Use of antibiotics in chronic prostatitis syndromes

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Chronic prostatitis is a common condition, with an incidence estimated at between 9%-14% of men worldwide. It is a medically controversial condition with significant attendant morbidity. According to a recent consensus report from the National Institutes of Health (NIH), chronic prostatitis patients fall into one of three categories: chronic bacterial prostatitis (category II prostatitis); chronic pelvic pain syndrome (category III prostatitis); or asymptomatic inflammation (category IV prostatitis). Prostatic tissues are best penetrated by drugs with a high pKa and high lipid solubility, such as quinolones, macrolides, tetracyclines, and sulfa drugs. Ciprofloxacin has been shown to be effective in the treatment of chronic bacterial prostatitis caused by Escherichla coli. The older quinolones demonstrate superiority against chronic bacterial prostatitis caused by gram-negative pathogens; the newer quinolones may be more effective against gram-positive pathogens and anaerobes. Despite continuing controversy, antimicrobial agents are the most common therapy employed in the treatment of chronic prostatitis. While some patients with nonbacterial (category III) prostatitis do improve with antibiotics, prolonged courses in the absence of documented infection or symptomatic improvement are not warranted. Prospective, randomized, placebo-controlled trials will hopefully lead to a clearer understanding of the role of antimicrobial agents in chronic bacterial prostatitis within the next year.

Key Words: prostatitis, antibiotic therapy, chronic pelvic pain syndrome

Introduction

Chronic prostatitis syndromes are among the most common and most poorly understood conditions in urology. Most urologists take a nihilistic attitude towards bacteriological localizing studies, since their primary (and often only) treatment modality for this condition is antibiotics.[1] This is despite the fact that roughly only 5% of these patients will grow established uropathogens in their prostatic fluid or urine. Many patients will improve with antibiotic therapy, however, which may be attributable to pathogens that are difficult to detect, or due to other effects of antibiotics. The purpose of this paper is to review the current literature on chronic prostatitis syndromes, with an emphasis on the potential role, uses and abuses of antibiotics in men with these difficult disorders.

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Epidemiology and classification

The incidence of chronic prostatitis has been estimated at between 9%-14% of men worldwide.[2,3] While considered a mild nuisance condition by many physicians, the impact of the disorder on quality of life is of similar magnitude to the impact of myocardial infarction or Crohn's disease.[4]

Since the initial work of Meares and Stamey in the late 1960s, prostatitis syndromes have been categorized according to the findings of a "four glass

test," based on inflammation and bacterial growth in the initial urine (VB1), midstream urine (VB2), expressed prostatic secretions (EPS), and post-massage urine (VB3).[5] Based on these results and the clinical presentation, patients could be classified as having urethritis, acute prostatitis, chronic bacterial prostatitis, chronic nonbacterial prostatitis or prostatodynia (Table 1). Unfortunately, the Meares-Stamey classification system has never been validated or shown to differentiate patients on the basis of prognosis or response to therapy. Indeed, fewer than 50% of recently surveyed urologists and primary care physicians even examine EPS, let alone perform the entire protocol.[6]

At a recent NIH consensus conference that was held on the subject of chronic prostatitis,[7] a new classification system proposed (Table 1). In the NIH classification, acute prostatitis is called category I, chronic bacterial prostatitis is category II, nonbacterial prostatitis is category IIIa and prostatodynia is category IIIb. Category III patients are now collectively referred to as having chronic pelvic pain syndrome (CPPS), which reflects both the predominance of pain in these patients and the uncertainty of the role of the prostate in producing the symptoms. A new category IV designates asymptomatic patients who have evidence for prostatic inflammation, either in the EPS or in prostate tissue biopsies. What constitutes inflammation by microscopy is controversial. While many authors use 10 WBCs per high-power field (hpf) as their upper limit of normal for EPS, this number has not been firmly established. Clearly, many patients with chronic prostatitis fluctuate between having low and high WBC counts over time,[8] and many asymptomatic patients have WBC counts in the abnormal range.

The spectrum of clinical symptoms is similar in patients with category II, IIIa and IIIb prostatitis. The chronic prostatitis syndromes are characterized by urogenital pain, often associated with voiding and erectile dysfunction. These symptoms may be continuous, intermittent or relapsing. Pain may be felt in the perineum, penis, scrotum, lower abdomen, back, or groin. Hematuria is rare, while hematospermia is more common. The primary symptom of these patients may be a feeling of relief after ejaculation, or severe post-ejaculatory pain. Age of onset is in late adolescence, with a median age of presentation in the mid- 40s. Onset may be gradual or sudden, but few patients have a history of prior acute prostatitis.

Category II prostatitis (chronic bacterial prostatitis)

Category II prostatitis is defined clinically as a patient with recurrent urinary tract infection (UTI) caused by bacteria that is localized to the prostate between episodes of infection. The laboratory definition is the presence of bacteria in the EPS and/or VB3 that is unique to these samples, or is at least present in significantly higher concentrations than what is found in VB1 or VB2. While some investigators insist on the clinical presentation of recurrent UTI to make the diagnosis of category II prostatitis, others feel that the

TABLE 1. **Classification systems for chronic prostatitis/chronic pelvic pain syndrome**

Acute UTI?	EPS/VB3 Culture	Elevated WBC in EPS or VB3?	Meares-Stamey Classification	NIH Classification	Comments
Yes	+	+	Acute Prostatitis	Category I	Urine culture sufficient to diagnose
No	+	+ or -	Chronic Bacterial	Category II	Some require recurrent UTI with uropathogens
No	-	+	Nonbacterial	Category IIa	WBC elevation may be intermittent
No	-	-	Prostatodynia	Category IIIb	Must rule out other pelvic pathology
No	+ or -	None	Category IV	Asymptomatic	

UTI: urinary tract infection EPS: expressed prostatic secretions VB3: post prostatic massage urine

identification of established uropathogens (eg. *E. coli*, enterococcus) localizing to the prostate in the presence of symptoms is sufficient. The most controversial patients are those who have bacteria that is localized to the prostate, but which are not considered typical uropathogens. These include gram- positive bacteria and anaerobes. Clearly, gram- positive bacteria such as coagulase- negative staphylococci can be found in the prostates of men with prostatitis, and they often are found within bacterial biofilms, which may hinder detection and treatment.[9,10] While some gram-positive bacteria may be harmless commensals, we have shown that many men with these bacteria in their EPS have associated elevated levels of oxidative stress, indicative of an active injury response.11 Furthermore, some of these men do have resolution of their symptoms with antibiotic therapy, which is also associated with sterilization of the prostate fluid and a decrease in oxidative stress. Other microorganisms—including ureaplasma, chlamydia and mycoplasma— have been found in the prostatic fluid and urethra of these men. A direct etiological role is yet to be proven, however.[12]

The hallmark of therapy for category II prostatitis is antibiotics. Because the "blood-prostate" barrier is intact in men with chronic prostatitis, antibiotics with a high pKa and high lipid solubility should be chosen. Classes of antibiotics with these features include the sulfas, quinolones, macrolides and tetracyclines.[13]

The most commonly used antibiotics in prostatitis are the quinolones. In a recent study by Weidner et al, 40 men diagnosed with chronic bacterial prostatitis were treated with ciprofloxacin (Cipro) for 4 weeks. Bacterial sterilization of the EPS was found in 92% of patients examined at 3 months, and in 80% of patients examined at 24 months.[14] Of note, no symptom outcome measure was reported. In a similar multicenter German study, 65 men with chronic bacterial prostatitis were treated for 4 weeks, and eradication of bacteria in EPS was found in 89% of patients at 1 month, which fell to 59% at 9 months.[15] The newer quinolones ofloxacin and levofloxacin have also been used in men with category II prostatitis, but detailed comparative studies are lacking.[16]

There has been a steady stream of newer quinolones, designed primarily to improve gram-positive and anaerobic coverage. We had excellent anecdotal experience with trovafloxacin in prostatitis, but the drug has been discontinued due to hepatic toxicity. The currently used "newer" quinolones are gatifloxacin (Tequin) and moxifloxacin (Avelox). While no published studies yet exist for their efficacy in prostatitis, their extended spectrum for gram-positive bacteria commonly found in these men is potentially appealing.[17] In patients with documented gram- negative infections, the "older" agents (ciprofloxacin, levofloxacin) should be used, as their minimum inhibitory concentrations (MICs) are superior for these bacteria.

Tetracyclines have a long history of moderate efficacy in bacterial prostatitis[18] with the added potential benefit of coverage for ureaplasma and chlamydia. Erythromycins have been used, as a result of their excellent penetration and coverage for common organisms seen in urethritis and prostatitis. Newer agents, such as clarithromycin[19] and azithromycin,[20] have documented prostatic penetration as well as the ability to penetrate bacterial biofilms.[21]

Regardless of the antibiotic chosen, a minimum course of therapy should be 4 weeks. Patients who do not respond after 4 weeks of therapy, however, should not be continued with long term therapy unless reculturing identifies bacteria.[13] Patients who improve, however, may require 8-12 weeks of therapy. Some men, particularly those with enlarged boggy prostates with large volumes of EPS, may benefit from regular prostatic massage combined with antibiotic therapy.[22,23] In patients with relapsing infections, a transrectal ultrasound may reveal prostatic calcification. While diffuse calcification along the surgical capsule of the prostate is a common finding in men with and without prostatitis and requires no therapy, larger stones located more centrally could represent a bacterial focus and these patients may benefit from transurethral resection of these stones. Patients with inefficient voiding and significant residual urine may benefit from combining antibiotics with an alpha blocker.[24] For men without an anatomic focus who have recurring prostatitis despite antibiotics with or without prostatic massage, longer courses of suppressive antibiotics may be necessary. For men on prolonged antibiotic therapy, it is important to be vigilant for complications that can occur with each class of agents, and to monitor for their occurrence (eg. tendon inflammation with quinolones, photosensitivity with tetracyclines).

Category III prostatitis (chronic pelvic pain syndrome)

The cause of category III prostatitis (nonbacterial prostatitis, prostatodynia, chronic pelvic pain syndrome) is unknown. Suggested etiologies for these disorders include occult infection, neurogenic voiding

dysfunction, an autoimmune or other inflammatory reaction, neuromuscular pelvic muscle spasm, or sterile urinary reflux into the prostate. Due to the similarities in symptoms with bacterial prostatitis, an occult infection with difficult to culture or entrapped microorganisms has been suspected. Indeed, most physicians "vote with their feet" for this possibility, as antibiotics are often the first and only therapies offered these men.[1]

There is clear evidence for the presence of bacteria in the prostates of men with category III prostatitis. Careful cultures of EPS will often show growth of gram- positive organisms such as staphylococcus epidermidis or *Corynebacteria,* and transperineal biopsies will often grow bacteria not found by other means.[25] As mentioned before, these bacteria may escape detection because they are protected within biofilms in the prostatic tissue.[10] We have used 16S ribosomal RNA (rRNA) techniques to detect bacterial signal in prostatic fluid of men with negative cultures and we demonstrated that presence of bacterial signal by this technique predicted response to empiric antibiotic therapy.[26,27] The key question that remains is whether these bacteria represent pathogens whose eradication would cure the clinical syndrome, or whether changes in the microenvironment of the prostates of men with CPPS promote the growth of otherwise harmless commensals.

Given that antibiotics are the most common therapy in CPPS, one would assume that properly designed clinical trials would have been done long ago to prove this point. There is actually no data yet published in the literature to support this contention. There are two recently completed studies, both currently in press, that address this issue and I am grateful to the lead authors of both studies for allowing me to summarize their findings here.

Nickel et al performed a multicenter study of 102 patients with prostatitis (II, IIIa and IIIb) who were treated with 12 weeks of ofloxacin. Overall, 57% of the patients felt moderate to marked improvement. Perhaps most surprisingly, there was no difference in response by culture results, anti-bacterial antibody status, or WBC count. In addition, no patient who was not improved by 4 weeks of therapy had a positive response in the subsequent 8- week course. Several interpretations are possible. Since there was no placebo control group, this may represent a placebo effect detected equally in all patients. It may mean that with or without positive cultures, 57% of men with prostatitis symptoms have true infections that can be treated by antibiotics. If most men with CPPS have true infections, however, it is unclear why such a large proportion of men fail antibiotic therapy, even when it is combined with prostatic massage or alpha blockers. It also does not explain the anecdotal finding of improvement in symptoms seen with corticosteroids or full immunosuppression,[28] which theoretically should make infection worse. Finally, the antibiotics may be helping by a mechanism completely independent of their antimicrobial effects. Antibiotics such as quinolones, tetracyclines and macrolides have direct anti-inflammatory properties in the absence of infection, blocking cytokines such as interleukin-1 (IL-1), IL-8 and tumor necrosis factor (TNF),[29-31] which coincidentally are the same cytokines found to be elevated in the semen and EPS of men with prostatitis.[32,33]

Recently, Dimitrakov et al performed a double blind, placebo- controlled trial using 6 weeks of ciprofloxacin treatment for men with category IIIb prostatitis. Men were excluded from the study if they had positive bacterial signal by 16S rRNA analysis. There was no difference in symptomatic improvement between the 100 men on ciprofloxacin and the 100 on placebo at 6 weeks, 6 months or 18 months. Significantly, 65% of men in the ciprofloxacin group had drug- related side effects vs 9% for placebo. This study supports the use of molecular techniques to exclude patients who have minimal chance for success with antibiotic therapy.

Category IV prostatitis (asymptomatic)

The two most common presentations of category IV prostatitis are leukospermia associated with infertility and elevated prostate-specific antigen (PSA) in the absence of cancer or significant benign prostatic hyperplasia (BPH). Leukospermia has traditionally been treated with antibiotics, and while resolution of the high WBC count is often achieved,[34] a positive impact on fertility is less common.[35] In patients with elevated PSA and symptoms consistent with prostatitis, many doctors will treat with antibiotics and recheck the PSA before doing a biopsy. Recently, Potts et al prospectively studied men with elevated PSAs and treated those with inflammation in EPS or VB3 with 4 weeks of antibiotics.[36] They found that 53% of men with inflammation had a normal PSA following therapy. Of the remaining patients whose PSA did not normalize, 31% had cancer.

Conclusion

Antibiotics remain the mainstays of therapy for all chronic prostatitis syndromes, although clear scientific

evidence for their efficacy is lacking. For patients with category II prostatitis, antibiotics can usually sterilize the prostate, however symptoms may remain and recurrences are common. Many patients with category III prostatitis who are treated with antibiotics will improve, but whether this is due to cryptic, undetected bacteria or to other effects of the antibiotics is unknown. Fortunately, the clinical efficacy of antibiotics is finally being studied in placebo-controlled trials, which should confirm or refute common prescribing practices in the near future. □

References

1. McNaughton Collins M, Fowler FJ Jr, Elliott DB, Albertsen PC, Barry MJ. Diagnosing and treating chronic prostatitis: do urologists use the four-glass test? *Urology* 2000;55(3):403.
2. Mehik A, Hellstrom P, Lukkarinen O, Sarpola A, Jarvelin M. Epidemiology of prostatitis in Finnish men: a population-based cross- sectional study. *BJU Int* 2000;86(4):443.
3. Roberts RO, Lieber MM, Rhodes T, Girman CJ, Bostwick DG, Jacobsen SJ. Prevalence of a physician-assigned diagnosis of prostatitis: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. *Urology* 1998;51(4):578.
4. Wenninger K, Heiman JR, Rothman I, Berghuis JP, Berger RE. Sickness impact of chronic nonbacterial prostatitis and its correlates. *J Urol* 1996;155(3):965.
5. Meares EM, Stamey TA. Bacteriologic localization patterns in bacterial prostatitis and urethritis. *Invest Urol* 1968;5(5):492.
6. Moon TD. Questionnaire survey of urologists and primary care physicians' diagnostic and treatment practices for prostatitis. *Urology* 1997;50(4):543.
7. Nickel JC, Nyberg LM, Hennenfent M. Research guidelines for chronic prostatitis: consensus report from the first National Institutes of Health International Prostatitis Collaborative Network. *Urology* 1999;54(2):229.
8. Wright ET, Chmiel JS, Grayhack JT, Schaeffer AJ. Prostatic fluid inflammation in prostatitis. *J Urol* 1994;152(6 Pt 2):2300.
9. Nickel JC, Costerton JW. Coagulase-negative staphylococcus in chronic prostatitis. *J Urol* 1992;147(2):398.
10. Nickel JC, Costerton JW, McLean RJ, Olson M. Bacterial biofilms: influence on the pathogenesis, diagnosis and treatment of urinary tract infections. *J Antimicrob Chemother* 1994;33(Suppl A):31.
11. Shahed AR, Shoskes DA. Oxidative stress in prostatic fluid of patients with chronic pelvic pain syndrome: correlation with gram positive bacterial growth and treatment response. *J Androl* 2000;21(5):669.
12. Ohkawa M, Yamaguchi K, Tokunaga S, Nakashima T, Shoda R. Antimicrobial treatment for chronic prostatitis as a means of defining the role of Ureaplasma urealyticum. *Urol Int* 1993;51(3):129.
13. Bjerklund Johansen TE, Gruneberg RN, Guibert J et al. The role of antibiotics in the treatment of chronic prostatitis: a consensus statement. *Eur Urol* 1998;34(6):457.
14. Weidner W, Ludwig M, Brahler E, Schiefer HG. Outcome of antibiotic therapy with ciprofloxacin in chronic bacterial prostatitis. *Drugs* 1999;58(Suppl 2):103.
15. Naber KG, Busch W, Focht J. Ciprofloxacin in the treatment of chronic bacterial prostatitis: a prospective, non-comparative multicentre clinical trial with long-term follow-up. The German Prostatitis Study Group. *Int J Antimicrob Agent*s 2000;14(2):143.
16. Tunkel AR, Scheld WM. Ofloxacin. Infect Control Hosp *Epidemiol* 1991;12(9):549.
17. Ball P. Moxifloxacin (Avelox): an 8-methoxyquinolone antibacterial with enhanced potency. *Int J Clin Pract* 2000;54(5):329.
18. Paulson DF, Zinner NR, Resnick MI, Childs SJ, Love T, Madsen PO. Treatment of bacterial prostatitis. Comparison of cephalexin and minocycline. *Urology* 1986;27(4):379.
19. Giannopoulos A, Koratzanis G, Giamarellos-Bourboulis EJ, Panou C, Adamakis I, Giamarellou H. Pharmacokinetics of clarithromycin in the prostate: implications for the treatment of chronic abacterial prostatitis. *J Urol* 2001;165(1):97.
20. Chiarini F, Mansi A, Tomao P et al. Chlamydia trachomatis genitourinary infections: laboratory diagnosis and therapeutic aspects. Evaluation of in vitro and in vivo effectiveness of azithromycin. *J Chemother* 1994;6(4):238.
21. Yasuda H, Ajiki Y, Koga T, Yokota T. Interaction between clarithromycin and biofilms formed by Staphylococcus epidermidis. *Antimicrob Agents Chemother* 1994;38(1):138.
22. Nickel JC, Alexander R, Anderson R et al. Prostatitis unplugged? Prostatic massage revisited. *Tech Urol* 1999;5(1):1.
23. Shoskes DA, Zeitlin SI. Use of prostatic massage in combination with antibiotics in the treatment of chronic prostatitis. *Prostate Cancer and Prostate Diseases* 1999;2(3):159.
24. Barbalias GA, Nikiforidis G, Liatsikos EN. Alpha-blockers for the treatment of chronic prostatitis in combination with antibiotics. *J Urol* 1998;159(3):883.
25. Berger RE, Krieger JN, Rothman I, Muller CH, Hillier SL. Bacteria in the prostate tissue of men with idiopathic prostatic inflammation. *J Urol* 1997;157(3):863.
26. Tanner MA, Shoskes D, Shahed A, Pace NR. Prevalence of Corynebacterial 16S rRNA Sequences in Patients with Bacterial and "Nonbacterial" Prostatitis. *J Clin Microbiol* 1999;37(6):1863.
27. Shoskes DA, Shahed AR. Detection of bacterial signal by 16S rRNA polymerase chain reaction in expressed prostatic secretions predicts response to antibiotic therapy in men with chronic pelvic pain syndrome. *Tech Urol* 2000;6(3):240.
28. Palapattu GS, Shoskes DA. Resolution of the Chronic Pelvic Pain Syndrome after Renal Transplantation. *J Urol* 2000;164(1):127.
29. Aoki Y, Kao PN. Erythromycin inhibits transcriptional activation of NF-kappaB, but not NFAT, through calcineurin-independent signaling in T cells. *Antimicrob Agents Chemother* 1999;43(11):2678.
30. Galley HF, Nelson SJ, Dubbels AM, Webster NR. Effect of ciprofloxacin on the accumulation of interleukin-6, interleukin-8, and nitrite from a human endothelial cell model of sepsis. *Crit Care Med* 1997;25(8):1392.
31. Yoshimura T, Kurita C, Usami E et al. Immunomodulatory action of levofloxacin on cytokine production by human peripheral blood mononuclear cells. *Chemotherapy* 1996;42(6):459.
32. Alexander RB, Ponniah S, Hasday J, Hebel JR. Elevated levels of proinflammatory cytokines in the semen of patients with chronic prostatitis / chronic pelvic pain syndrome. *Urology* 1998;52(5):744.
33. Nadler RB, Koch AE, Calhoun EA et al. IL-1beta and TNF-alpha in prostatic secretions are indicators in the evaluation of men with chronic prostatitis. *J Urol* 2000;164(1):214.
34. Branigan EF, Muller CH. Efficacy of treatment and recurrence rate of leukocytospermia in infertile men with prostatitis. *Fertil Steril* 1994;62(3):580.
35. Comhaire FH, Rowe PJ, Farley TM. The effect of doxycycline in infertile couples with male accessory gland infection: a double blind prospective study. *Int J Androl* 1986;9(2):91.
36. Potts JM. Prospective identification of national institutes of health category iv prostatitis in men with elevated prostate specific antigen. *J Urol* 2000;164(5):1550.