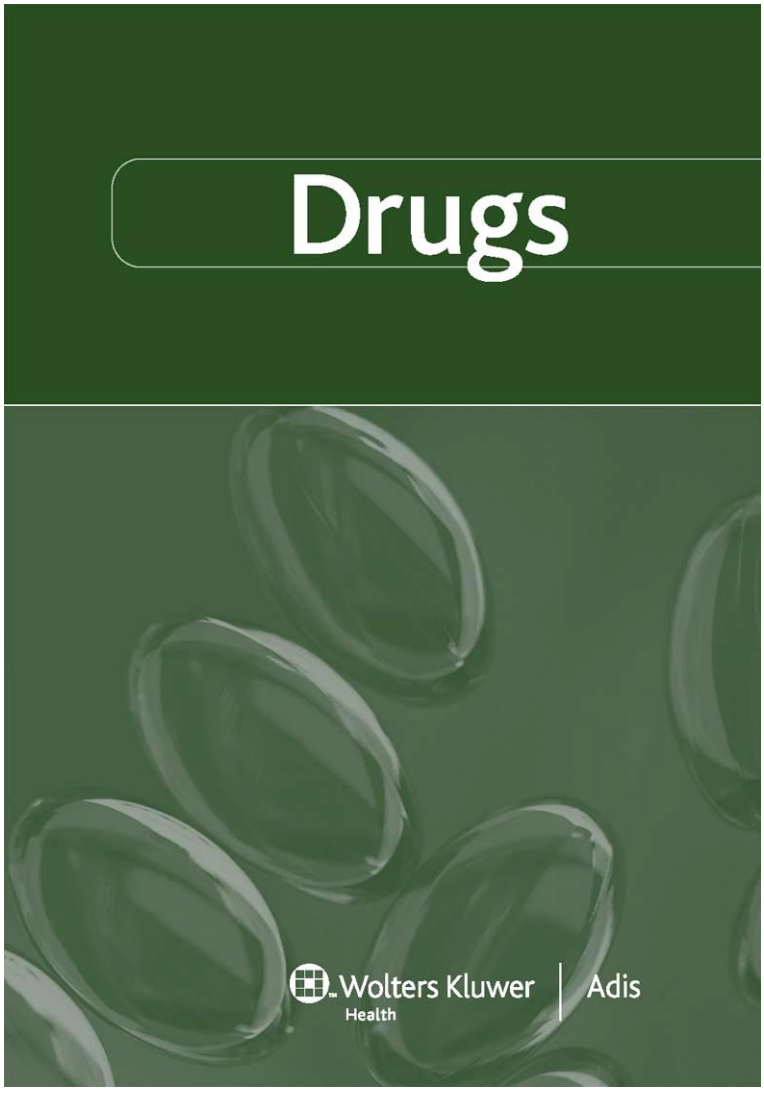

Drugs 2009; 69 (1): 71-84
0012-6667/09/0001-0071/$55.55/0

Chronic Prostatitis
Management Strategies

Adam B. Murphy, Amanda Macejko, Aisha Taylor and *Robert B. Nadler*

Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Contents

Abstract

The National Institutes of Health (NIH) has redefined prostatitis into four distinct entities. Category I is acute bacterial prostatitis. It is an acute prostatic infection with a uropathogen, often with systemic symptoms of fever, chills and hypotension. The treatment hinges on antimicrobials and drainage of the bladder because the inflamed prostate may block urinary flow. Category II prostatitis is called chronic bacterial prostatitis. It is characterized by recurrent episodes of documented urinary tract infections with the same uropathogen and causes pelvic pain, urinary symptoms and ejaculatory pain. It is diagnosed by means of localization cultures that are 90% accurate in localizing the source of recurrent infections within the lower urinary tract. Asymptomatic inflammatory prostatitis comprises NIH category IV. This entity is, by definition, asymptomatic and is often diagnosed incidentally

during the evaluation of infertility or prostate cancer. The clinical significance of category IV prostatitis is unknown and it is often left untreated. Category III prostatitis is called chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). It is characterized by pelvic pain for more than 3 of the previous 6 months, urinary symptoms and painful ejaculation, without documented urinary tract infections from uropathogens. The syndrome can be devastating, affecting 10–15% of the male population, and results in nearly 2 million outpatient visits each year. The aetiology of CP/CPPS is poorly understood, but may be the result of an infectious or inflammatory initiator that results in neurological injury and eventually results in pelvic floor dysfunction in the form of increased pelvic muscle tone. The diagnosis relies on separating this entity from chronic bacterial prostatitis. If there is no history of documented urinary tract infections with a urinary tract pathogen, then cultures should be taken when patients are symptomatic. Prostatic localization cultures, called the Meares-Stamey 4 glass test, would identify the prostate as the source for a urinary tract infection in chronic bacterial prostatitis. If there is no infection, then the patient is likely to have CP/CPPS.

For healthcare providers, the focus of therapy is symptomatic relief. The first therapeutic measure is often a 4- to 6- week course of a fluoroquinolone, which provides relief in 50% of men and is more efficacious if prescribed soon after symptoms begin. Second-line pharmacotherapy involves anti-inflammatory agents for pain symptoms and α-adrenergic receptor antagonists (α-blockers) for urinary symptoms. Potentially more effective is pelvic floor training/biofeedback, but randomized controlled trials are needed to confirm this. Third-line agents include 5α-reductase inhibitors, glycosaminoglycans, quercetin, cernilton (CN-009) and saw palmetto. For treatment refractory patients, surgical interventions can be offered. Transurethral microwave therapy to ablate prostatic tissue has shown some promise.

The treatment algorithm provided in this review involves a 4- to 6- week course of antibacterials, which may be repeated if the initial course provides relief. Pain and urinary symptoms can be ameliorated with anti-inflammatories and α-blockers. If the relief is not significant, then patients should be referred for biofeedback. Minimally invasive surgical options should be reserved for treatment-refractory patients.

1. Chronic Prostatitis

Prostatitis is a common cause of physician visits, accounting for 8% of visits to urologists.[1] The syndrome affects 2–16%[2-4] of men amounting to nearly 2 million outpatient visits per year in the US.[5] The prostatitis syndromes are diagnosed based on history and physical examination, but there are no specific physical findings or diagnostic laboratory tests. Moreover, there is limited understanding of the pathophysiology and optimal treatment for most patients.[6] In an attempt to improve treatment strategies and classify the syndrome to aid in future research, a panel of leading experts in prostatitis convened to develop the NIH consensus panel on redefining prostatitis. The NIH Chronic Prostatitis Symptom Index (NIH-CPSI) has become the established international standard for non-diagnostic symptom evaluation of prostatitis.[7] The index has been shown to be reliable, with validated versions in different countries. Results

Table I. National Institutes of Health (NIH) consensus definition and classification of prostatitis[10]

NIH classification	Definition
Category I – acute bacterial prostatitis	Acute infection of the prostate gland
Category II – chronic bacterial prostatitis	Recurrent infection of the prostate
Category IIIA – inflammatory CPPS	White cells in semen/EPS/VB3 (VB3 or post-prostatic massage)
Category IIIB – non-inflammatory CPPS	No white cells in semen/EPS/VB3
Category IV – asymptomatic inflammatory prostatitis	Abnormal semen analysis Elevated PSA values Incidental findings in biopsied prostate

CPPS = chronic pelvic pain syndrome; **EPS** = expressed prostatic secretions; **PSA** = prostate-specific antigen; **VB3** = voided bladder urine culture 3.

from numerous studies indicate that the NIH-CPSI total score, but not the subscales, show high internal consistency, can evaluate the severity of current symptoms and may be used as an outcome measure to evaluate the longitudinal course of symptoms with time or treatment.[8,9]

Prostatitis is now described by the NIH consensus classification of prostatitis syndromes as the following four distinct clinical entities (see table I).[10] Acute and chronic bacterial prostatitis syndromes represent the best understood, but least common, prostatitis syndromes; comprising 5–10% of symptomatic prostatitis. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) comprises 90–95% of prostatitis syndromes.[11]

1.1 Category I: Acute Bacterial Prostatitis

Acute bacterial prostatitis (ABP) patients present with acute symptoms of a urinary tract infection, such as urinary frequency, pelvic pain and painful urination. Many patients are acutely ill and have symptoms suggestive of systemic infection, such as malaise, fever and chills.[12] The presence of bacteria and white blood cells in the urine, termed bacteriuria and pyuria, are related to the infection of the prostate and bladder caused by uropathogenic bacteria, most commonly *Escherichia coli*.[13] The evaluation should involve a trans-abdominal ultrasound or bladder scan to assess for the volume of retained urine. Bladder outlet obstruction can be caused by the inflamed prostate. The physical exam does not involve a digital rectal/prostate exam because of the risk of causing severe pain and bacteraemia from manipulation of the infected prostate. Treatment involves antimicrobials and urinary drainage as patients may have obstructed urine flow as a result of prostatic inflammation.[14] Failure to clinically improve should prompt pelvic imaging (CT scan or MRI) to evaluate for the possibility of an abscess in the prostate, which would require drainage. Approximately 5% of men affected with ABP develop chronic bacterial prostatitis.[15]

1.2 Category II: Chronic Bacterial Prostatitis

Patients with chronic bacterial prostatitis experience recurrent episodes of bacterial urinary tract infection caused by the same organism, usually *E. coli*, other Gram-negative organisms or enterococci. The key to the diagnosis is isolating a uropathogen (a bacteria capable of infecting the urinary tract), which is present in higher concentrations in the prostate.[12] During a symptomatic infection, the bladder is also infected. About 25–43% of the time, patients present with a recurrent urinary tract infection; this infection should be treated with a non-prostate penetrating antibacterial such as nitrofurantoin or a β-lactam.[2] Between symptomatic episodes, the Meares-Stamey localization cultures (see figure 1) of the lower urinary tract can be used to document an infected prostate gland as the focus of these recurrent infections.[17] In 1991, Weidner and Schiefer[18] only found significant bacteriuria with uropathogens in 4.4% of patients with chronic prostatitis symptoms. Because recurrent infections could be caused by coexisting conditions, such as

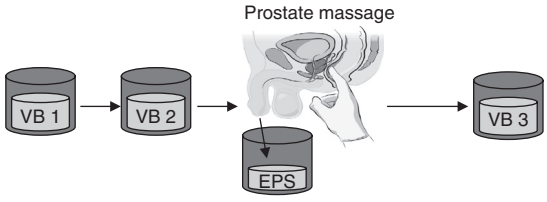

Fig. 1. Meares-Stamey 4 glass test. Each of the samples is collected during a urination with a prostatic massage to express fluid from the prostate after voided bladder 2 (VB2) is collected. The first 10mL of voided urine (VB1) represents the urethral flora. After 150–200mL of urine is voided, the midstream urine culture is collected (VB2), which represents the bladder flora. Following VB2, the physician performs the prostatic massage to collect expressed prostatic secretions (EPS). The EPS and the first voided 10mL after massage (VB3) are then collected and sent for culture and microscopic analysis. A positive finding for category II bacterial prostatitis includes a cultured colony count in the EPS or VB3 specimen greater than the VB1 and VB2 specimens by a factor of 10 or more. The 2 glass test utilizes only VB2 and VB3 with reasonable sensitivity.[16]

urinary tract stones, anatomical abnormalities and a poorly emptying bladder, a CT scan and measurement of residual urine after voiding should be performed.[6]

1.3 Category III: Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

The focus of this review is on CP/CPPS. CP/CPPS has not been scientifically demonstrated to be primarily either a disease of the prostate or the result of an inflammatory process.[19] The disease is named to recognize the limited understanding of the aetiologies of this syndrome for most patients and the possibility that organs other than the prostate gland may be important in the cause of this syndrome.[17] The new consensus definition recognizes genitourinary pain complaints as a primary component of this syndrome and includes several exclusion criteria, such as presence of active urethritis, urogenital cancer, urinary tract disease, urethral stricture or neurological disease affecting the bladder. Pain is the most prevalent symptom followed by urinary symptoms and sexual dysfunction.[20]

CP/CPPS can be categorized as inflammatory (IIIA) or non-inflammatory (IIIB), depending on the presence or absence of leukocytes in the collected expressed prostatic secretions and the subsequent urine sample collected. Category IIIA corresponds to the traditional classification of chronic nonbacterial prostatitis and category IIIB is comparable with the traditional classification of CPPS.[21] Patients with the inflammatory subtype of CP/CPPS (category IIIA) have leukocytes in their expressed prostatic secretions or post-prostate massage urine. In contrast, patients with the non-inflammatory subtype (category IIIB) have no evidence of inflammation, but the symptoms of CP/CPPS IIIA and IIIB are indistinguishable.

Because the focus of therapy for CP/CPPS is in symptom improvement, an expert panel developed the NIH-CPSI (see figure 2). It is a 9-item questionnaire scored in three domains: pain, urinary symptoms and quality of life (QOL) impact.[6] The NIH-CPSI has been validated and is used to monitor patient responses to interventions.[7]

1.4 Category IV: Asymptomatic Inflammatory Prostatitis

Asymptomatic inflammatory prostatitis (AIP) is diagnosed in patients who have no history of genitourinary tract pain complaints. Such patients often present to urologists because of elevated prostate specific antigen (PSA) and undergo a prostate biopsy to evaluate for prostate cancer.[14] Men with AIP can also be diagnosed while undergoing evaluation for infertility, where microscopic examination of expressed prostatic fluid reveals >10 leukocytes per high-power field, but the urine culture is negative.[19] Because these men are asymptomatic by definition, this entity is largely untreated and has an unknown clinical significance.[13,14]

1.5 Presentation of CP/CPPS

Men with CP/CPPS present with a variety of symptoms. Largely, they present with pelvic pain without evidence of urinary tract infection. The pain is in the perineum, rectum, prostate, penis, testicles and abdomen.[7] There are often symptoms of urinary obstruction (e.g. weak stream, straining) or lower urinary tract irritative symptoms (e.g. frequent or urgent urination), similar

NIH Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	☐ 1	☐ 0
b. Testicles	☐ 1	☐ 0
c. Tip of the penis (not related to urination)	☐ 1	☐ 0
d. Below your waist, in your pubic or bladder area	☐ 1	☐ 0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	☐ 1	☐ 0
b. Pain or discomfort during or after sexual climax (ejaculation)?	☐ 1	☐ 0

3. How often have you had pain or discomfort in any of these areas over the last week?

☐ 0 Never
☐ 1 Rarely
☐ 2 Sometimes
☐ 3 Often
☐ 4 Usually
☐ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

NO PAIN PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

☐ 0 Not at all
☐ 1 Less than 1 time in 5
☐ 2 Less than half the time
☐ 3 About half the time
☐ 4 More than half the time
☐ 5 Almost always

6. How often have you had to urinate again less than 2 hours after you finished urinating, over the last week?

☐ 0 Not at all
☐ 1 Less than 1 time in 5
☐ 2 Less than half the time
☐ 3 About half the time
☐ 4 More than half the time
☐ 5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

☐ 0 None
☐ 1 Only a little
☐ 2 Some
☐ 3 A lot

8. How much did you think about your symptoms, over the last week?

☐ 0 None
☐ 1 Only a little
☐ 2 Some
☐ 3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

☐ 0 Delighted
☐ 1 Pleased
☐ 2 Mostly satisfied
☐ 3 Mixed (about equally satisfied and dissatisfied)
☐ 4 Mostly dissatisfied
☐ 5 Unhappy
☐ 6 Terrible

Scoring the NIH Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3 and 4 =
Urinary Symptoms: Total of items 5 and 6 =
Quality-of-Life Impact: Total of items 7, 8, and 9 =

Fig. 2. National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI).[7]

to the symptom complex of benign prostatic hyperplasia (BPH). Sexual dysfunction often occurs and includes painful ejaculation, premature ejaculation or erectile dysfunction.[12] While most men experience stability of their symptoms, some experience variability in symptom severity. CP/CPPS is also associated with infertility.[6] Prostatitis, specifically in its chronic form, can be physically and psychologically devastating, diminishing the QOL of those affected. The QOL for a patient with CP/CPPS is similar to that experienced by patients with acute myocardial

infarction, unstable angina pectoris or active Crohn's disease.[2] Studies of the CP/CPPS cohort showed that the symptom severity decreases with time in most men and one-third of patients will have marked improvement in symptom severity.[22]

Of all NIH-CPSI symptoms, urinary frequency was associated with the least favourable QOL, followed by incomplete bladder emptying, pain frequency and pain intensity. The aforementioned CP/CPPS symptoms have a greater detrimental effect on QOL than pain symptoms and should represent the main therapeutic targets in affected patients.[23]

1.6 Epidemiology of CP/CPPS

Approximately 8.2% of men have prostatitis at some point in their lives. Estimates range from 2.2% to 16% in population-based studies.[1-3,21,24,25] Unlike prostate cancer and BPH, which affects elderly males, chronic prostatitis affects adult men of all ages.[3] Prostatitis-like symptoms occurred in 11.5% of men aged <50 years and in 8.5% of men aged ≥50 years.[2] Those with a history of prostatitis and sexually transmitted diseases also had an age-related increased risk of recurrent episodes.[5,25,26] Increased frequency of physical and sexual activity have been shown to be protective in African Americans.[26] Studies have also shown a substantial cost associated with prostatitis, with direct costs of care of $US4000 per patient per year (year 2004 value).[5]

1.7 Pathophysiology of CP/CPPS

The aetiology of CP/CPPS is inconclusive but several mechanisms have been proposed, including infectious, autoimmune, neurological and psychiatric diseases.[27] By definition, CP/CPPS is not infectious. However, Schaeffer et al.[28] reported findings using polymerase chain reaction to suggest that patients with CP/CPPS have a variety of bacterial DNA-encoding sequences, despite repeated negative culture results. This suggests the presence of a difficult-to-culture bacterium as the aetiological agent, similar to the role played by *Helicobacter pylori* in peptic ulcer disease. However, a case-controlled study found no difference in the rate of positive prostatic localization cultures between men with CP/CPPS and asymptomatic men.[29] This would imply that the bacteria are not the cause of the CP/CPPS symptoms, but it is unclear if there were differences in the virulence or infectious capability of the bacteria between asymptomatic men and the men with CP/CPPS.

Because of its similarity to interstitial cystitis, several authors speculate that CP/CPPS is not likely to be an organ-specific syndrome, but a urogenital manifestation of regional or systemic abnormalities.[19,30] The process may begin with an inciting agent (e.g. infection, dysfunctional voiding, trauma, autoimmune reaction) causing inflammation or neurological damage in and around the prostate (pelvic floor, bladder, perineum, etc.). If not effectively treated in the early stage, peripheral and then central sensitization could occur.[31] As a result, patients would develop pelvic floor neuromuscular dysfunction that may respond to targeted pelvic floor physical therapy.[19,32] The theory posits that once the CNS sensitization occurs, the patient enters a chronic neuropathic state. Because higher brain centres modulate pain and disability (depression, anxiety, coping mechanisms, etc.), cognitive behavioural therapy has been proposed as a treatment.[33]

Previously suggested risk factors include elevated cytokines and inflammation, abnormalities in bladder voiding function, androgen and estrogen imbalances, intra-prostatic reflux and psychological disturbances.[29,34-40] In a case-controlled study of men with CP/CPPS, other diseases seen at increased rates included non-specific urethritis, cardiovascular disease, neurological disease, psychiatric conditions, and hematopoietic, lymphatic or infectious diseases.[41] Studies are needed to discern whether these associated illnesses play a role in the aetiology of CP/CPPS.

1.8 Diagnosis

There is no gold standard for diagnostic testing for CP/CPPS.[27] The history of chronic pelvic pain in a man without documented infections supports the diagnosis of CP/CPPS. A history of

Table II. Interpretation of the Meares-Stamey 2 glass test (adapted from Nickel[44])

NIH category[a]	Pre-massage specimen (VB1/VB2)	Post-massage specimen (EPS/VB3)
Category II		
Microscopic evaluation	Possible WBCs	Has WBCs
Urine culture result	Possible positive culture with uropathogens	Negative culture
Category IIIA		
Microscopic evaluation	Possible WBCs	Has WBCs
Urine culture result	Negative culture	Positive culture with uropathogens
Category IIIB		
Microscopic evaluation	No WBCs	<10 WBCs per hpf
Urine culture result	Negative culture	Positive culture with uropathogens

a Category II chronic bacterial prostatitis can coexist with bacterial cystitis and VB1 and VB2 urine samples may contain WBCs and may also culture positive for uropathogenic bacteria. If confirmation of prostatitis is required, repeat after 3 days of nitrofurantoin or β-lactam therapy. The EPS and VB3 specimen should contain WBCs and uropathogenic bacteria. In category IIIA and IIIB, there should be no uropathogens growing in any of the specimens. On microscopic evaluation, the presence of ≥10 WBCs per hpf in EPS and VB3 defines category IIIA inflammatory chronic prostatitis/chronic pelvic pain syndrome.

EPS = expressed prostatic secretions; **hpf** = microscopic high power field; **WBCs** = white blood cells; **VB** = voided bladder.

recurrent or a recent urinary tract infection should raise suspicion for chronic bacterial prostatitis. In men with the potential for an infectious aetiology, the Meares-Stamey 4 glass or 2 glass tests are localization cultures used to differentiate CP/CPPS from chronic bacterial prostatitis and to sub-classify CP/CPPS into inflammatory (IIIA) and non-inflammatory (IIIB) types.[42] A positive Meares-Stamey localization culture would prompt a course of culture-specific antibacterials to treat chronic bacterial prostatitis.[16,43]

This localization culture technique can provide information on inflammation of the prostate (5–10 leukocytes per high-power field) to categorize type IIIA and IIIB (<5 leukocytes per high-power field),[44,45] but this subtyping does not alter management (see figure 1 for Meares-Stamey test description). The Meares-Stamey test can differentiate categories II, IIIA and IIIB with an accuracy exceeding 95%, simply on the basis of urinary white blood cell count and culture results (table II).[42] Chronic bacterial prostatitis is characterized by a history of symptomatic recurrent urinary tract infections documented by cultures with uropathogenic bacteria. If there was no documentation of positive urine cultures during symptomatic periods, microscopic analysis of the urine and urine culture should be obtained when the symptoms recur. The absence of positive urine culture with chronic pelvic pain, with or without obstructive or irritative voiding symptoms, supports the diagnosis of CP/CPPS. Confounding the diagnosis is the fact that up to 8% of men with presumed CP/CPPS and no history of positive urinary tract infections have positive prostate localization cultures. However, a similar number of asymptomatic men will also have positive localization cultures.[46]

Physical examination is non-specific for the diagnosis of CP/CPPS. However, abdominal ultrasound with examination can effectively rule out bladder distension from obstruction, and a digital rectal examination should be done to detect indurations or asymmetry as a screen for prostate cancer. A complete blood count and serum PSA are not clinically useful measures for CP/CPPS, although PSA elevations warrant further evaluation as it would in any situation.[29]

Imaging studies are usually low yield, but in men with painful ejaculation, a transrectal ultrasound may reveal an enlarged seminal vesicle, suggesting an obstructed ejaculatory duct. A recent case report by Nadler and Rubenstein[47] found that surgical removal of the enlarged seminal vesicle alleviated the patient's pain. The utility of transrectal ultrasonography has not been evaluated in this setting.

2. Treatment of CP/CPPS

There are non-curative but efficacious treatments for CP/CPPS. First-line pharmacotherapy includes antimicrobials, largely fluoroquinolones, and α-adrenergic receptor antagonists (α-blockers).[6] Second-line pharmacotherapy involves anti-inflammatories. Third-line pharmacotherapy includes 5α-reductase inhibitors, saw palmetto, quercetin, tricyclic antidepressants, phosphodiesterase inhibitors and glycosaminoglycans. There is only level III–IV evidence for the efficacy of third-line therapies. In general, these studies are small, uncontrolled studies with unclear enrolment protocols and non-validated outcomes. There are small, uncontrolled studies with unclear enrolment protocols and non-validated outcomes providing weak data for the efficacy of third-line approaches.[48]

2.1 Surgical Management

Surgical options are offered to often desperate, treatment-refractory patients. To ameliorate the symptoms, urologists have ablated prostate tissue via transurethral needle ablation (TUNA) of the prostate and transurethral microwave therapy. However, trials to evaluate TUNA did not show therapeutic efficacy.[31,49] Microwave therapy was evaluated in a small, randomized, sham-controlled study and showed benefit in treatment-refractory patients at 1 year with a 51% reduction in NIH-CPSI score.[50] Prostatectomies, surgical removal of the prostate, have largely been abandoned, as many men will have recurrent symptoms postoperatively.

2.2 Pelvic Floor Biofeedback

Recent studies suggest that the symptoms of CP/CPPS may be due to or associated with pelvic floor muscle dysfunction. Therapies aimed to improve relaxation and to teach proper use of the pelvic floor muscles, such as biofeedback physical therapy and pelvic floor re-education, could give symptomatic improvement.[51] In 2004, level IV evidence became available. A prospective, non-randomized, non-controlled study published in *European Urology*[51] involved 33 consecutively enrolled men with CP/CPPS. Each patient participated in a pelvic floor biofeedback re-educating programme. A rectal electromyogram probe was used to measure resting tone of the pelvic floor muscles, and was helpful for instruction on contraction and relaxation of the pelvic floor muscles. The mean total NIH-CPSI score decreased from 23.6 to 11.4 after treatment ($p < 0.001$). The mean value of the pelvic floor muscle tone was 4.9 at diagnosis (range 2.0–10.0) and decreased to 1.7 (range 0.5–2.8) after treatment ($p < 0.001$). The findings support the utility of biofeedback as an efficacious therapy in CP/CPPS. It also lends support to the theory that pelvic floor dysfunction (increased tone) is part of the pathogenesis of CP/CPPS.[51]

Similar non-randomized studies by Nadler[32] in 2002 and Ye et al.[52] in the Chinese literature from 2003 reported statistically and clinically significant improvement in 60 of 62 patients treated with biofeedback for 20 minutes, five times per week for 2 weeks. The patients showed improvement after two to three sessions without adverse reactions. In another uncontrolled study by Clemens et al.,[53] measures of pain, urgency and frequency all improved with pelvic floor biofeedback.

Randomized controlled trials are needed before biofeedback can be considered a first- or second-line therapy, but it is promising. The NIH-CPSI score improvements are more striking than the efficacy of long standing therapies, including α-blockers and anti-inflammatory drugs. The authors of this review frequently utilize this form of therapy in CP/CPPS management.

2.3 Antimicrobials

Fluoroquinolones are considered the first-line agent for acute and chronic bacterial prostatitis, and have cure rates of approximately 65%.[18,54,55] Levofloxacin has been found to have good antimicrobial activity against most uropathogens, and can concentrate intra- and extracellularly in the prostate in a 3 : 1 ratio compared with plasma concentrations.[56,57] CP/CPPS is considered non-bacterial. However, it is often treated with a course of antimicrobial therapy because of empirical success and is a

remnant of the fact that prostatitis subtypes were largely grouped together and antimicrobials would help the 5% of patients with acute or chronic bacterial prostatitis. Despite this, approximately 50% of patients with CP/CPPS can be expected to improve with fluoroquinolone therapy.[58] Recently, randomized controlled prospective trials have addressed this issue.[31]

In patients who can be considered to have CP/CPPS, who have been symptomatic for only a short duration (median 4 weeks) and have not previously been treated with antibacterials, response rates of up to 75% in patients who cultured non-uropathogenic bacteria have been obtained. The same was observed in patients who actually cultured typical uropathogens (patients with chronic bacterial prostatitis).[59]

However, patients with long-term CP/CPPS symptoms (median ~6.5 years) who had received multiple prior treatments (including antimicrobials) appear to have no significant benefit from active fluoroquinolone therapy because no significant reduction in scores on the NIH-CPSI relative to placebo has been shown.[60,61] Therefore, most urologists would treat a patient with a recent onset of symptoms consistent with CP/CPPS with a 4- to 6- week course of a fluoroquinolone or cotrimoxazole (trimethoprim/sulfamethoxazole). This may be repeated if significant benefit occurs. However, if there is no significant improvement after the initial antimicrobial course, additional courses of antimicrobials are not beneficial. Injudicious use of antimicrobials is implicated in the increasing prevalence of multidrug resistant organisms, such as extended-spectrum β-lactamase-producing bacteria.

2.4 α-Adrenergic Receptor Antagonists (α-Blockers)

CP/CPPS often presents with voiding symptoms, such as urgency, frequency and incomplete voiding sensation. These symptoms mimic BPH, in which α-blockers are the drug of choice. However, α-blockers are not US FDA approved for use in CP/CPPS. Randomized, placebo-controlled trials evaluating the α-blockers tamsulosin, terazosin and alfuzosin showed a statistically and probably clinically significant treatment effect with these agents.[62-64] Subgroup analysis found that men with more severe symptoms at baseline were significantly more likely to show improved urinary symptoms and pain reduction based on validated symptom questionnaires relative to those with mild symptoms using tamsulosin and doxazosin.[62,65] However, in a well powered, NIH Chronic Prostatitis Collaborative Research Network (CPCRN) trial of 6 weeks duration, on tamsulosin appeared to provide no additional benefit to placebo when used in CP/CPPS patients who were likely to be treatment-refractory, including to previous treatment with α-blockers.[64]

It could be concluded from these four trials that longer courses (12–14 weeks)[66] of α-blockers provide modest benefits when prescribed to α-blocker-naive CP/CPPS patients with shorter duration of disease, and that less selective agents are superior to highly selective α-blockers such as alfuzosin.[67] The NIH-CPCRN is conducting an ongoing randomized controlled trial comparing the effects of 12 weeks of alfuzosin 10 mg once daily with placebo in recently diagnosed α-blocker-naive CP/CPPS patients to test this hypothesis.[31]

On the basis of body of level II evidence, α-blockers can be considered first-line or part of multimodal therapy for CP/CPPS in patients who are naive to α-blocker therapy.[31]

2.5 Combination Therapy with α-Blockers and Fluoroquinolones

A study of 81 men from Seoul, Korea, compared 6 weeks of doxazosin 4 mg/day, 6 weeks of levofloxacin 500 mg/day and 6 weeks of combination therapy. The NIH-CPSI score reduction for levofloxacin was 50% versus only 21% for doxazosin at 6 weeks. The combination therapy was not significantly different from levofloxacin monotherapy.[68] In a Chinese study of 105 men randomized to tamsulosin, levofloxacin, or tamsulosin and levofloxacin, scores for pain, urinary symptoms and QOL were significantly improved by days 45 and 90 after all treatments.[69] The study, providing level II evidence for combining

an α-blocker and a fluoroquinolone, shows greater efficacy than monotherapy at 90 days, consistent with the therapeutic benefit seen with longer courses of α-blockers.[69]

Drawing conclusions from the available literature about the efficacy of the therapies is confounded by the duration of treatment in the studies and by whether the patients are therapy-naive or treatment-refractory.

2.6 Anti-Inflammatory Agents

Anti-inflammatory drugs have long been utilized in chronic pain syndromes to avoid narcotic use with modest benefit. A small, randomized, single-centre, placebo-controlled study with 17 patients evaluated zafirlukast (a leukotriene inhibitor) for 4 weeks. Of note, patients also received doxycycline. No difference in outcome was demonstrated in the treatment of CP/CPPS.[70]

Nickel et al.[71] randomized 161 patients to 6 weeks of the cyclo-oxygenase-2 selective NSAID rofecoxib at a dosage of 25 or 50 mg once daily, or placebo. Only high-dose rofecoxib provided statistically significant, but only modest clinically significant benefit compared with placebo treatment. Rofecoxib has since been removed from the market.

Since pelvic floor dysfunction is a theory behind the pathogenesis of CP/CPPS, muscle relaxants have been tried in combination with anti-inflammatory medications. In 2007, Tugcu et al.[72] published a placebo-controlled study of 90 treatment-naive men comparing 6 months of the α-blocker doxazosin 4 mg/day with triple therapy including doxazosin 4 mg/day, a muscle relaxant (tiocolchicoside 12 mg/day) and an anti-inflammatory (ibuprofen 400 mg/day). At 6 months, there was no difference between the triple therapy and α-blocker monotherapy, with a 56% reduction in NIH-CPSI score. The NIH-CPSI score reduction in both treatment arms was statistically significantly better than the placebo arm. This study provided level II evidence and showed no benefit from the addition of an anti-inflammatory and a muscle relaxant. This long-duration study does support the notion that chronic therapy with doxazosin improves NIH-CPSI scores.

2.7 5α-Reductase Inhibitors

Finasteride is a widely used 5α-reductase inhibitor for BPH. There is only level II evidence for its use in CP/CPPS. It inhibits the conversion of testosterone to the more potent dihydrotesterone, which slows the growth or reduces the size of prostate glands. Finasteride has been shown in small, poorly-controlled trials to provide some benefit in CP/CPPS. In 2004, Nickel et al.[73] performed a small, randomized, placebo-controlled study in 64 men. After 6 months of finasteride 5 mg/day compared with placebo, 75% versus 54% had a >25% decrease in NIH-CPSI score, but the actual magnitude of improvement did not reach statistical significance. The authors did not recommend finasteride as monotherapy in CP/CPPS, unless the patient had concomitant BPH. Rates of adverse events were similar between the two groups. In the treatment of BPH, the efficacy of finasteride may not be realized for up to 1 year and it is beneficial in men with large prostates. It is possible that longer studies in men with BPH and CP/CPPS are needed to demonstrate the utility of finasteride.

2.8 Glycosaminoglycans

Pentosan polysulfate is a semi-synthetic mucopolysaccharide that is structurally similar to the glycosaminoglycans of the bladder, which form a protective epithelial barrier. However, its efficacy in CP/CPPS may be due to its anti-inflammatory effects. It is FDA approved for interstitial cystitis, but not for CP/CPPS.[74]

In 2005, Nickel et al.[75] randomized 100 men with CP/CPPS to oral pentosan polysulfate 300 mg three times daily or placebo for 16 weeks. The results showed that pentosan polysulfate had a positive effect on the condition, but failed to show a statistically significant improvement in the total NIH-CPSI scores (−5.9 with pentosan vs −3.2 with placebo); however, it approached significance with a p-value of 0.068. Based on the clinical global improvement (CGI) assessment, patients receiving pentosan polysulfate did show a moderate to marked improvement relative to placebo (37% vs 18%, respectively). However, the

difference in the mean CGI scores between the two groups was not statistically significant. Patients in the pentosan polysulfate group showed a more significant improvement in QOL than those in the placebo group (−2.0 vs −1.0, respectively).

Pentosan polysulfate needs to be further evaluated with a larger randomized, placebo-controlled trial.

2.9 Phytotherapy

In Europe and Asia, phytotherapy with cernilton (CN-009) and quercetin is used for many medical conditions, including prostatitis. Saw palmetto is a berry extract used for the treatment of BPH as an over-the-counter preparation. However, phytotherapy has not been evaluated by the FDA and is not approved for CP/CPPS.[31]

Cernilton is an extract of bee pollen, and is presumed to have anti-inflammatory and anti-androgenic activity. Level IV open-label studies have reported some symptomatic improvement in CP/CPPS.[76]

Quercetin is a polyphenolic bioflavonoid commonly found in red wine, green tea and onions, with reported antioxidant, anti-histamine and anti-inflammatory properties. Dosages of 50–150 mg/day are well tolerated, but without effect on markers of inflammation such as uric acid or reactive oxygen species.[77] Level II evidence is provided by a double-blind, placebo-controlled trial using quercetin 500 mg twice daily for 1 month. Two-thirds of men experienced a 25% reduction in NIH-CPSI scores, which was significantly different from the placebo group ($p = 0.003$). In regards to efficacy, quercetin reduced the NIH CPSI score by a mean of 7.9 points, similar to the 9-point reduction seen with alfuzosin.[64] Quercetin was well tolerated and efficacious.[78] It competitively binds to DNA gyrase and should be used with caution with fluoroquinolones.[79]

Saw palmetto extract is an over-the-counter therapy often used by patients with BPH. Level II evidence was provided in 2004 when a randomized controlled trial was performed with 64 men with CP/CPPS comparing finasteride (5 mg/day) and saw palmetto (325 mg/day) for 1 year. The NIH-CPSI score decreased from 23.9 to 18.1 in the finasteride group and changed from 24.7 to 24.6 in the saw palmetto group. CP/CPPS patients treated with saw palmetto had no appreciable long-term improvement.[80] However, use of finasteride in this non-placebo-controlled study showed a statistically significant improvement in symptoms when given over 1 year.

2.10 Others

Anti-anxiolytics, tricyclic antidepressants and neuromodulatory agents (gabapentin and pregabalin) are used to treat the pain and associated symptoms of CP/CPPS, but no firm evidence is available to allow an evidence-based recommendation to be made.[45] Use of narcotics (opioids) in the management of the chronic pain of treatment-refractory CP/CPPS remains controversial and the real risks have to be weighed against the potential benefits. A recent review outlines the pros and cons of the use of opioids for the chronic non-malignant neuropathic pain experienced by patients with long-term treatment refractory CP/CPPS.[81]

2.11 Role of the Pharmacist

Pharmacists can aid patients with knowledge of the different NIH classifications of prostatitis. The pharmacist can also counsel patients on the therapeutic treatment options, potential adverse effects and the importance of compliance with all regimens. Pharmacists can screen for drug interactions, such as concomitant use of quercetin and fluoroquinolones, which may decrease compliance and efficacy. In this era of multidrug-resistant microbes, pharmacists can discourage patients with CP/CPPS from requesting multiple courses of antibacterials without documented infections. Given the fact that CP/CPPS is a diagnosis of exclusion, pharmacists can refer patients who are unresponsive to therapy for evaluation of serious underlying conditions.[32]

3. Conclusion

The aetiology of CP/CPPS is unknown, there is no cure and the focus of therapy is symptomatic

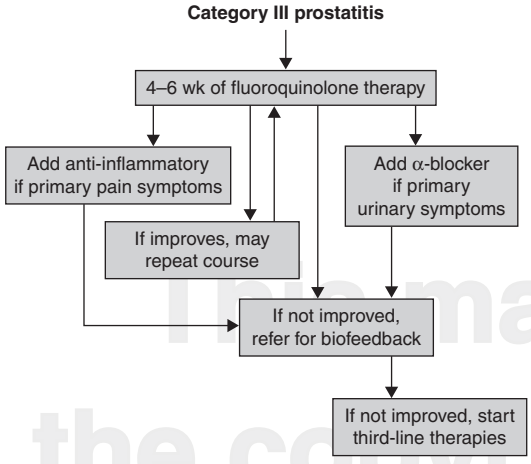

Fig. 3. Algorithm for the management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). After exclusion of other entities such as urinary tract infection, chronic bacterial prostatitis, urethral strictures, urogenital cancer, etc., with history, physical examination, microscopic urine exam, urine culture and measurement of post void residual, all patients with suspected CP/CPPS should undergo a National Institutes of Health Chronic Prostatitis Symptom Index questionnaire to better evaluate response to treatments. A trial of fluoroquinolone therapy is advised and may be repeated if there is a significant improvement in symptoms. α-Blockers and/or anti-inflammatory medications may be added depending on the predominance of symptoms. If this regimen does not improve the symptoms, then patients are referred for biofeedback. Third-line therapies such as finasteride or pentosan polysulfate can be tried thereafter. Surgical interventions are of limited use, but transurethral microwave therapy is a minimally invasive modality with demonstrated efficacy, especially in those with urinary symptoms.

relief. Our recommended treatment algorithm is presented in figure 3. CP/CPPS has many clinical presentations and treatment options, with fluoroquinolones as the only FDA-approved first-line agents. Combination therapy of an α-blocker for ≥12 weeks with a fluoroquinolone may be considered a multimodal first-line therapy. Differentiating CP/CPPS from the other NIH prostatitis subtypes helps healthcare professionals design treatment plans that optimize response. Furthermore, new research into biofeedback and pelvic floor muscle training suggests modest benefit that warrants its consideration as a second-line therapy. The diminution in NIH-CPSI scores were similar to levofloxacin monotherapy (51.7% vs 50.3%), but a randomized, controlled, comparative study is needed.

Acknowledgements

No sources of funding were used to assist in the preparation of this article. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Collins MM, Stafford RS, O'Leary MP, et al. How common is prostatitis? A national survey of physician visits. J Urol 1998 Apr; 159 (4): 1224-8
2. Nickel JC, Downey J, Hunter D, et al. Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. J Urol 2001 Mar; 165 (3): 842-5
3. Roberts RO, Jacobson DJ, Girman CJ, et al. Prevalence of prostatitis-like symptoms in a community based cohort of older men. J Urol 2002 Dec; 168 (6): 2467-71
4. Collins MM, Meigs JB, Barry MJ, et al. Prevalence and correlates of prostatitis in the health professionals follow-up study cohort. J Urol 2002 Mar; 167 (3): 1363-6
5. Calhoun EA, McNaughton Collins M, Pontari MA, et al. The economic impact of chronic prostatitis. Arch Intern Med 2004 Jun 14; 164 (11): 1231-6
6. Schaeffer AJ. Clinical practice: chronic prostatitis and the chronic pelvic pain syndrome. N Engl J Med 2006 Oct 19; 355 (16): 1690-8
7. Litwin MS, McNaughton-Collins M, Fowler Jr FJ, et al. 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
8. Litwin MS. A review of the development and validation of the National Institutes of Health Chronic Prostatitis Symptom Index. Urology 2002 Dec; 60 (6 Suppl.): 14-8; discussion 8-9
9. Schneider H, Wilbrandt K, Ludwig M, et al. Prostate-related pain in patients with chronic prostatitis/chronic pelvic pain syndrome. BJU Int 2005 Feb; 95 (2): 238-43
10. Krieger JN, Nyberg Jr L, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA 1999 Jul 21; 282 (3): 236-7
11. de la Rosette JJ, Hubregtse MR, Meuleman EJ, et al. Diagnosis and treatment of 409 patients with prostatitis syndromes. Urology 1993 Apr; 41 (4): 301-7
12. Habermacher GM, Chason JT, Schaeffer AJ. Prostatitis/chronic pelvic pain syndrome. Annu Rev Med 2006; 57:195-206
13. Nickel JC. The prostatitis manual: a practical guide to management of prostatitis/chronic pelvic pain syndrome. San Francisco (CA): Bladon Medical Publishing, 2002
14. Nickel J. Chronic prostatitis: current concepts and antimicrobial therapy. Infect Urol 2000; 13 (5a):s22-8
15. Lee YS, Han CH, Kang SH, et al. Synergistic effect between catechin and ciprofloxacin on chronic bacterial prostatitis rat model. Int J Urol 2005 Apr; 12 (4): 383-9
16. Schaeffer AJ. Epidemiology and evaluation of chronic pelvic pain syndrome in men. Int J Antimicrob Agents 2008 Feb; 31 Suppl. 1: S108-11

17. Weidner W, Ludwig M. Diagnostic management of chronic prostatitis. Prostatitis: etiopathology, diagnosis and therapy. Berlin: Springer-Verlag, 1994: 158-74
18. Weidner W, Schiefer HG. Chronic bacterial prostatitis: therapeutic experience with ciprofloxacin. Infection 1991; 19 Suppl. 3: S165-6
19. Potts J, Payne RE. Prostatitis: infection, neuromuscular disorder, or pain syndrome? Proper patient classification is key. Cleve Clin J Med 2007 May; 74 Suppl. 3: S63-71
20. Lee SW, Liong ML, Yuen KH, et al. Adverse impact of sexual dysfunction in chronic prostatitis/chronic pelvic pain syndrome. Urology 2008 Jan; 71 (1): 79-84
21. Pontari MA. Chronic prostatitis/chronic pelvic pain syndrome in elderly men: toward better understanding and treatment. Drugs Aging 2003; 20 (15): 1111-25
22. Propert KJ, McNaughton-Collins M, Leiby BE, et al. A prospective study of symptoms and quality of life in men with chronic prostatitis/chronic pelvic pain syndrome: the National Institutes of Health Chronic Prostatitis Cohort study. J Urol 2006 Feb; 175 (2): 619-23; discussion 23
23. Walz J, Perrotte P, Hutterer G, et al. Impact of chronic prostatitis-like symptoms on the quality of life in a large group of men. BJU Int 2007 Dec; 100 (6): 1307-11
24. Ku JH, Kim SW, Paick JS. Epidemiologic risk factors for chronic prostatitis. Int J Androl 2005 Dec; 28 (6): 317-27
25. Krieger JN, Lee SW, Jeon J, et al. Epidemiology of prostatitis. Int J Antimicrob Agents 2008 Feb; 31 Suppl. 1: S85-90
26. Wallner LP, Clemens JQ, Sarma AV. Prevalence of and risk factors for prostatitis in African American men: The Flint Men's Health Study. Prostate. Epub 2008 Sep 18
27. McNaughton Collins M, MacDonald R, Wilt TJ. Diagnosis and treatment of chronic abacterial prostatitis: a systematic review. Ann Intern Med 2000 Sep 5; 133 (5): 367-81
28. Hochreiter WW, Duncan JL, Schaeffer AJ. Evaluation of the bacterial flora of the prostate using a 16S rRNA gene based polymerase chain reaction. J Urol 2000 Jan; 163 (1): 127-30
29. Nadler RB, Collins MM, Propert KJ, et al. Prostate-specific antigen test in diagnostic evaluation of chronic prostatitis/chronic pelvic pain syndrome. Urology 2006 Feb; 67 (2): 337-42
30. Pontari MA. Chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: are they related? Curr Urol Rep 2006 Jul; 7 (4): 329-34
31. Nickel JC. Treatment of chronic prostatitis/chronic pelvic pain syndrome. Int J Antimicrob Agents 2008 Feb; 31 Suppl. 1: S112-6
32. Nadler RB. Bladder training biofeedback and pelvic floor myalgia. Urology 2002 Dec; 60 (6 Suppl.): 42-3; discussion 4
33. Nickel JC, Berger R, Pontari M. Changing paradigms for chronic pelvic pain: a report from the chronic pelvic pain/chronic prostatitis scientific workshop, October 19-21, 2005, Baltimore, MD. Rev Urol 2006; 8 (1): 28-35
34. Hochreiter WW, Nadler RB, Koch AE, et al. Evaluation of the cytokines interleukin 8 and epithelial neutrophil activating peptide 78 as indicators of inflammation in prostatic secretions. Urology 2000 Dec 20; 56 (6): 1025-9
35. Kaplan SA, Ikeguchi EF, Santarosa RP, et al. Etiology of voiding dysfunction in men less than 50 years of age. Urology 1996 Jun; 47 (6): 836-9
36. Hetrick DC, Ciol MA, Rothman I, et al. Musculoskeletal dysfunction in men with chronic pelvic pain syndrome type III: a case-control study. J Urol 2003 Sep; 170 (3): 828-31
37. Alexander RB, Brady F, Ponniah S. Autoimmune prostatitis: evidence of T cell reactivity with normal prostatic proteins. Urology 1997 Dec; 50 (6): 893-9
38. Naslund MJ, Strandberg JD, Coffey DS. The role of androgens and estrogens in the pathogenesis of experimental nonbacterial prostatitis. J Urol 1988 Nov; 140 (5): 1049-53
39. Kirby RS, Lowe D, Bultitude MI, et al. Intra-prostatic urinary reflux: an aetiological factor in abacterial prostatitis. Br J Urol 1982 Dec; 54 (6): 729-31
40. de la Rosette JJ, Ruijgrok MC, Jeuken JM, et al. Personality variables involved in chronic prostatitis. Urology 1993 Dec; 42 (6): 654-62
41. Pontari MA, McNaughton-Collins M, O'Leary MP, et al. A case-control study of risk factors in men with chronic pelvic pain syndrome. BJU Int 2005 Sep; 96 (4): 559-65
42. Nickel JC, Shoskes D, Wang Y, et al. How does the pre-massage and post-massage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? J Urol 2006 Jul; 176 (1): 119-24
43. Meares EM, Stamey TA. Bacteriologic localization pattern in bacterial prostatitis and urethritis. Invest Urol 1968; 5: 492-518
44. Nickel JC. The pre and post massage test (PPMT): a simple screen for prostatitis. Tech Urol 1997 Spring; 3 (1): 38-43
45. Nickel J. Chronic prostatitis/chronic pelvic pain syndrome: a decade of change. AUA Update Series 2006; 25: 309-16
46. Nickel JC, Alexander RB, Schaeffer AJ, et al. Leukocytes and bacteria in men with chronic prostatitis/chronic pelvic pain syndrome compared to asymptomatic controls. J Urol 2003 Sep; 170 (3): 818-22
47. Nadler RB, Rubenstein JN. Laparoscopic excision of a seminal vesicle for the chronic pelvic pain syndrome. J Urol 2001 Dec; 166 (6): 2293-4
48. Koulis H, Lam H. Prostatitis: a review of clinical management. US Pharmacist 2006; 31 (8): 107-16
49. Leskinen MJ, Kilponen A, Lukkarinen O, et al. Transurethral needle ablation for the treatment of chronic pelvic pain syndrome (category III prostatitis): a randomized, sham-controlled study. Urology 2002 Aug; 60 (2): 300-4
50. Kastner C, Hochreiter W, Huidobro C, et al. Cooled transurethral microwave thermotherapy for intractable chronic prostatitis: results of a pilot study after 1 year. Urology 2004 Dec; 64 (6): 1149-54
51. Cornel EB, van Haarst EP, Schaarsberg RW, et al. The effect of biofeedback physical therapy in men with chronic pelvic pain syndrome type III. Eur Urol 2005 May; 47 (5): 607-11
52. Ye ZQ, Cai D, Lan RZ, et al. Biofeedback therapy for chronic pelvic pain syndrome. Asian J Androl 2003 Jun; 5 (2): 155-8
53. Clemens JQ, Nadler RB, Schaeffer AJ, et al. Biofeedback, pelvic floor re-education, and bladder training for male chronic pelvic pain syndrome. Urology 2000 Dec 20; 56 (6): 951-5
54. Schaeffer AJ, Darras FS. The efficacy of norfloxacin in the treatment of chronic bacterial prostatitis refractory to

trimethoprim-sulfamethoxazole and/or carbenicillin. J Urol 1990 Sep; 144 (3): 690-3

55. Pust RA, Ackenheil-Koppe HR, Gilbert P, et al. Clinical efficacy of ofloxacin (tarivid) in patients with chronic bacterial prostatitis: preliminary results. J Chemother 1989 Jul; 1 (4 Suppl.): 869-71
56. Drusano GL, Preston SL, Van Guilder M, et al. A population pharmacokinetic analysis of the penetration of the prostate by levofloxacin. Antimicrob Agents Chemother 2000 Aug; 44 (8): 2046-51
57. Siegrist HH, Nepa MC, Jacquet A. Susceptibility to levofloxacin of clinical isolates of bacteria from intensive care and haematology/oncology patients in Switzerland: a multicentre study. J Antimicrob Chemother 1999 Jun; 43 Suppl. C: 51-4
58. Nickel JC, Downey J, Johnston B, et al. Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: a prospective multicenter clinical trial. J Urol 2001 May; 165 (5): 1539-44
59. Nickel J, Zadeikis N, Spivey M. Clinical significance of antimicrobial therapy in chronic prostatitis associated with non-traditional uropathogens [abstract]. J Urol 2005; 173: S30
60. Nickel JC, Downey J, Clark J, et al. Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: a randomized placebo-controlled multicenter trial. Urology 2003 Oct; 62 (4): 614-7
61. Alexander RB, Propert KJ, Schaeffer AJ, et al. Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. Ann Intern Med 2004 Oct 19; 141 (8): 581-9
62. Nickel JC, Narayan P, McKay J, et al. Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double blind trial. J Urol 2004 Apr; 171 (4): 1594-7
63. Cheah PY, Liong ML, Yuen KH, et al. Terazosin therapy for chronic prostatitis/chronic pelvic pain syndrome: a randomized, placebo controlled trial. J Urol 2003 Feb; 169 (2): 592-6
64. Mehik A, Alas P, Nickel JC, et al. Alfuzosin treatment for chronic prostatitis/chronic pelvic pain syndrome: a prospective, randomized, double-blind, placebo-controlled, pilot study. Urology 2003 Sep; 62 (3): 425-9
65. Evliyaoglu Y, Burgut R. Lower urinary tract symptoms, pain and quality of life assessment in chronic non-bacterial prostatitis patients treated with alpha-blocking agent doxazosin; versus placebo. Int Urol Nephrol 2002; 34 (3): 351-6
66. Mishra VC, Browne J, Emberton M. Role of alpha-blockers in type III prostatitis: a systematic review of the literature. J Urol 2007 Jan; 177 (1): 25-30
67. Lee SW, Liong ML, Yuen KH, et al. Chronic prostatitis/chronic pelvic pain syndrome: role of alpha blocker therapy. Urol Int 2007; 78 (2): 97-105
68. Jeong CW, Lim DJ, Son H, et al. Treatment for chronic prostatitis/chronic pelvic pain syndrome: levofloxacin, doxazosin and their combination. Urol Int 2008; 80 (2): 157-61
69. Ye ZQ, Lan RZ, Yang WM, et al. Tamsulosin treatment of chronic non-bacterial prostatitis. J Int Med Res 2008 Mar-Apr; 36 (2): 244-52
70. Goldmeier D, Madden P, McKenna M, et al. Treatment of category IIIA prostatitis with zafirlukast: a randomized controlled feasibility study. Int J STD AIDS 2005 Mar; 16 (3): 196-200
71. Nickel JC, Pontari M, Moon T, et al. A randomized, placebo controlled, multicenter study to evaluate the safety and efficacy of rofecoxib in the treatment of chronic nonbacterial prostatitis. J Urol 2003 Apr; 169 (4): 1401-5
72. Tugcu V, Tasci AI, Fazlioglu A, et al. A placebo-controlled comparison of the efficiency of triple- and monotherapy in category IIIB chronic pelvic pain syndrome (CPPS). Eur Urol 2007 Apr; 51 (4): 1113-7; discussion 8
73. Nickel JC, Downey J, Pontari MA, et al. A randomized placebo-controlled multicentre study to evaluate the safety and efficacy of finasteride for male chronic pelvic pain syndrome (category IIIA chronic nonbacterial prostatitis). BJU Int 2004 May; 93 (7): 991-5
74. Schaeffer A. Advances in the diagnosis and treatment of prostatitis. Urology 2002; 60 (6A): 1-44
75. Nickel JC, Forrest JB, Tomera K, et al. Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. J Urol 2005 Apr; 173 (4): 1252-5
76. Rugendorff EW, Weidner W, Ebeling L, et al. Results of treatment with pollen extract (Cernilton N) in chronic prostatitis and prostatodynia. Br J Urol 1993 Apr; 71 (4): 433-8
77. Egert S, Wolffram S, Bosy-Westphal A, et al. Daily quercetin supplementation dose-dependently increases plasma quercetin concentrations in healthy humans. J Nutr 2008 Sep; 138 (9): 1615-21
78. Shoskes DA, Zeitlin SI, Shahed A, et al. Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. Urology 1999 Dec; 54 (6): 960-3
79. Hilliard JJ, Krause HM, Bernstein JI, et al. A comparison of active site binding of 4-quinolones and novel flavone gyrase inhibitors to DNA gyrase. Adv Exp Med Biol 1995; 390: 59-69
80. Kaplan SA, Volpe MA, Te AE. A prospective, 1-year trial using saw palmetto versus finasteride in the treatment of category III prostatitis/chronic pelvic pain syndrome. J Urol 2004 Jan; 171 (1): 284-8
81. Nickel JC. Opioids for chronic prostatitis and interstitial cystitis: lessons learned from the 11th world congress on pain. Urology 2006 Oct; 68 (4): 697-701

Correspondence: Dr *Adam B. Murphy* and Dr *Robert B. Nadler*, Department of Urology, Northwestern University Feinberg School of Medicine, Tarry 16-703, 303 E. Chicago Avenue, Chicago, IL 60611, USA.
E-mail: a-murphy2@md.northwestern.edu and r-nadler@northwestern.edu