CLINICAL PRACTICE

Chronic Prostatitis and the Chronic Pelvic Pain Syndrome

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 38-year-old man reports pelvic pain, dysuria, and urinary urgency for the past 4 weeks. He has had several similar episodes over the past 2 years; urine cultures were not performed. He is sexually active and notes frequent discomfort after ejaculation. He is otherwise healthy and takes no medication. He does not have fever, chills, or flank pain. How should he be evaluated and treated?

THE CLINICAL PROBLEM

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N Engl J Med 2006;355:1690-8.

Prostatitis accounts for approximately 2 million outpatient visits per year in the United States, including 8% of all visits to urologists and 1% of those to primary care physicians.[1] The direct costs of care approach $4,000 per patient per year.[2] A classification system for the prostatitis syndromes has been developed by the National Institutes of Health (NIH) (Table 1).[3]

About 5 to 10% of men with symptoms of prostatitis have acute or chronic bacterial prostatitis,[4] conditions that are well defined according to clinical and microbiologic measures and that usually respond to antimicrobial therapy. Acute bacterial prostatitis is a life-threatening systemic infection, and its diagnosis and treatment are relatively straightforward and will not be discussed here. Chronic bacterial prostatitis is characterized by positive results on cultures of expressed prostatic fluid and is usually associated with recurrent urinary tract infections.[5] Men with chronic bacterial prostatitis may be asymptomatic between acute episodes or have mild pelvic pain or irritative symptoms on voiding (frequency, urgency). *Escherichia coli* cause approximately 75 to 80% of episodes. Enterococci and aerobic gram-negative rods other than *E. coli*, such as pseudomonas, are isolated in the remainder of the cases.

Most men with prostatitis, however, present with pelvic pain without evidence of urinary tract infection. This condition (NIH category III) is called the chronic pelvic pain syndrome and commonly manifests as pain in areas including the perineum, rectum, prostate, penis, testicles, and abdomen.[6] It is often associated with symptoms of obstruction (e.g., hesitancy, weak stream) or irritative symptoms on voiding. The symptoms usually remain stable or improve slightly over time, but some men have large fluctuations in the severity of symptoms.[7] In cross-sectional studies, the chronic pelvic pain syndrome is associated with reductions in the patient's quality of life similar to or greater than those associated with angina, congestive heart failure, Crohn's disease, and diabetes mellitus.[8] Both chronic bacterial prostatitis[9] and the chronic pelvic pain syndrome[10] have been associated with abnormalities in the semen and infertility.

Table 1. Categories of the Prostatitis Syndromes, According to the NIH Classification System.

Category	Symptoms
I. Acute bacterial prostatitis	Associated with severe symptoms of prostatitis, systemic infection, and acute bacterial urinary tract infection
II. Chronic bacterial prostatitis	Caused by chronic bacterial infection of the prostate with or without symptoms of prostatitis and usually with recurrent urinary tract infections caused by the same bacterial strain
III. Chronic pelvic pain syndrome*	Characterized by symptoms of chronic pelvic pain and possibly symptoms on voiding in the absence of urinary tract infection
IV. Asymptomatic inflammatory prostatitis	Characterized by evidence of inflammation of the prostate in the absence of genitourinary tract symptoms; an incidental finding during evaluation for other conditions, such as infertility or elevated serum prostate-specific antigen levels

* This category is subdivided into inflammatory (category IIIA) and noninflammatory (category IIIB) prostatitis.

EPIDEMIOLOGY

Chronic bacterial prostatitis has been associated with risk factors for urinary tract infection, including urethral catheterization or instrumentation. Although infections of the prostate with bacteria,[11] viruses,[12] and yeast[13] have been proposed as causes of the chronic pelvic pain syndrome, data to support these hypotheses are lacking and studies have failed to identify an association with sexually transmitted organisms, including *Chlamydia trachomatis, Ureaplasma urealyticum,* and *Trichomonas vaginalis*.[14] Cross-sectional studies of affected men have shown various abnormalities, including increased levels of cytokines, voiding dysfunction, immunologic dysfunction, and psychological disturbances (such as neurosis, psychosomatization, depression, and sexual problems),[15] but the role of these disorders in the development of prostatitis remains unclear.

STRATEGIES AND EVIDENCE

DIAGNOSIS

A history of recurrent urinary tract infections documented by cultures suggests the diagnosis of chronic bacterial prostatitis. If there was no documentation of positive urine cultures at the time of the previous symptomatic episodes, urinalysis and urine culture should be obtained when symptoms recur. In the absence of documented urinary tract infection, the presence of symptoms of chronic pelvic pain and possibly of obstruction or irritative symptoms on voiding support a diagnosis of the chronic pelvic pain syndrome. There are no reliable physical findings for either chronic bacterial prostatitis or chronic pelvic pain syndrome, but physical examination should be performed to rule out bladder distention and prostatic induration or asymmetry, conditions suggestive of prostate cancer. A complete blood count, other measures of inflammation, and serum prostate-specific antigen (PSA) testing are not helpful in the diagnosis of chronic bacterial prostatitis or the chronic pelvic pain syndrome.[16] PSA levels typically increase in the presence of acute urinary tract infection, and elevated values should be monitored after treatment of the infection until the values normalize. An elevated serum PSA level in the absence of infection warrants further evaluation, just as it does in men without urinary tract infection.

Chronic Bacterial Prostatitis

If recurrent urinary tract infections are confirmed, the patient should be evaluated for structural or functional abnormalities of the urinary tract with the use of computed tomography and measurement of residual urine after voiding. The yield on these tests (which in different studies has ranged from 23%[17] to approximately 50%[18]) depends on the patient's age and the presence of coexisting conditions; abnormal results (e.g., renal stones, obstruction) warrant urologic consultation. If no abnormalities are found and repeated cultures show the same bacterial strain, chronic bacterial prostatitis is the likely diagnosis.

To confirm that the prostate is the reservoir of bacteria between episodes of overt urinary tract infection, cultures to localize the area of infection are recommended. Because such testing is informative only if urine from the bladder shows no bacterial growth, any acute infection must first be treated; a beta-lactam antibiotic or nitrofurantoin

should be used, because these do not penetrate the prostate and therefore will not interfere with subsequent culturing of prostatic bacteria. The Meares–Stamey 4-glass test[19] involves the collection of sequential specimens of urine before and after prostatic massage and of prostatic fluid during prostatic massage (prostatic localization cultures); a simpler 2-glass test involving a midstream urine collection and prostatic massage after collection of the initial urine specimen correlates well with the 4-glass test (Fig. 1).[20,21] Cultures permit a comparison between quantifiable levels of bacteria in the prostate and those in the urethra. If pathogens are found only in the prostatic fluid or if the total amount of pathogens in the prostatic fluid is 10 times the levels found in the urethra, the patient is considered to have chronic bacterial prostatitis. Although the 4-glass test has long been the standard method of identifying chronic bacterial prostatitis, its accuracy and reliability have not been established. Furthermore, surveys of physicians have indicated that the 4-glass test is not widely used, even by urologists.[22]

Chronic Pelvic Pain Syndrome

There is no gold standard for diagnostic testing for the chronic pelvic pain syndrome.[15] The 4-glass or 2-glass test may provide information on prostatic inflammation (e.g., the number of white cells per high-power field), but this finding is not helpful in the diagnosis or management of the condition. Among men with presumed chronic pelvic pain syndrome and no history of urinary tract infection, up to 8% have been found to have positive prostatic localization cultures, but these findings have also been reported in a similar percentage of asymptomatic men.[23]

Urodynamic evaluation should be considered for patients with clinically significant lower urinary tract symptoms in addition to pelvic pain, since voiding dysfunction appears to be common among these patients and may respond to urologic interventions (such as treatment with an alpha-adrenergic blocker or transurethral incision of the bladder neck).[24] In general, imaging studies have a low yield. However, in patients with pain after ejaculation, transrectal ultrasonography may reveal enlargement of the seminal vesicle caused by obstruction of the ejaculatory duct; such an obstruction may be associated with or exacerbate the chronic pelvic pain syndrome. Isolated case reports suggest that the correction of the obstruction may relieve pain, although this cannot be proved because of a lack of data.[25]

TREATMENT

Chronic Bacterial Prostatitis

The initial treatment for chronic bacterial prostatitis involves the use of a prostate-penetrating antimicrobial agent (e.g., a fluoroquinolone or trimethoprim–sulfamethoxazole) that is effective against the pathogen identified by prostatic localization cultures. The usual course of therapy is 4 weeks, on the basis of high response rates in clinical trials using this duration, although different durations of therapy have not been directly compared (Table 2).

In randomized trials comparing different fluoroquinolones (given for 4 weeks), rates of clinical success at 6 months (defined as the resolution or improvement of symptoms) were between 75 and 89%, and the rates of bacteriologic cure were between 63 and 77%, depending on the particular agent used[26-29]; the rates for ciprofloxacin and levofloxacin[30] or lomefloxacin[29] did not differ significantly. A review of five retrospective case series involving a total of 70 men treated with trimethoprim–sulfamethoxazole for 90 days[31] reported cure rates of 31 to 67%. Since relapse (recurrence of infection by the same organism, as confirmed on urine cultures or in localization studies) occurs in approximately one third of patients,[26] patients should be followed after completion of the therapy and urine cultures should be repeated if symptoms recur. In practice, urine cultures should be repeated at 6 months, even in patients without recurrent symptoms, although the effect of this strategy has not been evaluated.

Although oral antimicrobial agents are the standard therapy, injection of antimicrobial agents into the prostate has also been proposed, and in one controlled study involving patients with prostatitis treated with local injections, the therapy significantly improved scores for symptoms and rates of bacterial eradication, as compared with those for controls.[32] One study in which some patients were prescribed alpha-blockers in combination with antimicrobial agents suggested that there were greater reductions in symptom scores and in the recurrence of positive results on prostatic-fluid cultures with combination therapy than with antimicrobial agents alone.[33] However, there

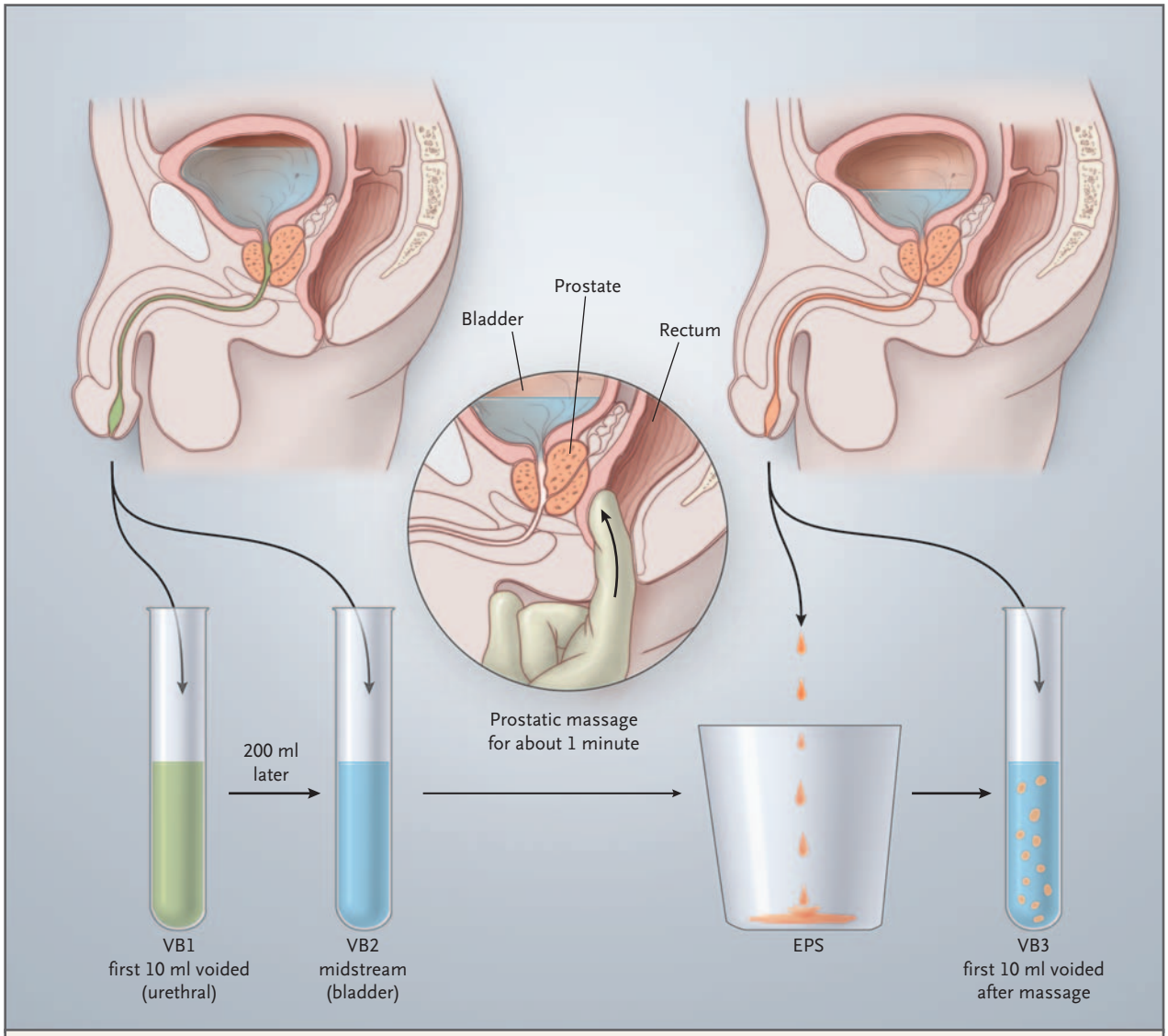

Figure 1. The Meares–Stamey 4-Glass Urine Test.

In the Meares–Stamey 4-glass test,[19] the initial 10 ml of the urinary stream, depicted as voided bladder 1 (VB1), represents the urethral specimen. A midstream specimen obtained from the bladder is depicted as voided bladder 2 (VB2). Prostatic massage is performed with gentle digital pressure moving from the lateral margin of the superior portion of a selected lobe of the prostate toward the apex, for approximately 1 minute (longer massage may inhibit the fluid outflow).[20] Several drops of expressed prostatic secretion (EPS) should emerge from the urethra within 2 to 3 minutes after the massage is completed. The EPS and the first 10 ml of urine after prostatic massage, depicted as voided bladder 3 (VB3), represent the microbiologic environment of the prostate. In the 2-glass test, only steps VB2 and VB3 are used, but the test still offers a reasonably accurate method of screening for prostatitis. Information used in this figure is from Nickel.[21]

were methodologic limitations to this study, including that the therapy was not clearly assigned randomly and the absence of a control group, and the results require confirmation.

If after antimicrobial therapy a patient has recurrent urinary tract infections caused by the same strain, localization cultures should be repeated. If the cultures confirm that the pathogen has not been eradicated, low-dose suppressive therapy with an agent shown to be effective against the patho-

Table 2. Treatment Regimens for Chronic Bacterial Prostatitis and the Chronic Pelvic Pain Syndrome.*

Condition	Medication	Dose	Adverse Effect
Chronic bacterial prostatitis	Antimicrobial agents		
	Fluoroquinolones	500 mg daily for 4 wk	Common: dizziness, restlessness, headache, diarrhea, nausea, rash Rare: convulsion, psychosis, severe hypersensitivity, tendon rupture
	Ciprofloxacin (Cipro, Bayer)†		
	Levofloxacin (Levaquin, Ortho-McNeil)†		
	Trimethoprim–sulfamethoxazole	160/800 mg twice daily for 4 wk	Common: anorexia, nausea, vomiting, rash, urticaria Rare: blood dyscrasias, hypersensitivity or photosensitivity, hepatic necrosis
Chronic pelvic pain syndrome	Alpha-blockers		Common: rhinitis, fatigue
	Alfuzosin (Uroxatral, Sanofi-Aventis)	10 mg twice daily for 12 wk	Rare: decrease in blood pressure, headache Contraindication: moderate hepatic insufficiency or with cytochrome P-450 3A4 inhibitors
	Doxazosin (Cardura, Pfizer)	Dose escalation from 1 to 4 mg, then effective dose daily for 12 wk	Common: decrease in blood pressure, headache
	Tamsulosin (Flomax, Boehringer Ingelheim)	0.4 mg once daily for 12 wk	Common: decreased ejaculate volume, headache Rare: absent ejaculate, decrease in blood pressure
	Terazosin (Hytrin, Abbott)	Dose escalation from 1 to 5 mg, then effective dose daily for 12 wk	Common: dizziness, decrease in blood pressure, headache

* There are no published clinical guidelines for the treatment of prostatitis or pelvic pain syndrome with antimicrobial agents or alpha-blockers. Examples of the drug classes are not comprehensive. Not all agents listed are approved by the Food and Drug Administration (FDA) for the treatment of prostatitis.
† This medication is approved by the FDA for this indication.

gen may be considered. Although this method has not been studied in randomized trials, generally it appears to be effective as long as suppression continues. Episodic repeated treatment of recurrent cystitis is an alternative.

Chronic Pelvic Pain Syndrome

Effective treatment for the chronic pelvic pain syndrome remains uncertain. Factors complicating the management of this condition include its probably multifactorial pathogenesis, lack of a gold standard for diagnostic testing, and the methodologic limitations of many treatment studies. Thus far, strategies have focused on symptomatic relief (Table 2).

Before initiating treatment, the severity of the symptoms and their effect on the patient's quality of life should be assessed. The NIH Chronic Prostatitis Symptom Index (Fig. 2) is a nine-item, self-administered tool that is reliable and valid and has been shown to be useful in assessing the patient's baseline status and responses to therapy (total scores range from 0 to 43 points, with higher scores indicating more severe symptoms).[6] A reduction of four to six points is generally agreed to be significant.

Alpha-Blockers

Several small, randomized, controlled trials[37-40] have shown improvements in the quality of life and relief from symptoms among men with the chronic pelvic pain syndrome who received alpha-blockers for 12 weeks[38] to 14 weeks.[37] Improvements in the mean scores on the NIH Chronic Prostatitis Symptom Index ranged from 57%[37] to 33%,[38,39] indicating a clinically and statistically significant change. However, a larger randomized trial involving 6 weeks of treatment with tamsulosin resulted in no significant improvement in scores according to the same index.[41] The dura-

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?

☐0 ☐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 have 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 had 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

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

Figure 2. The NIH Chronic Prostatitis Symptom Index.

Scores range from 0 to 43 points, with higher scores indicating more severe symptoms. This index has been translated into seven languages, including Chinese,[34] German,[35] and Spanish.[36] Information used in this figure is from Litwin et al.[6]

tion of symptoms, which varied from 1 year[37] to 9 years,[38] did not appear to influence the outcome. However, superior results in trials involving a longer duration of therapy suggest that a trial of 3 months or longer may be needed to assess therapeutic benefit. Adverse effects of alpha-blockers include dizziness, fatigue, and hypotension (in 16%, 16%, and 0.02% of patients, respectively, according to one report[37]) and decreased ejaculate volume (in 21% of patients in another report[38]).

Antimicrobial Therapy

Randomized, controlled trials have failed to support the use of antimicrobial agents in men with the chronic pelvic pain syndrome. Trials comparing ciprofloxacin (196 patients)[41] or levofloxacin (80 patients)[42] for 6 weeks with no treatment showed no significant benefit from active therapy in terms of a reduction in scores on the NIH Chronic Prostatitis Symptom Index. Because the mean duration of symptoms in these trials was 6.5 and 6.2 years, respectively, and because many of the patients had prior antimicrobial therapy, it is uncertain whether these results are generalizable to patients with a recent onset of symptoms or those who have not had a trial of antimicrobial therapy.

5α-Reductase Inhibitors

One randomized, placebo-controlled trial of finasteride showed that scores on the Prostatitis Symptom Severity Index and the International Prostatitis Symptom Survey decreased significantly after 1 year of treatment, but pain scores did not change significantly.[15] In another randomized, controlled trial, response rates at 6 months (defined as an improvement of more than 25% in scores on the NIH Chronic Prostatitis Symptom Index) were not significantly better for finasteride than for placebo (33% vs. 16%).[43] Rates of adverse effects were similar in the two groups.

Other Therapies

Studies of other proposed therapies for the chronic pelvic pain syndrome are limited. One small randomized, controlled trial showed significant improvement in symptoms in men treated with mepartricin, an aromatic heptane that lowers plasma and prostate estrogen levels, as compared with placebo.[44] Quercetin, a bioflavonoid with antioxidant properties that is available over the counter, was reported to produce significantly greater improvement than placebo according to scores on the NIH Chronic Prostatitis Symptom Index in another small randomized trial.[15] However, these observations require confirmation in larger studies.

Pentosan polysulfate, a plant-derived mucopolysaccharide similar to naturally occurring glycosaminoglycans that form a protective layer covering the epithelium of the urinary tract, was ineffective in reducing symptoms in a randomized trial in men with the chronic pelvic pain syndrome.[45] Another randomized trial in this population found no benefit from a cyclooxygenase-2 inhibitor (rofecoxib).[46] Other therapies for the chronic pelvic pain syndrome tested in small pilot studies that have shown no significant benefit include gabapentin,[46] muscle relaxants,[15] bee-pollen extract,[15] saw palmetto,[47] corticosteroids,[48] and allopurinol.[15]

Transurethral microwave thermotherapy, which is widely available, can achieve temperatures of more than 45°C within prostatic tissue. One small randomized trial (20 patients) suggested that transurethral microwave thermotherapy significantly improved the quality of life at 3 months, as compared with sham treatment[15]; four patients reported transient adverse effects, including hematuria, urinary tract infection, impotence, urinary retention, urinary incontinence, and premature ejaculation, but whether these patients received active or sham treatment was not stated.

Small uncontrolled studies have shown limited improvements in scores on the NIH Chronic Prostatitis Symptom Index with the use of biofeedback[49,50] and acupuncture.[51] Controlled trials involving sham treatment are required before recommendations can be made. Physical therapies, including prostatic massage and sitz baths, have been recommended but have not been adequately studied.

Urologic referral should be considered for men with the chronic pelvic pain syndrome who have significant lower urinary tract symptoms or continue to report symptoms after empirical therapy. Men with persistent symptoms of obstruction of the lower urinary tract or irritative symptoms on voiding could have obstruction of the bladder outlet, which is surgically correctable.

AREAS OF UNCERTAINTY

The causes of the chronic pelvic pain syndrome remain poorly understood and appear to encom-

pass heterogeneous conditions. Additional data are needed from large randomized trials to guide management of the condition.

GUIDELINES

There are no formal guidelines for the management of chronic bacterial prostatitis or the chronic pelvic pain syndrome.

CONCLUSIONS AND RECOMMENDATIONS

The first step in evaluating patients with pelvic pain and irritative symptoms on voiding, such as the patient described in the vignette, is to determine whether the symptoms are associated with infection of the urinary tract, the prostate, or both. If the patient had documented bacterial urinary tract infection, I would recommend treating the current infection on the basis of bacterial susceptibility with a drug that does not penetrate the prostate, such as nitrofurantoin, and then performing cultures to localize the area of infection. If the results were consistent with the presence of chronic bacterial prostatitis, I would recommend a 4-week course of therapy with an antimicrobial agent that penetrates the prostate, preferably a fluoroquinolone, with follow-up for recurrent infection.

In the absence of evidence of urinary tract infections that are associated with symptoms, an infectious cause is unlikely. In such cases, the therapy should be guided by the patient's preferences and its effects on symptoms monitored according to scores on the NIH Chronic Prostatitis Symptom Index. On the basis of data from randomized trials (although these are inconsistent), I would recommend a 12-week trial of alpha-blocker therapy, which can be continued if a good response is observed.

Urologic referral is recommended for patients with significant lower urinary tract symptoms in addition to chronic pelvic pain or in whom the response to empiric therapy is inadequate. Symptoms of discomfort after ejaculation, as in the patient described, might be associated with an uncommon but remediable problem such as obstruction of the ejaculatory duct.

Supported in part by a grant (U01 DK65277-04) from the NIH.

Dr. Schaeffer reports having received consulting fees from DepoMed, Ortho-McNeil, Pfizer, and Schwarz Biosciences, and research support from Bayer. No other potential conflict of interest relevant to this article was reported.

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