Levofloxacin and Its Effective Use in the Management of Bacterial Prostatitis

Review

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Prostatitis is well-recognised around the world as having a significant impact on men of all ages. It imposes a huge economic and medical burden upon healthcare systems, affecting 10–14% of all men. In acute bacterial prostatitis Gram-negative bacteria remain the principal pathogens responsible for this usually severe infection, with treatment requiring administration of a broad spectrum antibiotic for 2–4 weeks. Subsequent identification of the causative pathogen, along with susceptibility tests, allows antimicrobial therapy to be tailored to the individual patient. In contrast to acute prostatitis, the chronic form of the disease is more difficult to diagnose, usually presenting with general symptoms common to other pelvic pathologies. Optimal management of this condition is made more difficult by the fact that only 10% of patients with chronic prostatitis symptoms actually have a bacterial infection. The most likely pathogens responsible for chronic prostatitis are the common uropathogens and the role of Gram-positive bacteria in this situation remains unclear. The best routine method of differentiating between this condition and chronic pelvic pain syndrome is the use of the Meares-Stamey four-glass test or the two-glass test. Fluoroquinolones remain the first choice of therapy for chronic bacterial prostatitis, in particular levofloxacin which is as effective as ciprofloxacin but has added advantages of achieving better prostatic and seminal fluid penetration and can be administered once daily.

Introduction

Prostatitis affects a large number of men of all ages and ethnicities, making it a significant, but often overlooked global healthcare issue. In fact its impact may be huge, with one out of every two men estimated to suffer from prostatitis symptoms at some time in their life. This is reflected in statistics that show that in the United States alone approximately 2 million medical office visits per year are reported for this condition (1–3). The wide impact of prostatitis is supported by evidence from a range of sources. Bartoletti et al. (4) reported that prostatitis is the most frequently diagnosed illness in men under the age of 50, while other researchers have shown that, globally, 10–14% all men will be affected by prostatitis (5, 6). Due to the severe medical and social symptomatology, prostatitis has a significant negative impact on quality of life (7), associated as it is with sexual dysfunction including decreased desire, erectile problems and premature ejaculation (4). An increased incidence of chronic prostatitis is associated with predisposing factors, such as smoking, a high-calorie diet with low consumption of fruit and vegetables, and slow digestion. However, the mechanisms responsible for the pathogenesis of this disease remain unclear (4).

Classification consensus

The United States National Institutes of Health (NIH) established the International Prostatitis Collaborative Network with the aim of improving the diagnosis and treatment of prostatitis (1). One of their first initiatives was to develop a new prostatitis classification schedule comprising the following four categories: Category I, acute bacterial prostatitis; Category II, chronic bacterial prostatitis; Category III: chronic pelvic pain syndrome (including inflammatory and non-inflammatory chronic pelvic pain syndromes); and Category IV: asymptomatic inflammatory prostatitis. Patients are classified into one of these four categories according to findings from urine, ejaculate and prostatic secretions, looking specifically at localisation patterns of leucocytes and bacteriologic analysis using the Meares-Stamey four-glass test (8).

It is important to differentiate between acute and chronic forms of bacterial prostatitis. Although both forms are caused by prostatic infection, opti-

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mal treatment requires accurate diagnosis. However, there remains no clear consensus regarding the specific pathogenic causes of Categories III and IV, with a range of proposed aetiologies including immunological, neurological, psychosomatic or anatomical causes (4).

Acute bacterial prostatitis

The diagnosis of acute bacterial prostatitis does not generally present much difficulty for the urologist (9). Symptoms at the time of presentation include signs of general infection, such as chills and fever, as well as more specific signs, such as a swollen, painful prostate. In the latter situation prostatic massage is unlikely to be tolerated by the patient, and is contraindicated due to the likelihood of causing sepsis. Gram-negative bacteria are the most likely causative pathogens, and can usually be isolated from the urine. Empiric therapy should be started as soon as the diagnosis is made with fluoroquinolones and/or β-lactam antibiotics as the drugs of choice. Antimicrobial therapy can be tailored to suit the individual patient as soon as the causative pathogen has been isolated and susceptibility tests performed (9). Oral antimicrobial therapy is usually prescribed for a duration of 2–4 weeks, although the optimal length of therapy remains debatable. At present, there is no clear consensus regarding how long acute prostatitis should be treated, and research into shorter therapy schedules of less than two weeks is warranted (9).

Chronic bacterial prostatitis

The diagnosis of chronic bacterial prostatitis is more problematic, as the symptoms tend to be similar to those of chronic pelvic pain syndrome, and patients can be asymptomatic between episodes. Patients with chronic bacterial prostatitis may also present with recurrent urinary tract infections, which may be a predisposing factor responsible for their prostatic infection.

The diagnosis of this disorder is made more difficult by the fact that only approximately 10% of patients with symptoms of chronic prostatitis or chronic pelvic pain syndrome have a bacterial infection (10). Recent data from Italy demonstrated that 13.8% of male urological outpatients (764/5,540) had chronic prostatitis and pelvic pain syndrome, with an incidence at first presentation of 4.1% (225 outpatients) (11). Further analysis of the 764 outpatients with the symptoms of prostatitis revealed that only 102 (13.3%) had chronic bacterial prostatitis. However, a much higher proportion of men diagnosed with prostatitis receive antibiotic therapy. This highlights the necessity for accurate diagnosis and pathogen identification in order to optimise the management of chronic bacterial prostatitis.

The best laboratory method of differentiating between chronic bacterial prostatitis and chronic pelvic pain syndrome is the Meares-Stamey four-glass procedure (8). This test involves taking four cultures from the following samples: 1) the first 10 ml of urine voided; 2) a 10 ml midstream sample taken after voiding about 200 ml; 3) prostatic secretions following prostatic massage; 4) the first 10 ml of urine voided post-massage. As can be seen by the number of samples required, this test involves a relatively large amount of preparation which has, unfortunately, resulted in this procedure being significantly underused for the diagnosis of chronic bacterial prostatitis in the clinic. Therefore, to overcome this drawback, a two-glass test is recommended for routine practice. The samples required for the two-glass test include a midstream urine sample and the first 10 ml of urine voided after prostatic massage. By using these two samples the two-glass test provides a similar specificity and sensitivity as the four-glass test (12). However, it is imperative that either a two-glass or four-glass test must be carried out when investigating patients with suspected chronic bacterial prostatitis to ensure correct diagnosis and to enable optimal therapeutic management.

Pathogens associated with chronic bacterial prostatitis

The pathogens most likely to be responsible for causing chronic bacterial prostatitis are the common uropathogens, including *Escherichia coli* and *Klebsiella* spp. (13). At present, the role of other microorganisms, remains open to debate, with the possibility that the actual pathogens responsible for prostatic or urogenital infection are not being reliably identified by current microbiological techniques (Table 1).

Another area relating to chronic bacterial prostatitis for which there is no clear consensus involves the precise role played by Gram-positive bacteria in causing infection. This is shown by re-

Table 1. Pathogens associated with chronic bacterial prostatitis

Aetiologically recognised microorganisms (mostly uropathogens)	Pathogens remaining controversial
Escherichia coli	Coagulase-negative staphylococci
Klebsiella spp.	Streptococci
Proteus mirabilis	*Corynebacterium* spp.
Pseudomonas aeruginosa	*Chlamydia trachomatis*
Other Gram-negative bacteria	Genital mycoplasma
Enterococcus faecalis	Anaerobic bacteria
Staphylococcus aureus	Yeasts
	Herpes simplex virus 1 and 2
	Trichomonas vaginalis

ports published during the last decade which have identified a substantial increase in the presence of Gram-positive organisms, increasing from 23–40% (13, 14) to 81.5–85.0% (15). The question arising from this changing epidemiological data is whether chronic bacterial prostatitis is moving from a predominantly Gram-negative to a Gram-positive infection. Several studies have argued that the role of Gram-positive pathogens is increasing, while other researchers continue to raise doubts about the actual pathogenicity of Gram-positive bacteria in prostatic infection. The difficulty in assigning actual causation to the bacteria identified is highlighted in a recent study by Krieger et al. (16). In this investigation the four-glass test was used to identify pathogens in 470 men with chronic bacterial prostatitis. Results showed that Gram-positive bacteria were identified in 6% of patients, while Gram-negative bacteria were identified in 7%. Of greater relevance were the results from 49 untreated men who underwent two to four repeated four-glass tests. Of these, 20 had repeatedly negative results and 29 had at least one Gram-positive test. Further analysis of this latter group demonstrated no consistent localisation of Gram-positive bacteria in 27 (94%) of the patients. These results suggest that, in the majority of tests, the localisation of Gram-positive bacteria is not reproducible and, therefore, the involvement of these specific pathogens in chronic bacterial prostatitis remains unclear. Researchers concluded that these results were consistent with the findings that Gram-positive microorganisms are rarely identified in prostate biopsy tissue taken from patients with symptoms of chronic prostatitis.

Other pathogens have been implicated in chronic bacterial prostatitis, including *Chlamydia trachomatis* and *Mycoplasma* spp., although the role of these pathogens remains controversial. In order to clarify this, a recent systematic review investigated the role of *Ureaplasma urealyticum* and/or *C. trachomatis* in these infections. Results from this review demonstrated that detection of these by pathogens using the four-glass test did not show that they were actually responsible for causing chronic prostatitis or chronic pelvic pain syndrome (17). Researchers concluded that because these two microorganisms can reside in the urethra, and since prostatic secretions must pass through this site, currently available microbiological techniques are unable to provide accurate data on these organisms. Therefore, the presence of these organisms may not indicate prostatic infection but, rather, the presence of urethritis.

Fluoroquinolone-based treatment

Due to the need to provide rapid antibacterial treatment and the difficulty in ensuring reliable diagnosis, the great majority of bacterial prostatitis cases are treated empirically. Therefore, antibiotic agents prescribed for these patients need to possess a broad spectrum of activity against both Gram-positive and Gram-negative bacteria. In this situation, the fluoroquinolones have risen to prominence. They possess a broad antibacterial spectrum and favourable pharmacokinetic properties, with excellent penetration and accumulation in prostatic tissue and fluids compared with β-lactam antibiotics (18, 19) and high urinary excretion (20). These features have resulted in the fluoroquinolones being recommended by many professional bodies as the drugs of choice in chronic bacterial prostatitis. These include the 2006 European Association of Urology Guidelines on the Management of Urinary and Male Genital Tract Infections (21). Among the fluoroquinolones, levofloxacin stands out as possessing particular strengths in managing urogenital tract infections. Results from a study in which a single dose of levofloxacin 250 mg and ciprofloxacin 250 mg was administered concomitantly to volunteers demonstrated that both the plasma concentration and prostatic fluid penetration were significantly higher for levofloxacin (Table 2) (22). These results are supported by other studies and the exceptional pharmacokinetics of levofloxacin provide it with advantages over other fluoroquinolones when treating bacterial prostatitis (19).

Further evidence supporting the usefulness of levofloxacin in managing these infections was provided by a multicenter, randomised, double-blind clinical trial which compared the safety and efficacy of levofloxacin versus ciprofloxacin (15). A total of 377 patients with a history of chronic bacterial prostatitis and current clinical signs and symptoms were randomised to receive levofloxacin 500 mg once daily (n = 197) or ciprofloxacin 500 mg twice daily (n = 180) for 28 days. Analysis of the intent-to-treat group demonstrated that the clinical response rate, defined as clinical cure (all signs and symptoms resolved or remitted to base-

Table 2. Median concentrations of levofloxacin and ciprofloxacin in plasma and prostatic fluid 3-hours post-administration of a single 250 mg dose in healthy volunteers

Body fluid concentration (mg/l)	Levofloxacin 250 mg	Ciprofloxacin 250 mg
Plasma C_{max}	3.10	1.37[a]
Prostatic fluid	0.89	0.16[a]
Seminal fluid	3.25	2.59
Ejaculate	3.21	2.63

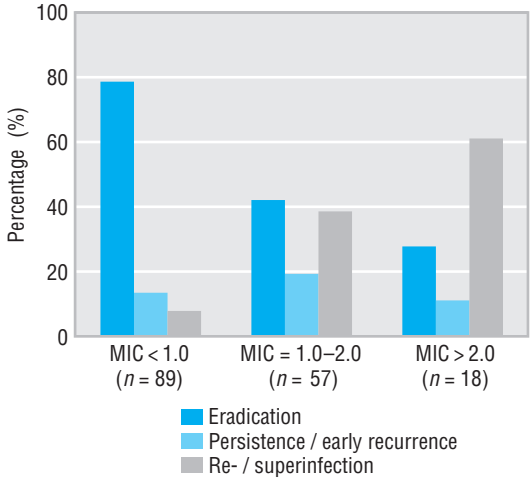
[a] $p < 0.05$ vs. levofloxacin.
Abbreviation: C_{max} = maximum serum drug concentration.
Adapted from reference (22).

Table 3. Post-therapy eradication rates following administration of levofloxacin 500 mg once daily or ciprofloxacin 500 mg twice daily for 28 days in men with chronic bacterial prostatitis

Pathogen	Levofloxacin (*n* = 136)		Ciprofloxacin (*n* = 125)	
	n	Eradicated (%)	*n*	Eradicated (%)
Escherichia coli	15	93.3	11	81.8
Enterococcus faecalis	54	72.2	45	75.6
Staphylococcus epidermidis	24	83.3	29	89.7
Staphylococcus haemolyticus	23	73.9	18	77.8
Streptococcus agalactiae	18	77.8	21	81.0
Streptococcus mitis	12	83.3	8	75.0
Coagulase-negative staphylococci	10	90.0	9	100.0
Overall susceptibility	—	94.7	—	90.6

Adapted from reference (15).

Figure 1. Minimum inhibitory concentrations of pathogens at 1 month after treatment with levofloxacin 500 mg once daily for 4 weeks



In case of (presumed) eradication or persistence/early recurrence: MIC of pathogens at baseline.
In case of re-/superinfection: MIC of pathogens up to 1 month after treatment.
Abbreviation: MIC = minimum inhibitory concentration.
Modified from reference (26).

line) plus clinical improvement (clear appreciated improvement in signs and symptoms) was 75.0% for levofloxacin vs. 72.8% for ciprofloxacin; 95% confidence interval (CI): –13.27–8.87. In addition, microbiologic eradication rates were similar for the two groups, being 75.0% for levofloxacin and 76.8% for ciprofloxacin; 95% CI: –8.98–12.58 (Table 3). Researchers concluded that using a once daily levofloxacin regimen was as effective as twice daily ciprofloxacin, both in terms of clinical and microbiological efficacy. Overall, the bacteriological eradication rates were similar to those reported for other fluoroquinolones, such as norfloxacin (23), ofloxacin (24) and ciprofloxacin (14, 25). Of added interest was the susceptibility data of 490 pathogens isolated at study entry. This revealed that significantly more organisms were susceptible to levofloxacin than ciprofloxacin (94.7 vs. 90.6%, respectively; $p < 0.001$).

Further evidence supporting the usefulness of levofloxacin in the urological setting is provided by results from an open-label, multicenter study carried out in 7 countries across Europe. This trial enrolled 117 patients with bacteriologically proven chronic bacterial prostatitis (median duration, 48 months) (26). Patients received levofloxacin 500 mg once daily for 28 days. The primary endpoint was microbiological efficacy at 1 month post-treatment. In addition to this, secondary endpoints included microbiological efficacy at 6 months and clinical response rates at 2 weeks of treatment and at 5–12 days, 1 month, 3 months, and 6 months post-treatment. Identification of 133 causative pathogens at baseline revealed 45.9% to be Gram-negative (27.1% *E. coli*) and 54.1% Gram-positive bacteria (13.5% *Enterococcus faecalis*, 10.5% *Staphylococcus epidermidis*). Microbiological eradication was achieved in 79% of patients at 1 month post-treatment follow-up, and this was maintained with 92% of these patients demonstrating sustained eradication at 6 months post-treatment follow-up. The correlation between minimal inhibitory concentrations (MICs) of levofloxacin on one side and eradication, persistence/early recurrence and re-/superinfection on the other side (Figure 1) showed a trend for the eradication to be higher for pathogens below 1 mg/l than for pathogens between 1–2 mg/l; re-/superinfecting pathogens had mainly MICs above 1 mg/l. This observation implies that high dosages may be more advantageous for the treatment of chronic bacterial prostatitis and could probably even be increased above the usually recommended dose of 500 mg once daily. In return, the length of treatment could probably be shortened, as has been shown for other indications, such as community-acquired pneumonia and acute pyelonephritis. When the dose was increased to 750 mg once daily, the duration could be shortened (27, 28).

Table 4. Clinical success rate post-treatment following administration of levofloxacin 500 mg once daily for 28 days

Assessment time-point post-treatment	Levofloxacin	
	Number of patients	Clinical success rate, patients (%; 95% CI)
Days 5–12	100	92 (92.0; 84.8–96.5)
1 month	106	82 (77.4; 68.2–84.9)
3 months	106	70 (66.0; 56.2–75.0)
6 months	105	65 (61.9; 51.9–71.2)

Abbreviation: CI = confidence interval.
Adapted from reference (26).

The clinical success rate is summarised in Table 4. Of interest is the fact that the long-term clinical success rate decreased over the 1–6 month post-therapy period, despite the excellent early results at days 5–12 following therapy. Therefore, bacterial prostatic infection may induce an, as yet undetermined, response in these patients, resulting in them becoming symptomatic again, despite earlier successful bacterial eradication. These results raise several interesting questions regarding the pathology of chronic bacterial prostatitis which require further investigation.

In regard to the safety analysis in this study (26), 15 patients (12.8%) reported adverse events, the majority being gastrointestinal (7 patients; 6.0%). Only in 6 of these 15 patients (5.1%) were the adverse drug reactions deemed to be possibly related to levofloxacin (3 patients with musculoskeletal and connective tissue disorders; 3 patients with gastrointestinal disorders). Treatment was discontinued in 4 patients (3.4%) due to adverse events. There was only one report of a serious adverse event (intestinal bleeding), and this was judged to be unrelated to the antimicrobial treatment.

Conclusion

It is imperative when managing a patient with suspected acute or chronic bacterial prostatitis that a clear and reliable diagnosis is made, which in the case of chronic disease requires a four- or two-glass test to be performed. Once the diagnosis has been made careful consideration should be given to likely pathogens and local susceptibility patterns before initiating empiric antibiotic therapy. Optimal management of acute bacterial prostatitis requires the initial administration of a broad spectrum antibiotic, which can then be tailored according to the results of sensitivity tests as they become available. When initiating antimicrobial therapy of chronic bacterial prostatitis, fluoroquinolones, in particular levofloxacin, remain the drugs of choice. This is due to their broad spectrum of antibacterial activity and favourable pharmacokinetic properties. Levofloxacin administered as a dose of 500 mg, once daily for 28 days, is effective and well tolerated, achieving results as good as ciprofloxacin 500 mg twice daily, but with significantly greater penetration into prostatic fluid. Levofloxacin should be considered as a drug of choice for treating chronic bacterial prostatitis, and this is well recognised in current international urological treatment guidelines (21).

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