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FEMALE UROLOGY (K KOBASHI, SECTION EDITOR)

# Painful Bladder Syndrome: An Update and Review of Current Management Strategies

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**Abstract** Interstitial cystitis/painful bladder syndrome (IC/PBS) remains a prevalent, but untreated disease with a poorly understood pathophysiology. Nonetheless, four main processes currently appear to be involved in producing IC/PBS symptoms: (1) disruption of the bladder GAG/proteoglycan layer, (2) upregulated immune/inflammatory response, (3) neural upregulation, and (4) pelvic floor dysfunction. Current and emerging therapies aimed at these potential targets will be the focus of this review with an update on IC/PBS therapy.

**Keywords** Interstitial Cystitis · Bladder Pain Syndrome · Chronic Pelvic Pain · Oral Treatment · Intravesical Treatment · Surgery

## Introduction

Our understanding of interstitial cystitis/painful bladder syndrome (IC/PBS) has evolved since the first description of interstitial cystitis in 1887 by Skene while describing a chronic inflammatory lesion of the bladder wall [1]. Guy Hunner further characterized a symptom complex of chronic bladder inflammation associated with a peculiar cystoscopic feature, the Hunner ulcer [2]. Descriptions of this complex expanded in Hand's work in 1949 when he presented varying endoscopic and histopathologic presentations of interstitial cystitis [3]. Currently, IC/PBS is recognized as a non-infectious chronic bladder disease characterized by pain and storage voiding symptoms (frequency, urgency, and nocturia) perceived to be related to the bladder [4••] Table 1.

In an attempt for standardization of this disease, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK, Bethesda, MD, USA) defined a number of criteria mainly based on exclusions in 1987 [5]. However, many feel these criteria are more suitable for research purposes and too restrictive for clinical application [6]. Therefore, the Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) adopted a more clinical definition for IC/PBS defining it 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" [7]. More recently, the American Urological Association (AUA) issued Guidelines on Diagnosis and Treatment of IC/PBS utilizing a systematic review of the literature up to 2009 [4••]. The primary focus of this review is an updated assessment of the current management options for IC/PBS.

## Epidemiology

Symptoms of IC/PBS overlap with other conditions including urinary tract infection, pelvic pain syndromes, and overactive bladder syndrome [8]. Therefore, its true incidence has been difficult to discern. Classically, symptom questionnaires have been used to estimate the incidence of IC/PBS [9]. The cohort in the 2004 United States Nurses Health Study (women ages 58 – 83 years old) indicated a prevalence of 2.3 % [10]. Notably, this estimate likely misses a substantial portion of the IC/PBS population since the disease also commonly

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**Table 1** Summary of IC/PBS treatments according to current AUA guidelines[4••] and grades of evidence[99]

| AUA Guidelines Treatment Recommendation | Treatment | Evidence Grade | References |
|---|---|---|---|
| First-Line | Dietary Modification | B | [26] Fisher |
| Second-Line | Pentosan Polysulfate | A | [38] Mullholland, [36] Parsons |
| | Pelvic Floor Physical Therapy | B | [33••] Fitzgerald |
| | Amitriptyline | B | [46] Foster |
| | Intravesical DMSO | B | [57] Sant, [86] Perez-Marrero, [87] Parkin |
| | Cimetidine | B | [48] Thilagarajah, [51] Dasgupta, [52] Seshadri |
| | Hydroxyzine | C | [57] Sant, [58] Theoharides |
| | Intravesical Heparin/Lidocaine | C | [77] Parsons, [83] Welk |
| Third-Line | Cystoscopy with Hydrodistension | C | [93] Cole, [94] Erickson, [95] Ottem |
| | Fulguration of Hunner Ulcers | C | [100] Hillelsohn |
| Fourth-Line | Sacral Neuromodulation | C | [114] Comiter, [115] Zabihi, [116] Ghazwani, [117] Gajewski |
| | Tibial Nerve Stimulation | C | [118] Gokylidiz, [119] O'Reilly |
| Fifth-Line | Cyclosporin A | B | [65] Sairanen,[66] Forrest |
| | Intravesical Botox-A | C | [106] Kuo, [108•] Shie |
| Sixth-Line | Surgical Reconstruction/ Diversion | C | [120] Rossberger |
| Uncategorized | Mycophenolate | A | [72] Yang |
| | Tanezumab | A | [76•] Evans |
| | Intravesical Liposome | C | [124] Chaung |
| | Hyperbaric oxygen | C | [128•] Tanaka |

afflicts women in younger age groups. Reviewing previously published data, the reported prevalence ranges from 1 – 11 % given the lack of standardization in methodology [11, 12]. Internet based questionnaires have also been used yielding similar results [13]. Berry et al. compiled an expert panel to arrive at a validated IC/PBS case definition [14]. Only 50 % of women that met criteria for IC/PBS had been evaluated by a urologist and 10 % carried the diagnosis of IC/PBS, further strengthening the fact that this disease is largely underreported. While these clinical tools remain helpful, most clinicians also agree that the diagnosis of IC/PBS often involves a process of exclusion of other sources of bladder pain and urinary symptoms including malignancy and infectious processes which can mimic IC/PBS symptoms [10]. Thus, while the estimated prevalence lies between 1 – 11 %, IC/PBS likely remains an underreported and also undertreated disease.

## Pathogenesis

Multiple hypotheses exist for the development of IC/PBS including infection, inflammation, autoimmune mechanisms, defects in the urothelial glycosaminoglycan layer, hypoxia, and central neurologic mechanisms [6, 15]. Bladder surface mucus creates a critical barrier between urine solutes and the underlying bladder [16]. Bladder surface mucus is composed of glycosaminoglycans (GAGs) and proteoglycans on the outer surface of the transitional cell apical membrane [17]. Disruption of this layer is thought to lead to migration of potassium (and possibly other components of the urine) across the mucosal surface, thereby depolarizing nerves and muscles and leading to tissue injury and pain. Hence, restoration and maintenance of the urothelial mucus GAG/proteoglycan layer remains one of the therapeutic paradigms for IC/PBS treatment.

Neuhaus, et al. employed a novel PCR technique to study detrusor receptor expression and found an upregulation of muscarinic (M2), purinergic (P2X1, P2X2) and histamine (H1) neurotransmitter receptors in patients diagnosed with IC/PBS [18]. Upregulation of muscarinic and purinergic receptors may possibly contribute to the typical storage voiding symptoms observed in IC/PBS patients [19, 20]. Likewise, upregulation of H1 receptors could contribute to the urothelial inflammatory response possibly involved in IC/PBS pathophysiology, especially given that some patients respond to oral antihistamines [21].

Upregulation of bladder neural afferent pathways has also been documented in IC/PBS. This finding may possibly explain the common pattern of initial storage voiding symptoms followed by the onset of bladder pain symptoms later [22]. Additionally, central hyperexcitability may be involved in the pathogenesis and/or maintenance of IC/PBS symptomatology. Increased activity in emotional arousal circuits may possibly explain the association of IC/PBS with several conditions including fibromyalgia, IBS and depression/anxiety disorders [23]. Thus, centrally-acting agents like amitriptyline and more peripherally-acting therapies like sacral neuromodulation may be helpful in addressing the neural upregulation involved in IC/PBS pathophysiology.

## Treatment for Interstitial Cystitis/Bladder Pain Syndrome

IC/PBS is often considered a spectrum disease with a wide array of presenting symptoms and severities. Thus, treatment is tailored to the individual patient. Frequently, a single treatment modality is unsuccessful at fully resolving IC/PBS symptoms, and a step-wise multimodal approach to therapy is often adopted [24]. Management strategies should range from least invasive to more invasive therapies [4••].

### Dietary Modification

Self-reported questionnaires have long identified dietary sensitivity in IC/PBS patients. Some studies report that up to 90 % of patients expressed sensitivity to food, beverage, and dietary supplements [25]. Citrus fruits, tomato products, alcohol, cola, and Mexican and Thai foods were among the most commonly reported comestibles that exacerbated IC/PBS symptoms. Interestingly, the only placebo-controlled IC/PBS dietary study to date failed to associate diet with symptoms in IC/PBS patients [26]. However, multiple questionnaire-based studies continue to support dietary associations with IC/PBS symptomatology [25, 27, 28]. There is currently no recommended IC/PBS diet beyond avoidance of problem food items. Diet may vary from patient to patient and, therefore, treatment in this regard remains highly individualized. Given the low risk of dietary modification, it is recommended as an initial treatment in patients with IC/PBS who have dietary sensitivities [28].

### Pelvic Floor Physical Therapy

On exam, tension and tenderness of the pelvic floor musculature and other somatic tissues are commonly present in patients with IC/PBS. In a series of 70 women with IC/PBS, 87 % were found to have levator pain on pelvic examination [29]. This levator pain is consistent with a myofascial trigger point, defined as a tender spot created by injury at the motor end plate as a result of acute, repetitive, or sustained muscle overloading [30]. Also, urodynamics in IC/PBS patients have revealed that pain episodes appear to parallel behavioral changes in sphincter more than detrusor changes [31]. Thus, there is reasonable evidence suggesting that pelvic floor dysfunction often accompanies and likely contributes to IC/PBS symptoms.

Pelvic floor physical therapy or manual trigger point release has been established to treat pelvic floor-related IC/PBS symptoms. Weiss demonstrated that 83 % of patients had moderate to marked improvement or complete resolution of pelvic pain after undergoing 8 – 12 weeks of manual pelvic floor physical therapy [32]. He also demonstrated a 65 % decrease in mean resting pelvic floor pressure on electromyography. Fitzgerald et al. performed a randomized multicenter trial comparing global therapeutic massage and myofascial physical therapy [33••]. This study revealed a 57 % improvement in the global assessment response rate in the myofascial physical therapy group compared to 21 % in the therapeutic massage group. Because it is relatively non-invasive and appears to benefit significantly a substantial portion of IC/PBS patients, pelvic floor physical therapy is recommended as one of the early interventions for IC/PBS according to recent AUA guidelines [4••].

### Oral Therapy

#### *Pentosan Polysulfate*

Pentosan polysulfate (PPS) is a semi-synthetic, sulfated polysaccharide, which is chemically and structurally similar to heparin and GAG [34]. A proposed mechanism is that the drug replaces the damaged parts of the GAG layer that lines the bladder [35]. It has been reported that PPS reduces bladder permeability based on the potassium sensitivity test [36]. Currently, PPS is the only oral therapy approved by the FDA for IC/PBS [37]. However, randomized controlled trials have shown mixed results in its efficacy. Mulholland and Parsons separately reported significantly improved pain and urgency symptoms from baseline at 3-month follow up [38, 39]. Conversely, Holm-Bentzen et al. failed to demonstrate any difference at 4-month follow up compared to placebo [40]. Increasing treatment doses does not appear to improve efficacy from the 100 mg TID dosing [41]. Diarrhea, abdominal pain, and rectal bleeding are the most common side effects and have been found to be dose-related. Alopecia was also noted in 5 % of patients in one study [41]. High-quality evidence demonstrates mixed support for this therapy. Therefore, given the moderate side effect profile, PPS is recommended as a second-line therapy for IC/PBS [4••].

*Amitriptyline*

Amitriptyline has been used to treat nocturnal enuresis in children [42] and is still often used to treat overactive bladder symptoms in adults [43]. Its exact mechanism of action in this regard remains unknown, but it is thought to work through central and peripheral anticholinergic actions including blockage of serotonin and noradrenaline reuptake as well as through central sedative and antihistaminic properties [44]. Another hypothesis is that low dose antidepressants may act centrally on limbic pain processing centers that are upregulated in patients experiencing chronic visceral pain [23, 45].

Amitriptyline has previously been designated as a second-line therapy in the treatment of IC/PBS [4••]. Titration is recommended starting at 25 mg and increasing to 75 – 100 mg. Foster et al. performed a multicenter, randomized, double-blind, placebo-controlled trial in amitriptyline-naïve patients in addition to behavioral modification [46]. A total of 231 patients were randomized and doses titrated to 75 mg if tolerated. Although the side effect profile was acceptable (nausea, drowsiness, sedation), there was no significant improvement in pain or voiding symptoms compared to placebo. Higher doses of amitriptyline were associated with higher response rates on statistical analysis. Amitriptyline has been shown to benefit a subset of patients, but its use is limited by tolerability of side effects [47]. Amitriptyline is typically offered as a second-line therapy for IC/PBS [4••].

*Cimetidine*

Patients with IC/PBS have demonstrated significant increases in the concentration of lymphocytes, T cells, and blood vessels in the bladder mucosa coupled with discontinuity of the basement membrane [48]. Multiple studies have implicated mast cell degranulation as an initiating factor in this inflammatory process [49, 50]. Cimetidine was speculated to improve symptoms via competitive inhibition of the $H_2$-receptor and was given to IC/PBS patients in 1987 [21]. Thilagarajah performed the first randomized, double-blind, placebo-controlled trial treating patients with oral cimetidine for 3 months [48]. Treatment groups had significant improvement in suprapubic pain and nocturia based on questionnaire data. There was no significant quantitative histologic difference in T cells between the pre- and post-treatment groups, leading the authors to consider that this drug has an immune-modulating effect on T cells. Long term data is limited in previous observational studies [51, 52]. Cimetidine is currently recognized as a second-line therapy according to recent AUA guidelines [4••].

*Hydroxyzine*

Hydroxyzine is an oral heterocyclic piperazine $H_1$-receptor antagonist [53]. It has been used for urticaria, pruritis, allergic rhinitis, and histamine-induced airway obstruction [54]. Given that a significant subset of patients with IC/PBS are prone to allergies [55] and that activated mast cells have been identified adjacent to nerve cells within the bladder wall [56], $H_1$-blockade may be beneficial in some patients. In a randomized, double-blind, placebo-controlled study using both PPS and hydroxyzine, there was no statistical difference in global response assessment in the hydroxyzine arm compared to placebo [57]. A nonrandomized case series reported a 40 % improvement in pain and voiding symptoms, which improved to 55 % in patients with a history of allergies [58]. Despite contradictory evidence, due to its low side effect profile and the potential benefit to a subset of IC/PBS patients, hydroxyzine remains a second-line therapy for IC/PBS.

## Immunotherapy Agents

Immune dysregulation has been postulated in patients with IC/PBS based on epidemiological, histopathological and clinical response criteria [59]. Evidence suggests that some IC/PBS patients respond to immunosuppressive drugs [60, 61]. Age and sex distribution are also similar to other patients with autoimmune disease [62], and there is a clinical concordance with other autoimmune diseases [63]. Therefore, immune-regulating therapies have been investigated as therapies for IC/PBS patients.

*Cyclosporin A*

Cyclosporin A is a calcineurin inhibitor, which blocks activation of T cells [64] and is thought to decrease bladder inflammation in IC/PBS patients. Previous open-label trials comparing cyclosporin A to PPS demonstrated a higher response rate with cyclosporin A [65]. Retrospective review from multiple tertiary centers in patients who had failed previous intravesical therapies demonstrated an 85 % response rate in patients with Hunner ulcers based on global response assessment. There was only a 30 % response rate in patients without Hunner ulcers [66]. Common side effects noted in the study were renal insufficiency, hypertension, and infection, thus requiring monitoring of serum creatinine and blood pressure. This may be a viable option in refractory IC/PBS patients, especially those with visible defects in the urothelium. The recent AUA guidelines list this as a fifth-line treatment option for IC/PBS [4••].

*Mycophenolate Mofetil*

Mycophenolate mofetil (MMF) is commonly used in transplant recipients as an antirejection agent. It has been successful in the treatment of autoimmune disorders such as inflammatory uveitis, systemic lupus erythematosis and lupus nephritis [67–69]. Given that there are data supporting the association with IC/PBS with these autoimmune diseases, MMF

has been investigated in the treatment of IC/PBS [70, 71]. However, the current data remain sparse and unfavorable. Yang performed a randomized, placebo-controlled trial to evaluate the efficacy of this drug in patients with refractory IC/PBS. The study was terminated prematurely given that the efficacy was no different than placebo [72].

*Tanezumab*

Tanezumab is a humanized anti-nerve growth factor (anti-NGF) monoclonal antibody that binds with high affinity to NGF, preventing it from interacting with receptors on nociceptive neurons. Inhibition of NGF signaling reduces pain-like behavioral responses in a number of animal models of visceral pain [73, 74]. Increased urinary and serum NGF has been found in IC/PBS patients [75]. A randomized, placebo-controlled, double-blind trial was performed using a dose of 200 ug/kg of intravenous tanezumab [76•]. This revealed a significant reduction in daily pain score, daily urgency episodes, and patient reported treatment benefit was positive. Further studies are needed to examine dosing regimen and clinical effects on IC/PBS patients, but anti-NGF remains a promising area of investigation in IC/PBS treatment. This modality was not evaluated by the recent AUA Guidelines.

Intravesical Agents

*Heparin and Buffered Lidocaine*

A variety of intravesical agents have been used throughout the years in addition to oral therapy or as second-line treatments [77]. Heparin is a sulfated polysaccharide that is thought to augment the protective effect of the natural bladder surface mucus GAG/proteoglycan layer [77, 78]. It has also demonstrated anti-inflammatory properties, including inhibition of angiogenesis and fibroblast proliferation [79, 80]. Sodium bicarbonate was found to increase lidocaine absorption through the lipid membrane [81]. Therefore, by combining these two mechanisms, both long-term and short-term benefits can be seen with instillation directly into the IC/PBS bladder.

Parsons was the first to present his data on 82 patients who underwent instillation of 40,000 U heparin, 8 mL of 1 % or 2 % lidocaine, and 3 mL of 8.4 % bicarbonate, resulting in significant symptom relief based upon the Patient Overall Rating of Improvement of Symptoms score [82]. Ninety-four percent of patients responded to 2 % lidocaine and 74 % responded to the 1 % lidocaine preparation. Parsons also reported that 4 – 12 months of therapy is often needed to obtain a beneficial response using a three times per week home dosing regimen [77]. Follow up studies have supported these findings as well as documented improvements in dyspareunia on validated questionnaires including Female Sexual Function Index and Pelvic Pain Urgency/Frequency symptom scale [83]. Sixty percent of patients experience temporary discomfort with instillation but this treatment option, overall, is typically well-tolerated as a second-line therapy [84].

*DMSO (dimethylsulfoxide)*

Dimethysulfoxide (DMSO) was first synthesized in 1867 as a by-product of the wood pulp industry [78]. DMSO subsequently was found to have anti-inflammatory, analgesic, and bacteriostatic properties [85]. In 1988, the first randomized, placebo-controlled trial using intravesical DMSO was performed [86]. Responses were assessed with urodynamics and voiding parameters, which demonstrated a 93 % improvement in the DMSO group versus 35 % in the placebo group. Subsequent studies revealed 50 – 90 % response rates in treatment groups [57, 86, 87]. Typical treatment regimens with weekly intravesical instillations comprise a total of 4 – 8 treatments. Self-administration techniques have also been described with similar efficacy [88]. Durable response rates have been documented up to 12 months [89•]. Recently, Stav et al. attempted to identify predictors in treatment failures in patients with IC/PBS. They found that small anesthetic capacity (<675 mL) was the only independent risk factor for treatment failure. The authors recommended that non-responders not continue after 3 weeks of intravesical treatment [89•]. Given the consistent data supporting its use and low side effect profile (bladder irritation, garlic-like taste, headache), some investigators have recommended DMSO as a first-line treatment for IC/PBS [90]. Currently, AUA guidelines recommend intravesical DMSO as a second-line therapy in IC/PBS [4••].

*Cystoscopy with Short Duration Hydrodistension*

Cystoscopic identification of glomerulations following hydrodistension or of Hunner ulcers is considered a prerequisite in the NIDDK criteria for IC/PBS [5]. However, it is well-documented that not all patients will demonstrate these findings on cystoscopy [91]. Also, cystoscopy alone can be useful to identify an alternate source for the patient's irritative voiding symptoms, such as bladder cancer or CIS [92]. There are no randomized data to support the use of low-pressure hydrodistension, but observational studies suggest some benefit in relief of symptoms [93–95]. Hydrodistension performed after instilling 10 mL of 4 % lidocaine intravesically demonstrated safe and therapeutic efficacy in IC/PBS patients in the office setting [96]. Patients had a significant improvement in O'Leary-Sant Score and 63 % had a durable response at 24 week follow up. However, this study did not report distension pressures or standardize the duration of treatment. High-pressure (>80 cm H20), long-duration hydrodistension (>10 min) should be avoided given the risk of bladder rupture and sepsis [97, 98]. AUA guidelines acknowledge the lack of

non-randomized trials and recommend low-pressure (60 – 80 cm H20), short duration (less than 10 min) hydrodistension as a third-line therapy [4••].

### *Fulguration of Hunner Ulcers*

Cystoscopy with fulguration of Hunner ulcers is also a third-line treatment recommendation listed in the AUA guidelines with Grade C clinical evidence [99]. Hillelsohn et al. performed a retrospective review of patients previously treated with fulguration in response to the AUA guidelines [100]. All patients had undergone previous oral and intravesical therapy. Seventy-eight percent reported improved or stable symptoms after therapy with an average follow up of 44.8 months. Interestingly, 45.8 % of patients required one or more additional fulguration session within 4 years of their initial treatment. Two of the original 59 patients ultimately required cystectomy for worsening of their condition. This suggests that fulguration of Hunner ulcers remains purely a treatment of IC/PBS symptoms rather than the underlying disease process.

In addition to fulguration, treatment of Hunner ulcers with Nd:YAG laser or injection with triamcinolone can be considered [101, 102]. A single treatment of these lesions has demonstrated a lasting response of between 7 – 12 months based on validated questionnaires [102]. If identified, Hunner ulcers should be treated given the low risk from intervention.

### *Intravesical OnabotulinumtoxinA*

Intravesical onabotulinumtoxinA (BTX-A) injection was first introduced in 2000 for use in spinal cord injury patients with urinary incontinence secondary to neurogenic detrusor overactivity [103]. BTX-A is a potent neurotoxin derived from the anaerobic bacterium Clostridium botulinum; it acts by inhibiting the release of acetylcholine at the neuromuscular junction, thereby decreasing muscle contractility at the injection site [104]. Animal models have demonstrated that BTX-A also inhibits sensory neuropeptide release including substance P and calcitonin gene-related peptide suggesting that it may have a potential benefit in the treatment of neurogenic inflammation [105]. A randomized study looking at hydrodistension versus BTX-A plus hydrodistension, demonstrated increased bladder capacity and long term pain relief in patients who received the combined therapy [106]. More recently, Gottsch, et al. performed a randomized, controlled trial of periurethral injection of BTX-A with no improvement in symptoms versus controls [107]. Thus, based on this evidence, BTX-A appears to require injection into the bladder to have a beneficial effect in IC/PBS patients.

More recent evidence suggests that multiple injections prove superior to a single injection of BTX-A [108•, 109]. Although there was no placebo control group, Shie et al. performed bladder biopsies prior to multiple BTX-A injections [108•]. They found overall significant improvement in visual analog pain scores and O'Leary-Sant scores. Histologic analysis also showed a decrease in inflammatory and apoptotic markers. Patients that demonstrated the greatest histologic changes underwent three repeated injections every 6 months.

Limitations of the BTX-A data continue to be the variability in treatment protocols and lack of randomized studies. However, this remains a growing area of interest in the management of IC/PBS given the amount of positive data that has surfaced.

## Neuromodulation

Neurogenic insult resulting in chronic perineuritis and neuroproliferation in the bladder wall has been proposed as another possible etiology of IC/PBS [110]. Sacral S3 nerve stimulation (SNS) is believed to block afferent bladder activity in somatic pathways as well as interfere with abnormal C-fiber activity [111]. SNS has also been found to decrease heparin-binding epidermal growth factor (HB-EGF) and anti-proliferative factor (APF) in IC/PBS also supporting this neurogenic hypothesis. [112].

Seigel et al. described benefit from sacral nerve stimulation in the treatment of intractable pelvic pain [113]. Previous studies had been limited by short follow up [114, 115] but more recent data have revealed durable results. In a retrospective review, 52 % of IC/PBS patients undergoing SNS underwent permanent implantation for greater than 50 % improvement in their pain symptoms [116]. Patients had persistent efficacy for an average follow up of 71.5 months. Another long-term, retrospective study of 78 patients revealed a 72 % response rate in pain and voiding symptoms with a median follow up of 61 months [117]. This study noted a 50 % revision rate, the most common reason being loss of efficacy.

Percutaneous tibial nerve stimulation (PTNS) has also been used for IC/PBS. Gokylidiz et al. performed a randomized trial of PTNS vs. routine care for IC/PBS patients. The PTNS group demonstrated improvements in overall QOL scores, sensory and affective McGill scores, and the pain component in the Female Sexual Function Index [118]. O'Reilly randomized refractory patients to laser PTNS and a sham group [119]. Although both arms demonstrated improvement in symptoms, there was no significant difference in pain scores.

The majority of the data for neuromodulation stems from small, nonrandomized trials. However, recent data has demonstrated durable response in refractory IC/PBS patients. Risks of invasive surgical procedures and the possible need for revision should be thoroughly explained to patients before offering neuromodulation for refractory IC/PBS. Currently, neuromodulation is included as a fourth-line therapy for IC/PBS treatment in recent AUA guidelines [4].

### Surgical Reconstruction/Urinary Diversion

AUA guidelines specify bladder augmentation, substitution cystoplasty and urinary diversion as the last line of therapy for IC/PBS patients. Typically these options are reserved for patients with low anesthetic bladder capacity (<300 cc) and/or Hunner ulcers [8]. There is a relative paucity of data on major lower urinary tract reconstruction in IC/PBS. In a retrospective review of IC/PBS patients undergoing urinary diversion, 10 of 13 (76 %) non-ulcer patients had persistent pain; however, 32 of 34 (94 %) of patients with classic Hunner ulcers did have symptom relief [120]. The surgical procedures included ileal conduit, supratrigonal cystectomy and ileocystoplasty, continent urinary diversion (Kock pouch), continent orthotopic diversion, and cecocystoplasty. Differentiating ulcer vs. non-ulcer subtypes may help improve outcomes when major reconstructive surgery is being considered.

### Emerging Therapies

#### *Intravesical Liposomes*

Liposomes (LP) are vesicles composed of concentric phospholipid bilayers separated by aqueous compartments [121]. Given that LP absorb to cell surfaces, they have been tested as a therapeutic agent to promote wound healing [122, 123]. LP animal models have also shown decreased bladder sensitivity to potassium chloride or acetic acid [123]. When compared to PPS, intravesical LP had statistically significant decreases in urinary frequency and nocturia as well as significant decreases in pain, urgency, and the O'Leary-Sant symptom score [124]. Dosing is typically weekly for 4 weeks and is well-tolerated by patients [125]. Initial studies have demonstrated promising results, but large-scale randomized studies are still warranted to assess the efficacy of this treatment.

#### *Hyperbaric Oxygen*

Hyperbaric oxygen (HBO) has been used to successfully treat patients with cyclophosphamide-induced hemorrhagic cystitis and chronic radiation cystitis [126, 127]. A pilot study examined 11 patients with refractory IC/PBS treated with 2 – 4 weeks of HBO therapy [128•]. Seven patients had improvement in pain scores and urgency/frequency symptoms lasting up to 2 years. This modality could be offered to refractory IC/PBS patients. Hyperbaric oxygen has also improved beneficial effects of DMSO when used concurrently [129].

## Conclusion

IC/PBS remains a prevalent, but untreated disease with a poorly understood pathophysiology. Nonetheless, research suggests that (1) disruption of the bladder GAG/proteoglycan layer, (2) upregulated immune/inflammatory response, (3) neural upregulation, and (4) pelvic floor dysfunction may all play a role in the pathophysiology of the disease. These constitute the main therapeutic targets for the IC/PBS treatments covered in this review. Despite the many advances and promising areas of investigation, IC/PBS treatment still remains highly individualized, often utilizing multiple treatment modalities in a stepwise approach from less invasive to more invasive treatments.

### Compliance with Ethics Guidelines

**Conflict of Interest** Dr. Anthony J. Dyer declares no potential conflicts of interest relevant to this article.

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- • Of importance
- •• Of major importance


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