Therapeutic management of Interstitial Cystitis/Bladder Pain Syndrome in humans

Nissrine Nakib, MD
Assistant Professor and Director of Female Urology
University of Minnesota Urology Department, MN, USA

Definition:
The American Urological Association (AUA) agreed with the definition of interstitial cystitis/bladder pain syndrome (IC/BPS) proposed by the Society for Urodynamics and Female Urology.

“An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes”.

The AUA selected this definition as it reduces the risk of delaying treatment unlike other definitions that require a waiting period of 6 months or longer before treatment starts. For example, the European Society for the Study of IC/BPS (ESSIC) define IC/BPS as a condition with chronic (> 6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or frequency with or without cystoscopic abnormalities.

IC/BPS is essentially an umbrella term that covers a spectrum of pain and cystoscopic findings. There is a distinct type, namely the Hunner lesion, which is different from other categories in terms of histopathology, gene expression, and inflammation. This only comprises approximately 10% of patients who present with BPS.

Obviously, the variability in definitions by internationally recognized societies and plethora of non-specific symptoms and comorbidities complicate the diagnosis of the disease.

Symptoms:
Pain is the hallmark symptom of IC/BPS, including sensations of pressure and discomfort. This is typically in the suprapubic region related to bladder filling but pain throughout the pelvis—in the urethra, vulva, vagina, rectum—and in extragenital locations such as the lower abdomen and back have also been reported. Patients often describe worsening of their pain with the consumption of certain foods or drinks and describe the triggering of “Flare ups”. Increased voiding frequency is almost universal (92% of one population).

Although women are estimated to have IC ten times more often than men, there is evidence to suggest that the incidence is higher than previously observed. Clinical findings and symptoms in men mirror those of female patients. They may present with suprapubic tenderness, external (perineal) tenderness, and internal (levator muscle) tenderness or spasticity.

Causes:
IC/BPS is, in theory, a complex and multi-factorial disease. There are several hypotheses being investigated as causality of the disease such as urothelial barrier permeability, glycosaminoglycans, mast cell, microbial infections, and neuroendocrine pathways.

Epidemiology:
Due to the inconsistency in definition, the prevalence of IC/BPS follows suit in variance. However, Over the years, the incidence of IC/BPS has been obtained through various surveys, clinical studies, questionnaires and self-reported studies, and is estimated to be 2.7%–6.5% of women aged ≥ 18 years (i.e. 3.3–7.9 million), whereas in men, the RAND Interstitial Cystitis Epidemiology study found it to be 1.9%–4.2%.

Many more may still be undiagnosed

IC/BPS is more prevalent in women above 40 years of age and lower socioeconomic status, but the data are somewhat unclear when it comes to factors such as race, medical history, etc. Although studies suggest an overall prevalence of IC/BPS was 306 per 100,000 in Austrian women, 265 per 100,000 in Japanese women, and 98 per 100,000 among Chinese women.
Associated Disorders:
IC/BPS is not an isolated pathological condition, and is often associated with such diseases as irritable bowel syndrome, vulvodynia, endometriosis, fibromyalgia, allergies, and several other disorders. These associations suggest that there may be a systemic dysregulation in some patients, and perhaps even a shared central pathogenesis and pathophysiology among the disorders.14,15,16,17

Furthermore, patients with IC/BPS frequently exhibit mental health disorders such as depression and anxiety. There is also evidence to show an increase in migraines, reduced sleeping quality, panic attacks, sexual dysfunction, and bladder contracture, among others.38,39 While these symptoms may be reactive in some IC/BPS patients, there is also some evidence that there may be a common biologic mechanism involved. For instance, a link between IC/BPS and panic disorder has been suggested from genetic linkage studies.20,21

The effects of IC/BPS on psychosocial functioning and quality of life (QoL) are many and not to be taken lightly. These include damaging work life, psychological well-being, personal relationships and general health.22 In addition, IC/BPS patients have significantly more pain, sleep dysfunction, catastrophizing, anxiety, stress, social functioning difficulties and sexual dysfunction due to pain, than do non-IC/BPS age-matched women. In fact, its impact on QoL is as severe as end-stage renal disease.23,24

Cost:
Quantifying the exact economic burden of IC/BPS on the American healthcare system is difficult because of the lack of an objective marker for diagnosis, however, cost of IC/BPS treatments, including outpatient and physician visits and patient expenses, such as medication and hospitalizations, were estimated to be around $230 million annually.25,26 These costs are greater than the mean annual per-person direct costs of diabetes mellitus, depression, hypertension, and asthma.27

Furthermore, because of the chronicity of this condition, these costs typically persist over years. The indirect costs of IC/BPS, including time away from work and lost productivity while working, are particularly significant because the condition primarily affects working age adults, and especially women aged 25-50 years. The psychosocial costs such as social, educational and career-related activities not pursued, as well as the emotional distress, depression, social isolation, and diminished QoL cannot be measured, but are almost certainly substantial.

Treatment:
Given that the underlying mechanism of IC/BPS is not well understood there is a paucity of definitive and generally effective treatments. In fact, many of the AUA guidelines are widely based on clinical principles and expert opinion. As such, treatment strategies generally proceed using more conservative therapies first, then progressively employing less conservative measures if there is inadequate symptom control for an acceptable QoL. At the moment, there is no way to determine which treatment will benefit which patients, however this is being evaluated by developing phenotypes using INPUT system (infection, neurologic/systemic, psychosocial, ulcers and tenderness of muscles). Accordingly, treatments are divided into different progressive groups to maintain a positive risk/benefit balance.28

First-Line Treatments:
These treatments should be offered to all patients. The first is to educate the patient on the complexity of IC/BPS, its often multifaceted nature, and association with other disorders. It is important to help them understand their disease process and set the expectation that given the above, their symptom control may require multiple trials of different treatment options before finding the one, or combination, that helps. Furthermore, patients should be informed that, given the chronic nature of IC/BPS, the typical course involves symptom exacerbations and remissions.

It is also important to implement self-care practices and behavior modifications that can improve their symptoms. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored a multicenter trial that focused on treatment-naive IC/BPS patients. All patients underwent a standardized education and behavioral modification program (EBMP), and 45% of patients (n=136) assigned to the EBMP were markedly or moderately improved on the Global Response Assessment. This emphasizes the significant benefits of self-care practices and behaviors.29

These behavioral modifications may include implementing stress management practices, as well as making dietary and fluid intake changes.30 It may be necessary to restrict fluids in some patients while increasing hydration in others. Certain foods are known to be common bladder irritants such as coffee or citrus products, however the use of an elimination diet to better identify trigger culprits can be a more specific and effective tool. The avoidance of certain exacerbating exercises, sexual intercourse, wearing of tight-fitting clothing, and constipation may also help. The application of heat or cold over the bladder, perineum or other trigger point areas has been shown to be effective in managing flare-ups, as are strategies such as meditation, imagery, and pelvic floor relaxation techniques. Sometimes over-the-counter products such as nutraceuticals, calcium glycerophosphates, and pyridium are utilized to control symptoms.30,31,32

Second-Line Treatments:
Many patients with IC/BPS often have concomitant pelvic floor tenderness. It is unclear whether the bladder pain causes the musculature tightness or whether the pelvic floor abnormality gives rise to the bladder pain. However, there is evidence that demonstrates an improvement in symptoms with manual physical therapy. In a study by Fitzgerald et al, ten 60-minute sessions of myofascial physical therapy (MPT) over 12 weeks showed a benefit over global therapeutic massage in IC/BPS patients. At 3 months, moderate to marked improvement was reported in 59% and 26% respectively. It is very important to note however that pelvic floor strengthening exercises (such as Kegel exercises) do not improve symptoms and in fact may even worsen the condition.33
Pain has a major impact on QoL. The approach to pharmacological pain management in IC/BPS patients is the same for other chronic pain patients. It is not possible to predict which drug is most likely to alleviate each patient’s pain. Therefore, the most likely effective course is a multimodal approach in which pharmacologic agents are combined with other. The goal of pharmacotherapy is to find the medication that provides the best pain relief with the least side effects, such as urinary analgesics and NSAIDS, and to limit, even avoid, narcotic use. However, during flare-ups, a pain treatment protocol with some flexibility to manage the breakthrough pain may be required.

Other medication options typically used as part of second line therapy include amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate. In a randomized controlled trial (RCT) amitriptyline was found to be superior to placebo (63% vs. 4%) at 4 months. As a tricyclic antidepressant, it is best to start low (10 mg) and increase slowly to 50-100 mg in order to minimize side effects of lethargy, sedation, and nausea, which are often reasons patients stop using it.

Cimetidine has also shown to be efficacious at a dose of 400 mg twice daily when compared with placebo in terms of improvement in pain and nocturia after 3 months of use in an RCT, but this was based only on 40 patients. Other observational studies with doses of 300 mg twice daily or 200 mg three times daily, showed that 44-57% patients had improvement in symptoms, but again there was a low number of patients. There were no adverse events (AEs) reported with this Histamine-2 (H-2) blocker.

As for hydroxyzine, an RCT showed that only 10% more patients experienced significant improvement over the placebo group when using 50 mg for 6 months titrated slowly from 10 mg. One observational study reported that 92% of patients had clinically significant improvement at a dose of 75 mg daily. Adverse events were mild and generally self-limiting; they included sedation and weakness. Interestingly, all the patients in the study had systemic allergies, therefore, and may represent a subset more likely to respond to this antihistaminic drug.

Pentosan polysulfate is the only oral drug specifically FDA-approved for IC/BPS. It has a similar structure to the glycosaminoglycan lining of the bladder and is thought to help repair it. However, the evidence to show its efficacy is lacking. There have been at least five RCTs of this drug and a meta-analysis of these studies showed a statistically significant improvement but a fairly weak clinical one. A more recent study showed no improvement at all. Of the options mentioned, amitriptyline has the strongest evidence supporting its use.

Intravesical instillations are also considered part of second line therapy. These include dimethyl sulfoxide (DMSO), heparin, and lidocaine. There were two randomized crossover trials that showed an improvement in patients receiving DMSO during which 50 ml of a 50% solution was instilled for 15 minutes at 2-week intervals. The first study evaluated patients at 1 month and showed a 58% improvement over placebo. The second at 3 months reported improvement of 47% when compared with a different instillation; there was no placebo.

Several observational studies using similar protocols ranging from weekly to monthly to as needed and follow-up intervals of a few months to several years reported efficacy rates of 25 to 90%. Side effects were minimal and included pain if left in too long.

There are no placebo controlled trials of heparin, a naturally occurring glycosaminoglycan, alone but there are some observational studies reporting improvement. When a preparation of 10,000 IU in 10 ml of sterile water was held in the bladder for 1 hour, repeated three times per week for 3 months, 56% of patients reported a clinically significant improvement.

There is one RCT using 200 mg of alkalized lidocaine daily for 5 consecutive days with 1-hour retention. At 3 and 10 days after treatment, 30% and 24% of patients, respectively, experienced clinically significant improvement compared with 10% and 11.5% in the placebo group. After 5 treatments, the improvement increased to 54% and 48% at 3 and 10 days post-treatment.

More often than not, these drugs are administered as a part of a “cocktail” that includes DMSO, heparin, sodium bicarbonate, a local corticosteroid, and/or a lidocaine preparation. Reported efficacy rates range from 61% to 70%, 49,50,51,52

The bottom line is that a one-size-fits-all approach to pharmacotherapy is bound to fail, and the paucity of evidence supporting the use of many of these drugs highlights the need for additional randomized, placebo-controlled trials.

**Third Line Therapies:**

These include cystoscopy with short-term (<10 minutes), low pressure (60-80 cm H2O) hydrodistension with possible fulguration if there are Hunner’s ulcers present. This procedure serves to examine the bladder properly, identify Hunner’s ulcers (sometimes more evident upon distension of the bladder), and finally to identify the anatomical, rather than the functional, capacity of the bladder. The efficacy of this treatment ranges from 30-90%, however, the evidence supporting this is mainly based on observational studies.

If Hunner’s lesions are present, then it is recommended that fulguration, with laser or cautery, and/or injection of triamcinolone be carried out. There are multiple observational studies showing significant or complete relief in pain with fulgurating of the lesion (from 75% to 86%). Similar results were seen with Nd:YAG lasers with sustained improvement in pain, urgency, and nocturia in 80-100% of patients. Patients are typically counseled that periodic retreatment may be necessary if symptoms recur.

Patients should be counseled that periodic retreatment is likely to be necessary when symptoms recur. Injection of corticosteroids resulted in 70% of patients reporting improvement with an average improvement duration of 7 to 12 months according to one study.
Fifth-Line Treatments:
Cyclosporin A (CyA) is an immunosuppressant medication. Studies have shown an overall improvement in symptoms ranging from 50-59%. Success was even higher (85%) among patients with Hunner’s lesions. Adverse events included increased serum creatinine, hypertension, alopecia, cutaneous lymphoma, mouth ulcers, and acute gout. Many were managed by decreasing the dose or requiring other medication to control the symptoms; others elected to stop the CyA.

Given the small number of patients in these studies, lack of long-term data, and potential for serious AEs, the risk/benefit balance remains a question. Clinicians prescribing this medication should be adept at dosing and monitoring for patient complications.

Fourth-Line Treatments:
These include intravesical injection of botulinum toxin A (BoNT-A) and a trial of neuromodulation.

BoNT-A involves inhibition of suburothelial neurotransmitter release of sensory neuropeptides and neurotransmitters. A randomized double-blind placebo-controlled trial was conducted in Taiwan where 40 patients received 100 units of BoNT-A and 20 patients received normal saline. The visual analog scale for pain showed overall success to be 63% in the treatment group versus 15% in the sham group at 8-week follow up.61 Other studies have shown the treatment groups to be no better than placebo.62

A more recent meta-analysis of treatments demonstrated that BoNT-A has one of the best outcomes according to global response assessment and significantly improves bladder capacity in IC/BPS patients.63 This inconsistency in results makes interpretation of the data very difficult when ascertaining the efficacy of BoNT-A.

Sacral neuromodulation (SNM) is a well-established treatment for overactive bladder and non-obstructive urinary retention, however it is not FDA-approved for use in IC/BPS. Nevertheless when implanted to treat the above associated symptoms it may also help with pain. Its efficacy is thought to be related to the gate-control theory. This states that non-painful stimulus closes the “gates” to painful stimulus. Another possible mechanism of action is that SNM reduces pelvic floor hypertonicity, which is often a symptom of patients with IC/BPS.64

There have been several studies to evaluate the outcomes of SNM in patients with painful bladder syndrome. Peters et al implanted 26 patients with interstitial cystitis, More than two-thirds of patients reported a moderate or marked improvement in urinary frequency, urgency, pelvic pain, pelvic pressure, incontinence, and overall quality of life.65

A subsequent randomized cross-over trial by the same authors compared SNM with pudendal nerve stimulation for IC. Of the 22 patients who underwent trial stimulation, 17 responded and received a permanent implant. The overall reduction in symptoms for pudendal and SNM was 59% and 44%, respectively.66 Other studies evaluated long-term outcome (>5 years) of SNM. The success rate was reported to be 72-77%, with mean reduction in visual analog scale pain scores by 41-63%.67,68,69

Sixth-Line Treatment:
Patients and clinicians should be aware that 100% pain relief is often not achievable; the focus of pain management is to minimize discomfort and maximize the patient’s ability to function in daily life. When all other options have been exhausted, then major surgery may be considered. Options include substitution cystoplasty and urinary diversion with or without cystectomy.71

In a substitution cystoplasty, all but the trigone of the bladder is removed. However, there is concern that this area may be a source of persistent pain. The patients most likely to fail this procedure are those who describe their pain mainly at the urethra and those with Hunner’s lesions.72

If the main problem is frequency along with the pain, then a urinary diversion can almost certainly prove effective. However, pain may persist. A published study reported that 10/14 patients who underwent cystourethrectomy and urinary diversion experienced persistent pelvic pain including four with subsequent pouch pain postoperatively.73

When considering these procedures, it is imperative to counsel patients, and they must be willing to understand and accept the potential morbidities and life-long changes associated with irreversible surgery, including the fact that the pain may persist.

Future direction:
Mesenchymal stem cell (MSC) therapy is considered a novel therapeutic approach in the treatment of several diseases. Injection of umbilical cord-blood-derived MSCs (UCB-MSCs) into the bladder of an IC rat model showed an improvement in the urothelial layer by stimulating epithelial regeneration. In this regard, UCB-MSCs were able to directly differentiate into epithelial cells and stimulate the EGF signaling cascade. For this reason, the use of UCB-MSCs is a promising strategy in the treatment of IC.75

Liposomes (LPs) are spherical vesicles composed of concentric phospholipid bilayers enclosing an aqueous interior. Intravesical administration of LPs has been shown to reduce bladder hyperactivity and may attach to injured uroepithelium, thereby assisting in the repair of leaky inflamed uroepithelium.76,77

The carrier potential of LPs may also be used to transport BoNT directly into the bladder without the need for intravesical injections, which may be associated with adverse events including urinary tract infection, urinary retention, pain, and hematuria. Results from initial studies have been inconsistent and proof of concept still needs to be demonstrated.78,79
Tacrolimus is a potent immunosuppressive drug and may also have local anti-inflammatory effects. Liposomes formulated with tacrolimus were recently tested as a potential treatment for IC/BPS. In rat models for chemotherapy-induced hemorrhagic cystitis and radiation cystitis, it was shown to significantly reduce inflammation and voiding changes. However, clinical trials are needed before liposomal tacrolimus can be used for the treatment of human IC/BPS.\textsuperscript{80,81}

It is well established that there are inflammatory processes in the bladder driven by vascular endothelial growth factor (VEGF). Therefore, increased angiogenesis at sites of inflammation and ulcers in IC/BPS can be targeted with ligands for the VEGF receptor.\textsuperscript{92}

As previously reported, intravesical lidocaine may be used to treat IC/BPS, as such, using elastomeric polymers, a continuous lidocaine-releasing intravesical system (LiRIS) was designed to be retained in the bladder through cystoscopy and to release therapeutic amounts of the drug into the urine over a period of 2 weeks. Nickel et al. reported on a small study in 16 women with IC/BPS who were treated with LiRIS; there were clinically meaningful reductions in pain, urgency, and voiding frequency. Furthermore, 5 out of 6 patients demonstrated resolution of their Hunner’s lesions on Day 14 (the day of removal). Extended follow up suggested that the relief in pain was maintained for several months thereafter.\textsuperscript{83,84}

Future large-scale placebo-controlled studies are still lacking and are needed to confirm the true value of any of these options in the treatment of IC/BPS.

References:


64. The efficacy of botulinum toxin A and sacral neuromodulation in the management of interstitial cystitis (IC)/bladder pain syndrome (BPS), what do we know? ICIR-S 2017 think thank, Bristol. Rahnama J MS, Marcelissen T, Apostolidis A, Veit-Rubin N, Schurch B, Cardozo L, Dmochowski R.


66. Peters KM, Feber KM, Bennett RC. A prospective, single-blind, randomized crossover trial of sacral vs pudendal nerve stimulation for interstitial cystitis. BJU Int. 2007; 100:835


82. Saban MR, Backer JM, Backer MV, et al. VEGF receptors and neuropilins are expressed in the urothelial and neuronal cells in normal mouse urinary bladder and are upregulated in inflammation. Am. J. Physiol. Renal Physiol. 2008;295(1)
