Painful Bladder Syndrome/Interstitial Cystitis/Bladder Pain Syndrome/Hypersensitive Bladder Syndrome – Global Concepts and Harmonization
W14, 15 October 2012 14:00 - 17:00

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**Aims of course/workshop**
This workshop is designed to present the way that the syndrome of bladder pain associated with voiding dysfunction is perceived around the world. It will discuss how it is defined, how it is diagnosed, and the various treatment algorithms that are used in North America, Europe, and Asia. It will discuss the different approaches currently employed and the published guidelines that highlight these approaches. A major portion of the program will be to contrast and compare the guidelines and see where the efforts of the last decade have been successful in harmonization and where the efforts seem to have failed and why they have failed.

**Educational Objectives**
This course is designed for an international audience and will provide a perspective from which to view the management of PBS/IC/BPS/HSB. It will not promote any one guideline, but rather focus on the importance of harmonizing the definitions, diagnosis, and management so as to improve clinical results into the future. A common language for nomenclature and definition, and a common basis for diagnosis will allow for better understanding, outcomes, and cooperation internationally as we research the etiology and best therapies for our patients. Clinicians, basic researchers, and pharmaceutical companies will benefit from an understanding of where there is agreement and where there is disagreement and the ways we can move forward. The immediate educational value lies in improving clinical diagnosis and management. Future developments will be presented with a focus on the implications of the National Institute of Health Multidisciplinary Approach to the Study of Pelvic Pain (MAPP).
Painful Bladder Syndrome/Interstitial Cystitis/Bladder Pain Syndrome/Hypersensitive Bladder Syndrome – Global Concepts and Harmonization

Jørgen Nordling, Tomohiro Ueda, Phil Hanno, Magnus Fall

The following is an extract from the paper Global concepts of bladder pain syndrome (interstitial cystitis) by Jørgen Nordling, Magnus Fall and Philip Hanno.

Over the last 20 years Painful Bladder Syndrome/Interstitial Cystitis/Bladder Pain Syndrome/Hypersensitive Bladder Syndrome has been viewed through a new paradigm. It is no longer considered primarily a bladder disease, but rather one of a number of chronic pain syndromes that is distinguished by being manifest through bladder related symptoms. The last two decades have seen a worldwide effort to try to standardize its nomenclature, definition, diagnosis, and treatment algorithm. Advances have been made, and it is hoped that this international effort will help to lead to better diagnostic and treatment approaches in the future. In this article we will detail current terminology and diagnostic approaches.

**Nomenclature and diagnostic algorithms**

**ESSIC guidelines**

The ESSIC (International Society for the Study of Bladder Pain Syndrome) guidelines are based on discussions during meetings and on the internet. After a major international meeting on interstitial cystitis in Japan in March 2003, 23 European urologists met in Copenhagen with the intention to give their input into the confused areas of what Interstitial Cystitis(IC) was and how it should be evaluated and treated. This resulted in the publication on evaluation in 2004 and the start of ESSIC in Copenhagen in June 2004. During the following years intense discussions resulted in the publication of the ESSIC recommendation on nomenclature and definition in 2008.

**Nomenclature**

The term “interstitial cystitis” lacked an agreed upon clinically useful definition, though a research definition developed by the National Institute of Diabetes, Digestive, and Kidney Diseases did have utility in the clinical research setting. The term Painful Bladder Syndrome as defined by the
International Continence Society 6 excluded 34% of patients having bladder pain and being classified by experts to have IC 7, and therefore was unsatisfactory for clinical use. The ESSIC group proposed to give the syndrome a new name which would better fit into existing pain taxonomy 8. This would also allow it to define it in a unique and clinically applicable manner. Bladder Pain Syndrome (BPS) ... would be diagnosed on the basis of chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary 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 morphological findings in bladder biopsies.

The presence of other organ symptoms as well as cognitive, behavioural, emotional and sexual symptoms should be addressed. 3,4

The diagnosis BPS is thus based solely on symptoms. As a diagnosis of exclusion, diseases that might cause bladder pain (confusable disease) were listed by the ESSIC along with how they can be excluded (table 1).
Patients with BPS demonstrate large variations in complaints, quality of life, cystoscopic and biopsy findings as well as in response to treatment and prognosis. These characteristics may be correlated only to a limited extent. In order to be able to study these correlations ESSIC introduced a schema related to subtypes of BPS (table 2).

The ESSIC diagnostic algorithm is illustrated in figure 1.
International Consultation on Incontinence (in conjunction with World Health Organization)

Painful Bladder syndrome including IC was the nomenclature used in the 3rd International Consultation on Incontinence in 2004. At the 4th International Consultation on Incontinence in 2008 Bladder Pain Syndrome was accepted as the name of the disease. An algorithm for evaluation and treatment was published (figure 2).
Asian Concepts and Guideline

Yukio Homma published a treatise on lower urinary tract terminology which was a plea for continuously challenging our verbiage for scientific validity. He proposes that frequency/urgency syndrome is characterized by frequency (frequent voiding) and urgency (strong desire to void). It is an inclusive term incorporating overactive bladder syndrome (OAB), hypersensitive bladder syndrome (HSB), and other conditions that are associated with frequency and urgency. Urgency in OAB is characterized by sudden onset and/or fear of leakage, while urgency in HSB is of a persistent nature and is associated with the fear of pain. OAB-wet is a subgroup. Painful bladder syndrome (PBS) is a subgroup of HSB with pain. Interstitial Cystitis (IC) is one of the diseases manifest by frequency/urgency and overlapping with HSB and PBS.

Two large multinational meetings organized by Dr. Tomohiro Ueda and held in Kyoto set in motion the process that ultimately resulted in a guideline reflecting the views of the Japanese Urological Association and urologists from Taiwan and Korea with a special interest in the condition. This East-Asian guideline defines interstitial cystitis as “a disease of the urinary bladder diagnosed by three conditions: lower urinary tract symptoms, bladder pathology, and exclusion of confusable diseases. The characteristic symptom complex is termed hypersensitive bladder syndrome (HBS), which is defined as bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain (figure 3).
The American Urological Association Guidelines Committee has released their first evidence-based clinical guideline on the what they term interstitial cystitis/bladder pain syndrome (IC/BPS) to aid health care providers in diagnosis and treatment of this condition. The condition is defined as “An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes.” It recommends the following in assessing both women and men for the condition:

- A full basic assessment, including a careful history, physical examination and laboratory examination to identify characteristic IC/BPS symptoms (including sensations of pain, pressure and discomfort perceived by the patient to be related to the bladder, absence of infection, as well as marked urinary urgency and frequency) and rule out confusable disorders (such as overactive bladder or, specifically in men, chronic prostatitis).
- Measurements of baseline voiding symptoms and pain levels (to which subsequent levels may be compared to measure treatment efficacy).
The consideration of cystoscopy and/or urodynamic studies to better assess complicated presentations or to confirm a diagnosis when assessment results are in doubt. While there are no existing cystoscopic or urodynamic findings specific for IC/BPS, these tests can be valuable in identifying lesions or alterations (Hunner’s lesions) in the bladder in patients with symptoms, and in ruling out other entities such as bladder cancer or urethral diverticula.

The full algorithm including treatment suggestions is displayed in figure 4.

IC/BPS: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symp-toms of more than six weeks duration, in the absence of infection or other identifiable causes

**Basic Assessment**

- History
- Frequency/Volume Chart
- Post-void residual
- Physical examination
- Urinalysis, culture
- Cytology if smoking hx
- Symptom questionnaire
- Pain evaluation

**First-Line Treatments**

- General Relaxation/Stress Management
- Pain Management
- Self-care/Behavioral Modification

**TREAT & REASSESS**

**Dx Urinary Tract Infection**

- Incontinence/OAB
- GI signs/symptoms
- Microscopic/gross hema-turia/sterile pyuria
- Gynecologic signs/symptoms

**Consider:**

- Urine cytology
- Imaging
- Cystoscopy
- Urodynamics
- Laparoscopy
- Specialist referral (urologic or non-urologic as appropriate)

NORMAL

**TREAT AS INDICATED**

**Second-Line Treatments**

- Appropriate manual physi-cal therapy techniques
- Oral: amitriptyline, ci-metidine, hydroxyzine, PPS
- Intravesical: DMSO, hepa-rin, Lidocaine
- Pain Management

**Third-Line Treatments**

- Cystoscopy under anesthesia w/ hydrodistension
- Pain Management
- Tx of Hunner’s lesions if found

**Fourth-Line Treatments**

- Neuromodulation
- Pain Management

**Fifth-Line Treatments**

- Cyclosporine A
- Intradetrusor BTX
- Pain Management

**Sixth-Line Treatments**

- Diversion w/ or w/out cystectomy
- Pain Management
- Substitution cystoplasty

NOTE: For patients with end-stage structurally small bladders, diversion is indicated at any time clinician and patient believe app-propriate.

**Clinical Management Principles**

- Treatments are ordered from most to least conserva-tive; surgical treatment is appropriate only after other treatment options have been found to be ineffective (except for treatment of Hunner’s lesions if detected)
- Initial treatment level depends on symptom severity, clinician judgment, and patient preferences
- Multiple, simultaneous treatments may be considered if in best interests of patient
- Ineffective treatments should be stopped
- Pain management should be considered throughout course of therapy with goal of maximizing function and minimizing pain and side effects
- Diagnosis should be reconsidered if no improvement within clinically-meaningful time-frame

**Research Trials**

Patient enrollment as appropriate at any point in treatment process

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The evidence supporting the use of Neuromodulation, Cyclosporine A, and BTX for IC/BPS is limited by many factors including study quality, small sample sizes, and lack of durable follow up. None of these therapies have been approved by the U.S. Food and Drug Administration for this indication. The panel believes that none of these interventions can be recommended for generalized use for this disorder, but rather should be limited to practitioners with experience managing this syndrome and willingness to provide long-term care of these patients post intervention.

**European Association of Urology (EAU) Guidelines**

EAU suggests that taxonomy be based on the axial structure of the International Association for the Study of Pain (IASP). *Bladder pain syndrome was found best to conform to current taxonomy.* The term “interstitial cystitis” is reserved for a subset of patients with verified signs of chronic inflammation extending submucosally. BPS is diagnosed on the basis of symptoms, examination, urine analysis, cystoscopy with hydrodistension and biopsy. (figure 5)
Conclusion

The 2003 Kyoto initiative of Dr Ueda inspired a number of international activities, since surprisingly divergent opinions were brought into the open. Further basic science and clinical research in this area was found vital. When comparing opinions in Europe, Asia and United States, there are interesting differences on how to interpret and weigh very basic clinical information such as symptoms, cystoscopy and biopsy findings. Even if divergences are diminishing, controversies on the understanding of BPS still remain in the present guidelines.


(16) Pain terms: a list with definitions and notes on usage. recommended by the IASP Subcommittee on Taxonomy. *Pain* 1979;6:249.
New aspects in immunological diagnosis of bladder pain syndrome/interstitial cystitis

Tomohiro Ueda, MD, PhD
Urology, Ueda Clinic
Kyoto Japan

Focus into symptom
Subjective assessment for IC

- Frequency/ urgency and pain

Why does it develop?
Hypersensitive Bladder

- IC symptom developed by multiple factors in the urine
- We should demonstrate the tool to detect these pathology such as the **neurometer** and **Narrow Band imaging (NBI)**
- Neurometer can detect **hypersensitivity** of the bladder epithelium
- NBI can detect **angiogenesis** of the bladder epithelium
CPT values in pts with IC

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<th>160</th>
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<th>100</th>
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<th>60</th>
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- **Aβ-fiber**
- **Aδ-fiber**
- **C-fiber**

Stimulation

5Hz  250Hz  2000Hz

"Hyper-sensitive"

- IC
- Control

p<0.01  p<0.05

February 2012 JUA Symposium

Video system center

Light Source

Flexible Cystoscope
Narrow Band Imaging System for Interstitial Cystitis

**Conventional White Light**

**Narrow Band Imaging (NBI)**

Brown at 415nm
Cyan at 540 nm

Bladder lesions are easily and clearly recognized by NBI

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Cystoscopic diagnosis

- IC specialist diagnoses it by symptom and cystoscopy in Japan
- Demonstrate bladder epithelial pathology
Immunogenic diagnosis of IC

Ulcer and Glomerulation

What happens?

Purpose

The correlation of the expression of angiogenic factors such as PDECGF/TP* and TGF-β with the severity of symptoms in patients with bladder carcinoma and interstitial cystitis.

* PDECGF/TP: platelet-derived endothelial cell growth factor/thymidine phosphorylase
Patient Profile

- Bladder carcinoma: 32
- Interstitial cystitis: 19
- Control: 3

Mean TP (units/mg protein)

Pain Symptom

2012JUAシンポジウム
Immunohistochemical staining of Angiogenic Growth Factors In Bladders with Glomerulation (n=38)

Possible mechanism of Glomerulation

Overexpression of angiogenic growth factors

Neovascularization and increase in weak abnormal capillaries

Rupture

Mechanical or congestive stress on these capillaries

Immunological diagnosis

- Overexpression of angiogenic factor
- Angiogenesis in the bladder epithelium
- Mast cell hyperactivity
- GAG deficiency
Multi-pathology of BPS/IC

- Mast cell
- Th2
- Uroplakin
- Angiogenesis
- Cytokine/Growth factor
- Urine
- Bacteria
- Chemicals
- Viruses
- Tumor
- Radiation
- Stress
- Epi thel ium
- Ur ine
- GAG
- Heparin-binding
- CD44
- TGF-β
- APF
- C-fiber
- Pain
- Defense mechanism suppressed
  - GAG, Uroplakin, APF
- Offense mechanism activated
  - Diet (acid, potassium, spicy food)
  - Stress (cold...)
  - Bacteria, chemicals, virus, tumor, radiation...

Immunological Pathology of BPS/IC

- Defense mechanism suppressed
- Offense mechanism activated
- Inflammation/angiogenesis
- C-fiber, Aδ-fiber
- NGF, VEGF, EGF, PDEGF/TP
- Chemokine, IL-6

What do you think of inflammation/angiogenesis?
- Is it a cause, a result or just a bystander??
What’s the problem of research on IC

- Symptom-based diagnosis (BPS or PBS) is useful for maximizing the power to identify potential patients of the disease.
- However, when bladder-targeting therapies (systemic or local) are considered, it is important to identify patients who exhibit pathological changes in the bladder. By using NBI, Neurometer?
- Thereafter, we should evaluate which factor(s) are most important as a defense or offense mechanism of IC (=BPS or PBS with bladder pathology).

Conclusion

- We have to demonstrate the pathology, which can induce IC like symptoms, such as bacterial cystitis, CIS and chemical cystitis.
- Moreover, we should provide an easy tool to detect hypersensitivity of the bladder and epithelial angiogenesis, such as the neurometer and NBI cystoscopy so as to facilitate diagnosis of IC by general urologists.
- Such tools would ensure that IC patients are not left to suffer from their disease alone without evaluation or treatment.
- 3rd ICICJ meeting in Kyoto will be held in March, 2013.
Notes
Record your notes from the workshop here