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Guideline

Clinical guidelines for interstitial cystitis/bladder pain syndrome

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Abbreviations & Acronyms
BCG = bacillus Calmette–Guérin
BPS = bladder pain syndrome
BW = bodyweight
DAMP = damage-associated molecular patterns
DMSO = dimethyl sulfoxide
GAG = glycosaminoglycan
HIC = Hunner-type interstitial cystitis
HSB = hypersensitive bladder
IC = interstitial cystitis
MBAD = mucosal bleeding after distension
MBSR = mindfulness-based stress reduction
NGF = nerve growth factor
NHIC = non-Hunner type interstitial cystitis
NSAIDs = non-steroidal anti-inflammatory drugs
OAB = overactive bladder
PBS = painful bladder syndrome
QoL = quality of life
s.c. = subcutaneously
TRPV = transient receptor potential vanilloid
VAS = visual analog scale
VEGF = vascular endothelial growth factor
ZO-1 = zonula occludens-1

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Abstract: The clinical guidelines for interstitial cystitis and related symptomatic conditions were revised by updating our previous guidelines. The current guidelines define interstitial cystitis/bladder pain syndrome as a 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. The characteristic symptom complex is collectively referred as hypersensitive bladder symptoms. Interstitial cystitis/bladder pain syndrome is divided into Hunner-type interstitial cystitis and bladder pain syndrome; Hunner-type interstitial cystitis and bladder pain syndrome represent interstitial cystitis/bladder pain syndrome with Hunner lesions and interstitial cystitis/bladder pain syndrome without Hunner lesions, respectively. So-called non-Hunner-type interstitial cystitis featured by glomerulations or bladder bleeding after distension is included in bladder pain syndrome. The symptoms are virtually indistinguishable between Hunner-type interstitial cystitis and bladder pain syndrome; however, Hunner-type interstitial cystitis and bladder pain syndrome should be considered as a separate entity of disorder. Histopathology totally differs between Hunner-type interstitial cystitis and bladder pain syndrome; Hunner-type interstitial cystitis is associated with severe inflammation of the urinary bladder accompanied by lymphoplasmacytic infiltration and urothelial denudation, whereas bladder pain syndrome shows little pathological changes in the bladder. Pathophysiology would also differ between Hunner-type interstitial cystitis and bladder pain syndrome, involving interaction of multiple factors, such as inflammation, autoimmunity, infection, exogenous substances, urothelial dysfunction, neural hyperactivity and extrabladder disorders. The patients should be treated differently based on the diagnosis of Hunner-type interstitial cystitis or bladder pain syndrome, which requires cystoscopy to determine the presence or absence Hunner lesions. Clinical studies are to be designed to analyze outcomes separately for Hunner-type interstitial cystitis and bladder pain syndrome.

Key words: bladder pain syndrome, guidelines, Hunner lesions, hypersensitive bladder symptoms, interstitial cystitis.

Introduction

We, a group of East Asian urologists, published clinical guidelines for IC and related conditions in 2009 and 2016.[1,2] Currently, these guidelines have been revised. The readers are kindly advised to look at the previous guidelines for the evidence before 2015; the descriptions and references in the previous guidelines have been shortened or removed for the sake of conciseness.

The scope of the guidelines is basically IC patients. However, there is no widely accepted definition of IC.[3] The lack of definition has incurred confusion by creating many terms; PBS,

BPS, HSB, IC/PBS and IC/BPS are examples.[4–7] The current guidelines have adopted IC/BPS as the umbrella term that covers patients complaining of characteristic HSB symptoms with no other obvious diseases. Those with OAB or other chronic pelvic pain syndrome, such as chronic prostatitis category 3, might present HSB symptoms, but not the target population of the guidelines.

Methods

We have updated the previous guidelines using materials identified by the PubMed database published from 2016 to end of 2019, including e-publications. Guidelines issued by the American Urological Association and the International Society for the Study of BPS (ESSIC) were also counselled.[4,6] We have not repeated the descriptions and references in the previous guidelines, but focused on recent evidence since the last publication.

Definition

The definition of IC/BPS is 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. The characteristic symptom complex is collectively referred as HSB symptoms.

IC/BPS is divided into HIC and BPS; HIC and BPS represent IC/BPS with Hunner lesions, and IC/BPS without Hunner lesions, respectively (Table 1). HIC has characteristic endoscopic findings and distinct inflammatory histopathology, whereas BPS lacks both of them.[8,9]

The previous guidelines used NHIC or HSB as a subcategory term.[1,2] NHIC is featured by glomerulations or bladder bleeding after distension, and HSB has no proven bladder pathology despite symptoms. These terms have been disused; glomerulations are not confidently pathological,[10] and NHIC and HSB are indistinguishable in terms of histopathology and gene expression.[8] Alternatively, NHIC and HSB are combined as a single group of BPS.

Epidemiology

The known prevalence of IC or conditions suggestive of IC ranged from 0.01% to 2.3%, with an approximately fivefold female dominance, although the criteria of IC are highly variable.[1,2] A study in the USA found IC prevalence from 2.70% to 6.53% in women. In Japan, 1.0% of the general population experienced bladder pain every day. The IC prevalence in Korea was reported to be 0.26% in women. The Taiwan National Database showed the prevalence was 21.8 out of 100 000 in 2002, and 40.2 out of 100 000 in 2013, respectively.[11]

Table 1 Definition of IC/BPS and its subgroups

	Description
IC/BPS	A 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
HIC	IC/BPS with Hunner lesions
BPS	IC/BPS without Hunner lesions

The symptom complex is termed as HSB symptoms.

Histopathology

We have first provided a histopathology section in the IC/BPS guidelines. Conventionally, the histopathology of IC/BPS has been referred as "non-specific."[12–15] Histological evaluation was regarded of minimal importance for the diagnosis, although most of the past studies on IC/BPS histopathology did not distinguish IC/BPS with and without Hunner lesions. Recent studies have shown significant histological differences between HIC and BPS (Table 2).[9,16]

HIC

Inflammation: Chronic inflammation is almost always observed in the bladder mucosa of HIC (Fig. 1). It is not confined in the Hunner lesion, but also found in the background (out of the Hunner lesions) area. In other words, HIC bladders show "pancystitis." The inflammatory cells are most densely distributed in the subepithelial region. They consist mostly of lymphocytes and plasma cells, with plasma cells far predominating in some cases. Lymphoid aggregates/follicles are observed in approximately 40% of patients.[16] A small number of eosinophils and neutrophils can be present. Dense neutrophilic infiltration suggestive of infectious acute inflammation is never seen.

Epithelial denudation: Another key histological finding of HIC is epithelial denudation. The epithelium diminishes in thickness and is frequently completely lost. The epithelial denudation or detachment is not artificial, and it sometimes occurs in a sloughing manner. Denudation is identified both in the Hunner lesions and in the background area, although more prominent in the former.[16] Increased microvessels, edema, fibrosis, hemorrhage and fibrin exudation are found in variable degrees, supposedly as the consequences of chronic inflammation and epithelial denudation.[8]

BPS

The bladder of BPS patients shows little, if any, inflammatory changes (Fig. 2). The epithelium is generally well-preserved. Biopsy specimens of BPS bladder are usually indistinguishable from the normal bladder.[16] However, in

Table 2 Histological differences between HIC and BPS

	HIC	BPS
Subepithelial chronic inflammation	Present	Absent or minimal
Types of infiltrating inflammatory cells	Lymphocytes and plasma cells are dominant. Plasma cell-rich area is often present	Plasma cells are few, even when there is slight inflammation
Lymphoid follicles	Often present	Extremely rare
Urothelial epithelium	Frequently denuded	Full layer is preserved

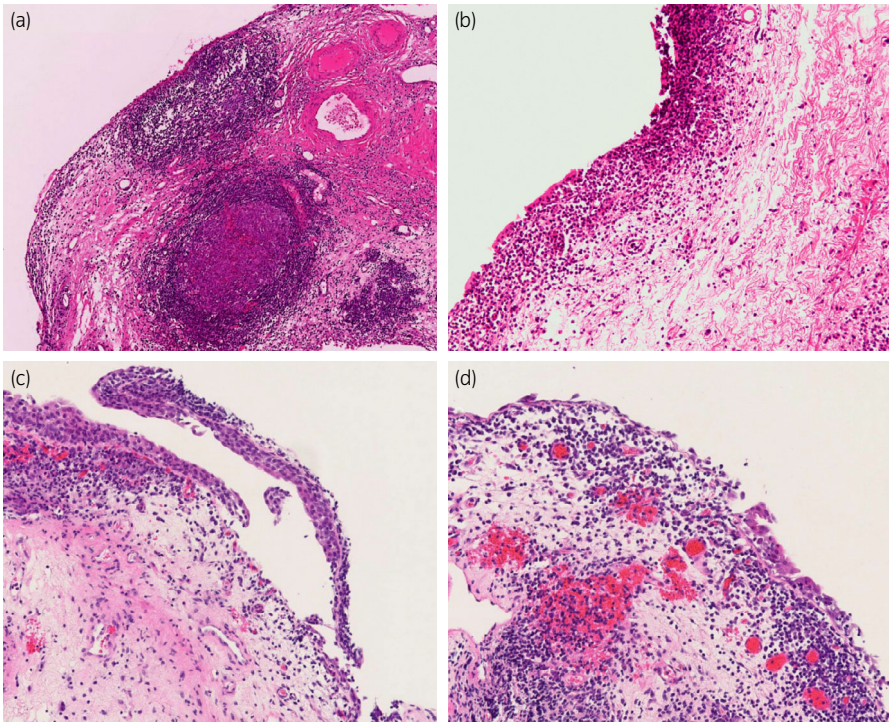

Fig. 1 Histopathology of HIC. Dense inflammatory cell infiltration is observed in the subepithelial region. (a) Lymphoid follicles are frequently present. (b) Linear inflammatory cell infiltration is present in the subepithelial region. (c) Epithelial denudation is often observed. Numerous plasma cells are present along with lymphocytes in HIC bladder. Microvessels are increased. The superficial layer of the epithelium is lost. (d) The epithelial cells in the basal layers show degenerative changes.

some cases, moderate-to-dense fibrosis is observed in the subepithelial stroma. A few scattered lymphocytes always reside in normal bladder mucosa by nature; no bladder mucosa is completely devoid of inflammatory cells.

Mast cells

A controversy is the etiological and clinical significance of mast cell infiltration. The confusion is attributable to several factors: inconsistent staining methods to identify mast cells, counting mast cells by human eyes, difficulty in obtaining a sufficient amount of detrusor muscle, few investigations in a HIC versus NHIC manner and little attention to the background inflammation.[17–22] The role of mast cells might be implicated differently between HIC and BPS.[23,24] Mast cells are unlikely to play a pivotal role in HIC pathogenesis, as mast cell infiltration is far less dense compared with other infiltrating inflammatory cells. The role might not be dismissed in BPS pathogenesis; mast cells are implicated in systemic disorders with afferent hypersensitivity and neurogenic inflammation.[25]

Pathophysiology

Pathophysiology of IC/BPS is undetermined, but would be totally different between HIC and BPS. Histopathologically, HIC bladder shows an immunological inflammatory reaction frequently accompanied by B-cell clonal expansion and epithelial denudation, whereas BPS shows little change.[9,16] Inflammation, which can be caused by autoimmunity, infection, exogenous substances or unknown mechanisms, would be the principle etiology of HIC. Meanwhile, functional defects of urothelial barrier, neurogenic inflammation, neural hyperactivity or extrabladder disorders might play the primary role in BPS pathophysiology.

Inflammation

Bladder inflammation, regardless of etiologies, might induce afferent nerve overactivity and HSB symptoms.[26]

Immunological inflammation: HIC is a distinct inflammatory disease in many aspects.[27] Histopathology of HIC bladders shows diffuse and intense inflammation.[9,16] The bladder tissue overexpresses many pro-inflammatory genes.[28,29] High serum or urinary concentrations of immunoglobulin and inflammatory markers, such as C-reactive protein, NGF and pro-inflammatory cytokines, are reported.[30–33] Deposits of immunoglobulin and complement are detected in the bladder as well.[34] Immune responses might be elicited by autoimmunity, infection or exogenous substances (see respective sections below).

Neurogenic inflammation and mast cells: Neurochemical transmitters can induce the central nervous sensitization and local inflammatory changes, referred to as neurogenic inflammation. Mast cells play a pivotal role in this local inflammation through synthesis of pro-inflammatory cytokines, recruitment of leukocytes and vascular remodeling.[35] Increased stromal fibrosis and mast cell counts are also reported in BPS.[36] Recent research casts doubt on the role mast cells in HIC (see Histopathology section).

Autoimmunity

Autoimmune disorders are common comorbidities of IC/BPS. Autoantibodies were detected in the serum or urine of IC/BPS patients.[1] Endogenous pathogens from degenerated cellular components (DAMP) might evoke the inflammatory reaction.[37] Autoimmunity against uroplakin induces

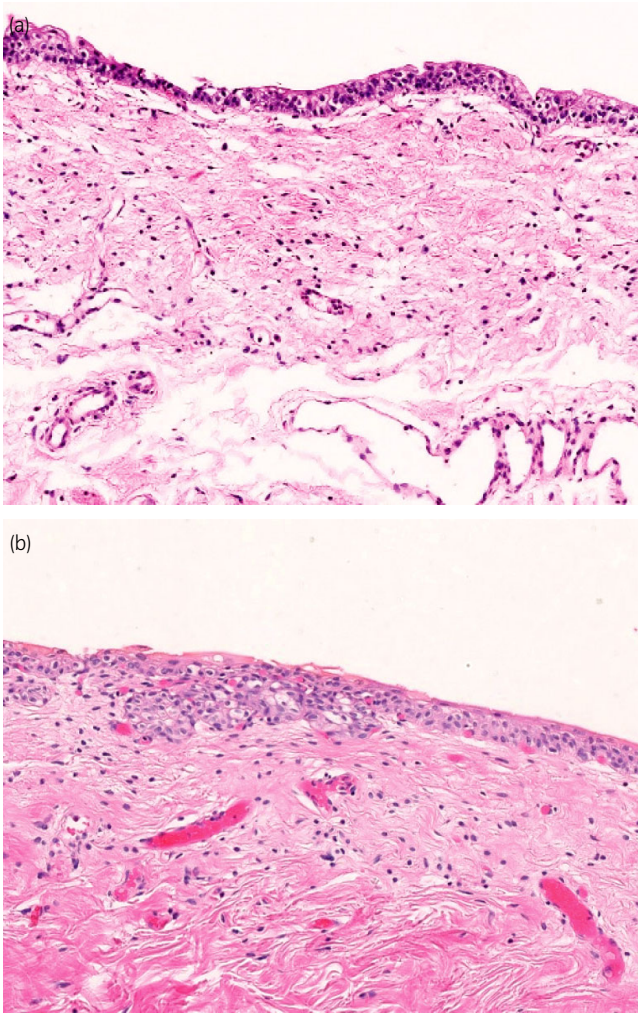

Fig. 2 Histopathology of BPS. Histopathology of the bladder biopsy is often unremarkable in BPS. (a) Subepithelial inflammation is not evident. (b) The epithelium is well-preserved in BPS.

subepithelial inflammation, serum antibody responses and voiding dysfunction in a murine model.[38]

Infection

An association of urinary tract infection with IC/BPS is suggested by a high positivity of urine cultures, altered urine bacterial flora[39,40] or the whole transcriptome analysis.[8] Increased frequency of Epstein–Barr virus infection is also reported in HIC patients.[41] Microorganism infection induces immune responses, especially in individuals with genetic susceptibility.[42,43]

Exogenous substances

Urinary substances might function as noxious or injurious stimuli. Consumption of specific diets triggers symptom worsening.[44,45] Urine alkalization by citrate improved HSB symptoms by reducing urine acidity.[46] Urinary metabolites of ketamine are known to induce bladder inflammation associated with immunological hypersensitivity.[47] Alternatively, DAMPs from the degenerated cells by toxic substances might promote immunological inflammations.

Angiogenesis

Elevated levels of VEGF, a pro-inflammatory growth factor, have been reported in HIC.[1,8,48–50] Given the inflammatory nature of HIC, increased angiogenesis might be a result from chronic inflammation. OnabotulinumtoxinA injections, which eliminate HSB symptoms, downregulate VEGFs.[51] Increased and dysregulated angiogenesis is also implicated with MBAD in BPS.[52]

Urothelial defects

Defect of the urothelial barrier results in entry of urine or urinary components into the bladder wall, causing afferent nerve hyperactivity and/or persistent inflammatory responses. Denudation or anatomical loss of urothelium, documented in HIC,[9,16] allows direct invasion of urine. Functional defect and increased urothelial permeability might be caused by abnormality of the GAG layer overlying the urothelium or impaired cell adhesion/proliferation.[53,54] Intravesical therapy with GAG substitutes is aimed to replenish the damaged GAG layer.[55] Downregulation of tight junction proteins, such as E-cadherin and ZO-1[56] or increased apoptotic activity, is reported.[54]

Neural hyperactivity

Increased mental stress and multiple sensitivities are seen in IC/BPS patients.[45,57] The bladder tissue of HIC showed elevated levels of NGF, TRPV channels, adenosine triphosphate and prostaglandins.[29,58,59] Increased sympathetic nerve activity was also reported in IC/BPS.[60–62]

Extrabladder disorders

IC/BPS patients are liable to functional somatic syndrome, including irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome and migraine.[60,63–65] Common neural hyperactivity and central nervous sensitization might be involved in the pathophysiology of IC/BPS and functional somatic syndrome. Neuronal cross-talk with pelvic organs might exaggerate bladder symptoms.[63] Somatoform disorder could be a predictor of IC/BPS.[66]

Diagnosis

The diagnosis of IC/BPS is made by HSB symptoms and exclusion of confusable diseases. Differential diagnosis of HIC and BPS warrants cystoscopy to determine the presence or absence of Hunner lesions. Diagnostic tests were classified into basic, suggested and optional according to recommendation level (Table 3).

Symptoms and QoL

The symptoms of IC/BPS are to be collectively called HSB symptoms; that is, 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. Simply, they are bladder pain and urinary frequency. The HSB symptoms are more severe in HIC than BPS.[67] Symptom severity is susceptible to dietary, environmental and mental stress with variable remissions and

Table 3 Clinical tests for diagnosis

Basic	Clinical history, physical examinations, urinalysis
Suggested	Symptom scores, QoL scores, frequency–volume chart, residual urine measurement, urine culture, urine cytology, blood test including prostate-specific antigen, cystoscopy, ultrasonography
Optional	Pelvic imaging tests, urodynamic studies, bladder biopsy, hydrodistension

Cystoscopy is mandatory to determine the presence or absence of Hunner lesions. Tests to exclude confusable diseases should be considered differently.

exacerbations.[45] Many symptom assessment tools are available, although a single specific questionnaire cannot offer complete assessment.[68] Significant symptomatic overlap between IC/BPS and OAB is recognized; bladder pain and urgency incontinence is more typical for IC/BPS and OAB, respectively.[69] The QoL is negatively affected by the HSB symptoms; for example, patients had lower economic status, sexual-related pain and sleep disorder in Taiwan.[70] Greater symptom impact, depressive symptoms and comorbidities were each associated with less work participation.[71]

Clinical examinations

Urinalysis usually has no abnormality. A urinary diary showed increased urinary frequency and constant small voided volumes all day.[72] High signal intensity of the bladder wall was related to IC/BPS on diffusion-weighted magnetic resonance imaging.[73]

Biomarkers

Numerous diagnostic biomarkers are explored including urinary or serum NGF,[30,74] urinary or serum pro-inflammatory cytokines or chemokines.[33,75] Intra-tissue increase in chemokines or receptors related to pro-nociceptive inflammatory reactions is reported. Urinary metabolomics identified an increased level of a sulfo-conjugated 5-beta reduced isomer of testosterone in IC/BPS.[76] However, there are no universally accepted biomarkers.[77,78]

Cystoscopy

Cystoscopy is required for the differential diagnosis of HIC and BPS, and is thus highly recommended.[3,67] The findings should be recorded in a standardized way.[1] A Hunner lesion is recognized as a reddish lesion associated with converging vessels, covering fibrin clots or scars (Fig. 3). The current guidelines first provide multiple characteristic endoscopic pictures of Hunner lesions for reference, as inconsistent diagnostic criteria for the lesions are suggested by a highly variable proportion of patients with Hunner lesions among hospitals.[79] It is crucially important to watch the bladder mucosa from the early phase of filling, as Hunner lesions might be obscured shortly after bladder distension. The lesions are more readily recognized by narrow-band imaging cystoscopy.[1]

Bladder biopsy

Bladder biopsy is not essential for diagnosis. However, HIC shows dense inflammatory infiltrates and epithelial denudation in the bladder.[16] The findings would be helpful for the definite diagnosis of HIC.

Diagnostic hydrodistension

The bladder looking normal before distension might undergo MBAD during emptying.[1] MBAD or glomerulations might represent unknown bladder pathology, although convincing evidence as a definite diagnostic criterion is lacking.[8,10]

Other diseases to be excluded

Many diseases can cause HSB symptoms thus to be excluded. The examples are bladder diseases (OAB, neurogenic bladder, bladder cancer, bladder calculus, radiation cystitis, chemical cystitis, ketamine-related cystitis), prostate and urethral diseases (benign prostatic hyperplasia, prostate cancer, prostatitis, urethral cancer, urethral diverticulum, urethral stricture), genitourinary infections (bacterial cystitis, urethritis, prostatitis), gynecological diseases (gynecological malignancies, endometriosis, uterine myoma, vaginitis, climacteric disturbance) or other conditions (polyuria, urinary stones).

Treatment

Treatments for IC/BPS are listed in Table 4 with the grade of recommendation.[1] Readers should refer to the previous guidelines[1,2] for the detailed evidence before 2015. Not mentioned this time are the treatments with no major progress during these past 4 years: amitriptyline, hydroxyzine, suplatast tosilate, steroid, cimetidine, L-arginine, citrate, and instillation of heparin, hyaluronic acid, oxybutynin, pentosan polysulfate, lidocaine, resiniferatoxin and BCG.

Conservative treatment

Patient education using a text- or video-based m-health system is useful for managing symptom flare-up.[80] MBSR, a standardized meditation program, might be effective for IC/BPS.[81] Symptoms significantly improved on the global response assessment in patients attending MBSR class (88%) compared with controls with usual care alone (36%, $P = 0.03$). Additional evidence for dietary therapy is shown by intensive systematic dietary manipulation, a strict dietary therapy with nutrient control, and restricted intake of tomatoes, tomato products, soybean, tofu products, spices, excessive potassium, citrus and high-acidity-inducing substances. IC/BPS patients ($n = 20$) on this dietary therapy for 1 year showed significant symptom improvement compared with controls ($n = 10$).[82]

Medical treatment

New recent evidence has added to pentosan polysulfate, cyclosporine A and antibacterial agents. Six agents (duloxetine, gabapentin, montelukast, NSAIDs, sildenafil and adalimumab) are mentioned this time, despite no new evidence available, as they were not described previously.[1,2] Certolizumab pegol and tacrolimus are newly described.

Pentosan polysulfate: Pentosan polysulfate might improve symptoms by repairing the damaged GAG layer of the urothelium, although the clinical study results are

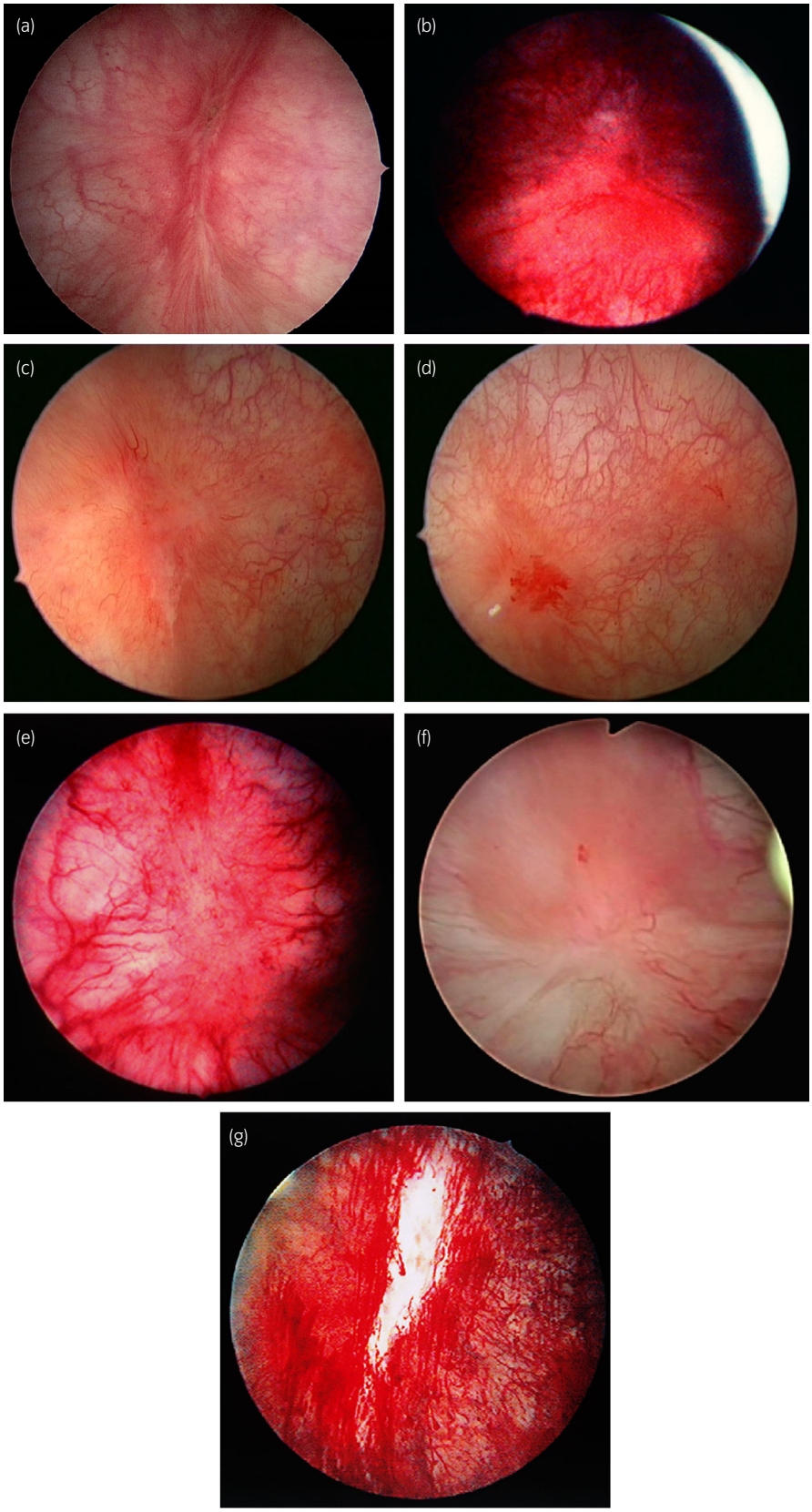

Fig. 3 (a–e) Cystoscopic findings of Hunner lesions. A Hunner lesion is a reddish mucosal lesion lacking in the normal capillary structure. (a) The lesion runs linearly to arch-like, (b) and with occasional branching. It is often associated with (c) detached urothelium (white tissue in the lower half), (d) covering clots, (e) converging vessels (vessels around the lesion apparently converge to the lesion) and (f) scars. (g) The lesion develops rupture and arterial bleeding by overdistension.

Table 4 Treatments for IC/BPS

Treatment	Grade of recommendation (level of evidence)	Suggested doses† or indication
Conservative treatment		
Behavior modification§	B (4)	
Stress reduction	B (2)	
Dietary modification	B (2)	
Physiotherapy§	B (2)	
Medical treatment		
Pentosan polysulfate	C (2, 2)‡	300 mg/day
Amitriptyline§	B (2, 2)	10–75 mg/day
Hydroxyzine§	C (4)	25–75 mg/day
Suplatast tosilate§	C (4)	300–600 mg/day
Cyclosporine A	C (2)	3 mg/kg BW/day
Steroid (prednisolone)§	C (4)	5–25 mg/day
Cimetidine§	C (2)	600 mg/day
Antibacterial agent	D (4, 2)	
L-arginine§	D (4, 2)	
Citrate§	C (4)	853 mg/day
Duloxetine	D (4)	
Gabapentin	C (4)	300–2100 mg/day
Montelukast	C (4)	10 mg/day
NSAIDs (piroxicam)	C (4)	40 mg/day
Sildenafil	C (2)	25 mg/day
Adalimumab	C (2)	40–80 mg/every 2 weeks, for 12 weeks, s.c.
Tacrolimus	C (5)	3 mg/day
Certolizumab pegol	C (2)	400 mg at weeks 0, 2, 4, and 8, s.c.
Intravesical instillation or bladder wall injection		
DMSO	B (2)	50 mL of 50% solution
Heparin§	C (3)	10 000 units
Hyaluronic acid§	C (3)	40 mg
Chondroitin sulfate	C (2, 2)	0.2–2%
Pentosan polysulfate§	C (3)	300 mg
Oxybutynin§	C (3)	0.01%
Lidocaine§	C (2)	4%
Resiniferatoxin§	C (4, 2)	10–100 nM
Botulinum toxin	B (3)	100–200 IU
Steroid	C (4)	40 mg/mL 10 mL
BCG§	D (2, 2)	
Hydrodistension	B/C (4)	
Other treatments		
Electrostimulation	B/C (2/3)	
Acupuncture	C (3, 3)	
Hyperbaric oxygen§	C (4, 2)	
Transurethral fulguration	B (3)	HIC only
Cystectomy or augmentation	C (4)	Last resort

†Only for the treatments with grade of recommendation B and C. ‡(level of evidence for efficacy, level of evidence for non-efficacy). §Refer to previous guidelines for detail (no major progresses in the past 4 years).

conflicting.[2] Pigmentary maculopathy associated with reading difficulty was reported in six IC/BPS patients receiving pentosan polysulfate over a median duration of exposure of 186 months (range 144–240 months).[83] Recent large cohort studies reported controversial results on the association between pentosan polysulfate exposure and subsequent diagnosis of maculopathy.[84,85]

Cyclosporine A: The efficacy of cyclosporine A was shown in open trials and a randomized study, especially for HIC. In an open-label study, four of 26 patients failing two or more prior treatments showed >50% reduction of symptom index at 3 months, with 75% (3/4) of the responders having Hunner lesions.[86] The dosage was started at 3 mg/kg and adjusted based on the serum level 2 h after the morning dose. Two patients withdrew because of hypertension or elevated serum glucose.

Antibacterial agents: Antibacterial agents were not recommended previously.[1] A recent report showed symptom reduction in 624 women with refractory chronic bladder pain and recurrent cystitis by full-dose first-generation antibiotics, such as cephalexin, nitrofurantoin or trimethoprim, in combination with methenamine hippurate for 383 days (mean), although just 16% of urine cultures were positive.[87] The results might warrant a future randomized controlled trial.

Duloxetine: Duloxetine is a serotonin-norepinephrine reuptake inhibitor. No statistically significant symptom improvement was found in 48 IC/BPS women who were prospectively treated for 2 months following an uptitration protocol to the target dose of 80 mg/day for 5 weeks.[88] There were five responders (10%) and 17 (35%) dropouts due to adverse events (nausea).

Gabapentin: Gabapentin, an anticonvulsant agent, was orally administered to 21 patients with refractory genitourinary pain including eight patients with IC/BPS. The dose was titrated from 300 up to 2100 mg/day. At 6 months, 48% of patients (63% of IC/BPS) reported subjective improvement of the pain. Gabapentin was well tolerated; just four patients dropped out as a result of side-effects.[89]

Montelukast: Montelukast is a blocker for cysteinyl leukotriene 1 receptors. A total of 10 female IC/BPS patients with detrusor mastocytosis received 10 mg montelukast daily. After 3 months, pain decreased from 46.8 to 19.6 mm on a VAS ($P = 0.006$), with urinary frequency and nocturia also decreasing significantly. No side-effects were observed.[90]

Non-steroidal anti-inflammatory drugs: A total of 37 patients received 75 mg doxepin (tricyclic antidepressant) and 40 mg piroxicam (cyclooxygenase inhibitor) daily. Medication was not tolerated by five. Of the remaining 32 patients, 26 experienced virtual total remission of symptoms, and six attained significant relief. Most patients who showed significant improvement had a return of symptoms after cessation of therapy.[91]

Sildenafil: Sildenafil enhances the effect of NO by inhibiting phosphodiesterase type 5. IC/BPS women were randomly assigned to a daily low-dose of sildenafil (25 mg, $n = 24$) or placebo ($n = 24$) for 3 months. The symptom index and problem indices, but not VAS pain score, significantly improved in the sildenafil group compared with the control group. All adverse events were mild-to-moderate and transient.[92]

Adalimumab: Adalimumab is a monoclonal antibody against tumor necrosis factor-alpha. IC/BPS patients were randomized to a loading dose of 80 mg subcutaneous adalimumab followed by 40 mg every 2 weeks ($n = 21$) or subcutaneous placebo for 12 weeks ($n = 22$).[93] Patients receiving adalimumab alone showed significant improvement in the symptom index, problem index and VAS pain score compared with baseline, although no statistically significant intergroup difference was detected. There were no major adverse events.

Certolizumab pegol: Certolizumab pegol is also a monoclonal antibody against tumor necrosis factor-alpha. IC/BPS patients were randomized to subcutaneous injection of 400 mg certolizumab pegol ($n = 28$) or placebo ($n = 14$) at weeks 0, 2, 4 and 8.[94] At week 18, certolizumab pegol attained a significantly greater decrease from baseline for a symptom index of 3.6 ($P = 0.03$), problem index of 3.0 ($P = 0.042$) and VAS pain score of 2.0 ($P = 0.02$) compared with the placebo. There were no significant adverse events.

Tacrolimus: Tacrolimus is a potent immunosuppressant. A 69-year-old woman, who had been diagnosed with primary Sjögren's syndrome 23 years ago, developed IC and was successfully treated with 3 mg tacrolimus and 30 mg prednisolone combination therapy.[95]

Intravesical instillation or bladder wall injection

DMSO: DMSO is a chemical solvent, and might exert symptomatic efficacy through the combined effect of anti-inflammatory activity, nerve blockade, smooth muscle relaxation and collagen synthesis inhibition. Randomized and non-randomized studies showed long-lasting efficacy, and the efficacy was favored for HIC.[1,96,97] Co-instillation with steroid and heparin was attempted.[98]

Chondroitin sulfate: Chondroitin sulfate is a glycoprotein. Single or combined instillation showed symptom improvement,[99] although the efficacy as a single agent was negated in a randomized double-blind controlled study.[100] Recent reports showed better effects than other intravesical agents.[101,102]

Botulinum toxin: Single-arm or randomized studies showed symptom relief by botulinum toxin injection, single or repeated, into the bladder wall.[103,104] The average duration of effect was approximately 6 months, and repeated injections are apparently required. It is uncertain whether the presence of Hunner lesions affects the efficacy of injection.[105,106] Instillation with gel as an alternative to bladder wall injection was attempted. Intravesical instillation of botulinum toxin premixed with gel as an alternative to bladder wall injection was attempted.[107]

Steroid: Submucosal injections of a corticosteroid in and around Hunner lesions consistently offered significant symptomatic improvement.[108,109]

Endoscopic surgery

Hydrodistension: Some reports reported an approximately 50% efficacy rate and efficacy persistence of a few months,[110,111] whereas others reported long-term efficacy of >1 year.[112] The putative mechanism for efficacy includes degeneration of afferent nerves, anti-inflammatory effect or reduction of multiple growth factors.59 Suggested procedures for hydrodistension were described previously.[1] Identifying the optimal patients is required; a study identified concomitant lumbar spinal stenosis and irritable bowel syndrome as poor outcome predictors.[112] Bladder rupture and necrosis are serious procedure-related complications.[113] Multiple sessions might not decrease bladder capacity.[114,115]

Transurethral ablation/fulguration: Many studies reported pain relief by transurethral electro- or laser ablation of the Hunner lesions, confirming efficacy persisting for a few months to 2 years post-treatment.[112,116–118] The procedure can be repeated on symptom recurrence. The surgery is usually combined with hydrodistension, and the concomitant

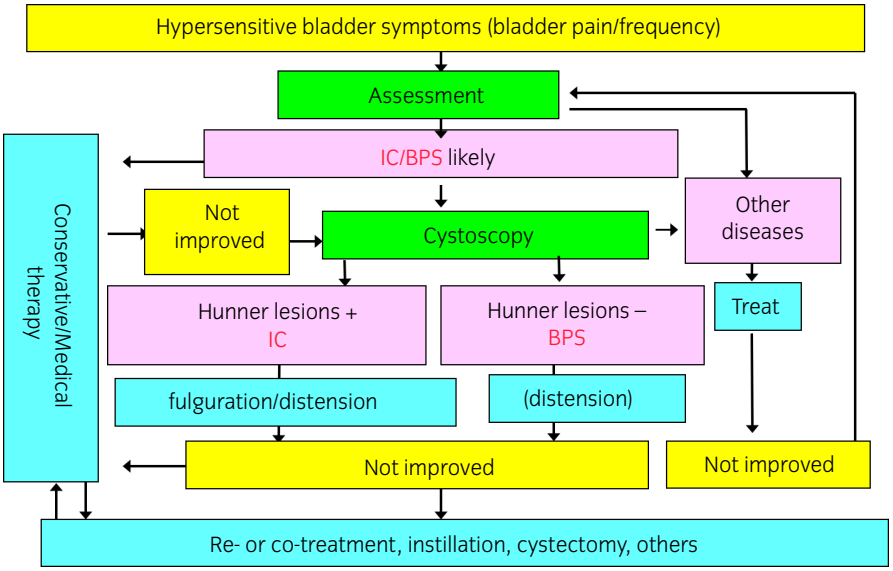

Fig. 4 Clinical algorithm for patients with HSB symptoms. Patients presenting with bladder pain and/or urinary frequency should be managed according to the algorithm. After proper assessment and exclusion of other confusable diseases, conservative or medical treatment might be initiated. Hunner lesions should be fulgurated once detected. Combined treatment with bladder instillation, bladder injection and electrostimulation should be considered. Cystectomy or urinary diversion is the last resort.

procedure was more effective in improving symptoms than ablation alone.[119] Decreasing bladder capacity by repetitive procedures is a concern and controversial.[120]

Cystectomy, substitution, urinary diversion

Surgical interventions including partial or complete cystectomy, bladder augmentation and urinary diversion would be the last resort for intractable symptoms and/or a severely contracted bladder.[121] Patients with HIC rather than BPS are the candidates. Supratrigonal cystectomy with subsequent bladder substitution using a bowel segment is the most common continence preserving technique.[122] Subtrigonal cystectomy with ureteral re-implantation or total cystectomy with urinary diversion is an alternative option, in which urethrectomy might not be required.[123] Urinary diversion alone without cystectomy might attain sufficient symptom relief.[124] Long-term postoperative observation is required to monitor symptom recurrence and morbidities, such as hydronephrosis and adenocarcinoma of the bowel segment.

Other treatments

Electrostimulation: The efficacy of permanent sacral nerve neuromodulation was shown in many studies and confirmed in a long-term observation.[125] Intermittent posterior tibial nerve stimulation or pudendal nerve stimulation also showed some efficacy.[126]

Acupuncture: A large placebo effect and contradictory results with limited and temporary efficacy were reported.[127,128]

Assessment of therapeutic effectiveness

Clinical studies for IC/BPS require special consideration for the study design, inclusion criteria and outcome measures, as described previously.[1] Most importantly, the study should specify the target patients as IC/BPS, HIC alone or BPS alone. When IC/BPS patients are included, separate analysis of HIC and BPS should be made to clarify the therapeutic effects for each category.

Clinical algorithm

An algorism is provided for patients presenting with HSB symptoms (simply bladder pain and/or urinary frequency; Fig. 4). The assessment consists of the basic evaluation (history taking, physical findings and urinalysis), and suggested or optional tests (see Table 3 for details). When other diseases are identified, appropriate treatments should be initiated. When IC/BPS is likely, cystoscopy is recommended to determine the presence or absence of Hunner lesions. Alternatively, conservative or medical treatments might be empirically initiated, with cystoscopy not carried out. When Hunner lesions are found on cystoscopy (HIC diagnosed), fulguration of lesions (preferably concomitantly with hydrodistension) is indicated. When Hunner lesions are not found (BPS diagnosed), hydrodistension under spinal or general anesthesia might be indicated. In any case, conservative or medical pain treatments should be considered concurrently. When sufficient improvement is not attained, re-evaluation, repeated treatment or combined treatment with bladder instillation, bladder injection and electrostimulation should be considered. Cystectomy or urinary diversion is the last resort.

Conflict of interest

None declared.

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Editorial Comment

Editorial Comment to Clinical guidelines for interstitial cystitis/bladder pain syndrome

The former Japanese Clinical Guidelines for interstitial cystitis (IC) and related conditions was published in 2009 and 2016.[1] Homma *et al*. revised the previous guidelines, completing articles identified by the PubMed database published from 2016 to 2019.[2]

In the current clinical guidelines, one of the characteristics is the categorization. IC/bladder pain syndrome (BPS) is utilized as a comprehensive term, and divided into Hunner-type IC (HIC) and BPS. Only HIC represents Hunner lesions, thus endoscopic findings are indispensable for the diagnosis.