PELVIC FLOOR DYSFUNCTION

Interstitial cystitis/bladder pain syndrome is difficult to diagnose. Here, updated guidelines on recognition, with tools to help the cause, and data on promising secondary treatments.

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The authors report no financial relationships relevant to this article.

IN THIS ARTICLE

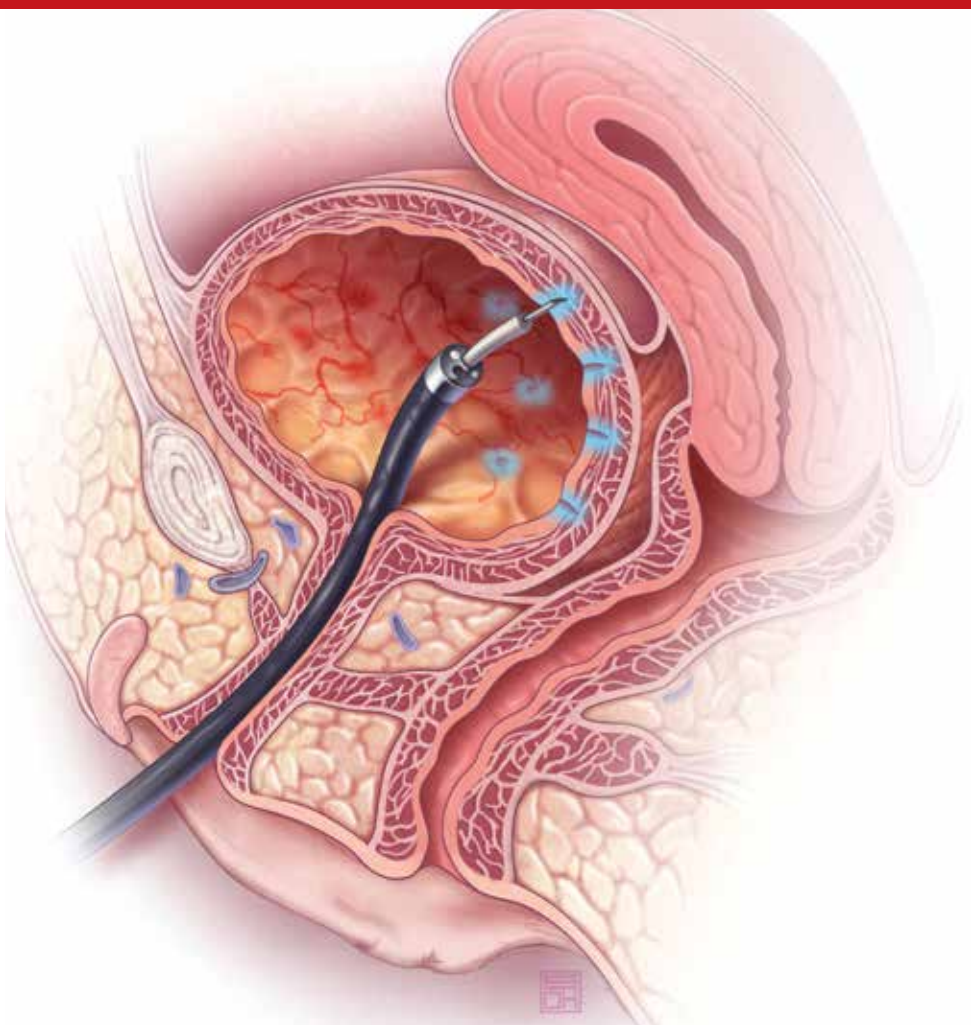
Interstitial cystitis (IC) is a debilitating disease that presents with a constellation of symptoms, including pain, urinary urgency, frequency, nocturia, and small voided volumes in the absence of other identifiable etiologies.[1] The overall prevalence of IC among US women is between 2.7% and 6.5%—affecting approximately 3.3 to 7.9 million women[2]—and it results in substantial costs[1,3] and impairments in health-related quality of life.[4] Unfortunately, there is a lack of consensus on the pathophysiology and etiology of this prevalent and costly disorder. Thus, therapies are often empiric, with limited evidence and variable levels of improvement.[5]

There has been no clear evidence that bladder inflammation (cystitis) is involved in the etiology or pathophysiology of the condition. As a result, there has been a movement to rename it "bladder pain syndrome." Current literature refers to the spectrum of symptoms as interstitial cystitis/bladder pain syndrome (IC/BPS).

Currently, the American Urological Association (AUA) defines IC/BPS as an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of infection or other identifiable causes.[6] This is still a broad, clinical diagnosis that has significant overlap with other pain syndromes but allows for treatment to begin after a relatively short symptomatic period.[7] Because gynecologists are frequently the main care provider for women, understanding the diagnosis and treatment options for IC/BPS is important to avoid delayed treatment in a difficult to diagnose population.

Recently, the AUA published an amendment to their 2011 management guidelines to provide direction to clinicians and patients regarding how to recognize IC/BPS, conduct valid diagnostic testing, and approach treatment with the goals of maximizing symptom control and patient quality of life.[7]

In this article, we review the AUA diagnostic and treatment algorithms and the results of recently published randomized trials comparing the efficacy of various treatment modalities for IC/BPS, including pentosoan polysulfate sodium (PPS; Elmiron, Janssen Pharmaceuticals, Titusville, New Jersey) and botulinum toxin (Botox, Allergan, Irvine, California) with hydrodistension.



Although more data are needed, short-term study results indicate that botulinum toxin-A injection into the bladder improves pain and bladder capacity in patients with interstitial cystitis/bladder pain syndrome that is refractory to conventional treatment.

Evaluation and treatment algorithms for IC/BPS: AUA guidelines

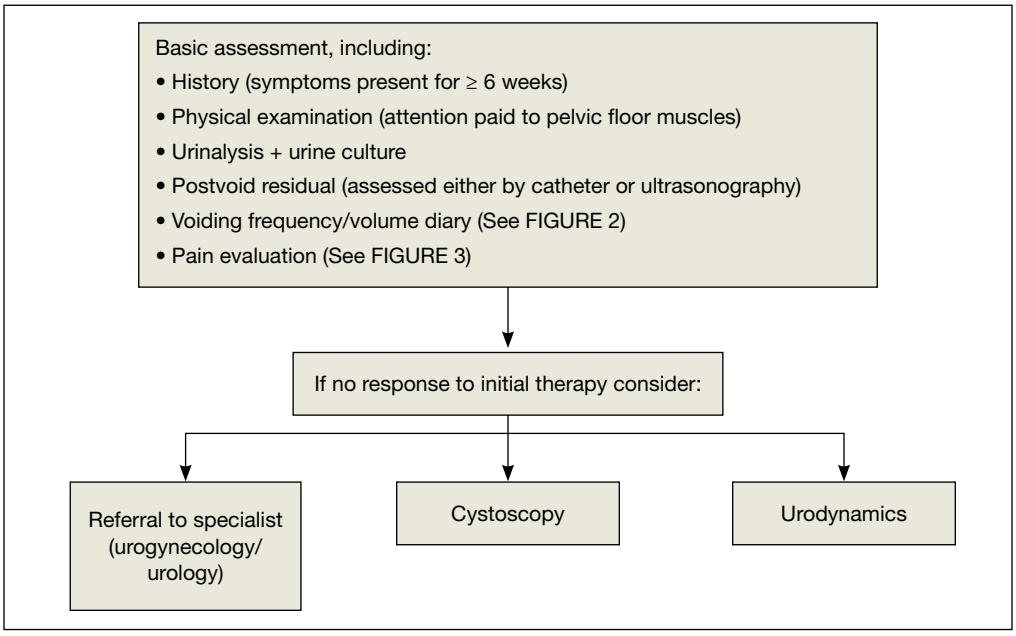
Hanno PM, Erickson D, Moldwin R, Faraday MM; American Urological Association. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol. 2015;193(5):1545–1553.

The diagnosis of IC/BPS can be challenging due to a wide spectrum of symptoms, physical examination findings, and clinical test responses. The AUA developed its diagnostic and treatment guidelines mostly based on expert opinion, but they do provide a framework to help clinicians determine whether or not treatment for IC/BPS is warranted. The primary principles for evaluation are presented in **FIGURE 1,** page 46.[7,8]

It is important to establish baseline voiding symptoms and pain levels with objective, validated instruments, including a voiding diary (**FIGURE 2,** page 46)[9] and such patient questionnaires as the O'Leary Sant Interstitial Cystitis Index (ICSI; **FIGURE 3,** page 47).[10] Characteristic IC/BPS voiding frequency is 10 or more times per day (to relieve pain, not to relieve a fear of wetting, which would be expected in a patient with overactive bladder).[8] The ICSI questionnaire should be used primarily to establish baseline

ILLUSTRATION: STEVE OH FOR OBG MANAGEMENT

FIGURE 1 AUA guidelines for diagnosing IC/BPS[7,8]



symptoms, not as a diagnostic tool. A score higher than 8 has been used as inclusion criteria for therapeutic trials, however.[11]

It is unnecessary to primarily perform cystoscopy or urodynamics, as there are no agreed-upon diagnostic criteria for these modalities for IC/BPS. They may be considered, however, if the patient does not respond to first- and second-line therapies. Additionally, potassium sensitivity testing is painful and, in view of the paucity of benefits, the risk/benefit ratio is too high to recommend for clinical care.

FAST TRACK

Ruling out urinary tract infection is a vital step in assessing patients for IC/BPS

Treatment: Conservative first

The treatment for IC/BPS should start with more conservative therapy (including behavioral management and physical therapy). If symptom control is inadequate, other modalities should be employed. Behavioral modifications should include:

- local heat/cold over the bladder and perineum
- avoidance of foods and fluids that are known to be common irritants (such as coffee and citrus)
- trial of elimination diet
- bladder training with urge suppression techniques.

As noted in FIGURE 1, first make sure that patients do not have a urinary tract infection. If culture results are negative and other criteria fit, consider the diagnosis of IC/BPS and offer therapies as outlined in the treatment algorithm (**FIGURE 4**).[7] Repeated treatment for negative results of urine cultures in patients with frequency, urgency, and bladder pain can lead to unnecessary antibiotics and delayed treatment of IC/BPS.

Treatments in FIGURE 4 are ordered from most to least conservative, and initial treatment depends on symptom severity, clinician judgment, and patient preference. If at any point in the patient's care the diagnosis

FIGURE 2 Voiding diary[9]

Date	Time	Measured amount of void	Did your have urine leakage, yes or no?	Severity of pain before voiding (0–10)

is questioned or treatments have been ineffective, referral to a specialist, including urogynecology or urology, may be appropriate.

Managing pain

Pain management is an important component at all levels of therapy, and pharmacologic pain management principles for IC/BPS should be similar to those for management of other chronic pain states. Options primarily include nonsteroidal anti-inflammatory drugs (NSAIDs) and urinary analgesics (pyridium). The use of narcotics presents the risks of tolerance and dependence. If their use is necessary, all narcotic prescriptions must come from a single source and should be used as a component of multimodality therapy to minimize narcotic use.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

IC/BPS should be considered in women who present with urgency, frequency, bladder pain, small voided volumes, and negative urine culture in order to avoid delayed diagnosis and treatment.

FIGURE 3 O'Leary Sant Interstitial Cystitis Index[10]

1. How often have you felt the strong need to urinate with little or no warning?
   - ❑ Not at all
   - ❑ Less than 1 time in 5
   - ❑ Less than half the time
   - ❑ About half the time
   - ❑ More than half the time
   - ❑ Almost always
2. Have you had to urinate less than 2 hours after you finished urinating?
   - ❑ Not at all
   - ❑ Less than 1 time in 5
   - ❑ Less than half the time
   - ❑ About half the time
   - ❑ More than half the time
   - ❑ Almost always
3. How often did you most typically get up at night to urinate?
   - ❑ Not at all
   - ❑ Once per night
   - ❑ 2 times per night
   - ❑ 3 times per night
   - ❑ 4 times per night
   - ❑ 5 or more times per night
4. Have you ever experienced pain or burning in your bladder?
   - ❑ Not at all
   - ❑ A few times
   - ❑ Fairly often
   - ❑ Usually
   - ❑ Almost always

FIGURE 4 Treatment algorithm for IC/BPS[7]

First-line treatments	• General relaxation/stress management • Pain management - primarily NSAIDs and urinary analgesics (ie, pyridium) • Patient education • Self-care/behavioral modification
Second-line treatments	• Appropriate manual physical therapy techniques and avoidance of Kegel exercises • Oral: amitriptyline, cimetidine, hydroxyzine, pentosan polysulfate (Elmiron) • Intravesical: Dimethyl sulfoxide, heparin, lidocaine
Third-line treatments	• Cystoscopy under anesthesia with hydrodistension • Pain management with care to minimize narcotic use • Treatment of Hunner lesions if found
Fourth-line treatments	• Intradetrusor botulinum toxin A • Neuromodulation • Pain management
Fifth-line treatments	• Cyclosporine A • Pain management

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Oral PPS is FDA approved for relief of bladder pain associated with IC/BPS

Nickel JC, Herschorn S, Whitmore KE, et al. Pentosan polysulfate sodium for treatment of interstitial cystitis/bladder pain syndrome: insights from a randomized, double-blind, placebo-controlled study. J Urol. 2015;193(3):857–862.

FAST TRACK

Although conservative options should be first-line therapy, consider second-line or multimodal treatment with oral PPS

In this multicenter, double-blind, randomized, placebo-controlled study, investigators evaluated the efficacy and tolerability of a decreased dose of PPS (100 mg daily) versus the current established dose (100 mg TID) in patients with IC/BPS.

Details of the study

A total of 368 participants (85.6% of whom were women) aged 18 to 78 years with questionnaire-diagnosed IC/BPS and no urinary tract infection for at least 6 months before screening were randomly assigned by a computer-generated randomization schedule in a 1:1:1 ratio to PPS 100 mg 3 times per day (FDA-approved dose), PPS 100 mg daily, or matching placebo. Safety assessments were performed at prespecified time points over 24 weeks. The primary efficacy endpoint was defined as a 30% reduction in ICSI total score. The study was powered to detect a 15% difference in the proportion of responders if there were 200 patients per treatment arm.

There was an interim analysis performed due to slow recruitment that led to early study termination, but all initially enrolled participants were included in the intention to treat analysis. Of the 368 patients, 162 (44%) withdrew from the study, with equal numbers in each arm. The treatment response rate was 40.7% for patients assigned to placebo, 39.8% for patients treated with PPS 100 mg once daily, and 42.6% for those treated with PPS 100 mg 3 times per day. These rates were not significantly different between groups.

Adverse events were equal between groups and included bladder pain, nausea, headache, and exacerbation of IC/BPS symptoms. Gastrointestinal events led to the withdrawal of 10% of participants in the placebo group and 11% to 13% in the PPS groups. No clinically meaningful change was noted in laboratory tests, vital signs, or physical examination.

Study expands data on oral PPS

This was a multicenter, double-blind, randomized study of adults diagnosed with IC/BPS based on symptoms. Earlier studies of PPS efficacy, which provided the data for FDA approval of oral PPS, employed strict cystoscopic criteria for IC/BPS diagnosis.[12] Although the study was terminated early due to low recruitment and there was a high drop-out rate, there still was a large number of patients in each treatment arm. Furthermore, although the responder rate did not differ between groups, this may have been due to lack of power at the recruited numbers.

This study is an important glimpse into the use of oral PPS in a broad population of patients with bladder pain, urgency, frequency, and nocturia. It further emphasizes the need for improved diagnostic criteria to provide individualized, efficacious treatment for patients with IC/BPS.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Clinicians should continue to recommend conservative treatments for IC/BPS, including behavioral modifications, stress management, and manual physical therapy techniques prior to initiation of medications. Oral PPS may still be considered as a possible second-line therapy or as multimodal therapy for patients with IC/BPS.

Botulinum toxin-A with hydrodistention shows short-term efficacy as advanced therapy

Kuo HC, Jiang YH, Tsai YC, Kuo YC. Intravesical botulinum toxin-A injections reduce bladder pain of interstitial cystitis/bladder pain syndrome refractory to conventional treatment—A prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial [published online ahead of print April 24, 2015]. Neurourol Urodyn. doi: 10.1002/nau.22760.

In this multicenter, randomized, double-blind, placebo-controlled trial in patients with IC/BPS refractory to conventional treatment, investigators evaluated the efficacy and tolerability of hydrodistention plus suburothelial injections of onabotulinum toxin A (BoNT-A; Botox).

Details of the study

Sixty patients (86.7% female) aged 20 to 82 who had failed 6 months of conventional treatment for IC/BPS were enrolled. In this particular study, diagnosis was established based on symptoms and glomerulations on cystoscopy during hydrodistension. Patients were included if they had failed 2 prior treatment modalities for IC/BPS. Participants completed a baseline voiding diary, ICSI questionnaire, and visual analogue scale (VAS) for patient self-reported pain. All patients also received video-urodynamic testing prior to therapy.

Eligible patients were randomly assigned in a 2:1 ratio to either receive 100 units of intradetrusor BoNT-A or injection with normal saline immediately following cystoscopic hydrodistension under general anesthesia. All patients received oral antibiotics for 7 days after therapy. Follow up was performed at 2, 4, and 8 weeks after treatment, with additional voiding diaries, symptom questionnaires, and VAS scores collected. At 8 weeks, a urodynamic study was performed.

The primary endpoint was reduction of pain on VAS score at the 8-week follow-up. With 60 participants, researchers had 85% power to detect a difference of 1.5 points on the VAS score between groups. Secondary outcomes included a composite global response assessment (GRA), ICSI scores, voiding diary parameters, and urodynamic findings.

No differences were noted in baseline measurements between the 2 groups except for VAS score, which was higher at baseline in the BoNT-A group ($P = .056$).

At 8 weeks, the BoNT-A group showed a significantly greater reduction than the saline group in the mean (SD) pain score (-2.6 [2.8] vs -0.9 [2.2], respectively; $P = .021$). Mean (SD) cystometric bladder capacity also increased significantly in the BoNT-A versus saline group (67.8 [164.3] vs -45.4 [138.5]; $P = .020$). Other secondary outcomes, including ICSI score, GRA, and functional bladder capacity as noted on voiding diary, improved significantly from baseline in both groups at 8 weeks.

Adverse events included dysuria, hematuria, urinary tract infection, and retention. There was a higher rate of dysuria noted in the BoNT-A compared with the saline group (40% vs 5%, respectively) at 8 weeks. There was only 1 urinary tract infection in each group, and only 1 patient had retention in the BoNT-A group, although study criteria for retention or need for self-catheterization was not provided.

Short-term efficacy, but more data needed

This was a well-designed trial evaluating the addition of BoNT-A to hydrodistension in a population of patients with refractory IC/BPS. The participants were mostly women

FAST TRACK

Pain and bladder capacity improved at 8 weeks in patients treated with BoNT-A versus saline injection

and relevant to a gynecologic population. When utilized for patients with overactive bladder, 100 units of intradetrusor injections of BoNT-A has rates of urinary tract infection and retention of approximately 33% and 5%, respectively.[13] Patients with IC/BPS undergoing this procedure should be counseled about these possible adverse effects. Furthermore, with a relatively short 8-week follow-up period, this study cannot be used to make any comments on long-term efficacy of this procedure.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although BoNT-A is not currently FDA approved for the treatment of IC/BPS, it is listed as fourth-line therapy for women with this condition. If initial therapies fail, it is appropriate to refer patients to a specialist, including a urogynecologist or urologist, where they may discuss BoNT-A therapy with or without hydrodistension.

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