

The Evaluation and Management of Interstitial Cystitis/Bladder Pain Syndrome

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Abstract

Interstitial cystitis or bladder pain syndrome is a frustrating symptom complex for both the patient and the clinician. Classic Hunner's lesion interstitial cystitis is clearly a bladder disease and treating the bladder improves symptoms. Non-Hunner's lesion interstitial cystitis or bladder pain syndrome likely has multiple aetiologies and in many cases the bladder is an innocent bystander in a bigger pelvic process. For many years, non-Hunner's lesion interstitial cystitis has been treated with bladder-directed therapies, with poor overall outcomes. This literature review article will review the diagnosis and management of interstitial cystitis and encourage the reader to look beyond the bladder to achieve symptom relief.

INTRODUCTION

Since interstitial cystitis was originally defined in 1887,¹ the nomenclature has shifted following further discoveries about the disease and its association with other issues outside the bladder. There is no definitive marker to diagnose interstitial cystitis, or bladder pain syndrome (IC/BPS), but diagnosis is symptom driven. The authors adopt the definition of IC/BPS from the Society for Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU), which states that IC/BPS is: "an unpleasant sensation (pain, pressure, and/or discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of

>6 weeks duration, in the absence of infection or other identifiable causes."² The authors further subcategorise patients into non-Hunner's lesions (HL) interstitial cystitis (N-HLIC/BPS) and HLIC. HLIC is a bladder disease with relatively straightforward treatment. N-HLIC/BPS is a syndrome requiring a multimodal approach that is tailored to individual patients.

Over time, the diagnosis of IC/BPS was oversimplified and patients that feel pain from their umbilicus to their knees were labelled with IC based on a validated questionnaire or a potassium sensitivity test. Unfortunately, this simplification failed to confirm whether the bladder was driving the symptoms. Many of these patients would see multiple healthcare

professionals and trial numerous treatments without benefit.³ It is now clear that clinicians must be astute, evaluate triggers that can impact the patient's symptoms, and use a multimodal approach to improve quality of life.

COMPREHENSIVE EVALUATION

A careful history and physical exam are critical in patients with symptoms of IC/BPS. These patients commonly have systemic comorbidities or symptom complexes, such as depression, fibromyalgia, chronic fatigue syndrome, Sjögren's syndrome, endometriosis, inflammatory bowel disease, migraines, and temporomandibular joint disorder.⁴ Furthermore, a systemic disease manifesting in the bladder may present as IC/BPS.

IC/BPS patients often present with urinary urgency and frequency and pelvic discomfort. Pelvic pain is usually worse with bladder filling and is relieved following voiding. Multiple pain triggers are found in patients labelled with IC/BPS, making treatment difficult. In a study of 193 IC/BPS patients, 73% reported pain sites outside the bladder or pelvic area, with those patients also experiencing more severe pain and depression.⁵ Evaluating the pelvic floor muscles during a pelvic exam is crucial. Pelvic floor dysfunction (PFD) and myofascial pain are found in up to 87% of patients diagnosed with IC/BPS.⁶ A study comparing MRI of women with IC/BPS to age-matched controls identified hypertonicity of the pelvic floor.⁷ A tight pelvic floor can refer pain to the pelvis, vulva, rectum, or perineum and result in obstructed voiding, leading to urinary hesitancy, urgency, and frequency.³

Pudendal neuropathy can be associated with symptoms of IC/BPS. Clinicians can identify IC/BPS by using the Nantes criteria: pain in the anatomical territory of the pudendal nerve, worsened by sitting, not causing patient to be woken at night, no objective sensory loss, and positive anaesthetic pudendal nerve block.⁸ Vulvodynia is the fourth most common IC-associated syndrome, affecting up to 48% of IC/BPS patients.⁹ Vulvodynia is a superficial pain, often localised to the opening of the vagina, triggered during penetration or with light touch.

Sexual dysfunction occurs frequently in IC/BPS patients and decreases their quality of

life.¹⁰ Patients should be specifically questioned about dyspareunia, vaginal dryness, orgasmic dysfunction, and sexual desire. Dyspareunia is often caused by PFD, but frequently vestibulodynia contributes to the condition.

Furthermore, anticipation of pain during intercourse increases pelvic floor tone, creating a pain cycle that is difficult to break. A full social history, including previous abuse (emotional, physical, or sexual), should be recorded. Many patients with IC/BPS have a history of abuse, which may be associated with more pain and fewer voiding problems.⁴

Gastrointestinal symptoms should be evaluated and treated. Bowel complaints are often associated with lower urinary tract symptoms, likely secondary to neural crosstalk of the pelvic organs.¹¹ Chronic constipation is a common issue in patients with IC/BPS, which may be caused by their underlying PFD or secondary to medications, such as opioids or antimuscarinics.³

Voiding diaries can be filled out by patients to quantify urinary symptoms.² Validated questionnaires are commonly used to quantify symptoms and assess changes during treatment, but questionnaires should not be used alone for the diagnosis of IC/BPS. The Interstitial Cystitis Symptom Index and Problem Index can show changes in symptoms over time.¹² Urodynamic studies can aid the diagnosis of patients with bladder outlet obstruction.

Urinalysis and urine culture must be checked to screen for infection or microscopic haematuria. Haematuria increases the suspicion of HLIC or another urological pathology and should prompt cystoscopy to visually evaluate the bladder and urine cytology to screen for cancer. If HL are identified, treatment should focus on these lesions first. Urothelial cancer can be a source of irritative voiding symptoms. A study of 600 patients treated for IC/BPS found that 1% of patients had urothelial cancer as the source of their irritative voiding symptoms, which resolved after treating the malignancy.¹³ Furthermore, patients with IC/BPS may be at higher risk of subsequently developing urothelial cancer according to a recent nationwide population-based study.¹⁴

NON-HUNNER'S LESION INTERSTITIAL CYSTITIS OR BLADDER PAIN SYNDROME

Treatment options are variable for IC/BPS but should focus on identified pain triggers, such as PFD. Given the complexity of IC/BPS, a multidisciplinary clinic is the most effective way to treat this patient population. The authors lead a clinic that involves urologists, gynaecologists, pelvic floor physical therapists, colorectal surgeons, integrative specialists, and pain psychologists who communicate together to tailor a multimodal therapy for each individual. A multidisciplinary clinic is extremely successful in managing IC/BPS patients, with very high patient satisfaction.³

Behavioural modifications and stress management

All patients should be offered first-line therapy with behaviour modifications, including an elimination diet to identify any food triggers. Most patients will report that stress flares their symptoms. Stress management is a crucial component to the multidisciplinary care of IC/BPS patients. Pain psychologists can address past and present life stressors and provide coping strategies to the chronic pain patient. Cognitive behavioural therapy can help patients develop coping strategies. Interpersonal therapy may help patients work through intimacy related issues. Emotionally expressive therapy may help address painful experiences prior to onset of their symptoms.⁴

Complementary therapies, including acupuncture, massage, guided imagery, and reiki, focus on the mind-body connection and may have a role in the treatment of IC/BPS. A recent systematic review of randomised control trials investigating acupuncture treatment of chronic pelvic pain in women found that acupuncture in combination with conventional treatment significantly reduced pelvic pain.¹⁵ Although there is a lack of robust clinical trials investigating complementary therapies, it is the authors' experience that they can be very helpful in managing symptoms of IC/BPS.

Oral and Intravesical therapies

The American Urological Association (AUA) guidelines detail a list of optional second-line

treatments for IC/BPS, including oral medications and intravesical therapies.² In the authors' experience, these may only be effective in a subset of patients with true bladder centric symptoms without HLIC.

Pentosan polysulfate (PPS) is a U.S. Food and Drug Administration (FDA) approved and is believed to help repair damage to the glycosaminoglycan layer of the bladder. In 1987, a randomised, multicentre, double-blinded, placebo-controlled study reported significant success with PPS.¹⁶ Over time, its efficacy has been questioned and a recent dose-ranging, placebo-controlled study revealed no significant difference between groups.¹⁷ In addition, there is recent concern about the development of pigmentary maculopathy following prolonged use of PPS.¹⁸ In the authors' opinion, given its limited efficacy, cost, and potential complications, PPS should be used with caution and with clear informed consent.

Cimetidine and hydroxyzine are thought to affect mast cell degranulation in the bladder wall. A prospective, randomised, placebo-controlled study of cimetidine was very effective in relieving symptoms.¹⁹ A subsequent multicentre randomised controlled trial compared hydroxyzine with oral PPS and reported that neither provided benefit to patients with IC.²⁰ Amitriptyline in combination with education and behavioural modification did not significantly improve IC/BPS symptoms compared to placebo, but with dose-escalation to ≥ 50 mg there was a significantly higher response rate.²¹ Despite lack of strong evidence, trials of cimetidine, hydroxyzine, and amitriptyline can be offered, but should be discontinued if there is lack of improvement.

Patients with symptoms of IC/BPS often use over the counter 'nutraceuticals', with ingredients such as aloe vera, quercetin, and calcium glycerophosphate. Although there may be benefits from some of these ingredients, the data are sparse. The authors often partner with naturopathic physicians to help guide patients on their supplement choices.

Intravesical dimethyl sulfoxide (DMSO) therapy is FDA approved and believed to provide anti-inflammatory, analgesic, and muscle relaxant properties. A literature review detailing

the impact of DMSO on IC/BPS revealed a lack of standardisation with short-term follow-up and suggested the importance of discovering potential biomarkers to subtype the precise patient for its use.²² Other therapy cocktails combine DMSO with heparin, lidocaine, sodium bicarbonate, intravesical PPS, chondroitin sulfate, and hyaluronic acid, and the guidelines recommend individualisation for each patient.²

Pelvic floor physical therapy

Pelvic floor physical therapy (PFPT) is a second-line treatment detailed in the AUA guidelines.² Physical therapists must be specially trained to perform intravaginal myofascial release; the therapy also involves the manipulation of the patient's external trunk and lower extremities. Treating the tenderness and tightness of the pelvic floor musculature can indirectly improve associated urinary, bowel, and sexual symptoms.⁴ The benefit of PFPT has been demonstrated in many studies, including a National Institutes of Health (NIH) sponsored trial that compared PFPT with internal pelvic muscle work against general therapeutic massage.²³⁻²⁶ In the authors' experience, most patients diagnosed with IC/BPS actually have PFD as the cause of their symptoms, and PFPT is a highly effective treatment pathway.

Trigger point injections

Trigger point injections (TPI) have been shown to improve pelvic pain. A study of 18 women showed that 72% had significant improvement of pain and 33% were pain free after their first TPI.²⁷ A cadaver study using a systematic standard template characterised the pelvic floor muscle injections and confirmed the ability to successfully deliver medications to the pelvic floor.²⁸ The authors use the aforementioned template with long-acting local anaesthetic for immediate relief and a corticosteroid for sustained relief. TPI are often used as an adjunct to PFPT. Most women tolerate a transvaginal approach in the office. Men with pelvic pain can have TPI carried out transrectally or through the perineum. One study of men with chronic pelvic pain syndrome reported improvement in about half of patients after TPI as an adjunct to PFPT.²⁹ Botulinum toxin is also being studied for injection into the pelvic floor for longer-term relief. Single

and repeat injections both show significant reduction in pelvic pain.³⁰ A study of 28 women with pelvic pain and IC/BPS or vulvodynia who underwent injection of 300 units of botulinum toxin reported improvement in 80% of patients at 24 weeks;³¹ however, further evaluation is warranted.

Pudendal nerve blocks

Patients with PFD commonly present with symptoms of pudendal neuralgia. Pudendal nerve blocks can be completed with or without trigger point injections. They can be carried out transvaginally or transgluteally. Improvement in pain after a pudendal nerve block suggests that the pudendal nerve is involved in the pain process. A series of pudendal nerve blocks with multidisciplinary treatments significantly improve patients' symptoms.³

Intravaginal medications

Local intravaginal medications, such as diazepam or baclofen, are used to manage IC/BPS symptoms. A study that evaluated treatment with vaginal diazepam reported 62% of patients demonstrated significant improvements in pain after one month.³² In a different study of women with hypertonic pelvic floor muscles on exam and electromyography reported no improvement in subjective outcomes or electromyography following vaginal diazepam versus placebo.³³ Vaginal diazepam has been reported in another study to significantly improve pain and pelvic floor function when used as an adjuvant therapy to PFPT and TPI.³⁴ Vulvodynia has been successfully treated with an analgesic cream containing baclofen and palmitoylethanolamide, an endogenous anti-inflammatory compound.³⁴

OnabotulinumtoxinA

The AUA guidelines list intravesical OnabotulinumtoxinA (Botox) injections as a fourth-line treatment for IC/BPS. Originally cited to relieve urgency and frequency, Botox may cause peripheral afferent desensitisation providing additional pain relief.³⁵ Literature reviews, including a recent meta-analysis, revealed that Botox consistently reduced morbidity, including a reduction in pelvic pain, urinary frequency, nocturia, and improved quality of life and bladder capacity.^{36,37} The authors offer intravesical Botox injections to relieve urgency and frequency but

only to patients who understand the risk of urinary retention.

Neuromodulation

Sacral neuromodulation for chronic pelvic pain is still considered experimental.³⁸ Sacral neuromodulation is FDA approved for the management of urge incontinence, faecal incontinence, and frequency-urgency syndrome, but it is not approved to treat pain caused by IC/BPS. Studies have shown sacral neuromodulation to be safe and efficacious over long treatment durations with the ability to alleviate pain and decrease narcotic medication use in refractory IC patients.³⁹⁻⁴¹ A meta-analysis of sacral neuromodulation for refractory IC patients reported a pooled overall success of 84% with improvement in pelvic pain, daytime frequency, nocturia, urgency, and average voiding volumes.⁴² Pudendal neuromodulation has shown excellent results for patients with N-HLIC/BPS and pudendal neuralgia.⁴³⁻⁴⁵ In a series of patients with pudendal pain, all had an improvement in pain, including six patients who had previously failed to respond to sacral neuromodulation.⁴⁴ A new implantable electrode with an external energy source (StimWave, Inc., Pompano Beach, Florida, USA) is approved for peripheral nerve pain, including action on the pudendal nerve. This allows clinicians to offer neuromodulation for patients with only pain and not voiding or bowel dysfunction.

Percutaneous tibial nerve stimulation has been shown to improve pelvic pain in medication-refractory patients. Specific studies for treating IC/BPS have reported conflicting results and further studies are needed.³⁸ Central, supraspinal modulation through brain stimulation may also benefit pelvic pain patients, specifically patients who have failed peripheral approaches, and has shown success in case reports, but additional studies are indicated.³⁸

HUNNER'S LESION INTERSTITIAL CYSTITIS

The presence of HL on cystoscopy is the key to distinguishing HLIC from N-HLIC/BPS. HL represent an inflamed vulnerable area of the bladder and appear as circumscribed, reddened

mucosal areas with small vessels radiating towards a central scar.⁴⁶ HLIC is rarer, representing roughly 10-15% of IC/BPS patients, and occurs through a separate disease process.³ A recent prospective trial of IC/BPS patients reported there is no distinct clinical phenotype to differentiate HLIC, suggesting that cystoscopy be conducted in all patients with IC/BPS to rule out HL.⁴⁷ HLIC patients are generally older, have a rapid onset of symptoms with more severe urinary frequency, and a decreased bladder capacity.⁴ HL may be more commonly found in male patients with IC/BPS.⁴⁸ HLIC patients have fewer comorbidities and less systemic involvement compared to N-HLIC/BPS.⁴⁹

First-line therapy

Dietary modification has been shown to reduce symptoms and improve quality of life within 3 months with continued efficacy for 1 year.⁵⁰ The specifically designed diet avoided tomatoes, spices, citrus, soybeans, and additional foodstuffs. In the author's experience, elimination diets are effective in a motivated patient, but are too cumbersome for most to adhere to. Diluting the toxins in the urine by increasing water intake can help patients with HLIC.

Cystoscopic treatment

AUA guidelines list hydrodistension (HD) as a third-line option for IC/BPS when other treatments have failed and recommend it be conducted under anaesthesia for <10 minutes with pressures around 60-80 cm H₂O.² Previously, HD was used to identify glomerulations that were thought to be pathognomonic for IC/BPS, but the presence or absence of glomerulations is nonspecific, so the only role of HD is to improve symptoms.² HD has been tried in up to 85% of patients with a diagnosis of IC/BPS.⁵¹ Although it is a popular intervention, there is weak evidence to support its effectiveness.⁵² In total, <20% of patients report excellent improvement after HD with mostly short-lived relief of <6 months.⁴

In the authors' practice, HD is performed to determine the anaesthetic bladder capacity as a prognostic variable and aid in electrocautery of HL, since the lesions split and crack, to define the true borders of the HL.⁴⁶ According to the guidelines, if HL are present, fulguration should be performed with laser or electrocautery.² The authors always perform a biopsy of a HL to rule

out carcinoma *in situ* and then use a roller ball on a resectoscope and rapidly fulgurate over the lesions to avoid a deep burn. Electrocautery has been shown to provide symptom improvement in many studies although the durability is variable. Many patients with fulguration alone will have recurrent symptomatic HL requiring repeat electrocautery.⁵³⁻⁵⁵ A long-term study of 76 patients who underwent a total of 214 electrocautery procedures for HL had significant improvement in pain, urgency, and frequency. Overall, 89.6% of patients noted some degree of symptom improvement, 56.3% noted a marked improvement, and 84.0% of patients reported electrocautery as the most beneficial treatment they received. The study also showed that there was no reduction in bladder capacity after single or multiple electrocautery treatments.⁵⁶ A retrospective review of patients who underwent their first HD with fulguration found that the extent of HL is associated with symptom severity and bladder capacity but did not predict the need for a repeat HD.⁵⁷

Injection of a corticosteroid into the HL at time of fulguration is an optional treatment according to AUA guidelines.² One study of HLIC patients who received a total dose of 400 mg of triamcinolone reported symptom improvement in 70% with an average duration of 7-12 months.⁵⁸ There are no substantial safety data for a 400 mg dose, so it is recommended to limit the total dose to 60 mg.²

Medical treatment

Cyclosporine A is an immunosuppressive agent used to suppress bladder inflammation in IC/BPS and is listed as a fifth-line treatment in the AUA guidelines.² Excellent outcomes have been reported for cyclosporine in IC/BPS, including superiority to PPS.⁵⁹⁻⁶¹ HLIC patients are more likely to benefit from cyclosporine.⁶² Following electrocautery, the authors routinely prescribe cyclosporine for patients with recurrent HL at a starting dose of 100 mg twice daily for 30 days followed by 100 mg once daily. The dose for IC/BPS is low, thus limiting toxicity, but monitoring blood pressure and renal function is necessary. A recent study monitored cyclosporine concentration in patients 2 hours after drug administration, creatinine, and blood pressure to effectively minimise toxicity. The cyclosporine concentration ranged widely, with no correlation

to treatment response, but was a useful tool to reduce the dose and minimise toxicity.⁶²

Reconstructive surgery

When all other therapies have failed, substitution cystoplasty or urinary diversion with or without cystectomy is an option according to the AUA guidelines.² Reconstructive surgery resulted in symptom resolution in 82% of patients with HLIC, but this surgery only benefited 23% of patients with N-HLIC/BPS.⁶³ A long-term, retrospective review of IC/BPS patients who underwent major surgery reported good symptom relief for those with disabling symptoms and that extended preoperative duration of symptoms may increase risk of persistent pain after surgery.⁶⁴ Another study found that augmentation with supratrigonal cystectomy significantly improved symptoms and increased bladder capacity in HLIC patients.⁶⁵ Reconstructive surgery can potentially benefit refractory HLIC patients; however, the patients should understand the risks of irreversible major surgery with associated lifelong changes and possibility of persistent pain.² An IC/BPS specialist should evaluate patients prior to considering surgery. According to the literature, the best response will be in patients with a small bladder capacity under anaesthesia and with an absence of neuropathic pain.² This treatment is not recommended for N-HLIC/BPS patients.

BIOMARKERS

No clear pathophysiologic explanation of IC/BPS has been determined, but some proposed mechanisms focus on the dysfunction of the bladder epithelium, extracellular matrix, and associated immune mediators. These cellular processes have been linked to specific chemical biomarkers in the urine, serum, and stool.^{66,67} More recently, proteomics of urine have identified a number of proteins associated with IC/BPS and a pattern of protein expression to differentiate patients with IC/BPS from asymptomatic controls.⁶⁸ To date, no biomarker has shown adequate sensitivity and specificity to provide diagnostic assistance yet, they offer the potential to differentiate between systemic and focal disorders or subclassify patients into specific phenotypes, which may allow for a more targeted treatment approach.

CONCLUSION

IC/BPS is a challenging symptom complex for the clinician to manage. Many patients are overwhelmed and burdened by the disease, especially after failing therapies directed at their bladders. HLIC is a bladder disease, responds to bladder directed therapy, and should be considered a separate disease from N-HLIC/BPS. A multidisciplinary approach is crucial for success in treating N-HLIC/BPS. It is critical to carefully phenotype these patients, identify pain triggers, and direct therapy towards these triggers. A

hypertonic pelvic floor is often overlooked during the evaluation of a patient with symptoms suggestive of IC/BPS. In the authors' opinion, identifying and treating PFD with physical therapy, trigger point injections, pudendal nerve blocks, integrative medicine treatments, psychological support, and neuromodulation offer the best success in the management of the refractory IC/BPS patient.

The bladder is often an innocent bystander in a bigger pelvic process. It is time to think beyond the bladder!

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