

Painful Bladder Syndrome: A Chronic Condition



Joel M. H. Teichman, MD, FRCSC

Presented at The University of British Columbia's Urology Update 2006, Vancouver, British Columbia.

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic bladder condition. IC/PBS is prevalent, representing 3% of diagnoses by Canadian urologists. However, it is underdiagnosed. The typical patient sees multiple physicians prior to diagnosis. In the US, older data shows that at least 800,000 women were diagnosed with IC/PBS, but recent studies yield an estimated prevalence at eight to 12 million Americans.

IC/PBS is diagnosed ten times more often in women than in men. The median age at diagnosis is 42 years. The average patient is symptomatic for two to seven years prior to being diagnosed. Misdiagnosis as urinary infection, or endometriosis is common. Although there is no currently accepted "gold standard" of diagnosis, research advances have yielded new understanding and management options.

Pathophysiology

Several theories have been advanced. The most compelling data implicates changes in the bladder epithelial mucin layer (glycosaminoglycan theory). A normal bladder is impermeable to urinary solute. The change in epithelial mucin permits urinary solute to cross the epithelium and enter the interstitium. Urinary potassium is thought to stimulate submucosal sensory nerves and produce urgency and pain. Inflammatory changes may occur secondary to solute "leak." Mast cells and histamine are increased. Histamine recruits other inflammatory mediators

Susan's case

Susan, 28, is a student who presents with suspected interstitial cystitis. She suddenly developed pelvic pain without any obvious triggers 2 months before. She denies any change in voiding habits.

Prior treatments

Susan's GP treated her empirically for a bacterial cystitis with nitrofurantoin macrocrystals. She returned 1 week later with no symptom improvement. A urine culture was performed and she was given an additional course of ciprofloxacin.

One week later Susan is no better. Her culture showed no growth. She was referred to a gynecologist specializing in endometriosis though it was felt that she did not have endometriosis; she was then referred to a urologist.

History

Susan claims to wake 8 times per night to void and believes this is a result of aging. She also urinates about every 45 minutes during waking hours. This has been consistently occurring for the past 9 years.

A more detailed history is unremarkable. She has no anterior vaginal wall tenderness. Her urinalysis is normal. However, her potassium test is strikingly positive.

Her story typifies the insidious progression of voiding frequency many patients feel (and accept) prior to the later onset of pain. Many patients feel that voiding frequency and pain are unrelated.

Lesson learned

Always request a voiding history from every pelvic pain patient.

For a second case, turn to page 99.

Table 1

Symptom triggers or exacerbations

- Intercourse (dyspareunia or ejaculatory pain affects 80%)
- Specific foods affect 50% (particularly citrus, bananas, spicy foods, tomatoes, chocolate, caffeine)
- Premenstrual or menstrual flares
- Bacterial cystitis
- Vaginal infection
- Stress

and induces substance P release. Increased sensory nerve density and C-fiber activation occur late and with dorsal root ganglion stimulation. Spinal cord involvement may also occur. Spinal cord involvement at the sacral micturition center (S2 to S4) may lead to neural cross-talk and other organs innervated by S2 to S4 (pelvic floor, vagina, rectum) may become symptomatic. Central sensitization may also be a factor in allodynia.

An alternate theory is that primary neurogenic inflammation occurs. There is no consistent evidence that IC/PBS is infectious or caused by an infection.

Clinical presentation

Patients generally present with chronic symptoms of:

- urinary urgency,
- frequency,
- nocturia and
- pelvic pain or discomfort.

The pelvic pain may be localized to the suprapubic area, lower quadrants, vagina, scrotum, perineum and lower back. Rarely, patients describe pelvic pain radiating into their medial thighs.



Dr. Teichman is an Associate Professor, Department of Urologic Sciences, University of British Columbia and Staff, Division of Urology, St. Paul's Hospital, Vancouver, British Columbia.

In the early phase of the disease, patients typically describe “pressure,” or “discomfort” rather than pain. In one study, the median duration from initial onset of voiding frequency to pelvic pain onset was two years (see Susan’s case).

In severe cases, patients often report:

- chronic sleep deprivation from nocturia and pain,
- limiting their daily chores to places where there is ready access to toilet facilities,
- difficulty working due to need for frequent access to toilet facilities,
- avoiding intercourse due to pain and
- frustration with their healthcare providers that they perceive have “failed” them.

Suicidal ideation occurs in up to 20%.

Findings during a typical physical exam are:

- a normal or dysphoric mood,
- suprapubic tenderness and
- bladder neck tenderness on vaginal exam.

Diagnosis

The history should elicit voiding frequency, nocturia, subjective sense of urinary urgency after voiding, the presence of pelvic pain (discomfort or pressure) if a patient forestalls micturition, dyspareunia (in a woman) and any triggers listed in Table 1.

Multiple conditions may produce similar symptoms of urgency, frequency, nocturia and pain, including several conditions that should be elicited: bacterial cystitis, bladder cancer (especially carcinoma *in situ*), urethral diverticulum, active genital herpes, bladder or distal ureteral stone, endometriosis, overactive bladder and irritable bowel syndrome. In IC/PBS, the clinician typically elicits:

- Absence of documented urinary infection while symptomatic
- Lack of symptom response to antibiotics
- Lack of urinary incontinence
- Lack of response to antimuscarinic agents

- No gross or microscopic hematuria
- Negative laparoscopy findings (no evidence of endometriosis)

Diagnostic criteria

Since 2003, there have been at least three international consensus conferences to adopt diagnostic criteria. To date, all conferences agree that diagnosis is largely clinical and requires excluding other conditions. There is currently no definitive diagnostic test that is widely accepted. However, several tests to rule out other conditions are routinely ordered:

- Urinalysis (often normal, although pyuria and microhematuria is seen in up to 20%)
- Urine culture (small voided volume may make clean catch technique difficult)

Other tests are considered optional:

- Urine cytology (a positive cytology implies high grade bladder cancer)
- Cystoscopy (should be done in any patient where bladder cancer is a risk)
- Voiding and intake diary (frequent, small voided volumes with no incontinence are typical)
- Validated questionnaires (interstitial cystitis symptom and problem indices, pelvic pain and frequency [PUF] questionnaire)
- Potassium test (controversial test, but positive in 66% to 92% of patients, see Susan's case)
- Lidocaine challenge
- Cystoscopy and hydrodistension under anesthesia

Cystoscopy

When the disease was codified in 1916 by Hunner, all patients had a pathognomic bladder ulcer found at cystoscopy, termed a "Hunner's ulcer." Most modern series show that Hunner's ulcers occur in < 7% of IC/PBS cases. Even the use of cystoscopy and hydrodistension has been challenged. A large National Institutes of Health sponsored trial found

Lucy's case

Lucy, 37, is referred for recurrent bacterial cystitis. Her "infections" began 18 months earlier, although she has noted nocturia 2-3 times for about 5 years and has voided every hour to 90 minutes during the day. Lucy believes she has an infection whenever she feels "burning" and "pain" in the suprapubic and urethral regions.

Triggers

Lucy notes premenstrual flares but denies food triggers. She reports dyspareunia and senses a "deep" pain near the suprapubic area.

Previously, she responded to antibiotics but does so no longer. She received a trial of tolterodine 4 years earlier with no relief of her voiding frequency and discontinued use due to dry mouth.

Examination

She has a moderately tender bladder neck and mild levator ani tenderness. A voiding diary showed no incontinence with frequent, small voided volumes (approximately 80 cc-100 cc every one hour to 90 minutes). Multiple urinalyses show 0-2 white blood cells. Multiple urine cultures show either no growth or low titers of *Staphylococcus epidermidis* or lactobacillus species. Cystoscopy was normal, other than reproducing her suprapubic pain with approximately 100 cc filling.

Lucy is given intravesical instillations of lidocaine, heparin and bicarbonate, which gives her 80% pain relief and resolves her dyspareunia. She is started on pentosan and hydroxyzine. At 6 months follow-up, her voiding frequency is every 2 hours, she has nocturia once and rarely has any pain, claiming when it does occur, "the pain is mild."

that only 60% of patients satisfied "traditional" cystoscopic criteria. A prospective study showed that the traditional cystoscopic findings of submucosal petechial hemorrhages ("glomerulations") occurs in normal and IC/PBS patients with equal frequency. In short, cystoscopic criteria are not reliable for diagnostic confirmation but helps to exclude bladder cancer.

Table 2

Common misdiagnoses

- Recurrent bacterial cystitis (see Lucy's case)
- Overactive bladder
- Endometriosis
- Chronic pelvic pain syndrome (or chronic prostatitis)
- Urethral syndrome (historical term that usually implies early phase interstitial cystitis/painful bladder syndrome [IC/PBS])
- Urethral stenosis (majority of women with "urethral stenosis" have normal caliber urethra)

Common misdiagnoses

Because of the many non-specific findings and lack of a definitive diagnostic test, patients are commonly misdiagnosed (Table 2).

A lack of response to treatments directed at any of these conditions should prompt consideration of possible IC/PBS as a diagnosis.

Management

Patient education is important. Many patients are reassured that they have a genuine condition causing their symptoms. Conversely, some patients are distressed that they have a chronic condition with no known cure. It is important to inform patients that their symptoms may be controlled with long-term therapy, in much the same way hypertension or diabetes mellitus are controlled, but not cured. A good patient education website is www.ichelp.org.

Specific management options (see Lucy's case) are listed in Table 3.

Pentosan

Patient counselling is important in order to achieve medication compliance. Pentosan typically requires six months of administration prior to the onset of improvement. Up to 70% of patients will improve

Table 3

Specific management options

- Dietary measures to reduce food triggers
- Use of calcium glycerophosphate prior to known food triggers
- Pentosan polysulfate, 100 mg p.o. t.i.d.
- Antihistamine: 25 mg of hydroxyzine p.o. q.h.s. or 20 mg of cetirizine p.o. q.h.s.
- Low-dose amitriptyline, 25 mg p.o. q.h.s.
- Cystoscopy and hydrodistension under anesthesia

with long-term pentosan therapy. Pentosan has multiple mechanisms of action, but is thought to replenish the bladder mucin coating. Side-effects occur in up to 8% of patients. GI side-effects (including diarrhea) are dose dependent. Alopecia occurs in up to 4% of patients and many patients are reluctant to initiate therapy once they are aware of the consequences. It is worthwhile to discuss with patients that alopecia here typically means more strands of hair fall out compared to normal when they comb or brush their hair, but "baldness like chemotherapy" is rare and their hair will grow back even on medication.

Antihistamines

Antihistamines often produce drowsiness and difficulty concentrating, side-effects that abate after drug tolerance occurs, typically after three weeks. Pentosan and hydroxyzine are synergistic.

Amitriptyline

Amitriptyline is used off-label. Inform patients that although it is an antidepressant drug at a much higher dosage, at a low dose (25 mg to 50 mg) it is used for chronic pain. Otherwise, patients may read the pharmacy printout, "your physician has diagnosed you with depression." Without understanding the reason for using amitriptyline off-label, some patients become angry when they feel their symptoms are being dismissed as if they are "crazy" and refuse

Table 4

Associated conditions

- Vulvodynia
- Endometriosis
- Pelvic floor dysfunction
- Fibromyalgia
- Irritable bowel syndrome

therapy. The extra time to educate patients on the rationale for the use of off-label medication gains their compliance.

Bladder instillations

Bladder instillations (see below) with alkalinized lidocaine, with or without heparin, may reduce the need for amitriptyline. Although efficacy has not been demonstrated in properly conducted trials, some patients find stress reduction techniques, such as yoga or pelvic floor physiotherapy, beneficial. Limited reports of S3 neurostimulation show promise in selected patients.

Several medications have been used as bladder instillations:

- Alkalinized lidocaine
- Alkalinized lidocaine with heparin
- Heparin
- Pentosan
- Chondroitin sulfate
- Dimethyl sulfoxide (with or without heparin, bicarbonate and corticosteroid)

Catheter technique seems important as many patients have severe urethral tenderness. A 10 Fr. hydrophilic catheter is recommended.

Narcotics

In severe refractory pain, narcotics may be used but may also exacerbate visceral pain. It may be prudent to have patients sign narcotic contracts, or defer narcotic prescriptions to a pain management specialist. Off-label use of high dose gabapentin (900 mg p.o. t.i.d.) may be helpful, although side-effects (*i.e.*, sedation, nightmares) are problematic.

Take-home message

- IC/PBS diagnosis requires a high index of suspicion
- Consider IC/PBS in patients who have failed therapies for recurrent bacterial cystitis, overactive bladder, chronic prostatitis and endometriosis
- Make sure patient is not at risk for bladder cancer
- Spend time with a patient to educate them on the condition and give them patient education websites (www.ichelp.org)
- Discuss with patients the rationale for multimodal therapy (*e.g.*, pentosan, off-label antihistamine, off-label amitriptyline)
- Set realistic expectations that response may take ≥ 6 months

Cystectomy

Cystectomy is rarely indicated and patients undergoing cystectomy for refractory pain should be counselled that their pain is unlikely to improve.

Associated conditions

IC/PBS patients have higher than expected incidence of concomitant diagnoses (Table 4).

It is thought that chronic pain stimulation and neural upregulation of the sacral spinal cord produces neural cross-talk, central sensitization and other efferent hyperstimulation of S2 to S4. A multi-disciplinary approach with urology, gynecology, gastroenterology and physical therapy may be helpful.

