Chapter 3
Diagnostic Criteria, Classification and Nomenclature for Bladder Pain Syndrome

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Introduction

The National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) formulated criteria for a diagnosis of interstitial cystitis (IC) in 1987 [1, 2]. These criteria were meant for scientific studies but by time there has been varying understanding of the substance of these criteria causing a lot of confusion. An illustration

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Table 3.1 Overview of mandatory features in publications for the diagnosis of interstitial cystitis (IC), painful bladder syndrome (PBS), bladder pain syndrome (BPS) and hypersensitive bladder syndrome (HSB, HBS)

		Mandatory feature			
Source	Name	Pain	Urgency	Frequency	Other
NIDDK, 1988 [1]	IC	No	No	No	Pain *or* urgency, glomerulations, Hunner's ulcer, other
Holm–Bentzen et al., 1987 [4]	IC is a subgroup of PB disease	Yes	No	No	
Witherow et al., 1989 [5]	PBS	Yes	No	Yes	
ICS, 2002 [6]	PBS	Yes	No	No	
	IC	Yes	No	No	IC = PBS + cystoscopic and histological features
EAU, 2010 [7]	PBS/BPS	Yes	No	No	
ICI, 2004 [8]	PBS/IC	Yes	No	No	
ESSIC, 2006, 2008 [9, 10]	BPS types	Yes	No	No	
ARHP, 2007 [11]	IC/PBS	Yes	No	No	Urgency *or* frequency
Homma, 2007, 2009 [12, 13]	HSB/HBS	No	No	No	
	PBS	Yes	No	No	
	IC	No	No	No	

of that fact is that the criteria were fulfilled by only one-third of patients thought to have IC by experts [3]. Moreover, pain is not a mandatory feature for the diagnosis. This is in contrast to all definitions published after 1987 [4–11] with the exception of the Japanese guideline (Table 3.1) [12, 13]. This guideline distinguishes hypersensitive bladder syndrome, painful bladder syndrome and interstitial cystitis and pain is only mandatory for the diagnosis of painful bladder syndrome (PBS). The International Continence Society (ICS) defined the term "PBS" as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology"[6]. The name IC was reserved for PBS with typical cystoscopic and histologic features. Logically IC should include some form of inflammation in the deeper layers of the bladder wall, whereas PBS should include pain in the region of the bladder. At the International Consultation on Interstitial Cystitis in Japan (ICICJ) in 2003, it became clear that the evaluation and diagnosis of patients differed enormously among centres in Europe, North America and Japan [14] and that a new approach was urgently needed.

Criteria for the diagnosis of a disease are needed if the target disease may be confused with other diseases (confusable diseases) because of overlapping features [15]. Symptoms and signs for use in diagnostic criteria do not need to be specific for the target disease. On the contrary, if a specific symptom or sign existed for the target disease, a diagnosis would only require the presence of the specific feature

Fig. 3.1 Schematic representation by *grey* areas of a diagnosis of BPS by exclusion of all confusable diseases (**a**) or by recognition of a typical combination of features of BPS (**b**)

and diagnostic criteria would not be necessary. For a diagnosis, the target disease has to be recognized in a pool of confusable diseases by exclusion of (all) confusable diseases or by recognition of a typical combination of features of the target disease (Fig. 3.1). For the diagnosis of bladder pain syndrome (BPS), the name we prefer for IC and PBS (see below), ideally both methods should be used because:

- Confusable diseases are more common than BPS, so recognition of a confusable disease is mandatory because many can be treated.
- Failure to diagnose a confusable disease if present would automatically incorrectly yield a diagnosis of BPS.
- Patients may have two diseases at the same time, a confusable disease and BPS.

The diagnosis of BPS is thus made on the basis of exclusion of confusable diseases in addition to the presence of a typical combination of symptoms and signs of BPS. If the main urinary symptoms are not explained by a single diagnosis (confusable disease or BPS), the presence of a second diagnosis should be considered.

Methods

ESSIC held meetings in 2003 and 2004 (Copenhagen, Denmark) on standardization of medical history, physical examination, laboratory tests, symptoms evaluation, urodynamics and technique and classification of cystoscopic and histologic findings [16]. Briefly, glomerulations represent submucosal bleedings at cystoscopy with hydrodistention, with grade 2 being large submucosal bleeding (ecchymosis) and grade 3 diffuse global mucosal bleeding. Detrusor mastocytosis is defined as mast cell counts exceeding 28 mast cells/mm^2 [16]. At ESSIC meetings in 2005 in Baden and 2006 in London, the following approach to the diagnosis of BPS was discussed:

- Selection of patients who need further evaluation for the presence of BPS.
- Definition of confusable diseases that may cause urinary symptoms.
- Classification of BPS.

Results

Name

Consensus was obtained that the name BPS better complies with our present knowledge and current nomenclature of other pain syndromes than the name IC or PBS. ESSIC realized that omitting the name "interstitial cystitis" might cause serious problems in different health systems by affecting reimbursement or the possibility for patients to gain disability benefits, and it was therefore decided that the name bladder pain syndrome/interstitial cystitis (BPS/IC) could be used parallel with BPS for the time being.

Selection of Patients

It was agreed that BPS would be diagnosed on the basis of chronic (>6 months) [7] pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistention and morphologic findings in bladder biopsies. The presence of other organ symptoms as well as cognitive, behavioural, emotional and sexual symptoms should be addressed.

Confusable Diseases

Diseases that were discussed and accepted as confusable diseases for BPS are listed in Table 3.2 with an indication on how they can be recognized or excluded.

Classification of BPS

Consensus was obtained that for the documentation of positive but not mandatory signs for the diagnosis of BPS, hydrodistention at cystoscopy was a prerequisite and if indicated also a biopsy to document histologic details of BPS. Cystoscopic features that were accepted as positive signs of BPS were glomerulations grade 2–3 or Hunner's lesions, or both (see below). Histologic findings that were accepted as positive signs of BPS were inflammatory infiltrates, granulation tissue, detrusor mastocytosis and/or intrafascicular fibrosis.

Table 3.2 Confusable diseases for bladder pain syndrome (BPS)

Confusable disease	Excluded or diagnosed by *
Carcinoma and carcinoma in situ	Cystoscopy and biopsy
Infection with	
Common intestinal bacteria	Routine bacterial culture
Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Mycoplasma genitalium, Corynebacterium urealyticum, Candida species	Special cultures
Mycobacterium tuberculosis	Dipstick; if "sterile" pyuria culture for *M. tuberculosis*
Herpes simplex and *Human Papilloma Virus*	Physical examination
Radiation	Medical history
Chemotherapy, including immunotherapy with cyclophosphamide	Medical history
Anti-inflammatory therapy with tiaprofenic acid	Medical history
Bladder neck obstruction and neurogenic outlet obstruction	Uroflowmetry and ultrasound
Bladder stone	Imaging or cystoscopy
Lower ureteric stone	Medical history and/or haematuria: Upper urinary tract imaging such as CT or IVP
Urethral diverticulum	Medical history and physical examination
Urogenital prolapse	Medical history and physical examination
Endometriosis	Medical history and physical examination
Vaginal candidiasis	Medical history and physical examination
Cervical, uterine and ovarian cancer	Physical examination
Incomplete bladder emptying (retention)	Post-void residual urine volume measured by ultrasound scanning
Overactive bladder	Medical history and urodynamics
Prostate cancer	Physical examination and PSA
Benign prostatic obstruction	Uroflowmetry and pressure-flow studies
Chronic bacterial prostatitis	Medical history, physical examination, culture
Chronic non-bacterial	Prostatitis medical history, physical examination, culture
Pudendal nerve entrapment	Medical history, physical examination, nerve block may prove diagnosis
Pelvic floor muscle related pain	Medical history, physical examination

CT = computed tomography; IVP = intravenous pyelogram; PSA = prostate-specific antigen.
* The diagnosis of a confusable disease does not necessarily exclude a diagnosis of BPS

Hunner's Lesion

Hunner's "ulcer" is not a chronic ulcer but rather a distinctive inflammatory lesion presenting a characteristic deep rupture through the mucosa and submucosa provoked by bladder distension. The word "ulcer" suggests that it can be seen at cystoscopy

without hydrodistention. Consequently, the name Hunner's ulcer was replaced by Hunner's lesion. The following definition by M. Fall was accepted: "The Hunner's lesion typically presents as a circumscript, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area. This site ruptures with increasing bladder distension, with petechial oozing of blood from the lesion and the mucosal margins in a waterfall manner. A rather typical, slightly bullous edema develops post-distension with varying peripheral extension". Despite the fact that cystoscopy with hydrodistension is not mandatory as part of the clinical evaluation for a diagnosis of BPS, it is highly recommended as it is virtually the best way to diagnose a Hunner's lesion with major therapeutic implications.

Types of BPS

BPS shows large variations among patients in clinical presentation, complaints, quality of life, cystoscopic and biopsy findings, response to treatment, clinical course and prognosis. It was generally appreciated that these characteristics may be correlated only to some extent. Diagnostic criteria and disease classification should facilitate future studies on these relationships. Consequently, types of BPS were defined based on the findings used to document positive signs for the diagnosis of BPS. The name BPS will be followed by a type indication that consists of two symbols: Symbols 1, 2 or 3 indicate findings at cystoscopy with hydrodistention and symbols A, B or C of biopsy findings. X indicates that no cystoscopy with hydrodistention (first symbol) or no biopsy (second symbol) was done (Table 3.3). BPS types thus also allow classification of patients with normal findings at cystoscopy with hydrodistention and normal biopsies as long as they fulfil the patient selection criteria and also confusable diseases are excluded (BPS type 1A; see Fig. 3.2 and Table 3.3).

Table 3.3 Classification of types of bladder pain syndrome on the basis of findings at cystoscopy with hydrodistension and of biopsies

		Cystoscopy with hydrodistension			
		Not done	Normal	Glomerulations[a]	Hunner's lesion[b]
Biopsy	Not done	XX	1X	2X	3X
	Normal	XA	1A	2A	3A
	Inconclusive	XB	1B	2B	3B
	Positive[c]	XC	1C	2C	3C

[a]Cystoscopy: Glomerulations grade 2–3
[b]With or without glomerulations
[c]Histology showing inflammatory infiltrates, detrusor mastocytosis, granulation tissue and/or intrafascicular fibrosis

Discussion

Why Do We Need New Criteria?

The NIDDK criteria for the diagnosis of IC were intended for use in scientific studies. These criteria, however, did not comprise more than one-third of patients considered to have IC by experts [3]. Pain was not a mandatory feature for the diagnosis in contrast to almost all definitions published after 1987 [4–10]. Moreover, patients under the age of 18 years were excluded as were those with voided volumes of more than 350 ml, thus making it difficult to study early stages of the disease. These considerations made the NIDDK criteria less useful in clinical situations and limited their value in scientific studies because the criteria only recognized a biased minority of the patient population. The need for the design of new diagnostic criteria is obvious. To avoid unacceptable discrepancies between scientific studies and clinical practice, it was considered essential that new diagnostic criteria could be used in both situations.

Why Is Pain a Prerequisite?

BPS is characterized by urinary bladder pain [4–10, 17, 18]. A recent study, however, demonstrated a correlation between pain bother in the IC problem index (burning, discomfort, pain or pressure) and the presence of pain in the IC symptom index of only 0.7 [19]. This finding underscores that many patients report a sensation of pressure or discomfort in the bladder/pelvic area and do not report this sensation as pain but rather as urgency (see below). The International Association for the Study of Pain (IASP; http://www.iasp-pain.org) definition of pain is: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [20]. Patients having microwave treatment for benign prostatic obstruction producing tissue damage at the bladder neck report the same sensation of pressure and discomfort in the bladder region [21–23]. The sensation is therefore by definition a pain sensation, but not described as such by the patient. Pain or the equivalent pressure, discomfort perceived to be related to the bladder, was, therefore, considered to be a prerequisite for the description of symptoms on the basis of which patients should undergo further investigations for BPS. The increase of pain on bladder filling was left out of the description because this association is not always present [18, 24, 25].

Why Is Urgency Not Included in the Description of Patients Who Need Further Evaluation for BPS?

Urgency is defined by the ICS as the complaint of a sudden compelling desire to pass urine, which is difficult to defer [6]. BPS is commonly mistaken for overactive bladder (OAB) and vice versa because the term "urgency" is used to describe

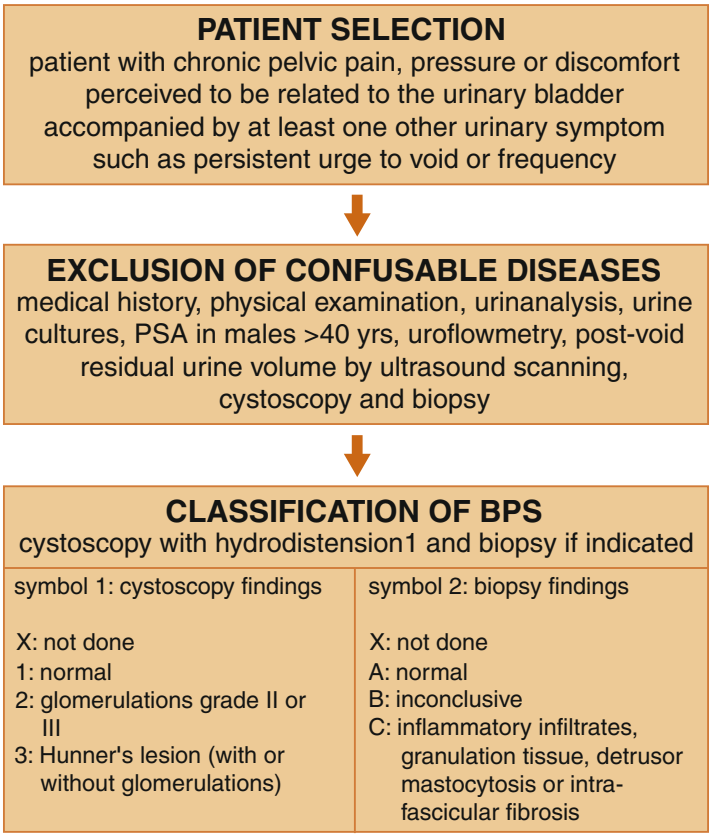

Fig. 3.2 Schematic representation of the proposed approach for the diagnosis of bladder pain syndrome (BPS)

the symptoms of both disorders. For some women, urgency is used to indicate the heightened need to make it to a toilet quickly to avoid getting wet, whereas other women consider urgency to mean a need to void as a way of avoiding intensifying pain, pressure or discomfort. The first group is most likely to have OAB, and the latter group can be expected to have BPS [18]. Urinary urgency was left out of the description of patients who need further evaluation for the presence of BPS for several reasons. First, urgency is the key symptom of OAB [17, 24], a major confusable disease for BPS, that is ten times more common than BPS [18]. Second, the clinical aspects of urgency are complex [6, 18, 24, 26–29]. At a meeting arranged by the Association of Reproductive Health Professionals in the United States in February 2007 involving 33 urologists, gynaecologists and nurses it was proposed to use the term "persistent urge" instead of urgency to avoid confusion with OAB [11]. Many patients find the strong, unpleasant urge to void the most dominant and disabling part of their symptoms, so patients (and doctors) are often confused because, with

the present terminology, a patient is not allowed to use the word urge to describe complaints. In the Oxford Advanced Learner's Dictionary of Current English urge is defined as "a strong desire", whereas urgency is defined as "needing prompt decision or action" [30]. So the words urgency and urge describe very well the difference between the sensation felt by the patient with OAB and the patient with BPS. Persistent urge was therefore included in the definition as a typical symptom, such as frequency. It must be stressed that the presence of these symptoms is not necessary to suspect or diagnose BPS.

Why is the Potassium Sensitivity Test Not Used as a Diagnostic Tool?

The potassium sensitivity test (PST) is based on the hypothesis that instilled potassium provokes symptoms such as pain and urgency when the bladder epithelium is abnormally permeable. The PST has been found positive in 66–83% of patients with BPS but also in similar proportions of patients with cystitis due to radiation and other causes, prostatitis and bladder cancer and even in one-third of healthy subjects [31–35]. The low sensitivity and specificity make the PST unsuitable as a diagnostic tool [36].

Why is the APF Test Not Used as a Diagnostic Tool?

The antiproliferative factor (APF) is a peptide secreted by bladder epithelial cells from patients with BPS [37]. APF inhibits bladder cell proliferation by means of regulation of cell adhesion protein and growth factor production. It has been detected in 86% of women with BPS, compared with 8% of asymptomatic control women, 12% of women with bacterial cystitis and 0% of women with vulvovaginitis, yielding sensitivity and specificity values of 91.4 and 90.6%, respectively. The test is advocated as a useful non-invasive means for diagnosing BPS in women [38]. However, no data on the clinical value of the APF test for the diagnosis of BPS are available to support this claim. Moreover, the test is not yet widely available, so the APF test cannot be recommended as a diagnostic tool to date.

Why Should Confusable Diseases Be Excluded?

In evidence-based medicine, diagnoses are based on medical history, physical examination and appropriate clinical investigations to eliminate diseases from the list of differential diagnoses (confusable diseases) and to confirm the final diagnosis.

BPS may occur together with confusable diseases such as chronic or remitting urinary infections or endometriosis.

Cystoscopy with hydrodistention and biopsies might in this situation document positive signs of BPS, thereby making a double diagnosis more probable. For therapeutic studies it makes sense to exclude patients who also have a confusable disease because symptoms and signs may be caused by BPS, the confusable disease or both. For prevalence studies of BPS, on the other hand, all cases with BPS should be included, also those with a confusable disease. This approach eliminates the need for separate diagnostic criteria for clinical practice and scientific studies.

Why Do We Need Various BPS Types?

Unravelling the cause of a disease usually begins with grouping patients with similar symptoms and signs. The hypothesis is that these patients have a disease with the same aetiology and pathogenesis that is better recognized in homogeneous than in heterogeneous groups. This has been the reason for dividing BPS patients into subgroups (types) based on positive signs. It is worth noting that the Hunner type of disease stands out as a specific type not only cystoscopically but also with reference to histopathology, response to treatment and complications [7, 39].

Why Do We Propose to Change the Name of IC?

Hanno recently stated that the term IC was not descriptive of the clinical syndrome or the pathologic findings in many cases. Moreover, the term IC is misleading because it directs attention only to the urinary bladder and inflammation [40]. The name IC excludes patients with typical IC symptoms but normal cystoscopic and histologic findings from disease classification in many countries around the world. The inability to classify these patients might have severe negative consequences for the patients, for example, in therapeutic, personal, social and many other aspects. IC, originally considered a bladder disease, is now considered a chronic pain syndrome [41]. These perceptions have led to the current effort to reconsider the name of the disorder [7, 40, 42, 43]. It is also the contention of the ESSIC that the existing terminology of IC hampers development in this area.

Why Do We Propose to Choose BPS as the New Name?

For some time now there has been much work going on in international organizations to create a logical and workable terminology for chronic (persistent) pain conditions. For background information we refer to the 2010 Guidelines on Chronic Pelvic Pain

issued by the European Association of Urology (EAU) [7]. The EAU definitions are in line with recent recommendations for terminology from the ICS [6] and use the axial structure of the IASP classification [20]. This implies a taxonomy-like approach under the umbrella term of chronic pelvic pain syndrome. Further identification is based on the primary organ that appears to be affected on clinical grounds. Urologic pelvic pain syndromes are divided into bladder pain syndrome, urethral pain syndrome, penile pain syndrome, prostate pain syndrome and others. More specific terminology is based on the identification of, for example, inflammation or infection [42, 44]. The classification system of chronic pelvic pain syndromes aims to draw together the expertise of many specialist groups. The impact of the classification of chronic pelvic pain syndromes thus goes far beyond the scope of IC. Another essential feature is that the nomenclature and knowledge of pathophysiologic mechanisms do not conflict with each other. In this context, the name bladder pain syndrome was considered the best new name for IC to date, because the name is in line with the other chronic pelvic pain syndromes and is in balance with the clinical presentation of the syndrome and the level of knowledge of its pathophysiology. We realize that changing the name of IC into BPS may have emotional implications, understandably for patients, but also for patient organizations with a scope limited to IC and for insurance and reimbursement in different health systems around the world. Considering these consequences, although BPS is the name of choice, ESSIC agrees that including IC in the overall term (BPS/IC) could be used in parallel to BPS during a transition period. In this context, it is worth remembering that a subgroup of BPS patients (representing the Hunner type of disease) presents interstitial inflammation and thus fulfils the requirements of the original term of IC.

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