

Interstitial cystitis/painful bladder syndrome: Symptom recognition is key to early identification, treatment

■ ABSTRACT

Once thought to be rare, interstitial cystitis (IC) is now believed to have a markedly higher prevalence. This potentially devastating disease is also known as painful bladder syndrome (PBS) and can significantly impact quality of life. It is diagnosed by its symptoms, as there are no proven pathological findings. Unfortunately, the symptoms of IC/PBS overlap those of other common disease states such as overactive bladder, endometriosis, urinary tract infection, and prostatitis, which complicates the differential diagnosis. Understanding the presenting symptoms of urinary frequency, urinary urgency, and pelvic pain in the presence of otherwise normal findings can enhance primary care providers' ability to appropriately identify the disease. Early identification may allow initiation of therapy or referral before the disease becomes refractory to standard treatment, which typically includes behavioral therapy and possibly multimodal drug therapy.

■ DEFINITION OF THE CONDITION

Interstitial cystitis (IC) is a chronic condition defined by its symptoms of urinary frequency, urgency, pelvic pain relieved with voiding, nocturia, and dyspareunia.¹⁻³ The International Continence Society advocates use of the term "painful bladder syndrome" (PBS), which it defines as "the complaint of suprapubic pain related to bladder filling, accompanied by

other symptoms such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology."⁴

■ PREVALENCE AND SOCIAL IMPLICATIONS

More common than previously appreciated

In the past, the prevalence of IC/PBS was seemingly low, likely because the diagnosis was based on a very restrictive and possibly inappropriate standard.

Historically, the diagnosis of IC hinged on a classic triad of factors: (1) symptoms, (2) the absence of any identifiable causes, and (3) the presence of bladder lesions on cystoscopy.⁵ Using this historical definition, the prevalence of IC/PBS was generally less than 0.1%. The reality is that cystoscopic findings are not always present in the patient with IC/PBS and that bladder lesions, if present at all, might be found only in advanced cases. This overly restrictive requirement may lead to misdiagnosis of patients presenting in the early stages of IC/PBS, resulting in a missed opportunity for earlier identification and treatment.

Today, most would agree that IC/PBS is a symptom-based disease and that its prevalence is markedly higher than 0.1%. Leppilahti et al surveyed 1,000 Finnish women and found a prevalence of 0.45%.⁶ Although this study was pivotal in that the authors used a symptom score to detect prevalence, they chose the O'Leary Sant symptom and problem indices, which are intended not for screening but for monitoring response to therapy.⁷

A recent study by Rosenberg and Hazzard⁸ challenged the findings from the Finnish study. They administered the pelvic pain and urgency/frequency patient symptom (PUF) scale, a validated screening tool (Table 1),⁹ in addition to the O'Leary Sant indices (Table 2) in a comparable group of 1,218 women in a primary care practice setting. The prevalence of IC/PBS was 0.57% with the O'Leary Sant indices and 12.6% with the PUF scale. The true prevalence may fall somewhere between these extremes.⁸

* **Dr. Rosenberg** reported that he has received consulting fees and honoraria from Indevus Pharmaceuticals/ESPRIT Pharma, Pfizer, and GlaxoSmithKline for consulting, teaching/speaking, and serving on advisory committees; honoraria and consulting fees from Verathon Medical for consulting and serving on advisory committees; honoraria from Eli Lilly and Auxilium Pharmaceuticals for teaching/speaking; a research grant from Sanofi-Aventis; and consulting fees and honoraria from Ortho-McNeil for consulting and teaching/speaking. **Ms. Newman** reported that she has received honoraria from Watson Pharmaceuticals, Pfizer, Astellas Pharma, GlaxoSmithKline, Novartis, and SCA Personal Care for teaching/speaking, as well as for serving on an advisory committee (for Watson) and for consulting (for SCA Personal Care). **Ms. Page** reported that she has no financial relationships that pose a potential conflict of interest with this article.

TABLE 1
Pelvic pain and urgency/frequency patient symptom (PUF) scale⁹

		Points					Symptom score	Bother score
		0	1	2	3	4		
1	How many times do you go to the bathroom during the day?	3–6	7–10	11–14	15–19	20+	_____	
2	a) How many times do you go to the bathroom at night?	0	1	2	3	4+	_____	
	b) If you get up at night to go to the bathroom, does it bother you?	Never	Occasionally	Usually	Always			_____
3	Are you currently sexually active? Yes _____ No _____							
4	a) If you are sexually active, do you now have or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always		_____	
	b) If you have pain, does it make you avoid sexual activity?	Never	Occasionally	Usually	Always			_____
5	Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, penis, testes, or scrotum)?	Never	Occasionally	Usually	Always		_____	
6	a) If you have pain, is it usually...		Mild	Moderate	Severe		_____	
	b) Does your pain bother you?	Never	Occasionally	Usually	Never			_____
7	Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always		_____	
8	a) If you have urgency, is it usually...		Mild	Moderate	Severe		_____	
	b) Does your urgency bother you?	Never	Occasionally	Usually	Always			_____
Symptom score (1, 2a, 4a, 5, 6a, 7, 8a)—Subtotal							_____	
Bother score (2b, 4b, 6b, 8b)—Subtotal								_____
Total score* (Symptom score + Bother score)							_____	

*In the published assessment of the PUF scale by Parsons et al,⁹ a total PUF score of 15 or greater was associated with an 84% likelihood of having a positive potassium sensitivity test, which is a strong predictor that interstitial cystitis may be present. In the authors' view, any PUF score greater than 5 warrants further investigation into a patient's symptoms.

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As part of a separate exploratory prevalence study, Rosenberg and Hazzard screened 3,883 asymptomatic men and women using the PUF scale.¹⁰ Subjects were excluded if they had prior genitourinary surgery or radiation therapy or a prior diagnosis of IC or PBS. The prevalence of IC/PBS in this population was 13.1%, and was twice as high among women as among men.¹⁰

These findings strongly suggest that physicians should more frequently consider IC/PBS in the differential diagnosis of patients who present with pelvic/bladder pain and urinary urgency and frequency.

Urgency can progress to debilitating pain

As the disease progresses, the social implications of IC/PBS can be devastating. Initially, the patient has urinary urgency, urinary frequency, and mild pain.

These symptoms, which overlap other disease states, frequently lead to multiple physician visits and numerous misdiagnoses. Over time, IC/PBS can become debilitating as the patient is voiding with tremendous frequency (up to several times an hour) simply to relieve the pain. The result can be marked limitations on the patient's lifestyle and professional life.

With disease progression, the severity of dyspareunia may interfere significantly with intercourse and sexual intimacy. Patients with IC/PBS are five times more likely to be treated for emotional disorders than those without the disease.¹¹

IC/PBS has the dubious distinction of possessing a disability code, which indicates how severely it can affect patients' lives.

Not every patient will suffer the refractory, debilitat-

TABLE 2**O'Leary Sant indices for symptoms and quality-of-life effects of interstitial cystitis/painful bladder syndrome****Section A: Urinary symptoms**

- A1. During the past month, how often have you:
- a) Had a burning feeling when you urinate?
 - b) Felt the strong need to urinate with little or no warning?
 - c) Had to urinate again within 10 minutes of urinating?
 - d) Had to urinate again less than 2 hours after you finished urinating?
 - e) Found it difficult to postpone urination?
- A2. Over the past month, in a typical day, about how many times did you urinate from the time you got up until the time you went to bed at night?
- A3. Over the past month, once you had the urge to urinate, how long could you usually wait comfortably before going to the bathroom?
- A4. Over the past month, how many times did you most typically get up at night?
- A5. Over the past month, how many times did you most typically get up at night to urinate?
- A6. Over the past month, when you did urinate at night, were you:
- a) Mostly awakened by the need to urinate?
 - b) Mostly awake already for other reasons?
- A7. Over the past month, how often did you leak or drip urine before you could reach the bathroom?
- A8. Over the past month, did you ever drip or leak urine:
- a) When you were running or doing vigorous exercise?
 - b) When you coughed, laughed, or sneezed?
 - c) When you were walking fast or walking up the stairs?
 - d) When you stood up from a chair?
 - e) When you were lying down or sleeping?

Section B: Pain symptoms

- B1. During the past month, how often have you experienced pain in your bladder? Was that pain or burning relieved by urinating?
- B2. During the past month, how often have you experienced any kind of discomfort or pressure in your bladder? Was that discomfort or pressure relieved by urinating?
- B3. During the past month, have you experienced:
- a) Pain or burning in your urethral area?
 - b) Discomfort or pressure in your urethral area?
 - c) Pain in your pelvis or lower abdomen?
 - d) A dull pain in the middle of your lower back?

Section C: Sexual function

- C1. Over the past month, how would you rate your level of sexual interest?
- C2. Over the past month, have you had any kind of sexual activity (ie, intercourse, masturbation)?
- C3. Over the past month, how often have you experienced pain or discomfort while having sexual intercourse?

Section D: General health

- D1. Thinking back, how long have you had urinary symptoms?
- D2. Over the past month, how did stress affect your urinary symptoms?
- D3. Thinking back, how long have you had any other symptoms of pain, burning, or discomfort?

Section E: Symptom relationship with menstrual cycle

- E1. Have you been pregnant in the past 12 months?
- E2. During the past 12 months, have you had any menstrual periods at all? How were your urinary symptoms affected when you stopped having periods?
- E3. How are the following affected during your menstrual period?
- a) Frequent urination
 - b) Pain or pressure in your bladder, lower abdomen, or urethral area
 - c) A dull pain in the middle of your lower back
 - d) Pain or discomfort while having sexual intercourse
 - e) Feeling tired

Section F: Quality of life

- F1. During the past month, how much has each of the following been a problem for you?
- a) A burning feeling when you urinate
 - b) Frequent urination during the day
 - c) Getting up at night to urinate
 - d) Need to urinate with little warning
 - e) Burning, pain, discomfort, or pressure in your bladder or urethral area
 - f) Pelvic pain or discomfort
 - g) Getting enough sleep
 - h) Concern about being too far away from the bathroom
 - i) Embarrassment about going to the bathroom too often
 - j) Concern about your sexual functioning
- F2. During the past month:
- a) Has your urinary condition kept you from doing the kinds of things that you would usually do?
 - b) Has your urinary condition limited your ability to take part in light sports, such as swimming or bowling?
 - c) Has your urinary condition limited the kinds of vigorous activity that you can do, such as running or participating in strenuous sports?
 - d) Has your urinary condition interfered with your normal social activities?
 - e) Has concern about your sexual functioning been a problem for you?
 - f) Has your urinary condition affected your mood?
 - g) Has your urinary condition caused you to worry about your health?
 - h) Has your urinary condition affected your sleep?
- F3. If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?

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ing course that IC/PBS can potentially create. As primary care providers recognize the true prevalence of the disease, it is hoped that more patients will receive timely and appropriate treatment.

■ PATHOGENESIS

Glycosaminoglycan disruption may be the key

The etiology of IC/PBS is not established and is controversial. Most literature supports the belief that its symptoms are associated with abnormal permeability of the epithelium in the lower urinary tract. Normally, the bladder epithelium is coated with a protective mucin layer that contains glycosaminoglycan (GAG).¹² Disruption of this normally impermeable structure allows penetration of the underlying urothelium by potentially caustic agents in the urine, thereby affecting nerves and muscles in the bladder wall.^{13,14} This process of nerve and muscle irritation will lead to the IC/PBS symptoms of urgency, frequency, and pain. The cause of initial injury to the GAG layer is unknown.

Supportive evidence for the role of a dysfunctional and irritated GAG layer in the pathogenesis of IC was recently provided with the identification of antiproliferative factor (APF).¹⁵ APF is a glycosylated frizzled-related peptide inhibitor of cell proliferation that is secreted by the epithelial cells in patients with IC/PBS. It is believed that APF inhibits repair of the GAG layer and normal turnover of the urothelium. APF has been heralded as a possible future marker of IC/PBS.

It has been proposed that irritation of the GAG layer initiates an inflammatory response, which in turn leads to further disruption (**Figure 1**).¹⁶ This model is particularly helpful in identifying the various targets for multimodal treatment of IC/PBS, which includes both repair of the disrupted GAG layer and stabilization of the inflammatory response.

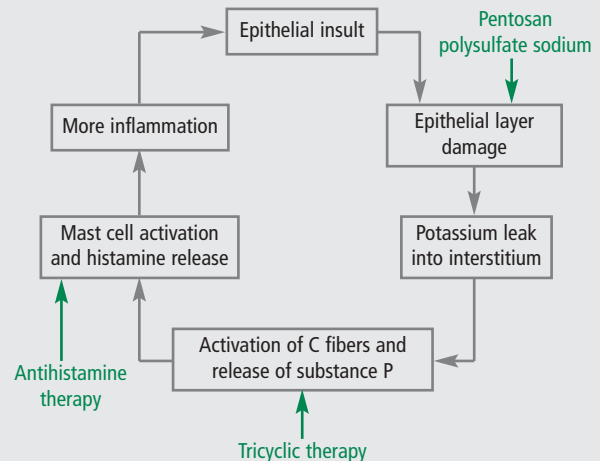
Other theories

Other theories on the pathogenesis of IC/PBS have been proposed,¹⁷ but the weight of evidence currently favors the GAG theory. Other factors—such as lymphatic, infectious, neurogenic, autoimmune, hormonal, and vasculitic components—have been investigated, but no studies have determined a role for any of these.¹⁸ Many believe that there may be a genetic component to IC/PBS, and this possibility is the subject of several ongoing studies.

■ PRESENTING SYMPTOMS

The classic symptoms of IC/PBS are a combination of urinary frequency, urinary urgency, nocturia, and blad-

Etiology of IC/PBS and the role of multimodal therapy



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FIGURE 1. Proposed model for the pathogenesis of interstitial cystitis/painful bladder syndrome (IC/PBS), along with various therapies targeted at different points in the pathogenic process.

der or pelvic pain that may be temporarily relieved by voiding. These symptoms may progress from mild and intermittent to severe and constant. Voiding is usually but not always involved, so that in the occasional patient the pain may not be perceived as being generated from the bladder, which can misdirect the diagnosis away from the urinary tract. As a result, the clinician may be misled to think of processes other than IC/PBS, such as endometriosis, vulvodynia, vaginitis, or prostatitis.

Diagnosis often lags symptom onset by years

On average, the patient with IC/PBS has had the disease for more than 7 years before actual diagnosis.² Typically patients are in their 20s to 40s at the time of diagnosis. As children, many of these patients were labeled incorrectly as having frequent urinary tract infections (UTIs) or pelvic pain of unknown etiology.

Urinary frequency is a common initial symptom. Some patients report that they void up to 15 times per day. Urgency and pain generally develop next.¹ As the disease progresses, it is thought that the GAG layer becomes more permeable, increasing the proportion of unprotected urothelium that is exposed to the caustic solutes in the urine. This exposure, in turn, initiates neurogenic upregulation and provokes a pain response.¹⁹ A significant difference in presentation between patients with overactive bladder and

patients with IC/PBS is that the former void frequently for fear of urine leakage, whereas the latter void frequently to relieve pain.

The patient with IC/PBS generally will present with pain (pelvic or bladder) as the most bothersome symptom. A frequent component of the pelvic pain is dyspareunia, which has been reported to occur in 63% of women with IC/PBS.¹ Although similar incidence data are not available for men, pain with sexual activity is common in both men and women with IC/PBS (Table 3).^{20–22}

Note history and patterns of symptom onset

The history of symptom onset is another clue in unraveling the disease. Patients will often recall that their symptoms generally occur in patterns of flares and remissions. The flares may last for several days and can be triggered by diet, allergies, stress, and sexual activity.⁴ Women will note this exacerbation of symptoms during the premenstrual week.

Flares are frequently misdiagnosed—and mistreated—as recurrent UTIs or prostatitis. Since the flare will generally resolve, clinicians often can be fooled that antibiotic therapy worked when in fact the resolution of symptoms was merely part of the disease's natural pattern. It is the recurrence of flares and the lack of identified microbes that should draw attention.

Interestingly, nearly 12 million primary care office visits per year result in the diagnosis of a UTI, yet urine culture results are negative in nearly half of these cases.²³

Prostatitis is a common diagnosis in men who present with symptoms of urinary urgency, frequency, and pain. Rarely, however, do these patients have an identifiable bacterial cause of their symptoms, and most are not helped by a prolonged course of antibiotics.^{24–26}

EVALUATION

The initial evaluation of IC/PBS starts with a detailed history of symptoms. Generally, the patient will note the onset of urinary urgency and frequency years before the onset of discomfort. Pain, which is relatively minor initially, becomes more prominent as the disease progresses. In fact, pain is generally what brings patients to the physician's office, since they usually adapt to urgency and frequency.

Surveys to assess symptoms

As mentioned earlier, two surveys are used commonly to assess the symptoms of IC/PBS—the O'Leary Sant indices and the PUF scale.^{7,9} The O'Leary Sant indices (Table 2) were developed for monitoring progress following treatment. The PUF scale (Table 1) was designed for screening. Patients with multiple and more

pronounced symptoms will have higher PUF scores and, consequently, a greater likelihood of IC/PBS.

Clinicians should keep in mind that surveys and questionnaires can never diagnose a disease but rather should be viewed as a tool in the decision-making process. Further, a survey may not always be practical for the busy clinician, in which case a few questions regarding the symptoms of urgency, frequency, nocturia, or pain will provide a good starting point.

No specific physical findings

No physical findings are specific to the patient with IC/PBS; however, many have noted exquisite tenderness at the bladder neck in both men and women. In men, this trigger point is at the perineum between the anus and scrotum; in women, it is at the anterior vaginal wall near the urethral orifice. Women with severe IC/PBS pain will report discomfort, pain, or both upon vaginal examination.

Laboratory tests play an exclusionary role

There are no laboratory findings that will identify IC/PBS. It is paramount, however, to exclude diseases that have similar symptoms, such as diabetes or UTI. A blood glucose test and a urinalysis are generally sufficient to rule out these processes. The need for urine cytology is frequently mentioned in the literature as a consideration in high-risk patients (eg, smokers) in order to rule out carcinoma. Urine cytology should certainly be performed for any patient with hematuria.

Further testing to support the diagnosis

With supportive information from the patient's symptoms, and in the absence of physical or laboratory abnormalities, treating for IC/PBS would not be unreasonable. However, there are further tests to isolate the bladder as the source of symptoms, and these may offer the patient and provider a greater degree of comfort. The typical patient with IC/PBS has gone from physician to physician for several years and has received myriad diagnoses. Educating patients by providing further evidence that IC/PBS is the problem is essential to initiating treatment and seeing it through to success.

Two tests that involve bladder catheterization can be helpful in this regard: the potassium sensitivity test and the anesthetic bladder challenge.

The potassium sensitivity test (PST) is based on the premise that potassium in the urine plays a major role in provoking symptoms in the patient with a defective GAG layer. When potassium is instilled into the bladder of a patient with suspected IC/PBS, it may induce the symptoms. Potassium will follow the osmotic gradient from the bladder, where its con-

centration is high, to the interstitium, where its concentration is low. Normally, this movement is blocked by the impermeable GAG layer. Parsons et al showed that potassium did not provoke symptoms of urgency and pain in healthy subjects unless the bladder mucosa had been injured with protamine.²⁷ The actual PST procedure assesses the symptoms induced when 40 mL of a solution of potassium chloride (0.4 mol/L) is instilled into the bladder in comparison with the symptoms induced by 40 mL of water.²⁸

The correlation between PST results and symptom-defined IC/PBS has been documented in numerous studies.²⁹ In one primary care study, the PST was used to evaluate 188 patients who had PUF scores of 5 or greater. Of these patients, 166 had a positive result on the PST, whereas the PST results of 26 controls (with a PUF score of 0) were all negative.³⁰

Although the utility of the PST is well documented in the literature,²⁹ it is still the subject of debate. One concern is that the PST measures the response to provoked pain. However, when properly performed, it is well tolerated.³¹

The anesthetic bladder challenge (ABC) is an alternative to the PST.³² It can be useful if the patient has active discomfort and the physician is attempting to determine if the origin of the pain is the bladder. The procedure entails intravesical administration of lidocaine and bicarbonate (to promote absorption of the lidocaine). The lidocaine is absorbed as a result of the disrupted urothelium. (This procedure is also used as treatment, as explained later.) If the instillation results in dissipation of symptoms, then one can be comfortable that the bladder is involved.

It is essential to note that the PST and the ABC are tools to assist in identifying a potential bladder origin for the symptoms of IC/PBS but that they do not confirm the disease. Because these tests involve catheterization, they may not be practical for all primary care providers. For those not comfortable performing the PST, assessment for anterior vaginal wall pain on physical examination may be a reasonable alternative, as a recent study showed a positive PST to be significantly correlated with such pain.³³

No consistent pathological findings

There is no pathological finding consistent with IC/PBS. Glomerulations (pinpoint-size petechial hemorrhages in the bladder), long thought to be the hallmark of the diagnosis, have been found equally in controls and IC/PBS sufferers. As a result, there is no diagnostic role for cystoscopy or bladder hydrodistension under anesthesia (distending the bladder well

TABLE 3

Symptoms that should prompt consideration of interstitial cystitis/painful bladder syndrome (IC/PBS)*

Pelvic and/or bladder pain—most patients with IC/PBS present with pain that is relieved upon voiding
Dyspareunia/pain with or following sexual intimacy (during vaginal penetration in women and upon orgasm and ejaculation in men)
Frequent symptoms that suggest urinary tract infection without microbes being identified
Frequent symptoms that suggest vaginitis
Urinary frequency or urgency with pain relieved by voiding
Nighttime urination with or without pain (generally two or more voids per night)

* Any of these symptoms may indicate IC/PBS; not all need be present.

above normal capacity, thereby stretching the mucosal and nerve fibers), although these procedures may have a role in treatment of the patient with refractory IC/PBS, as stretching of the bladder can offer temporary (3 to 6 months) relief from pain.

Office cystoscopy alone has a place in the evaluation only if hematuria or a positive cytology is noted during laboratory testing. Urodynamics have a role only if another process, such as detrusor overactivity, needs to be excluded. Caution is warranted, however, as the findings of urodynamic testing may not be specific to a disease process.

■ DIFFERENTIAL DIAGNOSIS

Symptoms suggestive of IC/PBS are listed in **Table 3**. However, when the clinician encounters the symptoms of pelvic pain, urgency, and frequency, the differential diagnosis can be quite extensive. The hierarchy of diagnosis may well depend on the clinician's specialty. The gynecologist, for example, may focus on endometriosis, pelvic inflammatory disease, vulvovaginitis, or UTI. The urologist may think UTI, overactive bladder, or prostatitis.

The key is to focus on the history and listen to the patient, as the assessment must make logical sense. If recurrent UTI is diagnosed, then a urine culture should be positive. The same rule applies to pelvic inflammatory disease. The diagnosis of prostatitis may not require a culture, but if the disease does not respond to therapy after a reasonable time (1 to 3 months), then another diagnosis should be entertained (for more information, see the article on pros-

tatitis in this supplement). If symptoms presumed to be due to overactive bladder are not responsive to antimuscarinics, then the diagnosis must be reconsidered. Endometriosis is certainly a common diagnosis; however, it has been shown to coexist with IC/PBS, the degree of pain does not correlate with the degree of endometriosis, and surgical treatment consisting of hysterectomy and oophorectomy does not always resolve the pain.^{34,35}

TREATMENT

Nonpharmacologic therapy is the cornerstone

Conservative or behavioral therapy is the cornerstone of treatment for the patient with IC/PBS. It involves educating patients about symptoms, behavior modification for urinary urgency and frequency, physical therapy for trigger point release, stress reduction, and dietary manipulation.

Certain foods, especially those rich in potassium, can cause bladder irritation. Foods commonly thought of as irritants include tomatoes, chocolate, citrus fruits and juices, coffee, alcohol, and carbonated beverages. The list can be fairly exhaustive, and each patient will respond differently. To help identify offending foods, a patient can be advised to keep a diary of foods consumed and symptoms that may result. A list of potentially aggravating foods can be found on the Web site of the Interstitial Cystitis Network (www.painfulbladder.com/handbook/).

Although it remains unclear whether stress is a precipitant or consequence of IC/PBS, alleviation of stress may help control symptoms or help patients cope with them.³⁶

Multimodal pharmacologic approach

The goals of pharmacologic therapy for IC/PBS are to restore bladder surface integrity, modulate neuronal dysfunction, and reduce any coexisting inflammation. These goals can be achieved by targeting the specific points in the postulated cycle of the disease (Figure 1) with a multimodal pharmacologic approach.¹⁶

Pentosan polysulfate sodium (PPS), the only oral medication currently approved by the US Food and Drug Administration (FDA) for the treatment of IC, provides the bladder with a compound structurally analogous to the GAG layer.³⁷ Although its mechanism of action is unknown, it is believed to facilitate restoration of the defective layer, thereby preventing further urothelial insult.³⁸ The approved dose of PPS is 100 mg three times per day. Unfortunately, patients may be slow to respond to PPS, as it sometimes takes several months before any relief is noted. Treatment

with PPS should continue for at least 6 months.

Hydroxyzine. To suppress mast cell degranulation, which is part of the inflammatory response, the addition of the oral antihistamine hydroxyzine is recommended. Hydroxyzine is unique among antihistamines in its ability to bring about this specific suppression.³⁹ Dosing starts at 25 mg, given at bedtime, and may increase to 50 to 100 mg/day during the allergy season.

Amitriptyline, an oral tricyclic antidepressant, is used in the IC/PBS patient to regulate pain and urgency in the bladder by modulating neuronal dysfunction. An additional benefit may be its antihistaminic properties. In an early study, amitriptyline (25 to 75 mg/day taken nightly) provided mild to moderate central pain modulation in 60% to 90% of patients with IC/PBS.⁴⁰ A recent placebo-controlled, double-blind study showed amitriptyline to be safe and effective in patients with IC/PBS for up to 4 months.⁴¹

The studies of oral medications for the IC/PBS sufferer have generally shown benefit, although a few have shown mixed results. This lack of uniformity may be due, in part, to the confusion surrounding the diagnosis of IC/PBS and the previously restrictive diagnostic criteria, which tended to isolate patients with very severe, possibly refractory, disease that may not respond to conservative therapy. As a recent example, the combination of PPS and hydroxyzine was not found to be helpful in a group of patients with IC/PBS,⁴² but this small cohort had fairly refractory disease as a result of the study's inclusion criteria.

In contrast, in a study in which patients were screened for the disease based on symptoms, initiation of PPS and hydroxyzine therapy early in the disease process was associated with improved outcomes.⁴³ This study compared outcomes between patients who had symptoms for less than 1 year and patients with symptoms for more than 1 year, finding a faster response to therapy in the former group. It is not unreasonable to conclude that early identification and intervention will result in more efficacious treatment; however, whether outcomes are improved with early intervention has not yet been proven and will need to be studied further.

The practice of triple therapy (with PPS, hydroxyzine, and amitriptyline) is speculative. We know how each medication functions in the treatment of IC/PBS, so it is thought that some patients may require all modalities.

Other medications and pharmacologic approaches

Other medications may be appropriate, depending on a patient's symptoms and response to therapy. Anti-

muscarinics may alleviate urgency and frequency but will not relieve pain associated with these symptoms. Phenazopyridine may subdue irritation and pain in the lower urinary tract. Judicious and responsible use of analgesics, including narcotics, may be appropriate in some cases.

Instillation therapy, which targets the bladder directly, offers another level of IC/PBS treatment for the experienced clinician. Intravesical dimethyl sulfoxide (DMSO) has been approved by the FDA for the relief of IC/PBS symptoms; unlike PPS, however, it does not address the deficient GAG layer.

Fairly recent additions to the armamentarium for IC/PBS include novel instillation therapies that use a combination of sodium bicarbonate, lidocaine, and heparin. The sodium bicarbonate allows neutralization, thereby facilitating absorption of the lidocaine, which in turn provides pain relief. Intravesical heparin is thought to play a role in restoration of the dysfunctional mucin layer.⁴⁴

Surgical options for refractory patients

Investigation of the use of implanted neurostimulators to reduce IC/PBS-associated pain is ongoing.⁴⁵ Although the role of surgery is quite limited, cystectomy with urinary diversion may be considered in refractory patients who have no other options.

■ APPROPRIATE FOLLOW-UP

Follow-up for patients with IC/PBS can be challenging. These patients have frequently had symptoms for an extended time and usually have received many different diagnoses. They may have become disillusioned with the health care community and wary of new treatments. Not uncommonly, patients have been told that their symptoms were “in their head,” which further alienates them from providers.

Follow-up at 1-month intervals for the first 3 months and then every 3 months thereafter offers an opportunity to monitor patients' progress and address their concerns. Since symptoms may be slow to respond, encouraging treatment compliance is important. The O'Leary Sant indices (Table 2)⁷ are a useful tool for following these patients.

■ WHEN TO REFER

When to refer the patient with IC/PBS depends on the comfort level of the provider. Some choose to refer upon identifying symptoms, whereas others may be comfortable with further evaluation, including the PST or ABC. Helping the patient is crucial, all the while understanding the limits of one's own abilities.

Specific findings during the evaluation that should trigger referral include hematuria, chronic UTI, pyuria, intractable pain, and confusing symptoms. If the primary care provider has initiated treatment and the symptoms do not respond after a reasonable amount of time (3 to 6 months), then further evaluation and consultation is appropriate. During this consultation, the patient can generally expect further tests, including cystoscopy and possibly urodynamic evaluation.

■ REFERENCES

1. Parsons CL. Interstitial cystitis: epidemiology and clinical presentation. *Clin Obstet Gynecol* 2002; 45:242–249.
2. Metts JE. Interstitial cystitis: urgency and frequency syndrome. *Am Fam Physician* 2001; 64:1199–1206.
3. Driscoll A, Teichman JMH. How do patients with interstitial cystitis present? *J Urol* 2001; 166:2118–2120.
4. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Am J Obstet Gynecol* 2002; 187:116–126.
5. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. *Urology* 1978; 12:381–392.
6. Leppilähti M, Tammela TLJ, 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.
7. O'Leary MP, Sant GR, Fowler FJ, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. *Urology* 1997; 49(Suppl 5A):58–63.
8. Rosenberg MT, Hazzard M. Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. *J Urol* 2005; 174:2231–2234.
9. 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.
10. Rosenberg MT, Hazzard MA. Prevalence of interstitial cystitis in a primary care setting. *Urology*. In press.
11. Hanno P, Baranowski A, Fall M, et al. Painful bladder syndrome. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. *Incontinence: Proceedings from the 3rd International Consultation on Incontinence*. Plymouth, UK: Health Publications; 2005: 1455–1520.
12. Hurst RE. Structure, function, and pathology of proteoglycans and glycosaminoglycans in the urinary tract. *World J Urol* 1994; 12:3–10.
13. Sant GR. Interstitial cystitis: pathophysiology, clinical evaluation and treatment. *Ann Urol* 1989; 3:172–179.
14. 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.
15. Keay SK, Szekely Z, Conrads TP, et al. An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. *Proc Natl Acad Sci USA* 2004; 101:11803–11808.
16. Evans RJ. Treatment approaches for interstitial cystitis: multimodality therapy. *Rev Urol* 2002; 4(Suppl 1):S16–S20.
17. Wei DC, Politano VA, Selzer MG, Lokeshwar VB. The association of elevated urinary total to sulfated glycosaminoglycan ratio and high molecular mass hyaluronic acid with interstitial cystitis. *J Urol* 2000; 163:1577–1583.
18. Sant GR, Theoharides TC. The role of the mast cell in interstitial cystitis. *Urol Clin North Am* 1994; 21:41–53.
19. Parsons CL. The therapeutic role of sulfated polysaccharides in the urinary bladder. *Urol Clin North Am* 1994; 21:93–100.
20. Parsons CL, Zupkas P, Parsons JK. Intravesical potassium sensi-

- tivity in patients with interstitial cystitis and urethral syndrome. *Urology* 2001; 57:428–432.
21. **Koziol JA, Clark DC, Gittes RF, Tan EM.** The natural history of interstitial cystitis: a survey of 374 patients. *J Urol* 1993; 149:465–469.
22. **Parsons CL, Albo M.** Intravesical potassium sensitivity in patients with prostatitis. *J Urol* 2002; 168:1054–1057.
23. **McIsaac WJ, Low DE, Biringier A, et al.** The impact of empiric management of acute cystitis on unnecessary antibiotic use. *Arch Intern Med* 2002; 162:600–605.
24. **Miller JL, Rothman I, Bavendam TG, Berger RE.** Prostatodynia and interstitial cystitis: one and the same? *Urology* 1995; 45:587–590.
25. **Collins MM, Meigs JB, Barry MJ, Walker Corkery E, Giovannucci E, Kawachi I.** Prevalence and correlates of prostatitis in the health professionals follow-up study cohort. *J Urol* 2002; 167:1363–1366.
26. **Schaeffer AJ.** Chronic prostatitis and the chronic pelvic pain syndrome. *N Engl J Med* 2006; 355:1690–1698.
27. **Parsons CL, Greenberg M, Gabal L, et al.** The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol* 1998; 159:1862–1867.
28. **Rosenberg M, Parsons CL, Page S.** Interstitial cystitis: a primary care perspective. *Cleve Clin J Med* 2005; 72:698–704.
29. **Parsons CL.** Prostatitis, interstitial cystitis, chronic pelvic pain, and urethral syndrome share a common pathophysiology: lower urinary dysfunctional epithelium and potassium recycling. *Urology* 2003; 62:976–982.
30. **Rosenberg MT, Page S, Roth L, et al.** A proactive approach to early identification and treatment in interstitial cystitis patients in the primary care setting. Poster presented at: Society for Infection and Inflammation in Urology symposium at the American Urological Association Annual Meeting; May 8–13, 2004; San Francisco, CA.
31. **Rosenberg MT, Page S, Roth L, et al.** Tolerability of the potassium sensitivity test for interstitial cystitis. Poster presented at: Research Insights into Interstitial Cystitis: A Basic and Clinical Science Symposium; October 30–November 1, 2003; Alexandria, VA.
32. **Moldwin R, Brettschneider N.** The use of intravesical anesthetics to aid in the diagnosis of interstitial cystitis. Poster presented at: Research Insights into Interstitial Cystitis: A Basic and Clinical Science Symposium; October 30–November 1, 2003; Alexandria, VA.
33. **Rosenberg MT, Hazzard MA, Sailor N, et al.** Correlation of elicited anterior vaginal wall pain with the potassium sensitivity test in the evaluation of interstitial cystitis. Poster presented at: Society for Infection and Inflammation in Urology symposium at the American Urological Association Annual Meeting; May 20–25, 2006; Atlanta, GA.
34. **Chung MK, Chung RR, Gordon D, Jennings C.** The evil twins of chronic pelvic pain syndrome: endometriosis and interstitial cystitis. *JSLs* 2002; 6:311–314.
35. **Chung MK.** Interstitial cystitis in persistent posthysterectomy chronic pelvic pain. *JSLs* 2004; 8:329–333.
36. **Rothrock NE, Lutgendorf SK, Kreder KJ, et al.** Stress and symptoms in patients with interstitial cystitis: a life stress model. *Urology* 2001; 57:422–427.
37. **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.
38. **Parsons CL.** Epithelial coating techniques in the treatment of interstitial cystitis. *Urology* 1997; 49(5A Suppl):100–104.
39. **Theoharides TC, Sant GR.** Hydroxyzine therapy for interstitial cystitis. *Urology* 1997; 49(5A Suppl):108–110.
40. **Hanno PM.** Amitriptyline in the treatment of interstitial cystitis. *Urol Clin North Am* 1994; 21:89–91.
41. **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.
42. **Sant GR, Probert KJ, Hanno PM, et al.** A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. *J Urol* 2003; 170:816–817.
43. **Rosenberg MT, Hazzard MA, Page SA.** Patient response in a screened population for interstitial cystitis. *Compr Ther.* In press.
44. **Parsons CL.** Current strategies for managing interstitial cystitis. *Exp Opin Pharmacother* 2004; 5:287–293.
45. **Peters KM, Konstandt D.** Sacral neuromodulation decreases narcotic requirements in refractory interstitial cystitis. *BJU Int* 2004; 93:777–779.

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