

A Practical Approach to Diagnosis and Treatment of Interstitial Cystitis

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ABSTRACT

Interstitial cystitis/painful bladder syndrome (IC/PBS) is characterized by pelvic pain, urinary urgency and frequency, and nocturia. The etiology of IC/PBS is unknown but likely multifactorial. It can be difficult to diagnose IC/PBS because of variable presentation. No definitive diagnostic tests and no established guidelines for the treatment of this condition exist. It is possible to distinguish IC/PBS from other similar conditions through careful history taking and physical examination. A variety of treatment options are available; multimodal therapy may offer patients the best outcomes.

KEYWORDS: Interstitial cystitis; Pelvic pain; Chronic pelvic pain; Painful bladder syndrome

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OVERVIEW OF INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME

Interstitial cystitis/painful bladder syndrome (IC/PBS) is characterized by urinary urgency and frequency, pelvic pain, and nocturia in the absence of infection or other obvious pathology [1,2]. The majority of patients initially present with only one symptom, often frequency/urgency or pelvic pain, and the full range of symptoms may not appear for years [3]. Symptoms may occur in a pattern of intermittent flares, which can be triggered by the menstrual cycle in women and by sexual intercourse or seasonal allergies in both men and women [4].

The symptoms of IC/PBS overlap with other common conditions such as endometriosis, overactive bladder, vulvodynia, and chronic nonbacterial prostatitis [5,6]. In addition, IC often coexists with some of these conditions, including endometriosis and vulvodynia [7-10]. There is no definitive diagnostic test for IC/PBS. As a result, some patients may go undiagnosed, often for several years [3], while experiencing frustration and reduced

quality of life. Many practitioners have come to rely on the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria to diagnose IC/PBS. These criteria include cystoscopic findings of glomerulations or Hunner's ulcer and symptoms of bladder pain or urinary urgency. Because many patients do not exhibit the full range of clinical signs and symptoms, the strict use of these criteria may result in up to 60% of cases being missed [11].

ETIOLOGY

The etiology of IC/PBS has not been clearly established. Theories include increased bladder surface permeability, neurogenic up-regulation, an autoimmune disorder, increased mast cell activity, or a combination of these factors [12,13]. Abnormally enhanced permeability of the bladder mucosal lining due to structural or molecular changes may allow irritating solutes such as potassium to diffuse into the urothelium, resulting in sensory nerve activation and tissue damage and leading to symptoms of urgency, frequency, and pelvic pain [14,15]. Bladder epithelial tissue from patients with IC/PBS shows an

increased number of mast cells compared with tissue from individuals without IC/PBS, indicating an inflammatory process [16,17]. Neurogenic inflammation or neural upregulation may also be involved in IC/PBS [18].

EVALUATION AND DIAGNOSIS OF IC/PBS

The typical diagnostic evaluation of a patient with suspected IC/PBS includes a detailed history, physical examination, and laboratory evaluations. The history should include detailed information on the occurrence and duration of voiding symptoms (urgency, frequency, nocturia) and any factors that aggravate or relieve symptoms. Pain that worsens with certain food or drink and bladder filling, and is relieved by bladder emptying, suggests IC [19]. The presence of urge incontinence suggests OAB. Symptoms that can distinguish chronic prostatitis from IC include obstructive voiding symptoms, ejaculatory problems, and impotence.

The history should also include severity, location, and frequency of pain. Patients with IC may experience generalized pelvic pain and/or pressure. Pain may be referred and range from mild to severe. Male and female patients with IC may also experience pain during or after intercourse. Dysuria may be present [20].

Questionnaires are available that can help screen for the symptoms of IC/PBS. The Pelvic Pain and Urgency/Frequency (PUF) Patient Symptom Scale[®] (Figure 1) and the O'Leary-Sant (OLS) Interstitial Cystitis Symptom and Problem Index Questionnaire[®] (Figure 2) look at symptoms specific to IC/PBS [21,22]. Both include questions about pain, urinary urgency, frequency, and nocturia, along with the impact of these symptoms on daily life. The PUF has additional questions regarding sexual dysfunction. A one-day voiding diary can also be helpful in capturing frequency of urination, nocturia, and symptoms before, during, and after voiding.

The physical examination should include a thorough general evaluation and a comprehensive pelvic examination for women and rectal examination for men. A pelvic exam of a female patient with IC/PBS will typically show pain/tenderness at the anterior vaginal wall/bladder base [13,23]. The cotton swab test will frequently provoke vulvodynia [24]. There may also be pelvic floor (levator) tenderness. The physical exam of a male patient with IC may show tenderness of the levator ani muscles on rectal examination [25].

Laboratory evaluations should include urinalysis and urine culture to rule out UTI [26]. Microscopic hematuria may also be present [27]. Urine cytology or cystoscopy should be

performed if the patient has risk factors for bladder cancer such as hematuria, smoking, and age > 40 years [28].

Optional tests are available to aid in the diagnosis of IC/PBS. The potassium sensitivity test (PST) [29] can help localize pain to the bladder. This test involves intravesical instillation of a potassium solution, which triggers symptoms of pain and urgency in patients with abnormal bladder-surface permeability [29]. However, this test is not specific for IC/PBS because it may be positive for other inflammatory bladder conditions such as acute bacterial or radiation cystitis [30]. The PST can also cause temporarily worsened pain and urgency in patients who are already experiencing pain. Therefore, this test is not universally accepted [31].

The Anesthetic Bladder Challenge (ABC), which involves intravesical instillation of an anesthetic cocktail, can also help localize pain to the bladder. It does not cause increased pain. This test is only effective in patients with current symptoms of pain or urgency [31].

Cystoscopy with hydrodistention is not necessary for diagnosis but may help with prognosis [1,28]. This procedure can help confirm the diagnosis of IC in a subset of patients with glomerulations or Hunner's ulcers, but has also shown false positives in patients without IC [11,32]. Urodynamic testing is not necessary for diagnosis but may be useful in ruling out detrusor instability [2].

TREATMENT

There are no universally accepted guidelines for the treatment of IC/PBS. Treatment is generally tailored to the individual patient, depending on the range and severity of symptom presentation. Nonpharmacologic and pharmacologic treatment options are available.

Many patients with IC/PBS experience symptom flares after eating certain foods, so dietary restrictions and ingestion of alkalinizing agents such as calcium glycerophosphate (Prelief; AkPharma Inc., Pleasantville, NJ) may be helpful for symptom relief [33-35]. Patients may be counseled to avoid certain foods or to keep a food diary to help establish which foods trigger their flares. Symptoms of IC/PBS can be exacerbated by stress, so lifestyle management programs such as meditation, counseling, or a support group can be beneficial [36]. Physical therapy can include treatment of pelvic floor dysfunction using biofeedback and/or electric stimulation to help identify and control pelvic floor musculature [37,38]. Bladder retraining involves gradually increasing intervals between voids. This

Figure 1. The Pelvic Pain and Urgency/Frequency (PUF) Patient Symptom Scale[®].
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		0	1	2	3	4	SYMPTOM SCORE	BOTHER SCORE
1	How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2	a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
	b. If you get up at night to go to the bathroom does it bother you?	Never	Mildly	Moderate	Severe			
3	Are you currently sexually active? YES_____ NO_____							
4	a. IF YOU ARE SEXUALLY ACTIVE , do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Occasionally	Usually	Always			
	b. If you have pain, does it make you avoid sexual intercourse?	Never	Occasionally	Usually	Always			
5	Do you have pain associated with your bladder or in your pelvis (vagina, lower abdomen, urethra, perineum, testes, or scrotum)?	Never	Occasionally	Usually	Always			
6	Do you have urgency after going to the bathroom?	Never	Occasionally	Usually	Always			
7	a. If you have pain, is it usually		Mild	Moderate	Severe			
	b. Does your pain bother you?	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 = (Add 1, 2a, 4a, 5, 6, 7a, 8a)	
BOTHER SCORE = (Add 2b, 4b, 7b, 8b)	
TOTAL SCORE (Symptom Score + Bother Score) =	

Figure 1 is adapted with permission from 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(4):573-578. Copyright 2000 C. Lowell Parsons, MD.

Figure 2. O'Leary-Sant (OLS) Interstitial Cystitis Symptom and Problem Index Questionnaire©. doi: 10.3834/uij.1944-5784.2009.10.11f2

Interstitial Cystitis Symptom Index:

Q1. *During the past month, how often have you felt the strong need to urinate with little or no warning?*

- 0. _____ not at all
- 1. _____ less than 1 time in 5
- 2. _____ less than half the time
- 3. _____ about half the time
- 4. _____ more than half the time
- 5. _____ almost always

Q2. *During the past month, have you had to urinate less than 2 hours after you finished urinating?*

- 0. _____ not at all
- 1. _____ less than 1 time in 5
- 2. _____ less than half the time
- 3. _____ about half the time
- 4. _____ more than half the time
- 5. _____ almost always

Q3. *During the past month, how often did you most typically get up at night to urinate?*

- 0. _____ none
- 1. _____ once
- 2. _____ 2 times
- 3. _____ 3 times
- 4. _____ 4 times
- 5. _____ 5 or more times

Q4. *During the past month, have you experienced pain or burning in your bladder?*

- 0. _____ not at all
- 2. _____ a few times
- 3. _____ almost always
- 4. _____ fairly often
- 5. _____ usually

Add the numerical values of the checked entries;
total score: _____.

Interstitial Cystitis Problem Index:

During the past month, how much has each of the following been a problem for you?

Q1. Frequent urination during the day?

- 0. _____ no problem
- 1. _____ very small problem
- 2. _____ small problem
- 3. _____ medium problem
- 4. _____ big problem

Q2. Getting up at night to urinate?

- 0. _____ no problem
- 1. _____ very small problem
- 2. _____ small problem
- 3. _____ medium problem
- 4. _____ big problem

Q3. Need to urinate with little warning?

- 0. _____ no problem
- 1. _____ very small problem
- 2. _____ small problem
- 3. _____ medium problem
- 4. _____ big problem

Q4. Burning pain, discomfort, or pressure in your bladder?

- 0. _____ no problem
- 1. _____ very small problem
- 2. _____ small problem
- 3. _____ medium problem
- 4. _____ big problem

Add the numerical values of the checked entries;
total score: _____.

Figure 2 is reprinted with permission from O'Leary MP, Sant GR, Fowler FJ Jr, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. *Urology*. 1997;49(suppl 5A):58-63. Copyright 1997 Elsevier, Inc.

technique is appropriate only in patients whose pain is under control [36,39]. Symptoms of IC/PBS can impact sexual relations for some patients. They can employ various strategies, including voiding before and after sex, to limit IC/PBS symptoms associated with sexual intercourse [37].

Pharmacologic treatment consists of multimodal therapy to address the multifactorial etiology of IC/PBS (Table 1) [40-42]. Pentosan polysulfate sodium (PPS) (Elmiron; Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ) is the only oral therapy approved by the FDA for relief of bladder pain or discomfort associated with IC/PBS [43]. In some clinical trials, PPS provided effective symptom relief for patients with IC/PBS, but patients

may need to remain on therapy for 3 to 6 months to achieve symptom improvement [44-47]. PPS is thought to repair the defective bladder-surface layer, potentially decreasing the leak of irritating solutes such as potassium through the bladder wall [15,43]. This drug may also have antihistamine properties [48]. Side effects are typically mild and include alopecia, gastrointestinal events, headache, and rare mild rectal bleeding. The recommended dosage is 100 mg tid [43].

Other medications have been used off-label to treat symptoms of IC/PBS. Hydroxyzine is used to treat increased mast cell activity [49]. One study of patients with IC/PBS showed at least a 40% reduction in symptom scores after 3 months of hydroxyzine use

Table 1. Pharmacological Therapies for IC/PBS [40-42].

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Treatment	Dose	Recommended Use in IC	Side Effects
Pentosan polysulfate sodium	100 mg tid	Treats underlying damage to the bladder lining; symptom relief is gradual	Hair loss, GI events, headache, rectal bleeding
Hydroxyzine	10-75 mg/day	For patients whose symptoms worsen during allergies	Drowsiness, constipation, dry mouth
Amitriptyline	10-100 mg/day	Analgesic, antihistamine, anticholinergic properties	Nausea, constipation, drowsiness
Gabapentin	300-3600 mg tid	Treats neuropathic pain	Nausea, constipation, drowsiness
Prednisone	25 mg/day	Antiinflammatory effect; use second-line for IC	Weight gain, hyperglycemia, hypertension
Cyclosporine	IV, up to 1.5 mg/kg bid	Immunosuppressant; use second-line for refractory IC	Hypertension, gingival hyperplasia; requires monitoring for renal toxicity
Intravesical Agents^a			
Dimethyl sulfoxide	50 mL instillation every 2 weeks	Pain relief	Pain following instillation; garlic-like taste or odor
Local anesthetics	1%-2% lidocaine; 0.5% bupivacaine	Pain relief	Pain following instillation
Glycosaminoglycan substitution	10,000 IU heparin	Repair of damaged bladder surface	
Corticosteroids	100 mg hydrocortisone; 40 mg triamcinolone	Immunosuppressive	

Abbreviation: IC, interstitial cystitis

^aMay be used separately or combined in therapeutic "cocktails"

[50]. In another study, hydroxyzine did not provide significant benefit when compared with placebo [46]. The most common side effect was sedation. Amitriptyline hydrochloride and anticonvulsants (eg, gabapentin) are used for neurogenic down-regulation. Both amitriptyline and gabapentin have sedative side effects and can modulate pain [15]. In a randomized, double-blind study, 63% of patients taking amitriptyline for IC/PBS reported satisfaction with the therapeutic outcome [51]. The most common side effect was dry mouth. Cyclosporine is thought to relieve IC/PBS symptoms by interrupting the inflammatory cascade in the bladder [52]. Two small studies of patients with severe IC/PBS showed improvement in pain and urinary symptoms after treatment with cyclosporine. Side effects were mild and typical for patients taking this drug [52,53]. Patients receiving cyclosporine should be monitored closely for the possibility of renal toxicity. Narcotics are given as a last resort to relieve pain. Consultation with a pain specialist may be indicated for complex cases.

Intravesical instillation therapy may also be used to treat symptoms associated with IC/PBS. Dimethyl sulfoxide (DMSO) intravesical therapy is approved by the FDA for the treatment of IC/PBS [54]. Clinical reports have indicated 50% to 70% improvement of IC/PBS symptoms with DMSO. Side effects include transient exacerbation of IC/PBS symptoms as well as a garlic odor on the breath [55]. Other off-label anesthetic solutions have been used intravesically, including sodium bicarbonate, lidocaine hydrochloride, and heparin sodium. An alkalized solution of heparin and lidocaine provided symptom relief in 75% to 94% of patients with IC/PBS [56]. Intravesical instillation can provide immediate relief to patients during symptom flares or while other treatments are taking full effect.

CONCLUSIONS

The symptoms of IC/PBS are similar to many conditions commonly seen in urologic practices. In order to make an accurate diagnosis, it is important to consider IC/PBS in all patients who present with pelvic pain or urinary urgency or frequency. Because of the multifactorial etiology of this disease, multimodal therapy should be used to treat the symptoms of IC/PBS.

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Conflict of Interest

Dr. Evans is an advisor and invited speaker for Ortho-McNeil Pharmaceutical, Inc.

Dr. Proctor is a consultant and a member of the speakers' bureau for Ortho-McNeil Pharmaceutical, Inc.

Dr. Moldwin is a consultant and invited speaker for Ortho-McNeil Pharmaceutical, Inc.

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