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REVIEW

# Interstitial Cystitis/Bladder Pain Syndrome: Role of Bladder Inflammation in Bladder Function

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## Abstract

**Purpose of Review** We performed recent literature review with the aim to address the updates in diagnosis and management of interstitial cystitis/bladder pain syndrome (IC/BPS).

**Recent Findings** There are multiple recently published studies that collectively lead to an organized stepwise plan for diagnosis and management of IC/BPS.

**Summary** IC/BPS is a common health condition that can be managed efficiently if the appropriate steps are taken in diagnosis and management.

**Keywords** Interstitial cystitis (IC) · Bladder pain syndrome (BPS) · Bladder inflammation · Bladder function

## Abbreviations

| | |
|---|---|
| IC/BPS | Interstitial cystitis/bladder pain syndrome |
| CPPS | Chronic pelvic pain syndrome |
| LUTS | Lower urinary tract symptoms |
| UTI | Urinary tract infection |
| HIC/BPS | Hunner (ulcerative) type IC/BPS |
| NHIC/BPS | Non-Hunner (non-ulcerative) type IC/BPS (NHIC/BPS) |
| AUA | American Urological Association |
| GAG | Glycosaminoglycan |
| NGF | Nerve growth factor |
| TRPV | Transient receptor potential vanilloid |
| ATP | Adenosine triphosphate |
| RTX | Resiniferatoxin |
| TLR-4 | Toll-like receptor-4 |
| HPA | Hypothalamo-pituitary-adrenal |
| ACTH | Adrenocorticotropic hormone |
| APF | Antiproliferative factornb |
| PET | Positron emission topography |
| fMRI | Functional magnetic resonance imaging |
| TNF-α | Tumor necrosis factor-α |
| HIF-1α | Hypoxia-inducible factor-1α |
| VEGF | Vascular endothelial growth factor |
| TGF-ß | Transforming growth factor-ß |
| ESSIC | European Society for the Study of IC/PBS |
| GUPI | Genitourinary pain index |
| ICSI | Interstitial cystitis symptom index |
| VAS | Visual analog scale |
| PPS | Pentosan polysulphate |
| DMSO | Dimethyl sulfoxide |
| EAU | European Association of Urology |

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## Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pelvic pain syndrome (CPPS) with unknown causes. It typically manifests as suprapubic pain (pelvic pain or bladder pain) related to bladder filling and lower urinary tract symptoms (LUTS), such as frequent urination with or without urgency and nocturia that lasts for at least 6 weeks [1–3]. It is frequently divided into two distinct disorders, "BPS," which frequently lacks an inflammatory component and

"IC," a chronic inflammatory disorder [4, 5]. The syndrome can also be divided into two groups based on the results of a bladder biopsy: Hunner (ulcerative) type IC/BPS (HIC/BPS) and non-Hunner (non-ulcerative) type IC/BPS (NHIC/BPS) [6, 7]. The syndrome has no known etiology, making diagnosis and treatment challenging [1, 8]. According to American Urological Association (AUA) recommendations, IC should only be diagnosed and treated in people who have had the typical symptoms for more than 6 weeks and are not responding to treatment [9].

## Etiology

### Chronic Inflammation

Bladder inflammation is assumed to be the main mode of IC/BPS mediation [10]. This idea has been supported by a number of observations in IC/BPS patients, including elevated levels of pro-inflammatory proteins in their serum and diffuse expression of inflammatory cells, localized lymphoid clusters, and B- and T-cell markers in their bladders [10, 11]. These inflammatory cells, which were primarily seen in the suburothelial region, were primarily lymphocytes and plasma cells with a small number of eosinophils and neutrophils. About 40% of patients with IC/BPS also had lymphoid clusters and follicles [12]. Furthermore, due to damage caused by chronic inflammation to the glycosaminoglycan (GAG) layer of the urothelium, which results in urothelial denudation, the superficial layer of urothelium is frequently damaged in those patients. In addition, abnormal bladder urothelial differentiation in IC/BPS bladders leads to a reduction in the production of cell surface defenses like proteoglycans, E-cadherin adhesion protein, tight junction proteins, zonula occludens-1, and bacteria-fighting molecules [13]. The voiding symptoms and pain in IC/BPS are primarily brought on by these alterations, which are associated with chronic mucosa inflammation [14]. Likewise, IC/BPS patients' bladder biopsies revealed higher mast cell counts, changes in interstitial cells, inflammatory cell infiltration, edema, fibrosis, and vascular lesions [15–17]. The elevation of inflammatory signals may cause apoptosis in IC/BPS bladders, presumably through TNF-α and p38 MAPK signaling pathways, as seen by the elevated levels of apoptotic signaling molecules, such as Bad, Bax, and cleaved caspase-3 [18].

The etiology of IC/BPS may potentially be driven by systemic inflammation [10]. Patients with IC/BPS have been found to have a wide range of somatic and functional abnormalities, concomitant diseases, and mental disorders [19, 20]. In patients with IC/BPS, functional somatic syndrome in particular is frequently observed [21]. Because inflammatory bladder illnesses, mental health issues like stress-related disorders, or even medical comorbidities may contribute to or exacerbate the symptoms of IC/BPS [22], different clinical signs, urodynamic results, and histological findings are frequently seen in IC/BPS patients [23].

### Alterations in Bladder Urothelium

Changes in the bladder urothelium are one of the most widely accepted explanations for the etiology of IC/BPS (1, 8, 14). Previous literature has correlated functional pain disorders, such as IC/BPS, to structural and functional changes in the epithelial layer (8). Defects in the urothelial barrier can allow water, urea, and other toxic materials to enter the deeper layers of the neural and muscular tissues, causing symptoms of urgency, frequency, and pain when the bladder is filled and emptied [24]. Additionally, because of this, the epithelial cells are forced to react to environmental toxins, mediators released by nerves or surrounding inflammatory cells, and bacteria and their byproducts. These responses alter the expression and sensitivity of a number of receptors and channels and even the release of mediators, which may have an impact on function [8].

Urothelium denudation has been consistently reported in IC/BPS patients especially in HIC/BPS [12, 25]. Disrupted urothelium permits the diffusion of urine toxins, leading to bladder inflammation, detrusor interstitial fibrosis, and afferent nerve hyperexcitability ultimately resulting in the pain and storage LUTS in IC/BPS patients [12, 25–27]. Loss of GAG layer was associated with a loss of biglycan and perlecan on the luminal layer [28], and intravesical therapy with chondroitin sulfate and GAG substitutes for IC/BPS patients was aimed to reconstitute the integrity of the epithelium through the binding of GAGs to proteoglycans with structural urothelium [29]. Bladder epithelial cell differentiation and maturation deficits have also been frequently reported in IC/BPS patients with reduced expression of the tight junction protein zonula occludens-1 and the adhesive protein E-cadherin, impaired cell adhesion, alleviated cell proliferation in the basal layers, increased urothelial apoptosis, and strengthened oxidative stress protein [1, 23, 30–32]. Accordingly, urothelial dysfunction ensues which can also be attributed to reduced expression of epithelial cell differentiation and maturation markers, including cytokeratin (CK)-5, CK-14, and CK-20 in IC/BPS bladders [1, 33–35]. Also, the mature cell marker CK20 and the cell proliferation proteins P63 and FGFR4 have been reported to be lower in patients with HIC or NHIC and grade 3 glomerulations than in other subtypes of NHIC and controls while the immature cell marker CK5 and the apoptotic protein BAX have been reported to be higher in HIC or NHIC and grade 3 glomerulations [36]. Paraneurons are specialized cells in the urethral epithelium which are identified by the neurotransmitter they express (e.g., acetylcholine, serotonin, or somatostatin) [8,

37, 38]. Because these cells are located close to sensory nerves, they may release multiple factors which may play a role in modulating sensory excitability and contribute to sensation and pain [8].

## Neuronal Hyperactivity

The myelinated Aδ fibers and the unmyelinated C fibers are two distinct types of bladder afferent nerves. Under typical circumstances, the Aδ fibers can detect bladder filling despite being non-nociceptive. On the other hand, the C fibers are nociceptive and become activated in pathological states, causing pain, nocturia, urinary incontinence, urgency, and frequency [39]. The increased sensory afferent activity in IC/BPS was connected to C fiber sensitization and resulted in bladder pain [40, 41]. The number of M2 and M3 receptors has been found to be more abundant in the lamina propria of IC/BPS bladders, and the number of suburothelial muscarinic receptors is correlated to the number of urgency symptom scores [42]. Additionally, IC/BPS bladders are said to have elevated levels of prostaglandins, adenosine triphosphate (ATP), transient receptor potential vanilloid (TRPV) channels, and nerve growth factor (NGF) [11, 43, 44]. Urgency and excessive detrusor activity have been reported in IC/BPS patients [14], and these symptoms have been explicitly linked to the upregulation of TRPV1 [45], P2 × 3 receptors [46], and the C-fiber pathway's hypersensitivity [47]. Inflammatory pain, frequency, and urinary urgency are also widely attributed to TRPV1 in IC/BPS [48]. Purinergic signaling is activated in IC-induced bladder hyperactivity by activating TRPV1 by vanilloids (capsaicin and resiniferatoxin (RTX)), which are involved in voiding function and pain perception. This is done by increasing intracellular calcium, inducing the release of NO and ATP, and ultimately evoking transient currents. Through TRPV1 signaling, NGF participates in the pathophysiology of OAB syndrome [14, 49]. Also, IC/BPS patients with bladder inflammation may experience pain episodes due to the increase in afferent nerve hyperactivity or hyperexcitability [50]. For instance, toll-like receptor-4 (TLR-4) has also been demonstrated to have a significant role in the sensitization of central pain. The distinct prevalence of pain conditions in male and female IC/BPS patients has been attributed to interactions between sex hormones and TLR-4-mediated inflammation [51]. As a result, notably in female IC/BPS patients, TLR-4-mediated inflammation was linked to unpleasant symptoms and nerve hyperactivity, including bladder pain, frequency, and urgency [14].

The hypothalamo-pituitary-adrenal (HPA) axis and sympathetic nervous system may both contribute to the etiology of IC/BPS [52]. Neuronal dysregulation occurs in IC/BPS patients due to dysfunction of either one of these pathways or both [53]. Stress has been proven to cause the feline sympathetic nervous system to produce more catecholamines in urine [54]. The HPA axis theory, which links stress to a rise in adrenocorticotropic hormone (ACTH) in people with IC, suggests that this may lead to a reduction in pain tolerance [55]. The bladder should be able to repair itself once any of these processes have taken place, just like it can in healthy people. However, because of the rise in antiproliferative factor (APF) activity, the bladder's ability to regenerate is compromised. The end stage of IC, in which the bladder is unable to restore its lining and permits the resulting persistent impairment, may be explained by the formation of APF [52].

In addition to previous peripheral mechanisms, central mechanisms are also thought to contribute to visceral hypersensitivity and pain. These include the ongoing activation of the dorsal horn neurons, which leads to changes in the spinal cord (also known as central sensitization), and the brain's processing of afferent signals [8]. Recent developments in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have improved our comprehension of how the central nervous system regulates the human bladder and other pelvic viscera [56]. Patients with CPPS, in particular, have been found to demonstrate extensive pain along with a pattern of brain structure and function that is also present in those with fibromyalgia, which is frequently regarded as the prototypical centralized pain disorder [8, 57].

## Autoimmunity

It has been well established that urothelial denudation, heightened immune responses in HIC/BPS, and autoimmunity to bladder tissue are related [58]. Autoantibodies have regularly been found in the serum and urine of IC/BPS patients, and autoimmune diseases have frequently been documented in IC/BPS patients [59]. Anti-urothelial autoantibodies have previously been discovered in IC patients [60–62]. Autoantibodies have been found in people with IC serum and bladder at high rates and titers [63, 64]. In a mouse cystitis model, autoimmunity to uroplakin-induced suburothelial inflammation, serum antibody response, and voiding dysfunction were seen [65]. Patients with IC/BPS have more mast cells in the bladder urothelium [66]. Inflammatory mediators including neuropeptide substance *P* and NGF are released by mast cells together with other proinflammatory cytokines and chemokines in IC/BPS, and these mediators are linked to the proliferation of nerve fibers [67–70]. Additionally, the bladder urothelium produces several neural signaling substances, including ATP and NGF, which activate mast cells and stimulate submucosal afferent neurons [24], causing voiding and bladder discomfort as well as structural alterations to the bladder wall [26]. Additionally, bladder issues have been often observed in people with systemic autoimmune diseases like Sjogren's

syndrome, systemic lupus erythematosus, and autoimmune thyroiditis. Histological evidence of immunoglobulin and complement deposits in the bladder has been found in these cases [71]. These individuals' symptoms of the lower urinary tract are like those of HIC/BPS patients [72, 73]. Additionally, well-known epidemiological characteristics of IC/BPS include a majority of females and a greater frequency of concomitant systemic autoimmune illnesses [74–76]. All the evidence points to the possibility that HIC/BPS is autoimmune in origin [58].

Tumor necrosis factor-α (TNF-α) levels were observed to be considerably higher in the serum, urine, and bladder tissue of IC/BPS patients, especially HIC/BPS patients [10, 77, 78]. TNF-α, a proinflammatory cytokine, causes excessive inflammation and bladder injury [79]. Mast cell activation, followed by TNF-α release, has been linked to the inflammatory response seen in IC/BPS [80]. TNF-α inhibitors could reduce bladder inflammation in an autoimmune IC/BPS model [81]. Adalimumab, an anti-TNF-α medication, significantly alleviated clinical symptoms in IC/BPS patients [82]. Certolizumab pegol is a TNF-α specific monoclonal antibody. Certolizumab pegol reduced mast cell degranulation, which resulted in the production of inflammatory mediators such as histamine, prostaglandin, leukotriene, serotonin, heparin, and serine protease [83].

It was recently established that immunological responses in HIC/BPS are linked to bladder infection [12, 84]. In people who are genetically predisposed to autoimmune disease, infection drives the pathogenesis [85–87]. During this process, microbial infiltration through the bladder mucosa may be aided by a dysfunctional urothelial barrier [88]. Epstein-Barr virus infection was shown to be more common in HIC/BPS patients [89]. As a result, immunological reactions against the urinary bladder are hypothesized to occur in HIC/BPS patients in association with infection [58].

### Abnormal Angiogenesis

Urinary frequency and bladder pain are associated with abnormal bladder angiogenesis in IC/BPS patients [90, 91]. Mucosal bleeding after distension in NHIC/BPS is likewise linked to increased and dysregulated angiogenesis [90]. In patients with IC/BPS, increased expression of hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor (VEGF) is linked to glomerulation formation [90]. Several investigations have shown that bladder glomerulations are related to increased VEGF expression, implying that glomerulations in IC/BPS bladders are caused by neovascularization [92, 93]. Angiogenesis is critical for bladder regeneration because it maintains blood vessels that give nourishment and oxygen via the VEGF signaling pathway and stimulates phosphorylation of Erk1/2, P38, and Akt [94]. The levels of VEGF in HIC/BPS are substantially higher [59, 84, 90, 91, 95]. TNF-α, VEGF, CD31, and transforming growth factor-ß (TGF-ß) expression have all been found to be significantly higher in IC/BPS patients [14]. Increased VEGF is linked to bladder inflammation in IC/BPS patients [96].

## Presentation and Diagnosis

### Symptoms

Pelvic discomfort with urine frequency and urgency is the most common symptom among IC/BPS patients. However, the following symptoms are also commonly observed [97]:

1. Lower abdominal discomfort with urine frequency and/or urgency
2. Suprapubic pain that worsens with a full bladder and lessens with an empty bladder
3. Urgency
4. Anal discomfort coupled with urinary symptoms in the absence of an anal abnormality
5. The sensation of incomplete emptying

The European Society for the Study of IC/BPS (ESSIC) and the AUA criteria are two of the most extensively used. According to ESSIC, symptoms include "chronic pelvic pain (> 6 months), pressure or discomfort considered to be attributable to the urinary bladder, associated with at least one other urinary symptom such as persistent urge to void or frequency." Diseases that could be the cause of the symptoms must be ruled out [98].

The number of voids each day, the sense of a continual urge to void, and the location, nature, and intensity of pain, pressure, or discomfort should all be recorded. It is also important to note dyspareunia, dysuria, ejaculatory pain in men, and the correlation of pain to menstruation in women. All patients should have a brief neurological exam to rule out an occult neurologic condition and an evaluation for incomplete bladder emptying to rule out occult retention. A complete hematuria workup should be undertaken in patients with unexplained hematuria, and patients with cigarette exposure should be evaluated due to the high incidence of bladder cancer in smokers [99]. A 1-day voiding log should be used at least to confirm the presence of a low volume frequency voiding pattern that is characteristic of IC/BPS. The genitourinary pain index (GUPI), interstitial cystitis symptom index (ICSI), or visual analog scale (VAS) should be used to assess pain and collect information about pain/discomfort location(s), intensity, and characteristics, as well as to identify factors that aggravate or ameliorate pain or discomfort [9].

## Physical Examination

An abdominal and pelvic examination should be performed to detect masses, tenderness, and the presence of hernias. The external genitalia, bladder base in females, and urethra in both sexes should be palpated during the pelvic examination. Both sexes' pelvic floor muscles should be palpated for tenderness and trigger points. Documentation of the pelvic support for the bladder, urethra, vagina, and rectum is recommended. A thorough examination is required to rule out vaginitis, urethritis, tender prostate, urethral diverticulum, or other potential sources of pain or infection [100].

## Investigations

A. Urine culture:
   It is critical, and all patients should perform it even if their urine analysis is normal [101].
B. Renal and bladder ultrasound:
   It is a bedside investigation that is simple and initial in the diagnosis. Here, we will observe a normal urinary tract ultrasound with pre-micturition low bladder volume as the patient cannot tolerate micturition [102].
C. Cystoscopy:
   Cystoscopy is required when the diagnosis is uncertain. Cystoscopy has the following advantages:
   1. Excluding diseases that cause analogous symptoms as stone, CIS, and malignancy.
   2. Any suspicious area should be biopsied.
   3. Hunner ulcer treatment and diagnosis [103]. Hunner lesion is a distinct inflammatory lesion with distinctive central fragility that ruptures with hydrodistension. It is usually a single lesion, but up to three lesions may be present. This lesion is usually visible prior to bladder distention. It appears as a circumscribed reddish mucosal area with small vessels radiating towards a central scar on cystoscopy [104].
   4. Glomerulations (pinpoint petechial hemorrhages) can be seen on cystoscopy, but they are non-specific for IC/BPS and are commonly seen in other conditions that co-exist with or are misdiagnosed as IC/BPS, such as chronic undifferentiated pelvic pain or endometriosis [105].
   5. The bladder capacity should be calculated.
D. Urodynamic study:

Has no bearing on the diagnosis, and no definite criteria exist [106]. Examination discomfort, detrusor overactivity, pelvic floor muscle dysfunction, and bladder outlet obstruction may be observed [9, 107].

## Management

There is no gold standard treatment for IC/BPS, but all treatments are currently being tested. Treatment focuses on pathogenesis and symptoms. Conservative management is the preferred first line of IC/BPS management, but other management lines are also used [98]. To break the cycle of pain, treatment is directed at the urothelial layer, nervous system, and/or immune system [108].

A. Non-pharmacological treatment:

On long-term follow-up, approximately half of the patients showed improvement in their symptoms [108]. Changes in behavior, stress reduction, dietary changes (avoidance of certain foods known to be common bladder irritants for IC/BPS patients, such as coffee or citrus products), and physical therapy (application of local heat or cold over the bladder or perineum) are all options. Timed voiding and bladder training are two behavioral modifications that can be used to increase voiding intervals. Physical therapy may include maneuvers to relieve trigger points in the pelvic, abdominal, and/or hip muscles; lengthen muscle contractures; and release painful scars and other connective tissue restrictions [108–110].

B. Oral pharmacological treatment:
   1. Amitriptyline: It is a tricyclic antidepressant that prevents the neurotransmitters serotonin and noradrenaline from being reabsorbed [111]. It is commonly used in the treatment of neuropathic pain. The starting dose is 25 mg per day, which is gradually increased to 100 mg per day if tolerated [108]. The main source of concern is medication side effects [111].
   2. Cimetidine: It is a histamine H2 receptor antagonist that, in some patients, hinders the effects of increased histamine release from mast cells on the bladder. After 3 months of treatment, one RCT found that oral cimetidine (400 mg twice daily) was more effective than placebo in terms of total symptoms, pain, and nocturia [108].
   3. Pentosan polysulphate (PPS): The drug may act as a buffer to control cell permeability by adhering to the bladder wall mucosal membrane, preventing irritating solutes in urine from reaching the cells. It has been used to treat BPS both orally and by instilling it into the bladder [112]. A meta-analysis of four randomized placebo-controlled trials of oral PPS with 448 patients found that it significantly improved pain, urgency, and frequency (success defined as a 50% reduction in symptoms) when compared to pla-

cebo. Subcutaneous heparin may improve the effects of oral PPS [108].

4. Oral cyclosporin A: Cyclosporin A is an immunosuppressive medication that affects T cells [113]. Patients with Hunner lesions responded better to cyclosporin A than others. The major drawback of this drug is that it causes nephrotoxicity, hair loss, hypertension, and immunosuppression in 94% of patients [108, 114].

C. Intravesical instillation:

The advantage of intravesical instillation is that it bypasses the systemic circulation. Several trials with various types of drugs and combinations have been conducted [108, 113, 114].

1. Glycosaminoglycan layer treatments: Heparin is the most used drug. The dose is 10,000 to 25,000 IU in 10 $cm^3$ sterile water three times per week for 3 months, with a 1-h retention period [115]. Other substances, such as hyaluronic acid and chondroitin sulfate, were investigated. A meta-analysis of 10 studies involving 390 patients revealed substantial improvements in pain scores (O'Leary-Sant and VAS scores) with both intravesical hyaluronic acid and combined hyaluronic acid and chondroitin sulfate [116].
2. Dimethyl sulfoxide (DMSO): DMSO is well known as a nonspecific anti-inflammatory agent that can penetrate the GAG layer of the bladder and has a direct effect on the detrusor muscle, even though the mechanism of action is unknown. Furthermore, DMSO may have anticholinesterase and neuromuscular blocking properties [117]. It is FDA-approved and recommended by the European Association of Urology (EAU). The dose is not standardized, but 50 mL of a 50% DMSO solution is typically instilled into the bladder once weekly for 6 weeks, followed by another 6 weeks and then monthly maintenance [108]. A study found that combining DMSO with heparin, hydrocortisone, and bupivacaine improved pain analog scale scores by 23–47% [118]. Chondroitin sulfate, on the other hand, demonstrated greater improvement (72.7% vs 14%, $P = 0.002$) and tolerability than DMSO, as well as less drop out (57% vs 27%) [119•].
3. Lidocaine: It is a local anesthetic with no standard dose in IC/BPS. In a multi-centric RCT, combining 200 mg of alkalinized lidocaine with sequential instillation of 8.4% sodium bicarbonate once daily for 5 consecutive days with 1-h retention significantly improved patients' symptomatology. Alkalinization increases lidocaine urothelial penetration and thus efficacy. However, by day 10, the effect had diminished [9]. It is also recommended by the EAU for the short-term relief of acute symptom flares [108].
4. Combinations of all above mentioned drugs: Several studies discussed various types of combinations, but there is still no gold standard in treatment. Small cohort studies provide the only evidence for these combination therapies [108].

D. Endoscopic treatment:

1. Hydrodistension: Short duration (less than 10 min), low pressure (60 to 80 cm $H_20$) after confirming that there is no pathology, hydrodistension makes Hunner's ulcer visible after mucosal cracking and also aids in determining bladder capacity [9]. Multiple studies, sorely missing a control group, found short durations of improvement with disparate outcomes, making it impossible to draw firm conclusions [9, 120•].
2. Transurethral treatment of Hunner lesions: The treatment of choice is fulguration (with laser or cautery) and/or injection of triamcinolone. Following treatment, a large proportion of patients reported significant or complete pain relief [108]. In a large study of 103 patients, 89% reported symptom relief with transurethral resection, with 40% reporting long-term efficacy of more than 3 years, but relapse and the need for retreatment were common [108]. In addition, there was no significant difference in efficacy between transurethral resection and transurethral coagulation in 126 patients with Hunner lesions [121•]. In one study, triamcinolone acetonide injection resulted in a 1-year remission period in terms of symptom control in approximately 43% of the patients, and the results were better in patients who were older and had more severe IC/BPS-related symptoms [122].
3. Botulinum toxin type A: Hyperstimulation of afferent nerve fibers due to urothelium regeneration failure is thought to be a major cause of bladder pain syndrome [123•]. Botulinum toxin type A inhibits neurotransmitter release, reducing detrusor overactivity [122]. However, it only provides short-term relief, and patients should be aware that they may require intermittent self-catheterization after treatment [9].

E. Neuromodulation:

Neuromodulation is currently not FDA-approved for the treatment of IC/BPS. At 6 months post-implant, 66% of patients reported clinically significant improvement, with

patients with pudendal implants reporting greater symptom relief than those with sacral implants, according to a study [9]. SNM was associated with a significant reduction in pelvic pain, frequency, nocturia, urgency, and interstitial cystitis problem score in a meta-analysis. The overall pooled treatment success rate was 84% [122]. The data on transcutaneous nerve stimulation are contradictory and did not show a significant improvement with a small number of participants.

F. Major surgery:

Substitution cystoplasty and urinary diversion with or without cystectomy are major surgeries. They should be provided to the patient only after all other options have been exhausted and a definitive diagnosis of IC/BPS has been made. Fibrotic bladder with low capacity and Hunner ulcers are predictors of success [9].

1. Supratrigonal cystectomy and augmentation: The benefits include the preservation of the ureteral orifices, which prevents anastomotic stricture and spontaneous micturition [124]. However, the failure rate can reach 23%, and a secondary cystectomy may be required [9, 124].
2. Supravesical urinary diversion: The benefits include avoiding urine contact with the bladder, which eliminates irritative symptoms, avoiding the risks of prolonged operative time and avoiding metabolic problems that are commonly reported with augmentation. The disadvantage is that keeping the bladder may allow pain to persist (9, 125, 126•).

## Conclusions

IC/BPS is a CPPS of unknown etiology that commonly presents with suprapubic pain associated with bladder filling and LUTS. Chronic inflammation, alterations in bladder urothelium, neuronal hyperactivity, autoimmunity, and abnormal angiogenesis have all been proposed as possible etiologies for the condition, although non confirmed. When diagnosing and treating IC/BPS, a high index of suspicion is required. Management can range from conservative management to major surgical management depending on the degree of patient bother and response to treatment, all of which targeting to break the cycle of pain. The preferred first line of management is always conservative management.

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## Declarations

**Ethical Approval** Our review article does not require an ethical approval as it just involves a retrospective review of literature.

**Conflict of Interest** The authors declare no competing interests.

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