ABSTRACT

Interstitial cystitis (IC), which affects an estimated 1 million people in the United States, is still incompletely understood. Its etiology and pathogenesis appear to be multifactorial, with epithelial dysfunction, sensory nerve up-regulation in the bladder, and mast cell activation playing central roles. Because the signs and symptoms of IC overlap with those of numerous other disorders, it is frequently misdiagnosed as a urinary tract infection, endometriosis, prostatitis, or a number of other conditions. IC may also be the actual cause of several pain and/or urinary frequency syndromes such as overactive bladder and chronic pelvic pain syndrome. Whereas the traditional diagnostic paradigm was based on findings in patients with severe and advanced disease and focused on procedures to establish the diagnosis, the current approach to diagnosis focuses on patient history, physical examination, laboratory findings, and symptom surveys. It is believed that such a clinically oriented approach will facilitate the detection and diagnosis of early and milder disease.

Interstitial cystitis (IC), a chronic bladder syndrome characterized by pelvic pain and urinary frequency and urgency, remains an enigmatic condition. Its etiology and pathogenesis are still incompletely defined, its true prevalence is not known because it is frequently misdiagnosed and underdiagnosed, and its definition has been hampered by the cumbersome and restrictive diagnostic criteria established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 1998 to help identify patients with IC. New criteria are expected to be published soon.

There are 2 forms of IC: “classic” or ulcerative IC, in which Hunner’s ulcers are present and bladder capacity is diminished, and the more common nonulcer type, which is characterized by glomerulations and submucosal hemorrhages. Classic IC was first described over 100 years ago, while nonulcer IC was first described in 1978.

To familiarize members of the pharmacy community with IC, its underlying causes, and its clinical presentation, this article reviews the epidemiology, etiology, and differential diagnosis of IC and addresses the implications of misdiagnosis.

Epidemiology

Current estimates suggest that at least 1 million people in the United States have IC. However, the true prevalence is difficult, if not impossible, to ascertain because population-based studies of IC tend to focus on women only, because there are differences of opinion on how to diagnose IC, and because IC is frequently misdiagnosed as some other bladder or pelvic disorder. Taking these factors into account, particularly the cases of urinary tract infection, prostatitis, overactive bladder, chronic pelvic pain of gynecologic or urologic
origin, and other conditions that are probably IC, increases the estimated number of people in this country with IC exponentially to 9 million to 14 million.

Although most cases of IC occur in women, it also occurs in men, as well as in children and adolescents. In fact, one population-based study, published in 1990, found that patients with IC were 10 to 12 times more likely than controls to have had bladder problems in childhood. Other findings from that study, which estimated that 500,000 persons in this country have IC, are summarized in Table 1.

The 2-fold disparity in prevalence estimates between the earlier population-based study, which relied on a confirmed IC diagnosis in women, and the more recent study, which relied on self-reports of a previous diagnosis of IC in men and women, underscores the need for appropriate epidemiologic studies, as does the probable underestimation of IC in men. Although studies have found that 10% of IC occurs in men, the actual prevalence is likely to be much higher because the cardinal symptoms of chronic prostatitis—urinary dysfunction, pelvic pain, and pain associated with sexual activity—overlap with those of IC. Comparative studies are also needed to determine if chronic prostatitis and IC are, in fact, the same condition.

Another issue that needs to be addressed by epidemiologic studies is whether urinary frequency and urgency in children represent a form of IC, as some believe, or whether they represent some other bladder disorder. The availability of noninvasive markers in the future to establish the diagnosis of IC and longitudinal follow-up studies of children over months and years should provide an answer.

Other epidemiologic findings of note include the over-representation of allergies, inflammatory bowel disease, and fibromyalgia in patients with IC and the possibility, as suggested in studies of twins, that there is a genetic susceptibility to IC.

**ETIOLOGY AND PATHOGENESIS**

Although numerous theories have been proposed to explain the pathogenesis of IC, none have been proven conclusively. Among the proposed causative factors are epithelial dysfunction, subclinical infection, mast cell abnormalities, vascular abnormalities, neurogenic inflammation, autoimmune phenomena, and up-regulation of sensory nerves in the bladder. Given the multiple factors that play a role in the pathogenesis of IC, a multifactorial etiology is far more likely than a single etiology. A proposed model that incorporates these factors, as well as the clinical histories of patients with IC, is shown in Figure 1.

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**Table 1. Overview of Findings from a Population-Based Study of IC**

- Women with a confirmed diagnosis of IC represented only 20% of cases presenting with symptoms suggestive of IC (eg, chronic painful bladder, sterile urine)
- Median age at symptom onset was 40 years
- Late deterioration in symptoms was unusual
- Up to 50% of patients experienced spontaneous remission of 1 to 80 months (mean, 8 months)
- Those with IC were twice as likely as controls to have a history of urinary tract infection
- IC was more common in patients of Jewish origin than in controls (14% vs 3%)
- Patients with IC ranked their quality of life lower than did patients undergoing chronic renal dialysis

IC = interstitial cystitis.
Data from Hanno and Held et al.

**Figure 1. Proposed Model for the Pathogenesis of IC**

Bladder Insult

↓

Epithelial Layer Damage

↓

Potassium Leak into Interstitium

↓

Activation of C-Fibers and Release of Substance P

↑

Mast Cell Activation and Histamine Release

↓

Repeat Bladder Insult

IC = interstitial cystitis.
The cascade of events leading to the development of IC begins with an insult to the bladder or urothelium, which is the layer of transitional epithelium in the wall of the bladder, ureter, and renal pelvis, external to the lamina propria, which often occurs after a bout of bacterial cystitis, childbirth, pelvic surgery, or use of urologic instrumentation.9 Whereas the injured urothelium in normal individuals heals after appropriate therapy, this is not the case in patients with IC. As suggested in recent studies, these patients have increased levels of antiproliferative factor, a unique protein in the urine of patients with IC, and decreased levels of epithelial growth factor in their urine that prevent normal epithelial healing.18

Over time, abnormalities develop in the glycosaminoglycan (GAG) layer, the defensive mucosal lining of the bladder epithelium, allowing irritating urinary metabolites such as potassium to leak into the submucosal space19 and cause depolarization of smooth muscle in the bladder and pelvis, as well as activation of sensory nerves. Leakage also causes an inflammatory reaction characterized by the proliferation and activation of mast cells and the subsequent release of histamine and other mediators that stimulate sensory nerve fibers and produce local tissue damage.9

The interaction between mast cells and activation of capsaicin-sensitive (C) nerve fibers, that are involved in pain transmission results in the release of substance P, a mediator of inflammation, and other neuropeptides, producing additional cell damage and further mast cell activation. As the effects of these actions continue, they produce further injury to local tissue—the GAG layer and bladder smooth muscle and eventually lead to fibrotic changes in the bladder. If this sequence of events is left untreated, the bladder will eventually decrease in size and its functional capacity will be severely compromised.9 In addition, repeated inflammation and activation of C-fibers can trigger neural up-regulation and neural changes in the spinal cord, causing chronic pelvic pain, urgency, and frequency.9

An integrated hypothesis of IC pathogenesis that incorporates both the cascade of events shown in Figure 1 and the role of neural up-regulation and neurologic “wind-up” in producing visceral organ allodynia, the pain resulting from a non-noxious stimulus, and hyperalgesia is shown in Figure 2.1 In this scheme, once the sensory nerves in the bladder are up-regulated, dorsal postganglia and the spinal cord also release substance P and other tachykinins, which are hormones that cause smooth muscle contraction and vasodilation. This leads to a state of neurologic wind-up, which is manifested by allodynia and hyperalgesia in the bladder and adjacent organs—for example, the pelvic floor, the gastrointestinal tract, the urethra, and the uterus and vagina.20 Involvement of these organs explains why many patients with IC also have pelvic floor dysfunction, gynecologic symptoms such as vulvodynia and pain associated with sexual activity, and gastrointestinal symptoms or disorders such as irritable bowel syndrome and inflammatory bowel disease.1

**Signs and Symptoms**

The symptoms of IC are urinary frequency/urgency and/or pelvic pain. In many cases, both in men and women with IC, pelvic pain is associated with sexual activity. Some patients have pain or urgency/frequency only, while others have both pain and urgency/frequency.4,21,22 However, in 1 study involving men and women with IC, 9% had pain only and 8% had urgency only.23

Symptoms can be mild or severe, or they can be occasional or constant. Some patients feel a constant urge that never goes away, even immediately after voiding, while others feel the need to void frequently but do not necessarily feel the urge to void all the time. Many patients find nocturia to be especially troublesome.24 However, many patients are able to identify certain triggers that make their symptoms worse—such as physical or mental stress or certain foods or beverages—and they

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**Figure 2. Integrated Hypothesis of IC Pathogenesis**

Urothelial Dysfunction

↓↓

Mast Cell Activation → C-Fiber Nerve Up-regulation

↓↓

Spinal Cord and Central Nervous System

“Wind-Up”

↑↓

Visceral Organ Hyperalgesia/Allodynia

↓↓

Urinary

↓

Gynecologic

↓

Pelvic Floor

↓

Gastrointestinal

IC = interstitial cystitis.
modify their behavior accordingly to lessen their symptoms. Some women also report that their symptoms vary in severity with their menstrual cycles.

Although urine cultures in patients with IC are usually negative, urinalysis is often positive for pyuria. When pyuria (presence of pus in the urine) is noted on dipstick urinalysis, it can lead to a mistaken diagnosis of bacterial cystitis and treatment with antibiotics.

**Differential Diagnosis**

Because the symptoms of IC are also seen in numerous other clinical conditions (Table 2), and because IC is essentially a symptom complex, diagnosis is largely one of exclusion. The differential diagnosis is therefore crucial in ruling out non-IC causes, establishing a diagnosis of IC, and instituting appropriate treatment. For example, IC should not be confused with changes in bladder function resulting from radiation therapy and treatment with agents such as cyclophosphamide, which also can cause severe cystitis. Similarly, carcinoma in situ of the bladder often mimics the symptoms of IC and must always be ruled out by repeated urinary cytology and bladder biopsy.

In contrast to ruling out the conditions listed in Table 2 to establish a diagnosis of IC, one should also consider the converse: that IC may be the actual cause of symptoms in patients who have been diagnosed with conditions whose symptoms are pain and/or frequency (Table 3). Patients with the frequency-urgency syndrome, painful bladder syndrome, or chronic pelvic pain syndrome most likely have IC.

**Diagnostic Strategies**

The diagnosis of IC has been likened to the “I can’t define it, but I know it when I see it” answer given by a Supreme Court Justice when he was asked to define pornography. Essentially, the diagnosis is grounded in the symptomatology of pelvic pain and urinary frequency/urgency that is chronic in nature and not adequately explained by any known urologic or other system pathology.

An updated paradigm for the diagnosis of IC that is grounded in the symptomatology is presented in Table 4. Emphasizing the patient’s history, physical examination, laboratory tests, and symptom surveys, it is a departure from the traditional NIDDK diagnostic paradigm that was based on the relatively rare occurrence of severe and advanced disease rather than on the more common occurrence of earlier and less severe disease.

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**Table 2. Clinical Conditions Presenting with Urinary Frequency, Urgency, and/or Pain**

<table>
<thead>
<tr>
<th>Infections</th>
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<td>Urinary tract infections</td>
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<td>Vaginal infections</td>
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<td>Sexually transmitted diseases</td>
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<th>Gynecologic</th>
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<tr>
<td>Malignancy</td>
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<td>Endometriosis</td>
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<td>Pelvic inflammatory disease</td>
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<td>Genital atrophy</td>
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<td>Pelvic floor dysfunction</td>
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<th>Urologic</th>
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<tr>
<td>Malignancy</td>
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<tr>
<td>Overflow incontinence</td>
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<tr>
<td>Chronic pelvic pain syndrome</td>
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<td>Bladder obstruction</td>
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<td>Open bladder neck</td>
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<tr>
<td>Chronic nonbacterial prostatitis</td>
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<tr>
<td>Pelvic floor dysfunction (prostate)</td>
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<tr>
<th>Neurologic</th>
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<tr>
<td>Detrusor hyperreflexia</td>
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<td>Parkinson’s disease</td>
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<td>Spinal tumor</td>
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<td>Multiple sclerosis</td>
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<tr>
<td>Neurogenic bladder (can present with frequency and incontinence)</td>
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**Table 3. Syndromes with Pain and/or Urinary Frequency That May Be Caused by IC**

- Pelvic pain syndrome (male and female)
- Chronic nonbacterial prostatitis
- Overactive bladder
- Painful bladder syndrome
- Urgency-frequency syndrome
- Recurrent urinary tract infection
- Nocturia
- Urethral syndrome
- Frequent vaginitis
- Urethritis

IC = interstitial cystitis.
disease. An important advantage of the updated, symptom-based approach, in which several diagnostic methods that were commonly used in the past are now considered optional, is that it avoids the risks, morbidity, and discomfort of invasive procedures.1

**HISTORY AND PHYSICAL EXAMINATION**

The diagnostic workup for IC begins with a comprehensive patient history and a thorough physical examination. The history should focus on IC symptoms, prior diagnoses of conditions known to overlap with IC (Table 3), and circumstances that exacerbate or lessen symptoms. Because pelvic pain due to IC may be felt at single or multiple locations in the pelvis,22,28 complaints of pain or discomfort anywhere between the navel and the thighs, front and back, should be noted.

The physical examination should include an assessment of the pelvic floor—during the bimanual examination in women and the digital rectal examination in men—to rule out pelvic floor dysfunction, which should be suspected in patients who describe stop/start voiding or difficulty in emptying the bladder completely unless they strain.

Rigid bands of muscle, which can be felt at the bottom of the vagina away from the bladder at the 5 o’clock and 7 o’clock positions in response to voluntary tightening of the urinary sphincter, are a distinct focus of pain in women with pelvic floor dysfunction. Pain elicited at the bladder base during the bimanual exam is typical in women with IC, but not diagnostic of IC if it is the sole finding of the physical examination.

**LABORATORY TESTS AND SYMPTOM SURVEYS**

Urinalysis and urine culture should be done to rule out bacterial infection, which is often concurrent with IC. In fact, IC is frequently misdiagnosed as urinary tract infection, particularly in women. Urine cytology should be done in addition in patients with IC symptoms who smoke, men aged 40 years or above, any patient who has hematuria, and any patient at risk for bladder cancer.

Because the presentation of IC differs from one patient to another, and because symptoms in the same individual may vary over time, symptom questionnaires can be extremely helpful in providing a complete picture of the patient’s symptoms, including those that the patient has not associated with the bladder or identified as a problem.

The commonly used symptom surveys that are especially useful in the diagnosis of IC are the O’Leary-Sant Symptom Index and Problem Index and the Pelvic Pain and Urinary/Frequency Patient Symptom (PUF) scale.30 Both are also helpful in monitoring a patient’s response to therapy. The indexes were the first to be reported and validated, and have gained wider acceptance than the more recently reported PUF scale. In routine clinical practice, the indexes and a voiding diary may be sufficient for diagnosis of IC if urine culture and cytology are negative.1 The PUF questionnaire, however, is more useful in distinguishing IC from urinary incontinence.31

For example, patients with detrusor instability, overactive bladder, or known urge incontinence will score in the urgency/frequency domains of the PUF scale, but not in the pelvic pain or dyspareunia domains. By comparison, most patients with IC will score in each of these domains. Thus, PUF scale scores in patients with detrusor instability or overactive bladder (typically around 10) are higher than PUF scale scores in asymptomatic individuals (typically ≤3) but lower than scores seen in patients with IC (>10 to ≥20). In contrast, patients with detrusor instability or overactive bladder will score fairly high on the O’Leary-Sant indexes because they include relatively few questions about pain.

Rising PUF scale scores also correlate directly with an increasing likelihood of a positive potassium sensitivity test (PST) in women with pelvic pain of gynecologic origin, while scores above 7 correlate with a

<table>
<thead>
<tr>
<th>Table 4. An Updated Paradigm for the Diagnosis of IC</th>
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<tbody>
<tr>
<td>• History and physical examination</td>
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<tr>
<td>• Laboratory tests and symptom surveys</td>
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<tr>
<td>    Urinalysis and urine culture</td>
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<tr>
<td>    Urinary cytology</td>
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<tr>
<td>    O’Leary-Sant Symptom and Problem Index</td>
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<tr>
<td>    Pelvic Pain and Urgency/Frequency Patient Symptom scale</td>
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<tr>
<td>• Optional diagnostic procedures</td>
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<tr>
<td>    Cystoscopy/cystoscopy with hydrodistention under anesthesia</td>
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<td>    Urodynamics</td>
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<td>    Potassium sensitivity test and anesthetic bladder challenge</td>
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<td>    Biopsy</td>
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<td>    Voiding diary</td>
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<td>    Urinary markers</td>
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IC = interstitial cystitis.
positive PST in men diagnosed with prostatitis. Thus, the PUF scale can be considered a surrogate for the PST in many cases.

**OPTIONAL DIAGNOSTIC PROCEDURES**

The diagnostic tests and procedures described below were typically used in the traditional diagnostic paradigm but are now considered optional in establishing the diagnosis of IC after obvious pathology—e.g., abnormal findings on physical examination, urinary tract infection, hematuria—has been ruled out.

**Cytoscopy and cytoscopy with hydrodistention under anesthesia.** Cytoscopy, which can be done as an in-office procedure in patients with suspected IC to exclude other intravesical pathology, particularly hematuria, cannot definitively rule in or rule out IC.

Cytoscopy with hydrodistention under anesthesia is no longer mandatory for the diagnosis of IC. Although it documents bladder inflammation (evidenced by glomerulations, hemorrhages, and ulcers), determines bladder capacity, excludes other diseases, and delineates degree and subtype inflammation, it is associated with risks, morbidity, and discomfort. Furthermore, the glomerulations documented by this procedure are not pathognomonic of IC, as demonstrated in a study of normal women undergoing tubal ligation that found glomerulations in 40%. However, a finding of diffuse glomerulations with markedly reduced bladder capacities (eg, 350 cc) generally indicates severe IC.

**Urodynamics.** Urodynamic testing cannot establish a diagnosis of IC. However, it can help in distinguishing stress incontinence from urge incontinence associated with IC and in the differential diagnosis of painful voiding disorders and the symptoms of overactive bladder. Patients with IC will generally have sensory urgency and instability, reduced bladder capacity, and pain with bladder filling at low volumes on simple urodynamic evaluation.

**PST and anesthetic bladder challenge.** The PST involves the instillation of a dilute solution of potassium into the bladder, where it is left for about 5 minutes. The patient is then asked to rate the degree of provocation of urinary urgency and frequency on a scale of 0 to 5, with 0 indicating no provocation and 5 indicating marked provocation. However, the PST is a test for epithelial permeability, and it is not specific for IC. Although the PST is positive in 75% of patients with IC, it is also positive in 25% of patients with detrusor instability and in 100% of patients with either radiation cystitis or bacterial cystitis. In addition, false-negative results occur in patients with severe IC and in patients recently treated with dimethyl sulfoxide, pentosan polysulfate sodium, or narcotic agents, or who have recently undergone hydrodistention.

Bladder challenge with an instilled anesthetic solution, which ascertains the source of pelvic pain, is an alternative to the PST. A report of significant pain relief after instillation generally indicates that the patient’s pain is generated in the bladder rather than elsewhere in the pelvis.

**Biopsy.** Because no specific finding on bladder biopsy can confirm or exclude a diagnosis of IC, it is not a required component of the diagnostic workup for IC unless a malignancy is suspected. However, elevated levels of mast cells in the specimen strongly suggest IC.

**Voiding diary.** A voiding diary can be extremely helpful in documenting abnormal urinary frequency. It can also be helpful in monitoring a patient’s progress after therapy has been instituted.

**Urinary markers.** The search for noninvasive techniques for IC diagnosis has led to the study of several urinary markers. Thus far, an antiproliferative factor (AFP) and glycoprotein GP-51 have been identified, with levels of AFP shown to be increased in patients with IC. At present, there are no commercially available tests to identify IC with these markers.

**IMPLICATIONS OF MISDIAGNOSING IC**

IC is frequently misdiagnosed. Consequently, many patients receive inadequate treatment or the wrong treatment, including repeated courses of antibiotics for a presumed infection or oral anticholinergics for presumed overactive bladder. This delays the correct diagnosis and allows early and mild disease to progress without appropriate treatment. In addition, the undue reliance on the restrictive diagnostic criteria of the traditional paradigm has led to significant underdiagnosis of IC, particularly in women with symptoms of overactive bladder (frequency, urgency, and/or urge incontinence), again leaving a large number of patients at risk for the wrong treatment.

**CONCLUSIONS**

IC, which affects an estimated 1 million and perhaps as many as 9 million to 14 million people in the United...
States, remains an enigmatic condition. Its etiology and pathogenesis are still not completely defined, although both are believed to be multifactorial.

Because the signs and symptoms of IC overlap with those of numerous other disorders, it is frequently misdiagnosed, and a careful differential diagnosis is needed. IC may also be the actual cause of several pain and/or urinary frequency syndromes such as overactive bladder and chronic pelvic pain syndrome.

In contrast to the traditional diagnostic paradigm, which involves restrictive criteria and focuses on procedures to establish the diagnosis, the current approach is to diagnose IC on the basis of patient history, physical examination, laboratory findings, and symptom surveys.

REFERENCES