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## Modified Meares-Stamey test

# Simplified prostatitis test is put to the test

Penny Allen

UT CORRESPONDENT



San Antonio—The Meares-Stamey four-glass test is the gold standard for localizing bacteria and assessing inflammation in the lower urinary tract of symptomatic men. The classifications of prostatitis—bacterial, nonbacterial, inflammatory, and noninflammatory—are based on it. But few clinicians actually perform the test.



Dr. Nickel

“It’s too expensive, it’s too difficult, and, in most patients, it doesn’t make any difference,” J. Curtis Nickel, MD, told *Urology Times*.

Before prescribing antibiotics for a man with prostatitis symptoms, some idea of whether bacteria are present in the lower urinary tract is important. Knowing that is all the more important in light of the Chronic Prostatitis Collaborative Research Network (CPCRN) study showing antibiotic therapy to be ineffective in heavily pretreated chronic prostatitis patients (*Arch Intern Med* 2004; 141:581-9). For these patients, “you have to do something,” said Dr. Nickel.

That “something” may be a simplified version of the Meares-Stamey test that analyzes just pre- and postprostatic massage urine; that is, midstream urine, then the initial stream after prostatic massage, “since you have to do a DRE anyway,” pointed out Dr. Nickel, who is professor of urology at Queen’s University in Kingston, Ontario.

Now he and other prostatitis experts in the National Institutes of Health’s multicenter CPCRN have examined whether the test could be useful in clinical practice. They presented the results of their analysis at the AUA annual meeting.

### Results compared

To gauge the accuracy of this approach, CPCRN investigators compared test data on 353 chronic prostatitis patients in the CPCRN database who had had complete

Meares-Stamey four-glass test results. They compared results of cultures and leukocyte counts of midstream and postprostatic massage urine specimens, known as VB2 and VB3 samples, with the complete results from VB1 (initial stream), VB2, expressed prostatic fluid (EPS), and VB3 specimens.

For analysis, the investigators carried out the Chi-square test to assess the association of leukocyte counts in EPS (used in the classic test) and VB3 specimens and constructed a receiver-operating-characteristic (ROC) curve to determine the optimal cutoff count of leukocytes in VB3 specimens that would predict the presence of leukocytes in EPS. Analysts also used 2x2 contingency tables to calculate the sensitivity and specificity of VB3 cultures in predicting EPS results and in predicting positive overall Meares-Stamey results.

The comparison of leukocyte counts in EPS and VB3 showed that leukocytes were highly likely ( $p < .0001$ ) to be present in EPS when any leukocytes were in the VB3 specimen. A cutoff of 3 leukocytes per high-power field in VB3 specimens predicted a count of 5<sup>+</sup> in EPS with a sensitivity of 76% and a specificity of 70%. A cutoff of 4 leukocytes per HPF in VB3 specimens predicted a count of 10 in EPS with a sensitivity of 62% and a specificity of 75%.

Finding bacteria in the VB3 specimen predicted bacteria in EPS with a sensitivity of 67.6% and a specificity of 96.5%. Localizing actual uropathogens to either EPS or VB3 confirmed a positive Meares-Stamey test.

Finding bacterial pathogens in the VB3 culture only predicted a positive Meares-Stamey test with a sensitivity of 75% and a specificity of 100%.

Although the modified test has a lower sensitivity than the Meares-Stamey test, “it’s better than doing no test at all,” said Dr. Nickel. Overall, the results are 96% to 98% accurate.

“We feel that we can actually say that this test is accurate enough for clinical practice,” he concluded. **UT**

# Quinolone-resistant *E coli* strain a major threat

Research also shows cytokines may serve as biomarkers for nonbacterial prostatitis

Mac Overmyer

UT CONTRIBUTING EDITOR

One by one, drug-resistant microbes have weakened or destroyed the efficacy of established antimicrobials. The appearance of a strain of urinary tract infection-associated *Escherichia coli* that is resistant to ciprofloxacin (Cipro, Proquin) is not necessarily a surprise, but it is a significant concern, according to Anthony J. Schaeffer, MD, chairman of the department of urology, Northwestern School of Medicine, Chicago.

A study documenting this resistant strain was one of several presented at the AUA annual meeting that merited comment from Dr. Schaeffer. Others included findings that PSA can remain elevated for extended periods following acute prostatitis, reports of two new markers for chronic prostatitis, and a study relating nanobacteria to prostatic stones in men with chronic pelvic pain syndrome.

**Ciprofloxacin-resistant *E coli* occur in 12% of UTIs overall, in only 2% of uncomplicated UTIs, but in 31% of all complicated UTIs. Risks for resistance are complicated UTI or previous exposure to quinolone antibiotics.**

"It has been understood for many years that the older, traditional drugs such as sulfa, penicillin, cephalosporin, and others have lost their efficacy due to the appearance of drug-resistant organisms. Unfortunately, we

are now seeing this same threat in a newer generation of broad-spectrum antimicrobials, the fluoroquinolones. This is a major problem," Dr. Schaeffer said.

Researchers from Japan found that 12.4% of *E coli* strains isolated from 202 patients with complicated or uncomplicated urinary tract infections were resistant to ciprofloxacin. Only 2.3% of the strains isolated from uncomplicated UTIs were resistant, but 30.6% of those from complicated UTIs were resistant. The investigators reported that patients who did not respond to a fluoroquinolone did respond to cephalosporin.



Dr. Schaeffer

**In nearly 80% of patients with acute prostatitis, PSA is elevated, and it can remain so for months.**

Dr. Schaeffer cautioned that sustained elevated PSA levels following acute prostatitis should not be misinterpreted.

"Although acute prostatitis is a rare condition, it can cause marked symptoms and changes in the prostate which will be evidenced by a marked rise in PSA. These changes can persist and can mislead in the direction of other diagnoses. The take-home message is to monitor the PSA until it ceases to diminish. When it is stable for several months, establish that finding as the nadir and proceed from there," he advised.

A multicenter retrospective Korean study of 225 patients with acute prostatitis showed that high fever was the most common complaint, and that *E coli* was the most frequently found organism. PSA was elevated (mean 26.5 [4.2 to 163.0] ng/mL) in 78% of the patients and remained elevated in more than half the patients through 12 weeks of therapy.

**New research shows evidence of biomarkers for chronic pelvic pain syndrome, or type III nonbacterial prostatitis.**

A study from Dr. Schaeffer's own lab identified two new biomarkers in expressed prostatic secretions that appear not only to have a high degree of sensitivity and specificity for CPPS, but may also shed light on the pathogenesis of the disease. The cytokine macrophage inflammatory protein-1alpha (MIP-1α) has a sensitivity of 72.4% and a specificity of 69.2%; monocyte chemoattractant protein-1 (MCP-1) has a sensitivity of 83.9% and a specificity of 90%. Combined, the two have a sensitivity of 88.7% and a specificity of 80%.

"Men with CCPS frequently have prostatic inflammation. This study indicates that they also have these two elevated cytokines. These may, in fact, be biomarkers for the disease. Further study is needed to determine how these biomarkers are modulated during the course of the disease and if treatment with anti-cytokines might be warranted," Dr. Schaeffer said.

**Some men with apparent CPPS have prostatic stones in which nanobacteria are implicated.**

"The association between inflammation and elevated cytokine levels suggests infection could play a role, at least in some cases of CPPS," Dr. Schaeffer explained. "Although bacteria are not traditionally associated with CPPS, a study of men with CPPS implicates nanobacteria in prostatic stone formation."

A study from The Cleveland Clinic, Weston, FL, found nanobacterial antigens or antibodies in 60% of urine samples and 40% of urine samples in 16 men with CPPS refractory to multiple prior therapies. Entry criteria for the study included prostatic calculi on transrectal ultrasound.

The men were treated with comET, a complex of 500 mg tetracycline, a proprietary nutraceutical, and an ethylenediaminetetraacetic acid suppository daily. The therapy specifically targets nanobacteria. Eighty percent of the patients showed a 25% symptom improvement, and 53% showed a 50% improvement. The therapy reduced the size of stones in at least half the men in the study. **UT**

## UT Table [ Sensitivity, specificity of biomarkers for CPPS

	Cutoff	Sensitivity	Specificity
MIP-1 alpha	146.13 pg/mL	72.4%	69.2%
MCP-1	703.85 pg/mL	83.9%	90%
MIP-1α+ MCP-1	MIP-1α 69.99 pg/mL MCP-1 1061.84 pg/mL	88.7%	80%

Source: Anthony J. Schaeffer, MD

# Two-pronged approach relieves refractory CPPS pain

Penny Allen

UT CORRESPONDENT

San Antonio—A combination of physical and psychological therapy for chronic pelvic pain syndrome (CPPS, or chronic nonbacterial prostatitis) can provide relief for many patients who have pain refractory to conventional treatments, according to researchers from Stanford (CA) University.

“We really have a big job to find out the cause of this disorder and the associated biomarkers,” Rodney Anderson, MD, professor of urology at Stanford University, said at the AUA annual meeting here. “But while we’re doing that, one of the things we found helpful is to do myofascial release of trigger points that can be found in and around the prostate gland and in the pelvic floor. More important, we have a psychologist who knows how to help patients positively affect the mind-body interaction.”

This combined physical therapy and psychological approach, said Dr. Anderson, is “difficult, time consuming, and not well reimbursed,” but it works. He and his team—a psychologist, a physical therapist, and a clinical research coordinator—saw moderate to marked improvement in nearly three-quarters of the 138 men they treated who had CPPS refractory to traditional therapy.

The men had symptoms for a median of 31 months, and some experienced symptoms for as long as 29 years. Therapy included four weekly physical therapy sessions using myofascial trigger point release, followed by eight biweekly treatments. At the same time, patients underwent a form of cognitive behavioral therapy called paradoxical relaxation therapy, receiving an hour of individual verbal instructions and a supervised practice session weekly, with a recommendation for daily 1-hour home practice sessions.

Based on the patient-reported perceptions of overall effects of therapy documented on a Global Response Assessment questionnaire, 72% of the men had moderate to marked improvement and a median 24% to 46% drop in their NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) total scores, respectively.

The team used the Stanford Pelvic Pain Syndrome Survey, including a pain visual analog scale (VAS), to evaluate patients’ progress. For those men with a clinical improvement, the median scores decreased

## At a Glance

**Combined approach** » Combination of physical and psychological therapies provides marked relief, study shows.

“We have a psychologist who knows how to help patients positively affect the mind-body interaction.”

RODNEY ANDERSON, MD

69% and 80% for pain and urinary symptoms, respectively. One-fifth (21%) got worse, with a 27% increase in pain scores.

### Trigger points and a paradox

The physical therapy used in this protocol goes beyond myofascial release techniques, physical therapist Tim Sawyer explained to *Urology Times*. He said he uses those techniques, including massage, and that the most important is trigger point release of myofascial trigger points in internal and external muscle groups that refer pain. A myofascial trigger point is a hyperirritable, sensitive spot within a taut band of skeletal muscle and its associated fascia. These trigger points occur frequently in the abdominals, psoas, gluteals, piriformis, quadratus lumborum adductor, pectineus, and paraspinal muscles externally and the levator ani, obturator internus, coccygeus, piriformis, sphincter ani, bulbospongiosus, and ischial cavernosus muscles internally.

The therapist must treat the trigger points that, when palpated, reproduce the patient’s symptoms, he said. For example, points in the anterior portion of the levator ani tend to refer pain and or symptoms to the tip of the penis, and points in the levator endopelvic fascia lateral to the prostate. These trigger points can also cause frequency and or urgency. To treat these points, Sawyer maintains pressure on them for about 60 seconds. The internal muscles are treated transrectally using finger pressure with the patient in the prone position. Patients also are instruct-



ed in a home treatment program.

The paradoxical relaxation therapy technique applied to men with pelvic pain was developed by psychologist David Wise, PhD. It includes a specific breathing technique to quiet anxiety and relaxation training that focuses attention on the effortless acceptance of tension (thus, the paradox) in specific areas of the body.

Dr. Anderson said this therapy probably is the more important part of the protocol. Genitourinary disorders, such as voiding dysfunction and ejaculatory pain, are intimately related to the autonomic nervous system and to the balance of smooth and striated muscle. Acute and chronic stress is known to affect these systems.

### Stress a perpetuating factor

“Most men and women whom we see with pelvic pain have a high level of stress, and anxiety as a perpetuating factor,” Sawyer said. “If this is not addressed, then any amount of trigger point release would be either temporary or unsuccessful.”

Although this study did not compare results of physical therapy with the psychological therapy alone and in combination, he said he definitely feels a difference in muscles and fascia once a patient starts practicing the paradoxical relaxation therapy.

The hard-to-design study compares these therapies with some kind of placebo. One audience member pointed out that patients who are sick and who get attention from a doctor, physical therapist, and a psychiatrist and who are told that this will make them better will likely get better.

“How can you convince us that there is some fundamental physiologic process you’re affecting by this therapy?” he asked.

Designing a placebo control for a therapy like this is difficult, but Dr. Anderson pointed out that the National Institute of Diabetes and Digestive and Kidney Diseases’ Chronic Prostatitis Clinical Research Network and the Interstitial Cystitis Clinical Research Network are working to design a sham procedure as a control. **UT**

# Chronic prostatitis is common condition in U.S. men

Primary care physicians diagnose and treat majority of cases, HMO-based study reveals



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San Antonio—A new estimate shows that chronic prostatitis, especially nonbacterial prostatitis, is common in American men, and that most diagnosis and treatment takes place in primary care.



Dr. Clemens

The incidence of chronic prostatitis was 4.9 per 1,000 men per year, and that of chronic nonbacterial prostatitis (chronic pelvic pain syndrome, or CPPS) was 3.3 per 1,000 men per year.

That translates to 270,000 new diagnoses of CPPS annually in the United States, said J. Quentin Clemens, MD, assistant professor of urology at the Northwestern University Feinberg School of Medicine, Chicago, who presented results of the analysis at the AUA annual meeting here.

Dr. Clemens and teams from Northwestern and Kaiser Permanente Northwest in Portland, OR, looked for all new diagnoses coded for chronic prostatitis in the HMO's database from May 2002 to May 2004 and reviewed charts of a sample of those patients to determine the proportion of different types of chronic prostatitis among those diagnoses.

The total male population between 25 and 85 years of age in the HMO's files during this time period accounted for 181,949 person-years. The team's database search for ICD-9 codes 601.1 (chronic prostatitis)

and 601.9 (prostatitis, not otherwise specified) yielded 1,223 men with the diagnoses. The analysts' random review of 413 of these patient charts showed 280 new diagnoses made by HMO physicians. Of these, 189 patients had type III prostatitis (CPPS), 58 had type I or II (attributable to infection), and 33 had type IV (inflammation found incidentally on prostate biopsy). Based on those figures, the team made estimates of incidence.

Those men had characteristics that are not necessarily typical of the men with CPPS whom urologists see, especially urologists at tertiary care centers involved with studying CPPS. Chronic pelvic pain syndrome has been defined, in part, by persistence of symptoms for 3 months or more. When men with symptoms of shorter duration were eliminated, the incidence was 1.2 per 1,000 men per year. When men without pain symptoms (thought by some to be necessary to diagnose CPPS) were excluded, the incidence was 2.6 per 1,000 men per year. Dysuria occurred in 46.6% of patients, perineal pain in 34.4%, testicular pain in 16.5%, pain in the bladder or pubic area in 15.9%, pain in the tip of the penis in 11.1%, and ejaculatory pain in 8.5%.

"Most of the symptoms were less complex and less long-standing than the typical male pelvic pain cohorts that have been studied at tertiary referral centers," possibly because men are not being diagnosed and treated first by urologists, Dr. Clemens told *Urology Times*. "We in urology feel that prostatitis is a urologic condition, but the diagnosis really is being made much more commonly by primary

care physicians."

In fact, in this HMO, primary care physicians made about three-fourths of the diagnoses. A majority of patients never saw a urologist. Only one-third of the men who were seen by a primary care doctor eventually saw a urologist.

## A new picture emerges

The picture of chronic prostatitis drawn by this study is different from what urologists are accustomed to. It shows that chronic prostatitis is much more common than had been believed, and that the clinical picture early in the syndrome is somewhat different from what urologists see.

Whether the data show that men are being treated successfully in primary care isn't clear, but this picture of less-complicated symptoms early on does present opportunities.

In fact, the new focus of chronic prostatitis studies being planned by the National Institute of Diabetes and Digestive and Kidney Diseases is on recently diagnosed patients.

"We feel that some of the standard treatments probably work much better in patients with new diagnoses—or at least that's the hypothesis, and that's what we want to check," Dr. Clemens said.

In the next few years, clinicians should learn whether early diagnosis and treatment can reduce the burden of this common condition. **UT**

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