DISTRIBUTED BY

OB/GYN SPECIAL EDITION

CMEZone.com Explore The Zone™

Special REPORT

CME CERTIFIED APRIL 2005

Interstitial Cystitis and The Gynecologic Practice: Improving Outcomes and Optimizing Care

This activity is supported by an educational grant from Ortho-McNeil Pharmaceutical, Inc.

ORTHO-McNEIL

FACULTY

Edward J. Stanford, MD, MS, FACOG, FACS
Director, Urogynecology
St. Mary's Good Samaritan
Centralia, Illinois

Dr. Stanford is a member of the speaker's bureau of Ortho-McNeil Pharmaceutical, Inc.

T. Fleming Mattox, MD, FACOG
Assistant Professor
Medical Director, Division of Urogynecology
University of South Carolina
Columbia, South Carolina

Dr. Mattox has received grant/research support from Eli Lilly & Co. and Schwartz and is a member of the speaker's bureaus of Novartis, Ortho-McNeil Pharmaceutical, Inc., and Pfizer.

MEDICAL WRITER

Joshua Kilbridge

Mr. Kilbridge discloses no relevant financial relationships, interests, or affiliations.

DISCLOSURE OF FINANCIAL INTEREST

All faculty members participating in continuing medical education programs sponsored by the University of Kentucky Colleges of Pharmacy and Medicine Continuing Office are expected to disclose any real or perceived conflict of interest related to the content of their presentations. Copies of faculty disclosures will be included in your program materials.

The University of Kentucky Colleges of Pharmacy and Medicine presents this activity for educational purposes only. Participants are expected to utilize their own expertise and judgment while engaged in the practice of medicine. The content of the presentations is provided solely by presenters who have been selected for presentations because of recognized expertise in their field.

Jointly sponsored by the University of Kentucky Colleges of Pharmacy and Medicine and McMahon Publishing Group.

UK UNIVERSITY OF KENTUCKY

NEEDS STATEMENT

New estimates of the prevalence of interstitial cystitis (IC) indicate that IC may affect as many as 20% of all women—a much higher percentage than once believed. One study found that of the 134 chronic pelvic pain cases presented to a gynecologist, 85% were associated with the bladder—a clinical sign of IC.

The exact pathophysiology of IC remains unknown; diagnosis relies heavily on the physician's ability to differentiate IC from various other disorders associated with pelvic pain. While relatively new diagnostic tools can help gynecologists make the correct diagnosis, the complex nature of diagnosing a disease that does not have a specific, definable cause and the finding that gynecologists often overlook the bladder as a cause of pelvic pain leads to an incorrect diagnosis. Furthermore, treatments associated with other pelvic pain disorders do not benefit IC-afflicted patients and may expose them to other treatment-related issues.

Gynecologists need further information on diagnosing and managing the IC patient, as well as information on incorporating the treatment of IC into their practices from an administrative perspective. New data on prevalence with regard to a patient's medical and family history may also help gynecologists with diagnosis.

ACCREDITATION STATEMENTS

This activity has been planned and implemented in accordance with the Essentials Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of University of Kentucky College of Medicine and McMahon Publishing Group. The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Kentucky College of Medicine designates this educational activity for a maximum of 2.5 Category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit actually spent in the educational activity.

LEARNING OBJECTIVES

At the completion of this activity, participants should be able to:

❶ Differentiate the clinical presentation of interstitial cystitis (IC) from other pelvic pain disorders.
❷ Employ diagnostic tools to identify patients with IC.
❸ Contrast current pharmacologic treatment options for managing the IC patient.
❹ Assess the financial significance of IC on clinical practice.
❺ Develop practice management procedures to properly handle IC-coding and reimbursement issues.

ESTIMATED TIME OF COMPLETION

This activity should take approximately 2.5 hours to complete.

TARGET AUDIENCE

This educational program is intended for healthcare professionals who treat and/or are interested in interstitial cystitis.

METHOD OF PARTICIPATION

There are no fees for participating and receiving credit for this activity. The participant should, in order, read the objectives and monograph and answer the multiple-choice post-test. Participation is available online at **www.CME-Zone.com**. Enter the project number "SR500" in the keyword field to directly access this activity and receive instantaneous participation. Or, complete the answer sheet with registration and evaluation on page 20. and mail to: Attn: Distance Education, Continuing Education Office, Colleges of Pharmacy and Medicine, University of Kentucky, 1 Quality St, 6th Fl, Lexington, KY 40507-1428. Certificates will be mailed to participants in approximately four weeks after receipt of the mailed or faxed submissions. This credit is valid through April 2006.

Release Date: April 1, 2005 Expiration Date: April 1, 2006

Interstitial cystitis (IC) is a heterogeneous disorder characterized by pelvic pain and urinary urgency and frequency.[1] Recent data suggest that IC may be far more common than previously thought—accounting for an unimagined proportion of patients in gynecologic practice.[1] Much remains to be elucidated with regard to IC, and theories abound regarding the etiology and pathophysiology of the disorder. Similarly, the diagnosis of IC is largely one of exclusion, and the clinical presentation mimics those of other, more common disorders. A typical patient may see multiple physicians before the correct diagnosis is made—frustrating both patients and clinicians. Mirroring the profusion of proposed disease mechanisms is a pharmacopoeia of treatment options ranging from antihistamines to gene therapy.[2] Although many physicians regard IC as a relatively rare disease for which no broadly effective treatment is available, recent studies have demonstrated that IC is quite common and can be treated successfully.[1,2] In fact, IC provides an excellent opportunity for practice building among gynecologists and other physicians.

This article describes the most current research into IC and outlines simple and reliable approaches to its diagnosis and treatment. Also described is an approach to building the management of patients with IC into a gynecologic practice, including information on coding, billing, and training staff.

Part I: What Is Interstitial Cystitis?

Epidemiology

Although the true prevalence and incidence of IC remain the subject of controversy and investigation, certain characteristics of the disorder are well described. IC is largely a disorder of adults; its onset is often between 30 and 70 years of age.[3] Previous study has shown that the median age at onset is 43 years[4]; however, Stanford et al recently found that the median age of women with IC is 38 years.[5] The difference is likely due to the diagnosis of early cases. Still, IC has been diagnosed in children.[6,7] The disorder is also far more common in women, who account for up to 90% of all cases.[8] For this reason, the gynecologic practice is uniquely positioned to incorporate and treat many patients with IC. It is also worth noting that IC is sometimes referred to as a "syndrome," which may be accurate for men with IC, because it overlaps significantly with prostatitis, but not for women, in whom the differential diagnosis is extensive.

Clinicians can be forgiven for believing that IC is a rare condition. Indeed, until relatively recently, estimates of the prevalence of IC were uniformly low, and few epidemiologic studies had been published. One early report cited a prevalence rate of 18.6 per 100,000 in women 20 years of age and older (10.6 per 100,000 for both sexes combined).[9] Other studies reported even lower rates, as low as 4.5 per 100,000 females.[10,11] Even some more recent estimates reflected a fairly rare disease, and the overall prevalence of IC in the United States is often reported to be approximately 700,000 cases.[12] A 1999 analysis of data from the population-based Nurses' Health Study, for example, suggested prevalence rates in women ranging from 52 per 100,000 to 67 per 100,000.[6] Although severalfold higher than previously reported estimates, this range still did not reflect a common condition.

One central problem in assessing the epidemiology of IC is the definition of the disorder itself. As previously noted, no reliable clinical definition currently exists. In research, the ways of defining IC vary between studies and are often overly restrictive. For example, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 1988 published strict diagnostic criteria for IC for research purposes; physicians have adopted and still rely on this old criteria today.[13] However, this NIDDK definition excludes all but advanced cases of IC, profoundly misrepresenting the epidemiology of the disease.[14]

Using different methods, several investigators have published data suggesting that the true prevalence of IC may be 10-fold higher than previous estimates. For example, Leppilahti et al used a validated IC questionnaire to evaluate the prevalence of IC in 1,331 female patients in Finland and reported a probable rate of 450 per 100,000.[15] Other investigators have leveraged new diagnostic techniques to evaluate the prevalence of IC in patient populations. The potassium sensitivity test (PST) was introduced in 1996 as a diagnostic test for IC.[16] The PST involves the intravesical infusion of 2 different solutions: sterile water, followed by a dilute potassium solution. The test result is considered positive for IC when patients experience pain or urgency/frequency on infusion of the potassium solution but not of the water. The PST can yield false-negative results but rarely produces false-positive results.[1] Using the PST, Parsons et al evaluated 466 women with IC and found that 78% tested positive, indicating a good degree of sensitivity.[17] In a separate group of 116 women with "urethral syndrome," 55% tested positive for IC. However, none of the 42 control subjects tested positive. The authors concluded that urethral syndrome likely represents a less severe, intermittent form of early IC.[17] These data demonstrate that the PST identified a large proportion of patients with IC, even those with milder, less advanced disease.

Parsons and colleagues then used the PST to perform a series of studies. In the first study, the authors screened 134 gynecologic patients who presented with chronic pelvic pain (CPP) and reported that 85% tested positive for IC.[18] The second study evaluated 244 consecutive, unselected gynecologic patients with CPP and included 47 control subjects.[19] The results confirmed previous findings; 81% of the women with CPP tested positive on the PST, whereas none of the control subjects had a positive result. In both of these studies, the subjects initially received clinical diagnoses ranging from endometriosis to vulvodynia, despite the presence of urologic symptoms (eg, urgency/frequency) in the majority. In fact, IC was diagnosed initially in only a very small minority; only 1.6% of the patients in the second study received an initial diagnosis of IC.[18,19]

Parsons and Albo conducted a further PST study in 44

men in whom prostatitis had been diagnosed.[20] In all, 84% of the subjects tested positive. In a similar study, Bernie et al examined 526 men and 25 women undergoing urodynamic evaluation for lower urinary tract symptoms.[21] In older men with lower urinary tract symptoms, the most common diagnosis is bladder outlet obstruction secondary to benign prostatic hyperplasia. However, 16% of the male subjects (and 24% of the female subjects) in this study had a positive PST result; these patients also had urodynamic findings significantly different from those of subjects with a negative PST result.

These findings indicate that IC is far more common than previously thought. In the United States, it is estimated that more than 9 million women experience CPP, many of whom consult a gynecologist for diagnosis and treatment.[22] If IC is the cause of CPP in 80% to 85% of these women, then the true prevalence of IC in US women is likely to be upward of 7 million—at least 10-fold higher than previous estimates.[1] A high prevalence was further corroborated by a study in which the PST was used in conjunction with a questionnaire (the Pelvic Pain and Urgency/Frequency [PUF] Symptom Scale). In a sample population of women, approximately 1 in 4 had PUF scores that predicted IC.[23]

These studies also strongly suggest that the majority of patients with IC are initially given an incorrect diagnosis. Indeed, most patients consult at least 5 physicians over a period of more than 4 to 7 years before being given a diagnosis of IC.[24,25] IC is not only far more common than is widely thought, it is also frequently undiagnosed or misdiagnosed. Because IC is a great mimicker of other disorders and the treatments for IC are specific to IC, patients with an incorrect diagnosis may be inappropriately treated, prolonging their suffering and increasing the economic burden through failed treatment and continued physician visits.[24,25]

Etiology and Pathogenesis

Although the cause of IC is not known, several specific theories have been proposed and investigated. Causes that have been explored include epithelial dysfunction, mast cell infiltration, infection, autoimmunity, neurogenic inflammation, and genetic, psychological, lymphatic, vasculitic, and hormonal factors.[1,24,26] With many of these proposed causes, few or no data are available to support their purported role in the disease. Because the responses of the bladder to harmful stimuli are limited—sensations of urinary urgency and pain—different causal factors produce similar symptoms.[1] Thus, IC may have multiple causes and may be influenced by different mechanisms in different patients.[1,12]

Several theories of etiology and pathophysiology have received the most attention. These hypotheses include epithelial dysfunction, mast cell activation, neurogenic inflammation, and autoimmunity.

Epithelial Dysfunction

One of the leading hypotheses holds that IC is caused by a defect in the urothelial surface lining the bladder. This theory has been promoted for more than 2 decades, and the defect is often called "leaky epithelium"—referring to changes in the permeability of the urothelial lining.[1,27-30]

Altered permeability of the bladder wall has been demonstrated by instilling various solutions, and also indirectly, through treatments designed to improve the GAG layer. Lilly and Parsons first demonstrated altered permeability by instilling a urea solution into the bladders of patients with IC and those of control subjects.[38] When the bladders were drained, the urine from the patients with IC contained a substantially lower concentration of urea than did the urine of the control subjects, suggesting that urea had been absorbed at a greater rate. To further test the GAG hypothesis, the authors then instilled protamine, a cation that disrupts the mucin layer, into the bladders of the control subjects. Following protamine administration and removal, the urea solution was instilled again, and this time instillation was associated with a 22% greater loss of urea in the control subjects ($P<0.02$ vs initial instillation). They also reported significant urinary urgency and discomfort. Treatment with heparin sulfate, a GAG thought to improve the integrity of the mucin layer, reduced these symptoms, and also the loss of urea in a third instillation of urea solution.[38]

It has been suggested that this latter experiment was flawed because protamine may cause direct damage to the bladder wall, leading to increased absorption of urea irrespective of GAG layer defects.[41] Nevertheless, this elegant experiment demonstrated 1) that the symptoms of IC could be reproduced in healthy individuals and 2) that the pseudo-IC could be relieved with heparin therapy.

The urothelial surface is coated by bladder surface mucin, a heterogeneous layer located between the lumen and endothelium that is composed of glycoproteins and sulfonated glycosaminoglycans (GAGs).[31,32] This GAG component is hydrophilic and binds a layer of water molecules that is thought to protect the urothelium from potentially harmful agents, including bacteria, proteins, and ions. Proponents of the leaky endothelium theory suggest that the GAG layer is deficient in patients with IC, allowing irritants in the urine to leak through the urothelium and cause inflammation, irritation, and numerous other reactions.[24]

Direct detection of a GAG deficiency has remained elusive. Morphologic studies have not identified substantial differences between the bladder surfaces of patients with IC and those of control subjects.[33-35] Some qualitative changes in the bladder epithelium have been noted in patients with IC and in a cat model of IC.[36-39] However, other investigators have questioned the validity of this animal model.[40]

Studies of the instillation of potassium solutions, as in the PST, also suggest altered permeability of the bladder surface. Potassium is normally present at high levels in urine (40-140 mEq/L). Whereas urinary potassium does not penetrate normal urothelium, it might diffuse through dysfunctional epithelium into the bladder muscularis—leading to the depolarization of nerves and muscle and tissue damage.[42] The corollaries of permeability to potassium are the symptoms of pain and urgency, evidenced by use of the PST. As previously discussed, the PST elic-

its these hallmark symptoms in patients with IC but causes virtually no symptoms in control subjects.[16-18,43] Because potassium does not cross normal urothelium, the results of PST experiments in patients with IC support the concept of epithelial dysfunction as a central component of the disease process.

Several oral and intravesical therapies have been developed and applied based on the leaky endothelium hypothesis. These treatments (eg, heparin sulfate, pentosan polysulfate sodium [PPS], hyaluronic acid) all mimic components of the GAG layer. In theory, these techniques coat the epithelium, improving its integrity and reducing its permeability. The benefits of these and other therapeutic options are discussed in detail later in this article.

Mast Cell Activation

Substantial evidence points to an important role for mast cells in IC. Numerous investigators have identified increased numbers of mast cells in the bladders of patients with IC. Individual studies have reported significantly increased numbers of mast cells in the bladder muscularis and submucosa.[44,45] The association with increased numbers of mast cells is stronger when IC is more advanced, as in patients with Hunner's ulcers (ulcerative IC), and when additional histologic regions are involved, including the lamina propria.[46-48] Overall, mastocytosis has been identified through histochemical means in 30% to 65% of patients with IC, although these numbers are likely to underestimate the presence of mast cells as a consequence of technical limitations in the fixation and preparation of samples.[32,45,49]

Mast cells in the bladders of IC patients are located close to the intrinsic nerves of the bladder wall, and mast cell activation may affect nerve health and function.[40,50] The degranulation, or activation, of mast cells (the presence of granules indicates inactivity of mast cells, and the absence of granules indicates that they are activated) in IC has been documented by light and electron microscopy, and also through biochemical means.[49,51-56] In an ultrastructural study, investigators reported a mast cell count of 6.6 +/- 4.8 per mm^2 in the bladders of control subjects, and 69.6% of these mast cells were considered to be intact (ie, not activated). In the bladders of IC patients, on the other hand, mast cell counts averaged 42.7 +/- 31.2 per mm^2, with only 20.1% intact—indicating a substantial increase in both number and activation.[51] One interesting finding of this study was that many mast cells in the IC patients were only partially degranulated, in contrast to the wholesale degranulation typically seen in allergic or anaphylactic reactions.[51,57]

Indirect evidence of the involvement of mast cells in IC comes from biochemical studies. When mast cells degranulate, either partially or completely, they release a multiplicity of potent mediators. These mediators are either preformed and stored within the granules (eg, heparin, histamine, proteases, certain cytokines) or synthesized de novo (eg, interleukin-6 [IL-6], prostaglandins, nitric oxide) on activation.[58-61] Release of some or all of these mediators can be elicited by immunologic and nonimmunologic stimuli, including allergens, sensory nerve stimulation, neuropeptides, acetylcholine, cytokines, toxins, and multiple other factors.[58,62-65] The mediators have powerful inflammatory effects on smooth muscle and the vascular epithelium—all important to the pathology of IC.[24]

Some of the mediators have been documented in patients with IC. Increased levels of histamine, for example, have been found in the bladder walls of patients with IC.[54] Increased urinary excretion of methyhistamine and the histamine metabolite 1,4-methylimidazole acetic acid (1,4-MIAA) has also been documented.[53,55] Slightly elevated levels of IL-6 have also been noted in IC patients.[66,67]

The etiologic relationship between mast cells and IC is not known; the involvement of mast cells may be either primary or secondary.[57] However, it is clear that mast cell numbers are increased in IC, and that a greater proportion of them are activated.[51-61] The many potent mediators contained in mast cells and released on activation draw attention to the involvement of mast cells in the pathophysiology of IC, regardless of their etiologic relationship. Several mast cell–targeted therapies have been developed with this involvement in mind.

Neurogenic Inflammation

Neurogenic inflammation has been proposed as a main pathophysiologic mechanism in IC.[40] It is clear that the sensory nerves of the bladder become activated, and that such activation is a central element of the disease.[1,68] Possible causes of sensory nerve activation include stimulation or injury of peripheral nerves by potassium or other substances in the urine, nerve regeneration after injury, central activation, and other factors.[1] The hypothesis of neurogenic inflammation holds that sensory nerves secrete inflammatory mediators (eg, substance P), producing local inflammation, hyperalgesia, and the symptoms of IC.[32,40]

Evidence supporting the hypothesis of neurogenic inflammation includes the following findings in patients with IC: increased levels of substance P in the urine, increased numbers of nerves in the bladder containing substance P, and a relationship between the concentration of substance P and the degree of pain reported by patients.[69] Substance P acts as a nociceptive neurotransmitter and as an inflammatory mediator. Release of substance P by the peripheral nerves produces an inflammatory cascade involving mast cell activation (among other effects) and the activation of neighboring nerve terminals.[32] The close association between mast cells and the intrinsic nerves of the bladder wall in patients with IC illustrates the plausibility of neurogenic inflammation as a contributor to IC. As proposed, this model has the advantage of integrating multiple pathophysiologic mechanisms: Neurogenic inflammation may lead to mast cell activation, localized inflammation, vascular changes, urothelial injury, and autoimmune effects (Figure 1). Possible causative factors triggering this cascade of events include stress, hormonal changes (eg, the menstrual cycle), and unidentified microbial factors or toxins in the urine.[40]

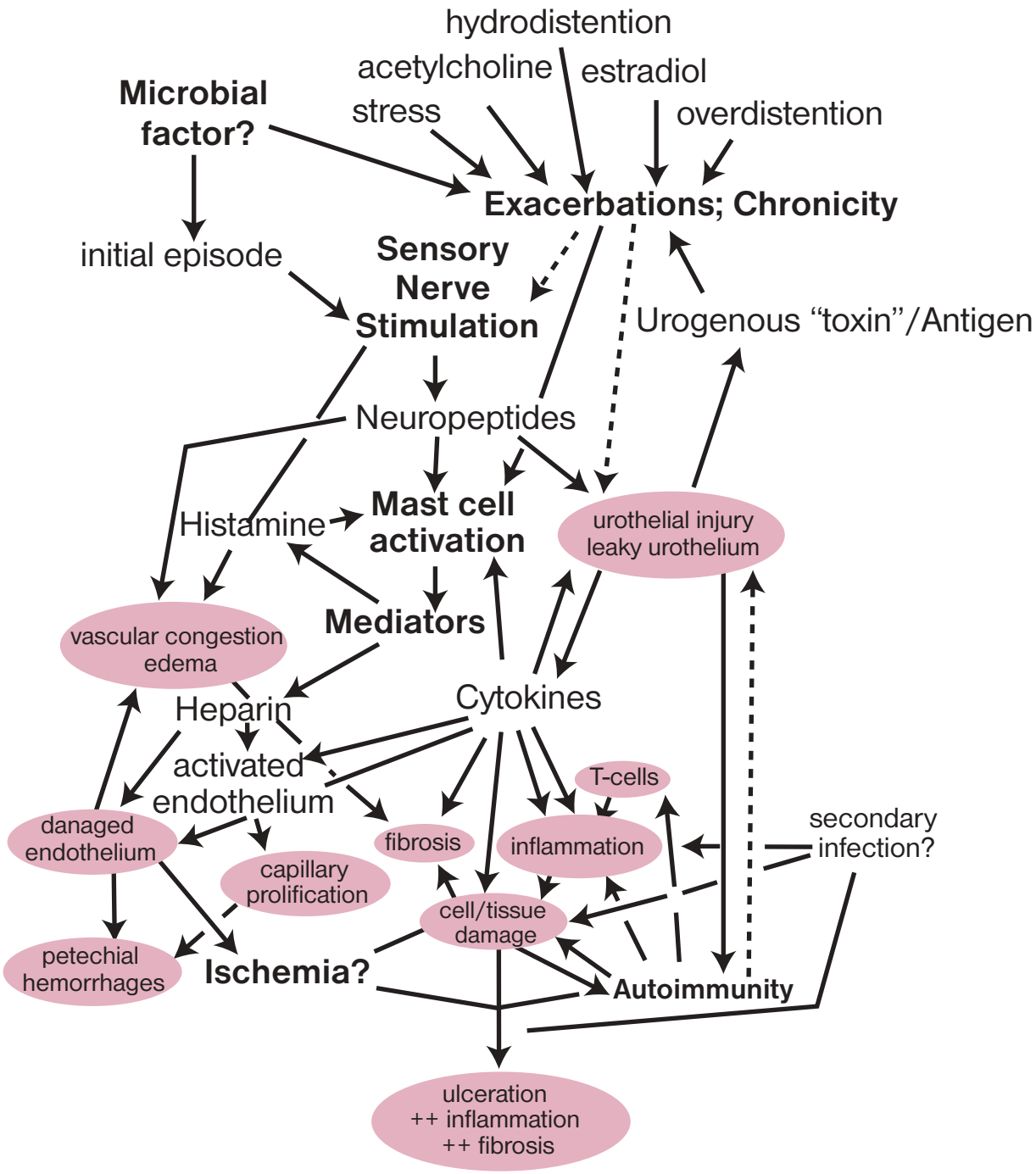

Figure 1. Proposed model of neurogenic inflammation.

Reprinted from *Urology*, 49, Elbadawi A., Interstitial cystitis: a critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis, p. 29, Copyright 1997, with permission from Elsevier.

Autoimmunity

Many of the clinical features of IC reflect an autoimmune component of the disease process. For example, the symptoms of IC, like those of many autoimmune diseases, are chronic and typified by flares and remissions. Investigators have also reported occasional associations between IC and other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.[70-72] Other suggestive features include the presence of inflammation in the absence of an identified pathogen, a high prevalence of antinuclear antibodies, and the occasional response of symptoms to steroids or other immunosuppressants.[32,73] Some investigators have reported elevated levels of bladder-specific autoantigens, although others have reported contradictory results.[72,74,75] It has been suggested that these changes are merely secondary to local damage to bladder tissues.[40]

Interaction of Multiple Etiologic/Pathophysiologic Factors

The heterogeneity of IC lends credence to the possibility that the disease may have multiple causes and pathologic components. Various forms of pathology have been identified in different patients, and the clinical response to the multitude of treatments also varies from patient to patient.[32] Therefore, it is possible, as some investigators have proposed, that several or all of these pathophysiologic processes are active simultaneously. This potential multiple-factor pathophysiology suggests a treatment program incorporating therapies directed at multiple disease mechanisms.

Part II: Diagnosis and Treatment Of Interstitial Cystitis

Although IC may seem enigmatic to many clinicians, significant strides have been made in its recognition and treatment. Physicians can now make use of effective strategies for diagnosis and therapy. These approaches can improve patient care and quality of life, and they provide an opportunity to build a gynecologic practice around this common and treatable disorder.

Diagnosing Interstitial Cystitis

Despite the lack of an inclusive clinical definition of IC, physicians' ability to diagnose early or mild disease has improved dramatically during the last 2 decades. As previously discussed, the NIDDK has published a consensus report on IC to provide a definition for research purposes.[13] In the absence of any other guidelines, this definition has been adopted by many physicians for the clinical recognition of IC. The NIDDK paper outlines specific inclusion and exclusion criteria.[13,14]

Although appropriate for many research goals, the NIDDK definition has proved far too restrictive for clinical use. In an oft-cited study, Hanno et al evaluated the utility of the NIDDK definition for clinical and research purposes.[14] The authors concluded that almost 90% of the patients in their study who met the NIDDK criteria did have IC, reflecting the value of these criteria for the selection of a homogeneous population for research. However, of the patients considered definitely or likely to have IC, more than 60% would have been given an incorrect diagnosis according to the NIDDK criteria.[14] Therefore, patients who meet the NIDDK criteria almost certainly have IC, but the opposite cannot be assumed.

Although the NIDDK criteria may not be suitable, a fairly simple diagnostic strategy can be constructed. The diagnostic method should include the following: 1) identifying the symptoms of pain and/or urinary urgency/frequency; 2) ruling out other definable causes of symptoms; 3) using 2 diagnostic tools (PUF Symptom Scale and PST). IC should be strongly suspected in a patient who presents with CPP and/or urinary urgency/frequency in the absence of any other definable cause (Figure 2).

Symptoms

At the foundation of a diagnostic strategy are the hallmark symptoms of IC: CPP and urinary urgency/frequency. It is important to keep in mind, however, that patients may present with only one of these symptoms, particularly early in the course of the disease. Up to 30% of patients with IC present without pelvic pain,[1] and approximately 15% present with pain as the only symptom.[76] In a recent retrospective study, Driscoll and Teichman examined the presentation of patients with IC.[77] The authors reported that 89% of the patients studied presented with only 1 symptom (pain, urgency/frequency, or nocturia). The median time from appearance of the initial symptom to the appearance of all symptoms was 2 years (mean, 5.5 years).[77]

Pelvic pain is the most typical symptom of IC and may be felt as dysuria or as pain in 1 or more anatomic locations (eg, suprapubic area, lower abdomen, lower back, medial thighs, inguinal area, urethra, vagina, vulva). Dyspareunia is also common in patients with IC.[1,17]

Several factors may influence the symptoms of IC. The duration of disease can affect the number and severity of symptoms; a longer duration is associated with more advanced disease. The level of recent sexual activity can influence symptoms, which may flare during or soon after intercourse.[1,18] Symptoms may also flare before the onset of menses in women.[1,18] Seasonal allergies can affect the severity of symptoms, and the patient should be assessed for these.[8] All of these factors contribute to the variable presentation of IC.

Because of its variable presentation, many physicians fail to detect IC until it becomes more symptomatic.[77] In the study by Driscoll and Teichman, the most common previous misdiagnosis was urinary tract infection (UTI), followed by gynecologic and other urethral diagnoses.[77] Of course, this is understandable because UTI is much more common than IC. If a patient presents with lower abdominal pain and dysuria, a UTI would be at the top of the list of possible diagnoses; it is the recurrent patient who should cause the clinician to suspect IC.

Identifying Other Causes of Symptoms

Ruling out other potential causes of symptoms is critically important because IC is a diagnosis of exclusion.

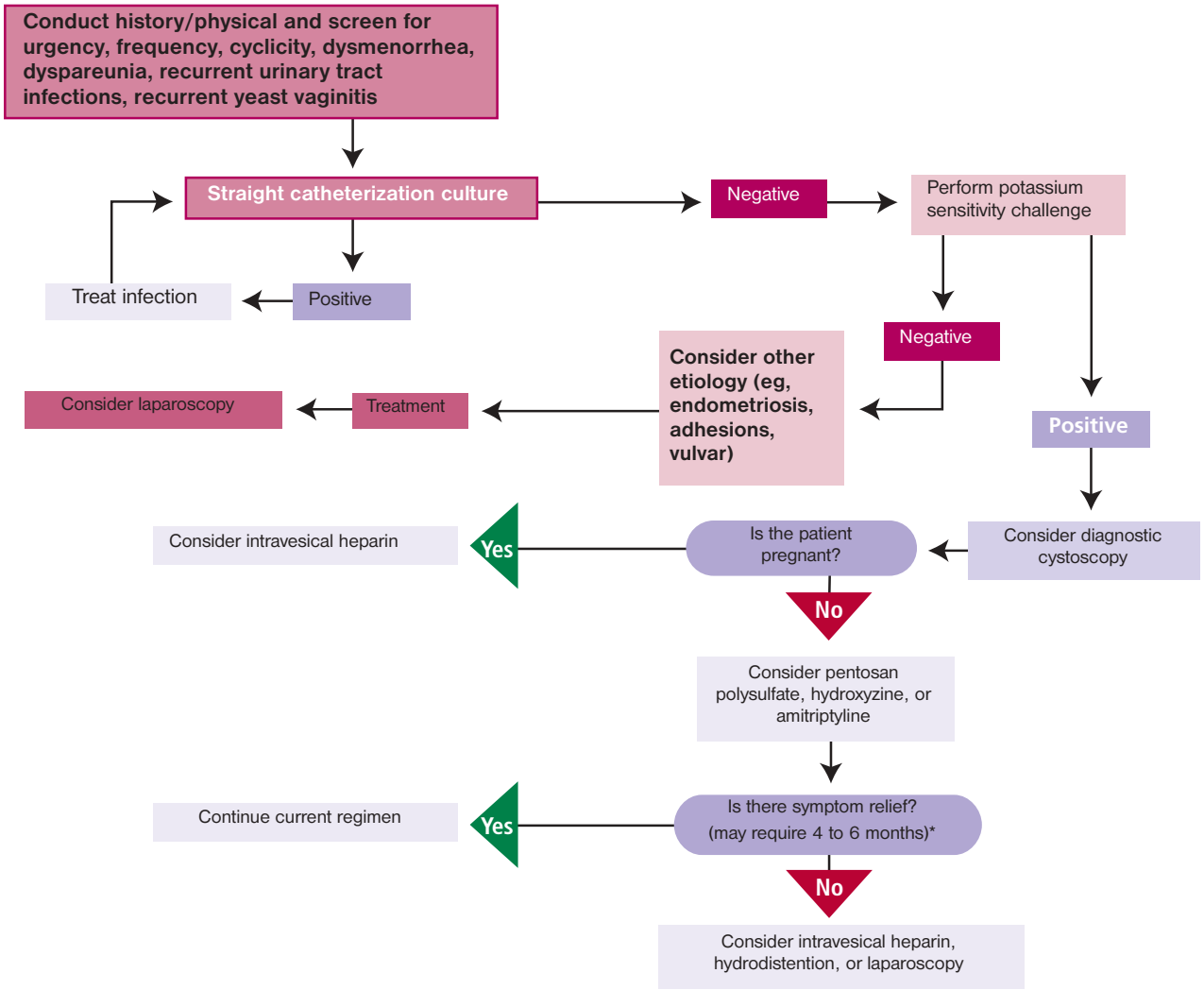

Figure 2. Algorithm for management of interstitial cystitis.

* Timing may vary per patient.
Source: Stanford EJ. Searching for the cause: chronic pelvic pain: a pocket guide. *OB/GYN Special Edition*. April 2003;18-19.

Patients with IC may be symptomatic for several years before their condition is properly diagnosed and treated. A patient presenting with CPP and/or urgency/frequency should be carefully evaluated for other causes before a diagnosis of IC is reached.

Conditions that must be ruled out before IC is diagnosed include the following: sexually transmitted diseases (eg, herpes simplex, *Chlamydia trachomatis* infection), recurrent UTI, irritable bowel syndrome, endometriosis, overactive bladder syndrome, vulvar and vaginal conditions, and abdominopelvic adhesions.[24,76] Data indicate that irritable bowel syndrome affects up to 35% of women with CPP; biopsy-proven endometriosis affects 33% of patients.[78,79] Stanford et al recently found that the bladder was the most common source of CPP (68%), followed by adhesions (64%), biopsy-proven endometriosis (28%), and vulvar pain (20%).[80] It was found that a workup designed to uncover sources of pain in the bladder and intraperitoneal causes would lead to a diagnosis in 95% of patients.[80]

Clinical History and Physical Examination

A careful history and physical examination should be conducted first. Important factors to ascertain include the following: duration of the symptoms (symptoms of longer duration more suggestive of IC); association of the symptoms with sexual intimacy or menses; whether allergies, stress, or specific foods trigger the symptoms; degree of urgency/frequency (if present); and previous medical history—in particular, visits to other physicians for CPP, urgency, or frequency (multiple consultations or referrals

Pelvic Pain and Urgency/Frequency 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 waking hours?	3-6	7-10	11-14	15-19	20+		
2a How many times do you go to the bathroom at night?	0	1	2	3	4+		
2b If you get up at night to go to the bathroom, to what extent does it usually bother you?	None	Mild	Moderate	Severe			
3 Are you currently sexually active? YES _____ NO_____							
4a IF YOU ARE SEXUALLY ACTIVE, do you now or have you ever had pain or urgency to urinate during or after sexual activity?	Never	Occasionally	Usually	Always			
4b Has pain or urgency ever made you avoid sexual activity?	Never	Occasionally	Usually	Always			
5 Do you have pain associated with your bladder or in your pelvis (vagina, lower abdomen, urethra, perineum, testicle, or scrotum)?	Never	Occasionally	Usually	Always			
6 Do you still have urgency shortly after going to the bathroom?	Never	Occasionally	Usually	Always			
7a If you have pain, is it usually		Mild	Moderate	Severe			
7b How often does your pain bother you?	Never	Occasionally	Usually	Always			
8a If you have urgency, is it usually		Mild	Moderate	Severe			
8b How often does your urgency bother you?	Never	Occasionally	Usually	Always			
					SYMPTOM SCORE (1, 2a, 4a, 5, 6, 7a, 8a) =		
					BOTHER SCORE (2b, 4b, 7b, 8b) =		
					TOTAL SCORE (Symptom Score + Bother Score) =		

0-4 = negative; 5-9 = 57% chance of potassium positive;
10-14 = 75%; 15-19 = 79%; 20+ = 93% chance

Figure 3. Pelvic Pain and Urgency/Frequency Patient Symptom Scale.

Reprinted from *Urology*, 60, 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,, pp. 573-578, Copyright 2002, with permission from Elsevier.

are suggestive of undiagnosed IC). Although CPP and urgency/frequency are the hallmark symptoms of IC, other symptoms are also frequently associated with the disease, including nocturia, dysuria, and dyspareunia.[76]

It is important to keep in mind that many patients may be accustomed to their urinary frequency, so that it does not seem abnormal. Therefore, patients should be asked to keep a 24-hour voiding log to document urinary frequency and voiding patterns.[24]

The physical examination may reveal a tender bladder or other painful sites. A pelvic examination in women may elicit tenderness of the anterior vaginal wall or bladder base.[76] Approximately 20% of female patients with IC also have vulvar vestibulitis.

Urinalysis and Urine Culture

A simple urinalysis and complete urine culture will serve to rule out many of the most common conditions.

Table 1. Score on the PUF Scale as a Predictor Of a Positive PST Result

PUF Score	Chance of Positive PST Result, %
10-14	75
15-19	79
≥20	94

PST, potassium sensitivity test; **PUF**, Pelvic Pain and Urgency/Frequency Symptom Scale

Adapted from *Urology*, 60, 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, Copyright 2002, with permission from Elsevier.

Infection of the bladder or urinary tract will become evident after urine culture. Hematuria may indicate bladder cancer or carcinoma in situ. Clinicians have long believed that patients who have hematuria should undergo a complete urologic workup, including cystoscopy or a referral for cytology. However, a recent study of women with IC described hematuria in a significant proportion of women who had no signs of malignancy.[81] These data suggest that hematuria is not a specific risk factor for bladder cancer in the absence of other risk factors (eg, age older than 40 years, smoking, family history of bladder cancer), and that the presence of blood in the urine is not an indication for cystoscopy..

Cystoscopy

Some clinicians may opt to perform cystoscopy regardless of the presence or absence of hematuria. Cystoscopy is required according to the NIDDK criteria, with the presence of either glomerulations or classic Hunner's ulcer necessary for a diagnosis of IC.[13] Indeed, many investigators routinely perform cystoscopy with or without hydrodistention to confirm the diagnosis of IC. With this technique, glomerulations appear as pinpoint hemorrhages or fissures with bleeding.[14,82] Hunner's ulcers may also be seen during cystoscopy, although these occur in only a small minority of patients.[24]

However, IC can be diagnosed successfully without the use of cystoscopy to document bladder damage. In fact, an interesting study of women undergoing tubal ligation found that mucosal glomerulations were present in women without symptoms of IC, suggesting that the presence of lesions may not be as strongly indicative of IC as generally thought.[83]

New Diagnostic Tools

Once other conditions have been ruled out in patients with physical examination findings and a presentation indicative of IC, clinicians can take advantage of 2 simple tools to complete their diagnosis of IC.

Pelvic Pain and Urgency/Frequency Symptom Scale The first new tool is the self-administered PUF screening questionnaire, which has been validated through correlation with the PST in urology and gynecology patients (Figure 3).[23] The PUF Symptom Scale is designed to elicit a balanced view of the patient's symptoms, including urgency/frequency, pelvic pain, and dyspareunia. Higher PUF scores indicate a greater likelihood of IC. When compared with PST results, patients' PUF scores appeared to correlate strongly with positive PST results (Table 1).[23] Patients with higher scores (eg, ≥10) can be further evaluated with the PST.

Potassium Sensitivity Test The PST can be performed easily in the clinician's office and helps to confirm a diagnosis of IC. The PST is based on the underlying dysfunctional urothelium, which allows potassium ions to cross into the bladder wall, depolarizing nerves and muscle and causing symptoms of pain and urgency.[1,18,42] First sterile water is instilled, then a potassium solution is instilled.[1] After the instillation of water (solution 1), the patient is asked to rate any pain and urgency on a scale from 0 (none) to 5 (severe). Five minutes after the water has been removed and the potassium chloride (solution 2) instilled, the patient is asked to rate pain and urgency again. Finally, the bladder is rinsed with sterile water. The patient is then asked to rate which solution caused greater discomfort (1, 2, or neither) and gauge the difference between the solutions (mild, moderate, or severe). The test result is considered positive if the patient's urgency or pain score is at least 2 and the potassium solution provoked the more severe symptoms.

The sensitivity of the PST has been questioned—in the initial evaluation of the PST in 466 women with IC, it yielded a positive result in only 78%.[17] However, in this study, as in most others, none of the control subjects (without IC) had a positive test result. To confirm a clinical diagnosis of IC, therefore, the PST is useful and sensitive. The combination of the clinical presentation, history, physical examination findings, urinalysis and urine culture results, PUF score, and PST result should provide adequate information to make an initial diagnosis of IC.

Table 2. Examples of Foods That May Aggravate Symptoms of IC

Citrus fruits, including cranberries
Caffeinated, carbonated, or alcoholic beverages
Certain cheeses
Chocolate
Hot spices (eg, cayenne pepper, curry), spicy foods
Mayonnaise
Nuts (except almonds, pine nuts, peanuts)
Onions
Salad dressing
Sour cream
Soy sauce
Tomatoes, tomato products (eg, paste, sauce)
Vinegar
Yogurt

IC, interstitial cystitis
Adapted from Moldwin RM, Sant GR. Interstitial cystitis: a pathophysiology and treatment update. *Clin Obstet Gynecol*. 2002;45:259-272.

Approach to Treatment

At first blush, the broad array of therapies available for the treatment of IC may appear overwhelming. Multiple causes and pathophysiologic mechanisms have been proposed, and there are treatments aimed at many of these potential disease mechanisms. Data from randomized, controlled trials are largely lacking for IC treatments. However, many of the treatments used empirically in IC have been applied successfully in other conditions and have been effective in IC.

Regardless of the therapeutic strategy, the goal of treatment is to reduce or eliminate the symptoms of IC

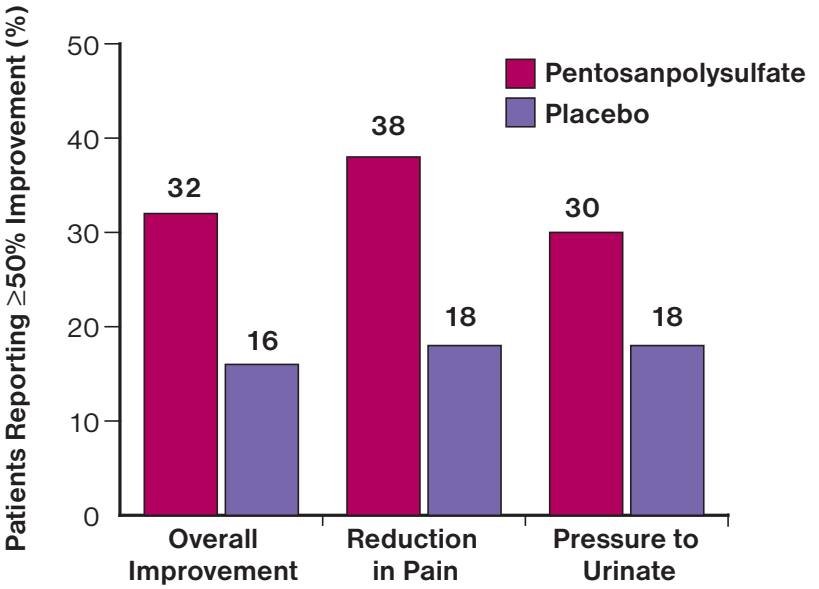

Figure 4. Three-month results of a randomized, double-blind, placebo-controlled trial of PPS In 148 subjects with IC.

Reprinted from *Urology*, 63, Chancellor MB, Yoshimura N., Treatment of interstitial cystitis., p. 87, Copyright 2004, with permission from Elsevier.

and improve quality of life. Because IC is a chronic disease, patients should be counseled regarding realistic expectations of treatment. Remission may be attained but should not be expected, and even when it is attainable, months of medical treatment may be required.[32] Exacerbations during periods of remission are common, and patients need to be encouraged that therapy is not failing. Often, asking the simple question of whether the current flare is as severe as prior ones (before the patient was on therapy) helps the patient to stay the course. As always, adherence to treatment is paramount, and patients should be strongly encouraged to remain compliant with the therapeutic regimen. Because of the heterogeneity of the disease, successful treatment may require several attempts with different agents or combinations of agents.

Counseling the Patient

Defusing patient frustration may entail more than education before treatment is initiated. Most patients with IC have consulted several physicians, including psychiatrists, for years before even receiving a diagnosis. This frustration with caregivers may be further complicated by fear, particularly if more threatening diagnoses, such as bladder cancer, have not been excluded. Therefore, patients should be counseled regarding the nature of IC—that it is nonmalignant and nonsystemic—and if necessary, they should be directed to psychosocial therapy to help deal with the frustration they experience because of the duration and effects of their symptoms.

Dietary and Behavioral Modification

Both pharmacologic and nonpharmacologic means should be used. In particular, dietary changes can affect symptoms. The use of a diary to track the intake of specific foods and beverages can help correlate certain problem foods with worsening symptoms. The theory is that the urinary metabolites of some foods may cross the damaged urothelium, further irritating the bladder and perpetuating the inflammatory state. Clinical trials evaluating the effects of specific foods have not demonstrated any effect on symptoms. However, anecdotal evidence suggests that diet can profoundly affect symptoms in some patients.[32]

A wide range of foods and beverages have been implicated in worsening the symptoms of IC (Table 2).[84] Food sensitivities vary greatly among patients, and some patients display no such sensitivity. One approach is to have patients begin with a fairly bland diet, adding 1 food at a time while monitoring for worsening symptoms. Any change in symptoms is likely to occur within 30 minutes to 6 hours after the food has been consumed.[32]

Some investigators recommend the use of bladder retraining protocols. Because IC is typified by urinary frequency, constantly voiding small volumes over time leads to a reduced bladder capacity, further worsening symptoms. A protocol has been described in which

patients progressively lengthen their voiding intervals to counteract this problem. One study reported a 50% reduction in urinary frequency, urgency, and nocturia with this technique.[85]

Medical Therapy

Medical therapies for IC include oral, subcutaneous, and intravesical agents. These drugs can be roughly categorized according to their intended point of action within the disease process.

Protection of the Mucosal Surface

The hypothesis of a GAG layer deficiency in IC states that symptoms are related to increased permeability of the urothelium. Therefore, a number of agents have been used to improve the integrity of the mucosal surface. These include oral and intravesical PPS,[86,87] intravesical or subcutaneous heparin,[88,89] and intravesical hyaluronic acid.[90] Oral chondroitin sulfate has also been used, but it has not been studied extensively in IC.[91] Mucosal agents act either by coating the epithelium directly or by detoxifying cations in the urine that harm the epithelium.[92]

Pentosan Polysulfate Sodium. The synthetic sulfated polysaccharide PPS is the most widely used of the mucosal agents and is also one of the few agents to be evaluated in double-blind, controlled trials.[2,30,92] One double-blind, prospective study randomized 148 subjects with IC to either of 2 groups: oral PPS (100 mg tid) or placebo.[86] After 3 months of treatment, a statistically significant proportion of patients reported a reduction in pain and pressure to urinate, and an overall improvement over baseline (Figure 4). A subsequent open-label study evaluated the long-term efficacy and safety of oral PPS in patients with IC.[93] The long-term use of PPS (100 mg tid) was associated with symptom relief that increased with the duration of treatment, continuing for 1 to 2 years. The frequency of adverse events was <4%, with reversible alopecia, diarrhea, nausea, headache, and rash the most common adverse events. It has been noted that in clinical practice, PPS may take up to 4 months to relieve pain and up to 6 months to decrease urinary frequency.[94] Nevertheless, on the basis of these trials and other studies, oral PPS was approved by the FDA for the treatment of IC and remains the only oral therapy approved for IC.[95]

An intravesical formulation of PPS has been investigated in preliminary research. This formulation is instilled directly into the bladder, and in theory it would effect a more rapid improvement in symptoms compared with the oral formulation. Investigators dissolved oral PPS preparations in 10 mL of normal saline solution with 3 mL of 8.4% sodium bicarbonate and either 10 mL of 1% lidocaine or 16 mL of 2% lidocaine.[96] The solution was instilled into the drained bladders of patients with IC, held for 10 to 20 minutes, and then voided. Doses ranged from 100 to 200 mg for women, and from 200 to 400 mg for men. A series of 17 patients underwent an average of 13 instillation procedures each. Symptoms were assessed on the PUF Symptom Scale. During the observation period, scores declined from an average of 24.1 to 17.8, suggesting substantial symptom relief. It should be emphasized that this procedure represents an off-label use of PPS.[95]

Intravesical and Subcutaneous Heparin. Heparin has been used for the treatment of IC since the 1960s. It is either instilled or administered subcutaneously. When instilled, heparin does not have systemic anticoagulant effects because it is not absorbed across the urothelium. Both routes of administration have been studied in patients with IC. In one study, 48 patients with IC self-administered intravesical heparin (10,000 U in 10 mL of sterile water) 3 times weekly for 3 months.[88] Fifty-six percent of the patients attained clinical remission after 3 months. Patients who continued therapy reported continued reductions in symptoms for up to 1 year. Subcutaneous heparin has been demonstrated to produce rapid relief of symptoms. One study of 8 patients reported long-term benefit over 1 year or more of treatment.[89]

Table 3. Additional Treatments for IC in Various Stages of Development

Agent	Characteristic
L-Arginine	Substrate for nitric oxide production
Misoprostol	Oral prostaglandin E_1 analog
Montelukast	Leukotriene D–receptor analog
Suplatast tosilate	Immunoregulator
Capsaicin	Activator of vanilloid receptor–1
Resiniferatoxin	Capsaicin analog
Preproenkephalin (delivered by gene therapy)	Opioid precursor
Intravesical liposomes	Mucosal enhancers
Gabapentin	Neuropathic pain agent
Carbamazepine	Neuropathic pain agent

IC, interstitial cystitis
Source: Adapted from Chancellor MB, Yoshimura N. Treatment of interstitial cystitis. *Urology*. 2004;63:85-92.

Table 4. CPT Codes for Alternative Treatments For IC

Treatment	CPT Code(s)
Biofeedback	
EMG	51784
Biofeedback training	90901
ADL (15-min increments)	97535
Electrical stimulation (15 min)	97032
Neuromodulation	
Ilioinguinal nerve block	64425
Pudendal nerve block plus E&M code	64430
Exenterative surgery	
Cystectomy, complete, with ureteroileal conduit	51590
Cystectomy, complete, with continent diversion by any technique	51596

ADL, Activities of Daily Living; **CPT**, Current Procedural Terminology; **E&M**, Evaluation and Management; **EMG**, electromyography

Intravesical Hyaluronic Acid. Reports of the use of intravesical hyaluronic acid suggest modest relief of symptoms.[90,97] One study noted a 71% response rate after 12 months of therapy with intravesical hyaluronic acid (40 mg weekly for 4 weeks, then monthly).[97] A later study evaluated 10 women with IC.[90] Subjects received 40 mg weekly for 6 weeks, then monthly thereafter for 6 months. The response rate was only 30% at 6 weeks, although relief of symptoms was satisfactory in those who responded. This agent is currently not available in the United States.

Mast Cell Inhibition

The involvement of mast cells in IC is certain, although their exact etiologic role has not been elucidated. Histamine is a major mediator released by activated mast cells and has been documented in the bladder wall of IC patients.[54] To counter these effects, antihistamines are commonly used in the treatment of IC. Hydroxyzine, an H_1-receptor antagonist, has been used extensively in patients with IC, although the clinical data regarding its effectiveness are limited. One open-label, nonconsecutive case series of patients with IC reported a 40% reduction in symptom scores in 90 patients who returned case report forms.[98] In a subgroup of patients with allergies, the reduction in symptom scores was 55%. Hydroxyzine acts by blocking mast cell activation, although its anticholinergic side effects may also contribute to symptom relief by reducing urinary frequency. In addition, hydroxyzine has sedative and anxiolytic effects.[2,98]

The H_2-receptor antagonist cimetidine has been evaluated in small, open-label trials.[99] It has been shown to produce some symptom relief but has not been tested in randomized, controlled trials.[91]

Pain Modulation

Various agents have been used to modulate the perception of pain in IC. Tricyclic antidepressants (TCAs), especially amitriptyline, are commonly used and are known to have pain-reducing effects. TCAs may be the systemic agents used most successfully for the treatment of pain in IC[94,100]; nevertheless, clinical data are lacking. One small study evaluated 3 weeks of amitriptyline (75 mg per day) in 25 patients with IC. The authors reported significant relief of pain, reduction of daytime urinary frequency and dyspareunia, and total remission in some patients.[101] One recent prospective, double-blind, controlled study of amitriptyline evaluated 50 patients with IC.[102] Subjects were randomized to amitriptyline or placebo for 4 months. Improvement in overall symptoms scores was significantly greater in the treatment group (P=0.005), as were reductions in pain and urgency (P<0.001). Anticholinergic effects were reported by 92% of patients. The mechanisms by which TCAs influence the symptoms of IC are not known.

The solvent dimethyl sulfoxide (DMSO) has been used as an intravesical therapy for IC. Its multiple effects include anti-inflammatory and analgesic effects, muscle relaxation, mast cell inhibition, and collagen dissolution.[103] Patients treated with DMSO in studies have experienced a 50% to 70% reduction of symptoms, although the relapse rate on discontinuation of therapy is 35% to 40%. Administration in combination with various other agents has been recommended to improve the response to DMSO, including hydrocortisone and other steroids, heparin, and sodium bicarbonate.[103] One side effect is a garlic-like breath odor that can last for up to 2 days.[2]

More traditional analgesic remedies have also been used in IC, including opioids and nonsteroidal anti-inflammatory drugs.[2]

Immunologic Modulation

Immune stimulants and suppressants have been used to varying degrees in IC. Bacillus Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis*, is used as an intravesical agent in both bladder cancer and IC.[2,32] Weekly instillation of BCG in IC patients was evaluated in a small, double-blind, controlled study.[104] The initial response rate was 60% (compared with 27% in the placebo group). During long-term follow-up, 89% of patients continued to demonstrate symptom relief. A later study failed to show any significant response to BCG in comparison with intravesical DMSO.[105] Further trials of BCG are currently under way.[32]

Cyclosporine, an immunosuppressant used in organ transplantation, was tested in a small, open-label study of 11 patients with IC.[106] Subjects received cyclosporine (2.5-5.0 mg/kg per day) for 3 to 6 months. The results were largely positive and statistically significant: the frequency of urination decreased, the volume of voided urine increased, and bladder pain either decreased or stopped completely in 10 patients. In most patients,

however, the symptoms returned soon after discontinuation. A recent trial evaluated 23 patients with IC after 1 year of treatment with cyclosporine.[107] The number of voidings per 24 hours, maximal bladder capacity, and mean voided volume all increased significantly compared with baseline (P<0.001 for each parameter). Eleven patients stopped treatment after 1 year; symptoms recurred in 9 patients within months.

Other Medical Therapies

Still more agents have been examined to varying degrees for use in IC. These include immunoregulators, pain modulators, and gene therapy (Table 3).

Multimodal Medical Therapy

To manage the multiple pathologic features of IC, clinicians may choose a multimodal approach to treatment. Combining agents from different classes can improve response to therapy by attacking the disease at several points. One common multimodal approach is to restore epithelial function with a heparinoid, treat neural activation (and pain) with a TCA, and control allergies with an antihistamine.[1] An example of this approach in patients with mild to moderate IC would be oral PPS (100 mg tid) plus hydroxyzine (25-100 mg each evening), and amitriptyline (25 mg each evening) as needed for pain. In patients who have advanced IC or do not respond to oral therapy, intravesical treatment may be required. Instillation of a combination of an anesthetic (eg, lidocaine), heparin and/or PPS (an off-label use), and sodium bicarbonate should provide rapid relief of symptoms. Instillation of such a combination should be performed weekly for 6 to 8 weeks, whereas oral therapy should be continued for 6 months or more, or until symptoms remit. Combination instillation therapy is also indicated for patients who experience significant symptom flares after remission.

Procedural Interventions

A number of surgical approaches are available when medical therapy fails. These include hydrodistention, laser resection of the bladder, and cystectomy with urinary diversion.[32] Neuromodulation is a recently developed procedure in which the sacral nerve is electrically stimulated. This technique as a treatment for IC has been the subject of recent interest, and initial studies suggest that it can relieve symptoms of IC.[108]

Part III: Incorporating Interstitial Cystitis Into the Gynecologic Practice

Incorporating IC into a gynecologic practice can be rewarding for patients and physicians. For patients with IC, many of whom spend years bouncing from physician to physician in search of an accurate diagnosis and effective treatment, the availability of a gynecologist with expertise in IC is invaluable. For gynecologists, IC represents an excellent opportunity to build a patient base and a new revenue model. The treatment of patients with IC is also highly gratifying—it is an opportunity to provide quality care to patients who sorely need it.

Several key factors are involved in incorporating IC treatment into a gynecologic practice. These include training staff members in IC management and learning appropriate coding and reimbursement strategies. Time is another factor. Some clinicians express concern that the treatment of IC is excessively time-consuming and thus not economically practical. The first part of this concern is valid: Because a patient with IC often requires an extensive history and examination and the development of a treatment strategy, time is taken up that might be used to treat other patients. However, focusing on the care of IC patients can actually provide many clinicians with the opportunity to increase revenue, regardless of the time commitment.

Training Staff in the Management of Interstitial Cystitis

The effective and efficient management of IC depends on a team-based approach. For a gynecologic practice, this begins with a committed and supportive clinical staff. All members should be thoroughly educated in the numerous facets of IC treatment so that they can be effective managers of patients' needs and physicians' time. Knowledge of the most recent coding and reimbursement issues will ensure proper billing for all evaluations and procedures.

As discussed previously, IC patients may express frustration after years of misdiagnoses and inappropriate treatment. Staff members should be able to provide comfort and assurance, in addition to information about IC. Because the disease is chronic and characterized by flares, adequate staff coverage is also important. Ideally, staff members can be trained in techniques common in IC care, such as instillation procedures.

Building an Interstitial Cystitis Practice: Marketing

An IC-focused gynecologic practice will benefit from a strong network. Referrals are a source of patients and a powerful support system. Such a network should include other gynecologists, urologists, family practitioners, gerontologists, internists, psychiatrists, and other professionals who may be helpful (eg, nutritionists and marriage counselors). Building and maintaining connections are central to a successful IC practice.

Clinicians should also consider advertising their practice, with an emphasis on IC expertise. Marketing materials can mention the surprising rate of underdiagnosis and misdiagnosis, along with the symptoms of IC. Opportunities for patient education will also help build reputation and increase exposure.

Economics of Interstitial Cystitis: Coding

Paramount to practice building is an accurate and thorough knowledge of the Current Procedural Terminology (CPT) codes, which are maintained by the American Medical Association.

Assessing New and Referred Patients

For patients who are part of a primary care practice, the initial visit may be either a detailed (code 99214) or comprehensive (99215) level of care. When patients are

physician-referred, as in many urologic and gynecologic settings, they are coded as an initial consultation, either level 4 or level 5 (99244 or 99245), depending on the amount of time required (this includes time spent reviewing records). Occasionally, patients are seeking a second opinion, which is coded 99274 or 99275, depending on the expenditure of time.

Urinalysis and urine culture are routinely performed for new and referred IC patients (81000 urinalysis; 87086, 87088, P9612, and 87181/87184 urine culture). At this time, the clinician determines the need for an in-office cystoscopy or cystoscopy and hydrodistention under anesthesia. The role of cystoscopy in the diagnosis of IC is currently a matter of debate.

If a cystoscopy (52000) is to be performed, a PST is often conducted first. When a PST is undertaken, a code can be assigned for each instillation (51700 × 2), and a J code is assigned for the potassium chloride solution (depending on local costs). Bladder washings for urinary cytology are also coded (51700). If bladder emptying must be assessed, either a catheterization (P9162), transabdominal ultrasound (76857, G0001), or nonimaging pelvic ultrasound (51798) may be performed. If the patient experiences significant pain or discomfort during the PST, an intravesical agent can be instilled (51700) to alleviate the symptoms. Typically, such a solution contains heparin (J1644 × 40 for 40,000 U), 10 mL of 1% lidocaine, and 3 mL of 8.4% sodium bicarbonate.[109] Alternatively, PPS may replace the heparin—this is an off-label use, and there is no corresponding J code.

If the physician determines that cystoscopy with hydrodistention is warranted, then the appropriate codes are 51700 for bladder irrigation and 52000 for the cystoscopy. Bladder biopsy (52204) is not generally indicated in IC patients but may be performed.

Treatment Phase

Once a diagnosis of IC is made, an office visit is scheduled. This visit is very important because the diagnosis and treatment options are explained by the physician and a treatment strategy is devised. Depending on the amount of time spent with the patient, this visit is coded as level 3 or level 4 (99213, 99214). The patient's expectations regarding treatment should also be discussed at this time. In accordance with the combination approach discussed previously, the patient is treated with multiple oral drugs (eg, PPS, hydroxyzine, amitriptyline). Patients are seen again at 1 month and 3 months following initiation of therapy to assess their response to treatment (and again at 6 months, particularly with PPS therapy). A level 3 or level 4 code (99213, 99214) is generally used for these visits, depending on the amount of time spent with the patient.

For patients with more advanced disease or for those who cannot take or do not respond to oral therapy, adjunctive intravesical therapy should be considered. Physicians may choose from a variety of intravesical therapies: heparin (J1644), bupivacaine (J3490), lidocaine (J2000), PPS (off-label; no code), and DMSO (J1212). The instillation procedure is also coded (51700), as is the clinic setting. If the procedure is performed by a physician extender,

the visit is coded 99211. If the physician is in attendance, it is coded 99212 or 99213. After 6 weekly instillations, a clinic visit is scheduled to assess response (99213, 99214).

Some patients choose to perform instillations of intravesical therapy at home. In this case, a physician extender trains the patient in self-catheterization techniques during a clinic visit (99211). The training can be coded as a simple catheterization (51701). Supplies are also provided and coded, including catheters (A4351), heparin (J1644), bupivacaine (J3490), and/or lidocaine (J2000).

Flares of Interstitial Cystitis

Intermittent flares are common in IC and may be provoked by any number of factors. It is important to implement a protocol within the practice to handle flares of IC. Patients should be seen immediately by staff members if a physician is not available and urinalysis performed to detect infection. The visit is coded 99211 and the urinalysis 81000, as previously discussed. If bacteriuria is detected, a full urine culture and sensitivity are obtained (87086, 87088, P9612, 87181/87184). Antibiotic therapy and analgesics are initiated within 48 hours.

If bacteriuria is not present, then immediate intravesical therapy is administered by the nursing staff, with oral analgesics as determined by protocol. Coding is identical to that for the previous instillations of intravesical therapy.

Other Therapies

A number of other therapies have been developed, aside from oral and intravesical medication. Some patients may require or request such measures, which include biofeedback techniques, neuromodulation, and, infrequently, surgery. These procedures and their codes are listed in Table 4 (page 12).

Conclusion

IC appears to be far more common than previously thought and is clearly misdiagnosed and underdiagnosed. Patients with IC suffer the consequences of this neglect, often spending years being evaluated by different physicians before an accurate diagnosis is made and treatment begun. The situation is the result, in part, of the mistaken notion that IC is excessively difficult to diagnose and not broadly amenable to treatment. Great improvements have been made in the area of diagnostic tools, and a wide variety of therapeutic options are now being used. Although PPS is the only oral therapy currently FDA-approved for the treatment of IC, other agents have also proved effective. Combination therapy (eg, PPS, hydroxyzine, amitriptyline) is a widely used treatment paradigm. Numerous new therapies are in various stages of development.

With these developments in hand, gynecologists are well-suited to the task of bringing IC patients into their practices. Indeed, a clinical focus on IC can benefit both the many IC patients in need of treatment and the gynecologic practice itself. Careful attention to the training of staff members, advertising, referral networks, and coding can help to build a successful and respected practice in IC.

References

1. Parsons CL. Interstitial cystitis: epidemiology and clinical presentation. *Clin Obstet Gynecol.* 2002;45:242-249.
2. Chancellor MB, Yoshimura N. Treatment of interstitial cystitis. *Urology*. 2004;63:85-92.
3. Jensen H, Nielsen K, Frimodt-Moller C. Interstitial cystitis: review of the literature. *Urol Int*. 1989;44:189-193.
4. Jones CA, Nyberg L. Epidemiology of interstitial cystitis. *Urology*. 1997;49:2-9.
5. Stanford EJ, Parsons CL, et al The median age of women with interstitial cystitis: demographic data from pentosan sulfate treatment trial [abstract]. Presented at: National Institutes of Health Interstitial Cystitis Symposium; May 2004; Alexandria, Va.
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. Mattox TF. Interstitial cystitis in adolescents and children: a review. *J Pediatr Adolesc Gynecol*. 2004;17:7-11.
8. Parsons CL Parsons JK. Interstitial cystitis. In: *Female Urology*. 2nd ed. Philadelphia: WB Saunders; 1996.
9. Oravisto KJ. Epidemiology of interstitial cystitis. *Ann Chir Gynaecol Fenn*. 1975;64:75-77.
10. Bade JJ, Rijcken B, Mensink HJ. Interstitial cystitis in the Netherlands: prevalence, diagnostic criteria and therapeutic preferences. *J Urol.* 1995;154:2035-2037; discussion 2037-2038.
11. Ito T, Miki M, Yamada T. Interstitial cystitis in Japan. *BJU Int*. 2000;86:634-637.
12. Ratner V, Taylor N, Wein AJ, Hanno PJ. Re: epidemiology of interstitial cystitis: a population based study. *J Urol.* 1999;162:500.
13. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. *J Urol*. 1988;140:203-206.
14. Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L Jr. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. *J Urol*. 1999;161:553-537.
15. Leppilahti M, Tammela TL, Huhtala H, Auvinen A. Prevalence of symptoms related to interstitial cystitis in women: a population based study in Finland. *J Urol.* 2002;168:139-143.
16. Parsons CL. Potassium sensitivity test. *Tech Urol*. 1996;2:171-173.
17. Parsons CL, Zupkas P, Parsons JK. Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. *Urology.* 2001;57:428-432; discussion 432-433.
18. 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.
19. 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.
20. Parsons CL, Albo M. Intravesical potassium sensitivity in patients with prostatitis. *J Urol*. 2002;168:1054-1057.
21. Bernie JE, Hagey S, Albo ME, Parsons CL. The intravesical potassium sensitivity test and urodynamics: implications in a large cohort of patients with lower urinary tract symptoms. *J Urol*. 2001;166:158-161.
22. 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.
23. 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.
24. Metts JF. Interstitial cystitis: urgency and frequency syndrome. *Am Fam Physician*. 2001;64:1199-1206.
25. Held PJ. Epidemiology of interstitial cystitis. In: Sant G (ed.). *Interstitial Cystitis*. New York: Springer-Verlag; 1990.
26. Theoharides TC. The mast cell as a neuroimmunoendocrine effector in interstitial cystitis. In: *Interstitial Cystitis*. Philadelphia: Lippincott–Raven Publishers; 1997:101-108.
27. Parsons CL, Schmidt JD, Pollen JJ. Successful treatment of interstitial cystitis with sodium pentosanpolysulfate. *J Urol*. 1983;130:51-53.
28. Parsons CL. Bladder surface glycosaminoglycan: efficient mechanism of environmental adaptation. *Urology*. 1986;27:9-14.
29. Parsons CL. Sodium pentosanpolysulfate treatment of interstitial cystitis: an update. *Urology*. 1987;29:14-16.
30. 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.
31. Ruggieri MR, Chelsky MJ, Rosen SI, Shickley TJ, Hanno PM. Current findings and future research avenues in the study of interstitial cystitis. *Urol Clin North Am*. 1994;21:163-176.
32. Moldwin RM, Sant GR. Interstitial cystitis: a pathophysiology and treatment update. *Clin Obstet Gynecol*. 2002;45:259-272.
33. Dixon JS, Holm-Bentzen M, Gilpin CJ, et al. Electron microscopic investigation of the bladder urothelium and glycocalyx in patients with interstitial cystitis. *J Urol*. 1986;135:621-625.
34. Nickel JC, Emerson L, Cornish J. The bladder mucus (glycosaminoglycan) layer in interstitial cystitis. *J Urol*. 1993;149:716-718.
35. Anderstrom CR, Fall M, Johansson SL. Scanning electron microscopic findings in interstitial cystitis. *Br J Urol*. 1989;63:270-275.
36. Moskowitz MO, Byrne DS, Callahan HJ, Parsons CL, Valderrama E, Moldwin RM. Decreased expression of a glycoprotein component of bladder surface mucin (GP1) in interstitial cystitis. *J Urol*. 1994;151:343-345.
37. Sant GR Uccia AA, Jr., Alroy J. Bladder surface glycosaminoglycans (GAGs) in interstitial cystitis. *J Urol*. 1986;135:175A.
38. Lilly JD, Parsons CL. Bladder surface glycosaminoglycan is a human epithelial permeability barrier. *Surg Gynecol Obstet*. 1990;171:493-496.
39. Press SM, Moldwin R, Kushner L. Decreased expression of GP-51 glycosaminoglycan in cats afflicted with feline interstitial cystitis. *J Urol*. 1995;153:288A.
40. Elbadawi A. Interstitial cystitis: a critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. *Urology*. 1997;49:14-40.
41. Lavelle J, Meyers S, Ramage R, et al. Protamine sulfate-induced cystitis: a model of selective cytodestruction of the urothelium. *Urology*. 2001;57:113.
42. 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; discussion 1866-1867.
43. Nickel JC, Barkin J, Forrest J, et al. Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium (PPS) for interstitial cystitis (IC). *J Urol*. 2001;165(suppl 5):67.
44. Larsen S, Thompson SA, Hald T, et al. Mast cells in interstitial cystitis. *Br J Urol*. 1982;54:283-286.
45. Feltis JT, Perez-Marrero R, Emerson LE. Increased mast cells of the bladder in suspected cases of interstitial cystitis: a possible disease marker. *J Urol*. 1987;138:42-43.
46. Johansson SL, Fall M. Clinical features and spectrum of light microscopic changes in interstitial cystitis. *J Urol*. 1990;143:1118-1124.
47. Aldenborg F, Fall M, Enerback L. Proliferation and transepithelial migration of mucosal mast cells in interstitial cystitis. *Immunology*. 1986;58:411-416.
48. Enerback L, Fall M, Aldenborg F. Histamine and mucosal mast cells in interstitial cystitis. *Agents Actions*. 1989;27:113-116.
49. Lynes WL, Flynn SD, Shortliffe LD, et al. Mast cell involvement in interstitial cystitis. *J Urol*. 1987;138:746-752.
50. Theoharides TC, Pang X, Letourneau R, Sant GR. Interstitial cystitis: a neuroimmunoendocrine disorder. *Ann N Y Acad Sci*. 1998;840:619-634.
51. Theoharides TC, Sant GR, el-Mansoury M, Letourneau R, Ucci AA Jr, Meares EM Jr. Activation of bladder mast cells in interstitial cystitis: a light and electron microscopic study. *J Urol.* 1995;153:629-636.
52. Elbadawi AE, Light JK. Distinctive ultrastructural pathology of nonulcerative interstitial cystitis: new observations and their potential significance in pathogenesis. *Urol Int.* 1996;56:137-162.
53. Holm-Bentzen M, Sondergaard I, Hald T. Urinary excretion of a metabolite of histamine (1,4-methyl-imidazole acetic acid) in painful bladder disease. *Br J Urol.* 1987;59:230-233.
54. Kastrup J, Hald T, Larsen S, Nielsen VG. Histamine content and mast cell count of detrusor muscle in patients with interstitial cystitis and other types of chronic cystitis. *Br J Urol.* 1983;55:495-500.

References

55. el-Mansoury M, Boucher W, Sant GR, Theoharides TC. Increased urine histamine and methylhistamine in interstitial cystitis. *J Urol.* 1994;152:350-353.
56. Boucher W, el-Mansoury M, Pang X, Sant GR, Theoharides TC. Elevated mast cell tryptase in the urine of patients with interstitial cystitis. *Br J Urol*. 1995;76:94-100.
57. Theoharides TC, Kempuraj D, Sant GR. Mast cell involvement in interstitial cystitis: a review of human and experimental evidence. *Urology*. 2001;57:47-55.
58. Galli SJ. New concepts about the mast cell. *N Engl J Med*. 1993;328:257-265.
59. Klein LM, Lavker RM, Matis WL, Murphy GF. Degranulation of human mast cells induces an endothelial antigen central to leukocyte adhesion. *Proc Natl Acad Sci U S A*. 1989;86:8972-8976.
60. Plaut M, Pierce JH, Watson CJ, Hanley-Hyde J, Nordan RP, Paul WE. Mast cell lines produce lymphokines in response to cross-linkage of Fc epsilon RI or to calcium ionophores. *Nature*. 1989;339:64-67.
61. Serafin WE, Austen KF. Mediators of immediate hypersensitivity reactions. *N Engl J Med*. 1987;317:30-34.
62. Spanos C, el-Mansoury M, Letourneau R, et al. Carbachol-induced bladder mast cell activation: augmentation by estradiol and implications for interstitial cystitis. *Urology*. 1996;48:809-816.
63. Carraway R, Cochrane DE, Lansman JB, Leeman SE, Paterson BM, Welch HJ. Neurotensin stimulates exocytotic histamine secretion from rat mast cells and elevates plasma histamine levels. *J Physiol*. 1982;323:403-414.
64. Lagunoff D, Martin TW, Read G. Agents that release histamine from mast cells. *Annu Rev Pharmacol Toxicol*. 1983;23:331-351.
65. Dimitriadou V, Buzzi MG, Moskowitz MA, Theoharides TC. Trigeminal sensory fiber stimulation induces morphological changes reflecting secretion in rat dura mater mast cells. *Neuroscience*. 1991;44:97-112.
66. Lotz M, Villiger P, Hugli T, Koziol J, Zuraw BL. Interleukin-6 and interstitial cystitis. *J Urol.* 1994;152:869-873.
67. Felsen D, Frye S, Trimble LA, et al. Inflammatory mediator profile in urine and bladder wash fluid of patients with interstitial cystitis. *J Urol*. 1994;152:355-361.
68. Letourneau R, Pang X, Sant GR, Theoharides TC. Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis. *Br J Urol.* 1996;77:41-54.
69. Chen Y, Varghese R, Chiu P, et al. Urinary substance P is elevated in women with interstitial cystitis. *J Urol*. 1999;161:4-26.
70. Fister GM. Similarity of interstitial cystitis (Hunner's ulcer) to lupus erythematosus. *J Urol.* 1938;40:37-51.
71. Oravisto KJ, Alfthan OS, Jokinen EJ. Interstitial cystitis. Clinical and immunological findings. *Scand J Urol Nephrol*. 1970;4:37-42.
72. Silk MR. Bladder antibodies in interstitial cystitis. *J Urol*. 1970;103:307-309.
73. Moran PA, Dwyer PL, Carey MP, Maher CF, Radford NJ. Oral methotrexate in the management of refractory interstitial cystitis. *Aust N Z J Obstet Gynaecol.* 1999;39:468-471.
74. Jokinen EJ, Alfthan OS, Oravisto KJ. Antitissue antibodies in interstitial cystitis. *Clin Exp Immunol.* 1972;11:333-339.
75. Anderson JB, Parivar F, Lee G, et al. The enigma of interstitial cystitis—an autoimmune disease? *Br J Urol.* 1989;63:58-63.
76. Parsons CL, Stanford EJ, Kahn BS, et al. Tools for diagnosis and treatment. *Female Patient*. 2002;27(suppl):12-17.
77. Driscoll A, Teichman JM. How do patients with interstitial cystitis present? *J Urol*. 2001;166:2118-2120.
78. Williams RE, Harmann KE, Sandler RS, Miller WC, Steege JF. Prevalence and characteristics of irritable bowel syndrome among women with chronic pelvic pain. *Obstet Gynecol.* 2004;104:452-458.
79. Howard FM (ed.). *Pelvic Pain: Diagnosis and Management*. New York, NY: Lippincott, Williams & Wilkins; 2000.
80. Stanford EJ, Koziol J, Feng A. The prevalence of endometriosis, interstitial cystitis, and vulvar pain in women presenting for laparoscopy for chronic pelvic pain. *J Minimal Invasive Gynecol.* 2005;12:43-49.
81. Stanford EJ, Parsons JK, McMurphy C. Microhematuria in women with interstitial cystitis. Society of Inflammatory and Infectious Urology at the American Urological Association; San Francisco, Calif. May 2004.
82. Mobley DF, Baum N. Interstitial cystitis. When urgency and frequency mean more than routine inflammation. *Postgrad Med*. 1996;99:201-204, 207-208, 214.
83. Waxman JA, Sulak PJ, Kuehl TJ. Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. *J Urol*. 1998;160:1663-1667.
84. Gillespie L. *You Don't Have to Live With Cystitis!* New York: Rawson Associates; 1996.
85. Parsons CL, Koprowski PF. Interstitial cystitis: successful management by increasing urinary voiding intervals. *Urology*. 1991;37:207-212.
86. 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.
87. Bade JJ, Laseur M, Nieuwenburg A, van der Weele LT, Mensink HJ. A placebo-controlled study of intravesical pentosanpolysulphate for the treatment of interstitial cystitis. *Br J Urol*. 1997;79:168-171.
88. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. *Br J Urol.* 1994;73:504-507.
89. Lose G, Jespersen J, Frandsen B, Hojensgard JC, Astrup T. Subcutaneous heparin in the treatment of interstitial cystitis. *Scand J Urol Nephrol*. 1985;19:27-29.
90. Porru D, Campus G, Tudino D, et al. Results of treatment of refractory interstitial cystitis with intravesical hyaluronic acid. *Urol Int.* 1997;59:26-29.
91. Theoharides TC, Sant GR. New agents for the medical treatment of interstitial cystitis. *Expert Opin Investig Drugs*. 2001;10:521-546.
92. Parsons CL. Epithelial coating techniques in the treatment of interstitial cystitis. *Urology*. 1997;49:100-104.
93. Hanno PM. Analysis of long-term Elmiron therapy for interstitial cystitis. *Urology.* 1997;49:93-99.
94. National Kidney and Urologic Disease Information Clearinghouse. Interstitial Cystitis. Bethesda, Md: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 2002. NIH Publication No 02-3220.
95. Elmiron [prescribing information]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; 2002.
96. Parsons CL, Davis EL. Pentosan polysulfate sodium intravesical instillation—end-organ therapy. *Practice Building Today*. 2003;18-22.
97. Morales A, Emerson L, Nickel JC, Lundie M. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. *J Urol*. 1996;156:45-48.
98. Theoharides TC, Sant GR. Hydroxyzine therapy for interstitial cystitis. *Urology*. 1997;49:108-110.
99. Seshadri P, Emerson L, Morales A. Cimetidine in the treatment of interstitial cystitis. *Urology*. 1994;44:614-616.
100. Coquoz D, Porchet HC, Dayer P. Central analgesic effects of desipramine, fluvoxamine, and moclobemide after single oral dosing: a study in healthy volunteers. *Clin Pharmacol Ther*. 1993;54:339-344.
101. Hanno PM, Buehler J, Wein AJ. Use of amitriptyline in the treatment of interstitial cystitis. *J Urol*. 1989;141:846-848.
102. van Ophoven A, Pokupic S, Heinecke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. *J Urol*. 2004;172:533-536.
103. Sant GR, LaRock DR. Standard intravesical therapies for interstitial cystitis. *Urol Clin North Am*. 1994;21:73-83.
104. Peters KM, Diokno AC, Steinert BW, Gonzalez JA. The efficacy of intravesical bacillus Calmette-Guérin in the treatment of interstitial cystitis: long-term follow-up. *J Urol*. 1998;159:1483-1486; discussion 1486-1487.
105. Peeker R, Haghsheno MA, Holmang S, Fall M. Intravesical bacillus Calmette-Guérin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized double-blind study. *J Urol*. 2000;164:1912-1915; discussion 1915-1916.
106. Forsell T, Ruutu M, Isoniemi H, Ahonen J, Alfthan O. Cyclosporine in severe interstitial cystitis. *J Urol*. 1996;155:1591-1593.
107. Sairanen J, Forsell T, Ruutu M. Long-term outcome of patients with interstitial cystitis treated with low dose cyclosporine A. *J Urol*. 2004;171:2138-2141.
108. Paszkiewicz EJ, Siegel SW, Kirkpatrick C, Hinkel B, Keeisha J, Kirkemo A. Sacral nerve stimulation in patients with chronic, intractable pelvic pain. *Urology*. 2001;57:124.
109. Henry R, Patterson L, Avery N, et al. Absorption of alkalized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. *J Urol.* 2001;165:1900-1903.

Post-test

1. **What are the hallmark symptoms of interstitial cystitis (IC)?**
   a. Nocturia, dysuria, dyspareunia
   b. Pelvic pain, nocturia, urinary urgency
   c. Nocturia, pelvic pain, dysuria
   d. Pelvic pain, urinary urgency, urinary frequency

2. **Approximately how many US women are estimated to have IC according to recent studies?**
   a. 700,000
   b. 9 million
   c. 7 million
   d. 67 per 100,000

3. **The approximate ratio of women to men with IC is _____.**
   a. 1:9
   b. 9:1
   c. 1:2
   d. 2:1

4. **One of the leading theories of the etiology of IC proposes a defect in the _____.**
   a. glycosaminoglycan layer of the urothelium
   b. bladder muscularis
   c. lamina propria of the bladder
   d. afferent nerve terminals

5. **The "leaky epithelium" and its treatment were modeled in healthy subjects through which experiment?**
   a. electron micrographic analysis of mast cells
   b. instillation of pentosan polysulfate sodium (PPS) into the bladder
   c. instillation of heparin, followed by protamine
   d. instillation of protamine, followed by heparin

6. **Which of the following is one of the main mast cell mediators in IC?**
   a. Leukotriene
   b. Histamine
   c. Interleukin-2
   d. Cytokines

7. **What are examples of other conditions that must be ruled out before IC is diagnosed?**
   a. Urinary tract infection (UTI), endometriosis, abnormal Pap smear
   b. UTI, hematuria, endometriosis
   c. UTI, endometriosis, abdominopelvic adhesions
   d. UTI, AIDS, endometriosis

8. **Cystoscopy should be performed to complete the diagnosis of IC to _____.**
   a. visualize glomerulations
   b. visualize Hunner's ulcers
   c. rule out bladder cancer in younger women
   d. Cystoscopy does not need to be performed to diagnose IC.

9. **According to recent data, the presence of hematuria on urinalysis in a patient with suspected IC _____.**
   a. indicates the presence of bladder cancer
   b. does not alone indicate a high risk for bladder cancer
   c. indicates the presence of IC
   d. does not indicate the presence of IC

10. **The potassium sensitivity test (PST) is associated with _____.**
    a. a low rate of false-negatives
    b. a low rate of false-positives
    c. poor sensitivity for IC
    d. 100% sensitivity for IC

11. According to a study by Parsons et al, Pelvic Pain and Urgency/Frequency Symptom Scale (PUF) scores of 10 to 14, 15 to 19, and ≥20 are associated with which rates of a positive PST result:
a. 5%, 27%, 60%, respectively
b. PUF scores are not positively associated with positive PST result.
c. 75%, 79%, 95%, respectively
d. approximately 100% for all PUF scores over 10

12. Which of the following symptoms always coexist in patients with IC?
a. Urinary urgency/frequency and nocturia
b. Urinary urgency/frequency and pelvic pain
c. Pelvic pain and dyspareunia
d. Patients may have only 1 symptom of IC.

13. Which of the following treatments theoretically improves the glycosaminoglycans layer?
a. PPS
b. Hydroxyzine
c. Amitriptyline
d. Dimethyl sulfoxide (DMSO)

14. Which of the following treatments is used to block pain in IC?
a. PPS
b. Hydroxyzine
c. Amitriptyline
d. Cimetidine

15. Which of the following treatments acts by blocking mast cell activation?
a. PPS
b. Hydroxyzine
c. Cimetidine
d. DMSO

16. Which of the following has not been studied extensively for the treatment of IC?
a. PPS
b. Hyaluronic acid
c. Heparin
d. Chondroitin sulfate

17. Which of the following combinations is a common initial treatment strategy in patients with IC?
a. PPS, heparin, hydroxyzine
b. PPS, hydroxyzine, amitriptyline
c. PPS, lidocaine, bupivacaine
d. PPS, bupivacaine, amitriptyline

18. Which of the following combinations is commonly used for the initial treatment of advanced IC?
a. Heparin, lidocaine, sodium bicarbonate (intravesical)
b. Heparin, lidocaine, PPS (oral)
c. Heparin, bupivacaine, amitriptyline (intravesical)
d. None of the above

19. According to Current Procedural Terminology (CPT), _____.
a. physicians can code for only 1 instillation per day.
b. physicians can code for each instillation in a PST
c. physicians can code for only 1 instillation per PST
d. physicians can code for PST once per day

20. If a physician extender performs an instillation for the treatment of IC, _____.
a. the CPT code is 99213
b. the CPT code is 51700
c. the CPT codes are 99211 and 51700 (if heparin is used, J1644 for each 1,000 units of heparin)
d. This procedure cannot be coded.

UNIVERSITY OF KENTUCKY

Answer Sheet & Evaluation Form

Release Date: April 1, 2005 **Expiration Date:** April 1, 2006

A score of 70% or higher on the post-test awards physicians 2.5 AMA PRA Category 1 credits and pharmacists 2.5 contact hours. To claim continuing education credit, individuals must complete the self-study activity, post-test, and evaluation. Please submit your answers only once through one of the methods listed below.

Participate online at:
CMEZone.com
Enter "SR500" in the keyword field

or Mail to: Attn: Distance Education
Continuing Education Office
Colleges of Pharmacy and Medicine
University of Kentucky
One Quality Street, 6th Floor
Lexington, KY 40507-1428

Must be postmarked by

Test Code: MDICGP06

Participant Information: (Please print)

Name:

Credentials: Soc. Sec. #: – –

Address:

City: State: Zip: –

Daytime Phone: – – Fax: – –

E-mail:

Signature: _____

Post-test Answers:

1.	a	b	c	d	**11.**	a	b	c	d
2.	a	b	c	d	**12.**	a	b	c	d
3.	a	b	c	d	**13.**	a	b	c	d
4.	a	b	c	d	**14.**	a	b	c	d
5.	a	b	c	d	**15.**	a	b	c	d
6.	a	b	c	d	**16.**	a	b	c	d
7.	a	b	c	d	**17.**	a	b	c	d
8.	a	b	c	d	**18.**	a	b	c	d
9.	a	b	c	d	**19.**	a	b	c	d
10.	a	b	c	d	**20.**	a	b	c	d

Evaluation:

Ratings:	*1=Poor*		*3=Satisfactory*		*5=Excellent*
Extent to which the objectives were achieved:	1	2	3	4	5
Potential impact on your practice:	1	2	3	4	5
Detail of information presented:	1	2	3	4	5
Overall evaluation of this CME/CPE activity:	1	2	3	4	5

Suggestions for future CME/CPE topics:

SR500