Cistite interstiziale/Sindrome del dolore vescicale (IC-BPS)

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**Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC):** a condition diagnosed on a clinical basis and requiring a high index of suspicion by the clinician, based on patient reported symptoms and exclusion of other disorders; there is a lack of consistent physical findings (ESSIC)

- Diagnosed on the basis of chronic pelvic pain, pressure, or discomfort perceived to be related to urinary bladder accompanied by at least one other urinary symptom: persistent urge to void or urinary frequency.

**Confusable (chronic) diseases as the cause of the symptoms must be excluded**
Overview

- BPS/IC encompasses a major portion of the "painful bladder" disease complex - including bladder and/or urethral and/or pelvic pain, irritative voiding symptoms (urgency, frequency, nocturia, dysuria), and sterile urine

- Painful bladder conditions with well-established causes include:
  - radiation cystitis
  - cystitis caused by microorganisms that are not detected by routine culture methodologies (broth culture)
  - systemic disorders that affect the bladder disorders
  - gynecologic disorders

Do subgroups exist?

- Japan, Taiwan and Korea have their own guidelines and label it as “hypersensitive bladder” (HSB): “bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain”.

- the terms IC, BPS/IC, BPS, HSB are used interchangeably and for the same syndrome!
Overview

- Symptoms are mostly allodynic, an exaggeration of normal sensations.
- There are no pathognomonic findings on pathologic examination.
- Petechial hemorrhages after hydrodistention is no longer considered the sine qua non of BPS/IC.
- BPS/IC is truly a diagnosis of exclusion. It may have multiple causes and represents a final common reaction of the bladder to different types of insults.
- In 1949 Hand described the first comprehensive review about the disease reporting 223 cases. The majority of his findings have relevance even today.” He notes, “small, discrete, submucosal hemorrhages, showing variations in form ... dot-like bleeding points ... little or no restriction to bladder capacity.” He portrays 3 grades of disease, with grade 3 matching the small-capacity, scared bladder described by Hunner. Sixty-nine percent were grade one and only 13% were grade three.
DEFINITION

- The ICS reserves the diagnosis of IC for patients with "typical cystoscopic and histological features," without further specifying these.

Hunner’s lesion
A positive finding that can confirm the diagnosis in patients who meet the definition criteria
- acute phase (inflamed, friable, denuded area)
- chronic phase (blanched, non-bleeding area)
- Provides a therapeutic option
Epidemiology

- Difficult to estimate precisely because of lack of clear diagnostic criteria
- >50% higher than previously thought
- ~90% of all patients with IC are women
- Estimates of IC/PBS prevalence have increased in USA 18 /100,000 habitants in 1975, 67 in 1995, 230 in 2005, 1 in 1000 women, increasing to more than 5 out of 1000 adult women, depending on diagnostic criteria, time frame, and geographic area (Fall 2008). However, other reports [Burkman 2004, Parsons 2004] have suggested that the incidence of IC in adult women is higher
Infection

- Diagnosis of BPS/IC is made only after a patient has been seen by a number of physicians and treated with antibiotics for presumed urinary tract infection without resolution of symptoms.

- "It is logical to suggest that even if organisms are not causative agents, their presence may lead to immune and host-cell responses that could initiate or exacerbate an inflammatory state."

The urothelium is heavily modified through the reversible distension of its urothelial cells. From Tajana G. Fisiopatologia clinica e biologia molecolare dell’urotelio. Minerva Urol Nefrol 2009; 61(3 suppl 1):1–29
Mast Cell Involvement

Mast cells have frequently been reported to be associated with IC, both as a pathogenetic mechanism and as a marker.

They are strategically localized in the urinary bladder close to blood vessels, lymphatics, nerves and detrusor smooth muscle.

MCs have been retained throughout the phylogenetic tree, their ability to produce hormonal, immune and neural substances resemble that of the unicellular organism. MCs are present in all mammals and may be necessary for survival of the species by regulating immunity, protecting the organism against external triggers, supporting pregnancy, augmenting delivery and also ensuring optimal conditions for procreation.

Abnormalities in autonomic (sympathetic) activity have been demonstrated in IC/BPS and this has been described both at a clinical and at an experimental level.

Studies strongly suggest that IC is a syndrome with neural, immune, and endocrine components in which activated mast cells play a central, although not primary, pathogenetic role in many patients.
**Bladder GAG Layer/Epithelial Permeability**

Organic cations in the urine neutralize the GAG layer producing increased permeability.

Potassium ions and other molecules pass into the urothelium or deeper.

Irritation, triggering inflammatory cells, and sending sensory signals.

Upregulation of sensory fibers.

The sensory signaling from the bladder affects other tissues as well as the bladder increased bowel permeability.

Increased bowel permeability (e.g., IBS) also signals back to the bladder causing increased bladder permeability by unknown mechanisms.

Communication is through the dorsal root ganglia. The pain signal is also transmitted to the brain where chronic pain can rewire the brain.

Signaling through the vagus nerve releases neurotransmitters and cytokines.

Activation of mast cells and macrophages that then increase bladder permeability.

Longterm effects on the brain, such as early life stress may potentiate some individuals toward IC/BPS by mechanisms that are not well understood.
ESSIC recommends that pathology report should include information about:

- **Epithelium** *(not present, present, dysplasia with grading, abnormal but no dysplasia—description)*;
- **L. Propria** *(normal, inflammation—description with a grading)*;
- **Detrusor muscle** *(abnormal muscle cells—describe, intrafascicular fibrosis—present/not present, mast cell count—at least 3 biopsies should be included in the counting and the biopsy with the highest number of mast cells per mm 2 should be reported)*;
- **Information on detrusor mastocytosis**: (a) less than 20 mast cells/mm 2 = no detrusor mastocytosis; (b) between 20 and 27 = grey zone; (c) 27 or more mast cells/mm 2 = detrusor mastocytosis.
Other Potential Causes of IC/BPS

- Pelvic floor dysfunction
- Visceral organ crosstalk
- Main question
  Does the intercommunication arise from cellular communication by migratory cells such as mast cells or the information is transmitted through neural communication and release of neurosecretory proteins that can alter one organ according to the status of another? There is evidence for both theories.
One can have pathology consistent with the diagnosis of IC, but there is no microscopic picture pathognomonic of this syndrome. So far the role of histopathology in the diagnosis of IC is primarily one of excluding other possible diagnoses.
DIAGNOSIS

- Considered one/part of the chronic visceral pain syndromes, affecting the urogenital and rectal area, well described but poorly understood (Including vulvodynia, orchialgia, penile pain, perineal pain, and rectal pain, various gynecologic conditions)

- Presumptive diagnosis can be made merely by ruling out known causes of frequency and pain/urgency in a patient with compatible chronic symptoms (Complete History&Physical examination, cultures, and cystoscopy)

- Cystometry in conscious IC patients generally demonstrates normal function, the exception being reduced bladder capacity and hypersensitivity.

- *Pain on bladder filling that reproduces the patient's symptoms is very suggestive of IC*
Typical appearance of glomerulations after bladder distention in a patient with nonulcerative interstitial cystitis.

Typical appearance of Hunner's ulcer in a patient with interstitial cystitis before bladder distention.
Glomerulations

- Absence of glomerulation can lead to false negative assessment of patients who present with clinical findings consistent with IC/BPS
- The finding of glomerulations on hydrodistention is variable and not consistent with clinical presentation
- Seen in many clinical situations
  - Radiation therapy, defunctionalized bladders, bladder cancer, chemotherapeutic or toxic drug exposure, normal bladders
Diagnosis

- Intravesical nitric oxide: a possible marker. In addition, recent studies have indicated that intravesical nitric oxide may be a potential marker to diagnose Hunner lesion. It has been shown that patients with Hunner lesions have high NO levels symptoms, while those without Hunner lesions have normal levels. While measurement is a simple procedure, it requires a nitric oxide measuring device that is as yet not generally available in urology departments. Research continues in this field.
PRINCIPLES OF MANAGEMENT

History/Initial Assessment

Initial assessment: frequency/volume chart, focused physical examination, urinalysis, and urine culture. Cytology and cystoscopy if indicated.

Initial Treatment

Patient education, dietary manipulation, nonprescription analgesics, and pelvic floor relaxation techniques. When these fail, or symptoms are severe and conservative management unlikely to succeed, oral medication or intravesical treatment can be prescribed.

Secondary Assessment

Further evaluation (urodynamics, pelvic imaging, and cystoscopy with bladder distention and possible bladder biopsy under anesthesia).
Pts. with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more advanced modalities (neuromodulation, pain clinic consultation, narcotic analgesia, and/or experimental protocols).

Surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urine stream

Philosophy of Management LAST STEP (augmentation).

Cautiously progress through a variety of treatments. One should encourage patients to maximize their activity and live as normal a life as possible, not becoming a prisoner of the condition. Although some activities or foods may aggravate symptoms, nothing has been shown to negatively affect the disease process itself.

Patients should feel free to experiment and judge for themselves how to modify their lifestyle without the guilt that comes from feeling they have harmed themselves if symptoms flare.
**ORAL THERAPY**

- **Tricyclic Antidepressants** (Amitriptyline) have three major pharmacologic actions:
  
  (1) central and peripheral anticholinergic actions
  
  (2) block the active transport system in the presynaptic nerve ending responsible for reuptake of serotonin and noradrenaline
  
  (3) sedative

- **Antihistamines**—Used since late 1950s, postulated that the local release of histamine may be responsible for, or accompany the development of IC.

- **Sodium Pentosan Polysulfate**—A heparin analog, thought to decrease the epithelial permeability
INTRA-vesical and IntraDetrusor Therapy

Intravesical instillation of one of a variety of preparations has remained a mainstay of treatment in the therapeutic armamentarium of IC.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Randomized Controlled Trial</th>
<th>% Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver nitrate</td>
<td>No</td>
<td>60%</td>
</tr>
<tr>
<td>Clorapactin WCS-90</td>
<td>No</td>
<td>60%</td>
</tr>
<tr>
<td>Dimethylsulfoxide</td>
<td>Yes</td>
<td>70%</td>
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<tr>
<td>Bacillus Calmette-Guérin</td>
<td>Yes</td>
<td>No proven</td>
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<tr>
<td>Resiniferatoxin</td>
<td>Yes</td>
<td>No proven</td>
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<tr>
<td>Hyaluronic acid</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Hyaluronic acid + Chondroitin s.</td>
<td>In press</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>No</td>
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<tr>
<td>Chondroitin sulfate</td>
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<tr>
<td>Lidocaine</td>
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<tr>
<td>Oxybutynin</td>
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<tr>
<td>Efficacy suggested</td>
<td>Doxorubicin</td>
<td>Anecdotal efficacy</td>
</tr>
<tr>
<td>Pentosan polysulfate</td>
<td>Yes</td>
<td></td>
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</tbody>
</table>
Dimethyl sulfoxide (DMSO)

- DMSO is a product of the wood pulp industry and a derivative of lignin
- It has exceptional solvent properties and is freely miscible with water, lipids, and organic agents
- Pharmacologic properties include membrane penetration, enhanced drug absorption, anti-inflammatory action, analgesic action, collagen dissolution, muscle relaxation, and mast cell histamine release
- It has been suggested that DMSO actually desensitizes nociceptive pathways in the lower urinary tract
- Some authors administer 50 mL of 50% DMSO as a bladder "cocktail" with 10 mg of triamcinolone 40,000 units of heparin, and 44 mEq of sodium bicarbonate
La BTA può trattare con successo i sintomi della IC/BPS insufficien
te comprensione dei meccanismi di esordio e di persistenza dei sintomi.

L’osservazione di modificazioni anatomiche e funzionali della sostanza grigia e bianca del SNC indica la necessità di uno studio più globale, per la scelta di un trattamento individualizzato. 

E’ improbabile che un singolo approccio terapeutico risulti efficace in tutti i pazienti.
The surgical therapy of IC is an option after all trials of conservative treatment have failed, a point that cannot be overemphasized.

IC, although a cause of significant morbidity, is a nonmalignant process with a temporary spontaneous remission rate of up to 50% and does not directly result in mortality.

Many surgical approaches have been employed for IC: Sympathectomy and intraspinal alcohol injections.

Differential sacral neurotomy.

Transurethral resection/laser of a Hunner's ulcer.

Supratrigonal cystectomy.

Urinary diversion with or without cystourethrectomy is the ultimate surgical answer to the dilemma of IC.
Intravesical liposome drug delivery

Intravesical LPs have shown safety and efficacy in non-clinical and clinical IC/BPS studies. Intravesical liposome (LP-08) reduces pain and urgency scores in symptomatic IC/BPS patients. Probability density functions for pain and urgency scores of patients at baseline, 8 and 12 weeks.
Intravesical liposome (LP-08) vs. standard of care oral pentosan polysulfate (PPS)
Thanks

...for these crimes, you will now be put to death by lethal injection.

Wait. WHAT?!!

You will now be put to death by lethal injection.

Oh thank God. I thought you said urethral injection.