002-00021
29. Magri V, Trinchieri A, Pozzi G, Restelli A, Garlaschi MC, Torresani E, Zirpoli P, Marras E, Perletti G. Efficacy of repeated cycles of combination therapy for the eradication of infecting organisms in chronic bacterial prostatitis. Int J Antimicrob Agents 2007;29(5):549–56. DOI: 10.1016/j.ijantimicag.2006.09.027
30. Magri V, Trinchieri A, Ceriani I, Marras E, Perletti G. Eradication of unusual pathogens by combination pharmacological therapy is paralleled by improvement of signs and symptoms of chronic prostatitis syndrome. Arch Ital Urol Androl 2007;79(2):93–8.
31. Los-Arcos I, Pigrau C, Rodríguez-Pardo D, Fernández-Hidalgo N, Andreu A, Larrosa N, Almirante B. Long-Term Fosfomycin-Tromethamine Oral Therapy for Difficult-To-Treat Chronic Bacterial Prostatitis. Antimicrob Agents Chemother. 2015 Dec 14;60(3):1854-8. DOI: 10.1128/AAC.02611-15
32. Kunishima Y, Takeyama K, Takahashi S, Matsukawa M, Koroku M, Tanda H, Tanaka T, Hirose T, Iwasawa A, Nishimura M, Takeda K, Suzuki N, Horita H, Yokoo A, Tsukamoto T. Gatifloxacin treatment for chronic prostatitis: a prospective multicenter clinical trial. J Infect Chemother. 2008;14(2):137–40. DOI: 10.1007/s10156-008-0593-4
33. Hu WL, Zhong SZ, He HX. Treatment of chronic bacterial prostatitis with amikacin through anal submucosal injection. Asian J Androl. 2002;4(3):163–7.
34. Nickel JC, Xiang J. Clinical significance of nontraditional bacterial uropathogens in the management of chronic prostatitis. J Urol. 2008;179(4):1391–5. DOI: 10.1016/j.juro.2007.11.081
35. 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(5):1539–44. DOI: 10.1016/S0022-5347(05)66344-6
36. Gutierrez J, Carlos S, Martinez JL, Liebana JL, Soto MJ, Luna Jde D, Piedrola G. A study of clinical response to antibiotic treatment in subjects with chronic bacterial prostatitis. Rev Esp Quimioter. 2004;17(2):189–92.
37. Guercini F, Pajoncini C, Bard R, Fiorentino F, Bini V, Costantini E, Porena M. Echoguided drug infiltration in chronic prostatitis: results of a multicentre study. Arch Ital Urol Androl. 2005;77(2):87–92.
38. Chen WM, Yang CR, Ou YC, Ho HC, Su CK, Chiu KY, Cheng CL. Combination regimen in the treatment of chronic prostatitis. Arch Androl. 2006;52(2):117–21. DOI: 10.1080/01485010500316113
39. Naber KG. Prostatitis. Nephrol Dial Transplant. 2001;16 Suppl 6:132–4. DOI: 10.1093/ndt/16.suppl_6.132
40. Wagenlehner FM, Naber KG. Antimicrobial treatment of prostatitis. Expert Rev Anti Infect Ther. 2003;1(2):275–82.
41. Wagenlehner FM, Naber KG. Prostatitis: the role of antibiotic treatment. World J Urol. 2003;21(2):105–8. DOI: 10.1007/s00345-003-0333-4
42. Wagenlehner FM, Naber KG. Fluoroquinolone antimicrobial agents in the treatment of prostatitis and recurrent urinary tract infections in men. Curr Urol Rep. 2004;5(4):309-16.
43. Wagenlehner FM, Naber KG. Fluoroquinolone Antimicrobial Agents in the Treatment of Prostatitis and Recurrent Urinary Tract Infections in Men. Curr Infect Dis Rep. 2005;7(1):9–16. DOI: 10.1007/s11908-005-0018-9
44. Wagenlehner FM, Weidner W, Sorgel F, Naber KG. The role of antibiotics in chronic bacterial prostatitis. Int J Antimicrob Agents. 2005;26(1):1–7, 39. DOI: 10.1016/j.ijantimicag.2005.04.013
45. Wagenlehner FM, Naber KG. Current challenges in the treatment of complicated urinary tract infections and prostatitis. Clin Microbiol Infect. 2006;12 Suppl 3:67–80. DOI: 10.1111/j.1469-0691.2006.01398.x
46. Wagenlehner FM, Weidner W, Naber KG. Therapy for prostatitis, with emphasis on bacterial prostatitis. Expert Opin Pharmacother. 2007;8(11):1667–74. DOI: 10.1517/14656566.8.11.1667
47. Croom KF, Goa KL. Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. Drugs. 2003;63(24):2769–802. DOI: 10.2165/00003495-200363240-00008
48. Fish DN. Levofloxacin: update and perspectives on one of the original 'respiratory quinolones'. Expert Rev Anti Infect Ther. 2003;1(3):371–87. DOI: 10.1586/14787210.1.3.371

49. Charalabopoulos K, Karachalios G, Baltogiannis D, Charalabopoulos A, Giannakopoulos X, Sofikitis N. Penetration of antimicrobial agents into the prostate. Chemotherapy. 2003;49(6):269–79. DOI: 10.1159/000074526
50. Nickel JC ZN, Spivey M, Wu SC. Clinical significance of antimicrobial therapy in chronic prostatitis associated with non-traditional uropathogens. in American Urological Association Annual Meeting. 2005. San Antonio: J Urol
51. Wagenlehner FM, Diemer T, Naber KG, Weidner W. Chronic bacterial prostatitis (NIH type II): diagnosis, therapy and influence on the fertility status. Andrologia. 2008;40(2):100–4. DOI: 10.1111/j.1439-0272.2007.00827.x
52. Naber KG. Management of bacterial prostatitis: what's new? BJU Int. 2008;101 Suppl 3:7–10. DOI: 10.1111/j.1464-410X.2008.07495.x
53. Wagenlehner FM, Naber KG, Bschleipfer T, Brähler E, Weidner W. Prostatitis and male pelvic pain syndrome: diagnosis and treatment. Dtsch Arztebl Int. 2009 Mar;106(11):175-83. DOI: 10.3238/arztebl.2009.0175
54. Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. Clin Infect Dis. 2010 Jun 15;50(12):1641-52. DOI: 10.1086/652861
55. Magri V, Perletti G, Bartoletti R, Cai T, Emelyanova I, Mehik A, Morgia G, Skerk V, Trinchieri A, Wagenlehner FM, Naber KG. Critical issues in chronic prostatitis. Arch Ital Urol Androl. 2010 Jun;82(2):75-82.
56. Wagenlehner FM, Pilatz A, Bschleipfer T, Diemer T, Linn T, Meinhardt A, Schagdarsurengin U, Dansranjavin T, Schuppe HC, Weidner W. Bacterial prostatitis. World J Urol. 2013 Aug;31(4):711-6. DOI: 10.1007/s00345-013-1055-x
57. Bowen DK, Dielubanza E, Schaeffer AJ. Chronic bacterial prostatitis and chronic pelvic pain syndrome. BMJ Clin Evid. 2015 Aug 27;2015:pii1802.
58. Rees J, Abrahams M, Doble A, Cooper A; Prostatitis Expert Reference Group (PERG). Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: a consensus guideline. BJU Int. 2015 Oct;116(4):509-25. DOI: 10.1111/bju.13101
59. Kurzer E, Kaplan S. Cost effectiveness model comparing trimethoprim sulfamethoxazole and ciprofloxacin for the treatment of chronic bacterial prostatitis. Eur Urol. 2002;42(2):163–6. DOI: 10.1016/S0302-2838(02)00270-1
60. Drusano GL, Preston SL, Van Guilder M, North D, Gombert M, Oefelein M, Boccumini L, Weisinger B, Corrado M, Kahn J. A population pharmacokinetic analysis of the penetration of the prostate by levofloxacin. Antimicrob Agents Chemother. 2000;44(8):2046–51. DOI: 10.1128/AAC.44.8.2046-2051.2000
61. Wagenlehner FM, Lunz JC, Kees F, Wieland W, Naber KG. Serum and prostatic tissue concentrations of moxifloxacin in patients undergoing transurethral resection of the prostate. J Chemother. 2006;18(5):485–9. DOI: 10.1179/joc.2006.18.5.485
62. Wagenlehner FM, Kees F, Weidner W, Wagenlehner C, Naber KG. Concentrations of moxifloxacin in plasma and urine, and penetration into prostatic fluid and ejaculate, following single oral administration of 400 mg to healthy volunteers. Int J Antimicrob Agents. 2008;31(1):21–6. DOI: 10.1016/j.ijantimicag.2007.08.025
63. Naber KG. Experience with the new guidelines on evaluation of new anti-infective drugs for the treatment of urinary tract infections. Int J Antimicrob Agents. 1999;11(3–4):189–96. DOI: 10.1016/S0924-8579(99)00014-X
64. Lipsky BA. Prostatitis and urinary tract infection in men: what's new; what's true? Am J Med. 1999;106(3):327–34. DOI: 10.1016/S0002-9343(99)00017-0
65. Stevermer JJ, Easley SK. Treatment of prostatitis. Am Fam Physician. 2000;61(10):3015–22, 3025–6.
66. Shoskes DA. Use of antibiotics in chronic prostatitis syndromes. Can J Urol. 2001;8 Suppl 1:24–8.
67. Iakovlev SV. Lomefloxacin: antimicrobial ability and clinico-pharmacokinetic basis for use in urogenital infections. Urologiia. 2002;(1):11–4.
68. Fowler JE, Jr. Antimicrobial therapy for bacterial and nonbacterial prostatitis. Urology. 2002;60(6 Suppl):24–6. DOI: 10.1016/S0090-4295(02)02300-2
69. Zvara P, Folsom JB, Plante MK. Minimally invasive therapies for prostatitis. Curr Urol Rep. 2004;5(4):320–6. DOI: 10.1007/s11934-004-0060-4

70. Skerk V, Krhen I, Kalenic S, Francetic I, Barsic B, Kuzmic AC, Derezic D, Jeren T, Kes P, Kraus O, Kuvacic I, Andrasevic AT, Tesovic G, Vrcic H. Guidelines for antimicrobial treatment and prophylaxis of urinary tract infections. Lijec Vjesn. 2004;126(7–8):169–81.
71. Liu H, Mulholland SG. Appropriate antibiotic treatment of genitourinary infections in hospitalized patients. Am J Med. 2005;118(7)Suppl:14-20. DOI: 10.1016/j.amjmed.2005.05.009
72. David RD, DeBlieux PM, Press R. Rational antibiotic treatment of outpatient genitourinary infections in a changing environment. Am J Med. 2005;118(7)Suppl:7-13. DOI: 10.1016/j.amjmed.2005.05.008
73. Perletti G, Skerk V, Magri V, Markotic A, Mazzoli S, Parnham MJ, Wagenlehner FM, Naber KG. Macrolides for the treatment of chronic bacterial prostatitis: an effective application of their unique pharmacokinetic and pharmacodynamic profile (Review). Mol Med Rep. 2011 Nov-Dec;4(6):1035-44. DOI: 10.3892/mmr.2011.575
74. Dickson G. Prostatitis--diagnosis and treatment. Aust Fam Physician. 2013 Apr;42(4):216-9.
75. Sanchez Navarro MD, Coloma Milano C, Zarzuelo Castaneda A, Sayalero Marinero ML, and Sanchez-Navarro A, Pharmacokinetics of ciprofloxacin as a tool to optimise dosage schedules in community patients. Clin Pharmacokinet, 2002. 41(14): 1213–20. DOI: 10.2165/00003088-200241140-00005
76. Rippere-Lampe KE, Lang M, Ceri H, Olson M, Lockman HA, and O'Brien AD, Cytotoxic necrotizing factor type 1-positive Escherichia coli causes increased inflammation and tissue damage to the prostate in a rat prostatitis model. Infect Immun, 2001. 69(10): 6515–9. DOI: 10.1128/IAI.69.10.6515-6519.2001
77. Velasco M, Horcajada JP, Mensa J, Moreno-Martinez A, Vila J, Martinez JA, Ruiz J, Barranco M, Roig G, Soriano E. Decreased invasive capacity of quinolone-resistant Escherichia coli in patients with urinary tract infections. Clin Infect Dis. 2001 Nov 15;33(10):1682-6. DOI: 10.1086/323810
78. Naber CK, Steghafner M, Kinzig-Schippers M, Sauber C, Sörgel F, Stahlberg HJ, Naber KG. Concentrations of gatifloxacin in plasma and urine and penetration into prostatic and seminal fluid, ejaculate, and sperm cells after single oral administrations of 400 milligrams to volunteers. Antimicrob Agents Chemother. 2001 Jan;45(1):293-7. DOI: 10.1128/AAC.45.1.293-297.2001
79. Giannopoulos A, Koratzanis G, Giamarellos-Bourboulis EJ, Stinios I, Chrisofos M, Giannopoulou M, Giamarellou H. Pharmacokinetics of intravenously administered pefloxacin in the prostate; perspectives for its application in surgical prophylaxis. Int J Antimicrob Agents. 2001 Mar;17(3):221-4. DOI: 10.1016/S0924-8579(00)00332-0
80. Scelzi S, Travaglini F, Nerozzi S, Dominici A, Ponchietti R, Novelli A, Rizzo M. The role of lomefloxacin in the treatment of chronic prostatitis. J Chemother. 2001 Feb;13(1):82-7. DOI: 10.1179/joc.2001.13.1.82
81. Horcajada JP, Vila J, Moreno-Martínez A, Ruiz J, Martínez JA, Sánchez M, Soriano E, Mensa J. Molecular epidemiology and evolution of resistance to quinolones in Escherichia coli after prolonged administration of ciprofloxacin in patients with prostatitis. J Antimicrob Chemother. 2002 Jan;49(1):55-9.
82. Lee YS, Han CH, Kang SH, Lee SJ, Kim SW, Shin OR, Sim YC, Lee SJ, Cho YH. Synergistic effect between catechin and ciprofloxacin on chronic bacterial prostatitis rat model. Int J Urol. 2005 Apr;12(4):383-9. DOI: 10.1111/j.1442-2042.2005.01052.x
83. Johnson JR, Kuskowski MA, Gajewski A, Soto S, Horcajada JP, Jimenez de Anta MT, Vila J. Extended virulence genotypes and phylogenetic background of Escherichia coli isolates from patients with cystitis, pyelonephritis, or prostatitis. J Infect Dis. 2005 Jan 1;191(1):46-50. DOI: 10.1086/426450
84. Cattoir V, Lesprit P, Lascols C, Denamur E, Legrand P, Soussy CJ, Cambau E. In vivo selection during ofloxacin therapy of Escherichia coli with combined topoisomerase mutations that confer high resistance to ofloxacin but susceptibility to nalidixic acid. J Antimicrob Chemother. 2006 Nov;58(5):1054-7.
85. Wang H, Chen ZH, Zhu YY, Wang T, Wu XJ. [Penetrability and therapeutic effect of vancomycin to the prostates of rats with bacterial prostatitis (BP) or BPH-BP]. Zhonghua Nan Ke Xue. 2006 Jun;12(6):490-5.
86. Wang H, Li ZC, Luo ZH, Chen ZH. [Penetrability of amikacin into prostate tissues in rat models of chronic bacterial prostatitis]. Zhonghua Nan Ke Xue. 2008 Jul;14(7):583-9.
87. Soto SM, Smithson A, Martinez JA, Horcajada JP, Mensa J, Vila J. Biofilm formation in

uropathogenic Escherichia coli strains: relationship with prostatitis, urovirulence factors and antimicrobial resistance. J Urol. 2007 Jan;177(1):365-8. DOI: 10.1016/j.juro.2006.08.081

88. Han CH, Yang CH, Sohn DW, Kim SW, Kang SH, Cho YH. Synergistic effect between lycopene and ciprofloxacin on a chronic bacterial prostatitis rat model. Int J Antimicrob Agents. 2008 Feb;31 Suppl 1:S102-7. DOI: 10.1016/j.ijantimicag.2007.07.016
89. Miri M, Shokri S, Darabi S, Alipour Heidari M, Ghalyanchi A, Karimfar MH, Shirazi R. Efficacy of Compound Therapy by Ginseng and Ciprofloxacin on Bacterial Prostatitis. Cell J. 2016 Spring;18(1):103-11. DOI: 10.22074/cellj.2016.3993
90. Meares EM, Stamey TA. Bacteriologic localization patterns in bacterial prostatitis and urethritis. Invest Urol. 1968 Mar;5(5):492-518.
91. Nickel JC. The Pre and Post Massage Test (PPMT): a simple screen for prostatitis. Tech Urol. 1997 Spring;3(1):38-43.
92. Krieger JN, McGonagle LA. Diagnostic considerations and interpretation of microbiological findings for evaluation of chronic prostatitis. J Clin Microbiol. 1989 Oct;27(10):2240-4.
93. Krieger JN, Ross SO, Limaye AP, Riley DE. Inconsistent localization of gram-positive bacteria to prostate-specific specimens from patients with chronic prostatitis. Urology. 2005 Oct;66(4):721-5. DOI: 10.1016/j.urology.2005.04.065
94. Cai T, Mazzoli S, Meacci F, Boddi V, Mondaini N, Malossini G, Bartoletti R. Epidemiological features and resistance pattern in uropathogens isolated from chronic bacterial prostatitis. J Microbiol. 2011 Jun;49(3):448-54. DOI: 10.1007/s12275-011-0391-z
95. Magri V, Wagenlehner FM, Montanari E, Marras E, Orlandi V, Restelli A, Torresani E, Naber KG, Perletti G. Semen analysis in chronic bacterial prostatitis: diagnostic and therapeutic implications. Asian J Androl. 2009 Jul;11(4):461-77. DOI: 10.1038/aja.2009.5
96. Strohmaier WL, Bichler KH. Comparison of symptoms, morphological, microbiological and urodynamic findings in patients with chronic prostatitis/pelvic pain syndrome. Is it possible to differentiate separate categories? Urol Int. 2000;65(2):112-6. DOI: 10.1159/000064850
97. Meier-Schroers M, Kukuk G, Wolter K, Decker G, Fischer S, Marx C, Traeber F, Sprinkart AM, Block W, Schild HH, Willinek W. Differentiation of prostatitis and prostate cancer using the Prostate Imaging-Reporting and Data System (PI-RADS). Eur J Radiol. 2016 Jul;85(7):1304-11. DOI: 10.1016/j.ejrad.2016.04.014
98. Ryu JK, Lee SM, Seong DW, Suh JK, Kim S, Choe W, Moon Y, Pai SH. Tc-99m ciprofloxacin imaging in diagnosis of chronic bacterial prostatitis. Asian J Androl. 2003 Sep;5(3):179-83.
99. Litwin MS, McNaughton-Collins M, Fowler FJ Jr, Nickel JC, Calhoun EA, Pontari MA, Alexander RB, Farrar JT, O'Leary MP. 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 Aug;162(2):369-75. DOI: 10.1016/S0022-5347(05)68562-X
100. Mazzoli S. Biofilms in chronic bacterial prostatitis (NIH-II) and in prostatic calcifications. FEMS Immunol Med Microbiol. 2010 Aug;59(3):337-44. DOI: 10.1111/j.1574-695X.2010.00659.x
101. Bartoletti R, Cai T, Nesi G, Albanese S, Meacci F, Mazzoli S, Naber K. The impact of biofilm-producing bacteria on chronic bacterial prostatitis treatment: results from a longitudinal cohort study. World J Urol. 2014 Jun;32(3):737-42. DOI: 10.1007/s00345-013-1145-9
102. Nickel JC, Olson ME, Costerton JW. Rat model of experimental bacterial prostatitis. Infection. 1991;19 Suppl 3:S126-30.
103. Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther. 2014 Aug;143(2):225-45. DOI: 10.1016/j.pharmthera.2014.03.003
104. Goto T, Nakame Y, Nishida M, Ohi Y. Bacterial biofilms and catheters in experimental urinary tract infection. Int J Antimicrob Agents. 1999 May;11(3-4):227-31; discussion 237-9.
105. Goto T, Makinose S, Ohi Y, Yamauchi D, Kayajima T, Nagayama K, Hayami H. Diffusion of piperacillin, cefotiam, minocycline, amikacin and ofloxacin into the prostate. Int J Urol. 1998 May;5(3):243-6. DOI: 10.1111/j.1442-2042.1998.tb00597.x
106. Naber KG, Giamarellou H. Proposed study design in prostatitis. Infection. 1994;22 Suppl 1:S59-60.
107. Skerk V, Mareković I, Markovinović L, Begovac J, Skerk V, Barsić N, Majdak-Gluhinić V. Comparative randomized pilot study of azithromycin and doxycycline efficacy and tolerability in the treatment of prostate infection caused by Ureaplasma urealyticum. Chemotherapy. 2006;52(1):9-11. DOI: 10.1159/000090234

108. Skerk V, Krhen I, Lisić M, Begovac J, Cajić V, Zekan S, Skerk V, Sternak SL, Topić A, Schönwald S. Azithromycin: 4.5- or 6.0-gram dose in the treatment of patients with chronic prostatitis caused by Chlamydia trachomatis--a randomized study. J Chemother. 2004 Aug;16(4):408-10. DOI: 10.1179/joc.2004.16.4.408
109. Skerk V, Krhen I, Lisić M, Begovac J, Roglić S, Skerk V, Sternak SL, Banaszak A, Strugar-Suica J, Vuković J. Comparative randomized pilot study of azithromycin and doxycycline efficacy in the treatment of prostate infection caused by Chlamydia trachomatis. Int J Antimicrob Agents. 2004 Aug;24(2):188-91. DOI: 10.1016/j.ijantimicag.2004.03.014
110. Skerk V, Schönwald S, Krhen I, Banaszak A, Begovac J, Strugar J, Strapac Z, Vrsalovic R, Vukovic J, Tomas M. Comparative analysis of azithromycin and ciprofloxacin in the treatment of chronic prostatitis caused by Chlamydia trachomatis. Int J Antimicrob Agents. 2003 May;21(5):457-62. DOI: 10.1016/S0924-8579(03)00056-6
111. Schaeffer AJ. Clinical practice. Chronic prostatitis and the chronic pelvic pain syndrome. N Engl J Med. 2006 Oct 19;355(16):1690-8. DOI: 10.1056/NEJMcp060423
112. Hofstetter A, Friesen A, Bishop-Freudling GB, Vergin H. [Co-trimoxazole concentration in the prostatic fluid of patients with subacute and chronic prostatitis]. Fortschr Med. 1984 Mar 8;102(9):244-6.
113. Smith JW, Jones SR, Reed WP, Tice AD, Deupree RH, Kaijser B. Recurrent urinary tract infections in men. Characteristics and response to therapy. Ann Intern Med. 1979 Oct;91(4):544-8. DOI: 10.7326/0003-4819-91-4-544
114. Grayson ML, Macesic N, Trevillyan J, Ellis AG, Zeglinski PT, Hewitt NH, Gardiner BJ, Frauman AG. Fosfomycin for Treatment of Prostatitis: New Tricks for Old Dogs. Clin Infect Dis. 2015 Oct 1;61(7):1141-3. DOI: 10.1093/cid/civ436
115. Cunha BA, Gran A, Raza M. Persistent extended-spectrum β-lactamase-positive Escherichia coli chronic prostatitis successfully treated with a combination of fosfomycin and doxycycline. Int J Antimicrob Agents. 2015 Apr;45(4):427-9. DOI: 10.1016/j.ijantimicag.2014.12.019
116. Gardiner BJ, Mahony AA, Ellis AG, Lawrentschuk N, Bolton DM, Zeglinski PT, Frauman AG, Grayson ML. Is fosfomycin a potential treatment alternative for multidrug-resistant gram-negative prostatitis? Clin Infect Dis. 2014 Feb;58(4):e101-5. DOI: 10.1093/cid/cit704
117. Tan T, Barry P, Reken S, Baker M; Guideline Development Group. Pharmacological management of neuropathic pain in non-specialist settings: summary of NICE guidance. BMJ. 2010 Mar 24;340:c1079. DOI: 10.1136/bmj.c1079
118. Seo Y, Lee G. Antimicrobial Resistance Pattern in Enterococcus faecalis Strains Isolated From Expressed Prostatic Secretions of Patients With Chronic Bacterial Prostatitis. Korean J Urol. 2013 Jul;54(7):477-81. DOI: 10.4111/kju.2013.54.7.477
119. Bates D, Parkins M, Hellweg R, Gibson K, Bugar JM. Tigecycline treatment of urinary tract infection and prostatitis: case report and literature review. Can J Hosp Pharm. 2012 May;65(3):209-15.
120. Nishikawa G, Ikawa K, Nakamura K, Yamada Y, Zennami K, Mitsui K, Narushima M, Ikeda K, Morikawa N, Sumitomo M. Prostatic penetration of meropenem in humans, and dosage considerations for prostatitis based on a site-specific pharmacokinetic/pharmacodynamic evaluation. Int J Antimicrob Agents. 2013 Mar;41(3):267-71. DOI: 10.1016/j.ijantimicag.2012.11.001

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