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Current standard of care in treatment of bladder pain syndrome/interstitial cystitis

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***Abstract*:** Bladder pain syndrome/interstitial cystitis (BPS/IC) is a debilitating, systemic pain syndrome with a cardinal symptom of bladder related pain with associated systemic symptoms. It is characterized by an inflammation that partially or completely destroys the mucus membrane and can extend into the muscle layer; however, the etiology and pathogenesis is still enigmatic. It has been suggested that mast cell activation, defects in the glycosaminoglycan layer, non-functional proliferation of bladder epithelial cells, neurogenic inflammation, microvascular abnormalities in the submucosal layer, autoimmunity and infectious causes may cause BPS/IC. Available treatment options include general relaxation techniques, patient education, behavioral treatments, physical therapy, multimodal pain therapy, oral (amitriptyline, cimetidine, hydroxyzine) and intravesical treatments (heparin, lidocaine, hyaluronic acid and chondroitin sulfate), hydrodistension and other more invasive treatments. Available treatments are mostly not based on a high level of evidence. Lack of understanding of disease mechanisms has resulted in lack of targeted therapies on this area and a wealth of empirical approaches with usually inadequate efficacy. The aim of this article is to review the available evidence on the pathophysiological mechanisms of BPS/IC as they relate to available treatment options.

Keywords: bladder pain syndrome, interstitial cystitis, pathophysiology, treatment

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Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a debilitating pain syndrome predominantly effecting females. Different terminologies have been used to describe this condition, resulting in inconsistencies and high variability in evidence synthesized from clinical practice and research data.[1] The term interstitial cystitis (IC) was first used by Skene in 1887 based on typical findings in cystoscopic examination, such as glomerulations, or the pathognomonic Hunner's ulcer in the bladder wall. In 2002, the International Continence Society defined painful bladder syndrome (PBS) or IC as "a clinical syndrome characterized by the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology", recommending the use of the term PBS, since IC is a histologic diagnosis *per se*.[2] This was followed in 2008 by suggestion of the use of the term bladder pain syndrome (BPS) by the European Society for the Study of Interstitial Cystitis alongside a proposed clinical phenotyping system based on cystoscopic and histological findings.[3] Later on, the American Urology Association and the European Association of Urology (EAU) promoted the use of a standardized terminology to define this condition, using slightly different definitions (summarized in Table 1). Taken together, all of the current standard definitions of BPS/IC agree on describing the condition as a pain syndrome defined by exclusion of other causes and pain mainly perceived as related to the bladder with co-existing lower urinary tract symptoms (such as urgency and frequency). The chronic nature of the pain is also highlighted, although the duration of pain required to have a diagnosis is described variably between 6 weeks and

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Table 1. Available terminologies used to define bladder pain syndrome/interstitial cystitis.

Society	Terms	Definitions
IASP[4]	IC BPS	Chronic pain, pressure and discomfort (with a duration of more than 3 months) associated with urinary urgency or frequency without any readily explainable cause (infection, neoplasm or structural abnormality).
ICS (ICI)[2]	IC PBS	Complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology.
ESSIC[3]	IC PBS	Chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies. The presence of other organ symptoms as well as cognitive, behavioral, emotional and sexual symptoms should be addressed.
EAU[5]	BPS	Persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and daytime and/or night-time urinary frequency. There is no proven infection or other obvious local pathology.
SUFU (AUA, CUA)[6]	IC BPS	An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms for more than 6 weeks' duration, in the absence of infection or other identifiable causes.
JUA[7]	IC BPS	The condition with chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by other urinary symptoms, such as persistent urge to void or urinary frequency in the absence of confusable diseases.

AUA, American Urology Association; BPS, bladder pain syndrome; CUA, Canadian Urology Association; EAU, European Urology Association; ESSIC, International Society for the Study of BPS; IASP, International Association for the Study of Pain; IC, interstitial cystitis; ICI, International Consultation on Incontinence; ICS, International Continence Society; JUA, Japanese Urology Association; PBS, painful bladder syndrome; SUFU, Society for Urodynamic and Female Urology.

6 months, Although all of the clinical guidelines recognize the misleading character of the term "interstitial cystitis", all guidelines apart from the EAU guideline kept it as a term included in all of the terminologies.

BPS/IC is contemporarily seen as a biopsychosocial disorder necessitating a multidisciplinary approach in the clinical management. The use of a multidisciplinary phenotyping system, UPOINT (urinary, psychosocial, organ-specific, infection, neurologic and/or extrapelvic/systemic pain, and tenderness of pelvic floor),[8] is recommended[5] to better characterize what domains are involved in each patient with the hope of directing multimodal therapy and improving patient outcomes. In one study, a phenotype directed approach resulted in clinically significant improvement in BPS/IC symptoms at 1 year follow-up.[9] Also, there is evidence to suggest that improvement in one domain can lead to a favorable effect in the others.[10]

The prevalence of BPS/IC is also highly variable, with different numbers being reported depending on the definition and diagnostic criteria used, the method used to investigate and characteristics of the populations studied. The reported prevalence rates range between 0.06% and 30%. In the United States, the estimated prevalences reported were between 2.7% and 6.5% of women ⩾18 years old[11] and 1.9–4.2% of men.[12] BPS/IC is also considered as a rare disease (ORPHA:37202), which is defined in Europe as any disease that effects less than one person in 2000.

BPS/IC is essentially a diagnosis of exclusion of confusable diseases. Cystoscopy is often performed

to exclude underlying pathologies such as vesical stones, bladder cancer or urethral diverticula and to look for the typical changes in the bladder mucosa such as glomerulations on cystodistension and Hunner's lesion. However, cystoscopy evaluation is not mandatory in diagnosis or the follow-up of BPS/IC and it is recommended that the diagnosis of this condition should not be delayed until cystoscopy and can be made based on clinical findings only.[13] Numerous biomarkers have been studied, such as urinary and serum nerve growth factor (NGF), pro-inflammatory cytokines and receptors related to pro-nociceptive inflammatory reactions. However, to date there is no clinically useful biomarker that can be used in diagnosis or follow-up of the condition. Therefore, BPS/IC remains largely unknown in many aspects, including its epidemiology, pathophysiology and clinical characteristics. That has direct implications on its treatment, which is still symptomatic with limited efficiency, adding to the suffering of patients with this condition.

Recent establishment of dedicated funding schemes to support rare disease research can potentially lead to an increase in basic scientific and clinical research in this area. It has been recognized that rare disease research requires special research methodologies such as data collection, data analysis and international collaborations as opposed to research on more prevalent diseases that the scientific communities are more familiar with. Taken together we could expect to see better quality basic scientific and clinical research in this area in the near future. Accordingly, the aim of this article is to review the current evidence on the pathophysiology of BPS/IC with a view to determining the most promising targets for possible novel treatments.

Methods

We performed a narrative review of the available literature. A search on *Medline*, *PubMed* and *Embase* databases was conducted to cover the period between 2000 and 2021. All publications reporting on the treatment of IC/PBS were included. Publications written in languages other than English were excluded. The following keywords were used for the search: IC, BPS, chronic cystitis, painful bladder, hypersensitive bladder, treatment. Additionally, reference lists of the existing guidelines were screened for relevant studies.

Etiology and pathophysiology

Although the pathophysiologic mechanisms underlying BPS/IC are still enigmatic, several theories attempted to explain the mechanisms underlying this condition. The current evidence on the pathophysiology of BPS/IC has been reviewed in detail recently by others. Here we will only summarize what is known on the subject as an introduction to the Treatment section[7,14–16] (Figure 1).

A widely accepted theory in the pathophysiology of BPS/IC identifies an initial damage/defect in the mucosal lining of the bladder that triggers the chronic inflammatory state. The urothelium has a specialized structure containing polysaccharides (chondroitin sulfate and hyaluronic acid) in the superficial layers and glycoproteins in the deep layers.[17] This structure results in a non-adherent and strictly impermeable layer to the bacteria and irritant substances in urine. A deficiency or damage to the components of this permeability barrier may lead to leakage of urine constituents into the suburothelial spaces and the bladder wall.[18] Abnormal expression of uroplakins, chondroitin sulfate and tight junction proteins have been detected in bladder biopsies of patients with BPS/IC.[19] Substances in urine such as potassium ion can leak through the urothelium and cause depolarization in muscle and nerve cells, trigger inflammatory cascades and degranulate mast cells, leading eventually to the development of lower urinary tract symptoms (LUTS).

In addition to its barrier function, the urothelium also plays a role in sensory transduction by detecting physiological and chemical stimuli in the bladder wall and releasing signaling molecules.[20] Although the mechanisms by which the urothelium contributes to sensory functions of the bladder are not completely elucidated, several substances released by the urothelial cells (such as substance P, acetylcholine and ATP) can stimulate bladder afferent neurons.

Chronic inflammation is also thought to play a role in pathogenesis of BPS/IC. Infiltration of mast cells, leucocytes and lymphocytes has been demonstrated in the suburothelial layers and bladder wall together with increased vasculature and thickened bladder wall in bladder biopsies of some patients with bladder pain. This is supported by clinical observations that the patients frequently report an initial urinary tract infection (UTI) that started their chronic pain. Recurrent

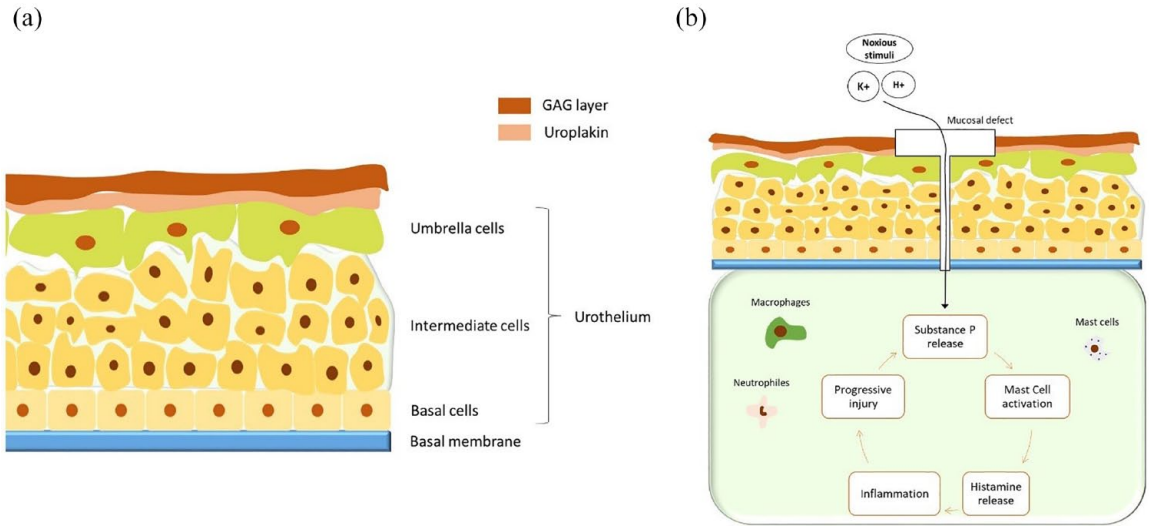

Figure 1. Schematic presentation of normal bladder urothelium (a) and proposed pathogenesis of bladder pain after an initial damage to urothelium (b) GAG, glycosaminoglycan.

urinary infections are more common during childhood in patients who develop the disease in adulthood and the symptoms of cystitis are similar to the symptoms of bacterial cystitis. Nevertheless, up to now there has been no robust evidence for the presence of any microorganisms or their genetic material in urine or biopsy samples of women with BPS/IC compared with controls. Although the mechanisms by which infections induce pain are not understood, experimental studies revealed that the induction of *Escherichia coli* mutant defective for O-antigen biosynthesis causes allodynia, which persisted a for long time after the infection was cured.[21] Therefore, BPS/IC could still be a sterile/persistent inflammation state that was initiated by an initial microbial cystitis.

Mast cell proliferation and activation has been studied extensively to elucidate their role in bladder immune response. Increased amounts of mast cells are found in the suburothelial space in patients with type 3 BPS/IC.

Mast cells secrete vasoactive factors, neurotrophins and cytokines, leading to visceral inflammation and neurogenic inflammation. Increased excitability and the loss of inhibition on peripheral afferents (Aδ and C fibers) initiate a central sensitization by increasing the neural input to the central nervous system. Clinically a hyperalgesia and allodynia can result from this upregulated central and peripheral reactivity. Nevertheless, mast cell count and perineural inflammatory are lacking in non-lesion BPS/IC. Different inflammatory mediators, such as nitric oxide, leukotriene D4 or blockade of interferon-gamma-inducible protein-10, are increased in all types of BPS/IC bladder.[22]

Another hypothesis proposes that BPS/IC can be a local manifestation of a systemic syndrome. Furthermore, some studies have reported an increased sympathetic tone with decreased cortisol level. These facts suggest that there may exist an autonomic etiology. In addition, some disorders, such as irritable bowel syndrome, pelvic floor tension myalgia, abdominal wall myalgia, vulvodynia, migraine, anxiety and depression, have been related to BPS/IC.[23–25]

In summary, the exact pathophysiology of BPS/IC is not completely understood. BPS/IC likely has a multifactorial etiology where a combination of a defect in the urothelium starts mast cell activation that then leads to activation of silent C-fibers in the suburothelial tissues and a sustained state of inflammation with increase in inflammatory mediators, resulting in a symptom complex typical of BPS.

Treatment

Standard treatments

BPS/IC is a chronic condition that has a significant impact on the quality of life (QoL) of

patients. BPS/IC affects QoL more than being on long-term hemodialysis, having Crohn's disease, systemic lupus erythematosus or rheumatoid arthritis. Therefore, the main target for treatment of BPS/IC is to improve QoL.[26]

A cure for BPS/IC has not been developed currently. Due to a lack of understanding of the pathophysiology, treatment targets are poorly defined and current management mainly focuses on palliation of symptoms. Being a pain syndrome of unknown cause with systemic manifestations a holistic approach with multimodal treatment emphasizing active involvement of patients is important. Behavioral, psychological, pharmacological, endoscopic and surgical therapies need to be considered simultaneously.

The first step in management of patients with BPS/IC includes patient education on the disease as well as discussion on the risks and benefits of available treatment options. It has been shown that providing information improves therapy adherence and its response.[27] A main target for drug treatment of patients with BPS/IC is relief of pain. Pain management would ideally be achieved within a multidisciplinary unit, such as a pain management team, consisting of physiotherapists, psychologists and doctors. Additionally, behavioral and cognitive treatments need to be considered to address social and psychological stress.[28] Pharmacotherapy includes a wide range of drugs, such as urinary analgesics, non-steroidal anti-inflammatory drugs and narcotic analgesics. Amitriptyline, or alternatively nortriptyline, is a tricyclic antidepressant which has demonstrated BPS/IC symptom improvement in up to 50% of patients when compared with placebo plus behavioral modification. Amitriptyline can be initiated at low doses (10 or 25 mg) and increased gradually to 75–100 mg as tolerated. Due to the role of mast cells in BPS/IC, anti-histaminic drugs (such as hydroxyzine, cimetidine) can also be used.

Pentosan polysulfate is the first medication approved by FDA for the indication of BPS/IC. The clinical efficacy of pentosan polysulfate in reducing pain, urgency and frequency vary widely between 21% and 56% compared with placebo.[29] The main adverse effects of oral pentosan polysulfate include diarrhea, vomiting, rectal bleeding and alopecia.

Intravesical treatments represent another option that can be used in BPS/IC patients. Drugs are administered in high concentrations in the bladder, raising the bio-availability and diminishing side-effects. Lidocaine is a local anesthetic which can be administered intravesically. It is usually administered with alkalization to improve urothelial penetration. Symptom improvement can be achieved in 30–50% of patients with intravesical instillation,[8] which can be increased up to 70% when combined with bicarbonate and heparin. Another intravesical agent that can be used is dimethylsulfoxide (DMSO). DMSO showed between 47% and 87% of symptom improvement with minor side effects.

Intravesical GAG replenishment therapies with hyaluronic acid (HA) and chondroitin sulfate (CS) have been shown to be effective in palliation of symptoms. Instillation of HA and CS aims to restore the glycosaminoglycan (GAG) layer lining the urothelium. Although the clinical efficacy of these therapies has been demonstrated in randomized controlled trials[30,31] the magnitude of effect is generally limited and combination therapies are required.

Investigational treatments

The following molecular targets have been investigated to treat BPS/IC.

Transient receptor potential channels. The family of transient receptor potential (TRP) channels has been recognized to play a crucial role in LUT dysfunction.[32] TRP channels V1,2,4, M8 and A1 are mostly expressed in the urethra and bladder, and they receive the sensation of tension and/or chemical irritation. Although TRP channels are predominantly expressed in afferent neurons, they are also found in the urothelium, interstitial cells, and detrusor and urethral smooth muscle.[33] TRP channels are mostly located in the plasma membrane and are responsible for the transportation of Ca, Mg and metal ions across the cell membrane. TRP channels play a role in many physiological processes such as sensory functions (sensation of pain and heat), hemostatic functions, and vasomotor functions and muscle contraction.[34]

The best-defined receptor in the family of TRP channels is the vanilloid 1 (TRPV1) receptor. Low pH, painful stimulus and vanilloids activate these channels. Capsaicin and resiniferatoxin are natural ligands of TRPV1 and cause desensitization by activating this receptor.[35] Resiniferatoxin is 1000 times more potent than capsaicin.[36]

Intravesical capsaicin therapy has been used effectively in the treatment of detrusor overactivity (DOA) in patients with neurogenic bladder.[37,38] For treatment of idiopathic DOA, intravesical resiniferatoxin therapy has been controversial.[39–43] The main reason for limited use of TRPV1 antagonists is the observation of significant increase in body temperature in the initial clinical trials with the first generation of TRPV1 antagonists.[44]

On the other hand, TRPV1 antagonists have been investigated in clinical trials for treatment of conditions associated with chronic inflammatory pain, such as osteoarthritis[45] and chronic cough.[46] Although the potential of TRPV1 receptors is exciting as targets to block pain sensation, current clinical studies have not used TRPV1 antagonists in the context of lower urinary tract dysfunction (LUTD). TRPV4 has been investigated as another target in BPS/IC after demonstration of lack of cystitis induced pain in TRPV4 knock-out mice.[47] Although TRPV4 antagonism emerged as a target in treatment of bladder dysfunction and pain, there is no clinical data to support their use yet.

In particular, the new TRPV1 blocker GRC 6211 has been shown to reduce the frequency of reflex bladder contractions in rats.[38,48]

Cannabinoid system. Cannabinoids are lipophilic molecules with anti-nociceptive and anti-hyperalgesic properties. Two types of endocannabinoids have been identified in mammals: N-arachidonoyl ethanolamide (anandamide) and 2-arachidnoylglycerol. Cannabinoids are metabolized by two enzymes: fatty acid amido hydrolase (FAAH) and monoacylglycerol lipase.[49] Cannabinoids bind to type 1 and 2 cannabinoid receptors and can be taken either endogenously or exogenously. Endogenous cannabinoids are synthesized 'on demand' and FAAH enzyme inhibitors can also increase the activity of endogenous cannabinoids by reducing their metabolism.

The first time that cannabinoids were effective in controlling urination and the emergence of some LUTS was when multiple sclerosis patients used cannabinoids to control symptoms such as pain, spasticity and LUTS.[50]

Two types of peripheral cannabinoid receptors (CRs), CR1 and CR2, have been identified, expressed in humans in both the detrusor muscle and the urothelium, and in nerve endings in the bladder and urethra.[51] It is thought that CRs in the bladder are located close to the ends of the sensory nerves. It is not known exactly what role cannabinoids have in the control of LUT, but the demonstration that patients with both idiopathic and neurogenic detrusor overactivity (DOA) due to multiple sclerosis increase the expression of CR type 1 in the detrusor muscle makes KR1 receptors an attractive target in Overactive Bladder (OAB) and IC treatment. CRs can also be found co-localized/co-located with TRPV1 and other TRPs and purinergic receptors.

The efficacy of cannabinoids in the treatment of LUTS has been investigated in several clinical trials with neurogenic bladder patients. In patients with multiple sclerosis, improvements in urgency and incontinence episodes up to 50% have been reported.[50,52–54]

In the treatment of bladder pain, a FAAH inhibitor, ASP3652, has been tested in women with mild/moderate symptoms of BPS/IC.[55] This clinical trial failed to demonstrate any improvement in pain symptoms and LUTS as compared with placebo. Nevertheless, its use was safe without any psychotropic side-effects that would be expected to occur with the use of cannabinoids. Insufficient dosing and the hypothetical lack of the capacity of the studied molecule to penetrate into bladder afferents may explain the observed effects.

On the other hand, it is important to highlight that, despite the fact that cannabinoids are generally well tolerated, they are associated with an increased risk of psychosis, myocardial infarction, hypertension, heart failure and stroke.[56] Thus, it is necessary to design multicenter randomized controlled trials in order to assess cannabinoids' safety, QoL changes, urodynamic findings, LUTS improvement and cost–effectiveness issues.

Purinergic system. There are many studies on the effects of ATP, one of the extracellular nucleosides, on different tissues and through purinergic receptors in different subtypes, on many short- and long-term biological effects. Purinergic receptors may be involved in a wide range of processes, such as neurotransmission, muscle contraction, chemical sensory stimulation, secretion, vasodilation and regulation of immune response. Moreover, it has been suggested that they play a role in

many pathological conditions such as cancer, cardiopulmonary insufficiency, diabetes, skin and bone diseases, pain, and bladder and bowel dysfunction.[57] P2 receptors are found in almost every cell membrane and are mainly divided into two groups: P2X (ATP gated ion channels) and P2Y (G protein coupled receptors).[58] P2X receptors-7 (P2X1–7) and P2Y-9 receptors (P2Y1,2,4,6,11–14) have been identified in mammals.[57]

In parasympathetic neurons, in addition to the acetylcholine system, ATP release is also known to play a role in bladder contraction (atropine resistant contraction). This atropine resistant component can be up to 50% in experimental animals, while it is known to be much less in healthy human bladder.[59] It is known that ATP release from parasympathetic nerve endings plays a role in bladder contraction with P2X1 receptors. ATP is released from the urothelium with the tension stimulus created with the bladder filling, and the sensory stimulation is carried to the central nervous system by the P2X3 receptors in the urothelium, suburothelial interstitial cells and afferent nerve endings, and urination is initiated.

ATP released from urothelium can affect afferent nerves, interstitial cells/myofibroblasts or detrusor smooth muscle by autocrine and paracrine mechanisms. A molecule has recently been reported in the molecular mechanisms by which the umbrella cells lining the bladder wall convert mechanical stimulation to chemical stimulation. In mice, this newly described mechanosensor, the Piezo 1 channel, increases Piezo-dependent cytosolic Ca concentrations with ATP release in the urothelium after mechanical stimulation.[60] As a result, purinergic receptors play a role in both bladder contraction and bladder sensory stimulation. ATP released from efferent nerves causes bladder contraction, while ATP released from urothelium activates afferent nerve endings.

There is just one clinical trial, a phase IIa study, evaluating the efficacy of this system in treating BPS/IC. Thus, gefapixant, which is a selective P2X3-containing receptor antagonist, was assessed in patients diagnosed with BPS. After the 4 weeks of treatment, gefapixant-treated patients had a decrease in pain ($p = 0.019$) as well as an improvement in urinary urgency and in both Patient's and Clinician's Global Impression of Change compared with placebo ($p = 0.038$).[61,62]

Despite the fact that this approach seems interesting as a future BPS/IC treatment, there is not enough evidence yet to use it now. Further clinical trials are needed to study carefully its efficacy as well as its safety.

Newly emerging treatments

Intravesical liposomes are water filled vesicles made of an outer phospholipid layer that have been used as topical drug carriers. The instilled liposomes have been traced using fluorescent dyes and were detected to be attached in the urothelial surface, suggesting a mechanism of action involving restoration of the urothelial barrier function.[63] Also, the major constituent of the liposomes, sphingomyelin, could have exerted an anti-inflammatory effect.[64] Water filled (empty) liposomes have been used in clinical trials of BPS/IC, being compared against oral pentosan polysulfate in clinical studies, demonstrating equal efficacy for both agents.[65]

Onabotulinum (BoNT-A) toxin filled liposomes have also been trialed in pilot clinical studies in patients with BPS/IC,[66] showing no superiority against placebo. Intradetrusor injection of BoNT-A can be effective in palliation of symptoms in patients with BPS/IC by chemical denervation and inhibition of sensory functions of the bladder and by exerting anti-inflammatory actions.[67,68]

Therefore, the clinical safety of both empty and drug-filled intravesical liposomes has been demonstrated; however, the mechanism of action and the clinical efficacy of this novel therapeutic agent are yet to be discovered.

Conclusion

The etiology, pathogenesis and clinical features of BPS/IC are poorly defined, resulting in poorly defined targets when developing treatment strategies. Available treatments mainly aim to restore the uroplakin layer, while another line of treatment aims at modifying sensory pathways at the urothelium, all of which appear to have limited efficacy or be associated with important side-effects. Recently, epidemiologic studies demonstrating an association between BPS/IC and other pain syndromes (fibromyalgia, restless bowel syndrome and chronic fatigue syndrome) together with development of a standardized terminology and classification system can pave the

way for a better understanding of this disease. Also, recent development of a Europe-wide reference network can be hoped to lead to better quality research in understanding the disease, developing better research methodologies in rare disease research and defining novel targets for treatment.

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Conflict of interest statement

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