REVIEW

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Bladder Pain Syndrome (Interstitial Cystitis) Consensus 2019: The Report of the Turkish Continence Society Bladder Pain Syndrome/ Interstitial Cystitis Working Group

Mesane Ağrısı Sendromu (İnterstisyel Sistit) Konsensus 2019: Türkiye - Kontinans Derneği Mesane Ağrısı Sendromu/İnterstisyel Sistit Çalışma Grubu Raporu

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Abstract

Bladder pain syndrome is an important chronic pain syndrome which seriously reduces the patients' quality of life. It is a diagnosis of exclusion. It is defined as a clinical diagnosis composed of chronic (>6 months) pain/pressure/discomfort that is primarly perceived from the bladder and/or pelvis, and accompanied by urgency and/or frequency of urination. Throughout this paper, the definition, characteristic features, diagnostic tests and attempts, interpretation of the findings and the different treatment algorithms suggested by different organizations will be discussed.
Keywords: Bladder Pain syndrome, Interstitial cystitis, Chronic pelvic pain

Öz

Mesane ağrısı sendromu, hastaların yaşam kalitesini ciddi şekilde azaltan önemli bir kronik ağrı sendromudur. Bir dışlama tanısıdır. Öncelikle, mesane ve/veya pelviste hissedilen ve sıkışma ve/veya pollakürinin de eşlik ettiği, kronik (>6 ay) tarzda, ağrı/basınç/rahatsızlık hissi olarak kendini gösteren klinik bir tablodur. Bu yazıda tanımı, karakteristik özellikleri, tanı testleri ve girişimleri, bulguların yorumlanması ve farklı kuruluşların önerdiği farklı tedavi algoritmaları tartışılacaktır.
Anahtar Kelimeler: Mesane ağrısı sendromu, İntertisyel sistit, Kronik pelvik ağrı

Introduction

Bladder pain syndrome (BPS) is an important chronic disease without a specific etiologic explanation that requires a high index of suspicion for its clinical diagnosis. It is primarily a diagnosis of exclusion (1). After excluding diseases with similar presentations, BPS/interstitial cystitis (IC) is diagnosed clinically when symptoms comprise chronic (>6 months) pain/pressure/discomfort that is perceived to be primarily originating from the bladder and/or pelvis, and accompanied by urgency and/or frequency of urination (1,2). There is no consensus regarding the nomenclature, definition and optimal management strategy of BPS/IC (3).

Recently, patients with Hunner lesions have been terminologically categorised as "Classical IC" or "BPS type 3C" that implied a BPS/IC subtype with distinct pathological and endoscopic features and more severe symptomatology (3,4). In an effort to enhance the recognition and comprehension and to align with insurance requirements, naming this disease as BPS/IC (rather than BPS) is advocated. Throughout this paper, the term BPS/IC will be used to imply BPS.

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Epidemiology

Owing to the intricacies surrounding its clinical diagnosis and non-standardised management, epidemiological studies about BPS/IC have generated somewhat conflicting and controversial results. The European Association of Urology (EAU) guidelines have reported a prevalence of 0.06%-30% (5), while in the US it ranges between 0.067% and 2% (6-9). The more recent US-based RAND study reported a prevalence rate of 2.9%-4.2% (10). The prevalence in women and men ranged between 0.004%-11.2% and 0.01%-6.2%, respectively (11,12). The prevalence in children was noted to be extremely low (13). Warren has proposed a familial background for BPS/IC (14).

According to the literature, the incidence of BPS/IC is in the range of 1-15/100,000/year (2). EAU guidelines have reported an incidence between 0.005% and 0.05% (5). The incidence in women and men ranged between 1.2 21/100,000/year and 0.6-4/100,000/year, respectively (15-17).

Female to male ratio of BPS/IC is 5-10:1 (11,16,18,19). A variation based on race or ethnicity probably exists (20-22).

Characteristics and Natural Course of BPS/IC

Patients diagnosed with BPS/IC frequently exhibit extravesicular symptom constellations or syndromes (2,23-25). Fibromyalgia, chronic fatigue syndrome, temporomandibular disorder and irritable bowel syndrome are among the common diagnoses that accompany BPS/IC (26-33). Similarly, systemic lupus erythematosus, Sjogren's syndrome, Sicca syndrome and allergic conditions may coexist in patients diagnosed with BPS/IC (18,30,33-39). The prevalence of pelvic pain, vulvar pain, headache and lower back problems have been reported to be higher in BPS/IC patients (30-32,38-40). Diagnoses like fibromyalgia, migraine, temporomandibular joint disorder and depression are more frequent in patients without characteristic bladder lesions when compared to those with BPS/IC type 3C (41). Psychological disturbances such as depression, anxiety and panic disorder have a higher prevalence in patients diagnosed with BPS/IC (31,32,38,39,42-45). Sexual dysfunction is common in females with BPS/IC (46-48). A negative correlation has been observed between diabetes mellitus and BPS/IC (33).

BPS/IS is commonly diagnosed in the 4th decade of life and later (17). It has a subacute onset with the classical symptom complex being evident over a rather short period of time. BPS/IC is a progressive disease with evolution into its final phase in approximately 5 years after which no significant alteration in symptom severity is usually expected (49). Symptomatic fluctuation is commonly seen with BPS/IC (2). Despite the fluctuating pattern of symptoms, overall disease severity does not exhibit significant long-term variation (50). Some patients may experience phenotypic progression from an organ-specific disease to a regional or generalised pain syndrome (38,51,52).

Diagnosis

As described above, diagnosing BPS is not straightforward due to the variations in symptomatic presentation and lack of concrete diagnostic criteria. Despite being composed of fundamental elements like careful history taking and physical examination; and objective assessment methods such as cystoscopy and hydrodistension, bladder biopsy and urodynamic study, the diagnostic algorithm of BPS/IC is far from ideal. Diagnosis of BPS/IC requires exclusion of diseases with similar presentations and a high index of suspicion based on the clinical experience of the physician.

History

Characteristic features of the pain, triggering factors, accompanying lower urinary tract symptoms, and other symptoms that may be related to pelvic organs must be questioned during history taking. Common to all guidelines, the diagnosis of BPS/IC necessitates the presence of pain/pressure/discomfort perceived to be originating from the bladder and accompanying lower urinary tract symptoms, such as increased daytime and/or nocturnal urinary frequency and the exclusion of diseases that may be responsible for a similar symptomatology (5).

Definition and accurate characterisation of the pain is vital to the diagnosis. Patients usually relate this pain, pressure, or discomfort to their bladder that commonly increases with bladder fullness. Pain is most frequently localised to the suprapubic region, and migration to the thigh, vagina and rectum is not uncommon.

The diseases that need to be excluded include; bladder cancer or carcinoma *in situ*, specific and non-specific urogenital infections, malakoplakia, radiotherapy/chemotherapy involving or targeting pelvis, bladder stones, bladder neck contracture, distal ureteric stone, cystocele, rectocele, urethral diverticulum, endometriosis, vaginal atrophy, vulvodynia, vaginal candidiasis, gynaecological malignancies such as cervical, uterine or ovarian cancer, prostate cancer, benign prostatic hyperplasia, overactive bladder, chronic prostatitis and pudendal nerve entrapment.

Since, pain is the main parameter that needs to be assessed while evaluating treatment response, it must be graded before initiating the treatment in an effort to monitor symptomatic improvement. The most reliable methods for this are visual analogue score (pain scores ranging from 1 to 10) and the 5-item verbal assessment (no pain, mild, moderate, severe, very severe pain) (5).

Following general physical examination, some diagnostic tests and procedures may need to be conducted.

Laboratory Tests

Urine analysis and culture (if needed, based on urine analysis findings) must be done in all patients. Patients at risk for bladder cancer should be evaluated by urine cytology. It is recommended to do vaginal and endocervical culture to rule out genital tract infection in women.

Cystoscopy

Cystoscopy in BPS/IC is an integral part of the evaluation and serves to exclude other diseases of the bladder and detect glomerulations or Hunner's lesions. Glomerulations are defined as petechial mucosal haemorrhages that occur after bladder distension (Figure 1). This oozing type of capillary bleeding may look like a "waterfall" and its intensity may impair endoscopic vision. The term "Hunner's ulcer" is replaced by "Hunner's lesion" since the lesion being described is not in the form of a true ulcer but rather is composed of an inflammatory reaction. Hunner's lesion is defined by a well-circumscribed hyperaemic mucosal region with a central scar that is adherent to a fibrin layer or coagulum and radially oriented capillaries (Figure 2). In addition to inspecting for suspicious lesions, the cystoscopy for BPS/IC workup should involve random mucosal biopsies from 3 different regions of the bladder to rule out diagnoses like carcinoma *in situ*, eosinophilic cystitis and tuberculous cystitis. Histopathological examination of the biopsy sample(s) obtained from Hunner's lesion (if present) usually reveals a chronic inflammatory reaction characterised by the infiltration of lymphocytes, plasma cells, macrophages, neutrophilic and eosinophilic granulocytes and an abundance of mast cells. In general, the presence of Hunner's lesion is associated with more severe symptomatology and a decreased bladder capacity (3,53).

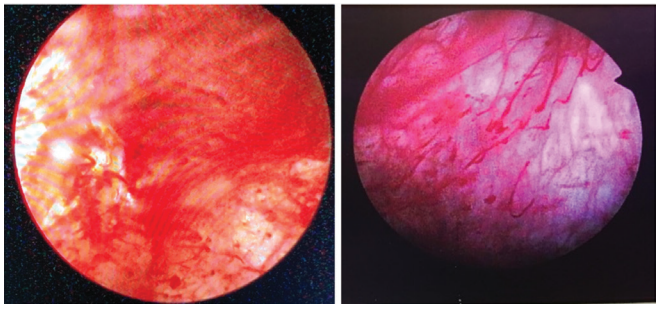


Figure 1. Cystoscopic view of a glomerulation

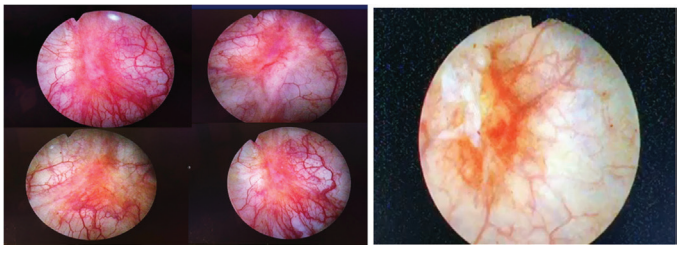


Figure 2. Cystoscopic view of a Hunner's lesion

ESSIC (International Society for the study of BPS) guidelines recommend cystoscopy and hydrodistension in order to classify patients with BPS (54) (Table 1). Similarly, EAU guidelines stand in favour of cystoscopy under general anaesthesia to define BPS/IC subtypes according to ESSIC criteria (Grade of recommendation: strong) (5). ESSIC classification of cystoscopic findings is defined as follows: "Grade 0, normal appearing mucosa"; "Grade I, petechial bleeding in at least 2 quadrants"; "Grade II, submucosal bleeding covering a wide area (ecchymosis)"; "Grade III, diffuse mucosal bleeding"; and "Grade IV, disturbed integrity of the mucosal lining (+/- bleeding/oedema)" (3,54).

Urodynamic Studies

There is no consensus regarding the indications and utility of urodynamic studies in the workup of BPS. Generally, these are reserved for complex cases (3,55).

Potassium Sensitivity Test (Parson's Test)

Parson's test is used to assess the permeability of bladder epithelium to potassium. However, a positive test result is inadequate in elucidating the underlying pathophysiological mechanism as it is unable to discriminate between the increased permeability of the mucosal lining and the hypersensitivity of regional afferent nerves.

Biomarkers

Several biomarkers such as, substance P, uroplakin III-δ4, interleukin-6, cyclic guanosine monophosphate, uromodulin, kininogens, inter-α-trypsin inhibitor heavy chain H4, nitric oxide, nerve growth factor, heparin-binding epidermal growth factor-like growth factor (HB-EGF) have been tested within the context of BPS/IC. However, only antiproliferative factor (APF) has been identified as a potential diagnostic tool (56-59). APF is apparently released from the damaged bladder epithelial cells and it prevents self-regeneration of the mucosal lining. Patients with BPS/IC have increased urinary levels of APF.

GP-51 is a glycoprotein that can be detected in transitional epithelial cells and urine. Moskowitz et al. (56) have demonstrated decreased GP-51 immunostaining in the bladder

Table 1. ESSIC classification of BPS according to cystoscopy, hydrodistension and biopsy results

	Cystoscopy and Hydrodistension			
	Not done	**Normal**	**Glomerulation**	**Hunner's lesion**
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Insufficient	XB	1B	2B	3B
Positive	XC	1C	2C	3C

BPS: Bladder pain syndrome

biopsy samples of BPS/IC patients. Despite being inferior to APF, GP-51's specificity for the diagnosis of BPS/IC is noteworthy, making it a promising biomarker that can be used in the workup of BPS/IC.

In conclusion, while the ideal diagnostic algorithm of BPS/IC continues to be debatable, exclusion of similar diseases is a must.

Cystoscopy, urodynamic studies, potassium sensitivity test and some biomarkers may be used as adjuncts to history and physical examination for the diagnosis of BPS/IC. Except some of the cystoscopic findings and few of the biomarkers that are still under investigation, none of the diagnostic tests have specific findings attributable to BPS/IC. Consequently, the diagnosis of BPS/IC requires the recognition of specific symptom combinations and exclusion of other diagnoses that may lead to a similar clinical Picture (Table 2).

Treatment

Treatment of BPS/IC should aim at improvement in symptoms and quality of life while minimising the related side effects or complications. It is important to note that cure is not possible with the available options, and the ideal treatment requires a multidisciplinary approach. Generally, individualising treatment pathways and making treatment-related decisions based on the clinical phenotype will increase the success rates (Table 3) (60,61).

Treatment recommendations stated in clinical guidelines and the grades of recommendation assigned to each treatment option are summarised in Tables 4, 5 and 6 (62).

Current treatment of BPS/IC involves initiation with conservative options and progression to more invasive modalities depending on the degree of improvement. Constituents of this step-wise approach exhibit differences between guidelines. Tables 7 and 8 summarise the treatment recommendations of ICI and AUA, respectively.

Recommendations of American Urological Association regarding the treatment of BPS/IC (63):

Step 1: Conservative Treatment Options

Patient education, diet advices, behavioural modifications, revisiting voiding habits, psychosocial support, pelvic floor physiotherapy, acupuncture and trigger point injections constitute the conservative treatment options for BPS/IC. With only patient counselling and psychological support, a symptomatic improvement in the range of 45%-50% can be expected (64). Minimising the amount of dietary consumables (coffee, tea, sodas, alcohol, apple, apricot, banana, peach, citrus, tomato, hot and spicy food, vinegar, artificial sweetener, etc.) that may trigger BPS/IC-related symptoms is highly recommended (61,65).

Timed voiding and manoeuvres that can suppress the urge to void can help with reducing the frequency of urination, increasing bladder capacity and counteracting the desire to void that is provoked by urgency and/or pain (66). It is possible to achieve symptomatic improvement in 45%-88% of the patients with behavioural modifications (67).

Several psychosocial problems, such as depression and anxiety, may arise due to the chronic nature of BPS/IC (68). Stress management strategies, such as regular physical exercise, meditation and yoga may serve well to tackle the psychological burden of BPS/IC (69).

Patients who exhibit trigger point tenderness in the pelvic floor may benefit from physiotherapy (+/- biofeedback), myofascial release, or intravaginal massage. Physical therapy that is done by pelvic floor physiotherapists, can lead to symptomatic improvement in 50%-62% of the patients (70,71).

Step 2

2.a. Oral Treatment Options

Amitriptyline

Placebo-controlled studies have reported superior results in terms of symptomatic improvement with a 4-month treatment course of amitriptyline (63% vs 4%). The incidence of side effects was significantly higher in the amitriptyline group than in the placebo arm (92% vs 21%) (72). Less than half of the patients can tolerate the threshold dose of amitriptyline (50 mg and above) that is necessary to obtain clinically meaningful results (73).

Cimetidine

Thilagarajah et al. (74) have shown that cimetidine is superior to placebo for symptomatic improvement, with a side effect profile similar to that of placebo.

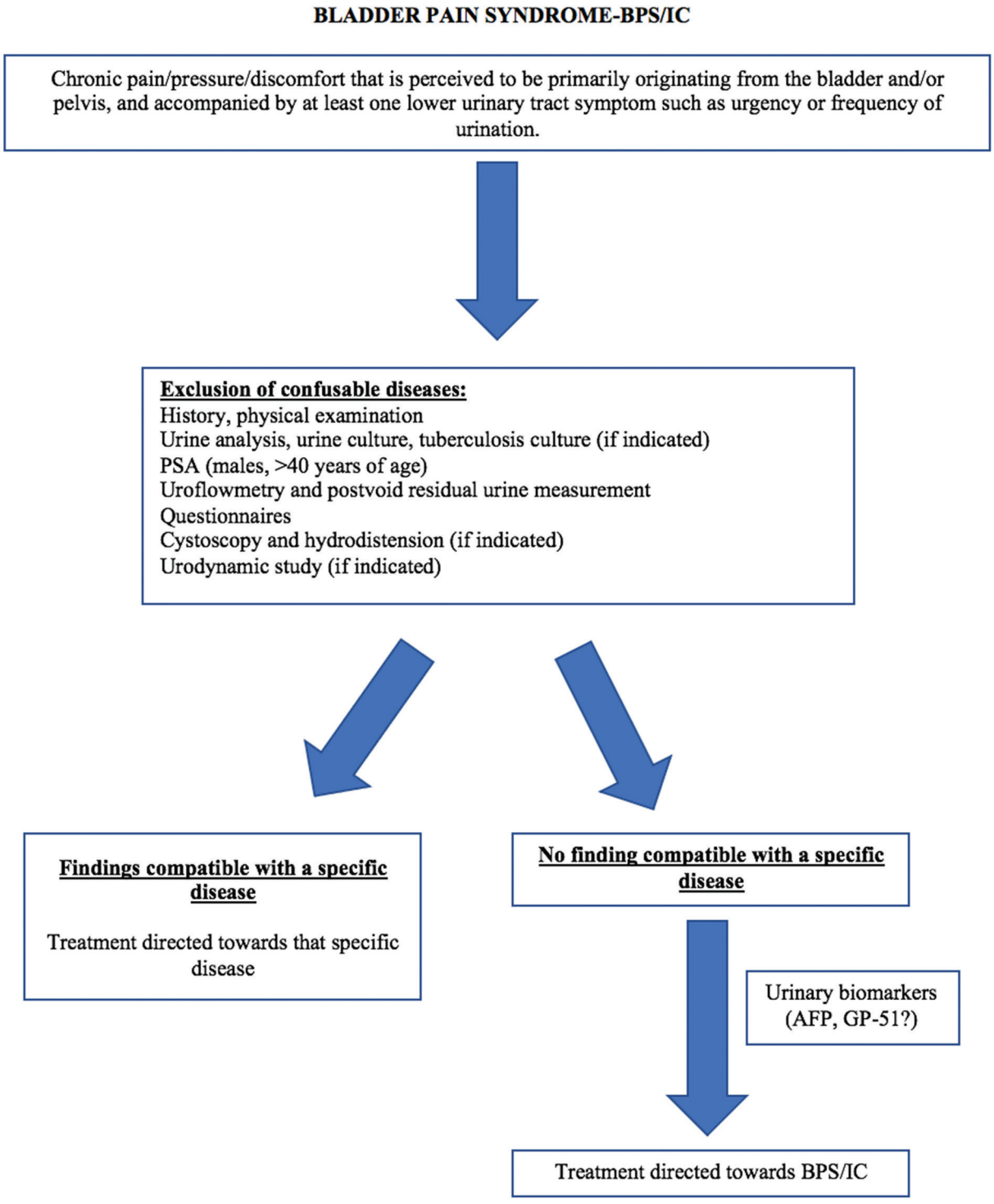
Hydroxyzine

The randomised controlled study that investigated the efficacy of hydroxyzine has demonstrated insignificant differences between the placebo and hydroxyzine groups (13% vs 23%, respectively), while hydroxyzine + pentosan polysulphate (PPS) combination performed better than PPS monotherapy (40% vs 28%, respectively) (75).

Pentosan Polysulphate

Oral PPS is approved by the Food and Drug Administration (FDA) for the treatment of BPS/IC. It acts by replenishing the deficient glycosaminoglycan (GAG) layer of the bladder. It also inhibits the histamine release from mast cells and has anti-inflammatory properties. The recommended dose is 300 mg/day (100 mg, TID) according to the pivotal placebo-controlled studies.

Table 2. Management algorithm of BPS/IC. (2,3)



The success (more than 50% of symptomatic improvement) rates of oral PPS in terms of the effect it had on pelvic pain, urgency and day and night time frequency have been reported to be 37%, 28%, 54% and 48%, respectively in a meta-analysis that included approximately 500 patients. It was found to be superior to placebo for every symptom that may be attributable to BPS/IC, except nocturia. The treatment efficacy of PPS becomes clinically detectable in 3-6 months. It has been shown that PPS performs better in BPS/IC type 3C than in non-lesion type BPS/IC. Treatment response has been correlated more with treatment duration, rather than dosage (76).

Table 3. Clinical phenotype-based treatment algorithm (61)		
Clinical phenotype		**Possible treatment options**
Urinary*		Behavioural treatment, Anticholinergics, Intravesicular treatment (Heparin, DMSO, HA, CS, PPS, Oxybutynin), Hydrodistension, Botulinum toxin A, Sacral neuromodulation, Radical surgery
Psychosocial		Stress management and psychosocial support
Organ-specific*	**Hunner's lesion (-)**	Amitriptyline, Cimetidine, Hydroxyzine, PPS, Quercetin, Intravesicular agents (DMSO, Heparin, HA, CS, alkalinised lidocaine, PPS), Hydrodistension, Botulinum toxin A, Radical surgery
	Hunner's lesion (+)	Cyclosporin A, Endoscopic treatment (Fulguration, laser ablation, resection, steroid injection), Hyperbaric oxygen, Radical surgery
Infectious		Antibiotic(s)
Neurologic/systemic		Gabapentanoids, Hydroxyzine, Cimetidine, Sacral neuromodulation
Sensitivity		Pelvic floor physiotherapy, Massage therapy, Acupuncture, Trigger point injections

This algorithm has been adapted from Nickel et al. (60)
*Phenotypes present in the majority of the patients, CS: Chondroitin sulphate, DMSO: Dimethylsulfoxide, HA: Hyaluronic acid, PPS: Pentosan polysulphate

Table 4. Oral and conservative treatment options in BPS/IC and the grades of recommendation assigned to each option in the clinical guidelines (3)

Treatment options		EAU	AUA	ICI	RCOG	CUA
Conservative treatment	Multimodal treatment (pain management, behavioural, psychosocial and educational)	A	Clinical principle	C	-	A
	Stress management	-	Clinical principle	C	D	B
	Individualised diet advices	C	Clinical principle	C	D	B
	Physiotherapy	A	Standard	C	B	B
	Acupuncture	-	-	-	D	B
	Pelvic floor-trigger point injections	-	-	-	-	D
Oral treatment	Gabapentin	-	-	C	-	C
	Amitriptyline	A	Optional	B	B	B
	Cimetidine	Limited benefit	Optional	C	B	B
	Hydroxyzine	-	Optional	D	Not recommended	B
	Sodium pentosan polysulphate (PPS)	A	Optional	D	Not recommended	D
	PPS + subcutaneous heparin	A	-	-	-	-
	Antibiotic(s)	-	Not recommended	D	Not recommended	-
	Suplatast tosilate	-	-	D	-	-
	Glucocorticoids **(long-term)**	Not recommended	Not recommended	-	Not recommended	-

EAU: European Association of Urology, AUA: American Urological Association, ICI: International Consultation on Incontinence, RCOG: Royal College of Obstetricians and Gynaecologists, CUA: Canadian Urological Association

Gabapentanoids

Studies with relatively lower level of evidence have shown that gabapentin may alleviate the pelvic pain associated with BPS/IC in 50% of the patients (77).

Quercetin

Based on the positive results it had achieved within the context of male chronic pelvic pain syndrome treatment, quercetin has been tested for the management of BPS/IC with some success in some observational studies (78).

2.b. Intravesicular Treatment Options

Intravesicular treatment alternatives may be utilised when oral options fail or if a multimodal approach is deemed necessary for a better outcome.

Dimethylsulfoxide (DMSO)

DMSO is an organic compound with anti-inflammatory and analgesic effects. It is instilled intravesically (50 mL of 50% solution, left inside the bladder for 30-60 minutes, weekly

Table 5. Intravesicular treatment options in BPS/IC and the grades of recommendation assigned to each option in the clinical guidelines (62)

Treatment options		EAU	AUA	ICI	RCOG	CUA
Intravesicular treatment	DMSO	Not recommended	Optional	B	C	B
	PPS	A	-	D	-	C
	HA	B	-	D	B	C
	CS	B	-	D	D	Da
	Heparin	C	Optional	C	D	C
	Lidocaine	A[b]	Optional	C	B	B
	Oxybutynin	Limited benefit	-	D	-	C
	BCG	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
	Capsaicin/ resiniferatoxin	-	-	Not recommended	Not recommended	Not recommended

DMSO: Dimethylsulfoxide, PPS: Pentosan polysulphate, HA: Hyaluronic acid, CS: Chondroitin sulphate, BCG: Bacillus Calmet Guerin, [a]: within the context of multimodal treatment, [b]: in conjunction with sodium bicarbonate, EAU: European Association of Urology, AUA: American Urological Association, ICI: International Consultation on Incontinence, RCOG: Royal College of Obstetricians and Gynaecologists, CUA: Canadian Urological Association

Table 6. Other treatment options in BPS/IC and the grades of recommendation assigned to each option in the clinical guidelines

Treatment options		EAU	AUA	ICI	RCOG	CUA
Cystoscopic interventions	Hydrodistension (brief and under low pressure)	Not recommended	Optional	C	D	C
	Fulguration of Hunner's lesion	B	Recommended	C	Recommended	B
	Intralesional (Hunner's) triamcinolone injection	-	Recommended	-	-	-
Other treatment options	BTX-A	C	Optional	D	B	C
	BTX-A + hydrodistension	A	-	-	-	-
	Sacral neuromodulation	B	Optional	C	D	C
	Cyclosporin A	-	Optional	-	D	C
Radical surgery	Urinary diversion or augmentation cystoplasty +/- cystectomy	A	Optional	C	D	C

BTX-A: Botulinum toxin A, EAU: European Association of Urology, AUA: American Urological Association, ICI: International Consultation on Incontinence, RCOG: Royal College of Obstetricians and Gynaecologists, CUA: Canadian Urological Association (3)

administrations for a total of 6 weeks, monthly boosters may be needed) for the treatment of BPS/IC (79). A randomised controlled comparison with normal saline has demonstrated superior objective (93% vs 35%, respectively) and subjective (53% vs 18%, respectively) improvement rates in the DMSO arm (80). The overall safety profile of DMSO is favourable. Halitosis (garlic-like odor) and a temporary symptomatic flare-up that may be seen following the initial doses represent DMSO-specific side effects (81). Intravesicular DMSO has been approved by the FDA for the treatment of BPS/IC.

Heparin

Heparin is a structural analogue of GAGs and acts by replenishing the deficient urothelial GAG layer in BPS/IC. Intravesicular heparin treatment has been associated with a symptomatic improvement in the range of 56%-73% at 3 months follow-up (81,82). Parsons et al. (83) have shown that the combined intravesicular administration of lidocaine and heparin can lead to symptomatic relief persisting for 12 hours.

Hyaluronic Acid

Observational studies have reported symptomatic improvement rates in the range of 30%-87% with hyaluronic acid that is a GAG analogue (84,85). Its intravesicular administration can be combined with other agents, such as chondroitin sulphate (86).

Chondroitin Sulphate

Chondroitin sulphate is another GAG analogue that is instilled into the bladder for the treatment of BPS/IC. It can lead to symptomatic improvement in 31%-39% of the patients according to the results of placebo-controlled studies (87,88).

Table 7. Step-wise approach to BPS/IC treatment, ICI, 2017 (62)

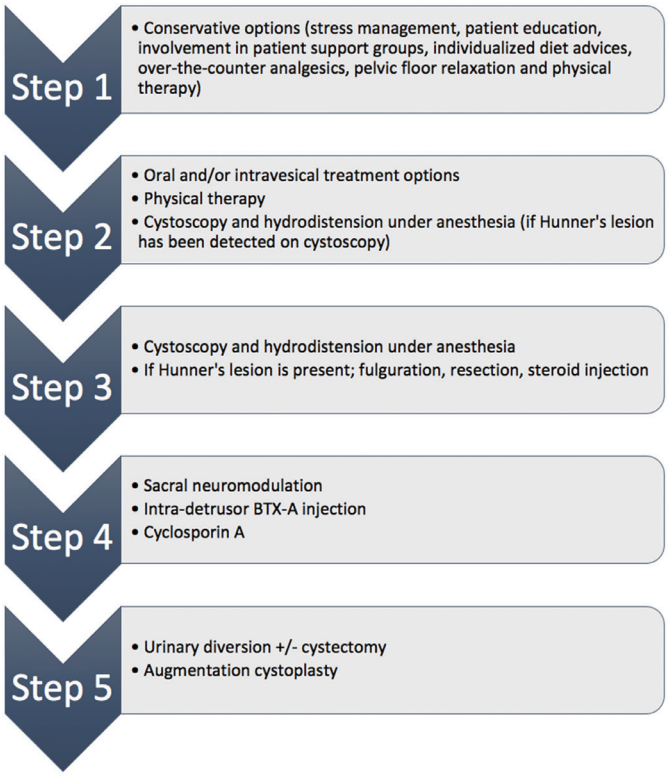
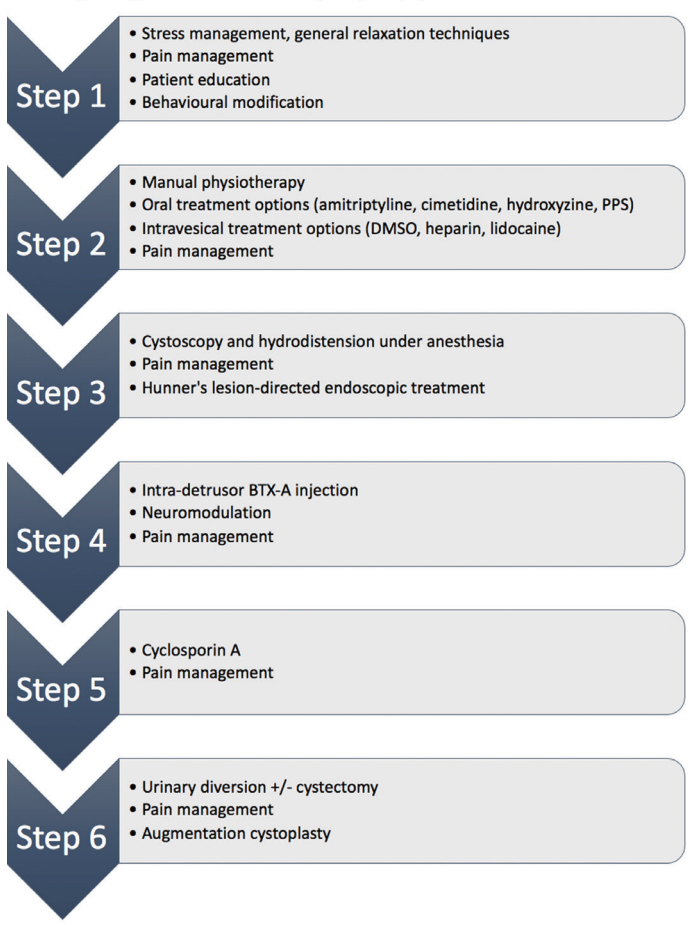


Table 8. Step-wise approach to BPS/IC treatment, AUA, 2015 (63)



Lidocaine

Lidocaine can be administered intravesically to manage acute exacerbations of BPS/IC. Alkalinisation with sodium bicarbonate or electromotive drug delivery techniques can enhance its diffusion into the bladder wall (89,90). In their placebo-controlled randomised study, Nickel et al. (91) have demonstrated that alkalinised lidocaine can provide profound short-term symptomatic improvement; spanning the 5-day treatment period and the 10-day window post-treatment.

Pentosan Polysulphate (PPS)

Intravesicular administration can potentiate the clinical efficacy of PPS. A placebo-controlled study has shown 40% symptomatic improvement rate (92). This rate can be increased to 62% when combined with oral PPS (93). Combined (oral + intravesicular) PPS treatment has been recommended by the EAU guidelines with a high level of evidence (1b) and strong grade of recommendation.

Step 3: Cystoscopic Interventions

Hydrodistension

Several observational studies have reported treatment success rates ranging from 18% to 56% with cystoscopy and hydrodistension (94,95). However, there is a significant variation between different hydrodistension protocols. Generally, it is advised that hydrodistension should be kept brief (3 minutes) and performed under low pressure (<80 cm H20) (61).

Endoscopic Procedures Directed at Hunner's Lesion(s)

Targeting cystoscopically detected Hunner's lesion(s) with electrofulguration, neodymium: yttrium-aluminium-garnet laser coagulation and triamcinolone injection can provide relatively higher (70%-100%) and more durable (7-12 months) success rates (96,97).

Step 4: Other Treatment Options

Intradetrusor Botulinum Toxin A (BTX-A) Injection

Kuo (82) compared intradetrusor BTX-A injection (100U vs 200U) and hydrodistension with hydrodistension alone in a randomised fashion and found out that the success rate at 3 months follow-up was significantly higher (72% vs 48%, respectively) in the combined treatment arm. The efficacy was similar between the different BTX-A doses, with 100U having a more favourable side effect profile.

Sacral Neuromodulation

According to the results of observational studies; it is possible to achieve treatment success (more than 50% of symptomatic improvement) with sacral neuromodulation in 42%-95% of the patients (98). Complications such as infection, migration and malfunction together with a revision surgery rate of 27%-50% should be kept in mind while recommending this option to the patients.

Step 5: Cyclosporin A

The randomised controlled study in which cyclosporin A was compared with PPS in a head-to-head fashion has demonstrated superior results in terms of treatment efficacy in the cyclosporin A arm (59% vs. 13%, respectively) (99). Side effect profile (hypertension, nephrotoxicity and immunosuppression) and the need to do regular serum level monitoring are the main obstacles precluding its adoption into routine practice.

Step 6: Radical Surgery

Urinary diversion +/- cystectomy can be considered as the last treatment option in refractory cases. Alternatively, supratrigonal/subtrigonal cystectomy and augmentation cystoplasty can also be recommended. Based on the findings gathered in retrospective studies, it can be concluded that radical surgery can be an option for patients who exhibit cystoscopic findings with decreased bladder capacity under anaesthesia and those with severe symptomatology who have exhausted numerous treatment efforts. Patients should be counselled about the possibility of pain persisting despite cystectomy.

Conclusion

- Patients must be counselled (about the disease's chronic course, need for long-term treatment, the impossibility of achieving cure, etc.) while planning the management strategy.
- A step-wise approach needs to be implemented, as recommended by the guidelines.
- Clinical phenotype-directed, individualised and multimodal approach optimises outcomes.
- Multiple options exist; however, cure is not possible with any of them.
- Aim should be to improve the symptoms and quality of life.
- Further research is warranted.

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