

# CLINICAL COURIER®

Vol. 24 No. 30

August 2006

ISSN 0264-6684

#### ACCREDITATION STATEMENT

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 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This program has been approved for 1.2 contact hours of continuing education by the American Academy of Nurse Practitioners. Program ID 0608282.

Release Date: August 2006

Expiration Date: August 31, 2007

# DIAGNOSIS AND MANAGEMENT OF INTERSTITIAL CYSTITIS/ PAINFUL BLADDER SYNDROME

#### PROGRAM CHAIR

#### John B. Forrest, MD

Clinical Associate Professor of Urology  
University of Oklahoma  
Health Sciences Center—Tulsa  
Urologic Specialists of Oklahoma, Inc.  
Tulsa, Oklahoma

#### PROGRAM CO-CHAIR

#### Daniel R. Mishell, Jr, MD

Lyle G. McNeile Professor in Obstetrics  
Chair and Professor  
Department of Obstetrics and Gynecology  
Keck School of Medicine  
University of Southern California  
Los Angeles, California

Jointly sponsored by



This program is made possible by an educational grant provided by



**ORTHO WOMEN'S HEALTH & UROLOGY**  
A DIVISION OF ORTHO-MCNEIL PHARMACEUTICAL, INC.

## FACULTY

### Charles W. Butrick, MD

Director, The Urogynecology Center  
Overland Park Regional Hospital  
Overland Park, Kansas

### Robert J. Evans, MD

Chief of Surgery  
Moses Cone Health System  
The Urology Center  
Greensboro, North Carolina

### Fred M. Howard, Jr, MD

Professor of Obstetrics and Gynecology  
University of Rochester School of Medicine and Dentistry  
Rochester, New York

### J. Curtis Nickel, MD, FRCS

Professor of Urology  
Queen's University  
Department of Urology  
Kingston General Hospital  
Kingston, Ontario, Canada

### Lee P. Shulman, MD, FACOG, FACMG

Professor and Chief  
Division of Reproductive Genetics  
Northwestern University  
Feinberg School of Medicine  
Chicago, Illinois

### Diane A. Smith, RN, MSN, CRNP

UroHealthcare LLC  
Newtown Square, Pennsylvania

### Edward J. Stanford, MD, MS, FACOG

Director, Center for Advanced Pelvic Surgery  
Centralia, Illinois

### Kristene E. Whitmore, MD

Chief of Urology  
Professor of Urology and Ob/Gyn  
Drexel University  
Medical Director  
Pelvic and Sexual Health Institute at Graduate Hospital  
Philadelphia, Pennsylvania

## TARGET AUDIENCE

This continuing education program has been developed to meet the educational needs of urologists, urogynecologists, obstetricians/gynecologists, and nurse practitioners who are involved in the diagnosis and treatment of interstitial cystitis (IC)/painful bladder syndrome (PBS).

## EDUCATIONAL OBJECTIVES

The goals of these materials are to generate awareness about chronic pelvic pain syndromes (CPPS) and to discuss the evolving diagnostic and management options for CPPS/IC. Upon completion of this newsletter, participants should be able to:

- Identify IC/PBS as a condition that is highly prevalent but frequently misdiagnosed and/or underdiagnosed
- Clarify the benefits of earlier diagnosis and treatment of IC/PBS
- Discuss how a diagnostic and treatment system for IC/PBS may be necessary to promote clarity in communication, leading to earlier diagnosis and appropriate treatment
- Develop diagnostic and treatment recommendations based on the best available clinical and research experience that would meet the needs of clinicians and patients

## DISCLAIMER

The content and views presented herein are those of the authors and do not necessarily reflect those of the Dannemiller Memorial Educational Foundation, Ortho Women's Health and Urology, or SynerMed® Communications. This material is prepared based on a review of multiple sources of information, but it 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.

## METHOD OF PARTICIPATION

This *Clinical Courier*® should take approximately 1 hour to complete. The participant should, in order, review the educational objectives contained in the newsletter, read the newsletter, answer the 10-question multiple-choice posttest, and complete the evaluation. The posttest and evaluation form are at the end of the newsletter. 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 participant views on future educational needs. To receive credit for this activity, follow the instructions provided on the posttest. This credit is valid through August 31, 2007. No credit will be given after this date.

## DISCLOSURE OF UNLABELED OR INVESTIGATIONAL DRUGS

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration (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/participants should appraise the information presented critically and are encouraged to consult appropriate resources for any product or device mentioned in this program.

## FACULTY DISCLOSURE

In accordance with the ACCME, the Dannemiller Memorial Educational Foundation requires that any person who is in a position to control the content of a CME activity must disclose all relevant financial relationships he or she has with a commercial interest.

Accordingly:

**Charles W. Butrick, MD**, has received grant/research support from Advanced Bionics and has been a consultant for and served on the speakers bureau for Advanced Bionics and Ortho Women's Health and Urology.

**Robert J. Evans, MD**, has received grant/research support from Ortho Women's Health and Urology, has been a consultant for Medtronic Inc. and Ortho Women's Health and Urology, and has served on the speakers bureau for American Medical Systems, Astellas Pharma Inc., Boehringer Ingelheim, GlaxoSmithKline, Medtronic, Inc., Novartis, Ortho Women's Health and Urology, and Solvay Pharmaceuticals.

**John B. Forrest, MD**, has received grant/research support from, has been a consultant for, and has served on the speakers bureau for Ortho-McNeil Pharmaceuticals, Inc.

**Fred M. Howard, Jr, MD**, has been a consultant for Ethicon Inc. and Ortho Women's Health and Urology and has served on the speakers bureau for TAP Pharmaceutical Products Inc.

**Daniel R. Mishell, Jr, MD**, has been a consultant for Barr Laboratories, Inc., Berlex Inc., and Ortho Women's Health and Urology, and has served on the speakers bureau for Ortho Women's Health and Urology.

**J. Curtis Nickel, MD, FRCS**, has received grant/research support from, has been a consultant for, and has served on the speakers bureau for Ortho Women's Health and Urology.

**Lee P. Shulman, MD, FACOG, FACMG**, has received grant/research support from Wyeth, has been a consultant for Berlex Inc., and Ortho-McNeil Pharmaceutical, Inc., and has served on the speakers bureau for Berlex Inc., Ortho Women's Health and Urology, and Wyeth.

**Diane A. Smith, RN, MSN, CRNP**, has served on the speakers bureau for Novartis, Ortho-McNeil Pharmaceutical, Inc., and Pfizer.

**Edward J. Stanford, MD, MS, FACOG**, has no financial interests to declare.

**Kristene E. Whitmore, MD**, has received grant/research support from Advanced Bionics, Astellas Pharma Inc., Medtronic Inc., Ortho-McNeil Pharmaceutical, Inc., Pfizer, and Vivus Inc., and has been a consultant for Boehringer Ingelheim, Boston Scientific, Eli Lilly and Company, Medtronic Inc., and Ortho-McNeil Pharmaceutical, Inc., and has served on the speakers bureau for Astellas Pharma Inc., Boehringer Ingelheim, Eli Lilly and Company, Ortho-McNeil Pharmaceutical, Inc., and Pfizer.

## NONFACULTY DISCLOSURE

The medical writer, Maxine Losseff, has no financial interests to declare.

The Dannemiller staff and SynerMed® Communications staff who were involved in the development of this activity have no financial relationships with any commercial interests that are relevant to this activity.

To resolve identified conflicts of interest, the educational content was fully peer reviewed by a physician member of the Dannemiller Clinical Content Review Committee who has nothing to disclose. The resulting certified activity was found to provide educational content that is current, evidence based, and commercially balanced.

The content of this newsletter was developed from a scientific meeting held April 7, 2006, in Chicago, Illinois. We would like to thank the following persons for their contributions: C. W. Butrick, MD, R.J. Evans, MD, F.M. Howard, Jr., MD, J.C. Nickel, MD, FRCS, L.P. Shulman, MD, FACOG, FACMG, D.A. Smith, RN, MSN, CRNP, E.J. Stanford, MD, MS, FACOG, and K.E. Whitmore, MD.

*Clinical Courier*® is a specialty newsletter reporting on clinical/biomedical issues. The publishers reserve copyright on all published materials, and such materials may not be reproduced in any form without the permission of SynerMed® Communications. This newsletter was developed and produced and is jointly sponsored by the Dannemiller Memorial Educational Foundation and SynerMed® Communications.

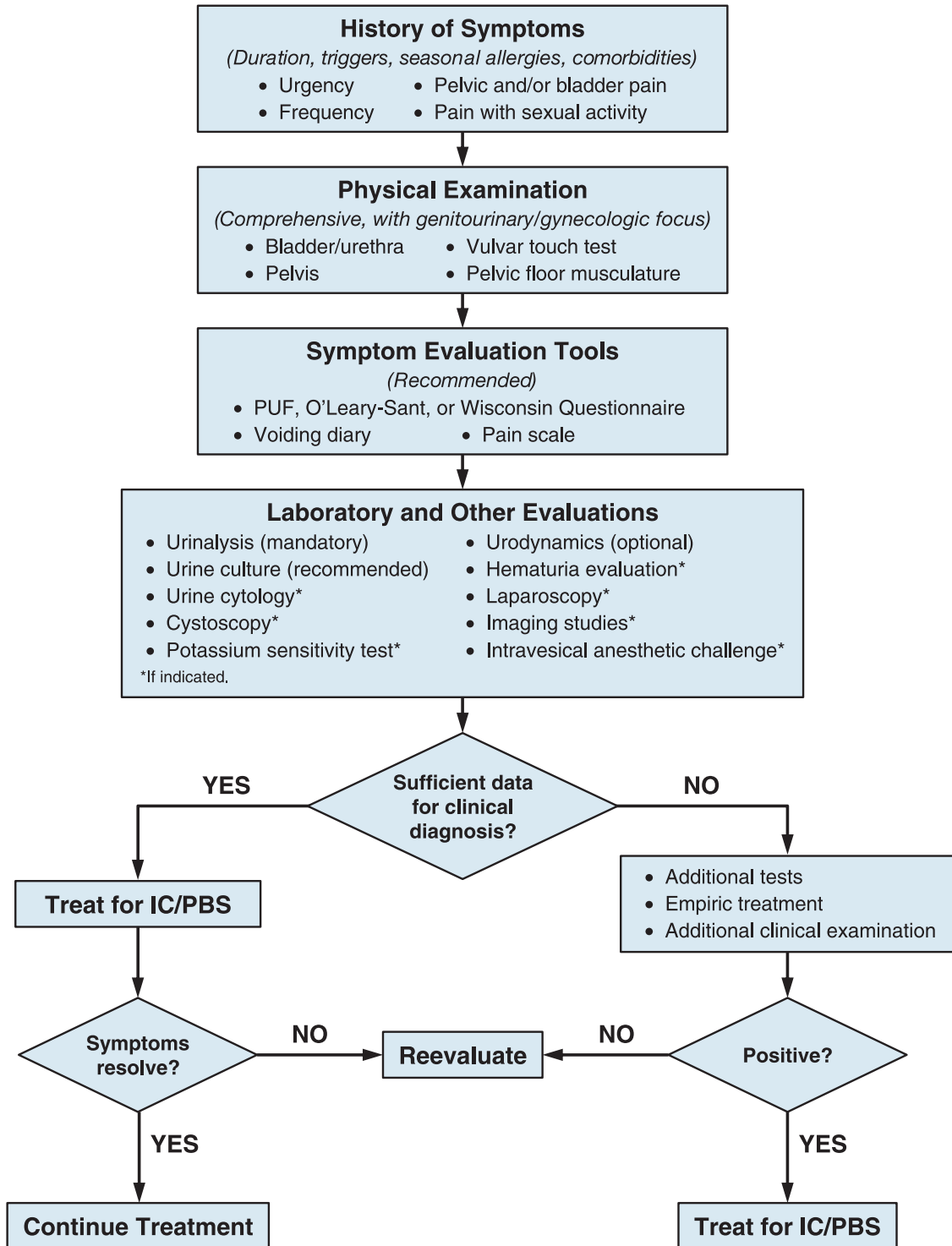
Please direct all correspondence to:

SynerMed® Communications  
Department 103  
518 Route 513  
PO Box 458  
Califon, NJ 07830



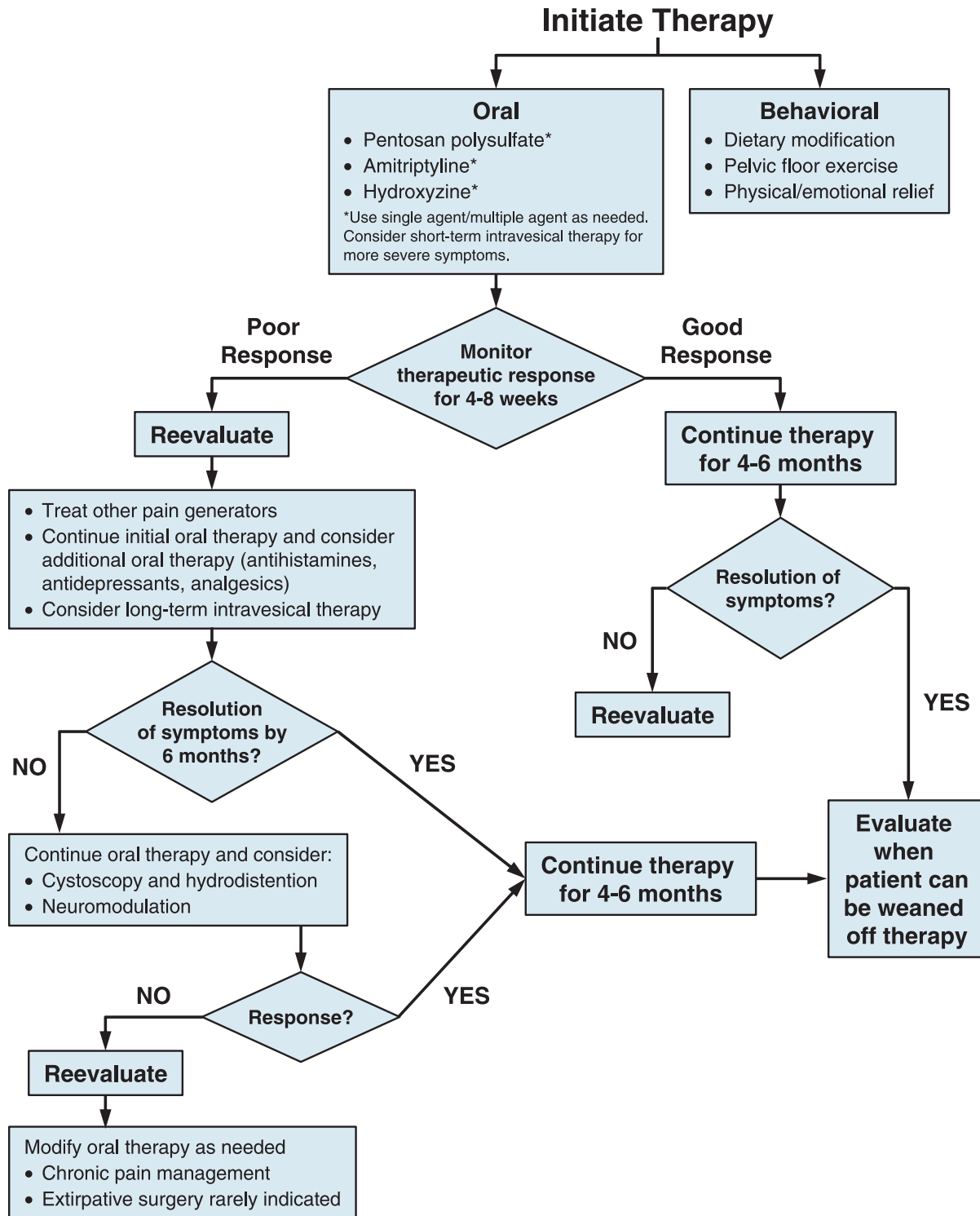
ALGORITHM #1

# Consensus Panel Recommendations for the Evaluation and Diagnosis of Patients With Suspected IC/PBS



ALGORITHM #2

## Consensus Panel Recommendations for the Treatment of Patients With Established IC/PBS Diagnosis



## ACCREDITATION STATEMENT

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 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This program has been approved for 1.2 contact hours of continuing education by the American Academy of Nurse Practitioners. Program ID 0608282.

Release Date: August 2006

Expiration Date: August 31, 2007

# DIAGNOSIS AND MANAGEMENT OF INTERSTITIAL CYSTITIS/ PAINFUL BLADDER SYNDROME

## INTRODUCTION

Interstitial cystitis/painful bladder syndrome (IC/PBS) is an underdiagnosed and frequently inadequately treated disorder that is one of several pathologic conditions with the primary symptom of chronic pelvic pain (CPP). Optimal management of IC/PBS is limited by the fact that standardized guidelines have not been developed to ensure a consistent and effective means for diagnosis and treatment. To this end, a group of experts in urology, urogynecology, and gynecology met on April 7, 2006, in Chicago, Illinois, to discuss the importance of early and accurate diagnosis of the disorder and establish treatment guidelines that might help physicians optimize care and improve outcomes of patients.

The purpose of the meeting was to review key pathophysiologic/clinical features and diagnostic tests for IC/PBS and propose ways to encourage its inclusion by primary care physicians in the differential diagnosis of CPP. The ultimate goal is to help prevent the many unnecessary surgical procedures that are performed and therapies that are given as a result of failure to diagnose IC/PBS. The group was charged with developing diagnosis and treatment algorithms to assist clinicians with early identification and appropriate treatment of IC/PBS via a standardized management protocol.

## IC/PBS: NEED FOR IMPROVED RECOGNITION AND FOCUSED CARE

IC/PBS is a chronic bladder disease that affects about 9 times as many women in the United States as men.<sup>1</sup> Nickel and colleagues found that 7.9% of women and 0.4% of men among 8712 patients visiting 48 urology practices over 2 weeks in Canada had IC/PBS.<sup>2</sup> Because IC/PBS often presents with symptoms common to other urogynecologic disorders, such as pelvic pain, urgency, nocturia, and increased frequency of urination, its diagnosis can be missed by the clinician. The underrecognition of IC/PBS is evident in the following statistics: about 15% of the adult female population will have the symptom of CPP, and approximately 12% of gynecologic referrals are based on this complaint.<sup>3,4</sup> The pain of as many as 85% of women with CPP is caused by a bladder etiology.<sup>5</sup> It is estimated that about 9 million women in the United States have IC/PBS.<sup>3,5</sup> Nevertheless, most patients with IC/PBS will see at least 5 different physicians over the course of at least 5 years before the diagnosis of IC/PBS is made.<sup>6,7</sup>

Estimates of prevalence rates of IC/PBS vary widely, from 67 to 230 per 100,000 women having clinically confirmed disease.<sup>6,8</sup> In clinical practice,

IC/PBS is frequently misdiagnosed as endometriosis, recurrent urinary tract infection (UTI), overactive bladder (OAB), or vulvodynia, leading many patients with pelvic pain to undergo multiple diagnostic laparoscopies and extirpative surgical procedures that fail to resolve the pain, before IC/PBS is initially considered.<sup>7,9,10</sup> In fact, in one study, 79% of women whose chronic pain was not relieved after hysterectomy were subsequently diagnosed as having IC/PBS, highlighting the importance of early and accurate diagnosis to prevent unnecessary surgery.<sup>9</sup>

---

**Most patients with IC/PBS will see at least 5 different physicians over the course of at least 5 years before the diagnosis of IC/PBS is made.**

---

Equally important, undiagnosed and untreated IC/PBS can have a negative impact on quality of life. The persistence of unpredictable, often debilitating symptoms despite repetitive treatment attempts and diagnostic testing causes excessive psychological strain.<sup>11</sup> This in turn can lead to maladaptive physical and emotional responses, such as depression, impaired mental health, poor social functioning, and worsening pain.<sup>10-12</sup> The psychological cost is exacerbated by the time and physical toll of continuing physician visits, new treatment trials, and the progressively worsening pelvic pain—a cycle that is not broken until the correct diagnosis is confirmed.

The last decade has been a period of increasing awareness of IC/PBS, but much work still needs to be done in educating clinicians to recognize and treat IC/PBS earlier and more aggressively. Forrest and colleagues showed that duration of bladder symptoms correlates with severity of IC/PBS and likewise with the time to improvement after initiating therapy.<sup>13</sup> Thus, more rapid identification and initiation of treatment can improve the time to response and degree of benefit associated with appropriate therapeutic intervention. Among the steps recommended to achieve this result are:

- Increasing the likelihood of earlier diagnosis of IC/PBS among gynecologists and primary care physicians
- Altering the diagnostic paradigm to one of inclusion (“think about the bladder”) rather than exclusion
- Making IC/PBS a first-line consideration in the differential diagnosis for CPP
- Broadening the definition of IC/PBS to include markers and diagnostic criteria associated with the current understanding of the disease

With these modifications to the current approach to CPP, clinicians can develop a comprehensive understanding of where IC/PBS fits into the diagnostic paradigm and provide better patient care.

## TOWARD AN IMPROVED UNDERSTANDING OF THE DISEASE PROCESS

The view of IC/PBS as a problem of bladder urothelial dysfunction may be considered just the tip of the iceberg. Traditionally, IC/PBS has been diagnosed based on findings of bladder pain, urgency, and visualization of glomerulations or Hunner's ulcers during cystoscopy with bladder hydrodistention, but this constellation of signs and symptoms is now known to be present in only 20% to 50% of patients with IC/PBS.<sup>14</sup> Other pathologic aspects of the disorder, such as abnormal epithelial permeability, as well as neurogenic processes responsible for the pain aspect, must be considered for diagnosis, patient care, and outcomes to be improved.

### GAG Defect as a Primary Cause

Although there are numerous hypotheses regarding the primary cause of IC/PBS, no single etiology has been established, and most experts believe it is a multifactorial process that starts with one of several urologic insults, such as immune-mediated injury, chronic inflammation, deficient bladder defenses, or obstruction of vascular or lymphatic vessels.<sup>15</sup> The natural history of IC/PBS then involves a cascade of events, in which bladder insult leads to epithelial layer dysfunction, C-nerve fiber activation, and proliferation of mast cells.<sup>16</sup> Without appropriate treatment, these processes become aggravated over time, leading to a vicious cycle of progressively worsening tissue damage, scarring, and fibrosis (Figure 1).<sup>17</sup>

A key concept currently accepted for describing the defect underlying all the observed pathophysiologies in IC/PBS is based on the belief that breakdown of the glycosaminoglycan (GAG) layer, the semipermeable protective coating that covers the bladder epithelium and protects against leakage of urinary irritants such as potassium and urea into the bladder wall, is the primary trigger of the cascade. In a healthy bladder, this

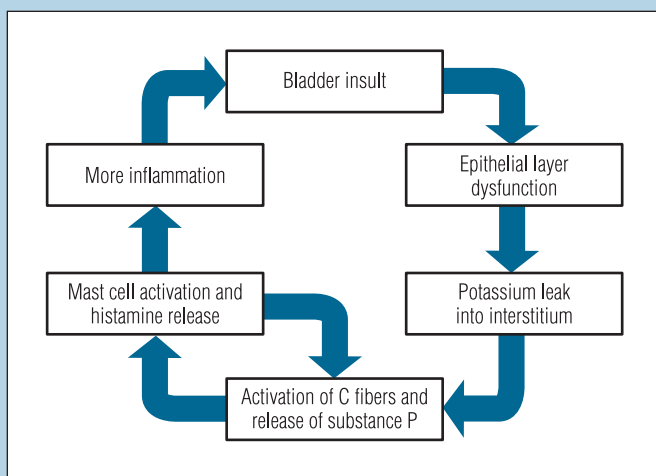
mucous layer acts as a barrier that prevents damage to the underlying nerves and muscles and impedes bacterial adherence. If the GAG layer is impaired or inefficient, the irritants in the urine are able to penetrate the bladder wall, initiate the pathologic cascade, damage tissue, cause pain, and disrupt the normal reparative process of the GAG layer.<sup>7,18,19</sup> Addressing this altered permeability of the bladder epithelium has become a focus for IC/PBS treatment strategies.

### Natural History of Bladder Pain: the Neurogenic Cascade in IC/PBS

Also contributing to this disease process is the concept of spinal cord "windup," the repetitive stimulation of C fibers in the dorsal horn and upregulation of sensory nerves in the bladder that cause the pain characteristic of IC/PBS.<sup>16,20</sup> The ability to perceive pain from internal organs is a function of the afferent sensory system, which in some organs projects to the central nervous system, thereby linking the viscera to the pain centers of the brain.<sup>21</sup> The bladder has the highest neural density of tissues within the pelvis.<sup>20</sup> A large group of visceral nerves are "silent" until a prolonged noxious stimulus such as inflammation causes them to become activated.<sup>21</sup> With ongoing stimulation from inflammation, during which there is prolonged release of neurotransmitters such as substance P, the threshold for neuronal stimulation decreases (allodynia) so that the amount of stimulation required to send a signal to the cerebral cortex is reduced.<sup>20</sup>

As the neurologic stimulation escalates because of hyperalgesia and allodynia, conditions of widespread pain and discomfort begin, and there may be progressive damage to the pelvic floor or the gastrointestinal organs, as well as gynecologic and urinary symptoms.<sup>16</sup> Based on the duration and severity of these alterations taking place within the dorsal horn, the changes can become permanent, a process known as *centralization*. With this neural upregulation, patients begin to experience exaggerated reflex output and viscerovisceral hyperalgesia, and muscle spasticity.<sup>20</sup> In these circumstances, the pain threshold is reduced so that minimal contact can induce a response (eg, the extreme sensitivity to a Q-tip test in patients with vulvodynia). In addition, pain in one organ will cause discomfort in a neighboring organ because of their shared innervation, leading to multiple pain generators and a self-perpetuating cycle of pain. This progressive and variable regional pain syndrome with multiorgan presentation complicates the diagnosis of IC/PBS.

**FIGURE 1**  
**VICIOUS CYCLE OF IC/PBS<sup>17</sup>**



IC, interstitial cystitis; PBS, painful bladder syndrome.

Copyright© MedReviews, LLC. Reprinted with permission of MedReviews, LLC. Evans RJ. Treatment approaches for interstitial cystitis: multimodality therapy. *Rev Urol.* 2002;4(suppl 1):S16-S20. Reviews in Urology is a copyrighted publication of MedReviews, LLC. All rights reserved.

## RECOGNIZING THE PATIENT WITH IC/PBS: CLINICAL SIGNS, SYMPTOMS, AND CHALLENGES

Factors confounding the prompt and effective diagnosis and treatment of IC/PBS in the clinical setting are the complexity of the underlying disease processes—the characteristic signs and symptoms that overlap with a wide range of diseases—and the fact that IC/PBS is not simply a result of a damaged organ but rather is a chronic visceral pain syndrome.<sup>20</sup> A patient may present to a gynecologist with the symptoms of dysmenorrhea, dyspareunia, or vulvodynia or to a urologist with a history of recurrent UTIs, urethral pain, or symptoms of OAB. The pain can be in the lower abdomen, inguinal area, labia, vaginal-perineal region, lower back, or thigh.<sup>22</sup>

### Indistinguishable Signs and Symptoms

Many women consider their gynecologists their primary providers of medical care. Because the clinical presentations of IC/PBS and CPP of gynecologic origin are quite similar, gynecologists may be the primary healthcare providers responsible for early diagnosis of IC/PBS. If IC/PBS is not diagnosed during these primary care visits, years can be spent pursuing unproductive investigations and unnecessary treatments that facilitate progression

of the condition. This delay need not occur if clinicians begin to think of IC/PBS as a relatively common disease and make it part of their evaluation protocol. The key to differentiating IC/PBS from gynecologic or other urologic disorders is to routinely consider IC/PBS in the differential diagnosis of CPP, even when there is evidence of coexistent disease processes.

The symptom overlap observed in IC/PBS and gynecologic/urologic disorders, including generalized pelvic pain; voiding symptoms such as frequency, urgency, or nocturia; pain during intercourse; or menstrual exacerbation, is a major reason IC/PBS remains an undiagnosed disorder in many patients presenting to gynecologists with unresolved pelvic pain.<sup>10</sup>

The principal syndromes to be considered in the differential diagnosis of IC/PBS are recurrent UTI, endometriosis, and OAB, although the other entities include a number of urethral, infectious, and vulvovaginal conditions. An accurate evaluation includes a thorough history, a physical examination including pelvic examination, and use of appropriate objective assessment tools that are used for the diagnosis of IC/PBS, such as the Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF) and potassium sensitivity test (PST) (Table 1).<sup>10,14,22</sup> Most important, in all cases of CPP, it is important to consider IC/PBS as part of the differential diagnosis, even when there is evidence of coexistent gynecologic disease processes. For instance, in several studies, 69% to 81% of patients being seen for recurrent UTIs or endometriosis had positive PST tests, indicating that these patients likely had IC/PBS.<sup>23-25</sup> In addition, in the OB/GYN Practice Study, a trial involving 1066 patients in 8 gynecologic practices, use of the PUF questionnaire to predict the probability of IC/PBS in a general gynecologic practice population indicated an estimated rate of probable IC/PBS of 25.7%.<sup>26</sup> These data suggest that IC/PBS is much more prevalent in the female population than was previously believed and that this disorder is often a source of pain for patients thought to have other gynecologic/urologic conditions.

Because IC/PBS is a progressive disorder, the management goal must be to establish a specific diagnosis early in the disease course, when symptoms are intermittent and before the neurologic upregulation that can lead

to chronic pain begins. Only by performing a thorough physical examination, taking a comprehensive history, including IC/PBS in the differential, and identifying and treating all sources of pelvic pain will clinicians effectively identify and provide relief to the large group of patients with IC/PBS.

**Data suggest that IC/PBS is much more prevalent in the female population than was previously believed.**

## EFFECTIVE DIAGNOSTIC AND SCREENING TOOLS FOR IDENTIFYING PATIENTS WITH IC/PBS

Although the characteristic symptoms of IC/PBS are well documented, the substantial overlap with features of other disorders mandates a focused screening and thorough differential diagnosis to rule out other potential causes of the urgency/frequency and/or pelvic pain, symptoms that characterize this condition. In addition to the history and physical examination, urinalysis and urine culture are the first step in ruling out disorders that mimic IC/PBS, such as UTI and bladder cancer. The absence of bacteria or blood cells in a voided urine specimen is characteristic of IC/PBS. If microscopic hematuria is observed on urinalysis, however, a complete urologic workup, including cystoscopy, should be used to rule out malignancy.<sup>22,27</sup>

The principal screening and diagnostic tools used to identify IC/PBS are described below.

### Screening Tools

#### PUF

The PUF is used to screen patients for IC/PBS symptoms, and it has been found to correlate closely with the PST, a reliable indicator of IC/PBS. The PUF is a short, self-administered questionnaire that assesses urinary patterns and pain parameters, with total scores ranging from 1 to 35 (Figure 2, page 4). The PUF has been validated for clinical use by both gynecologic and urologic patients in a study in which most patients were eventually diagnosed as having IC/PBS.<sup>28</sup> In this study, healthy controls scored 2 or less, and 84% of patients with scores greater than 15 had positive PSTs. Although the PUF has the shortcoming of not including measures of nocturia and sleep loss due to pain, it has reasonable sensitivity and specificity for the diagnosis of IC/PBS.<sup>28</sup> The PUF is also a valuable tool for following response to therapy, although the sensitivity for measuring improvements over time has not yet been validated.

#### O'Leary-Sant IC Symptom Index and Problem Index

The O'Leary-Sant questionnaire is designed to evaluate symptom severity and its relevance to IC/PBS. Each of the 2 indices contains 4 items that measure urgency and frequency of urination, nighttime urination, and pain or burning. Each question on the IC Symptom Index (ICSI) is assigned a score of 0 to 5, and questions on the Problem Index are scored from 0 to 4. Patients with IC/PBS generally score 6 or more on each index. The scale has been validated for internal consistency and reliability.<sup>29</sup> This questionnaire was shown to be responsive to change over time in 2 studies following patients' responses to treatment; thus, this index can be a valuable follow-up tool.<sup>30,31</sup>

The O'Leary-Sant indices provide important insight into IC/PBS symptoms and changes over time, but the endpoints they address are limited. They do not evaluate sexual dysfunction or symptom severity, so they are intended to be combined with other screening tools, such as the PUF, that address these additional symptom areas.

**TABLE 1**

### KEY FEATURES OF AN IC/PBS-SPECIFIC EXAMINATION AND DIFFERENTIAL DIAGNOSIS<sup>10,14,22</sup>

- History and physical examination
  - Including pain history, previous diagnoses, pelvic examination, and digital palpation of urethra and bladder base
- Objective assessment tools
  - PUF, urinalysis and culture, PST
- Other possible tests
  - Cystoscopy (?), intravesical challenge
- Differential diagnosis
  - Consider
    - IC/PBS
    - Endometriosis
    - Overactive bladder
    - Vulvodynia
    - Urethral diverticula
    - Uterovaginal prolapse
    - Vaginitis

IC, interstitial cystitis; PBS, painful bladder syndrome; PUF, Pelvic Pain and Urgency/Frequency Patient Symptom Scale; PST, potassium sensitivity test; PBS, painful bladder syndrome.

**FIGURE 2**

**PELVIC PAIN AND URGENCY/FREQUENCY PATIENT SYMPTOM SCALE**

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	a. Do you now or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always			
	b. Has pain or urgency ever made you avoid sexual activity?	Never	Occasionally	Usually	Always			
4	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			
5	a. If you have pain, is it usually		Mild	Moderate	Severe			
	b. Does your pain bother you?	Never	Occasionally	Usually	Always			
6	Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always			
7	a. If you have urgency, is it usually		Mild	Moderate	Severe			
	b. Does your urgency bother you?	Never	Occasionally	Usually	Always			
8	Are you currently sexually active? Yes _____ No _____							
<b>SYMPTOM SCORE (1, 2a, 3a, 4, 5a, 6, 7a)</b>								
<b>BOTHER SCORE (2b, 3b, 5b, 7b)</b>								
<b>TOTAL SCORE (Symptom Score + Bother Score)</b>								

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

PST, potassium sensitivity test.

©2000 C. Lowell Parsons, MD. Used with permission.

**University of Wisconsin IC Scale**

The Wisconsin scale is based on responses to 7 primary questions that are included in a longer symptom questionnaire; the complete form includes another 18 queries, regarding other body systems and other symptoms, designed to distract the patient from preconceived responses to IC/PBS-focused questions. This scale has been validated for clinical trials. It also has been shown to be responsive to improvement over time with treatment.<sup>31,32</sup>

**Diagnostic Tests**

**PST**

The PST is a sensitive indicator of bladder dysfunction that can be performed in a clinician's office (Figure 3).<sup>22</sup> The PST is based on the premise that, unlike healthy bladder walls, the altered GAG epithelium in IC/PBS will allow potassium (instilled directly into the bladder as potassium chloride in solution with sterile water) to pass into the bladder. If it is able to pass through the bladder wall, potassium, an irritant, will trigger a pain response and/or a sense of urgency. Up to 90% of patients diagnosed with IC/PBS have positive PSTs, as do 81% of gynecologic patients with pelvic pain; less than 2% of healthy women experience pain or urgency symptoms during the PST.<sup>25,28</sup>

The PST correlates closely with the results of the PUF and can be indicative of a diagnosis of IC/PBS in patients with pelvic pain.<sup>25,28</sup> The PST cannot, on its own, reliably distinguish IC/PBS from other disorders of bladder origin.<sup>22</sup>

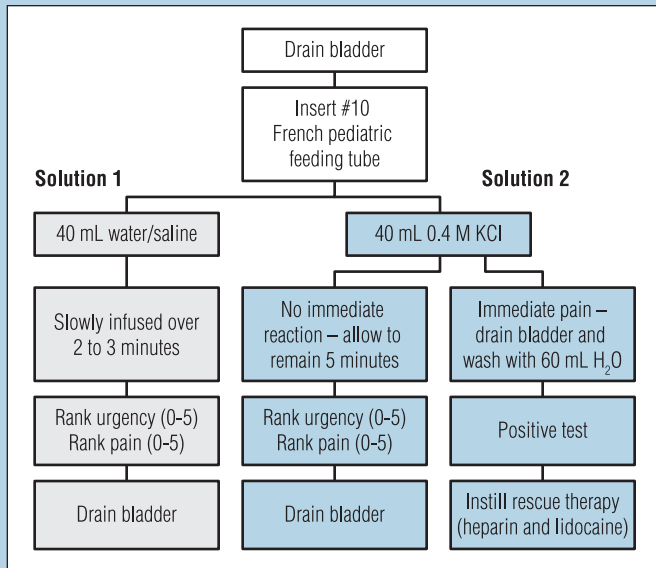
**Intravesical Anesthetic**

Henry and coworkers first described the use of intravesical administration of lidocaine in the management of IC/PBS in 2001, and today this technique has both diagnostic and treatment implications.<sup>33</sup> Although lidocaine will not pass through the bladder epithelium, alkalization of 5% lidocaine by use of an equal amount of 8.4% sodium bicarbonate buffered bladder contents and allowed absorption of instilled lidocaine, as demonstrated by the immediate relief of symptoms.<sup>33</sup> In this way, intravesical administration of an anesthetic solution can distinguish the bladder as the site of pain origin in patients with suspected IC/PBS, although the technique has not yet been validated for widespread use.

Preliminary results from a study in which a buffering solution of lidocaine and sodium bicarbonate was used to also deliver heparin or pentosan polysulfate sodium (PPS) and caused relief of symptoms, indicates promise for intravesical instillation as a treatment modality as well. Instillation of the solution into the bladder 3 to 7 times per week for at least 2 weeks afforded

**FIGURE 3**

**PROTOCOL FOR A POTASSIUM SENSITIVITY TEST TO PREDICT IC/PBS: PAIN IN RESPONSE TO INFUSION OF POTASSIUM CHLORIDE SUGGESTS BLADDER DISEASE<sup>22</sup>**



IC, interstitial cystitis; PBS, painful bladder syndrome.

Adapted with permission from Parsons CL. Diagnosing chronic pelvic pain of bladder origin. *J Reprod Med.* 2004;49:235-242.

sustained pain relief to 85% of 40 patients with IC/PBS who completed the study.<sup>27</sup> With confirmation of these results in additional trials, this technique could prove to be a valuable method of delivering immediate relief of the pain and urgency of IC/PBS.

**Cystoscopy With Bladder Hydrodistention**

Although the presence of submucosal hemorrhages or glomerulations on cystoscopy is part of the National Institute of Diabetes and Digestive and Kidney Diseases research parameters for diagnosis of IC/PBS, it is not predictive of pathology and does not correlate with symptoms; the biopsy is not diagnostic of IC/PBS and the presence of glomerulations is not specific for IC/PBS.<sup>34</sup> The primary indication for cystoscopy in the assessment of pelvic pain is to rule out malignancy in patients with hematuria and/or abnormal urinary cytology, and cystoscopy is no longer widely used as a standard diagnostic procedure in suspected IC/PBS.

**Biomarkers and the Disease Process**

Interest in the mechanism for bladder repair from tissue damage has led to identification of a number of potential biologic markers that might prove valuable for identifying IC/PBS from urine samples. Although the list of urinary factors tested as biomarkers of IC/PBS is relatively long—including norepinephrine, substance P, kallikrein, GAG, and mast cell mediators—the 2 most likely current candidates to establish diagnosis of IC/PBS early in the course of the disorder are antiproliferative factor (APF) and glycoprotein (GP)-51.

**APF**

Identified and described by Keay and colleagues at the University of Maryland in Baltimore, APF is a modified frizzled 8 protein-related peptide (a group of recently discovered proteins) that is present in high concentrations in the bladder epithelial cells of patients with IC/PBS.<sup>35</sup> APF inhibits

bladder cell proliferation by downregulating cell adhesion protein and growth factor production, including a profound decrease in heparin-binding epidermal growth factor-like growth factor (HB-EGF) and an increase in epidermal growth factor (EGF), insulin-like growth factor (IGF)-1, and IGF binding protein (IGFBP)-3.<sup>36,37</sup> As cell proliferation declines, it may lead to the characteristic epithelial thinning or ulceration seen in IC/PBS.<sup>37</sup> Whether APF directly decreases cell proliferation or reflects abnormal bladder function/disease—that is, whether it is a primary or secondary influence—is not known, but the presence of high levels of APF in the urine is clearly a marker of IC/PBS (Table 2).<sup>37,38</sup> APF has been observed in the urine of 94% of patients with IC/PBS and correlates with 94% sensitivity and 95% specificity for the presence of IC/PBS. Only about 10% of patients with other urogenital disorders will exhibit APF elevations.<sup>37</sup> In addition, APF levels have been shown to return to normal in IC/PBS patients undergoing certain therapies, such as hydrodistention of the bladder or sacral nerve stimulation, further suggesting a correlation between APF levels and the disease process in IC/PBS that warrants continued investigation.<sup>39,40</sup>

**GP-51**

GP-51, a urinary glycoprotein that is a key component of the mucin lining of the urinary tract, has been suggested as a marker for IC/PBS by Byrne and colleagues.<sup>38</sup> First identified as a protective element of the GAG layer of animal bladders, GP-51 has since been identified in the mucin of human transitional epithelium and shown to prevent bacterial access to underlying epithelial cells.<sup>38</sup> Produced and secreted by transitional epithelial cells of the genitourinary tract, GP-51 is present in human urine and decreased in bladder biopsies and urine of patients with IC/PBS. Furthermore, the GP-51 levels in the urine of patients after cystectomy were nearly identical to those of patients with IC/PBS, establishing the bladder, as opposed to the upper urinary tract, as the primary source of GP-51.<sup>38</sup>

**Other Markers Under Investigation**

The biology and histology of IC/PBS, including changes in GAG permeability and denudation or thinning of the bladder epithelium, suggest that regeneration of bladder tissue may be defective. Epithelial growth factors present in human urine that may be associated with epithelial cell regeneration and differentiation include EGF, IGF, IGFBP-3, HB-EGF, platelet-derived growth factors-A and -B, fibroblast growth factors-1 and -2, and transforming

**TABLE 2**  
**POTENTIAL BIOMARKERS FOR IC/PBS: LIKELY CANDIDATES<sup>37,38</sup>**

APF	GP-51
<ul style="list-style-type: none"> <li>Glycosylated peptide made by bladder epithelial cells from patients with IC/PBS</li> <li>Inhibits bladder cell proliferation via effects on cell adhesion and growth factor production</li> <li>Present in 94% of IC/PBS patients but &lt;10% of controls with or without urogenital disease</li> <li>94% sensitivity; 95% specificity</li> </ul>	<ul style="list-style-type: none"> <li>Glycoprotein produced and secreted by transitional epithelial cells of the bladder lining</li> <li>May be a strategic factor in the primary defense mechanism of the bladder</li> <li>Urine levels correlate with clinical diagnosis of IC/PBS                             <ul style="list-style-type: none"> <li>Reduced in IC/PBS</li> <li>Equivalent levels in IC/PBS and postcystectomy patients</li> </ul> </li> </ul>

IC, interstitial cystitis; PBS, painful bladder syndrome; APF, antiproliferative factor; GP-51, glycoprotein-51.

growth factor- $\beta$ .<sup>41</sup> Enzyme-linked immunosorbent assay testing of the urine of women with IC/PBS, healthy, asymptomatic controls, and women with bacterial cystitis revealed that HB-EGF levels were significantly lower ( $P<.001$ ), and EGF ( $16.13 \pm 1.52$  ng/mL), IGF-1 ( $18.94 \pm 3.46$  pg/mL), and IGFBP-3 ( $16.32 \pm 4.60$  ng/mL) levels were higher in the urine of women with IC/PBS than in urine of asymptomatic controls ( $8.02 \pm 0.90$  ng/mL,  $8.53 \pm 2.87$  pg/mL, and  $6.93 \pm 3.42$  ng/mL, respectively). Urine EGF and IGF-1 levels were higher in patients with IC/PBS than in those with bacterial cystitis ( $6.99 \pm 1.31$  ng/mL and  $14.97 \pm 3.58$  pg/mL, respectively).<sup>41</sup> These differences indicate complex changes in the bladder of women with IC/PBS and/or infection, but whether these growth factors may be used as markers to diagnose IC/PBS has not been established, although they remain an interesting subject for future research.

If patterns of expression of APF and GP-51 continue to support the potential of these proteins as biologic markers and diagnostic test measures, the incidence of rapid identification of IC/PBS could increase substantially. The development of noninvasive urinary tests for APF or GP-51 would provide rapid and safe means to ensure early diagnosis of IC/PBS in patients with pelvic pain, urinary frequency, or other characteristic symptoms; it might also provide a means for following disease progression or efficacy of drug therapy. With these tools, clinicians could improve response time to treatment, avoid unnecessary and invasive treatments for misdiagnosed disease, and restore years of improved quality of life to their patients.

## TREATMENT OPTIONS: AN UPDATE ON IC/PBS THERAPIES

Because of the elusive etiology of IC/PBS, many forms of treatment have been attempted. From excision of glomerulations to bladder distention to instillation of silver nitrate, oxychlorosene sodium, neomycin, and other agents, the treatment of IC/PBS has been changing with improved understanding of the underlying disease process. Some new therapies for management of IC/PBS are described below, including those designed to address the defective GAG layer currently believed to underlie IC/PBS pathophysiology and to treat neurogenic pain.

### Oral Therapy

PPS is a synthetic sulfated polysaccharide that has been tested in several studies of IC. Mulholland and coworkers treated 110 patients with 300 mg/day oral PPS for 3 months.<sup>42</sup> Based on investigator evaluation, overall improvement was reported by 26% of patients treated with PPS compared with 11% of placebo patients ( $P=.03$ ); the drug was extremely safe, with an adverse-event profile similar to that of placebo. In another study, 148 patients with IC received 100 mg PPS TID or placebo.<sup>43</sup> After 3 months, 32% of PPS-treated patients versus 16% of placebo patients had experienced a significant (50%) decrease in pain and urgency. More PPS-treated than placebo-treated patients experienced an increase of 20 mL or more in voided urine volume (40% vs 24%, respectively;  $P=.02$ ). The efficacy and safety of PPS for the relief of IC symptoms in this study confirmed previous data.<sup>43</sup>

Nickel and colleagues recently established the dose-response pattern of PPS in a 32-week study involving 380 adults with IC of at least 6 months' duration.<sup>44</sup> Comparing dosages of 300, 600, and 900 mg/day in a randomized, double-blind, double-dummy, parallel-group fashion, the researchers noted that all 3 dosage levels delivered clinically relevant and significant improvements in symptoms over baseline ( $-3$ ,  $-3.8$ , and  $-3.3$ , respectively, on ICSI scores;  $P<.001$ ), with no significant difference in

efficacy among dosage groups. They also observed that response continued to improve over the course of the study, indicating that duration of therapy rather than dosage appears to be more relevant to symptom improvement. Most adverse events were mild and resolved without alteration or discontinuation of therapy (Figure 4).<sup>44</sup>

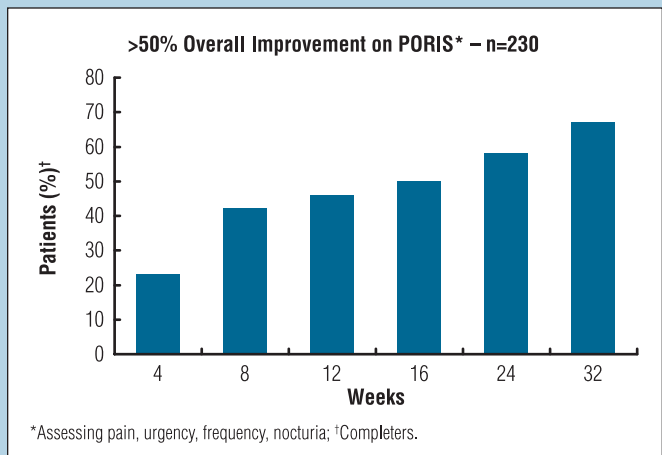
A recent report from Europe suggested that the immunosuppressive agent cyclosporine A (not approved for indicated use) may be more effective than PPS for the treatment of IC, albeit with some safety issues.<sup>45</sup> After treating 64 patients with 1.5 mg/kg BID cyclosporine A or 100 mg TID PPS for 6 months, the investigators found that cyclosporine provided superior improvements to those with PPS in clinical outcome measures, from frequency in 24 hours ( $-6.7 \pm 4.7$  vs  $-2.0 \pm 5.1$ , respectively;  $P<.001$ ) and voided volume ( $59 \pm 57$  mL vs  $1 \pm 31$  mL, respectively;  $P<.001$ ) to improvement on O'Leary-Sant symptom score sums ( $-15.0 \pm 9.4$  vs  $-3.1 \pm 4.3$ , respectively;  $P<.001$ ). There were, however, more severe and more common adverse events in the cyclosporine group, including gingival pain and hyperplasia, paresthesias, abdominal pain, and muscle pain. Increased blood pressure and serum creatinine levels with cyclosporine warrant careful follow-up as well. In addition, a post hoc analysis showed that the best efficacy with cyclosporine was achieved in the older population, which might reflect long-standing inflammatory pathophysiology.<sup>45</sup>

### Antidepressants

Experience with the antidepressant amitriptyline suggests a potential role for tricyclic antidepressants in the treatment of IC.<sup>46</sup> Among 94 patients with IC treated with amitriptyline for a mean of 16.5 months (mean self-titrated bedtime dose, 55 mg) and followed up for a mean of 19 months, 15% of patients expressed excellent overall satisfaction with therapy and 31% rated their satisfaction as good. The dropout rate, primarily for nonresponse to treatment, was 31% after a mean treatment period of 6 weeks at a mean dose of 70 mg. Common adverse events included dry mouth, weight gain, constipation, sedation, and nausea. The authors concluded that amitriptyline could be used safely and effectively to treat IC, although the side effects necessitate careful and judicious administration, preferably at bedtime.<sup>46</sup>

FIGURE 4

### PENTOSAN POLYSULFATE SODIUM TREATMENT PROVIDES SIGNIFICANT IMPROVEMENT OF IC/PBS SYMPTOMS THAT INCREASES WITH DURATION OF TREATMENT<sup>44</sup>



PPS, pentosan polysulfate; PORIS, Patient's Overall Rating of Symptom Index. Adapted with permission from Nickel JC et al. *Urology*. 2005;65:654-658.

## Hydroxyzine

Although common antihistamines have not proven to be effective in treating IC, the histamine-1 receptor antagonist hydroxyzine has been shown to yield some relief of IC symptoms. Hydroxyzine is believed to work by inhibiting neurogenic bladder mast cell activation as well as via its established anticholinergic, anxiolytic, and analgesic properties.<sup>47</sup> In one open-label study, hydroxyzine reduced IC symptoms by 40% (based on visual analog scales) in 95 of 140 patients with symptomatic IC. Among patients with bladder mastocytosis or histories of allergies, symptom relief was as great as 55%.<sup>48</sup>

## Intravesical Therapy

Several drugs have been developed that were designed to coat the bladder epithelium as a means of preventing transit of toxins that might otherwise pass through a deficient GAG layer in IC. Dimethyl sulfoxide (DMSO), a compound that was first synthesized in the mid-19th century, has recognized anti-inflammatory, immunologic, analgesic, and bacteriostatic properties. As early as 1968, DMSO was used to treat IC with substantial success. The only placebo-controlled study of DMSO in IC, however, was performed in 1988 by Perez-Marrero and colleagues, who treated 33 patients with biopsies suggestive of IC with intravesical administration of 50% DMSO or placebo.<sup>49</sup> The investigators found that the active drug provided both subjective and objective improvement of symptoms of pain, urgency, and frequency as well as urodynamic function compared with placebo. DMSO is administered as a series of bladder instillations at 1 to 2-week intervals for 4 to 8 treatments, with maintenance therapy every 1 to 2 months as necessary. It is an effective, well-tolerated, and easily administered treatment for early IC.

## Multimodal Therapy

There are numerous treatment strategies for IC/PBS available, and as a rule treatment should build from more conservative forms of therapy to increasingly aggressive interventions, with the ultimate goals of symptom relief and improved quality of life. Multimodal therapy is the basis of optimal care of patients with IC/PBS.

---

**Multimodal therapy is the basis of optimal care of patients with IC/PBS.**

---

It is becoming accepted that use of the safe and effective oral agent PPS should be the foundation of pharmacologic therapy, with intravesical administration of the drug currently under investigation for greater early symptom control.<sup>50</sup> Combination drug therapy can be tried if there is evidence of pelvic floor dysfunction, particular trigger points, an allergic component with mast cell activity, and/or other sources of pain, such as irritable bowel syndrome, vulvodynia, or endometriosis. Combining PPS with antihistamines, analgesics, antispasmodics, or antidepressants may enhance relief for patients who do not respond to monotherapy, and non-pharmacologic approaches such as bladder training and biofeedback may be added as needed.<sup>50</sup>

Finally, if drug therapy fails to eliminate the pain, secondary therapy with peripheral nerve stimulation has been shown to be very effective for patients with resistant disease. In 5 studies evaluating the efficacy of sacral nerve stimulation in the management of pelvic pain, this approach yielded notable improvements in the realms of urinary frequency, pain, and/or normalization of biomarkers such as HB-EGF and APF.<sup>40,51-54</sup> Removal of the bladder should be considered a last resort, to be used only for patients for whom other forms of management have failed.

## ALGORITHMS FOR IC/PBS MANAGEMENT

Given the growth in understanding of IC/PBS and advances in diagnosis and screening as well as in treatment, it now should be considered essential to outline a simple and rational approach for caring for patients who present with CPP. The goal of standardization is to provide a universal tool for assessment of patients presenting with pelvic pain to facilitate earlier identification of patients with IC/PBS and thereby ensure prompt, appropriate treatment and improved outcomes. The purpose of this consensus conference, therefore, was to establish acceptable guidelines for addressing CPP in the physician's office and to build algorithms for screening, diagnosis, and treatment that would aid in better management of IC/PBS. The results follow.

---

**The goal of standardization is to provide a universal tool for assessment of patients presenting with pelvic pain to facilitate earlier identification of patients with IC/PBS and thereby ensure prompt, appropriate treatment and improved outcomes.**

---

## Screening and Diagnosis

In working toward consensus on diagnosis and treatment algorithms to aid clinicians in recognizing symptoms and optimizing outcomes of IC/PBS, the expert panel aimed for inclusion of an adequate depth of evaluation without overwhelming detail to ensure the positive identification of patients with IC/PBS. As can be seen in Algorithm #1, their decisions led to a flow-chart, with consecutive steps that include a symptom history, a complete physical examination, use of recommended symptom evaluation tools, and a range of relevant laboratory assessments. Beginning with the history, clinicians should investigate patterns of urgency, frequency, and pelvic and/or bladder pain, including pain with sexual activity, and ascertain how long the symptoms last and whether there are any particular triggers, comorbidities, or seasonal allergies that might correlate with the condition. PUF, voiding diaries, or pain scales should be used in the consideration of the bladder as the origin of CPP.

A comprehensive physical examination with a genitourinary/gynecologic focus should be supplemented with urinalysis, with additional laboratory testing if needed. For many patients, the results of these tests will lead to reliable clinical diagnoses, but if the underlying pathology still is not clear, a PST and an anesthetic challenge should confirm the diagnosis of IC/PBS.

## Treatment

With the diagnosis of IC/PBS, oral and behavioral therapy (eg dietary modification) should be started immediately following the protocols of the treatment algorithm (Algorithm #2). Because of its safety and efficacy, current standards recommend initiating therapy with oral administration of PPS, with amitriptyline and/or hydroxyzine added as needed for allergic or neurogenic targets. In more severe cases, intravesical therapy may provide rapid relief of debilitating pain and symptoms. Patients who respond to first-line therapy can eventually be weaned off drugs. Those who continue to be symptomatic, however, should receive additional appropriate adjunctive therapies and potentially be given long-term intravesical medication. The patient who is still symptomatic 6 months after initiating therapy may require cystoscopy and hydrodistention with or without ulcer ablation or neuromodulation of the sacral nerve.

Very few patients will continue to be symptomatic, but those who do not respond to any of the above interventions may require chronic pain management. Extirpative surgery is rarely warranted.

## CONCLUSION

IC/PBS is a more common disorder than has been previously thought and is responsible for substantial morbidity if left undiagnosed and untreated. Increased understanding of the visceral and neurogenic components of IC/PBS has led to important advances in screening and diagnostic tests and improved pharmacologic therapies. If gynecologists and primary care clinicians, who are often the first healthcare practitioners to whom patients present with the characteristic complaints of IC/PBS, begin to consider the bladder among the possible sources of CPP, more patients will be managed earlier and more aggressively, potentially sidestepping the neurogenic sensitization that can make IC/PBS such a painful and debilitating condition. It is hoped that the diagnosis and treatment algorithms provided here will be a valuable guide to help clinicians make informed and appropriate choices and prevent progression of this challenging condition.

## REFERENCES

1. National Kidney and Urologic Diseases Information Clearinghouse. Interstitial cystitis. Available at: <http://kidney.niddk.nih.gov/kudiseases/pubs/interstitialcystitis/index.htm>. Accessed January 24, 2006.
2. Nickel JC, Teichman JM, Gregoire M, Clark J, Downey J. Prevalence, diagnosis, characterization, and treatment of prostatitis, interstitial cystitis, and epididymitis in outpatient urological practice: the Canadian PIE Study. *Urology*. 2005;66:935-940.
3. 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.
4. Walker EA, Katon WJ, Jemelka R, Alfrey H, Bowers M, Stenchever MA. The prevalence of chronic pelvic pain and irritable bowel syndrome in two university clinics. *J Psychosom Obstet Gynaecol*. 1991;12 (suppl):65-75.
5. 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.
6. Curhan GC, Speizer FE, Hunter DJ, Curhan SG, Stampfer MJ. Epidemiology of interstitial cystitis: a population based study. *J Urol*. 1999;161:549-552.
7. Metts JF. Interstitial cystitis: urgency and frequency syndrome. *Am Fam Physician*. 2001;64:1199-1206.
8. Leppilahti M, Sairanen J, Tammela TL, Aaltomaa S, Lehtoranta K, Auvinen A. Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finland. *J Urol*. 2005;174:581-583.
9. Chung M. Interstitial cystitis in persistent posthysterectomy chronic pelvic pain. *JSL*. 2004;8:329-333.
10. Parsons C, Stanford E, Kahn B, Sand P. Tools for diagnosis and treatment. *Female Pat*. 2002;suppl:12-17.
11. Azevedo K, Payne CK. The psychosocial economic impact of invisible chronic disease: examining the experience of patients with interstitial cystitis. *Urology*. 2001;57(suppl 1):118.
12. Rothrock NE, Lutgendorf SK, Kreder KJ. Coping strategies in patients with interstitial cystitis: relationships with quality of life and depression. *J Urol*. 2003;169:233-236.
13. Forrest JB, Sebastianski P, O'Brien-Westbrook M. Observations on the clinical factors affecting the treatment outcomes of interstitial cystitis. Poster presented at: 11th Scientific Meeting of the International Pelvic Pain Society; August 5-7, 2004; Chicago, Ill.
14. Nickel JC. Interstitial cystitis: a chronic pelvic pain syndrome. *Med Clin North Am*. 2004;88:467-481, xii.
15. Messing E. Interstitial cystitis and related syndromes. In: Walsh P, Retik A, Stamey T, Vaughan E, eds. *Campbell's Urology*. 6th ed. Philadelphia: WB Saunders Co; 1992:982-1005.
16. Sant GR. Etiology, pathogenesis and diagnosis of interstitial cystitis. *Rev Urol*. 2002;4:S9-S15.
17. Evans RJ. Treatment approaches for interstitial cystitis: multimodal therapy. *Rev Urol*. 2002;4:S16-S20.
18. Parsons CL, Boychuk D, Jones S, Hurst R, Callahan H. Bladder surface glycosaminoglycans: an epithelial permeability barrier. *J Urol*. 1990;143:139-142.
19. Burkman R. Chronic pelvic pain of bladder origin: epidemiology, pathogenesis and quality of life. *J Reprod Med*. 2004;49:225-229.
20. Butrick CW. Interstitial cystitis and chronic pelvic pain: new insights in neuropathology, diagnosis, and treatment. *Clin Obstet Gynecol*. 2003;46:811-823.
21. Cervero F. Sensory innervation of the viscera: peripheral basis of visceral pain. *Physiol Rev*. 1994;74:95-138.
22. Parsons CL. Diagnosing chronic pelvic pain of bladder origin. *J Reprod Med*. 2004;49:235-242.
23. Porru D, Politano R, Gerardini M, et al. Different clinical presentation of interstitial cystitis syndrome. *Int Urogynecol J Pelvic Floor Dysfunct*. 2004;15:198-202.
24. Stanford EJ, Koziol J, Feng A. The prevalence of interstitial cystitis, endometriosis, adhesions, and vulvar pain in women with chronic pelvic pain. *J Minim Invasive Gynecol*. 2005;12:43-49.
25. Parsons CL, Dell J, Stanford EJ, Bullen M, Kahn BS, Willems JJ. The prevalence of interstitial cystitis in gynecologic patients with pelvic pain, as detected by intravesical potassium sensitivity. *Am J Obstet Gynecol*. 2002;187:1395-1400.
26. Dell JR. OB/GYN Practice Study. Poster presented at: Research Insights Into Interstitial Cystitis: A Basic and Clinical Science Symposium; October 30-November 1, 2003; Alexandria, Va.
27. Parsons CL. Evidence-based strategies for recognizing and managing IC. *Contemp Urol*. 2003;15:22-35.
28. 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.
29. O'Leary MP, Sant GR, Fowler FJ, Whitmore KE, Spolarich-Kroll J. The Interstitial Cystitis Symptom Index and Problem Index. *Urology*. 1997;49:58-63.
30. Lubeck DP, Whitmore K, Sant GR, Alvarez-Horine S, Lai C. Psychometric validation of the O'Leary-Sant Interstitial Cystitis Symptom Index in a clinical trial of pentosan polysulfate sodium. *Urology*. 2001;57:62-66.
31. Probert K, Mayer R, Wang Y, et al. Responsiveness of symptom scales for interstitial cystitis. *Urology*. 2006;67:55-59.
32. Goin JE, Olaleye D, Peters KM, Steinert B, Habicht K, Wynant G. Psychometric analysis of the University of Wisconsin Interstitial Cystitis Scale: implications for use in randomized clinical trials. *J Urol*. 1998;159:1085-1090.
33. Henry R, Patterson L, Avery N, et al. Absorption of alkalinized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. *J Urol*. 2001;165:1900-1903.
34. Tomaszewski JE, Landis JR, Russack V, et al. Biopsy features are associated with primary symptoms in interstitial cystitis: results from the interstitial cystitis database study. *Urology*. 2001;57:67-81.
35. Keay S, Szekely Z, Conrads TP, et al. An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. *Proc Natl Acad Sci USA*. 2005;101:11803-11808.
36. Available at: <http://www.ichelp.org/cafeica/Vol03No03.html>. Accessed July 31, 2006.
37. Keay SK, Zhang CO, Shoenfelt J, et al. Sensitivity and specificity of antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor as urine markers for interstitial cystitis. *Urology*. 2001;57:9-14.
38. Byrne DS, Sedor JF, Estojak J, Fitzpatrick KJ, Chiura AN, Mulholland SG. The urinary glycoprotein GP51 as a clinical marker for interstitial cystitis. *J Urol*. 1999;161:1786-1790.
39. Chai TC, Zhang CO, Shoenfelt JL, Johnson HWJ, Warren J, Keay S. Bladder stretch alters urinary heparin-binding epidermal growth factor and antiproliferative factor in patients with interstitial cystitis. *J Urol*. 2000;163:1440-1444.
40. Chai TC, Zhang C, Warren JW, Keay S. Percutaneous sacral third nerve root neurostimulation improves symptoms and normalizes urinary HB-EGF levels and antiproliferative activity in patients with interstitial cystitis. *Urology*. 2000;55:643-646.
41. Keay S, Zhang CO, Kagen DI, et al. Concentrations of specific epithelial growth factors in the urine of interstitial cystitis patients and controls. *J Urol*. 1997;158:1983-1988.
42. 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.
43. Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR, Webster G. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. *J Urol*. 1993;150:845-848.
44. Nickel JC, Barkin J, Forrest J, et al. Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. *Urology*. 2005;65:654-658.
45. Sairanen J, Tammela TL, Leppilahti M, et al. Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. *J Urol*. 2005;174:2235-2238.
46. van Ophoven A, Hertle L. Long-term results of amitriptyline treatment for interstitial cystitis. *J Urol*. 2005;174:1837-1840.
47. Minogiannis P, El-Mansoury M, Betances JA, Sant G, Theoharides TC. Long-term results of amitriptyline treatment for interstitial cystitis. *Int J Immunopharmacol*. 1998;20:553-563.
48. Theoharides TC, Sant GR. New agents for the medical treatment of interstitial cystitis. *Expert Opin Investig Drugs*. 2001;10:521-546.
49. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol*. 1988;140:36-39.
50. Dell JR, Parsons CL. Multimodal therapy for interstitial cystitis. *J Reprod Med*. 2004;49:243-252.
51. Comiter CV. Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: a prospective study. *J Urol*. 2003;169:1369-1373.
52. Maher CF, Carey MP, Dwyer PL, Schluter PL. Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. *J Urol*. 2001;165:884-886.
53. Peters KM, Carey MP, Konstandt DB. Sacral neuromodulation for the treatment of refractory interstitial cystitis: outcomes based on technique. *Int Urogynecol J Pelvic Floor Dysfunct*. 2003;14:223-228.
54. Siegel SW, Paszkiewicz E, Kirkpatrick C, Hinkel B, Olsson K. Sacral nerve stimulation in patients with chronic intractable pelvic pain. *J Urol*. 2001;166:1742-1745.

# DIAGNOSIS AND MANAGEMENT OF INTERSTITIAL CYSTITIS/ PAINFUL BLADDER SYNDROME

Release Date: August 2006  
Expiration Date: August 31, 2007

## CME POSTTEST/REGISTRATION/EVALUATION

### 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 and newsletter, answer the 10-question multiple-choice posttest, and complete the program evaluation. If you wish to receive CME credit, please mail or fax a copy of your completed answers to:

**The Dannemiller Memorial Educational Foundation**  
**Attention: 06-874B**  
**5711 Northwest Parkway, Suite 100**  
**San Antonio, TX 78249-3360**  
**Phone: (800) 328-2308**  
**Fax: (210) 697-9318**

## POSTTEST/SELF-ASSESSMENT

- The prevalence of CPP in women who have pain of bladder etiology is:
  - Up to 35%
  - Up to 55%
  - Up to 85%
- The etiology of IC/PBS is believed to be multifactorial.
  - True
  - False
- The bladder has the \_\_\_\_\_ neural density in the pelvis.
  - Highest
  - Lowest
- IC/PBS is defined as:
  - An end-organ disease
  - A visceral pain syndrome
  - A gynecologic disorder
- Which of the following are symptoms of IC/PBS?
  - Pelvic pain, urinary urgency, dyspareunia
  - Dysmenorrhea, urinary frequency, vulvodynia
  - Abdominal pain, vaginal-perineal pain, lower back pain
  - All of the above
- Which of the following screening tools are used to help diagnose IC/PBS?
  - PUF
  - O'Leary-Sant IC Symptom Index
  - University of Wisconsin questionnaire
  - All of the above
- Recognition of biomarkers for IC/PBS might:
  - Confuse the diagnostic picture
  - Help early diagnosis of IC/PBS
  - Eliminate IC/PBS from the differential diagnosis
- Efficacy of mucosal surface protectors \_\_\_\_\_ the GAG theory of underlying pathophysiology in IC/PBS.
  - Disproves
  - Does not address
  - Supports
- Multimodality therapy is the basis for optimal care of patients with IC/PBS.
  - True
  - False
- Because of proven efficacy and safety, \_\_\_\_\_ should be first-line therapy for IC/PBS.
  - PPS
  - Amitriptyline
  - PPS and amitriptyline

## CME REGISTRATION/POSTTEST ANSWER FORM/EVALUATION

### To ensure credit, type or print all information legibly.

Full name: \_\_\_\_\_

MD/DO/NP/RN/Other: \_\_\_\_\_

Street: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ ZIP Code: \_\_\_\_\_

### NURSES (required for certificate):

State of licensure: \_\_\_\_\_ License# \_\_\_\_\_

Would you like your certificate sent to you via email?

Yes (address below)  No, please send my certificate via US mail.

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 of activity completion: \_\_\_\_\_

### CREDIT EXPIRATION: August 31, 2007

Record your posttest answers by filling in the blank with the correct letter from the corresponding question:

1.\_\_\_\_ 2.\_\_\_\_ 3.\_\_\_\_ 4.\_\_\_\_ 5.\_\_\_\_ 6.\_\_\_\_ 7.\_\_\_\_ 8.\_\_\_\_ 9.\_\_\_\_ 10.\_\_\_\_

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 an outcome survey regarding the material presented. (Your email address will be used for education purposes only. It will not be sold or shared with anyone outside our organization.) May we contact you? (Please check one.)

Yes, via email (address above)  No, please do not contact me.

- The program objectives were fully met.  
Strongly Agree    Agree    Disagree    Strongly Disagree
- The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.  
Strongly Agree    Agree    Disagree    Strongly Disagree
- The educational activity has enhanced my professional effectiveness in treating patients.  
Strongly Agree    Agree    Disagree    Strongly Disagree    Not Applicable
- The educational activity will result in a change in my practice behavior.  
Strongly Agree    Agree    Disagree    Strongly Disagree    Not Applicable
- The information presented was without promotional or commercial bias.  
(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 trade names are used, those of several companies must be discussed in the activity.)  
Strongly Agree    Agree    Disagree    Strongly Disagree
- What new information did you learn during this program?  
\_\_\_\_\_  
\_\_\_\_\_
- Recommendations for topics of future presentations.  
\_\_\_\_\_  
\_\_\_\_\_

If CME credit and a certificate are desired, please mail/fax this completed form or a copy of it. Keep a copy of this form for your records until you receive your certificate.

**The Dannemiller Memorial Educational Foundation**  
**Attention: 06-874-B**  
**5711 Northwest Parkway, Suite 100**  
**San Antonio, TX 78249-3360**  
**Phone: (800) 328-2308 Fax: (210) 697-9318**

Editor, *Clinical Courier*<sup>®</sup>  
SynerMed<sup>®</sup> Communications  
Department 103  
518 Route 513  
PO Box 458  
Califon, NJ 07830

Presorted Standard  
US Postage  
**PAID**  
Permit 22  
Midland, MI

**CME MATERIALS  
ENCLOSED**

**CLINICAL  
COURIER**<sup>®</sup>

Vol. 24 No. 30

**DIAGNOSIS AND MANAGEMENT OF  
INTERSTITIAL CYSTITIS/PAINFUL  
BLADDER SYNDROME**

---