CLINICAL COURIER®

Vol. 22 No. 32 October 2004 ISSN 0264-6684

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Dannemiller Memorial Educational Foundation and SynerMed® Communications. The Dannemiller Memorial Educational Foundation is accredited by the ACCME to provide continuing medical education for physicians.

DESIGNATION OF CREDIT

The Dannemiller Memorial Educational Foundation designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Release date: October 2004 Expiration date for credit: October 31, 2005

CHRONIC PELVIC PAIN OF BLADDER ORIGIN:

A Focus on Interstitial Cystitis Case Studies: Patients Who Fail Endometriosis Therapy

PRESENTED BY

U.S. Department of Health and Human Services

The Office on Women's Health

IN COOPERATION WITH

American Medical Women's Association

American Urogynecologic Society

National Association of Nurse Practitioners in Women's Health

Jointly sponsored by

Dannemiller Memorial Educational Foundation and SynerMed® Communications.

SynerMed® Communications

This activity is made possible by an educational grant provided by Ortho-McNeil Pharmaceutical, Inc.

ORTHO-McNEIL

STATEMENT OF NEED

Interstitial cystitis is commonly misdiagnosed in women as overactive bladder, recurrent urinary tract infection, or endometriosis; in men it is often mistaken for prostatitis. The impact of interstitial cystitis on a patient's quality-of-life (QOL) is significant – these women score lower on QOL inventories than do dialysis patients; in men, the impact is comparable to that of patients with myocardial infarction, angina, or Crohn's disease. Therefore, effective diagnostic methods, understanding of epidemiology and demographics, and proper identification of nonpharmacologic and pharmacologic options are necessary for the management of interstitial cystitis.

METHOD OF PARTICIPATION

This newsletter should take approximately 1 hour to complete. The participant should, in order, read the objectives and newsletter, answer the 10-question multiple-choice post-test, placing answers on Registration/Post-Test Answer Form/Evaluation on foldout page. The evaluation form provides each participant with the opportunity to comment on the quality of the instructional process, the perception of enhanced professional effectiveness, the perception of commercial bias, and his or her views on future educational needs. To receive credit for this activity, follow the instructions provided on the post-test and evaluation form. This credit will be valid through October 31, 2005. No credit will be given after that date.

EDUCATIONAL OBJECTIVES

Upon completion of this program, participants will be able to:

- Differentiate between chronic pain of pelvic versus bladder origin
- Discuss the epidemiology and demographics of chronic pelvic pain and interstitial cystitis
- Discuss the theories underlying the pathophysiology of interstitial cystitis
- Discuss the impact of interstitial cystitis and chronic pelvic pain on quality of life
- Describe the evolving roles of the Pelvic Pain Urgency and Frequency Patient Symptom Scale, Potassium Sensitivity Test, and other diagnostic tools in identifying patients with interstitial cystitis
- Identify nonpharmacologic and pharmacologic options for the management of interstitial cystitis

TARGET AUDIENCE

Obstetrician/gynecologists, urologists, family physicians, nurse practitioners, and physician assistants.

STEERING COMMITTEE

Jean L. Fourcroy, MD, PhD, MPH
Assistant Professor/Urology
Uniformed Services University of the Health Sciences
Walter Reed Army Hospital
Bethesda, Maryland

Wanda K. Jones, DrPH
Deputy Assistant Secretary for Health
Office on Women's Health
Department of Health and Human Services
Washington, DC

Daniel R. Mishell Jr, MD
Lyle G. McNeile Professor and Chairman
Department of Obstetrics & Gynecology
Keck School of Medicine
Los Angeles County & University of Southern California
Women's & Children's Hospital
Los Angeles, California

C. Lowell Parsons, MD
Professor of Surgery/Urology
School of Medicine
University of California, San Diego
San Diego, California

FACULTY DISCLOSURE STATEMENTS

The Dannemiller Memorial Educational Foundation requires that the faculty participating in a continuing medical education activity disclose to participants any significant financial interest or other relationship (1) with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in an educational presentation, or (2) with any commercial supporters of the activity. The presenting faculty reported the following:

Wanda K. Jones, DrPH
No financial or other relationship.

Jean L. Fourcroy, MD, PhD, MPH
No financial or other relationship.

Daniel R. Mishell Jr, MD
Speaker's Bureau: Ortho McNeil Pharmaceutical, Inc.

C. Lowell Parsons, MD
Consultant/Scientific Advisor: Ortho-McNeil Pharmaceutical, Inc.

Discussion of Off-Label/Investigational Uses of Pharmaceutical Products: This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by FDA.

The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings. Further, attendees should appraise the information presented critically and are encouraged to consult appropriate resources for any product or device mentioned in this program.

The content and views presented in this educational activity are those of the authors and do not necessarily reflect those of the Dannemiller Memorial Educational Foundation, the US Department of Health and Human Services' Office on Women's Health; the American Medical Women's Association; the American Urogynecologic Society; the National Association of Nurse Practitioners in Women's Health; SynerMed® Communications, or the program grantor, Ortho-McNeil Pharmaceutical, Inc.

This material is prepared based on a review of multiple sources of information, but is not exhaustive of the subject matter. Therefore, healthcare professionals and other individuals should review and consider other publications and materials on the subject matter before relying solely on the information contained within this educational activity.

CLINICAL COURIER®

Vol. 22 No. 32 October 2004 ISSN 0264-6684

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Dannemiller Memorial Educational Foundation and SynerMed® Communications. The Dannemiller Memorial Educational Foundation is accredited by the ACCME to provide continuing medical education for physicians.

DESIGNATION OF CREDIT

The Dannemiller Memorial Educational Foundation designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Release date: October 2004 Expiration date for credit: October 31, 2005

CHRONIC PELVIC PAIN OF BLADDER ORIGIN: A FOCUS ON INTERSTITIAL CYSTITIS CASE STUDIES: PATIENTS WHO FAIL ENDOMETRIOSIS THERAPY

INTRODUCTION

Interstitial cystitis (IC) is a cause of chronic pelvic pain syndrome (CPPS) of bladder origin characterized by pelvic pain and urinary urgency and frequency. Historically, IC has been considered a rare disorder that is difficult to diagnose and manage. Recently, studies have demonstrated that IC is much more common than previously believed and may affect as many as 1 in 4.5 women.[1] There have been important recent advances in the diagnosis and management of IC that provide clinicians with the ability to diagnose women early in the disease process and effectively treat women even with severe or long-standing IC.

This issue of *Clinical Courier*® will focus on the assessment and management of IC in women. The objective of this activity is to provide practical information and guidelines that can be utilized to expedite the care provided to patients with chronic pelvic pain (CPP) symptoms that are eventually determined to be of bladder origin. To facilitate this objective, 2 case studies will be presented and reviewed.

OVERVIEW AND MAGNITUDE OF THE PROBLEM

The American College of Obstetricians and Gynecologists (ACOG) defines CPP as "non-cyclic pain of 6 or more months' duration that localizes to the anatomic pelvis, abdominal wall at or below the umbilicus, lumbosacral back, or the buttocks, and is of sufficient severity to cause functional disability or lead to medical care."[2] The CPP can be of reproductive tract, genitourinary, gastrointestinal, psychologic, or neurologic origin, and the pain is either noncyclic or intermittent. Severity of the pain need not be associated with abnormal physical findings, and a normal physical examination does not exclude the presence of IC.

CPP is estimated to affect about 15% of women of reproductive age in the United States; 1 in 3 women will experience pelvic pain at some time during her life.[3,4] The morbidity associated with CPP is substantial: CPP is the cause of 40% of laparoscopies and 18% of hysterectomies performed in the United States.[5,6] The annual direct and indirect healthcare costs associated with CPP are very high: in 1996, the total direct and indirect costs in the United States were estimated at $3.3 billion.[4]

A wide range of medical conditions can cause CPP; among the most common causes are endometriosis, recurrent urinary tract infections (UTIs), overactive bladder (OAB), vulvodynia, and IC. Each of these conditions, except endometriosis, may cause CPP, along with symptoms of urinary urgency and frequency. Recent studies estimate that 80% to 85% of women with CPP of unknown etiology have IC.[7] In addition to CPP and urinary urgency and frequency, women with IC often also experience nocturia, premenstrual flares, pain that worsens with bladder filling and eases with bladder emptying, and/or pain associated with sexual intercourse. Women with IC typically first experience symptoms during their 30s, however, similarities in clinical presentation of IC and other causes of CPP, as well as infrequent consideration of the bladder being a source of pelvic pain, often result in misdiagnoses and inappropriate, and often ineffective, treatments. It has been estimated that women who are ultimately diagnosed with IC consult 5 to 8 healthcare professionals before an accurate diagnosis is made, resulting in an average age range of 42 to 46 years at diagnosis.[8,9]

Recent studies estimate that 80% to 85% of women with CPP of unknown etiology have IC.[7]

There is a wide spectrum of symptoms of IC ranging from mild and intermittent pelvic pain and infrequent nighttime voiding (≤ twice per night) to debilitating pain and significant nighttime voiding (>12 times per night). The chronicity and severity of IC symptoms often have a substantial impact on quality of life (QoL): nearly 50% of patients with IC are unable to work full-time, and more than 60% of patients complain of dyspareunia.[10] Patients with IC are at greater risk of emotional problems than the general population and score worse on QoL questionnaires than do patients receiving hemodialysis.[10,11] The symptoms of IC may be exacerbated by allergic conditions, certain foods or beverages, and physical and/or emotional stress.

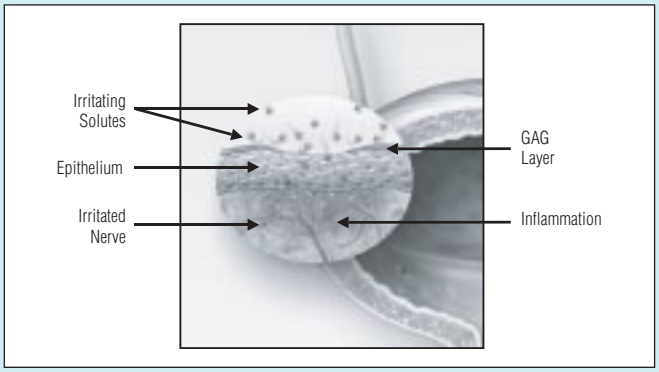
PATHOPHYSIOLOGY

The pathogenesis of IC is unclear but is believed to be multifactorial, and multiple pathologies can coexist within the same patient. Investigators have identified specific bladder abnormalities in patients with IC that increase their pain response to urine solutes. Specifically, it is believed that an initial insult or alteration to the bladder causes damage to the glycosaminoglycans (GAG) layer of the bladder surface, allowing leakage and transvesical passage of urea and potassium into the interstitium (Figure 1, page 2).[12] The GAG layer (mucus) inhibits bladder infections by preventing bacteria from adhering to urothelial surfaces and prevents passage of caustic components of urine into the bladder wall. Exposure to potassium causes interstitial tissue damage and pelvic pain, as well as urinary urgency and frequency—the symptoms of IC. Pelvic pain can also occur in the absence of actual bladder tissue damage.[13]

Investigators have identified increased levels of the neuropeptic substance P (SP) in the bladder tissue of patients with IC. SP, which is secreted from sensory nerve endings, transmits pain information, stimulates inflammation, and can trigger mast-cell secretion, particularly in the bladder submucosa.[14] Patients with IC have been shown to have an increased number of C-fibers, or pain-carrying nerves, that carry and release SP. Granules inside mast cells contain histamines that can cause inflammation. Degranulation of mast cells facilitates the abnormal release of histamines; it has been theorized that this

FIGURE 1

ROLE OF GAG LAYER IN IC: DEFECTIVE EPITHELIAL BARRIER[12]



process may cause the initial insult or damage to the GAG layer, allowing potassium to irritate the bladder interstitial tissue.

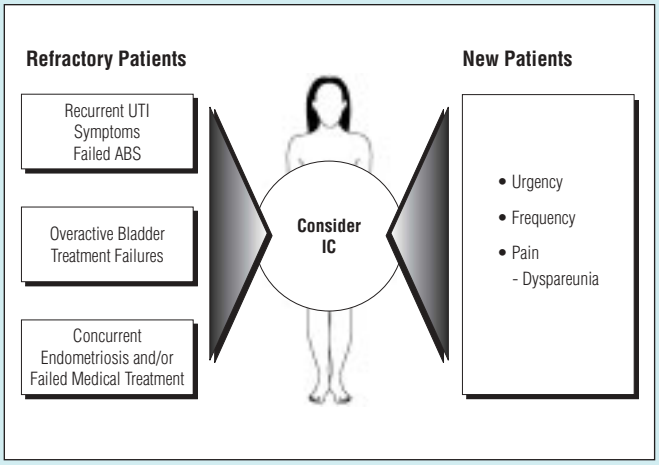
DIAGNOSIS

The diagnosis of IC needs to be made clinically, because there is an absence of gross histologic changes in the bladder tissue and an absence of abnormal laboratory assays or biomarkers. The diagnosis of IC has been made by exclusion after ruling out bladder or urinary tract infections, vaginal or sexually transmitted infections, endometriosis, and bladder cancer (Figure 2). IC should be suspected to be present in all women with refractory UTI who have failed to respond to multiple courses of antimicrobial therapy, as well as in women with refractory OAB who have not responded to anticholinergic treatment, and in women with persistent symptoms of endometriosis who have failed standard therapies including oral contraceptives or leuprolide. Any patient who presents with urinary urgency and frequency and clinical signs of CPP, in the absence of definable pathology, should be evaluated for IC.

Any patient who presents with urinary urgency and frequency and clinical signs of CPP, in the absence of definable pathology, should be evaluated for IC.

FIGURE 2

WOMEN WHO SHOULD BE SUSPECTED OF HAVING IC



Until recently, it was believed that the presence of Hunner's ulcers, which were visualized during cystoscopy with hydrodistention, was necessary to confirm a diagnosis of IC. It has been determined that fewer than 10% of patients with IC will have a Hunner's patch.[15] Consequently, it is the recommendation of the editorial faculty that cystoscopy with hydrodistention is now reserved for women with microscopic or gross hematuria to rule out abnormalities of the urethral or bladder surface, or for patients with CPP and risk factors for bladder cancer (cigarette smoking and older age).

A diagnosis of IC is based upon patient history and presenting signs and symptoms, along with a negative urinalysis, sterile urine culture, and normal urinary cytology (Table 1). Upon physical examination, women with IC may exhibit suprapubic tenderness, anterior vaginal wall/bladder base tenderness, levator muscle spasm, and rectal spasm. The physical examination can rule out other causes of CPP, such as vulvodynia, vaginitis, urethral diverticula, uterovaginal prolapse, and pelvic floor dysfunction. Additional diagnostic tests that may be useful for some women include a cystometrogram with urodynamic testing, an intravenous pyelogram, and transvaginal ultrasound.

TABLE 1

DIAGNOSING IC

- Patient History and Symptoms
  - Urinary urgency and frequency
  - Pelvic pain (>3 months)
    - Premenstrual flares
    - Flares with diet, allergies, sex
- Physical Examination
  - Suprapubic tenderness
  - Anterior vaginal wall/bladder base tenderness
  - Levator muscle spasm
  - Rectal spasm
- Laboratory Analyses
  - Urinalysis ± culture
  - Cytology of urine

The Pelvic Pain Urgency and Frequency (PUF) Patient Symptom Scale is an important addition to assist in the diagnosis of IC (Figure 3, inside fold-out). The PUF is an 8-question symptom scale that can readily distinguish IC from other abdominopelvic conditions (including UTI and gynecologic causes of CPP). The PUF requires approximately 5 minutes to complete. It measures both the presence and severity of IC symptoms: frequency, urgency and pain, and includes 2 questions that address symptoms associated with sexual activity. The maximum score of the PUF is 35; high scores (≥10 points) indicate a high probability that the patient has IC. Nearly all healthy women have low PUF scores (≤2 points). Patients with PUF scores ≥5 points have been shown to have a 55% likelihood of having IC; the likelihood of IC increases to 74% with a PUF score >10 points.[1] It is recommended that the PUF scale should be routinely administered to all women who complain of CPP. Women with a PUF score of at least 5 points should be suspected of having IC and should be assessed and managed accordingly.

Another addition to the IC diagnostic armamentarium is the potassium sensitivity test (PST), which identifies patients who respond with pain and/or urgency to the introduction of potassium chloride (KCl) into the bladder. A positive PST indicates abnormal epithelial permeability and is a reliable indication that the CPP is of bladder origin. However, a positive PST does not definitively diagnose IC and a negative result does not always rule out IC.[16] Although approximately 79% of patients with IC have a positive PST, other bladder diseases, including acute bacterial cystitis and radiation cystitis, can also cause a positive PST result and should be ruled out by appropriate

diagnostic tests.[17] Women who have recently undergone heparin treatment, bladder hydrodistention, or bladder instillations with dimethyl sulfoxide (DMSO), or patients receiving pain medications can have false negative PST results. It is estimated that approximately 85% of gynecology patients who have CPP have a positive PST.[1,7]

The initial step of the PST consists of the very slow introduction of 40 mL of sterile water (or normal saline solution) into the bladder through a thin catheter to assess the baseline of pain perception and urgency after bladder filling (using a 0- to 5-point scale, with 5 indicating the most severe pain). The water is retained in the bladder for up to 5 minutes before it is emptied through the catheter. The next step is the introduction of 40 mL of 0.4 M KCl solution into the bladder through the same catheter. The KCl solution is retained for up to 5 minutes unless severe pain occurs. The patient re-evaluates her level of pain/urgency; any increase of 2 or more points over the score obtained with sterile water indicates a positive PST result. A negative PST result occurs when a patient has a pain or urgency response to the KCl solution that is less than 2 points greater than the score obtained with sterile water.[13,16]

Recent investigations have found a significant correlation between a high PUF score and a positive PST result.[1] Ninety-one percent of patients with a PUF score range between 20 – 24 have been shown to have a positive PST, and 76% of patients with a PUF score range between 15 – 19 have been shown to have a positive PST. In contrast, healthy women nearly always have low PUF scores (<2) and 0% positive PST results.[1] These findings support the use of the PUF as an initial diagnostic technique to screen women with CPP for the presence of IC; the PST can be reserved for patients with symptoms suggestive of IC but low PUF scores (2 to 15 points). A diagnosis of IC is suggested by a PUF score of more than 15.

MANAGEMENT

Currently, there are 2 pharmacologic therapeutic modalities approved by the US Food and Drug Administration (FDA) for the management of IC—intravesical instillations of DMSO and oral pentosan polysulfate sodium (PPS). Intravesical DMSO instillations have been used to manage the pain and urinary symptoms of IC for nearly 30 years, with moderate success.[18-21] They are administered in the office or by the patient at home on a weekly or every other week schedule for 6 to 8 weeks. The procedure, which can be painful, involves instilling 50 mL of an aqueous solution (50%) of DMSO through a catheter into the bladder, where it is retained for up to 15 minutes before being expelled.[22] The mechanism of action is unknown, and the process can produce a garlic-like taste and/or odor on the breath or skin for up to 3 days after treatment.[22] Patients are advised to have kidney and liver function tests every 6 months during treatment with DMSO, because renal and hepatic abnormalities can occur with DMSO treatment.[23] Remissions following DMSO are rarely complete, and additional treatment courses can reduce the duration of remissions. DMSO therapy is being used less frequently than previously.

PPS is the only oral drug approved by the FDA for the management of IC (Table 2).[24] PPS is believed to act by replenishing the defective GAG layer, acting as a buffer to control cell permeability, and preventing irritating solutes from reaching uroepithelial cells. The FDA-recommended dosage is 300 mg/d taken as a 100-mg capsule 3 times daily; an evolving regimen to enhance patient compliance (not FDA approved) utilizes 200 mg taken twice daily.[25,26] PPS is well tolerated with no known drug-drug interactions.[24] PPS gradually repairs the damaged urothelium; the recommended course duration is at least 2 to 4 months for patients with mild to moderate IC, and at least 6 to 12 months for women with moderate to severe disease.[27]

Clinical trials have demonstrated the efficacy of PPS in reducing IC-associated pain and symptoms of urinary urgency and frequency.[28-30] A dose-ranging study demonstrated that symptomatic improvement increased with duration of therapy, but not with increased dosage (Figure 4).[31] This study also found that

TABLE 2

PPS

- The only FDA-approved oral therapy for management of IC[24]
  - Proven effective in multicenter studies[12,27]
- Resembles protective GAG layer that insulates bladder lining against urine[39]
- Reduces painful symptoms/provides long-term remissions[30]
- Provides relief of IC pain in many patients in 3 to 6 months[24]
  - Some patients experience pain relief in only 4 weeks[40]

PPS treatment significantly reduced potassium sensitivity as measured by the PST.[31]

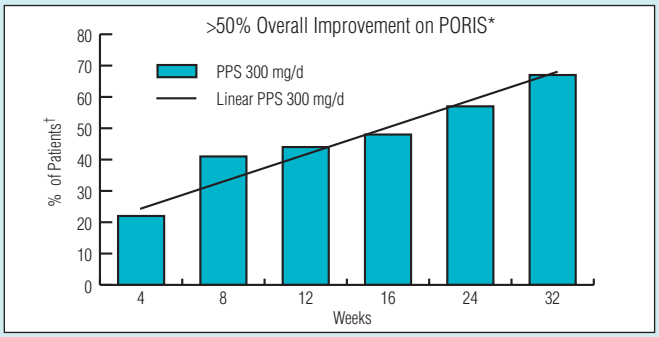
Adjunctive pharmacologic therapies for IC include analgesics, anticholinergics, antispasmodics, and antihistamines. Tricyclic antidepressants, particularly amitriptyline (not FDA approved), taken at bedtime to facilitate pain relief, inhibit histamine secretion from mast cells and have anticholinergic properties.[32] Intravesical heparin, while not FDA-approved for the treatment IC, has been found to be beneficial as monotherapy or in combination with DMSO in providing relief of pain and enhancing the duration of clinical remission.[33,34]

Nonpharmacologic interventions are often utilized to supplement the pharmacologic modalities, but are rarely utilized alone. Patients should be encouraged to remove from their diet foods high in acidity, such as alcohol, tomatoes, and chocolate. Foods that contain caffeine or artificial sweeteners should also be discouraged or eliminated. Behavior therapies, including bladder-training techniques, relaxation and distraction techniques, and pelvic floor relaxation exercises, can help patients to lengthen the interval between voids, but are rarely effective by themselves to treat patients with long-standing IC. Other recommendations include taking hot sitz baths and applying heating pads to the perineal area prior to intercourse and ice packs after intercourse.

Women with severe IC may benefit from immediate, though temporary, relief of the urgency/pain symptoms associated with IC by the administration of anesthetic intravesical solutions, or "therapeutic cocktails." The anesthetic solutions combine either heparin (10,000 to 40,000 units) or PPS (1 or 2 100-mg capsules dissolved in 10 cc of buffered normal saline) (not FDA approved) as the active agent, in combination with 3 cc of 8.4% sodium bicarbonate and 10

FIGURE 4

PPS: SYMPTOMATIC IMPROVEMENT INCREASES WITH DURATION OF TREATMENT[31]



*PORIS = Patient's overall Rating of Improvement of Symptoms index assessing, pain, urgency, frequency, and nocturia.

†Completers.

cc of 1% lidocaine or 16 cc of 2% lidocaine.[33,35,36] The woman assumes a dorsal lithotomy position, and the solution is instilled into an empty bladder using a small catheter. The solution is retained in the bladder for up to 30 minutes or until the patient needs to void. Clinical investigators suggest a series of 9 instillations - 3 during the first week and 1 per week for the next 6 weeks - to provide maximal pain relief and to reduce urinary urgency.

CASE STUDIES

Case Study #1

A 19-year-old nulliparous woman presented with complaints of lower abdominal pain, lower back pain, and dyspareunia.

History of Present Illness

The patient reported a history of recurrent UTIs as a child and a history of seasonal allergies. She first complained of pelvic pain 3 years earlier, shortly after menarche. The pain was initially mild and intermittent, but quickly increased in severity. She reported that the pain was exacerbated by sexual intercourse and urination, and increased 1 week prior to menses. She stated upon questioning that she had significantly reduced her fluid intake to reduce the frequency of urination.

The patient was initially diagnosed empirically as having endometriosis and was treated with oral contraceptives, which provided her little to no pain relief. A laparoscopy was performed for ablation of endometrial implants but produced minimal or no pain relief. Ovarian cysts were removed during a second laparoscopy, which provided minimal to no relief of the pelvic pain. At age 19, the patient underwent a third laparoscopy during which no pelvic disease was found.

Physical Examination

The patient was a slender woman who complained of chronic suprapubic pain and painful urination. She reported that she was engaged to be married but had been unable to have sexual intercourse for the past year due to the pelvic pain. She had been prescribed amitriptyline (10 to 25 mg) for pain. She had no bacterial etiology that would indicate UTI or STI, and the treatments prescribed for her initial diagnosis of endometriosis had been unsuccessful.

Current Diagnostic Assessment

The patient was suspected of having IC and was administered the PUF questionnaire. Her PUF score of 21, in addition to her history, clinical presentation, and the absence of any bacterial etiology, supported a diagnosis of IC.

Short-Term Treatment Plan

The patient was prescribed oral PPS (300 mg/d). In addition, a series of intravesical instillations of an anesthetic solution was administered to provide prompt pain relief. She was taught relaxation and bladder training techniques, and directed to modify her diet, removing foods high in acidity, caffeine, or artificial sweeteners.

Follow-Up

Three months after initiation of treatment, the patient reported significant improvement in her pelvic pain. She had increased her fluid intake and was having sexual intercourse without pain. She was directed to stop taking the amitriptyline but to continue on oral PPS for at least another 3 months. She was also told to slowly reintroduce (one at a time) the foods she had removed from her diet, unless she experienced symptomatic flares.

Discussion

Women with IC are frequently misdiagnosed with either recurrent UTI or endometriosis. Patient 1 had a history of recurrent UTIs and CPP; however, she had not had any urine cultures to determine the validity of the UTI diagnoses. She had a history of seasonal allergies and dyspareunia, both of which are commonly reported among women with IC. Although she had independently reduced her fluid intake to minimize voiding, Patient 1 did not readily offer this information until the clinician asked her about possible bladder symptomatology. It is important for clinicians to directly inquire about urinary frequency and urgency, as well as dyspareunia, because few patients volunteer this information. Recognizing that the bladder can be a source of CPP—and being highly aware of the likelihood of IC when patients present with CPP and urinary urgency/frequency—can prevent unnecessary diagnostic surgeries and pharmacologic interventions.

Case Study #2

A 35-year-old gravida 3 para 3 woman was referred by a pain-management center for definitive treatment of CPP. Her clinical presentation included lower abdominal pain, spasms of her back and legs, an inability to stand for long periods of time, vulvodynia, and a burning sensation after sexual intercourse.

History of Present Illness

The patient reported a sudden onset of CPP 4 years earlier that, despite numerous treatments and surgeries, was ongoing. In addition to her presenting complaints, she noted exacerbations of the pain prior to menses and during the spring and fall seasons. The first gynecologist with whom she consulted diagnosed her empirically as having endometriosis. Minimal endometriosis was found during her first laparoscopy and the lesions were ablated. The pain continued for another year, and the patient consulted a second gynecologist who also performed a laparoscopy for endometriosis. As with the first procedure, few lesions were observed and all were ablated. However, the pain continued and the patient consulted a pain-management center.

The patient was referred from the pain-management center to a third gynecologist for consultation regarding a hysterectomy. The third gynecologist also performed a diagnostic laparoscopy, but found no endometriosis, and advised against a hysterectomy. The patient continued to experience pain and sought a fourth gynecologist who performed a fourth laparoscopy and whose gross findings included endometriosis and chronic pelvic inflammatory disease (PID). The patient underwent a hysterectomy; however, histologic findings demonstrated no endometriosis, no adenomyosis, and no salpingitis.

Current Diagnostic Assessment and Treatment Plan

The pelvic pain continued after the hysterectomy, and the patient became depressed and suicidal. Her psychiatrist referred her to a urologist who suspected a diagnosis of IC and performed a PST, which was positive. Her PUF score was 22. The urologist diagnosed the presence of IC and prescribed oral PPS (300 mg/d) and hydroxyzine (not FDA approved), an antihistamine, and a mild anti-anxiety medication (starting with 25 mg every night at bedtime and progressing to 50 mg every night). She also received a series of 9 bladder instillations with an anesthetic solution.

Follow-Up

The patient was seen after 3 and 6 months, and again at 1 year. By the 6 month follow-up visit, the patient was no longer depressed or suicidal, and reported that her pain was markedly improved. She continued receiving oral PPS for a total of 12 months.

Discussion

Endometriosis affects 70% to 90% of women with CPP and is considered a common identifiable cause of CPP.[6] However, recent data indicate that 1 in 3 women with endometriosis have concurrent IC, and some clinicians consider endometriosis and IC "evil twins."[37,38] In a recent prospective study, 60 women with CPP underwent concurrent laparoscopy, cystoscopy, and hydrodistention.[38] Fifty-eight of the 60 women were subsequently diagnosed as having IC, and 56 were diagnosed with endometriosis (80% of whom had biopsy-proven endometriosis). Of the 56 women diagnosed with endometriosis,

54 had concurrent IC, and 54 of the 58 women diagnosed with IC had concurrent endometriosis.[38] This study illustrates the importance of considering the bladder as a source of CPP among patients who present with symptoms suggestive of endometriosis.

It is strongly recommended that the PUF questionnaire be administered prior to any diagnostic laparoscopy or hysterectomy for CPP, in order to rule out the presence of IC, which can be treated pharmacologically.

Patient 2 underwent 4 laparoscopic procedures and a hysterectomy to manage CPP that was erroneously attributed to endometriosis, despite finding only minimal or no endometrial lesions and the knowledge that endometriosis rarely causes bladder symptomatology. In addition, Patient 2 reported a childhood history of seasonal allergies and noted exacerbations of her CPP during allergy seasons, a finding that can be considered an indication of IC. Nevertheless, none of the 4 treating gynecologists had considered that her CPP could be of bladder origin. It is strongly recommended that the PUF questionnaire be administered prior to any diagnostic laparoscopy or hysterectomy for CPP, in order to rule out the presence of IC, which can be treated pharmacologically.

REFERENCES

1. Parsons CL, Dell J, Stanford EJ, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology* 2002;60:573-578.
2. ACOG Committee on Practice Bulletins - Gynecology. ACOG Practice Bulletin No. 51. Chronic pelvic pain. *Obstet Gynecol* 2004;103:589-605.
3. Walker EA, Katon WJ, Jemelka R, et al. The prevalence of chronic pelvic pain and irritable bowel syndrome in two university clinics. *J Psychosom Obstet Gynaecol* 1991;12:65-75.
4. Mathias SD, Kuppermann M, Liberman RF, Lipschutz RC, Steege JF. Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. *Obstet Gynecol* 1996;87:321-327.
5. Howard FM. The role of laparoscopy in chronic pelvic pain: promise and pitfalls. *Obstet Gynecol Surv* 1993;48:357-387.
6. Gambone JC, Mittman BS, Munro MG, Scialli AR, Winkel CA. Consensus statement for the management of chronic pelvic pain and endometriosis: proceedings of an expert-panel consensus process. *Fertil Steril* 2002;78:961-972.
7. Parsons CL, Bullen M, Kahn BS, Stanford EJ, Willems JJ. Gynecologic presentation of interstitial cystitis as detected by intravesical potassium sensitivity. *Obstet Gynecol* 2001;98:127-132.
8. Curhan GC, Speizer FE, Hunter DJ, Curhan SG, Stampfer MJ. Epidemiology of interstitial cystitis: a population based study. *J Urol* 1999;161:549-552.
9. Propert KJ, Schaeffer AJ, Brensinger CM, et al. A prospective study of interstitial cystitis: results of longitudinal followup of the interstitial cystitis database cohort. The Interstitial Cystitis Data Base Study Group. *J Urol* 2000;163:1434-1439.
10. Ratner V, Slade D, Greene G. Interstitial cystitis. A patient's perspective. *Urol Clin North Am* 1994;21:1-5.
11. Moldwin RM, Sant GR. Interstitial cystitis: a pathophysiology and treatment update. *Clin Obstet Gynecol* 2002;45:259-272.
12. Parsons CL. The therapeutic role of sulfated polysaccharides in the urinary bladder. *Urol Clin North Am* 1994;21:93-100.
13. Parsons CL, Greenberger M, Gabal L, Bidair M, Barme G. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol* 1998;159:1862-1866.
14. Pang X, Marchand J, Sant GR, Kream RM, Theoharides TC. Increased number of substance P positive nerve fibres in interstitial cystitis. *Br J Urol* 1995;75:744-750.
15. Theoharides TC, Sant GR. New agents for the medical treatment of interstitial cystitis. *Expert Opin Investig Drugs* 2001;10:521-546.
16. Parsons CL, Zupkas P, Parsons JK. Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. *Urology* 2001;57:428-433.
17. Parsons CL. Prostatitis, interstitial cystitis, chronic pelvic pain, and urethral syndrome share a common pathophysiology: lower urinary dysfunctional epithelium and potassium recycling. *Urology* 2003;62:976-982.
18. Stewart BH, Shirley SW. Further experience with intravesical dimethyl sulfoxide in the treatment of interstitial cystitis. *J Urol* 1976;116:36-38.
19. Stout L, Gerspach JM, Levy SM, et al. Dimethyl sulfoxide does not trigger urine histamine release in interstitial cystitis. *Urology* 1995;46:653-656.
20. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol* 1988;140:36-39.
21. Barker SB, Matthews PN, Philip PF, Williams G. Prospective study of intravesical dimethyl sulphoxide in the treatment of chronic inflammatory bladder disease. *Br J Urol* 1987;59:142-144.
22. Sant GR. Intravesical 50% dimethyl sulfoxide (Rimso-50) in treatment of interstitial cystitis. *Urology* 1987;29:17-21.
23. RIMSO-50® (brand of dimethyl sulfoxide irrigation, U.S.P.) [package insert]. Irvine, CA; Edwards Lifesciences. 2004.
24. Elmiron®. Physicians' Desk Reference®. 58th ed. Montvale, NJ: Thomson PDR; 2004. p. 2438-2439.
25. Dell J, Parsons C. Intravesical instillation therapy using PPS in patients with interstitial cystitis. Poster presented at: Research Insights into Interstitial Cystitis. Alexandria, Virginia; October 30-November 1, 2003.
26. Rosenberg M, Page S, Roth L, al. e. Pentosan polysulfate sodium for the treatment of interstitial cystitis: Rapid (1-month) and sustained symptom relief. Paper presented at: Research Insights into Interstitial Cystitis (A Basic and Clinical Science Symposium), October 30-November 1, 2003; Alexandria, Virginia.
27. Parsons CL, Benson G, Childs SJ, et al. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosan polysulfate. *J Urol* 1993;150:845-848.
28. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosan polysulfate. *J Urol* 1987;138:513-516.
29. Mulholland SG, Hanno P, Parsons CL, Sant GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. *Urology* 1990;35:552-558.
30. Hanno PM. Analysis of long-term Elmiron therapy for interstitial cystitis. *Urology* 1997;49:93-99.
31. Parsons CL, Forrest J, Nickel JC, et al. Effect of pentosan polysulfate therapy on intravesical potassium sensitivity. *Urology* 2002;59:329-333.
32. Hanno PM. Amitriptyline in the treatment of interstitial cystitis. *Urol Clin North Am* 1994;21:89-91.
33. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. *Br J Urol* 1994;73:504-507.
34. Kuo HC. Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome and interstitial cystitis. *J Formos Med Assoc* 2001;100:309-314.
35. Bade JJ, Laseur M, Nieuwenburg A, van der Weele LT, Mensink HJ. A placebo-controlled study of intravesical pentosan polysulfate for the treatment of interstitial cystitis. *Br J Urol* 1997;79:168-171.
36. Parsons CL, Davis EL. Pentosan polysulfate sodium intravesical instillation: end-organ therapy. *Practice Building Today.* September 2003:18-22.
37. Clemons JL, Arya LA, Myers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. *Obstet Gynecol* 2002;100:337-341.
38. Chung MK, Chung RR, Gordon D, Jennings C. The evil twins of chronic pelvic pain syndrome: endometriosis and interstitial cystitis. *JSLS* 2002;6:311-314.
39. Hurst R, Roy J, Min K, et al. A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. *Urology* 1996;48:817-821.
40. Nickel JC, Forrest J, Barkin J, Payne C, Mosbaugh P. Safety and efficacy of up to 900 mg/day polysulfate sodium (Elmiron) in patients with interstitial cystitis. *Urology* 2001;57:122-123.

FIGURE 3

PELVIC PAIN AND URGENCY/FREQUENCY (PUF) PATIENT SYMPTOM SCALE

Patient's Name:_____ Today's date: _____

Please circle the answer that best describes how you feel for each question.

		0	1	2	3	4	SYMPTOM SCORE	BOTHER SCORE
1	How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2	a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
	b. If you get up at night to go to the bathroom, does it bother you?	Never bothers	Occasionally	Usually	Always			
3	Are you currently sexually active? YES _____ NO _____							
4	**a. IF YOU ARE SEXUALLY ACTIVE,** do you now or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always			
	b. If you have pain, does it make you avoid sexual activity?	Never	Occasionally	Usually	Always			
5	Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, penis, testes, or scrotum)?	Never	Occasionally	Usually	Always			
6	a. If you have pain, is it usually		Mild	Moderate	Severe			
	b. Does your pain bother you?	Never	Occasionally	Usually	Always			
7	Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always			
8	a. If you have urgency, is it usually		Mild	Moderate	Severe			
	b. Does your urgency bother you?	Never	Occasionally	Usually	Always			
							SYMPTOM SCORE (1, 2a, 4a, 5, 6a, 7, 8a)	
							BOTHER SCORE (2b, 4b, 6b, 8b)	
							TOTAL SCORE (Symptom Score + Bother Score) =	

Total score ranges are from 1 to 35.
A total score of 10-14 = 74% likelihood of positive PST; 15-19 = 76%; 20+ = 91% Potassium Positive

Printed with permission.

Editor: *Clinical Courier®*
SynerMed® Communications
Department 163
518 Route 513
PO Box 458
Califon, NJ 07830

Presorted
Standard
US Postage
PAID
A&E Mailers

CLINICAL COURIER®
Vol. 22 No. 32

IMPORTANT CME MATERIALS ENCLOSED

CHRONIC PELVIC PAIN OF BLADDER ORIGIN: A FOCUS ON INTERSTITIAL CYSTITIS CASE STUDIES: PATIENTS WHO FAIL ENDOMETRIOSIS THERAPY

Release date: October 2004

CME REGISTRATION/POSTTEST ANSWER FORM/EVALUATION (04-726C)

Expiration Date for credit: October 31, 2005

Instructions:

Please mark your answers on the CME Registration/Posttest Answer Form/Evaluation.

This activity should take approximately 1 hour to complete. The participant should, in order, read the educational objectives contained in this newsletter, answer the 10-question multiple-choice posttest, below, and complete the registration/evaluation form. If you wish to receive CME credit and a certificate, please mail/fax a copy of your completed answers to:

If CME credit and a certificate are desired, please mail/fax this completed form or a copy of it to:

Dannemiller Memorial Educational Foundation
Attention: 04-726C
5711 Northwest Parkway, Suite 100, San Antonio, TX 78249-3360
Fax (210) 697-9318 Phone: (800) 328-2308

Expiration date for credit: October 31, 2005

POSTTEST/SELF ASSESSMENT (Circle the single most appropriate answer below.)

1. It is estimated that IC may effect as many as ___ in ___ women: have IC?
   a. 1 in 4.5
   b. 1 in 7
   c. 1 in 15
   d. None of the above

2. What percentage of laparoscopies are performed in the US are for CPP?
   a. 18%
   b. 23%
   c. 31%
   d. 40%

3. What percentage of women with CPP of unknown etiology have IC?
   a. 30% to 35%
   b. 45% to 52%
   c. 66% to 74%
   d. 80% to 85%

4. Which of the following symptoms of CPP is specific to IC?
   a. Nocturia
   b. Urinary urgency and frequency
   c. Dyspareunia
   d. All of the above
   e. None of the above

5. The most prevalent hypothesis describing the pathophysiology of IC concerns:
   a. The presence of unusual organisms in bladder cells
   b. An alteration of the GAG layer
   c. Decreased levels of Substance P
   d. Allergic reactions

6. Cystoscopy with hydrodistention should be performed:
   a. To confirm a diagnosis of IC
   b. On women with microscopic or gross hematuria
   c. On all women who smoke cigarettes
   d. All of the above

7. Recent data indicate that ___ in ___ women with endometriosis have concurrent IC?
   a. 1 in 3
   b. 1 in 5
   c. 1 in 7
   d. none of the above

8. IC should be suspected in women with:
   a. Recurrent UTIs
   b. Recalcitrant OAB
   c. History or suspicion of endometriosis
   d. All of the above
   e. None of the above

9. Oral PPS is believed to act by:
   a. Reducing bladder capacity
   b. Neutralizing acidity in the bladder
   c. Exerting muscle-relaxing properties
   d. Replenishing a defective GAG layer

10. Which of the following diagnostic findings is suggestive of IC?
    a. A PUF score ≥10 points
    b. A positive PST result
    c. History of cyclic or noncyclic CPP with urinary urgency/frequency
    d. All of the above

PROGRAM EVALUATION

Full Name_____ MD/DO/Other_____

Street _____

City _____ State _____ ZIP Code _____

PHYSICIANS: Are you licensed in the US? (circle) YES or NO

Email Address _____ @ _____

I certify that I completed this CME activity: The actual amount of time I spent in this activity was: _____hours _____minutes

Signature _____ Date Completed_____

The Dannemiller Memorial Educational Foundation would appreciate your comments regarding the quality of the information presented. Later, via email, we would also like to send you a website link to a follow-up survey regarding the material presented. May we contact you? (Please check one.)

___ Yes, via Email. ___ No, please do not contact me.

1. The program objectives were fully met.
   Strongly Agree Agree Disagree Strongly Disagree

2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.
   Strongly Agree Agree Disagree Strongly Disagree

3. The educational activity has enhanced my professional effectiveness to treat patients.
   Strongly Agree Agree Disagree Strongly Disagree NA

4. The educational activity will result in a change in my practice behavior.
   Strongly Agree Agree Disagree Strongly Disagree NA

5. The information presented was *without* promotional or commercial bias.
   Strongly Agree Agree Disagree Strongly Disagree

   (When answering this question, please refer to the following guidelines set forth by the ACCME regarding commercial bias and fair balance: *Discussion of commercial products must be free of bias for or against any one product and must present objective information about each product discussed: only generic names of therapeutic options should be used, however if trades names are used, those of several companies must be discussed in the activity.*)

6. Comments/suggestions regarding *this* material. _____

_____

7. Recommendations for topics of *future* presentations. _____

_____