



European Opinion on PBS/IC Characterizations

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Introduction

ESSIC (European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome) discussed definitions, methods and diagnostic criteria for painful bladder syndrome/interstitial cystitis in Copenhagen (Denmark), Baden (Austria) and London (UK) between 2003 and 2006 followed by e-mail discussions.

After long and intensive discussions, ESSIC agreed on the basis of consensus:

1. to no longer to use the name interstitial cystitis, neither alone nor in combinations
2. to use the name **bladder pain syndrome** (BPS), followed by a type indication; in a transition period the name bladder pain syndrome/interstitial cystitis (BPS/IC) could be used parallel with BPS
3. that the diagnosis of bladder pain syndrome (BPS/IC) will be made on the basis of
 - a. the symptom of chronic pain related to the urinary bladder accompanied by at least one other urinary symptom such as daytime and night-time frequency, *and*
 - b. exclusion of confusable diseases as the cause of the symptoms, *and*
 - c. cystoscopy with hydrodistension and biopsy if indicated*
4. that BPS/IC type indications consist of two symbols: the first symbol corresponds to cystoscopy with hydrodistension and the second to biopsy:
 - first symbols 1, 2 or 3 indicate increasing grade of severity at cystoscopy with hydrodistension
 - second symbols A,B or C indicate increasing grade of severity of biopsy findings
 - X indicates not done for both

*if indicated to document the type of BPS/IC

In this document, names were changed into BPS/IC where appropriate even if during the presentation themselves the names painful bladder syndrome and/or interstitial cystitis were used.

ESSIC website: <http://www.essic.eu>

Diagnosis and standard investigations for BPS/IC

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As a specific definition and characterisation of Interstitial Cystitis (IC) seems unlikely if basic patient evaluation is not performed in a standardized way, several European physicians interested in IC met in Copenhagen in May 2003 in an attempt to reach a consensus on how to perform the evaluation of patients with suspected IC. This group of colleagues later on, together with others, formed ESSIC (European Society for the Study of IC/PBS).

In 2004 ESSIC published the following recommendations regarding the diagnosis and standard investigations for BPS/IC.²

Medical History: The thorough general medical history should specifically focus on and elaborate bladder related previous conditions and surgery, pain characteristics and location.

Physical Examination: The common physical examination should specifically elaborate and focus on vaginal examination in females and digital rectal examination in males contributing to pain localisation and mapping.

Laboratory Tests: Urine dipstick, urine culture in all patients; if sterile pyuria culture for TB; urine cytology in risk groups; investigations for vaginal *Ureaplasma* and *Chlamydia* in females and prostatitis in men are optional.

Symptom Evaluation: Voiding diary with volume intake and output for 3 days at initial evaluation; at follow-up only number of voidings during day and night time is necessary; O'Leary-Sant Symptom Score supplemented as basic symptom score supplemented with the Quality of Life Score from the International Prostate Symptom Score; Pain should be recorded using a Visual Analogue Scale (VAS) for pain during the last 24 hours (to fit with the voiding diary).

Urodynamics: As IC and overactive bladder (OAB) may coexist and as bladder outlet obstruction in males can be a differential diagnosis it is recommended to perform filling cystometry with a filling rate of 50 ml/sec (to comply with the revised Potassium Test - see below) to look for instability, volume at first desire to void and cystometric capacity. In females, flowmetry, post void residual urine volume and pressure-flow study are optional. In males, a flowmetry should be done in all, and if maximum flow rate <20

ml/sec a pressure-flow study and measure of residual urine volume should be done.

Potassium Sensitivity Testing: The revised Potassium Test has shown prognostic value in bladder irrigation studies, but is considered optional. If performed it should be performed as described by the initiators.¹

Cystoscopy and Morphological Findings: Please refer to the presentation and abstract by Magnus Fall, Thursday Session 4.

Morphology: Please refer to the presentation and abstract by Kirsten Bouchelouche, Thursday Session 4.

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Cystoscopic and morphological findings in BPS/IC

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Skene¹ and Hunner² are the great pioneers in Interstitial Cystitis (IC) history. Their discovery of a new disease was based on important observations of morphologic and endoscopic bladder wall changes. According to their definition, IC was a true inflammatory disorder. Subsequently it was realised that patients lacking the typical signs of inflammation may present similar symptoms. The 1987 NIDDK definitions recognised the Hunner lesion as one of automatic inclusion, suburothelial glomerulations as one of several positive factors, also including a long list of exclusions.³

Recently, there has been decreasing emphasis on objective parameters focusing on symptom based diagnostics. With such a broadening scope of inclusion another diagnostic term has been found to be more accurate. Bladder pain syndrome (BPS) or Painful bladder syndrome has been suggested as appropriate umbrella terms,

encompassing various presentations and subsets of patients.⁴⁻⁶ Quite recently, this concept was brought forward by a structured classification system based on objective parameters, designed by the European Society for the Study of Interstitial Cystitis (ESSIC).^{7,8}

There is controversy as to the proportion of various subgroups of BPS/IC patients in different settings and centers. Likewise, the value of various measures for diagnosis and treatment is subject to intense discussion. We have repeatedly expressed our contention that identification of relevant BPS/IC subcategories is mandatory for progress in the search for etiology and pathogenesis, to establish comparability between scientific studies and ultimately for optimal care of our patients. *E.g.* urethral pain syndrome, although scientifically less well studied, has to be distinguished from BPS/IC. Certainly, the Hunner type of disease (classic IC) has to be distinguished from other BPS/IC presentations, hitherto denominated non-ulcer IC.⁹⁻¹² There are reasons to believe that the latter entity on its part is heterogenic.

In my talk various examples of endoscopic and histopathologic findings will be presented. It has to be acknowledged that, at this stage, a limitation is that a decisive factor for the outcome of endoscopy as well as histopathologic assessment is interest and experience. Nevertheless, there is every reason to devote greater attention to those indispensable tools. When supplemented by good markers these tools may be used to categorise with an adequate precision.^{13,14}

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Mast Cells in BPS/IC

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The etiology of Painful Bladder Syndrome/ Interstitial Cystitis (BPS/IC) is currently unknown. An increased number of activated mast cells are often seen in the bladder wall of BPS/IC patients. This has led to the theory that mast cells may play a pathogenic role, at least in a subgroup of patients with BPS/IC. Upon activation mast cells release several kinds of inflammatory mediators.

The ESSIC meeting 2003 in Copenhagen resulted in recommendations on how to perform the evaluation of patients suspected having IC. The recommendations were accepted by all the participants and were published 2004 in *European Urology*¹.

In the ESSIC recommendations, it is described what should be included in the evaluation of IC patients: the medical history, laboratory tests, symptom evaluation, urodynamics, cystoscopy and morphology. In the new ESSIC classification of BPS/IC presented at this meeting morphology is included. This presentation will focus on the

ESSIC recommendations on how to take biopsies, number of biopsies, biopsy handling, mast cell counting and the pathology report.

In brief, the ESSIC recommendations on morphology are:

Biopsies: During cystoscopy the bladder is distended to full capacity. After draining the bladder, bladder biopsies are taken at roughly half full bladder capacity. Large forceps should be used and the biopsy should include detrusor muscle.

Number of biopsies: At least 3 biopsies from the two lateral walls and bladder dome should be taken in addition to biopsies from lesional areas. The biopsies are fixed immediately.

Biopsy handling: Biopsies are treated conventionally according to routine procedures of the dept. of pathology. It is recommended to make H&E staining and a connective staining. Tryptase staining is now recommended for mast cell counting by the ESSIC group. One biopsy section is used to ensure the presence of detrusor muscle.

Mast cell counting: A grid containing 25 squares each square measuring 0.21 mm² is used for mast cell counting. The counting of mast cells in the detrusor is preferably made in 20 squares but a least 7 squares should be counted. At least 3 biopsies should be used for mast cell counting and the total number of mast cells per mm² is calculated. If biopsies for mast cell counting do not contain detrusor muscle new biopsies must be obtained. For mast cell counting the tryptase staining is, for the time being, recommended.

- less than 20 mast cells/mm² : no detrusor mastocytosis
- between 20 and 28 cells/mm² : grey zone
- more than 28 mast cells/mm² : detrusor mastocytosis

The pathology report: The report should include information about epithelium (not present, present, dysplasia with grading, abnormal but no dysplasia), propria (normal, inflammation, other findings) detrusor muscle (normal, abnormal), intrafascicular fibrosis (not present, present) and mast cell count (the biopsy with the highest number should be reported).

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ESSIC approach to the design of diagnostic criteria in confusable diseases

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Classification criteria for the diagnosis of a disease are necessary if the disease in question (*target disease*) may be confused with other diseases because of overlapping features (*confusable diseases*).¹ Classification criteria (diagnostic criteria) may co-exist with other criteria for other purposes such as prognostic, activity or outcome criteria. In contrast to common belief, 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 and diagnostic criteria were not necessary. As is the case when individual people or music compositions are recognized, diseases can be recognized by their specific combination of features.

For a diagnosis, the target disease (BPS/IC) has to be recognized in a pool of confusable diseases (see Fig.1). In addition to recognition of the specific combination of features of the target disease, the target disease could also be identified when all confusable diseases are excluded. For the diagnosis of BPS/IC both methods should be used because:

- confusable diseases are more common than BPS/IC and many can be treated
- failure to diagnose a confusable disease (unclassifiable confusable disease, unknown confusable disease or false-negative diagnosis of confusable disease) would automatically incorrectly yield a diagnosis of BPS/IC
- patients may have a confusable disease plus BPS/IC

Erasmus MC

PBS/IC and confusable diseases

| | |
|------------------------------------|---|
| carcinoma | bladder neck obstruction |
| carcinoma <i>in situ</i> | neurogenic outlet obstruction |
| infection with intestinal bacteria | bladder stone |
| infection with | lower ureteric stone → upper UT imaging |
| <i>Mycobacterium tuberculosis</i> | urethral diverticulum |
| <i>Chlamydia trachomatis</i> | endometriosis |
| <i>Ureaplasma urealyticum</i> | vaginal candidiasis |
| <i>Mycoplasma hominis</i> | cervical, uterine and ovarian cancer |
| <i>Mycoplasma genitalis</i> | incomplete bladder emptying (retention) |
| <i>Corynebacterium urealyticum</i> | prostate cancer → PSA |
| Candida species | benign prostatic obstruction |
| <i>Herpes simplex</i> | chronic bacterial prostatitis } → culture |
| <i>Human Papilloma Virus</i> | chronic non-bacterial prostatitis } → culture |
| radiation cystitis | pelvic floor muscle related pain |
| chemotherapy-induced cystitis | puddendal nerve entrapment → nerve block |
| cyclophosphamide-induced cystitis | PBS/IC |
| tiaprofenic acid-induced cystitis | |
| overactive bladder → urodynamics | |

ESSIC consensus 2005-2006

Figure 1. Slide showing BPS/IC and confusable diseases

If both methods are used, a diagnosis of the target disease is made on the basis of exclusion of confusable diseases and confirmation by the presence of the specific combination of symptoms and signs.

If the main urinary symptoms are not explained by a single diagnosis (confusable disease or BPS/IC), a second diagnosis is possible and should be looked for. This approach is very useful in clinical practice as more than one disease commonly coincide. For scientific studies it is usually to be preferred for obvious reasons to include only patients who fulfil the criteria of the target disease and who do *not* also have a confusable disease. For prevalence studies of the target disease, however, all cases with the target disease, *with or without* an additional confusable disease, should be included. This approach eliminates the need for separate criteria for clinical practice and scientific studies, thus avoiding a lot of confusion and incorrect use of criteria.

At the Annual Meetings of the European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome (ESSIC) in 2005 and 2006, followed by e-mail discussions, consensus was obtained on a list of diseases that can be confused with interstitial cystitis/painful bladder syndrome (IC/PBS) and how they can be diagnosed or excluded (for the latest version see: www.essic.eu/pdf/ESSICconsensus2006.pdf). The proposed actions for the diagnosis of BPS/IC can be summarized as follows:

1. **selection of patients** that need further evaluation for the presence of BPS/IC on the basis of the symptom of (chronic) pain related to the urinary bladder accompanied by at least one other urinary symptom
2. **exclusion of confusable diseases** as the main cause of urinary symptoms on the basis of:
 - a. medical history and physical examination
 - b. dipstick urinalysis, various urine cultures and serum PSA in males over 40 years
 - c. flowmetry and post-void residual urine volume by ultrasound scanning
 - d. cystoscopy and, if indicated*, biopsy
- 3) **confirmation of BPS/IC** by hydrodistension at cystoscopy and, if indicated**, biopsy

* if needed to make a diagnosis

** if needed to make a diagnosis or to document the type of BPS/IC

Consensus was obtained to distinguish types of BPS/IC on the basis of whether cystoscopy with hydrodistension is performed and/or biopsies are taken, and if so, the findings. Consensus was also obtained to no longer use the name interstitial cystitis but instead to use bladder pain syndrome (BPS) in order to comply with the current nomenclature of other pain syndromes. Further details will be presented by Jørgen Nordling in the next presentation.

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ESSIC classification of BPS/IC

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Interstitial Cystitis (IC) is a clinical diagnosis primarily based on symptoms of urgency, frequency and pain in the bladder and or pelvis.

International Continence Society (ICS) prefers the term Painful Bladder Syndrome (PBS) defined 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”.¹ ICS reserves the diagnosis IC to typical cystoscopic and histological features, without further specifying these. Logically IC should include some form of demonstrable inflammation in the bladder wall, while PBS should include pain in the region of the bladder.

The most successful attempt to define a clinical useful definition of IC was the NIDDK inclusion and exclusion criteria established at a workshop in 1987 and revised after a workshop in 1988. The NIDDK criteria included some positive findings like glomerulations after bladder distension and the finding of a Hunner’s lesion and a lot of exclusion criteria. The NIDDK criteria have worked well in a scientific setting, but the criteria were only fulfilled by 1/3 of patients thought to have the disease.

The European Society for the Study of IC/PBS (ESSIC) has approached the problem of defining and classifying the disease from a somewhat different angle. First a consensus on standardisation of investigational procedures were obtained and published in 2004 followed by a meticulous going through possible confusable diseases. After mapping confusable diseases, the definition of BPS/IC could focus on positive findings. The original ICS definition needed some corrections so after the ESSIC meeting in London 2006 and an additional e-mail discussion the following definition was approved (the name was changed from painful bladder syndrome to bladder pain syndrome to fit the taxonomy of pelvic pain syndromes):

The diagnosis of bladder pain syndrome (BPS/IC) will be made on the basis of the symptom of pain related to the urinary bladder, accompanied by at least one other urinary symptom such as daytime and night-time frequency, exclusion of confusable diseases as the cause of the symptoms and cystoscopy with hydrodistension and biopsy if indicated.

To be able to stratify patients based on cystoscopy with hydrodistension and bladder morphology,² the following classification system was developed (Fig. 2).

| | | cystoscopy with hydrodistension | | | |
|--------|-----------------------|---------------------------------|--------|-----------------------------|------------------------------|
| | | not done | normal | glomerulations ¹ | Hunner's lesion ² |
| biopsy | not done | XX | 1X | 2X | 3X |
| | normal | XA | 1A | 2A | 3A |
| | inconclusive | XB | 1B | 2B | 3B |
| | positive ³ | XC | 1C | 2C | 3C |

Figure 2. Classification of types of BPS/IC on the basis of findings at cystoscopy with hydrodistension and of biopsies.

¹ cystoscopy: glomerulations grade 2-3

² with or without glomerulations

³ histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

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