

Diagnosis and Treatment of Chronic Abacterial Prostatitis: A Systematic Review

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Purpose: The optimal management of chronic abacterial prostatitis is not known. A systematic review of the literature was done to answer the following questions: Are there accurate, reliable tests to diagnose chronic abacterial prostatitis? Are there effective therapies for it?

Data Sources: Studies were identified by searching MEDLINE (1966 to 1999), the Cochrane Library, and bibliographies of identified articles and reviews and by contacting an expert.

Study Selection: Diagnostic test articles were included if they reported on controlled studies; treatment articles were included if they reported on randomized or controlled trials. No language restrictions were applied.

Data Extraction: For each selected article, two investigators independently extracted key data on study design, patient characteristics, diagnostic test or treatment characteristics, and outcomes.

Data Synthesis: 19 diagnostic test articles and 14 treatment trials

met the inclusion criteria. The disparity among studies in design, interventions, and other factors precluded quantitative analysis or pooling of the findings. Diagnostic test articles included 1384 men (mean age, 33 to 67 years) and evaluated infection; inflammation, immunology, and biochemistry; psychological factors; and ultrasonography. Treatment trials included 570 men (mean age, 38 to 45 years) and evaluated medications used to treat benign prostatic hyperplasia, anti-inflammatory drugs, antibiotics, chemotherapy, and miscellaneous medications. No trial was done in the United States.

Conclusions: There is no gold-standard diagnostic test for chronic abacterial prostatitis, and the methodologic quality of available studies of diagnostic tests is low. The few treatment trials are methodologically weak and involved small samples. The routine use of antibiotics and α -blockers to treat chronic abacterial prostatitis is not supported by the existing evidence.

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Previously considered the purview of urologists, patients with prostate conditions are also cared for by primary care physicians. Because the three prostate diseases (benign prostatic hyperplasia, prostate cancer, and prostatitis) can coexist, they are sometimes confused with one another. The symptom complexes of chronic prostatitis and benign prostatic hyperplasia overlap (1), so that older men with chronic prostatitis may receive a misdiagnosis of benign prostatic hyperplasia. In addition, because prostatitis can increase prostate-specific antigen levels (2, 3), unnecessary prostate biopsies and detection of clinically insignificant prostate cancer may result. Because of the interrelations among these conditions, improved knowledge of chronic prostatitis among primary care physicians could positively affect the quality of care given to patients with benign prostatic hyperplasia and prostate cancer.

From 1990 to 1994, persons with a diagnosis of prostatitis accounted for almost 2 million outpatient visits per year in the United States, accounting for 8% of visits to urologists and 1% of visits to primary care physicians (4). Although chronic prostatitis is common, it is enigmatic (5) and has been called "a wastebasket of clinical ignorance"

(6). The hallmark of chronic prostatitis is its symptom complex of pelvic area pain and lower urinary tract symptoms (7, 8). The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) (Figure) is a reliable, valid, self-administered index that measures symptoms of chronic prostatitis and their impact on daily life (9). The health status impact of chronic prostatitis as measured by the Sickness Impact Profile is within the range of scores for patients with a history of myocardial infarction, angina, or Crohn disease (10).

The wide scope of recommended treatments for chronic prostatitis indicates how little is known about what causes the condition and how to diagnose and treat it. Chronic prostatitis often causes frustration on the part of the physician (11, 12), confusion and dissatisfaction on the part of the patient (13, 14), variable thresholds for referral (15), and potentially inappropriate antibiotic use (4).

We sought to examine the evidence regarding the operating characteristics of diagnostic tests and the effectiveness of therapies for chronic abacterial prostatitis. We briefly describe the clinical presentations of prostatitis as summarized in two recent reviews (16, 17).

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

| | | |
|--|--|---|
| <p>Pain or Discomfort</p> <p>1. In the last week, have you experienced any pain or discomfort in the following areas?</p> <p>a. Area between rectum and testicles (perineum) Yes No <input type="checkbox"/>₁ <input type="checkbox"/>₀</p> <p>b. Testicles <input type="checkbox"/>₁ <input type="checkbox"/>₀</p> <p>c. Tip of the penis (not related to urination) <input type="checkbox"/>₁ <input type="checkbox"/>₀</p> <p>d. Below your waist, in your pubic or bladder area <input type="checkbox"/>₁ <input type="checkbox"/>₀</p> | | <p>6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?</p> <p><input type="checkbox"/>₀ Not at all <input type="checkbox"/>₁ Less than 1 time in 5 <input type="checkbox"/>₂ Less than half the time <input type="checkbox"/>₃ About half the time <input type="checkbox"/>₄ More than half the time <input type="checkbox"/>₅ Almost always</p> |
| <p>2. In the last week, have you experienced:</p> <p>a. Pain or burning during urination? Yes No <input type="checkbox"/>₁ <input type="checkbox"/>₀</p> <p>b. Pain or discomfort during or after sexual climax (ejaculation)? <input type="checkbox"/>₁ <input type="checkbox"/>₀</p> | | <p>Impact of Symptoms</p> <p>7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?</p> <p><input type="checkbox"/>₀ None <input type="checkbox"/>₁ Only a little <input type="checkbox"/>₂ Some <input type="checkbox"/>₃ A lot</p> |
| <p>3. How often have you had pain or discomfort in any of these areas over the last week?</p> <p><input type="checkbox"/>₀ Never <input type="checkbox"/>₁ Rarely <input type="checkbox"/>₂ Sometimes <input type="checkbox"/>₃ Often <input type="checkbox"/>₄ Usually <input type="checkbox"/>₅ Always</p> | | <p>8. How much did you think about your symptoms, over the last week?</p> <p><input type="checkbox"/>₀ None <input type="checkbox"/>₁ Only a little <input type="checkbox"/>₂ Some <input type="checkbox"/>₃ A lot</p> |
| <p>4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?</p> <p><input type="checkbox"/>₀ <input type="checkbox"/>₁ <input type="checkbox"/>₂ <input type="checkbox"/>₃ <input type="checkbox"/>₄ <input type="checkbox"/>₅ <input type="checkbox"/>₆ <input type="checkbox"/>₇ <input type="checkbox"/>₈ <input type="checkbox"/>₉ <input type="checkbox"/>₁₀</p> <p>NO PAIN AS PAIN AS YOU CAN IMAGINE</p> | | <p>Quality of Life</p> <p>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?</p> <p><input type="checkbox"/>₀ Delighted <input type="checkbox"/>₁ Pleased <input type="checkbox"/>₂ Mostly satisfied <input type="checkbox"/>₃ Mixed (about equally satisfied and dissatisfied) <input type="checkbox"/>₄ Mostly dissatisfied <input type="checkbox"/>₅ Unhappy <input type="checkbox"/>₆ Terrible</p> |
| <p>Urination</p> <p>5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?</p> <p><input type="checkbox"/>₀ Not at all <input type="checkbox"/>₁ Less than 1 time in 5 <input type="checkbox"/>₂ Less than half the time <input type="checkbox"/>₃ About half the time <input type="checkbox"/>₄ More than half the time <input type="checkbox"/>₅ Almost always</p> | | <p>Scoring the NIH-CPSI Domains</p> <p><i>Pain:</i> Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3, and 4 = _____</p> <p><i>Urinary Symptoms:</i> Total of items 5 and 6 = _____</p> <p><i>Quality-of-Life Impact:</i> Total of items 7, 8, and 9 = _____</p> |

Definitions and Classification of Prostatitis

The umbrella term *prostatitis* is frequently used to refer to several types of prostatitis, each of which has different characteristics and proposed treatments. Although the traditional classification system for prostatitis developed by Drach and colleagues (18) is popular, it has never been tested (Table 1). Because the cause of prostatitis is unclear, Drach and colleagues' etiology-based classification system may contribute to the confusion (7). A chronic prostatitis

classification system recently established by the NIH (19), based closely on the traditional classification, uses the term *chronic pelvic pain syndrome* to reflect the uncertainty about whether chronic nonbacterial prostatitis and prostatodynia are, in fact, related to the prostate gland (Table 1). The NIH classification system has not been validated.

The diagnosis of chronic prostatitis is generally based more on history than on physical examination findings or results of investigative studies. Although the four-glass test

(20), also known as the bacterial localization study, has for decades been the standard test for categorizing chronic prostatitis as infectious, inflammatory, or noninflammatory (21–23), its accuracy and reliability have not been clearly demonstrated. Furthermore, surveys of physicians have indicated that it is not widely used (24–27).

Although type I prostatitis (acute bacterial prostatitis) is relatively straightforward to diagnose and treat, it accounts for few cases of prostatitis. Chronic prostatitis is much more common and is more difficult to diagnose and treat. Of the types of chronic prostatitis, type II (chronic bacterial prostatitis) is rare; both types I and II account for only 5% to 10% of cases of prostatitis (28). Despite the paucity of such cases, antimicrobial therapy was prescribed in 45% of visits by men with genitourinary symptoms and a diagnosis of chronic prostatitis (4). Because more than 90% of cases of prostatitis are type III (chronic abacterial prostatitis), we focused our review on this type. We did not examine type IV prostatitis (asymptomatic inflammatory prostatitis) because this condition is diagnosed incidentally during evaluation for other disorders.

Epidemiology

Unlike benign prostatic hyperplasia and prostate cancer, which are predominantly diseases of older men, prostatitis affects men of all ages. Compared with men 66 years of age or older, the odds of a diagnosis prostatitis are 1.6-, 2.6-, and 2.1-fold greater in men 18 to 35 years of age, 36 to 50 years of age, and 51 to 65 years of age, respectively (4). The histologic prevalence of prostatitis ranges from 6% to 44% (16) and from 35% to 98% (29). Although these reviews provide compelling evidence that histologic prostatitis is common, the prevalence of clinically evident or symptomatic prostatitis is of greater importance to the patient and physician. Roberts and colleagues (30) estimated the prevalence of medically diagnosed prostatitis to be 11%.

Etiology

The cause of prostatitis is unknown in more than 90% of cases; the remaining 5% to 10% of cases are bacterial (28). The older literature describes potential determinants of the condition, such as sex hormone levels, diet, past

Table 1. Classification and Definition of Prostatitis*

| Traditional Classification† | | NIDDK Classification‡ | |
|-------------------------------|---|--|---|
| Category | Definition | Category | Definition |
| Acute bacterial prostatitis | Recovery of bacteria from prostatic fluid, purulence of fluid, and systemic signs of infectious illness (fever, chills, myalgia) | Type I (acute bacterial prostatitis) | Acute infection of the prostate |
| Chronic bacterial prostatitis | Recovery of bacteria in significant numbers from prostatic fluid in the absence of concomitant urinary infection, or significant systemic signs (as in acute bacterial prostatitis) | Type II (chronic bacterial prostatitis) | Recurrent infection of the prostate |
| Nonbacterial prostatitis | No recovery of significant numbers of bacteria from prostatic fluid, but the fluid consistently reveals microscopic purulence | Type III (chronic abacterial prostatitis/chronic pelvic pain syndrome) | No demonstrable infection |
| Prostatodynia | No recovery of significant bacteria or purulence in the prostatic fluid, but patients have persistent urinary urgency, dysuria, poor urinary flow, and prostatic discomfort | Type IIIA (inflammatory chronic pelvic pain syndrome) | Leukocytes in semen, expressed prostatic secretions, or post-prostatic massage urine |
| | | Type IIIB (noninflammatory chronic pelvic pain syndrome) | No leukocytes in semen, expressed prostatic secretions, or post-prostatic massage urine |
| | | Type IV (asymptomatic inflammatory prostatitis) | No subjective symptoms; detected by prostate biopsy or by the presence of leukocytes in expressed prostatic secretions or semen during evaluation for other disorders |

* NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases.

† Adapted from reference 8.

‡ Adapted from Summary Statement, National Institutes of Health/NIDDK Workshop on Chronic Prostatitis, 7–9 December 1995.

genitourinary disease, stress, psychological factors, allergy, and marital status (16). More recent studies have examined age (4, 30–33), ethnicity (4), infectious agents (including viral and sexually transmitted diseases) (34–42), uric acid levels (43, 44), sexual activity (31, 45, 46), autoimmunity (47, 48), prostatic cysts and calculi (49, 50), proinflammatory cytokines (51), and prostate biopsy (52).

Methods

We sought to answer two questions: Are there accurate, reliable tests to diagnose chronic abacterial prostatitis? Are there effective therapies for it?

Inclusion Criteria

Diagnostic Articles

Articles on diagnostic tests were included if they described a control group in addition to a group of men with a clinical diagnosis of chronic abacterial prostatitis.

Treatment Articles

Articles on treatment were included if they reported on randomized controlled trials or controlled clinical trials involving men with chronic abacterial prostatitis; described a control group that received placebo, sham intervention, or active pharmacologic or device therapy for chronic abacterial prostatitis; and provided outcomes data.

Identification of Relevant Articles

Diagnostic Articles

Diagnostic studies were identified by searching MEDLINE from 1966 through March 1999 using a previously developed strategy (53). The search combined 10 exploded Medical Subject Headings (*physical examination, medical history taking, professional competence, sensitivity and specificity, reproducibility of results, observer variation, diagnostic tests-routine, decision support techniques, Bayes theorem, and mass screening*) and 2 text word categories (*physical exams and sensitivity and specificity*). The resulting search set was combined with the term *prostatitis* (exploded). The search strategy identified four studies that met inclusion criteria. The addition of the terms *nonbacterial prostatitis, chronic abacterial prostatitis, chronic pelvic pain syndrome, laboratory techniques and procedures, and blood chemical analysis* yielded six more studies. The remaining nine studies assessed were identified by review of study bibliographies, the Cochrane Library, and review articles.

Treatment Articles

Randomized or controlled clinical trials of abacterial prostatitis were identified by searching MEDLINE from 1966 to March 1999. The search strategy combined an optimally sensitive search strategy for trials developed for the Cochrane Collaboration with the Medical Subject Headings (including all subheadings) *prostatitis, chronic nonbacterial prostatitis, chronic abacterial prostatitis, chronic pelvic pain syndrome, and prostatodynia* (54). The Cochrane Library, reference lists of identified trials, and previous reviews were also searched for additional trials. An expert in prostatitis (J. Curtis Nickel, MD) was asked to identify additional trials. No language restrictions were applied.

The MEDLINE search retrieved 60 potential studies for inclusion. Twelve studies met inclusion criteria, and an additional 4 were identified by using the alternative searching methods. Two studies were excluded because they included men with bacterial prostatitis (55, 56).

Data Abstraction and Appraisal of Study Quality

Diagnostic Articles

The study characteristics, patient demographic information, diagnostic procedure and assessment instruments, and results were abstracted independently by two reviewers. Discrepancies were resolved by discussion. The main outcome was the sensitivity and specificity of the diagnostic test. Secondary outcomes were factors associated with chronic abacterial prostatitis. As a measure of methodologic study quality for diagnostic test research, we assessed whether articles met the seven methodologic standards outlined by Reid and colleagues (57).

Treatment Articles

The study characteristics, patient demographic information, enrollment criteria, therapy allocation, adverse effects, outcomes, and reasons for dropout were extracted independently by two reviewers. The main outcome was the efficacy of treatment for chronic abacterial prostatitis compared with placebo, sham, or active control in improving urologic symptom scale scores or global report of urinary tract symptoms. Secondary outcomes were changes in the prostate examination, uroflowmetry, urodynamics, analysis of urine, expressed prostatic secretions and seminal fluid, and prostate ultrasonography.

Statistical Methods

The 14 clinical trials that met our inclusion criteria differed in terms of interventions, study duration, assessment measures, and clinical outcomes. This disparity precluded quantitative analysis or pooling of findings across trials.

Results

Are There Accurate, Reliable Tests To Diagnose Chronic Abacterial Prostatitis?

Nineteen diagnostic test articles including 1384 men (mean age, 33 to 67 years of age) met the inclusion criteria. Four studies described the ethnic characteristics of the study sample (31, 47, 51, 58). Four studies reported the sensitivity and specificity of the test (50, 59–61). Twelve studies were done in the United States. One study was reported in a language other than English (62). No study met more than two of the seven methodologic standards (57); 12 met only one. Seven studies were more etiologic than diagnostic in nature; therefore, the standards did not always apply.

The diagnostic test articles evaluated infection (31, 39, 59, 63); inflammation, immunology, and biochemistry (47, 51, 60, 64–68); psychological factors (15, 58, 69); and ultrasonography (50, 61, 62, 70) (Table 2).

Infection

Although by definition men with chronic abacterial prostatitis do not have evidence of bacterial infection on routine cultures, investigators have postulated that fastidious or uncommon organisms that are undetected by conventional cultures cause the condition. Shortliffe (63) and Berger (31) and their colleagues examined the role of such organisms as *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Staphylococcus* species, *Streptococcus* species, and anaerobic bacteria. Neither study identified an infectious cause of chronic abacterial prostatitis. In contrast, one study (39) using the four-glass test revealed positive cultures from prostatic secretions; coagulase-negative staphylococci were the most common isolates (68%).

The bacterial localization study, or four-glass test, is the textbook standard test for chronic prostatitis. This segmented, quantitative culture technique of the lower urinary tract involves an initial-stream urine sample, a mid-stream urine sample, a sample of expressed prostatic secretion obtained after prostate massage, and a post-pros-

tatic massage urine sample. No studies that met our criteria evaluated the validity or diagnostic accuracy of the four-glass test. To simplify this test, Nickel (59) evaluated a two-glass test (the Pre and Post Massage Test), which involves culture and microscopic examination of urine obtained only before and after prostatic massage. With the four-glass test used as the gold standard, Nickel's "two-glass test" had a sensitivity and specificity of 91%, respectively, for classifying men with prostatitis.

Inflammation, Immunology, and Biochemistry

Investigators have postulated that chronic abacterial prostatitis is an inflammatory or immunologic process. Anderson and Weller (64) evaluated leukocyte counts and leukocyte cell types in prostatic secretions as indicators of prostatic inflammation. Men with chronic abacterial prostatitis had more leukocytes and macrophages than did controls.

Alexander and colleagues (51) found a strong correlation between levels of interleukin-1 β and tumor necrosis factor- α in the semen of men with the chronic pelvic pain syndrome. This finding suggests that seminal proinflammatory cytokines may provide an objective measure of disease in these patients (51). The lack of correlation between cytokine levels and the leukocyte count in expressed prostatic secretions suggests that leukocyte counts do not distinguish a meaningful subpopulation of symptomatic patients. Nadler and coworkers (65) also found higher levels of interleukin-1 β in men with inflammatory chronic abacterial prostatitis and noninflammatory chronic abacterial prostatitis than in controls. In contrast to Alexander and colleagues, Nadler and coworkers found a direct correlation between the leukocyte count and interleukin-1 β level in expressed prostatic secretions. Neither study reported sensitivity or specificity. Alexander and colleagues also found that some men with chronic abacterial prostatitis have evidence of an autoimmune response to prostatic proteins (47).

Investigators have hypothesized that immunologic analysis may be a better diagnostic tool than the bacterial localization study. Two small studies (66, 67) suggested that immunologic analysis of prostatic fluid for antigen-specific antibodies may aid in the differential diagnosis between bacterial and abacterial prostatitis. Neither study provided the sensitivity or specificity.

Zinc has been examined as a marker of prostatic secre-

Table 2. Studies of Diagnostic Tests for Chronic Abacterial Prostatitis*

| Study (Reference) | Focus | Patients, n | Mean or Median Age, y | Diagnostic Procedure and Assessment Instruments | Results and Comments |
|---|---|---|-----------------------|--|---|
| Infection | | | | | |
| Shortliffe et al. (63) | Antibody titers in men with CAP or BP | 44 men with CAP 25 controls 15 men with BP | – – – | EPS antibodies against several organisms measured by ELISA | 9 of 44 men with CAP had detectable antichlamydial antibody titers compared with 3 of 25 controls and 2 of 13 patients with BP (results not statistically significant) |
| Berger et al. (31) | Case-control study of infectious agents in men with suspected CAP | 34 men with CAP 50 controls | 40 33 | Analysis of urethral and EPS secretions for <i>Chlamydia</i> species; four-glass test (bacterial localization cultures); EPS leukocyte count | <i>C. trachomatis</i> was not isolated from any patient or control; 11 of 27 men with CAP had >1000 leukocytes/mm ³ in EPS compared with 0 of 44 controls (<i>P</i> < 0.001) |
| Lowentritt et al. (39) | Bacterial infection in prostatodynia | 22 men with prostatodynia 16 controls | 40 31 | 2-glass urine cultures and ELISA | 9 men (41%) with prostatodynia and 1 control (6%) had positive EPS cultures (<i>P</i> < 0.025); no IgG immune differences were found between patients and controls |
| Nickel (59) | Screening for prostatitis with culture and microscopic examination of urine before and after prostate massage | 39 men with CAP 14 men with BP 59 patients from the literature† | – – – | The "Pre and Post Massage Test" (2-glass test); the Meares–Stamey was the gold standard | The 2-glass test led to the same diagnosis in 91% of patients; sensitivity and specificity were 91% |
| Inflammation, immunology, and biochemistry | | | | | |
| Anderson and Weller (64) | Examination of leukocyte counts and cell types as indicators of prostatic inflammation | 43 men with CAP 20 controls | 39 35 | Urine and EPS analyzed for bacteria and leukocytes | Compared with controls, men with CAP had significantly higher EPS leukocyte counts (4543 ± 760 cells/mm ³ vs. 887.88 ± 111 cells/mm ³ ; <i>P</i> < 0.01) and significantly more macrophages (942 ± 135 cells/mm ³ vs. 115 ± 25 cells/mm ³) |
| Alexander et al. (51) | Differences in cytokines interleukin-1β and levels of tumor necrosis factor-α in semen of men with CAP | 18 men with CAP 8 controls | 38 33 | Seminal plasma measured by using two-antibody ELISA | Mean ± SE levels of interleukin-1β were 246 ± 63 pg/mL in patients with CAP and 27 ± 10 pg/mL in controls (<i>P</i> < 0.05); levels of tumor necrosis factor-α were 98 ± 39 pg/mL in patients with CAP and 17 ± 8 pg/mL in controls (<i>P</i> < 0.05); inflammation may be a feature of CAP |
| Nadler et al. (65) | Differences in interleukin-1β levels in men with CPPS | 19 men divided into 4 groups (2 CPPS+, BPH, control) | – – | EPS measured by ELISA | Mean levels of interleukin-1β were higher in men with inflammatory CPPS (113.84 pg/mL) than in controls (11.72 pg/mL; <i>P</i> < 0.05); direct correlation was found between leukocyte count in EPS and interleukin-1β levels in EPS (<i>R</i> = 0.65; <i>P</i> < 0.05); interleukin-1β may be useful in classification of CPPS, and cytokines may play a role in the pathogenesis of CPPS |
| Alexander et al. (47) | Autoimmune component of CPPS by examining T-lymphocyte reactivity to seminal plasma | 10 men with CAP or CPPS 15 controls | – – | Assay of seminal plasma to detect specific proliferation of peripheral helper T lymphocytes | 3 men with CPPS and 0 controls had a specific recall antigen proliferation response to seminal plasma; some men with CPPS may have an autoimmune component to their disease |
| Wishnow et al. (66) | Immunologic response to gram-negative bacterial antigens in men with BP and CAP | 4 men with CAP 10 controls 6 men with BP | – – – | EPS IgA, IgG, and IgM levels measured by using solid-phase radioimmunoassay | BP was immunologically distinguishable from nonbacterial inflammation of the prostate |
| Shortliffe and Wehner (67) | Immunologic measures that may differentiate CAP from BP | 23 men with CAP 21 controls 23 men with BP | – – – | EPS IgA and IgG to Enterobacteriaceae were measured by using solid-phase radioimmunoassay | Higher levels of total IgA and IgG were found in men with CAP compared with controls (<i>P</i> < 0.001 and <i>P</i> < 0.02); however, lack of significant antibodies to common Enterobacteriaceae suggested that unidentified antigens may be responsible for the symptoms in this syndrome |

Continued on following page

Table 2—Continued

| Study (Reference) | Focus | Patients, <i>n</i> | Mean or Median Age, <i>y</i> | Diagnostic Procedure and Assessment Instruments | Results and Comments |
|---|---|---|------------------------------|---|---|
| Marmar et al. (68) | Zinc levels as an additional variable in the classification of prostatitis | 41 men with CAP and BP 17 controls | – – | EPS analyzed for bacterial culture, leukocyte count, and zinc assay | Zinc levels were significantly lower in men with CAP (24.4 ± 15.9 mg/dL) and BP (21.4 ± 12.4 mg/dL) than in controls (46.8 ± 20.8 mg/dL) and men with prostatodynia (50.2 ± 13.2 mg/dL) |
| Zaichick et al. (60) | Differences in zinc levels in men with CAP | 28 men with CAP 22 controls 28 men with BPH 13 men with cancer | 49 49 64 67 | EPS obtained by digital rectal examination was analyzed for zinc levels | No difference in zinc levels was seen among the CAP, control, and BPH groups, but a significant decrease was seen in men with prostate cancer ($P < 0.001$); sensitivity and specificity were calculated for cancer (93% and 96%) but not CAP |
| Psychological factors de la Rosette et al. (15) | Personality variables in CAP | 50 men with CAP 50 men seen for vasectomy | 40 39 | Nederlandse Verkote MMPI§ | Depression and a tendency to somatize were key variables that distinguished patients with chronic prostatitis from patients undergoing vasectomy |
| Berghuis et al. (58) | Psychological and physical factors associated with CAP | 51 men with CAP 34 controls | 41 38 | MMPI; Brief Symptom Inventory; Personal Attributes Inventory; prostate-specific antigen level; EPS cell counts; electromyography | Patients with CAP scored higher than controls for hypochondriasis, depression, hysteria, and somatization and lower on masculine instrumentality scales; groups did not differ significantly in perineal muscle tension |
| Egan and Krieger (69) | Psychological factors in men with painful CAP | 20 men with CAP 20 men with chronic low-back pain | – – | MMPI and a structured interview using DSM-III criteria for major depression | The CAP group differed from the low-back pain group in the impact of pain problem on their personal relationships; 60% (12 of 20) of men with CAP met criteria for major depression |
| Ultrasonography Doble and Carter (61) | Ultrasonographic findings in prostatitis | 200 men 35 controls | 40 36 | TRUS scans were analyzed for parenchymal signs associated with chronic prostatitis; the Meares–Stamey test was the gold standard | 7 of 8 ultrasonographic signs were associated with symptoms of prostatitis compared with controls; sensitivity increased with higher leukocyte counts, but specificity was not sufficient to differentiate clinical groups |
| de la Rosette et al. (70) | Ultrasonographic findings in CAP | 22 men with CAP 22 men "without complaints" | 41 35 | TRUS | CAP cannot be diagnosed with certainty by TRUS, although many abnormalities were seen on TRUS |
| Sauvain et al. (62) | Power Doppler ultrasonography to improve detection of prostate cancer or inflammation of the prostate | 17 men with CAP 15 controls 25 men with BP 23 men with cancer | – – – – | Power Doppler ultrasonography of the peripheral prostate | Isolated capsular artery sometimes present in 9 of 17 men with CAP |
| de la Rosette et al. (50) | TRUS as a complement to digital rectal examination in diagnosing prostatitis | 32 men with CAP 81 men with BPH | – – | TRUS analyzed by using automated analysis of ultrasonographic prostatic images compared with digital rectal examination; prostate histology was the "gold standard" | Sensitivity of TRUS with automated analysis was 90.6%; specificity was 64.2% |

* BP = bacterial prostatitis; BPH = benign prostatic hyperplasia; CAP = chronic abacterial prostatitis; CPPS = chronic pelvic pain syndrome; DSM-III = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition; ELISA = enzyme-linked immunosorbent assay; EPS = expressed prostatic secretions; MMPI = Minnesota Multiphasic Personality Inventory; TRUS = transrectal ultrasonography.

† Includes men with CAP and BP. Results of segmented cultures were available for the 59 patients and were reevaluated.

‡ The CPPS group was divided into inflammatory (>10 leukocytes per high-power field in EPS) and noninflammatory (≤ 10 leukocytes per high-power field in EPS).

§ The Dutch short form of the MMPI.

|| Includes men with chronic prostatitis ($n = 105$), prostatodynia ($n = 54$), and borderline prostatitis ($n = 41$).

tory function. Marmar and associates (68) found that zinc levels in men with chronic abacterial prostatitis and men with bacterial prostatitis were significantly lower than those in controls and men with prostatodynia; the investigators

concluded that measurement of zinc levels may help in the differential diagnosis and classification. In contrast, Zaichick and colleagues (60) found no differences in zinc levels among patients with chronic abacterial prostatitis,

Table 3. Summary of Clinical Trials of Treatment of Chronic Abacterial Prostatitis*

| Study (Reference) | Intervention | Patients, <i>n</i> | Mean Age, <i>y</i> | Study Duration | Outcomes and Assessment Instruments | Results | Adverse Events and Dropouts |
|---|--|--|--------------------|----------------|---|--|---|
| Finasteride and α-blockers | | | | | | | |
| Leskinen et al. (71) | Finasteride, 5 mg, vs. placebo | Finasteride: 31† Placebo: 10† | – | 12 months | Symptom changes, by Prostatitis Symptom Severity Index score, prostatism score, and pain evaluation; uroflowmetry; prostate-specific antigen level; prostate volume | Symptom scores decreased significantly in the finasteride group ($P < 0.001$, Prostatitis Symptom Severity Index; $P < 0.05$, prostatism score), but groups did not differ significantly for pain; groups differed significantly for changes in prostate volume ($P < 0.03$) and serum prostate-specific antigen level ($P < 0.02$) | Finasteride: 3 patients had partial impotence; 4 dropouts Placebo: 2 dropouts |
| de la Rosette et al. (75) | Alfuzosin, 2.5 mg three times daily, vs. placebo | Alfuzosin: 10‡ Placebo: 10‡ | 39.4 | 6 weeks | Symptom changes by symptom score; urodynamics | Symptom score ($P = 0.01$), maximal flow ($P = 0.01$), flow time ($P = 0.03$), and time to maximal flow ($P = 0.01$) improved in the alfuzosin group; only change in maximal flow was significant compared with placebo | Alfuzosin: transient decrease in systolic blood pressure in 4 patients; slight decrease in libido in 2 patients |
| Dunzendorfer et al. (77) | Phenoxybenzamine, 10 mg twice daily, vs. placebo | Phenoxybenzamine: 17 Placebo: 13 | 39 | 12 | Symptom changes (pain evaluation); erythrocyte and leukocyte counts in urine after prostate palpation | Improvements in pain outcomes ($P < 0.05$) at 6 weeks. Decreased erythrocyte count in urine with phenoxybenzamine ($P < 0.001$) at 12 weeks | Phenoxybenzamine: orthostatic symptoms, aspermia |
| Osborn et al. (82) | Phenoxybenzamine, 10 mg/d for 3 days, then twice daily; baclofen, 5 mg three times daily for 3 days, then 10 mg three times daily; placebo (crossover trial) | 37‡ | 42 | – | Symptom response and peak urine flow | Satisfactory symptomatic response: phenoxybenzamine, 50% (13/27); baclofen, 37% (10/27); placebo, 8% (4/10) ($P = 0.027$ § for phenoxybenzamine vs. placebo); groups did not differ for peak urine flow | 10 dropouts Phenoxybenzamine: reflux ejaculation |
| Anti-inflammatory medications | | | | | | | |
| Muraro (73) | Seaprose S, 30 mg, plus hyperthermia (seven 1-hour sessions at 42.5–43.5 °C) vs. hyperthermia alone | Combination therapy: 10 Monotherapy: 10 | 42.5 | 2 weeks | Symptom changes by instrumental tests (uroflowmetry and transurethral prostatic echography) | Decrease in spontaneous pain: combination therapy, 70%; monotherapy, 11.1%. Decrease in pain on palpation: combination therapy, 70.6%; monotherapy, 20% | None reported |
| Wedren (76) | Pentosan polysulfate sodium, 100 mg twice daily, vs. placebo | Pentosan polysulfate: 15 Placebo: 15 | 37.7 | 3 months | Symptom changes by physician rating of treatment and symptom score; uroflowmetry | Physician-rated improvement of myalgia and arthralgia ($P < 0.01$) | Pentosan polysulfate: diarrhea, in 2 patients, 5 dropouts Placebo: 1 dropout |
| Antibiotics | | | | | | | |
| Simmons and Thin (81) | Minocycline, 100 mg twice daily, vs. diazepam, 5 mg | Minocycline: 20 Diazepam: 21 | – | 3 months | Symptom changes; polymorphonuclear leukocyte counts in expressed prostatic secretion | Groups did not differ in symptom improvement; decrease in leukocyte count in expressed prostatic secretions was 35.2% with minocycline and 8% with diazepam | Minocycline: esophagitis in 1 patient, 2 dropouts |
| Thermotherapy | | | | | | | |
| Nickel and Sorenson (72) | TUMT (1-hour session at 45–60 °C) vs. sham treatment | TUMT: 10 Sham: 10 | 45.3 | 21 months | Symptom changes by quality-of-life score, American Urological Association index, prostatitis symptom frequency and severity; subjective global assessment | At 3 months, quality-of-life score ($P < 0.05$) and prostatitis symptom severity scores ($P < 0.05$) were improved; for subjective global assessment (for >50% improvement), TUMT, 70% (7/10), and sham, 10% (1/10) | Transient and resolved in 4 men (for example, hematuria) |

Table 3—Continued

| Study (Reference) | Intervention | Patients, <i>n</i> | Mean Age, y | Study Duration | Outcomes and Assessment Instruments | Results | Adverse Events and Dropouts |
|------------------------|--|--|-------------|----------------|--|--|--|
| Montorsi et al. (74) | TRMH, 3 groups: 1) 1 session/wk for 4 weeks; 2) 1 session/wk for 6 weeks; 3) 2 sessions/wk for 3 weeks (42.5 ± 0.5 °C) | Group 1: 18† Group 2: 17† Group 3: 19‡ | 38.2 | 26 months | Subjective changes in symptoms (modified Boyarsky scale); self-rated improvement in quality of life; uroflowmetry; ultrasonography of the prostate | Subjective symptom score significantly improved in all patients at long-term follow-up; 50% of men reported improvement in quality of life | "Almost all" men had transient hematuria; 2 had urinary tract infection, 1 had epididymitis, 1 had hemospermia |
| Vassily et al. (78) | TRMH vs. sham treatment (6 sessions over 2 weeks); all patients received antibacterial and anti-inflammatory therapy | TRMH: 80 Sham: 20 | — | — | Symptom changes by symptom scores; prostate secretion analysis and spermography | Symptomatic improvement: TRMH, 75%; sham, 52.5% Prostate secretion analysis: "significant improvements in both groups" | None reported |
| Shah et al. (79) | TRMH [four 1-hour sessions at 43.8 °C vs. sham treatment (37 °C)] | TRMH: 15† Sham: 15† | — | 2–3 weeks | Symptom changes by symptom score; treatment was successful if improvement was >50% | Treatment success with TRMH was 68%, 57%, and 55% at end of treatment and 6 weeks' and 3 months' follow-up, respectively; placebo effect of 10% | No significant complications were reported; 2 dropouts in the sham treatment group |
| Strohmaier et al. (83) | 2 TRMH (39.5 °C or 43 °C, 1 or 2 sessions per week); parallel medication (doxycycline or placebo) | 17‡ (14 analyzed) | 30–50 | 2–4 weeks | Subjective symptoms; urinalysis; urodynamics | Marked subjective improvement in all patients; urodynamic variables unchanged | None reported |
| Miscellaneous | | | | | | | |
| Persson et al. (44) | Group 1: allopurinol, 300 mg, plus placebo Group 2: allopurinol, 300 mg twice daily Group 3: placebo | Group 1: 18 Group 2: 16 Group 3: 20 | — | 240 days | Subjective discomfort scale; urate (serum, urine, expressed prostatic secretion) and xanthine concentrations; leukocyte count | Subjective discomfort improvement (<i>P</i> = 0.003) and "significant effects" on urate and xanthine concentrations | None reported; 20 dropouts across all groups |
| Okada et al. (80) | PPC (amino acid preparation) vs. pollen extract | PPC: 32 Pollen extract: 30 | — | 4 weeks | Subjective symptoms; changes in prostate (tenderness, swelling, and sclerotic change) | Moderate to excellent improvement in subjective symptoms: PPC, 50.5%, pollen extract, 36.7%; alleviation of prostate swelling rated excellent: PPC, 76.9%, pollen extract, 35.7% | "No severe side effects" |

* TRMH = transrectal microwave hyperthermia; TUMT = transurethral microwave hyperthermia.

† Men with inflammatory chronic pelvic pain syndrome, previously known as chronic nonbacterial prostatitis.

‡ Includes men with prostatodynia.

§ Based on three-arm trial. *P* value for statistical significance 0.05/3 = 0.019.

benign prostatic hyperplasia, and controls; however, patients with cancer had significantly lower zinc levels. Neither study provided information on sensitivity and specificity.

Psychological Factors

The possible role of psychological factors in chronic prostatitis has been examined (15). Lack of treatment response has been attributed to three main factors: neuroti-

cism, psychosomatization, and sexual problems. None of these ideas has been substantiated.

Berghuis and associates (58) examined both psychological and physical factors. They found that patients with chronic abacterial prostatitis consistently scored higher than controls on measures of hypochondriasis, depression, hysteria, and somatization and lower on masculine instrumentality scales. Patients did not differ from controls in perineal muscle tension as measured by electromyography.

In another study (69), more than half of the patients with chronic abacterial prostatitis met criteria for major depression. None had received this diagnosis previously or were receiving medication for depression; major depression may therefore be an underrecognized condition in men with chronic abacterial prostatitis. Depression and a tendency to somatize were key variables that distinguished patients with chronic abacterial prostatitis from controls (15). The psychological profile of patients before the onset of chronic prostatitis symptoms was not reported; therefore, causality cannot be determined. None of the studies provided the sensitivity and specificity.

Ultrasonography

Several studies have examined ultrasonography as a diagnostic test for chronic prostatitis. Doble and Carter (61) found that seven of eight ultrasonographic signs were significantly associated with the presence of symptoms of chronic prostatitis compared with controls; sensitivity and specificity were calculated for each sign. Although the sensitivity of ultrasonography increased with higher leukocyte counts, the signs were not sufficiently specific to differentiate clinical groups. Similarly, even though several abnormalities were apparent on sonograms, transrectal ultrasonography could not diagnose chronic abacterial prostatitis with certainty in patients compared with controls (70). Sauvain and coworkers (62) used power Doppler ultrasonography to characterize hypoechoic areas in the peripheral areas of the prostate gland. Although an isolated capsular vessel was observed in 9 of 17 patients with chronic prostatitis, the sensitivity and specificity of this sign were not given. Using automated analysis of ultrasonographic prostatic images with prostatic histology as the gold standard, de la Rosette and colleagues (50) found a relatively high sensitivity but low specificity for the diagnostic test.

Are There Effective Therapies for Chronic Abacterial Prostatitis?

Fourteen treatment trials met our inclusion criteria. Of these, 7 were randomized, controlled trials (71–77) and 7 were controlled trials (44, 78–83). Five studies used placebo and three used sham intervention. A total of 570 participants (mean age, 38 to 45 years) were included. No studies reported the ethnic characteristics of participants. The duration of the studies ranged from 2 weeks to 1 year; maximum follow-up was 26 months. None of the studies

were done in the United States, and 4 were published in a language other than English (73, 77, 80, 83). All studies included information on symptom improvement, which was the primary outcome.

The articles studied medications used to treat benign prostatic hyperplasia (71, 75, 77, 82), anti-inflammatory medications (73, 76), antibiotics (81), thermotherapy (72, 74, 78, 79, 83), and miscellaneous medications (44, 80) (Table 3).

Medications Used To Treat Benign Prostatic Hyperplasia

Because the symptom complexes of chronic abacterial prostatitis and benign prostatic hyperplasia overlap, investigators have hypothesized that drug therapy for benign prostatic hyperplasia (such as finasteride and α -blockers) may help some men with chronic abacterial prostatitis. One trial (71) investigated whether the 5α -reductase inhibitor finasteride improved symptoms associated with inflammatory chronic pelvic pain syndrome, using validated symptom indices for prostatitis (72) and benign prostatic hyperplasia (84) plus a one-question, unvalidated pain evaluation. Compared with placebo, finasteride therapy reduced symptom scores for prostatitis and benign prostatic hyperplasia. However, pain ratings did not differ significantly between groups. Although the authors speculate that a reduction in prostate volume may alleviate symptoms, the mechanism by which finasteride would improve symptoms in patients with chronic abacterial prostatitis remains unknown.

de la Rosette and associates (75) examined use of the α -blocker alfuzosin in men with both inflammatory and noninflammatory chronic pelvic pain syndrome. Compared with placebo, the treatment group did not have significant reduction in symptoms. Duzendorfer and colleagues (77) investigated diphenoxylbenzamine therapy. In contrast to de la Rosette and associates, they found statistically significant improvements in several pain outcomes at 6 weeks of follow-up. The treatment group had orthostatic symptoms, but the number of patients with this side effect and the duration or severity were not described. In another study of α -blockers, 37 patients were enrolled in a double-blind crossover trial of phenoxybenzamine, baclofen, and placebo; treatments were given in random order and were each given for 1 month. Phenoxybenzamine improved symptoms in 50% of patients (82).

Anti-Inflammatory Medications

Muraro (73) compared the efficacy and safety of treatment with seaprose S (a proteolytic enzyme reported to have anti-inflammatory action) plus local prostatic hyperthermia with that of monotherapy with hyperthermia in 20 men with chronic abacterial prostatitis. No adverse effects were seen. Muraro found that spontaneous pain and pain on palpation were reduced more in the combination treatment group than in the monotherapy group. The duration of follow-up was not reported, and whether the pain instrument used was validated is unclear. Wedren (76) examined the efficacy of pentosan polysulfate sodium, an anti-inflammatory agent that has been used to treat interstitial cystitis. The treatment group ($n = 15$) was noted to have improvement in symptoms; however, the only symptoms that improved were physician-rated nonspecific myalgias and arthralgias. One third of the men receiving pentosan polysulfate sodium dropped out of the study.

Antibiotics

Although antibiotics are frequently used to treat chronic abacterial prostatitis, only one small randomized, controlled trial has addressed the efficacy and safety of antibiotic treatment for this condition (81), and that study had methodologic flaws. The control group was given diazepam rather than placebo; however, no evidence indicates that diazepam is superior to placebo in treating chronic abacterial prostatitis. The investigators found no difference in symptom improvement between the antibiotic (minocycline) and control groups.

Thermotherapy

Investigators have hypothesized that heat delivered to the prostate gland may either accelerate the natural resolution of an inflammatory response or alter the afferent nerve fibers that might transmit pain symptoms from an inflamed prostate (72). Five studies have evaluated transrectal microwave hyperthermia (TRMH) or transurethral microwave thermotherapy for chronic abacterial prostatitis; three of the studies used sham treatments.

Vassily and coworkers (78) noted greater symptom improvement in the TRMH-treated group (80 patients) than in the sham treatment group (20 patients). The investigators used a modified version of a validated prostatitis symptom index (72), raising questions about the validity of the instrument. The side effect profile was not described.

Another trial (79) compared TRMH with sham treatment in 30 men with inflammatory or noninflammatory chronic pelvic pain syndrome. The symptom assessment instrument was not described. Treatment success, defined as greater than 50% improvement in symptoms, was seen in 55% of men in the TRMH group at 3 months of follow-up. No complications were reported. Montorsi and associates (74) evaluated various treatment schedules of TRMH in men with inflammatory or noninflammatory chronic pelvic pain syndrome. Unlike in the studies that included a sham-treated control group, patients were randomly assigned to receive one of three therapeutic heat regimens that differed in total dose of heat delivered and in the time interval between each session. The symptom index used was an unvalidated modification of the Boyarsky index, which measures symptoms of benign prostatic hyperplasia. Symptoms significantly improved in all patients at long-term follow-up (26 months), and quality of life improved in 50% of men. Strohmaier and colleagues (83) randomly assigned patients to one of two therapeutic heat regimens that differed in total dose of heat delivered. Although TRMH did not affect objective measures, such as uroflow, residual volume, and urinalysis, marked improvement in symptoms was noted at 6 months (83).

One study investigated the safety and efficacy of transurethral microwave thermotherapy in 20 men (72). The strengths of the study included use of validated prostatitis symptom indices, a validated benign prostatic hyperplasia symptom score (84), and a quality-of-life question. Patients who received transurethral microwave thermotherapy had significantly improved symptom scores compared with sham-treated patients at 3 months of follow-up. However, 20% of patients experienced diverse temporary side effects, including hematuria, impotence, premature ejaculation, urinary tract infection, urinary retention, and urinary incontinence.

Miscellaneous Medications

Persson and Ronquist (43) theorized that backflow of urine into prostatic ducts causes prostatic inflammation by increasing concentrations of metabolites that contain purine and pyrimidine bases. Subsequently, a double-blind controlled study of allopurinol treatment in 54 men with 330 days of follow-up was performed (44). Although this small trial showed improvements in patient-reported symptoms, investigator-graded prostate pain, and bio-

chemical variables, the data provided, the measures used, and the statistics presented do not conclusively support the idea that changing the amounts of purine and pyrimidine bases in urine and prostatic secretions relieves symptoms (85, 86).

Okada and colleagues (80) compared an amino acid preparation, PPC with pollen extract (control group). Because no evidence indicates that pollen extract is effective in the treatment of chronic abacterial prostatitis, this control group is unsatisfactory. Improvement in symptoms was measured, although it is unclear whether a validated instrument was used. Fifty-one percent of the PPC-treated group (32 patients) compared with 37% of the pollen-treated group (30 patients) noted “moderate to excellent” symptom improvement. The statistical significance of this finding was not reported. The researchers reported no severe side effects, but they did not elaborate on other side effects that may have occurred.

Discussion

We have summarized a wide and complex body of literature and have shown the limitations of published primary research in terms of providing results in a valid and standardized fashion. We found that 1) no gold-standard diagnostic test exists for chronic abacterial prostatitis, including the widely recommended bacterial localization test (the four-glass test); 2) existing diagnostic studies are of low methodologic quality; 3) the few treatment trials are methodologically weak, have small samples, and were not done in the United States; and 4) more and better diagnostic, etiologic, and treatment studies are needed. The heterogeneity of the patient populations studied, the tests and treatments examined, and the outcomes measured precluded formal meta-analysis and quantitative estimation of efficacy.

Although experts may recommend or support an empirical course of antibiotics for chronic abacterial prostatitis (7, 17, 87), this practice is not supported by the existing evidence on disease etiology and treatment outcomes; further scrutiny is warranted. In addition, even though a recent review stated that α -blocker treatment is “likely to be beneficial” in chronic abacterial prostatitis (88), the routine use of α -blockers was not supported by the available evidence.

Our results support the following recommendations for clinical care and research:

1. The NIH chronic prostatitis classification system should be used to classify patients and code diagnoses.

2. Future studies of diagnostic and etiologic tests (including the unvalidated four-glass test) are needed and should meet methodologic standards, such as inclusion of the sensitivity and specificity of the test.

3. Clinicians who choose to perform the four-glass test should consider using the pre- and post-massage test (two-glass test) to classify patients with chronic prostatitis.

4. Because the symptom complex remains the hallmark of chronic abacterial prostatitis, the NIH-CPSI should be used to quantify symptoms and the impact on quality of life in men in whom the condition is suspected.

5. Routine use of antibiotics or α -blockers for chronic abacterial prostatitis is not supported by the existing evidence and deserves further scrutiny. In small studies, thermal therapy appears to have clinically significant benefit; further evaluation is merited.

6. Treatment trials in the United States are needed. Such trials should report important patient characteristics (such as ethnicity), details of the study design, assessment measures, and clinical outcomes. The Chronic Prostatitis Collaborative Research Network, which is funded by the National Institute for Diabetes and Digestive and Kidney Diseases, is planning the first of a series of adequately powered, randomized, controlled, double-blind clinical trials over the next several years (for more information, contact Kathleen Propert, ScD; kpropert@cceb.upenn.edu).

7. Physicians should understand the impact of chronic prostatitis on quality of life and potential for lost productivity. They should avoid routine use of unsubstantiated treatments that have greater potential for adverse events and costs versus benefits.

Addendum: After preparation of this article, a small (30 patients) randomized, controlled trial of 1 month’s duration was conducted in the United States. It compared the bioflavonoid quercetin with placebo for treatment of chronic abacterial prostatitis. Compared with placebo, quercetin was well tolerated and produced significant improvement in NIH-CPSI symptom scores ($P = 0.003$) (89).

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