CLINICAL
INVESTIGATION

Novel treatments of interstitial cystitis/bladder pain syndrome based on pathophysiology

Interstitial cystitis/bladder pain syndrome is characterized by bladder pain associated with urgency, frequency, nocturia, dysuria and sterile urine. Recent studies revealed that these bladder dysfunctions could originate from chronic inflammation or urothelial insult and proceed to a cascade of tissue reactions, which finally ascends to the CNS. The principles for treatment of interstitial cystitis/bladder pain syndrome are based on controlling the dysfunctional epithelium by continual replenishment of the glycosaminoglycan layer, inhibiting neurological hyperactivity by administration of amitriptyline or imipramine, suppression of allergies with antihistamines, and pain control with nonsteroidal anti-inflammatory drugs, COX-2 inhibitors or tranquilizers. Intravesical treatment with heparin, hyaluronic acid, chondroitin sulfate, Bacillus Calmette–Guérin, dimethylsulfoxide, resiniferatoxin, or botulinum toxin A has shown early effectiveness in some patients. Surgical treatment should be reserved for those who have no response to medical therapy.

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Interstitial cystitis (IC)/bladder pain syndrome (BPS) is a syndrome of mystery in urology. IC/BPS is characterized by bladder pain associated with urgency, frequency, nocturia, dysuria and sterile urine. The diagnosis of IC/BPS is based on the symptomatology and urological findings, including characteristic cystoscopic features after hydrodilatation under anesthesia [1]. Recent data on diagnosis show that cystoscopic hydrodistention findings might not be sensitive or specific; diagnosis of IC/BPS is suggested primarily on the basis of history. Cystoscopic hydrodistension was once considered as a diagnostic tool for selecting IC patients, but is not currently believed to be so. The National Institute of Diabetes and Digestive and Kidney diseases (NIDDK) criteria are used to select more uniform patients for clinical research [2] and is today widely used in Asia for the diagnosis of IC [3]. Many patients fulfilling the Asian definition of IC and the NIDDK criteria might not have bladder pain and do not, therefore, fulfill the definition of BPS. Although this disease has been noted for more than a century, the pathogenesis and diagnosis remain unclear and should be based on exclusion of other diseases [4,5]. The American Urological Association recently published a guideline for the diagnosis and treatment of IC/BPS. The guideline suggested IC/BPS is best identified and managed through use of a logical algorithm, such as is presented in the guideline [6].

IC/BPS has been classified into the classic and nonulcer types based on cystoscopic findings. Classic IC, also called Hunner's ulcer, is found in 5–55% of IC/BPS patients and is characterized by observable bladder ulcerations after hydrodilatation [7,8]. The Hunner lesions are not true ulcers and do not look like ulcers. They are therefore widely underdiagnosed. Nonulcer IC, also called early

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 1085

IC, is characterized by glomerulations and petechia formation after hydrodilatation under anesthesia, as described in the Asian IC guideline [3]. Patients with nonulcer disease were on average 20 years younger at the time of diagnosis [8]. Accumulated evidence indicates that IC is a heterogeneous syndrome. The recent findings clearly demonstrate that the two subtypes of IC represent separate disease entities [9]. Although many pathogeneses of IC have been proposed, the actual etiology remains unclear [10]. Possible etiologies include:

- A postinfection autoimmune process;

- Mast-cell activation induced by inflammation, toxins or stress;

- Urothelial dysfunction and increased permeability of the urothelium;

- Neurogenic inflammation resulting in serial reactions including potassium ion diffusion, mast-cell activation, upregulation of sensory fibers, release of neuropeptide (substance P) and bladder pain.

Nickel *et al.* recently proposed an UPOINT-phenotyping system to classify women with IC/BPS according to clinically relevant urinary, psychosocial, organ specific, infection, neurological/systemic, and tenderness domains [11]. Increased symptom duration leads to a greater number of domains, and domains that function outside of the bladder predict a significant impact on symptoms [11]. Patients reported more pain than controls in all reported body areas. The increased pain phenotype was associated with poorer psychosocial adjustment and diminished physical quality of life [12].

Since the pathogenesis of IC/BPS remains unclear, the current goals of treatment are largely based on symptomatic relief. The principles for treatment of IC are based on:

- Controlling the dysfunctional epithelium by continual replenishment of the glycosaminoglycan (GAG) layer;

- Inhibiting neurological hyperactivity;

- Suppression of allergies and;

- Pain control.

A certain percentage of patients treated have successful results for the short term, however, most patients experience symptom relapse during long-term follow up and need continual treatment with several different therapeutic modalities. This article reviews the recent novel treatments for IC/BPS based on the present evidence for possible pathophysiological mechanisms.

Since the definition and diagnostic criteria of IC has not gained universal consensus, using IC as a diagnosis of the syndrome of bladder pain and frequency urgency results in great confusion over which patients actually have the disease, and so BPS has recently been introduced. However, controversy still exists and this also influences the results of the studies performed on IC/BPS patients due to the heterogeneity of patient selection. Thus, the treament outcome might vary greatly in different studies using different methods of selecting patients.

Chronic inflammation in IC/BPS

The cause of IC/BPS has been considered by most urologists to result from long-standing inflammation of the bladder [13]. Bladder histological analysis shows infiltrates of mast cells, eosinophilic leukocytes and T-lymphocytes. This suggests that the disease is mediated by the immune system in some of the patients with IC/BPS [13]. However, the triggering factor that leads to the disease is still unknown. In previous reports, histological evidence has shown several marked changes in various tissue elements. First, abnormal behavior of urothelial cells disrupts the permeability barrier. Second, vascular lesions include endothelial cell injury and suggest a slow microcirculation. Third, neural changes include a combination of degenerative and regenerative features [14,15].

The chronic pain symptomatology in IC/BPS may be due to CNS sensitization and persisting abnormality, or activation of the afferent sensory system in the urinary bladder [16]. Increased central c-fos expression has been demonstrated in animal models of neurogenic detrusor overactivity and chronic inflammation. Elimination of rat spinal neurons expressing NK1 receptors reduces bladder overactivity and spinal c-fos expression induced by bladder irritation [17,18]. If the neurogenic inflammation in the dorsal root ganglia can be eliminated gradually through intravesical treatment, the visceral pain in IC/BPS might thus be relieved.

Recent findings have proposed several pathophysiological mechanisms, including epithelial dysfunction, activation of mast cells, neurogenic inflammation, autoimmunity and occult infection. Therefore, treatments targeting these pathophysiologies have been investigated [19]. One of the most common findings in bladder mucosal biopsies from IC/BPS patients is denudation or thinning of the bladder epithelium, suggesting an altered regulation of urothelial homeostasis. Other bladder abnormalities include increased nerve fiber density and inflammatory cell infiltration [13]. Previous reports on bladder biopsies of patients with IC/BPS have

confirmed the involvement and presence of eosinophils, macrophages in the urothelium and mast cells in the detrusor. However, a high proportion of patients have completely normal bladder morphology. Involvement of eosinophils is also supported by urine cytology showing increased urinary eosinophil cationic protein in the urine of patients with IC/BPS [20,21]. Mast cells have been considered as crucial effector cells for the immune response implicated in the pathogenesis of IC/BPS [13].

Neurogenic inflammation of IC/PBS

There is increasing evidence for the role of neurogenic inflammation in the pathophysiology of several diseases, including asthma, arthritis, migraine and possibly IC/BPS [22]. Preliminary studies have shown an increase in levels of immunoreactive substance P and NGF in the bladder tissue and urine [23,24]. The primary nerves involved in neurogenic inflammation are thought to be mainly C-fibers, although A-δ fibers also play a role. Recently, purinergic receptor P2X3 deficient mice have been shown to have hyporeflexic bladders and reduced pain-related behavior, indicating that P2X3 is critical for peripheral pain responses and afferent pathways controlling urinary bladder volume reflexes [25]. The P2X3 receptors have also been shown to localize on the suburothelial C-fibers and detrusor muscles, and co-localize with other sensory receptors, such as transient receptor potential vanilloid receptors, NK1, CGRP, tyrosin kinase A and other sensory-related receptors [26]. Any insult to the urothelium or directly to the bladder wall may induce a cascade of inflammatory reactions and produce painful inflammation, such as in IC/BPS [27].

From the above evidence, it is possible to postulate that IC/BPS syndrome might be induced sequentially by:

- Urothelium injury: such as in acute bacterial cystitis, intravesical foreign body, intravesical instrumentation and surgical bladder trauma;

- Suburothelial inflammation from urothelium, endogenous toxin or allergic reaction;

- Chronic inflammatory cell infiltration in the suburothelium and detrusor after the acute reaction;

- Chronic scar formation in the suburothelium and detrusor;

- Increased inflammatory reaction in the dorsal horn ganglia and corresponding sacral cord.

It is possible that IC/BPS is a progressive disease that evolves from early- to late-stage bladder conditions. Insult to the visceral organ initiates an inflammatory process in the organ. The inflammatory reaction will proceed along the sensory nerves in the dorsal root ganglia as well as the sacral cord. The sensory impulse will also ascend to the corresponding cortical gyrus. Therefore, any injury or inflammation in the urinary bladder will not only activate an inflammatory process in the bladder wall but also in the sacral cord and cerebral cortex. Patients might have an early inflammatory reaction and produce characteristic IC/BPS symptoms, including bladder pain, urgency, frequency and a positive KCl-sensitivity test. If the insult does not continue, the defense mechanism will solve the inflammation and patients may have symptom relief after symptomatic treatment. However, if the bladder insult continues, the inflammatory reaction will be raised to a higher level and cause permanent inflammation printing. Some patients with chronic IC/BPS might have referred pain due to the presence of high-level inflammation.

Urothelial dysfunction in IC/BPS

Previous reports indicate that the urothelium plays a pivotal role as a barrier between urine and its solutes and the underlying bladder. Bladder surface mucus is a critical component of this function [28–30]. The biologic activity of mucus that imparts this barrier function is generated by the highly anionic polysaccharide components (GAGs), which are extremely hydrophilic and trap water at the outer layer of the umbrella cell. In patients with IC/BPS, disruption of the urothelial barrier may initiate a cascade of events in the bladder, leading to symptoms and disease. Specifically, urothelial dysfunction leads to the migration of urinary solutes, in particular, potassium, which depolarizes nerves and muscles and causes tissue injury [31,32]. Consequently, it is imperative to understand the biologic effects by which the urothelium changes its growth behavior and the expression pattern of signal transduction molecules under these effects.

GAG is a part of the normal bladder epithelium and protects the bladder mucosa from bacterial adhesion and penetration by toxic substances in the urine [33]. A subset of patients with frequency–urgency syndrome has a leaky epithelium and K^+ cations can diffuse subepithelially and provoke urgency frequency. Intravesical KCl instillation at a concentration of 0.4 M was found to provoke symptoms in 4.5% of healthy people, 70% of patients with IC/BPS, 18% of IC/BPS patients treated with heparin, and 100% of patients with irradiation cystitis [30].

Intravesical sulfated polysaccharide (PPS) was found to restore injured urothelium to normal [34].

Studies of urothelial differentiation in IC/BPS also demonstrated that the acquisition of a transitional cell morphology occurred in some IC-derived cell lines, suggesting a subset of patients with IC/BPS might have a failure of urothelial cytodifferentiation, which might contribute to the disease and bladder dysfunction [28]. Abnormal expression of molecular markers has been found in IC/BPS bladder biopsies. Abnormal expression of uroplakin, chondroitin sulfate and tight junctional protein ZO-1 strongly suggests abnormal differentiation in bladders with IC/BPS, whereas elevated E-cadherin expression may represent an adaptation to increased bladder permeability [35].

Ki-67 is a commercially available monoclonal antibody that reacts with a nuclear antigen expressed in proliferating cells, but not in quiescent cells. Expression of this antigen occurs preferentially during the late G1, S, G2, and M phases of the cell cycle, while in cells in the G0 phase the antigen cannot be detected [36]. To confirm the results of a TUNEL stain we have compared the ratio of proliferating and apoptotic cells in a pathologic assay. The preliminary data showed that Ki-67 positive cells are rare in IC/BPS patients compared with controls [37].

VEGF, which plays a key role in bladder inflammation, is closely associated with the vascular alterations observed in patients with IC/BPS. In addition, recent findings indicate that VEGFRs and coreceptors (neuropilins; NRP) are strongly expressed in both the human bladder urothelium and in a human bladder cancer cell line (J82) and that the expression of NRP2 and VEGF-R1 is significantly down regulated in subjects with IC/BPS compared with control subjects [15]. These results suggest that urinary VEGF may gain access to the bladder wall via their receptors. According to this evidence, and the inflammation data from histological analysis, investigating the relationship of VEGF proteins and their receptor/co-receptor in the abnormal urothelium of patients with IC/PBS might clarify the role of VEGF in the pathogenesis of urothelial dysfunction in IC/BPS.

In previous research, some evidence has strongly suggested abnormal differentiation in the IC/BPS urothelium with a loss of E-cadherin and altered differentiation markers is independent and occurs independently of inflammation [38]. However, some results show a less proliferative phenotype, with increased expression of E-cadherin in IC/BPS. Some evidence showed that elevated E-cadherin may represent an adaptation to increased bladder permeability [35,39]. Our preliminary results indicated that the distribution of E-cadherin is different in patients with IC/

BPS with different maximal bladder capacities [40]. Therefore, the role of E-cadherin in the pathophysiology of IC/PBS is still controversial.

Previously published results and data confirm that IC/BPS involves an aberrant differentiation program in the bladder urothelium that leads to altered synthesis of several proteoglycans, cell adhesion and tight-junction proteins, and bacterial defense molecules such as GP51. Therefore, replacement therapy with GAG has been widely used for treatment of IC/BPS [41]. However, further correlation of the expression of the proteoglycan core proteins and differentiation related markers with inflammation scores in IC/BPS bladder biopsies revealed that the abnormalities in urothelial differentiation and loss of barrier function in IC/BPS were independent of inflammation [41].

Expression of intercellular adhesion molecules ICAM-1, P-, and E-selectin is highly positive in bladders with IC/PBS but not in controls. ICAM-1 binds to cellular adhesion molecules, which is necessary for initiation of inflammation. The results support different degrees of bladder inflammation in IC/BPS [42]. Increased ICAM-1 intensity was found in IC/BPS patients. The ICAM-1 intensity was higher in those who responded to bladder hydrodistention plus hyaluronic acid instillation. By blocking the ICAM-1 receptors, hyaluronic acid presumably alleviates the inflammatory process [43].

Bladders with IC/BPS showed morphological changes indicative of apoptosis. TUNEL staining showed apoptotic cells in the microvascular endothelial cells, but not in the endothelial cells of venules. Bladder microvascular endothelial cells may play an important role in the pathogenesis of IC/PBS [44]. Bladder epithelial cells from patients with IC/PBS exhibited profoundly decreased proliferation, decreased expression of cyclic D1 and JNK, and increased paracellular permeability compared with normal urothelial cells. Experiments in serum-free medium showed that the proliferation rate of explanted bladder epithelial cells from patients with IC/BPS was significantly decreased compared with that of control cells, indicating an intrinsic abnormality in IC/BPS cell proliferation. This abnormality may be caused by APF, which induces reversible inhibition of HB-EGF production and normal bladder epithelial cell proliferation [45]. APF treatment caused significant increases in the paracellular permeability of normal bladder epithelial cell monolayers and the attenuation of tight junctions compared with mock APF, similar to changes seen in IC cells. APF treatment also decreased expression of the tight-junction proteins ZO-1 and occludin [39,46].

Effect of chronic inflammation on urothelial dysfunction

Chronic suburothelial inflammation might inhibit normal basal cell proliferation and affect apical urothelial function. Treatment of urothelial dysfunction cannot be based solely on replacement of defense glycoproteins in the bladder urothelium. Furthermore, bladder inflammation caused by intravesical irritants or in patients with IC/BPS leads to acute afferent nerve activity and to long-term plasticity that lowers the threshold for nociceptive and mechanoceptive afferent fibers [47,48]. Chronic sensitization of afferent fibers might involve both peripheral and central mechanisms. A rise in bladder NGF in the muscle or urothelium initiates signals that are transported along the afferent nerves of the bladder to the dorsal root ganglion or spinal cord [49,50]. Based on these data, successful treatment of IC/BPS should aim at several targets including urothelial defense defects and suburothelial inflammation.

Treatments targeting urothelial dysfunction
■ Oral PPS

PPS has a heparin-like structure and is widely used for the treatment of IC/BPS. In the initial study of Parsons *et al.*, >50% improvement in frequency, nocturia, urgency and pain was found in 62 IC/BPS patients treated with 300–400 mg of PPS per day for 4 months [34]. In a randomized, double-blind, dose-ranging trial involving 380 patients treated with 300, 600 and 900 mg PPS per day for 32 weeks, the O'Leary-Sant Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index showed significant improvement in 49.6, 49.6, and 45.2% of patients, respectively. The authors concluded that the response to treatment was not dose dependent and the duration of therapy appeared to be more important than the dose [51]. However, in another earlier double-blind study, the results of treatment with PPS 400 mg per day over 4 months were not significantly different from the response in the placebo group [52]. A secondary analysis of 128 subjects treated with PPS 300 mg/day revealed that 75% of patients were satisfactory to PPS treatment at end point [53]. A good outcome was found associated with longer PPS intake (>12 months) [54]. A recent study of therapeutic effect of PPS on osteoarthritis suggested that PPS treatment prevents inflammatory intracellular responses induced by IL-1β through inhibition of phosphorylation of certain MAPKs, p38 and ERK in cultured chondrocytes [55]. Further investigation of the action mechanism of PPS is necessary.

■ Intravesical heparin therapy

Heparin is known to mimic the GAG layer structure, and, therefore, it is rational to treat IC/BPS with intravesical heparin with the aim of replenishment of the defective GAG layer in the bladder. Parsons *et al.* treated 48 IC/BPS patients with intravesical heparin 10,000 IU three-times per week for 3 months. They reported 56% of patients had improvement in a 3-day voiding diary and cystometrograms at 3 months. The authors concluded that intravesical heparin controlled symptoms in >50% of IC/BPS patients [55]. Kuo treated 40 IC/BPS patients who had a positive KCl test with intravesical heparin 25,000 IU retained for 2 h, twice per week for 3 months. The symptom scores of 29 (72.5%) patients improved by >50%. Urodynamic study revealed significant improvement in the first sensation of filling and bladder capacity after heparin treatment [56]. In patients who respond symptomatically to intravesical GAG-substitution therapy, the cystometric bladder capacity is increased, whereas nonresponders do not experience such change [57]. Although there is no consensus on the dose, therapeutic frequency, or the treatment duration in intravesical heparin therapy, it has been suggested that intravesical heparin therapy should start at a higher frequency in the acute stage, with a reduced frequency in the subacute stage. Treatment should continue intermittently in the maintenance stage, and should not stop, even in nonresponders.

A combination of heparin and alkalinized lidocaine has recently been used to treat IC/BPS patients [58]. Parsons *et al.* used 40,000 U heparin with 3 ml 8.4% sodium bicarbonate and 1 (Group 1) or 2% (Group 2) lidocaine for intravesical treatment three-times per week for 2 weeks. Significant immediate symptom relief after a single treatment was noted in 75 and 94% of Group 1 and 2 patients, 50% of Group 2 patients had symptom relief for 4 h and 80% of Group 2 patients reported significant sustained symptom relief after 2 weeks. In a recent study, Nickel *et al.* found that 102 patients with IC/BPS who received daily intravesical instillation of alkalinized lidocaine (200 mg lidocaine, alkalinized with 8.4% sodium bicarbonate solution to a final volume of 10 ml) for 5 days provided sustained amelioration of symptoms beyond the acute treatment phase [59].

■ Intravesical hyaluronic acid

Hyaluronic acid is a nonsulfated mucopolysaccharide component of the GAG layer and is believed to be present in subepithelial connective tissue to protect the bladder wall from irritants in the urine. Intravesical treatment with this agent has been investigated in IC/BPS patients. Morales *et al.*

treated 25 IC/BPS patients refractory to any treatment with 40 mg hyaluronic acid weekly for 4 weeks and then monthly [60]. They found an initial 56% positive response rate at week 4, and a 71% positive response rate at week 12. The response was maintained until week 20, but decreased after week 24 [60]. A recent prospective, nonrandomized study with a 3-year follow up in 20 IC/BPS patients revealed subjective continuing improvement in pain and frequency, with 55% of patients treated with intravesical hyaluronic acid choosing to continue treatment for symptomatic relief [61]. Shao *et al.* found intravesical instillation of 40-mg weekly in the first month followed by two monthly instillations may prolong the effect of bladder hydrodistention in patients with severe IC symptoms [62]. Engelhardt *et al.* treated 70 patients of IC/BPS with intravesical hyalurnan and found that 50% of responders had complete bladder symptom remission at 5 years follow up, 41.7% of the patients with symptom recurrence was improved with hyaluronan maintenance therapy [63].

■ **Intravesical chondroitin sulfate**
Chondroitin sulfate is a major component of the GAG layer and comprises a third of the total proteoglycans on the bladder surface. A deficit of chondroitin sulfate proteoglycans on the bladder urothelium has been detected in IC/BPS patients [64]. In total, 18 IC/BPS patients who had a positive KCl test had intravesical instillation of 40 ml of 0.2% chondroitin sulfate once per week for 4 weeks, followed by one treatment per month for 12 months. Of the 18 patients treated, 13 (66.7%) had improvement in lower urinary tract symptoms [65]. Intravesical chondroitin sulfate has been demonstrated to produce a physiological effect of decreasing recruitment of inflammatory cells in an acute rat model of the damaged bladder, supporting the use of intravesical GAG replenishment for bladder disorders with a loss of impermeability [66].

In a multicenter clinical study to evaluate efficacy and safety of intravesical chondroitin sulfate for the treatment of IC/BPS, Nickel *et al.* found 47% of 53 enrolled patients had response at week 10, and 60% at week 24 [67]. However, in a later multicenter, randomized, double-blind, parallel study of 6-week treatment of intravesical sodium condroitin sulfate, the authors did not detect a significant difference between the treament group and vehicle-control group [68]. The second multicenter study of an eight weekly instillation of 20 ml of 2% chondroitin sulfate further revealed the response rate was 38% for the treatment group and 31.3% for the vehicle control group. No significant difference was noted in the IC symptom scores and visual analog score (VAS) pain scores between groups [69].

■ **Cystoprotek**
Cystoprotek was formulated with natural GAG components (each capsule contains glucosamine sulfate 120 mg, chondroitin sulfate 150 mg, sodium hyaluronate 10 mg) to improve GAG integrity, and quercetin 150 mg and rutin 20 mg to reduce bladder-wall inflammation. In a noncontrolled study, Cystoprotek® was found to be effective in 37 patients with IC. Patients received six capsules per day for 6 months and the global assessment scale was reduced from 9.0 to 4.3, the symptom index dropped from 15.3 to 6.9 and the problem index from 13.1 to 5.4 [70]. A recent open-label, uncontrolled study enrolling 250 patients with IC/BPS revealed the VAS of pain could be reduced by approximately 50% in patients overall. The improvement was statistically significant in patients with more severe symptoms [71].

■ **Liposomes treatment**
Intravesical liposomes instillation has been shown to be effective in a bladder hyperactivity rat model. The intercontraction interval showed an increase of 156.8% after liposomes instillation [72,73]. A 4-weekly intravesical instillation of 80 mg/40 ml liposomes was found to be significantly decreased in urinary frequency and nocturia in 12 patients with IC/BPS, an effect similar to that in the PPS group [74]. Among 17 IC/BPS patients who were treated with 4-weekly liposomes instillations or twice a week instillations for 4 weeks, the O'Leary-Sant Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index total score and pain score were significantly improved without any unanticipated adverse events of [75].

Treatments targeting acute suburothelial inflammation

■ **Antihistamines**
The activation of mast cells in the bladder wall has been postulated to play an important role in the pathogenesis of IC/BPS, especially in bladder-pain symptoms [76]. Although an average 40% reduction of symptoms was demonstrated with 25–75 mg hydroxyzine daily for 3 months [77], a recent study conducted by the Interstitial Cystitis Clinical Trial Group revealed no significant difference in clinical efficacy between hydroxyzine and PPS [78].

■ **Amitriptyline**
Amitriptyline is a tricyclic antidepressant with central and peripheral anticholinergic effects. It has antihistamine sedation effects and inhibits serotonin and norepinephrine reuptake. Hanno *et al.* first reported a 95% improvement in bladder pain

and daytime frequency after treatment with amitriptyline [79]. In a recent double-blind, controlled study, van Ophoven *et al.* found a response rate of 64% in 94 patients treated with amitriptyline 12.5–150 mg (mean 55 mg) for 6 weeks. However, adverse effects were noted in 84% of patients, which resulted in a 31% drop-out rate [80]. A recent multicenter, randomized, double-blind, placebo-controlled clinical trial of amitriptyline revealed the rate of response was 55% in the amitryptiline group and 45% in the control group (p = 0.12). Of the subgroup with a higher drug dose (50 mg per day or greater) the response rate was 66 and 47%, respectively (p = 0.01). This study suggested amitryptiline may be beneficial in patients who can achieve a daily dose of 50 mg or greater [81]. Triple combined therapy with gabapentin, amitryptiline, and a nonsteroidal anti-inflammatory drug was recently found to be effective in patients with IC/BPS and caused no significant adverse effects [82].

Treatment targeting chronic suburothelial inflammation

■ Corticotherapy

Soucy *et al.* treated 14 patients with ulcerative IC/BPS refractory to first-line therapies [83]. The patients received 25 mg of prednisolone daily for 1–2 months, which was then tapered to the minimum required for pain relief. Among the nine patients who continued to use prednisolone, 38% had reductions in O'Leary index scores and pain decreased by 88%, while five patients dropped out from the study. The overall result showed a reduction of 22% in symptom scores and 69% improvement in pain. Submucosal injection of triamcinolone was recently found to be effective in 70% of patients with Hunner's ulcer as assessed by Patient Global Impression of Change [84].

■ Cyclosporine A

In a recent report, Sairanen *et al.* found that cyclosporine A was superior to PPS in all clinical outcome parameters measured at 6 months. In a prospective, randomized study comparing cyclosporine A 1.5 mg/kg bid with PPS 100 mg three-times per day, the micturition frequency decreased by 6.7 times per day in the cyclosporine group versus 2.0 times in the PPS group. The clinical response rate was 75% for the cyclosporine A group compared with 19% for PPS. However, more adverse events were noted in cyclosporine A group than in the PPS group [85].

■ Intravesical DMSO treatment

DMSO provides an anti-inflammatory effect, analgesia, muscle relaxation, and alteration of the collagen

response and has an influence on conduction and neurotransmission in sensory nerves. At concentrations of 10%, DMSO inhibits mast-cell secretion, but an initial increase in mast-cell secretion and worsened lower urinary tract symptoms have been noted at a concentration of 50% [86]. Relief of symptoms was reported in 50% of IC/BPS patients treated with 50 ml of 50% DMSO retained for 15–20 min, given once per week for 2–3 months. However, the relapse rate was 35–40% over a 24-month follow up [87]. The high concentration of DMSO has been thought to harm the bladder wall, resulting in a contracted bladder after repeated instillations. Melchior *et al.* found a 40% concentration of DMSO completely and irreversibly abolished contractions of rat bladders [88]. A recent study found 65.5% of patients who completed a DMSO cocktail-solution treatment experienced a >50% symptomatic improvement. Presence of advanced cystoscopic glomerulations, microscopic hematuria and urodynamics detrusor underactivity, however, may adversely affect treatment [89].

■ Intravesical Bacillus Calmette–Guérin Treatment

Intravesical Bacillus Calmette–Guérin (BCG) is an immunological therapy for superficial bladder cancer and is known to stimulate the Th1 cytokine profile. The use of BCG in the treatment of IC/BPS aims to modulate immunologic and allergic responses in the IC/BPS bladder wall [90]. In a double-blind, placebo-controlled study, 30 IC/BPS patients meeting NIDDK criteria received 6-week treatments with Tice strain BCG instillation or a placebo and were followed up for 8 months. There was a 60% response rate in the treated patients and a 27% rate in the control group [91]. In the long-term follow up, 89% of patients who responded favorably after the 6-week BCG treatment continued to have an excellent response at 24–33 months [92]. However, the Interstitial Cystitis Clinical Trials Group recently reported the results of a multicenter, randomized, double-blind, placebo-controlled trial of intravesical BCG for the treatment of refractory IC/BPS. Among 265 patients who received BCG or a placebo and were followed up for 34 weeks, the response rate was 12% for the placebo and 21% for BCG (p = 0.062). Only marginal statistical significance was observed in the secondary outcomes (voiding diary, pain, urgency and IC-symptom index). Although the safety profile was acceptable, intravesical BCG treatment was considered ineffective in treatment of refractory IC/BPS [93]. In a continuing study, patients who had no response to BCG treatment were offered treatment with open-label BCG, using the same course of treatment and follow up, the response rate was only 18%; therefore, the use of intravesical BCG for IC/BS is no

longer considered for patients with IC/BPS [94].

■ Bladder hydrodistention

Cystoscopy with hydrodistention and biopsy is the first choice for diagnosis, classification and treatment. Although hydrodistention is effective for relief of bladder symptoms of IC/BPS, the symptoms usually recur within 2 weeks and repeat hydrodistention is necessary. Prolonged hydrodistention under epidural anesthesia with an intravesical pressure equal to the mean arterial pressure of the patient has been shown to give long-term effects. Glemain *et al.* treated 65 consecutive IC/BPS patients and found this treatment was effective in 60% of patients at 6 months and 43.3% at 1 year [95]. Yamada *et al.* also had similar therapeutic results. In their study, adjuvant hydrodistention under epidural anesthesia was effective for 70% of patients for >3 months [96]. Rose *et al.* found that distention with electromotive drug administration in the doctor's office setting was as effective as hydrodistention of the bladder in the operating room [97].

Targeting the suburothelial inflammation & detrusor

■ Intravesical vanilloids

Vanilloid receptors (VR1) have been found to locate on the urothelial cells, suburothelial sensory afferents and smooth muscle cells. VR1 co-localizes with P2X3 receptors, mediating stretch, pain and noxious stimuli. Desensitization of VR1 receptors may deplete terminal nerve endings and end pain [26,98]. The most popular vanilloid agents used for clinical trials in IC/BPS are capsaicin and resiniferatoxin (RTX). A total of 36 patients with hypersensitive disorders and bladder pain were randomized to receive intravesical capsaicin 10 nM or a placebo twice weekly for 1 month. All patients had at least a 6-month history of frequency, nocturia, urgency and symptoms of pelvic pain. Significant improvement in frequency and nocturia was noted in the capsaicin-treated patients at the 6-month follow up. Both groups experienced a significant reduction in pain at the end of treatment and at the 6-month follow-up evaluation. However, no improvement in urgency was experienced after capsaicin instillation [99]. Intravesical capsaicin therapy was also investigated in Taiwan. The author had treated 10 patients with IC/BPS and 10 with hypersensitive bladders. Capsaicin in a 10 nM concentration was instilled intravesically once per week for 6 weeks. There was a short response period in eight patients with hypersensitive bladders (3–5 days) and in two IC/BPS patients (2–3 days). Nevertheless, no side effects were reported except for severe irritative symptoms

after treatment [100].

Lazzeri *et al.* treated 18 IC/BPS patients with single dose of 10 nM RTX or a placebo. Significant improvements in frequency, nocturia and pain scores were noted at 30 days, but therapeutic effects were reduced at 3 months [99]. The same author further treated five women with IC/BPS with prolonged intravesical infusion of 10 nM RTX for 10 days. The pain score (6.7–3.2) decreased after treatment and remained significantly lower at 3 months. Frequency (11.3–8.7 times) and nocturia (3.6–1.9 times) were also reduced at 3 months [101]. In a preliminary study, Kuo found multiple intravesical treatments with RTX 10 nM once weekly for 4 weeks was well tolerated and reduced bladder pain and increased the symptom score in 58% of 12 women with chronic IC/BPS [Kuo HC, Unpublished Data, 2006]. Although these preliminary studies seem promising, a recently reported multicenter, randomized, placebo-controlled trial to assess the efficacy and safety of single-dose RTX to treat IC/BS revealed no significant difference between RTX and a placebo [102]. In 163 IC/BPS patients treated with 10, 50, or 100 nM RTX, or a placebo in single intravesical treatment and followed up over 12 weeks, RTX did not improve the overall symptoms, pain, urgency, frequency, nocturia, or average void volume at 12 weeks. The bladder pain induced by RTX instillation increased with higher doses [102]. However, in a recent study comparing intravesical RTX instillation plus hydrodistention and hydrodistention alone, it was revealed that the treatment was effective in relieving pain but was not effective in improving lower urinary tract symptoms [103].

■ Intravesical botulinum toxin A

Botulinum toxin A (onabotulinumtoxinA, Botox®) is an inhibitor of acetylcholine release at the presynaptic neuromuscular junction. Inhibition of acetylcholine release results in regional decreased muscle contractility at the injection sites. This chemical denervation is a reversible process, and axons resprout in about 3–6 months. VR1 receptors are co-localized with P2X3, CGRP, or substance P in the urothelium and suburothelial sensory fibers. A significant decrease was noted in P2X3-immunoreactivity of suburothelial fibers at 4 weeks with a further decrease at 16 weeks after Botox injection in the responders of detrusor overactivity [104]. The study speculated that onabotulinumtoxinA might reduce production/uptake of neurotrophic factors, and regulate expression of VR1 and/or P2X3. In an animal model, Chuang *et al.* found that intravesical onabotulinumtoxinA

blocked acetic acid-induced bladder pain responses and inhibited CGRP release from afferent nerve terminals [105]. Intravesical onabotulinumtoxinA injections might not only reduce bladder sensitivity in IC/BPS patients but also induce desensitization in the CNS through affecting the over-expression of activated proteins in the dorsal horn ganglia [106].

Smith *et al.* treated 13 IC/BPS patients with 100–200 U of Dysport or onabotulinumtoxinA submucosally in the trigone and bladder base and found that 69% of patients had subjective improvement after onabotulinumtoxinA injections. The symptom index improved by 71%, problem index by 69%, and bladder pain by 79%. They concluded that onabotulinumtoxinA might have an antinociceptive effect on bladder afferent pathways in IC/BPS patients [107]. In another study, Kuo used suburothelial injections of onabotulinumtoxinA to treat ten women with IC/BPS and improved results were reported in seven women. All patients with therapeutic effects had dysuria after treatment [108]. The functional bladder capacity recorded in a voiding diary significantly increased and the daily frequency and pain score significantly decreased after treatment. However, only cystometric capacity showed a significant increase (287 ± 115 vs 210 ± 63.8 ml; p = 0.05) in all urodynamic parameters. The author also noted that trigonal injections did not result in symptom or urodynamic improvement. Nevertheless, no adverse effects were reported.

The effect of onabotulinumtoxinA on IC/BPS patients was further confirmed by a recent study. Giannantoni *et al.* treated 14 patients with injections of 200 U of onabotulinumtoxinA in 20 ml saline at 20 sites in the trigone and bladder base. In total, 12 patients (85.7%) reported subjective improvement at 1 and 3 months, scores on the VAS decreased, frequency decreased and bladder capacity increased significantly. Two patients reported dysuria and intermittent clean catheterization was needed [109]. The same authors evaluated the 1-year efficacy and tolerability of intravesical onabotulinumtoxinA injection [110]. Among 13 patient,s 86.6% reported subjective improvement at the 1- and 3-month follow-ups. At the 5-month follow up the beneficial effects persisted in 26.6% and at 12 months after treatment, pain recurred in all patients. Dysuria persisted in four patients at 3 months and in 2 at 5-month follow up. Nevertheless, the authors found that intravesical onabotulinumtoxinA treatment reduced bladder pain, improved psychosocial functioning and well being [111].

We have compared the clinical effectiveness of intravesical onabotulinumtoxinA injections followed by cystoscopic hydrodistention and hydrodistention alone in 67 patients with IC/BPS. onabotulinumtoxinA 200 U and 100 U were given in 15 and 29 patients and hydrodistention alone in 23 patients. The IC symptom score significantly decreased in all three groups, but VAS reduction, increases of functional bladder capacity and cystometric bladder capacity were significant only in the onabotulinumtoxinA groups at 3 months. Of the 44 patients in the onabotulinumtoxinA groups 31 (71%) had a successful result at 6 months, 24 (55%) at 12 months and 13 (30%) at 24 months [112]. In the investigation of the level of NGF mRNA in bladder tissue at baseline and after onabotulinumtoxinA injection, it was found that NGF levels in the bladder tissue are significantly increased in patients with IC/BPS and decreased to the normal range after onabotulinumtoxinA treatment [113]. The bladder tissue NGF levels were significantly decreased to normal levels after treatment in responders but not in nonresponders. Another recent study using 100 U onabotulinumtoxinA to treat women with IC/BPS by 10 trigonal injection sites found all patients had subjective improvement at 1- and 3-month follow up. The treatment remained effective in >50% of the patients for 9 months. The authors concluded that trigonal injection of onabotulinumtoxinA is a safe and effective treatment for refractory IC/BPS [114].

The largest cohort of onabotulinumtoxinA treatment for patients with IC/BPS was recently reported [115]. Intravesical injection of 100 U of onabotulinumtoxinA immediately followed by cystoscopic hydrodistention under intravenous general anesthesia was performed in 67 patients with IC/BPS. Changes of the urodynamic parameters, O'Leary-Sant Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index, VAS for pain, functional bladder capacity, and global response assessment (GRA) were evaluated at baseline and 6 months after onabotulinumtoxinA injection. Significant improvement was shown after intravesical injection of 100 U of onabotulinumtoxinA. Baseline and 6 months after injection scores were: Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index: 23.6 ± 5.9 vs 15.2 ± 8.5; p = 0.000; VAS: 5.3 ± 2.2 vs 3.3 ± 2.4; p = 0.000; functional bladder capacity: 136 ± 77.6 vs 180 ± 78.2; p = 0.000; and GRA: 0.3 ± 0.8 vs 1.4 ± 1.0; p = 0.000. Intravesical onabotulinumtoxinA injection appears to be a safe and effective therapeutic option for analgesia and increased bladder capacity for patients with IC/PBS.

The relationship between urothelial apoptosis and chronic bladder inflammation in the bladder wall

of IC/BPS and after intravesical onabotulinumtoxinA injections was recently investigated [116]. Single onabotulinumtoxinA injection improved clinical symptoms, pain score and daytime frequency in 23 patients. In the histological analysis, mast-cell activity stain and apoptotic cell count did not decrease significantly; Bax and p-p38 but not tryptase content showed a significant decrease after a single BoNT-A injection. In the 11 patients receiving three repeated onabotulinumtoxinA injections, significant decrease of pain score (5.80 ± 2.27 vs 3.03 ± 2.30; $p = 0.000$), glomerulations degree (1.80 ± 1.06 vs 1.20 ± 1.06; $p = 0.026$) and GRA (0.30 ± 0.92 vs 1.20 ± 1.06; $p = 0.000$) were noted after treatment. The tryptase, Bax, p-p38 contents and apoptotic cell counts all showed significant decrease. SNAP25 content in the bladder also decreased after onabotulinumtoxinA treatments, which confirmed the therapeutic effect of repeated onabotulinumtoxinA injections. This study confirmed that chronic inflammation and apoptotic signaling molecules can be significantly reduced after repeated onabotulinumtoxinA injections in IC/BPS bladders. The immunohistochemistric improvement is associated with clinical symptom improvement. Repeated onabotulinumtoxinA injections is necessary to achieve a higher success rate in treatment of IC/BPS.

Repeated onabotulinumtoxinA injections plus hydrodistention might provide a better outcome in treating IC/PBS. If repeated onabotulinumtoxinA injections can relieve bladder pain and increase bladder capacity in responders, the result might provide evidence of urothelial repair and reduction of suburothelial inflammation in IC/BPS responders. Chronic suburothelial inflammation might alter urothelial function and cell differentiation, and onabotulinumtoxinA injection might reduce the inflammation and restore a healthy urothelium, thereby improving the clinical symptoms of IC/BPS.

Targeting dorsal root ganglia & sacral cord inflammation: neuromodulation
Sacral nerve stimulation is thought to act via stimulation of somatic afferents, which inhibit the transmission of afferent messages arising from the bladder [117]. Therefore, sacral nerve stimulation has been applied to improve urgency, frequency and urge incontinence as well as IC/BPS symptoms [118]. Although currently the US FDA has not approved sacral nerve stimulation for this indication, several studies have demonstrated promising results.

Peters *et al.* found that sacral neuromodulation decreased narcotic requirements and subjective pelvic pain in 21 patients with refractory IC/BPS [119].

In another neuromodulation model, significant improvement in frequency, urgency and quality of life was noted in 51 women after posterior tibial nerve stimulation for 30 min weekly for 10 weeks [120]. In 33 women with IC/BPS, improvement in frequency, pain, voided volume, and bladder capacity was seen after percutaneous sacral nerve root stimulation [121]. Although the mechanisms of neuromodulation remain unclear, this therapeutic modality has been used to treat IC/BPS patients who are refractory to conventional therapies.

Zabihi *et al.* performed bilateral caudal epidural sacral neuromodulation in 30 patients with chronic pelvic pain and IC/BPS and found 23% of them had a successful trial stimulation and were permanently implanted. On average, patients reported a 42% improvement in their symptoms [122]. Powell *et al.* presented their long-term experience with sacral neuromodulation of a quadripolar permanent lead. Long-term success was noted in 92.3% of 13 patients with this device, however, 50% of them required device explantation [123]. Another study revealed that the explanation rate was 28% in 78 patients with IC/BPS. The commonest reason for explantation was poor outcome (54% of the failed patients), and the revision rate was 50% due to lack of stimulation sensation and worsening of symptoms [124]. It is essential to investigate the role of sacral neuromodulation in the treatment of IC/BPS. Patients should be carefully informed of the rates of explantation and revision of devices [125].

Bladder augmentation & cystectomy
Cystourethrectomy with urinary diversion or bladder augmentation is the ultimate option for the treatment of refractory IC/BPS, particularly in patients with intractable pain. Augmentation cystoplasty increases bladder storage capacity and may relieve bladder pain and frequency–urgency symptoms in patients with IC/BPS. Lotenfoe *et al.* achieved an overall success rate of 73% with cystourethrectomy and colonic urinary diversion [126]. They noted the success rate was 88% in patients with bladder capacities <400 ml, but only 20% in patients with capacities >400 ml. These results raise the possibility that in some IC/BPS patients, the visceral pain might originate from central sensitization or psychological pain rather than the visceral organ itself. Trigonal sparing orthotopic caecocystoplasty was reported to be effective in intractable IC/BPS after a 9-year follow up. However, problems with complications such as *de novo* clean intermittent self-catheterization, recurrent symptoms and carcinoma remain unsolved [127]. In another study, 14

of 18 patients treated with substitution enterocystoplasty (trigonal sparing) were pain free, 15 had resolution of dysuria and 12 could void spontaneously [128]. Bladder autoaugmentation has also been used to try to treat refractory IC/BPS patients. Bladder autoaugmentation without cystectomy resulted in reduced bladder pain but only a limited increase in bladder capacity in long-term follow up [Kuo HC, Unpublished Data]. In a large series single-center report, patients with refractory IC/BPS received subtotal cystectomy and bladder augmentation, or supravesical urinary diversion with intact bladder. Of these patients, 13 were later operated on with cystectomy due to persistent pain 12 months after the primary procedure. Overall, 74% of patients were free of pain, 68% were satisfied with the end result [129]. In appropriately selected patients, bladder augmentation provides an excellent treatment option to improve bladder capacity, achieve socially acceptable continence, and stabilize renal function [130].

Other new therapies for refractory IC/BPS

Numerous new therapeutic modalities have been developed in recent years, including cimetidine for BPS [131], hormonal manipulation with leuprolide acetate and oral contraceptive pills [132], hyperbaric oxygen [133,134], and doxycycline [135]. These treatments have shown good early-response rates. In a double-blind, sham-controlled study to evaluate the safety, efficacy and feasibility of hyperbaric oxygenation for IC/BPS, van Ophoven *et al.* found that a total of 30 treatment sessions of hyperbaric oxygenation appeared to be a safe, effective and feasible therapeutic approach to IC/BPS [136]. The therapeutic effects require further clarification. In a recent randomized, double-blind, placebo-controlled Phase II study of tanezumab, a humanized monoclonal antibody that specifically inhibits NGF as a treatment for IC/BPS, tanezumab was found to significantly reduce urgency-episode frequency. The most common adverse events are headache and paresthesia [137].

Multimodal therapy for IC/BPS

Since the etiology of IC/BPS is thought to be multifactorial, multiple therapies might produce synergistic effects and better outcomes. Patients with moderate to severe levels of the disease may require a multimodal therapeutic approach using oral PPS as a foundation of medication, combined with intravesical PPS instillation [138], or combined sequential cystoscopic hydrodistention in combination with intravesical hyaluronic aid instillation [139], or a combination of intravesical hyaluronic acid with chondroitin sulfate [140]. Patients with severe bladder

pain may require combined alkalinized lidocaine and heparin instillation, which provides up to 12 h of relief from urgency and pain [141]. Intravesical instillation of combined hyaluronic acid and alkalinized lidocaine may provide both immediate and sustained relief of symptoms in severe IC/BPS patients [142]. Nonpharmacologic approaches, such as bladder training, biofeedback and dietary changes can also provide supplementary relief, and should be added to the treatment of refractory IC/BPS [143,144].

Conclusion

Treatment of IC/BPS should be based on the possible pathophysiology. Lifestyle modification, oral analgesics, antihistamine, intravesical hyaluronic acid with or without chondroitine, GAG replenishment, neuromodulation, intravesical onabotulinumtoxinA injections and bladder augmentation have proven effective in a number of patients. Alkalinized lidocaine can be used as 'rescue' instillation. Amitriptyline has proven effective in a previous randomized study and has been shown to be effective in another study using higher doses in treatment of severe bladder pain. A combination of several therapeutic modalities to yield a better outcome is feasible. Several previously considered novel and effective treatments have been proven ineffective in the treatment of IC/BPS, such as BCG, resiniferatoxin, chondroitin sulfate, and so on. Large-scale randomized, controlled studies should be performed to reveal the actual therapeutic effectiveness of novel treatments.

Future perspective

Currently, the definite etiology of IC/BPS remains unclear. The management of IC/BPS is directed to pain relief. It is believed that IC/BPS may have multiple etiologies including alterations in urothelial permeability, abnormal sensory nerve stimulation, and mast-cell activation are inter-related simultaneously. This complexity of mechanisms results in the chronicity of IC/BPS and an unsatisfactory response to single-modality treatment. Several intravesical therapies cannot eradicate bladder pain and bothersome urinary symptoms in most patients with IC/BPS, suggesting restoration of epithelial integrity can only partially repair the damaged urothelial barrier but not the submucosal inflammation or possible central sensitization pain process that characterizes IC/BPS. It is believed that IC/BPS also represents a visceral neuropathic pain syndrome mediated by upregulation of nerves in the pelvis, spinal cord and brain. OnabotulinumtoxinA acts by cleaving the SNAP-25 complex in the presynaptic terminal, which prevents formation of the SNARE system. The release

Executive summary
Pathophysiology
■ The actual etiology of interstitial cystitis (IC)/bladder pain syndrome (BPS) remains unclear; the possible etiologies include:
- A postinfection autoimmune process;
- Mast-cell activation induced by inflammation, toxins or stress;
- Urothelial dysfunction and increased permeability of the urothelium;
- Neurogenic inflammation.
Therapeutic basis
■ The principles for treatment of IC/BPS are based on:
- Controlling the dysfunctional epithelium by continual replenishment of the glycosaminoglycan layer;
- Inhibiting neurological hyperactivity;
- Suppression of allergies and;
- Pain control with nonsteroidal anti-inflammatory drugs, COX-2 inhibitors or tranquilizers. Since the etiology of IC is thought to be multifactorial, multiple therapies might produce synergistic effects and better outcomes.
Previous treatment modalities
■ Amitriptyline is effective in higher doses in treatment of severe pain. Several previously considered novel and effective treatments have proven ineffective in treatment of IC/BPS, such as Bacillus Calmette–Guérin, resiniferatoxin, chondroitin sulfate, and so forth.
Future perspective
■ In future, repeated intravesical onabotulinumtoxinA injections plus glycosaminoglycan replenishment might provide a prospective treatment outcome for patients with IC/BPS refractory to convention therapies.

of acetylcholine, CGRP, substance P and glutamate decreased and then the nociceptive fiber discharge reduced after intravesical onabotulinumtoxin A injection. More and more evidence has shown that intravesical onabotulinumtoxinA injection is a minimally invasive treatment option for IC/BPS. Repeated intravesical onabotulinumtoxinA injections plus GAG replenishment might provide a prospective treatment outcome for patients with IC/BPS.

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