Guidelines

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/chronic pelvic pain syndrome. Chronic bacterial prostatitis is mainly caused by Gram-negative uropathogens. The role of Gram-positives, such as staphylococci and enterococci, and atypicals, such as chlamydia, ureaplasmas, mycoplasmas, are still debateable. For treatment, fluoroquinolones are considered the drugs of choice because of their favourable pharmacokinetic properties and their antimicrobial spectrum, with the best evidence supporting ciprofloxacin and levofloxacin. The optimal treatment duration is 28 days. Relapse and reinfection due to antimicrobial resistant pathogens are major problems in chronic bacterial prostatitis. The increasing resistance of *E. coli* against fluoroquinolones in many countries is of great concern in that respect. In patients with pathogens resistant to fluoroquinolones, but susceptible to trimethoprim-sulfamethoxazole, a three month course of treatment with trimethoprim-sulfamethoxazole can be administered. In patients with pathogens resistant to fluoroquinolones and trimethoprim-sulfamethoxazole, currently no recommendation can be given. Clinical trials with other antibiotics are urgently needed in this patient population.

Key words: Chronic bacterial prostatitis; Refractory chronic bacterial prostatitis; Antibiotic treatment; Antimicrobial resistance; Chronic pelvic pain syndrome.

Summary of recommendations: 1. The fluoroquinolone drug class is the first choice systemic treatment for chronic bacterial prostatitis, with the best evidence supporting use of ciprofloxacin and levofloxacin (GoR A). 2. Other drugs with evidence of efficacy include: gatifloxacin (discontinued in the US), lomefloxacin, moxifloxacin (no clinical data), prulifloxacin (not available in the US), and trimethoprim-sulfamethoxazole (GoR B). 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 promising oral alternatives to the fluoroquinolones. In patients with pathogens resistant to fluoroquinolones and trimethoprim-sulfamethoxazole, currently no recommendation can be given. Clinical trials with other antibiotics are urgently needed in this patient population (GoR A). 6. In refractory chronic bacterial prostatitis repeated treatment or antimicrobial prophylaxis is recommended using antimicrobials to which the pathogen is susceptible. More studies of this important issue are however warranted (GoR C). 7. Interventions are only recommended in patients with chronic bacterial prostatitis who have proven bladder outflow obstruction (GoR C). 8. There are insufficient data on alternative and complementary medicine approaches for patients with chronic bacterial prostatitis (GoR D).

1. INTRODUCTION

Approximately 10% of men with symptoms of chronic prostatitis/chronic pelvic pain syndrome 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 chronic bacterial prostatitis (NIH category II) and represent the focus of this consultation. Most cases of chronic bacterial prostatitis are caused by Gram-negative uropathogens. The role of Gram-positive and atypical bacteria is still debateable. 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 syndrome is one of the most common problems encountered in urologic practice. Classification of the prostatitis syndrome is based on the clinical presentation of the patient, the presence or absence of white blood cells in the expressed prostatic secretions (EPS), and the presence or absence of bacteria in the EPS.[1] Prostatitis is described as chronic when symptoms are present for at least three months.

1.2. Classification

The internationally-accepted classification of the prostatitis syndrome follows the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)/ National Institutes of Health (NIH) recommendations (Table 2).[2] There are four categories of 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 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, proven by adequate microbiological tests, with documented 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 are not associated with prostatic infection proven by standard microbiological methods in patients with chronic symptoms, termed chronic prostatitis/chronic pelvic pain syndrome (NIH category III), or in patients who have no symptoms but have proven prostatic inflammation, termed asymptomatic prostatitis (NIH category IV).

1.3. Epidemiology

The incidence of bacterial prostatitis may be higher than previously reported.[5] A recent study evaluated new physician-diagnosed prostatitis cases in a managed care population over a two-year interval.[6] The incidence of acute or chronic bacterial prostatitis was 1.26 cases per 1,000 men per year.

2. METHODS

We defined one major question, "What is the optimal antimicrobial therapy for patients with chronic bacterial pro-

statitis?" This question was then divided into four issues:

1. What is the first choice antimicrobial drug category and which drugs have the best evidence for clinical efficacy?
2. What is the optimal duration of therapy?
3. What is the desired length of follow-up?
4. What is the major outstanding issue for treatment?

2.1. Review of the literature

We searched the major databases covering the last 10 years (e.g., 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 and antimicrobial*. Similar searches were also conducted using the search term *chronic bacterial prostatitis* in binary combinations with the terms: *trimethoprim, refractory, antibiotic resistance, surgery, TURP and prostatectomy*. To identify papers not yet indexed in the major databases, we reviewed the tables of contents of the major journals of urology and other relevant journals, for the last three months. Papers published in non-reviewed supplements were not included. There is also a microbiological rationale supporting restriction of the literature search to the last 10 years, because in most areas a minimal inhibitory concentration (MIC) shift has taken place in the pathogens causing chronic bacterial prostatitis.

The studies were rated according to the level of evidence and the strength of recommendations. The Oxford Centre for Evidence Based Medicine have produced a widely accepted adaptation of the work of the Agency for Health Care Policy and Research (AHCPR).[7] The ICUD consultations use a modified version of the Oxford system which can be directly "mapped" onto the Oxford system.[8]

2.1.1. Results

These searches identified a total of 1,656 articles, including 1,014 articles published from 1999-2008. Review of the titles and abstracts of the 1,014 identified articles, identified a total of 72 articles that met the criteria for detailed analysis and rating. These 72 articles were reviewed in detail for how well each study was designed and carried out using a standard checklist adopted from the CONSORT statement (available at http: //www.consort-statement.org).

2.2. Rating of the literature

Of the 72 articles reviewed in detail, in total 57 papers met the criteria for rating (Table 1). According to the hierarchy of study types these papers included: no systematic reviews or meta-analyses, three randomized clinical trials, three non-randomized cohort studies, two case-control studies, six case series, 27 articles incorporating expert opinion, two cost-effectiveness studies, and 14 *in vitro*, laboratory or animal model studies (Table 1).

2.2.1. Results

Results are shown in table 1.

Three Level 1 studies (LoE 1b) were identified: three randomized clinical trials.[9-11] These studies included a total of 655 participants (Table 1).

The committee identified four Level 2 studies (two studies with LoE 2a, two studies with LoE 2b): two non-randomized cohort studies[12-13] and two case series.[14-16] These studies included a total o 359 participants (Table 1).

The committee identified 25 level three studies including: one non-randomized cohort study,[17] two case-control studies,[18-19] four case series,[20-23] 16 expert opinion reviews[24-39] and one cost-effectiveness study.[40] These studies included a total of 652 participants with chronic prostatitis (Table 1).

The committee identified 25 Level 4 studies including: 11 articles based on expert opinion,[41-51] one cost-effectiveness study,[52] and 14 in vitro, laboratory, or animal model studies.[53-66] These studies included no participants with chronic bacterial prostatitis (Table 1). Although the Delphi process can be used to give 'expert opinion' greater authority, we identified no article that used this approach.

3. CLINICAL PRESENTATION AND RECOMMENDED EVALUATION OF PATIENTS WITH CHRONIC BACTERIAL PROSTATITIS

Chronic bacterial prostatitis is characteristically associated with recurrent urinary tract infections caused by the same bacterial strain. Chronic bacterial prostatitis represents the most frequent cause of recurrent urinary tract infections in young and middle aged men. Chronic bacterial prostatitis can be a devastating disease, characterized by relapsing febrile episodes, if not treated adequately from the beginning. Potential complications include: urosepsis, prostatic abscess and acute urinary retention.

Accurate diagnosis of chronic bacterial prostatitis (NIH category II) depends on quantitative segmental bacteriological localization cultures and EPS microscopy. The classical four-glass procedure, first described by Meares and Stamey, remains the gold standard.[67] Nickel et al validated a simpler test to assess inflammation/infection as a screening test in primary care patient populations. The two-glass test is a reasonable alternative when EPS cannot be obtained or when microbiological assistance is not available, because EPS should be examined expeditously. Interpretation of localization test results can follow various definitions that have been evaluated, but the NIH definition is the most accepted.

3.1. Microbiology

A bacterial strain is considered a pathogen if the colony forming unit (CFU) concentration in EPS or post-prostate massage voided urine is at least 10 times higher than in midstream or first-void urine. The bacterial spectrum of chronic bacterial prostatitis has been carefully investigated in patients from tertiary care institutions.[4, 68] Similar to the experience with acute prostatitis, these series report that facultative Gram-negative bacilli (especially *E. coli*) were responsible for the great majority of cases. Recent reports from clinical series of patients have reported a preponderance of Gram-positive cocci.[10, 39] In these latter series, the median duration of patients' symptoms was 3.5 weeks. One recent report however describes that cultures suggesting localization of Gram-positive bacteria are not consistent in more than 90% of patients.[69] Nevertheless, most reports suggest that the bacterial spectrum resembles that of complicated urinary tract infections, with a preponderance of enterobacteria. *P. aeruginosa* and Enterococci are found less frequently, but are more difficult to treat.

3.2. Other issues related to clinical assessment

3.2.1. 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.[14] Therefore, semen culture is not sufficient to diagnose chronic bacterial prostatitis.[14]

TABLE 1. – Evidence Table: Studies of Chronic Bacterial Prostatitis Treatment that Include Original Data, Systematic Reviews or Meta-analysis, Expert Opinion, or Other Data (1999-2008).

Study Type	**Lead author, year, reference**	**Subjects**	**Design Aspects**	**Critical Findings**	**Rating of Evidence**
Systematic reviews and Meta-analyses					
	None				
Randomized clinical trials					
	Naber, 2002[9]	182	Multicenter, lomefloxacin 400 mg once daily vs. ciprofloxacin 500 mg twice daily for 4 weeks.	At 5-9 days, 4-6 weeks, 3 and 6 months after therapy eradication rates were 80, 72, 74, and 63% in the lomefloxacin group and 84, 81, 82, and 72% in the ciprofloxacin group.	1b, Positive (non-inferiority)
	Bundrick, 2003[10]	377	Multi-center, levofloxacin 500 mg once daily or ciprofloxacin 500 mg twice daily for 28 days	Microbiologic eradication rates 75% for levofloxacin and 76.8% for ciprofloxacin; 6-month relapse rates were similar.	1b, Positive (non-inferiority)
	Giannarini, 2007[11]	96	randomized to receive a 4-week oral course of either prulifloxacin 600 mg or levofloxacin 500 mg once daily.	6 months after therapy, microbiological cure rate was 72.73% for prulifloxacin and 71.11% for levofloxacin (p=0.86)	1b, Positive (non-inferiority)
Non-randomized cohort studies					
	Naber, 2000[12]	65	Multi-center study of ciprofloxacin 500 mg bd for 28 days	Eradication rates were 32/39 (82.1%) after 3 months, 26/34 (76. 4%) after 6 months and 13/22 (59.1%) after 9 months.	2a, Positive
	Kunishima, 2008[17]	10	Multi-center, 200 mg gatifloxacin twice daily for 4-8 weeks	58.1% symptomatic response rate 4 weeks after treatment	3, Positive
	Naber, 2008[13]	117	Multi-center open-label study of levofloxacin 500 mg once daily (p.o.) for 28 days. Patients were followed for 6 months.	Microbiological eradication rate was 82/98 (83.7%) at 1 month and the continued eradication rate was 52/57 (91.2%) at 6 months post treatment.	2a, Positive
Case-control studies	Nickel, 2008[19]	146 (average symptom duration was 8.4 weeks, median 3.5).	Multi-center study comparing levofloxacin or ciprofloxacin for 4 weeks with 6 months of follow-up	Bacteria eradication rate was 74.0% not different from men with no localization of pathogenic bacteria.	3, Positive
	Hu, 2002[18]	50	Amikacin 400 mg daily for 10 days via submucosal anal (30 cases) or intramuscular injection (20 cases).	"Cure rate" 33.3% for anal submucosal injection vs. 5% for IM injection (P<0.05)	3, Positive
Case-series	Weidner, 1999[14]	40	*E. coli* chronic bacterial prostatitis treated with 4 weeks of ciprofloxacin 500 mg bid with 12-24 months follow-up.	Microbiological eradication was 92% at 3 months and 70-80% 12-24 months after treatment.	2b, Positive
	Nickel, 2001[23]	14	Various regimens	57% "moderate to marked improvement," similar to response in patients with category III.	3, Positive
	Gutierrez, 2004[22]	105	Various regimens	Symptoms either disappeared or diminished, irrespective of whether positive cultures remained.	3, Positive
	Guercini, 2005[21]	320 with symptoms of chronic prostatitis	Antibiotic cocktails (based on cultures) with betamethasone by prostate infiltration, weekly for 3 doses.	68% of patients were "cured clinically."	3, Positive

Study Type	Lead author, year, reference	Subjects	Design Aspects	Critical Findings	Rating of Evidence
	Chen, 2006[20]	7	Combination of ciprofloxacin, doxazosin, allopurinol and biofeedback perineal massage.	Bacterial eradication rate was 71% after ciprofloxacin treatment during a follow-up of 6 months.	3, Positive
	Magri, 2007[15-16]	137	Combination therapy with ciprofloxacin, azithromycin, alfuzosin and a S. repens extract for 6 weeks.	64.2% microbiological response at the end of Rx. Of 49 patients showing persistence or reinfection at the end of treatment, 36 completed a second combination therapy cycle: 27 patients (75%) showed eradication. The cumulative eradication rate was 83.9%.	2b, Positive
Expert opinion					
	Naber, 1999		Review of guidelines	For chronic bacterial prostatitis, a category of its own is proposed rather than using the general category of complicated UTI.	4, Positive
	Lipsky, 1999[45]		Review	Trimethoprim-sulfamethoxazole or, preferably, a fluoroquinolone for 6 to 12 weeks.	4, Positive
	Stevermer, 2000[50]		Review	Antibiotics are continued for at least 3 to 4 weeks, although some men require treatment for several months.	4, Positive
	Shoskes, 2001[48]		Review	Ciprofloxacin has been shown to be effective. Newer quinolones may be more effective against gram-positive pathogens and anaerobes.	4, Positive
	Naber, 2001[26]		Review		3, Positive
	Iakovlev, 2002[44]		Review		4, Positive
	Fowler, 2002[43]		Review (minimal data)	Fluoroquinolone antibiotics given for 2 to 4 weeks will cure about 70%.	4, Positive
	Wagenlehner, 2003, 2004, 2005, 2006, 2007[32-38]		Reviews of pharmacokinetics and pharmacodynamics	Fluoroquinolones are the first choice.	3, Positive
	Croom, 2003[25]		Review	28 days of oral levofloxacin 500mg daily achieved similar clinical and bacteriological response rates to oral ciprofloxacin 500mg twice daily.	3, Positive
	Fish, 2003[42]		Review	Important role of levofloxacin.	4, Positive
	Naber, 2003[28]		Review of antimicrobial penetration into prostate tissue and seminal fluid	Fluoroquinolone concentrations at the site of infection should be sufficient for treatment of susceptible pathogens.	3, Positive
	Charalabopoulos, 2003[24]		Review of antimicrobial penetration into prostate tissue and secretions	Of agents, beta-lactam drugs penetrate poorly. Good to excellent penetration into prostatic fluid and tissue has been demonstrated with many antimicrobial agents, including tobramycin, netilmicin, tetracyclines, macrolides, quinolones, sulfonamides and nitrofurantoin. Pharmacokinetic studies of antimicrobials use heterogenous methodology. Antibiotic concentrations in prostatic fluid suitable for treatment of infections are only found with fluoroquinolones, macrolides, lincosamides and trimethoprim.	3. Positive

Study Type	Lead author, year, reference	Subjects	Design Aspects	Critical Findings	Rating of Evidence
	Skerk, 2004[49]		Croatian guidelines	Ciprofloxacin is the drug of choice.	4. Positive
	Nickel, 2005[77]		Review		3, Positive
	Zvara, 2002[51]		Review	Minimally invasive therapies (intraprostatic injections) in the treatment of chronic prostatitis are not a standard of care.	4. Negative
	Liu, 2005[46]		Review	Recommend fluoroquinolones, especially levofloxacin and gatifloxacin.	4, Positive
	David, 2005[41]		Review	Only trimethoprim and the fluoroquinolones possess both the appropriate bactericidal activity and the ability to diffuse into the prostate. Levofloxacin shows particularly good penetration.	4, Positive
	Wagenlehner, 2008[29]		Review	Follow up of at least 6 months is necessary. Most fluoroquinolones with this indication should be sufficient for susceptible pathogens.	3, Positive
	Naber, 2008[27]		Review	The fluoroquinolones (2-4 weeks) are the first choice, in particular levofloxacin is as effective as ciprofloxacin but shows a better prostatic penetration and is given once daily.	
Cost-effectiveness Studies					
	Kurzer, 2002[40]	hypothetical cohort of 100 men	Model comparing 90 days of trimethoprim-sulfamethoxazole and 14, 28 and 60 days of ciprofloxacin.	Ciprofloxacin 500 mg twice daily for 28 days appears to be the most cost effective treatment.	3, Positive
	Sanchez-Navarro, 2002[52]	50	Analysis of pharmacy and chart records		4, Positive
In vitro, laboratory, or animal model studies					
	Drusano, 2000[66]	Population pharmacokinetic analysis of prostate penetration by levofloxacin 33 subjects	Monte Carlo simulation of Levofloxacin concentrations in plasma and prostate tissue after repeated administration of 500 mg levofloxacin orally	Mean prostate tissue/ plasma concentration ratio was 4.14. 70% of the population had a penetration ratio in excess of 1.0	3, Positive
	Wagenlehner, 2006, 2008[30-31]	12 healthy volunteers and 39 TURP patients	Concentrations of moxifloxacin in plasma, urine, prostatic fluid, prostate tissue.	Moxifloxacin might be a good alternative for the prostatitis treatment.	3, Positive
	Rippere-Lampe, 2001[60]	Rat model		Cytotoxic necrotizing factor type 1-positive uropathogenic *E. coli* caused more inflammation-mediated and histological damage than isogenic CNF1-negative mutants despite similar bacterial counts.	4, Positive
	Velasco, 2001[63]	83 patients with FQ resistant E. coli isolates	Comparison of quinolone resistant E. coli isolates of invasive urinary tract infection and prostatitis cases versus cystitis cases	Quinolone resistance of invasive cases was 8% versus 20% in cystitis cases. Quinolone resistant E. coli is less likely to produce invasive disease than susceptible E. coli.	4, Positive

Study Type	Lead author, year, reference	Subjects	Design Aspects	Critical Findings	Rating of Evidence
	Naber, 2001[59]	10 normal volunteers	Gatifloxacin concentrations in plasma, urine, ejaculate, prostatic and seminal fluid, and sperm cells.	Good penetration into prostatic and seminal fluid suggest that gatifloxacin may be a good alternative.	4, Positive
	Giannopoulos, 2001[54]	50	Pefloxacin concentrations in serum and prostate tissue after 800 mg intravenuous pefloxacin were determined in BPH tissue using a microbiological plate assay	Tissue levels of pefloxacin were well above MICs of common bacteria causing bacterial prostatitis. Pefloxacin could be a satisfactory alternative for surgical prophylaxis and treatment of bacterial prostatitis	4, Positive
	Scelzi, 2001[61]	12 TURP patients	Lomefloxacin concentrations in serum and prostate tissue after 400 mg oral application	Tissue/ serum ratio was > 2 in prostatic capsule and > 1.6 in adenomatous tissue. Lomefloxacin could be an efficacious therapeutic option for treatment of chronic prostatitis	4, Positive
	Horcajada, 2002[56]	23 *E. coli* isolates	Emergence of quinolone-resistance in faeces of patients with prostatitis treated with ciprofloxacin for 1 month.	11 of 23 patients, developed quinolone-resistant strains, during and just after therapy. 2 months after treatment, these were completely displaced by quinolone-susceptible *E. coli.*	4, Positive
	Lee, 2005[58]	Rat model	Catechin, an extract of green tea.	Combination treatment of catechin and ciprofloxacin had synergistic effect.	4, Positive
	Johnson, 2005[57]	17 *E. coli* prostatitis isolates	Molecular analysis	Prostatitis isolates exhibited more virulence factors than cystitis isolates (n=23).	4, Positive
	Cattoir, 2006[53]	1	Quinolone resistance me-	chanisms in an *E. coli* clinical isolate (Ar2).	4, Positive
	Wang, 2006, 2008[64-65]	Rat model	Vancomycin and amikacin evaluated	Higher antibiotic concentration in the prostate tissues than in sera.	4, Positive
	Soto, 2007[62]	32 *E. coli* prostatitis isolates		Strains causing prostatitis produced biofilm in vitro more frequently than those causing other urinary tract infections and had a higher frequency of hemolysin (p = 0.03 and 0.0002, respectively).	4, Positive
	Han, 200855	Rat model		Lycopene may have a synergistic effect with ciprofloxacin in prostatitis treatment.	4, Positive

3.2.2. Imaging studies and urodynamics

The role of transrectal prostate ultrasound and urodynamic investigations was evaluated in a prospective study of 164 men. This study found that these investigations had no role in discriminating chronic bacterial prostatitis from chronic prostatitis/ chronic pelvic pain syndrome.[70]

In one study magnetic resonance imaging of four acute bacterial prostatitis and five chronic bacterial prostatitis cases were compared to prostate cancer, benign prostatic hyperplasia and chronic prostatitis/chronic pelvic pain cases.[71] Bacterial prostatitis showed some features similar to carcinoma suggesting that magnetic resonance imaging may provide little diagnostic specificity.

In another study 19 patients with chronic bacterial prostatitis were compared to controls and patients with chronic pelvic pain syndrome.[72] Hot uptake was found in 68% of chronic bacterial prostatitis patients and 70% of patients with chronic pelvic pain syndrome. Therefore, the data suggest that imaging procedures are of limited or no benefit in diagnosing chronic bacterial prostatitis or in predicting response to treatment.

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

The NIH-CPSI provides a standardized assessment of prostatitis symptoms.[73] The NIH-CPSI was designed as a tool for monitoring response in clinical trials of chronic prostatitis/chronic pelvic pain syndrome rather than as a diagnostic tool. Only limited data are available to validate use of this instrument in assessing the clinical response to therapy in patients with chronic bacterial prostatitis.

4. PRINCIPLES OF THERAPY

4.1. Antimicrobial treatment

Appropriate antimicrobial therapy represents the cornerstone of successful treatment for patients with bacterial pro-

statitis. For effective antimicrobial therapy the pathogens at the site of infection must be exposed to a drug concentration sufficient to inhibit bacterial growth or even eradicate the pathogens from that site. Although it remains unproven in humans, evidence suggests that bacteria in prostatic tissue may survive in a milieu protected by biofilms.[62, 74] Although the efficacy of antimicrobial therapy is markedly less against biofilm-associated bacteria, fluoroquinolones and macrolides are more active in biofilm than other antimicrobials, e.g. beta-lactams or aminoglycosides.[75]

A rather extensive review on pharmacokinetic studies of antimicrobial agents and their penetration into the prostate has been performed by Charalabopoulos et al.[24] If only studies with a suitable methodology are used, e.g. assessment of antibiotic concentrations in prostatic fluid, than antibiotic concentrations in prostatic fluid sufficiently high to treat chronic infections in the prostate are only found with fluoroquinolones, macrolides, lincosamides and trimethoprim. Encompassing pharmacokinetic and pharmacodynamic aspects, the fluoroquinolones are considered the drugs of choice for antimicrobial treatment of chronic bacterial prostatitis. All clinical studies within the last 10 years have been performed with fluoroquinolones.

Because clinical experience suggests that relapse and reinfection are common observed in patients with chronic bacterial prostatitis, only the results of clinical studies with a follow-up of at least six months is recommended.[76] 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 1). However, clinical experience suggests that prostatitis due to *P. aeruginosa* or enterococci seem to cause more failures. Therefore fluoroquinolones with a broad anti-bacterial spectrum, like levofloxacin, gatifloxacin, or moxifloxacin with improved activity against Gram-positive pathogens might be a better option in case of enterococci, although comparative RCT data suggest that these agents are equivalent to results of ciprofloxacin treatment. Levofloxacin was investigated in two recent clinical studies. The study by Bundrick et al.[10] was a randomized double-blind multicenter study comparing levofloxacin 500mg once daily to ciprofloxacin 500mg twice daily and found levofloxacin was equivalent to ciprofloxacin. Microbiological eradication was however only followed up to four weeks and patients were not required to have documented bacteriuria with the localizing bacterial "pathogens." In this study, the microbiological eradication rate by patient at four weeks was 75% in the levofloxacin group and 77% in the ciprofloxacin group. The specific eradication rate of *E. faecalis* was 72% with levofloxacin and 76% with ciprofloxacin. The eradication rate of *P. aeruginosa* was not indicated in this study. The other recent study by Naber et al.[13] was a non-randomized patient cohort study investigating levofloxacin 500mg once daily, patients were not required to have documented bacteriuria with the localizing bacterial "pathogens." The study also used different classification schemes for the diagnosis of chronic bacterial prostatitis.

The corresponding[10] total eradication rate at four weeks was 79%, and at six months 92%. The specific eradication rate of *E. faecalis* in the comparable classification scheme to the Bundrick study[10] was 56% (10/18) and of *P. aeruginosa* 100% (3/3).

4.2. Duration of antibiotic treatment and clinical follow-up

We identified no clinical studies comparing different durations of antibiotic treatment. Almost all studies used a four week treatment regimen.[9-13,19] In one study treatment with gatifloxacin was four to eight weeks,[17] but this was not a comparative study. 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.[40] Based upon these results in chronic bacterial prostatitis, an oral fluoroquinolone should be given for at least four weeks after the initial diagnosis (LoE 2, GoR B).

Follow up in most clinical studies was at least 6 months,[9-14, 19-20] which therefore should also be performed in clinical routine (LoE 2 GoR B).

4.3. Procedures

One study investigated amikacin 400 mg daily administered for 10 days via submucosal anal or intramuscular injection.[18] This study reported inferior results. Non-systemic application of antibiotics is therefore not recommended (LoE 3, GoR C).

No published study from the last 10 years evaluated interventions in chronic bacterial prostatitis. Expert opinions only recommend interventions in patients with chronic bacterial prostatitis who have proven bladder outflow obstruction although this has not been validated in studies (LoE 4, GoR C).

4.4. Alternative and complementary medicine approaches

One animal study investigated catechin, a green tea extract, in combination with ciprofloxacin in the treatment of chronic bacterial prostatitis.[58] The authors reported a statistically significant decrease in bacterial growth and improvements in prostatic inflammation compared with the ciprofloxacin only group.[58] Further studies are necessary to validate these observations.

One retrospective clinical study evaluated results of a 6-week course of combination therapy with ciprofloxacin, azithromycin, alfuzosin and a *Serenoa repens* extract in patients with chronic bacterial prostatitis.[15] Microbiological eradication rates were between 75.5% and 82.3%, and clinical success rates between 78.8% and 85.7%, depending on the pathogens isolated and were thus not higher than in those studies with antibiotics alone.[10,13] Thus, there are insufficient data on alternative and complementary medicine approaches for patients with chronic bacterial prostatitis (LoE 4, GoR D, no recommendation possible.)

4.5. Refractory patients

There are limited data available on treatment outcomes for patients who fail initial therapy for chronic bacterial prostatitis. One study investigated 36 patients with relapsing chronic bacterial prostatitis. 16 Of these 36 patients, 27 (75%) were cured by a second cycle of combination pharmacological therapy with antibacterial agents (ciprofloxacin/azithromycin), alpha-blockers (alfuzosin) and the phytotherapeutic, *Serenoa repens*. No other study evaluated patients with recurrent disease. More studies of this important issue are therefore warranted, therefore currently no recommendation can be given for refractory patients.

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, 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 with urinary tract infections and other urogenital infections, such as gonorrhea (for which fluoroquinolones are no longer recommended in the USA). In patients with pathogens susceptible to trimetho-

prim-sulfamethoxazole and resistant to fluoroquinolones, expert opinion recommends a three-month course of treatment with trimethoprim-sulfamethoxazole LoE 4, GoR C). In patients with pathogens resistant to fluoroquinolones and trimethoprim-sulfamethoxazole, currently no recommendation can be given.

Clinical trials with other antibiotics are therefore urgently needed in this patient population (LoE 4, GoR A).

6. FUTURE RESEARCH

The microbiological success of treatment of chronic bacterial prostatitis mainly depends upon the antimicrobial´s pharmacological properties in the prostate and the susceptibility of the pathogens. Future research should therefore especially be directed to the activity of other antibiotics, not tested up to now, and substances active in biofilm, to evaluate possible synergism, in the treatment of chronic bacterial prostatitis.

Table 2. – 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

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