



Variations in bladder pain syndrome/interstitial cystitis (IC) definitions, pathogenesis, diagnostics and treatment: a systematic review and evaluation of national and international guidelines

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Received: 7 February 2019 / Accepted: 22 April 2019 / Published online: 9 May 2019
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Abstract

Introduction and hypothesis Interstitial cystitis (IC) and bladder pain syndrome (BPS) are challenging and encompassing hypersensitivity disorders of the lower urinary tract. A variety of national and international guidelines have been published including guidance on nomenclature, definitions, etiopathology, diagnostics and treatment. A lack of universally established clinical guidance is apparent. The aim of this review is to evaluate key guidelines on this area of practice, identify variations, compare their recommendations and grade them using AGREE II.

Methods Literature searches were performed using the PUBMED and CINAHL database from January 1, 1983, to December 1, 2018, referring to the search strategy of AUA. Ten national and international guidelines were included into the analysis. We assessed the guidelines with the updated AGREE II.

Results Symptoms congruent in all guidelines are: pain, pressure, discomfort and frequency, urgency and nocturia. Urinalysis is a prerequisite for diagnostics, cystoscopy for most and urodynamics not part of the routine assessment. Treatment options are recommended stepwise. The highest level of evidence and consensus was identified for oral therapies. Nine guidelines had an overall quality score $\geq 50\%$ and three scored $\geq 70\%$ (AUA, GG, RCOG).

Conclusions The guidelines are congruent in symptom reporting, quite congruent in diagnostics and vary to a high degree on treatment recommendations. The complexity of BPS and emerging evidence indicate the need for regular updating of the guidelines and a wider consensus.

Keywords Bladder pain syndrome · Interstitial cystitis · Diagnostics · Treatment · Guidelines · AGREE II

On behalf of CHORUS: An International Collaboration for Harmonising Outcomes, Research and Standards in Urogynaecology and Women's Health

The paper was presented as a short podium presentation at the IUGA 2018 in Wien

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Introduction

Interstitial cystitis (IC) or bladder pain syndrome (BPS) is a challenging and encompassing hypersensitivity disorder of the lower urinary tract [1]. Both conditions are recognized as genitourinary pain syndromes of still enigmatic etiology.

The prevalence of IC in the USA was shown to be up to 0.5% in the adult population [2]. A newer study showed variations in the prevalence rates for IC/BPS according to diagnostic criteria from 2 to 17.3% among the general population [3, 4], and underdiagnosis is discussed based on a symptom-based study [5].

The criteria for interstitial cystitis were defined in 1987 by the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) for scientific studies. The criteria turned out to be restrictive, being fulfilled by only one third of patients [6], and did not mirror the problems of a majority of BPS

patients in a clinically feasible approach. To inform clinical practice, a variety of international and national guidelines, adopting less restrictive criteria, were introduced [7–17]. These guidelines highlighted the clinical issues of patients with BPS in terms of nomenclature, definitions, diagnostics, pathoetiology and treatment. However, a worldwide evidence-based consensus on the diagnosis and treatment of BPS is lacking. The objective of this study was to systematically evaluate key contemporary guidelines, focusing on the variations in definitions, diagnostics and treatment, compare their recommendations and grade the guidelines using the AGREE II tool.

Materials and methods

A systematic review was conducted to identify published international and national guidelines on IC/BPS. Literature searches were performed using the PUBMED and CINAHL database from January 1, 1983, to December 1, 2018, using the following search strategy referring to the AUA guideline [10]: “interstitial cystitis” OR “Painful bladder syndrome,” OR “Bladder pain syndrome” OR IC/PBS OR “Chronic pelvic pain” AND “guideline” NOT “case reports” NOT “comment” NOT “editorial” NOT “letter”. All references ($n = 521$) of relevant reviews were checked to ensure inclusion of most of the guidelines (Fig. 1). Sixteen guidelines were found as per search criteria. Six guidelines were excluded: four guidelines were outdated, one guideline was an Indian expert opinion [18], and one consensus statement of the International Association

for the Study of Pain (IASP) was too unspecific for the BPS/IS syndrome [19]. Ten guidelines were included into the analysis, including one amendment (AUA) [7–13, 15, 20, 21] (Table 1).

All 5 authors assessed the methodological rigor and transparency using the Appraisal of Guidelines Research and Evaluation II (AGREE II) instrument, which contains 23 items grouped in 6 domains: (1) scope and purpose; (2) stakeholder involvement; (3) rigor of development; (4) clarity and presentation; (5) applicability; (6) editorial independence [22, 23]. The authors independently rated each item on a 7-point scale, with 1 being the lowest and 7 the highest rating. For evaluation, the gradings 0–3 were classified as unsatisfactory quality on item, grading 4 as neutral and grading 5–7 as satisfactory quality on item. Every item for which the grading differed by more than 1 point on the original 7-point scale was discussed in a consensus meeting. Reviewers in turn explained the rationale for their rating and had the opportunity to revise it where appropriate. There is no defined threshold for the domain scores of the AGREE II tool to make a distinction between high- and low-quality guidelines, albeit some authors consider domain scores < 50% pragmatically as low quality. Inter-rater variability for agreement between raters was investigated for the complete guideline data, and Fleiss’ kappa coefficient was used to determine the overall agreement and significance. A kappa value < 0.00 indicates poor, 0.00–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial and 0.81 to 1.00 almost perfect agreement. The AUG and GG written in German were rated by two German-speaking authors (JP, CB), and the inter-rater agreement was expressed by Cohen’s kappa.

Fig. 1 Data collection

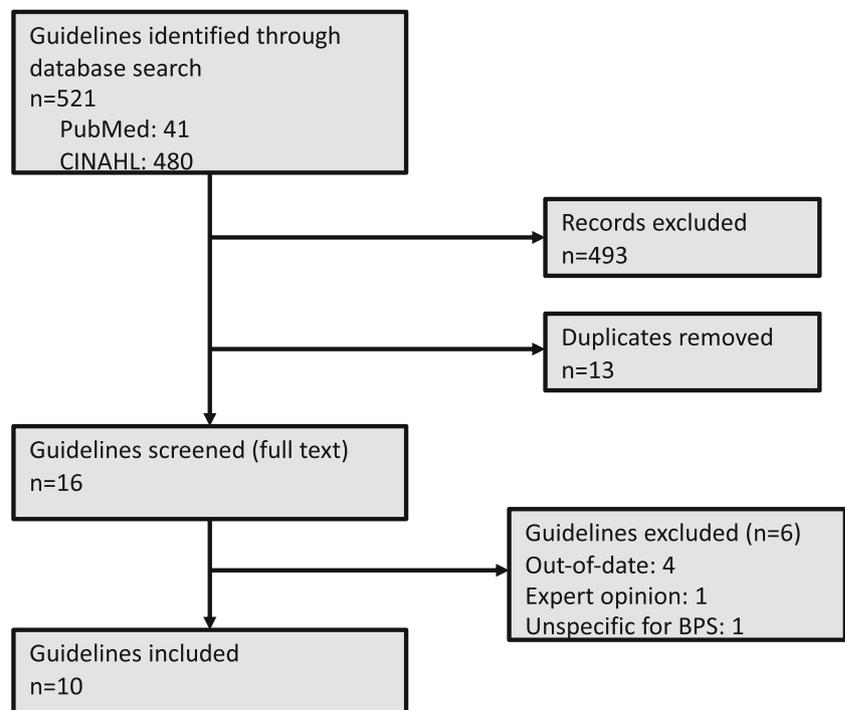


Table 1 BPS/IC Guidelines of national and international societies

Guideline	Year of publication	Abbreviation
International Consultation on Incontinence-Research Society	2011	ICI-RS
European Society for the Study of IC/PBS	2008	ESSIC
American Urological Association	2011, amendment 2015	AUA
Austrian Guideline Pelvic Pain Syndrome	2012	AUG
Canadian Urological guideline	2016	CUA
European Association of Urology	2009	EAU
German Guideline S2K (conjoint guideline of Austrian, German and Swiss societies)	2018	GG
Japanese Urological Association	2009	JUA
Royal College of Obstetricians and Gynecologists	2016	RCOG
Spanish Urological Guideline Bladder Pain Syndrome	2015	SUG

Evidence

Recommendations are based on observational, retrospective or randomized controlled studies as well as clinical principles and expert opinions. Rating of the level of evidence and grade of recommendation was performed according to the Oxford EBM Scale [24]. Most recommendations are based on level of evidence 2–4, and grades of recommendation vary between the guidelines depending on the actuality and the subjective weighting of the experts in the guideline group (ICI-RS, EAU, SUG). Clinical practice recommendations were applied because most treatments demonstrate limited efficacy in a subset of patients that is not readily identifiable a priori (AUA, CUA, JUA and RCOG).

The recommendations of the GG are expressed linguistically and are based on an online-consensus procedure; percentage of consensus was calculated for each recommendation.

Results

Terms and definitions

All international and national guidelines refer to the term agreed upon by the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction, which defines BPS as “the unpleasant sensation (pain, pressure, discomfort) perceived in relation to filling of the bladder” [25] (Table 2). Duration of the pain ranges from at least 4–6 weeks to at least 6 months. The AUA justifies the short duration because it allows treatment to begin after a relatively short symptomatic period. The SUG accepts a range between 3 and 6 months to establish the diagnosis with regard to the arbitrariness of criteria involved in the BPS. The ICI-RS and EAU use the axial structure of the IASP based on region, system, temporal characteristics of pain, patient’s statement of intensity and etiology.

Most guidelines reserve the name “interstitial cystitis” for BPS with typical cystoscopic and histological features [26]. The ESSIC and GG stress that the term IC is misleading because it directs attention only to the urinary bladder and inflammation and excludes patients with typical IC symptoms but normal cytosopic and histological findings from disease classifications [8]. The panel’s guideline proposes to use the term “persistent urge” instead of urgency to avoid confusion with overactive bladder. By contrast, the JUA proposes a new symptom syndrome, “hypersensitive bladder syndrome” (HBS), defined as bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain similar to the overactive bladder syndrome [14].

Diagnosis

Required symptoms in all guidelines (in line with the definition of BPS) are: pain, pressure, discomfort and frequency, urgency and nocturia (Table 2). Discomfort especially in the early phase of bladder filling is part of the main symptom complex in the JUA [27]. Dyspareunia and sexual symptoms are not specific for BPS but should be evaluated (AUA, CUA, EAU, GG JUA). Triggers such as coffee, alcohol, citrus fruits, tomatoes, carbonated beverages and spicy foods are also addressed with or without food diaries (AUA, CUA, GG, JUA, RCOG, SUG).

There is general agreement between the guidelines on the recommended initial evaluation. They all emphasize a full clinical history, examination and appropriate investigations to discover other causes of pelvic pain (Table 3). The diagnosis of BPS can be made by excluding confusable diseases and identifying concomitant diseases (fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, Sjögren’s syndrome, chronic headaches, vulvodynia) and may be confirmed by the presence of the specific combination of symptoms and signs of BPS (ICI-RS, ESSIC). Questionnaires [28] can be used as tools to assist with diagnosis (except for the ICI-RS, ESSIC, EAU). The CUA differentiates the several types of questionnaires

Table 2 Terms, definitions and symptoms for BPS/IC used in different guidelines

Terms, definitions and symptoms	Guideline supporting definition
Pelvic pain, pressure or discomfort	ICI-RS, ESSIC, AUA, AUG, CUA, EAU, GG, RCOG, SUG
Associated with lower urinary tract symptoms	ICI-RS, ESSIC, AUA, AUG, CUA, EAU, GG, JUA, RCOG, SUG
Frequency, urgency or nocturia	ICI-RS, ESSIC, AUA, AUG, CUA, EAU, GG, JUA, RCOG, SUG
Suprapubic pain and throughout the pelvis	ICI-RS, ESSIC, AUA, AUG, CUA, EAU, GG, JUA, RCOG
Discomfort especially in early phase of bladder filling	AUA (should be evaluated), CUA, EAU, GG, JUA
Dyspareunia, sexual symptoms	JUA
Triggers, local factors	AUA, AUG, CUA, GG, JUA, RCOG
Term: bladder pain syndrome (BPS)	ICI-RS, AUG, EAU, GG, RCOG, SUG
Term: BPS/interstitial cystitis	ESSIC, AUA, CUA, EAU, GG
Term: interstitial cystitis	JUA (hypersensitive bladder syndrome)
Duration: 4–6 weeks	AUA
Duration: 3–6 months	SUG
Duration: 6 months	AUG, EAU
Classification by findings at cystoscopy/biopsies	ICI-RS, ESSIC, GG
Classification by findings at cystoscopy not recommended	SUG

and reminds us that none of the surveys have sufficient specificity to serve as a sole diagnostic indicator. The RCOG points out that there is a good correlation between the IC Symptom Index and Pelvic Pain and Urgency/Frequency symptom scores, but poor correlation for quality of life (QoL) [29]. A psychological examination is mentioned in 6/10 guidelines: The RCOG evaluates the effect of BPS on QoL [30, 31] and considers referring patients with refractory BPS for psychological support. Furthermore, a brief pain inventory gives a better assessment of baseline pain and response to treatment than simple analog scales [32]. Urine analysis (cytology and culture) is part of the basic assessment in all of the guidelines in order to

exclude an infection. Bladder activity diaries are considered in 6/10 guidelines. A post-void residual is recommended only when a history of poor emptying is obtained and/or the bladder is palpable on examination (AUA, AUG, CUA, EAU). Additional tests are variable (Table 4) only if treatment of pain due to other possible causes is not effective. For the JUA cystoscopy with hydrodistension and bladder biopsy is a prerequisite for diagnosing BPS. For the RCOG cystoscopy does not confirm or exclude the diagnosis of BPS, but is required to diagnose or exclude other conditions that mimic BPS [33]. The ICI-RS stresses that there is no pathognomonic histology and that the role of histopathology in the diagnosis is primarily

Table 3 Basic evaluation of IC/BPS patients with personal history, diaries and subjective assessment and urine analysis. See Table 5 for explanation of Levels of Evidence

Evaluation	Guideline supporting recommendation
Detailed history	ICI-RS, ESSIC, AUA, AUG, CUA (mandatory C/4), EAU, GG, JUA, RCOG, SUG
Physical/pelvic examination	ICI-RS, ESSIC, AUA, AUG, CUA (mandatory C/4), EAU, GG, JUA, RCOG, SUG
Exclude confusable disease	ICI-RS, ESSIC, AUA, AUG, CUA, EAU, GG, JUA, RCOG, SUG (2a/B)
Questionnaires	AUA, AUG, CUA (all C/3), GG, JUA, RCOG (B), SUG
Psychological examination	AUA, AUG, RCOG (C/D), GG, JUA, SUG (4/C)
Pain body maps	AUA
Visual analog scales	AUA, RCOG (D)
Urine analysis	ICI-RS, ESSIC, AUA, AUG, CUA (optional 4/C), EAU, GG, JUA, RCOG (C), SUG
Bladder activity diary	AUA, AUG, CUA (all 3/C), GG, RCOG, SUG (4/C)
Post-void residual urine vol.	AUA, AUG, CUA (optional 4/C), EAU, GG (only men)

Table 4 Advanced evaluation of IC/ BPS patients

Diagnostic tests	Guideline supporting definition
Cystoscopy, all patients	ESSIC, AUG, CUA (3/C), EAU, GG, JUA, RCOG, SUG
Cystoscopy, no prerequisite	ICI-RS (consider), AUA
Bladder biopsy	ESSIC, CUA, EAU, GG (not prerequisite for diagnosis), SUG
Urodynamics	AUG, EAU, SUG (for men)
Urodynamics (not in the routine)	ICI-RS (consider), AUA, CUA (4/C), GG, RCOG (if OAB, C), SUG (for women)
Potassium Test	EAU, JUA, SUG (consider)
Urine markers	EAU, GG (consider), JUA, SUG (consider, 3)
Ultrasound	ICI-RS, AUA, AUG, CUA (optional, C), EAU, GG
Endoscopy	ICI-RS (in complicated BPS)
Laparoscopy	ICI-RS (in complicated BPS), AUA (consider)
Intravesical anaesthetic bladder challenge	CUA (3/C)
Further imaging evaluation (X-ray, CT, MRI)	CUA, ICI-RS, JUA, SUG, RCOG

one of exclusion [34]. In most of the guidelines, urodynamics are only recommended if OAB symptoms are present. Expressively undesired are the potassium test (AUG, CUA, RCOG) and urine markers (RCOG), whereas other guidelines propose a consideration. According to all guidelines, MRI is not mandatory (SUG consider), and X-ray examination [35], further imaging (ICI-RS) and ultrasound/pelvic imaging (CUA 4/C) are optional overall to investigate/exclude any suspected additional pelvic or abdominal pathology. RCOG only stated that any suspected additional pelvic or abdominal pathology should be appropriately investigated.

Treatment

A wide variety of IC/PBS treatments are proposed with different levels of effectiveness in all guidelines except the ESSIC guideline, which has no treatment section [7–15, 31, 36, 37] (Table 5). The treatment options are gradually escalated depending on severity of symptoms.

All guidelines apply the fundamental principle of using the most conservative therapies and passing to systemic conservative therapies if symptom control is inadequate for an acceptable quality of life. Therefore, clinical principles of education and lifestyle modifications come first (Table 5); physical, pharmacological and, ultimately, surgical therapies are reserved for patients where previous therapies failed. However, the different guidelines use different scoring systems to express evidence of treatment, preventing a 1:1 comparison of the recommendations.

Regarding conservative therapies, all guidelines provide recommendations on patient and dietary education as well as physiotherapy for pelvic floor relaxation. The role of complementary medicine was mentioned in 5/9 guidelines with the highest level of recommendation in the GG (possibly useful by all authors).

Oral medication of the antihistamine type (hydroxyzine, cimetidine), leukotriene-receptor antagonist type (montelukast), tricyclic antidepressant type (amitriptyline) and noradrenergic and specific serotonergic antidepressant type (mirtazapine) are rated by all (except the SUG guidelines) with quite high levels of recommendation. Only pentosan polysulfate sodium exceeds the recommendation of the aforementioned drugs with a level of evidence 1 (ICI-RS), 1a (EAU), +100 (GG) and -A (RCOG; -A means high level of evidence but not recommended). Cyclosporin A and anticonvulsants are classified lower, as they are favored by some (EAU, resp. AUG/GG) but to a much lesser extent by other guidelines (RCOG, resp. ICI-RS/EAU). Correspondingly low evidence is given for analgesics and muscle relaxants. Anticonvulsants and steroids are also recommended to a lower degree because of side effects and lacking efficacy. Long-term oral antibiotics or glucocorticoid administration, intravesical instillation of BCG or resiniferatoxin as well as high-pressure, long duration hydrodistension should be explicitly avoided according to the AUA.

Of the intravesical treatments, lidocaine, cortison, pentosan polysulfate sodium, heparin and dimethyl sulfoxide are recommended by most of the guidelines with similar evidence, followed by a lower degree of recommendation for chondroitin sulfate, hyaluronic acid, resiniferatoxin, capsaicin, bacillus Calmette Guerin and oxybutynin. Drug application supported by electromotive-drug administration (EMDA) is only taken into consideration by European societies.

Of the minimally invasive treatment options, the transurethral resection has the highest level of evidence followed by neuromodulation, hydrodistension and intravesical botox injection (\pm injection into the trigone). One common statement of all guidelines is that surgical intervention is the last step.

The AUA panel's observation was that most treatments may benefit a subset of patients that is not readily identifiable before treatment and that, nowadays, no treatment is of reliable benefit

Table 5 Treatment options with level of evidence and grade of recommendation

Therapeutic interventions	ICI-RS	AUA	AUG	CUA	EAU	GG (%)	JUA	RCOG	SUG
Conservative treatment									
Patient education	3/C	CP	+	A	3/B	+100	B	D	4/C
Physiotherapy	3/C	CP	+	B	3/B	+95	C	B	4/C
Relaxation, psychotherapy, support groups	4/C	CP	+	B	3/B	+95	B	D	//
Diet	4/C	CP	+	B	3/C	+100	B	D	4/C
Bladder training	//	CP	//	B	3/B	//	//	//	Possible
Complementary therapy (acupuncture)	//	//	+	B	//	p100	C	maybe	//
Oral treatments									
Hydroxyzine (anti-allergy)	1/D	C	//	B	1b/A	p100	C	-B	//
Cimetidine/Montelukast	3/C	B	//	B	2b/B	p90/p95	C	B	//
Corticoids	//	C	//	//	3/C	//	C	-	//
Cyclosporin A	3/C	C	//	C	1b/B	w100	C	D	//
Amitriptyline/Mirtazapine	2/B	B	+	B	1b/A	+80/p1-00	B	B	//
Oxybutinin	4D	//	+	C	3/C	//	C	//	//
Analgetics	4/C	//	+	//	2b/C	s100	//	+	//
Gabapentin or Pregabalin	4/C	//	+	C	3/C	p90	//	//	//
Pentosan polysulfate sodium	1/D	B	//	D	1a/A	+100	B	-A	//
Nifedipin	//	//	//	//	//	p95	//	//	//
Tizanidin	//	//	//	//	//	p95	//	//	//
Tamsulosin	//	//	//	//	//	w95	//	//	//
Quercetin	4/D	//	//	C	//	//	//	//	//
Antimicrobial therapy	4/D	-B	//	//	3/C	p85	-D	-	//
Intravesical treatments									
Dimethyl sulfoxide	2/B	C	+	B	1b/A	-100	B	C	//
Pentosan polysulfate sodium	4/D	B/C	+	D	1b/A	100	B	-A	//
Intravesical heparin	2/B	C	+	C	3/C	p100	B	D	//
Hyaluronic acid	4/D	//	+	C	2b/B	s100	D	B	//
Chondroitin sulfate	4/D	//	+	D	2b/B	s100	D	D	//
Resiniferatoxin/Capsaicin	-1/A	A	//	-B	1b/C	//	D	-	//
Lidocaine/corticoids	2/C	B	//	B	1b/A	p95	B	B	//
Bacillus Calmette Guerin	-1/A	B	//	-B	A	//	D/c	-	//
Oxybutinin	4/D	//	//	C	3/C	//	C	//	//
Electromotive-drug administration	//	//	+	//	3/B	s100	//	//	//
Other treatments									
Bladder hydrodistension	3/C	C	+	C	3/C	s100	B	D	2nd line
Botox + hydrodistension	4/D	C	+	C	1b/A	p100	D	B	//
Botox + injection in trigone	4/D	C	+	C	3/C	p100	D	B	//
Neuromodulation	3/C	C	+	C	1b/B	w75-90	C	D	//
Transurethral resection	3/C	C	+	B	3/B	w80	B	If HL*	//
Cystoplasty/surgical treatment	3/C	C	+	C	3/A	w80	C	//	//
Emerging therapies									
Hyperbaric oxygen	//	//	//	2/3	//	w90	C	//	//
PDE-5 inhibitors	//	//	//	2	//	p90	//	//	//
TNF-alpha inhibitors	//	//	//	-	//	//	//	//	//
Cannabinoide	//	//	//	-	//	//	//	//	//
Intravesical liposomes	//	//	//	-	//	//	//	//	//

Table 5 (continued)

Therapeutic interventions	ICI-RS	AUA	AUG	CUA	EAU	GG (%)	JUA	RCOG	SUG
Orthomolecular therapy	//	//	//	//	//	p80	//	//	//
Phenotype-directed multimodal therapy	//	//	//	B	//	//	//	//	//

Body of evidence strength is categorized as grade A (well-conducted RCTs or exceptionally strong observational studies), grade B (RCT with some weaknesses) or grade C (observational studies), and evidence strength is linked to statement type (standards, recommendation or options)

The ICI-RS, EAU and SUG use the categorization of the system Centre for Evidence-Based Medicine (Oxford) in the modified version by Sackett (available from: <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009>). The AUA, CUA, JUA and RCOG categorize the evidence in A (high), B (moderate), C (low), D (very low) or CP (clinical practice) according to their scientific and methodological consistency. (– = not recommended, + = recommended, *Hunner’s lesion), for instance –1/A = no recommendation with high level of evidence

The recommendations of the GG are expressed linguistically (– = not recommended, + = recommended, s = should be evaluated, p = possible, w = without recommendation) and are based on an online-consensus procedure; percentage of consensus is calculated for each recommendation as a number, for instance p90 = possible, 90% consensus

// = not mentioned

to most or all patients. To give more specific treatment recommendations, the EAU und CUA divide the therapy algorithm into columns of non-ulcer or classic BPS and recommend multimodal treatment plans [38]. The CUA and JUA address emerging therapies such as hyperbaric oxygen, PDE-5 inhibitors or phenotype-directed multimodal therapy, which include BPS management according to urinary, psychosocial, organ-specific, infectious and neurological findings. TNF-alpha inhibitors, cannabinoids and intravesical liposomes are so far not recommended, but it is possible that future research will influence actual recommendations.

BPS in pregnancy is evaluated only by the RCOG guideline, stating that the effect of pregnancy on the severity of BPS symptoms can be variable and that treatment options such as amitriptyline for oral and heparin for intravesical treatment are considered safe in pregnancy. DMSO should be avoided because of its teratogenic effect in animal studies [39].

Pathogenesis and molecular patterns

There are various hypotheses about the pathogenesis of the BPS, including infection, inflammation, autoimmune mechanisms, defects in the urothelial glycosaminoglycan layer, hypoxia and central neurological mechanisms (Table 6). The EAU states that “the etiology and pathophysiology of BPS remains a mystery, although central neurologic mechanisms probably play a role” [9]. The JUA and GG give the most extensive overview on the pathogenesis, whereas other guidelines (ESSIC, AUA, CUA, RCOG) do not address this topic. There is general consensus that BPS seems to result from a defective or dysfunctional bladder epithelium causing inflammation. It involves no identification of injury to justify inflammatory activity and endocrine-neurological disorder [40–42]. Concerning the role of infection in relation to the BPS, the guidelines are not consistent.

AGREE

Nine guidelines had an overall quality score $\geq 50\%$ and 3 scored $\geq 70\%$ (AUA, GG, RCOG). Across all guidelines, the AGREE II domain with the highest score was “scope and purpose” (76.3%). The “applicability domain” scored $< 50\%$, which hampers the clinical utilization. All other domains scored between 57.2 and 69.7%. The GG as the most detailed and comprehensive guideline scored the best in all domains, but it was only rated by the two German-speaking raters. The inter-rater agreement for the guidelines written in English was slight to moderate (Fleiss’ kappa, 0.17 to 0.48) among the five raters after two revisions on agreement (Table 7).

The guidelines were based on high-quality literature, and most of them included the level of evidence of the

Table 6 Mechanisms of pathogenesis

Factor	Guideline
Defective or dysfunctional bladder epithelium	ICI-RS, ESSIC, AUG, GG, JUA
Neurogenic inflammation	ICI-RS, ESSIC, AUG, GG, JUA
Prostanoids	ICI-RS, GG
Mast cell activation	GG, JUA, SUG
Infection	AUG, GG, JUA
Urinary toxic agents	GG, JUA
Hypoxia	ESSIC, AUG, JUA
Microcirculation	GG
Impaired pelvic health	GG, JUA
Immunity and allergy	ESSIC, AUG, GG, JUA
Emotion/psyche/autonomic nervous system	GG, JUA, SUG (–)
Endometriosis	GG
Microbiome	GG
Genetics	GG (possible)
Interaction among pathogenic factors	GG, JUA

Table 7 AGREE II scores of the guidelines (in every domain and in mean)

	% Mean	ICI	ESSIC	AUA	AUG	CUA	EAU	GG	JUA	RCOG	SUG
Scope and purpose											
Obtained score		80	77	95	25	84	87	41	78	95	76
Max. score		105	105	105	42	105	105	42	105	105	105
Min. score		15	15	15	6	15	15	6	15	15	15
% Domain	76.3	72.2	68.9	88.9	52.8	76.7	80	97.2	70	88.9	67.8
Stakeholder involvement											
Obtained score		56	61	75	15	60	76	35	62	83	67
Max. score		105	105	105	42	105	105	42	105	105	105
Min. score		15	15	15	6	15	15	6	15	15	15
% Domain	57.2	45.6	51.1	66.7	25	50	67.8	80.6	52.2	75.6	57.8
Rigor of development											
Obtained score		206	132	244	45	182	174	93	201	249	205
Max. score		280	280	280	112	280	280	112	280	280	280
Min. score		40	40	40	16	40	40	16	40	40	40
% Domain	64.1	69.2	38.3	85	30.2	59.2	55.8	80.2	67.1	87.1	68.8
Clarity of presentation											
Obtained score		77	54	59	31	90	80	35	83	89	72
Max. score		105	105	105	42	105	105	42	105	105	105
Min. score		15	15	15	6	15	15	6	15	15	15
% Domain	68.8	68.9	43.3	48.9	69.4	83.3	72.2	80.6	75.6	82.2	63.3
Applicability											
Obtained score		77	57	91	23	84	63	41	91	84	74
Max. score		140	140	140	56	140	140	56	140	140	140
Min. score		20	20	20	8	20	20	8	20	20	20
% Domain	48.4	47.5	30.8	59.2	31.25	53.3	35.8	68.8	59.2	53.3	45
Editorial independence											
Obtained score		47	61	54	13	53	62	27	27	62	52
Max. score		70	70	70	28	70	70	28	70	70	70
Min. score		10	10	10	4	10	10	4	10	10	10
% Domain	69.7	61.7	85	73.3	37.5	71.7	86.7	95.8	28.3	86.7	70
% OQS		60.8	52.9	70.3	41	65.7	66.4	83.9	58.7	79.0	62.1
Fleiss' kappa		0.29	0.21	0.17	1 ^a	0.17	0.32	1 ^a	0.22	0.48	0.19

Domain scores were calculated by the following formula: (obtained score - minimum possible score)/(maximum possible score - minimum possible score). The maximum possible score was: maximum possible score × number of items in domain × number of appraisers. The minimum possible score was: minimum possible score × number of items in domain × number of appraisers

Overall quality scores (OQS) and inter-reader variability (Fleiss' kappa)

^a Cohen's kappa (only two rater)

recommended clinical approach. At times the intended user of the guideline was not clearly defined, and several did not describe the author's conflicts and competing interests in detail.

Discussion

The different guidelines are very congruent in symptom reporting and quite congruent in diagnostics through detailed history, pelvic examination, exclusion of urinary tract

infection and other mimicking or confusable diseases. As defined by the ESSIC guidelines, the mother of all guidelines and published first in 2008, BPS is determined by symptoms and their location, as subsequently reflected in common by the other guidelines. Pain, pressure, discomfort and frequency, urgency and nocturia are the most prevalent symptoms and part of the BPS definition. A worldwide evidence-based consensus is lacking on whether chronic pelvic pain perceived to be related to the bladder is a prerequisite for a diagnosis of BPS and on the value of cystoscopy with hydrodistention and biopsies for the management of patients with BPS. As long as

pathognomonic tests for the BPS are lacking, pain, located in and around the bladder, associated with bladder filling and voiding, will remain the main guiding symptom, and treatment remains symptomatic.

The diagnosis of BPS is made on the basis of exclusion of confusable diseases and identification of concomitant diseases. However, according to some guidelines, the same pathology can be both confusable and concomitant, as in the case of “irritable bowel syndrome” (RCOG), “endometriosis” (RCOG and CUA guidelines), “OAB” (CUA guideline) and “pelvic floor disorders” (CUA guideline). Other guidelines consider “endometriosis” as a confusable disease (SUG and Japanese guidelines) and “irritable bowel syndrome” as a concomitant disease (AUA, ICI and EAU guidelines).

Some of the guidelines have the layout of a comprehensive scientific monograph (CUA, EAU, JUA, RCOG), but also act as a practical review of the evidence-based management of individual patients and summed up with expert recommendations [18]. The high variety of levels of evidence regarding treatments might be due to the different release dates of the guidelines (2008–2018).

Patients with IC/BPS frequently exhibit mental health disorders, such as depression and anxiety [43], and there is some evidence of a common biological mechanism involved. BPS as a chronic condition can negatively influence patient perceptions, functioning and treatment response. This suggests an association of BPS with psychosocial co-morbidities and that one condition reinforces the other [44]. The psychosomatic aspect of the disease is neglected in most of the guidelines; it is mentioned in the ICI-RS, GG and RCOG proposing a practical multidisciplinary care model and referral to a psychologist or psychosomatic expert since many BPS patients have associated psychological co-morbidities [45]. The EAU also mentions the psychological aspect as both a cause and effect of persistent pelvic pain, so in the section of chronic pelvic pain. Concerning psychological intervention, the SUG refers to the role of the doctor whose role and counseling is patient centered, providing primarily reassurance. Communication and counseling skills for the management of patients with BPS are essential as our body of knowledge on the etiopathology of the disease is ambiguous.

Strengths and limitations

There are some general weak points to consider for guideline assessment. Guidelines may have both methodological problems and conflicts of interest [46]. The guideline development groups are often represented by urologists, and it would be worth including stakeholders from other relevant professional groups such as gynecologists, pain experts, sexologists and psychologists to obtain a balanced and interprofessional recommendation. The weighting of expert recommendations may be biased and depends on the group composition. Some

persons have been authors in more than one guideline. We also decided not to consider the full version of the EAU guideline as this is only available to EAU members.

Indeed, most of the guidelines are more intended to give an easily accessible and applicable resource for clinicians based on the latest evidence and showing that the evidence lacks some diagnostic and treatment options. Regarding the complexity of the BPS and the growing research in the field, none of the guidelines seem to be robust for the next couple of years as newer research emerges [47]. Much research is also ongoing in pathoetiology, and it is possible that urine markers or composition of the vesical microbiome will become part of the diagnosis and treatment of BPS. The German S2k Guideline on IC as the newest guideline involved the latest diagnostic and treatment options.

Interpretation

It is known that up to 20% of strong recommendations, especially when based on opinion rather than trials, from practice guidelines may be retracted [46]. All BPS guidelines include not only recommendations based on trials but also opinions. The New York Times reported in 2004 that some simple clinical practice guidelines are not routinely followed to the extent they might [48]. On the other hand, it was also shown that guidelines may make recommendations that are stronger than the supporting evidence [47]. In response to many of these shortcomings of guidelines, CHORUS intends in the future to facilitate and develop consensus on core diagnostics, treatment and outcomes based on the most commonly reported ones but primarily on a wider and multifaceted stakeholder involvement. Thus, CHORUS aims to provide an overview for future working groups dealing with BPS. Patients and public representatives are key members of such work initiatives and should be included in care research and recommendations too.

Conclusion

The different guidelines are very congruent in symptom reporting and quite congruent in diagnosis, and they vary to a high degree regarding treatment options, also in respect to the level of evidence. Nine guidelines had an overall quality score of $\geq 50\%$ and three scored $\geq 70\%$ (AUA, GG, RCOG). After two revisions, the inter-rater agreement was slight to moderate, which reflects the different interpretation of data. Regarding the complexity of the BPS and growing research, the guidelines will have to be updated subsequently. Inclusion of patients' and public representatives will be an integral component in the future.

Compliance with ethical standards

Conflicts of interest None.

Details of ethics approval There is no need for ethical approval for a systematic review.

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