Urological Perspective on Persistent Pelvic Pain

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The AUA guideline defines IC/BPS as an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder associated with lower urinary tract symptoms of more than 6 weeks duration in the absence of infection or other identifiable causes.
Interstitial Cystitis (IC)
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”
Chronic Pelvic Pain

Definition

- Difficult to diagnose
- Difficult to treat
- Difficult to cure

Frustration for patient and physician
Epidemiology

- Epidemiology studies of BPS/IC suffer from the lack of a universally accepted definition
- The first population-based study included patients with IC in Helsinki: 18.1 per 100,000 women and 10.6 per 100,000 population
- 35–2400 per 100,000 in the United States
- 1.2 per 100,000 in Japan
- Female to male preponderance of 5:1
- “Interstitial Cystitis-The Great Enigma”
Prevalence

- Large European study undertaken in 2004 found that chronic pain occurs in 19% of adults.
- Seriously affecting the quality of their social and working lives.
- There are some differences between countries but not much spread is seen.
- Recent study in the UK found a prevalence of CPP of 14.8% in women over 25 years.
Chronic Pelvic Pain

Etiology: United Kingdom Primary Care Database

Diagnosis Distribution

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>37.7%</td>
</tr>
<tr>
<td>Urinary</td>
<td>30.8%</td>
</tr>
<tr>
<td>Gynecological</td>
<td>20.2%</td>
</tr>
</tbody>
</table>

- 25-50% of women had more than one diagnosis
- Severity and consistency of pain increased with multisystem symptoms
- Most common diagnoses:
  - endometriosis
  - adhesive disease
  - irritable bowel syndrome
  - interstitial cystitis
Urological aspects

1. **Pain may be associated with urological symptoms**
2. **A detailed history** of lower urinary tract functions should be taken
3. **Dysfunctions of the lower urinary tract** may exacerbate symptoms, as pain may interfere with the function of the lower urinary tract
4. **Micturition** in all its aspects should be addressed
5. Special attention should be paid to the **influence of micturition** on the experience of pain
Chronic pelvic syndrome

- **Prostate pain syndrome (PPS)** is the occurrence of persistent or recurrent episodic pain (which is convincingly reproduced by prostate palpation)
- **Scrotal pain syndrome** is the occurrence of persistent or recurrent episodic pain localized within the organs of the scrotum
- **Testicular pain syndrome** is the occurrence of persistent or recurrent episodic pain perceived in the testes
- **Epididymal pain syndrome** is the occurrence of persistent or recurrent episodic pain perceived in the epididymis

*no proven infection or other obvious local pathology*

Associated symptoms: suggestive of lower urinary tract or sexual dysfunction
Chronic pelvic syndrome cont.

- **Penile pain syndrome**: occurrence of pain within the penis that is not primarily in the urethra
- **Urethral pain syndrome** = occurrence of chronic or recurrent episodic pain perceived in the urethra
- **Post-vasectomy scrotal pain syndrome** is a scrotal pain syndrome that follows vasectomy absence of proven infection or other obvious local pathology associated with negative cognitive, behavioral, sexual or emotional consequences symptoms suggestive of lower urinary tract and sexual dysfunction
Bladder pain syndrome (BPS/IC)

should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom such as daytime and/or night-time increased urinary frequency.

The nature of pain is key to disease definition:

1. pain, pressure or discomfort perceived to be related to the bladder, increasing with increasing bladder content
2. located suprapubically, radiating to the groins, vagina, rectum or sacrum
3. relieved by voiding but soon returns
4. aggravated by food or drink
Phenotyping of interstitial cystitis/bladder pain syndrome

**Non-ulcerative**
- Non-ulcerative IC presents with pinpoint hemorrhages, also known as glomerulations, in the bladder wall
- **glomerulations** associated with IC/BPS diagnosis and pathogenesis
- are not likely to be a phenotypic feature of IC/BPS
- the severity of glomerulations may be associated with disease prognosis

**Ulcerative**
- 5–57% of **Hunner’s ulcers** or patches, which are red, bleeding areas on the bladder wall
- smaller bladder capacity
- more bladder-centric symptoms
- fewer comorbid non-bladder conditions
- proven bladder pathology compared to the non-Hunner lesion phenotype
Despite extensive scientific effort, the precise etiology of PBS/IC is still an enigma with no generally accepted treatment.

- **Mast cells** are thought to have a pivotal role in IC.
- They are multifunctional immune cells that contain highly potent inflammatory mediators such as histamine, leukotrienes, serotonin and cytokines.
Aetiology cont.

Epithelial alterations

• A defect in the glycosaminoglycan- (GAG) –layer is a pathogenetic explanation to IC that has been proposed

• Inhibition of urothelial bladder cell proliferation
  the bladder epithelial dysfunction might be the fact that the cells produce an inhibitor of heparin-binding epidermal growth factor-like production in IC

• Autoimmune mechanisms show certain similarities with other known autoimmune phenomena
Aetiology cont.

• **Neurobiology** autonomic nerve changes, but the findings are far from uniform

• **Toxic agents** Toxic constituents in the urine may cause injury to the bladder in PBS/IC
Chronic Pelvic Pain

Interstitial Cystitis

• **Description:** chronic pain syndrome whose causes remains elusive with no generally accepted treatment

• **Symptoms:**
  1. Urinary urgency and frequency
  2. Pain is worse with bladder filling; improved with urination
  3. Pain is worse with certain foods
  4. Pressure in the bladder and/or pelvis
  5. Pelvic Pain in up to 70% of women
  6. Present in 38-85% presenting with chronic pelvic pain
Interstitial cystitis/bladder pain syndrome

**Description:** chronic pain syndrome whose causes remain elusive with no generally accepted treatment

**Overlap** irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, anxiety disorders, other syndromes not directly related to the urinary bladder

**Symptoms:**
- Urinary urgency and frequency
- Pain is worse with bladder filling; improved with urination
- Pain is worse with certain foods
- Pressure in the bladder and/or pelvis
- 70% of women
- Present in 38-85%
**Diagnosis**

**Required symptoms in all guidelines are:** pain, pressure, discomfort and frequency, urgency and nocturia

**Potassium test** is an **office-based examination** in which solutions of sterile water and 0.4N KCl are sequentially instilled into the bladder and the subject asked to rate the degree of urge and pain produced by the instillation.

**Cystoscopic findings** of Hunner’s ulcer and glomerulations

Both might be found in patients without IC/PBS, and be absent in patients classified by experienced researchers as having IC/PBS.

**Urodynamics** *In the Interstitial Cystitis database approximately 14% of IC/PBS patients had overactive detrusors*
**Interstitial Cystitis Symptom Index**

• Q1. … how often have you felt the strong need to urinate with little or no warning?
• Q2. … how often have you had to urinate less than 2 hours after you finished urinating?
• Q3. … how often did you most typically get up at night to urinate?
• Q4. … have you experienced pain or burning in your bladder?

**Scoring Grade**
1. Not at all
2. A few times
3. Almost always
4. Fairly often
5. Usually
The diagnostic criteria

- Diagnostic criteria used varied amongst urologists
- **Pathology on bladder biopsies**
- The presence of **mast cells** in biopsies was used as a criterion for **79%** of the urologists
- The presence of **voiding symptoms** was reported in most of the patients who met the diagnostic criteria of the individual urologists
- **Frequency** was the most common (**87% of patients**) symptom
- **Pain** in the region of the bladder was reported in **61%** of the patients
Inclusion criteria

• **Hunner’s ulcer** – automatic inclusion or Pain on bladder filling relieved by emptying

• **Pain** (suprapubic, pelvic, urethral, vaginal or perineal)

• **Glomerulations** on endoscopy

• **Decreased bladder compliance** on cystometry

2 positive factors necessary for inclusion
Exclusion criteria

1. <18 years old
2. Benign or malignant bladder tumors Radiation cystitis
3. Tuberculous cystitis Bacterial cystitis, Vaginitis
4. Cyclophosphamide cystitis Symptomatic, urethral diverticulum Uterine, cervical, vaginal or urethral Ca, Active herpes
5. Bladder or lower ureteral calculi
6. Waking frequency <5 times in 12 hrs. Nocturia <2 times
7. Symptoms relieved by antibiotics, urinary antiseptics, urinary analgesics (for example phenazopyridine hydrochloride)
8. Duration <12mos
9. Involuntary bladder contractions (urodynamics) Capacity >400cc, absence of sensory urgency
10. Absence of an intense urge to void during cystometry
11. A frequency of urination, while awake, of less than eight times per day
12. A diagnosis of bacterial cystitis or prostatitis within a 3-month period
Management

• **General agreement** between All guidelines

• **Fundamental principle:** USE the most conservative therapies and passing to systemic conservative therapies if symptom control is inadequate for an acceptable QoL
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer subtype and phenotype-oriented therapy for the treatment of Bladder Pain Syndrome (BPS).</td>
<td>Strong</td>
</tr>
<tr>
<td>Always consider offering multimodal behavioural, physical and psychological techniques alongside oral or invasive treatments of BPS.</td>
<td>Strong</td>
</tr>
<tr>
<td>Administer amitriptyline for treatment of BPS.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer oral pentosane polysulphate for the treatment of BPS.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer oral pentosane polysulphate plus subcutaneous heparin in low responders to pentosane polysulphate alone.</td>
<td>Weak</td>
</tr>
<tr>
<td>Administer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.</td>
<td>Weak</td>
</tr>
<tr>
<td>Administer intravesical pentosane polysulphate before more invasive treatment alone or combined with oral pentosane polysulphate.</td>
<td>Strong</td>
</tr>
<tr>
<td>Administer submucosal injection of botulinum toxin type A (BTX-A) plus hydrodistension if intravesical instillation therapies have failed.</td>
<td>Strong</td>
</tr>
<tr>
<td>Only undertake ablative organ surgery as the last resort and only by experienced and BPS-knowledgeable surgeons.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer intravesical hyaluronic acid before more invasive measures.</td>
<td>Weak</td>
</tr>
<tr>
<td>Offer intravesical chondroitin sulphate before more invasive measures.</td>
<td>Weak</td>
</tr>
<tr>
<td>Offer transurethral resection (or coagulation or laser) of bladder lesions, but in BPS type 3 C only.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer neuromodulation before more invasive interventions.</td>
<td>Weak</td>
</tr>
<tr>
<td>Offer dietary advice.</td>
<td>Weak</td>
</tr>
</tbody>
</table>
Interstitial cystitis association dietary recommendations Foods to Avoid

- Milk / Dairy Products
- Vegetables
- Meats and fish
- Seasonings
- Preservatives and additives
- Fruits
- Carbohydrates and grains
- Beverages
- Miscellaneous

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# Drug Therapy

<table>
<thead>
<tr>
<th>Drug therapy</th>
<th>RCT</th>
<th>% Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline; tricyclic antidepressants</td>
<td>yes</td>
<td><strong>42%</strong></td>
</tr>
<tr>
<td>Antibiotic regimens</td>
<td>yes</td>
<td><strong>48%</strong></td>
</tr>
<tr>
<td>Anticholinergics and antispasmodics</td>
<td>no</td>
<td>anecdotal</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>no</td>
<td><strong>50%</strong></td>
</tr>
<tr>
<td>Benzydamine</td>
<td>yes</td>
<td><strong>0%</strong></td>
</tr>
<tr>
<td>Chloroquine derivatives</td>
<td>no</td>
<td><strong>50%</strong></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>yes</td>
<td><strong>65%</strong></td>
</tr>
<tr>
<td>Cortisone308 and other steroids</td>
<td>no</td>
<td><strong>80%</strong></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>no</td>
<td><strong>90%</strong></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>no</td>
<td><strong>71%</strong></td>
</tr>
<tr>
<td>Gapapentin</td>
<td>no</td>
<td>anecdotal</td>
</tr>
<tr>
<td>Hormones</td>
<td>no</td>
<td>anecdotal</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>yes</td>
<td><strong>31%</strong></td>
</tr>
<tr>
<td>L-Arginine</td>
<td>yes</td>
<td>not effective</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>no</td>
<td><strong>50%</strong></td>
</tr>
<tr>
<td>Misoprostgil</td>
<td>no</td>
<td><strong>48%</strong></td>
</tr>
<tr>
<td>Montellukast</td>
<td>no</td>
<td><strong>90%</strong></td>
</tr>
<tr>
<td>Nalmefene</td>
<td>yes</td>
<td>not effective</td>
</tr>
</tbody>
</table>
Intravesical Treatments

• Intravesical drugs are administered due to poor oral bio-availability establishing high drug concentrations within the bladder, with few systemic side-effects

• Disadvantages include the need for intermittent catheterization which can be painful in BPS patients, cost and risk of infection

1. Local anesthetics (Intravesical lidocaine, Alkalization of lidocaine improves its pharmacokinetics)
   
   Combination of heparin, lidocaine and sodium bicarbonate gave immediate symptom relief in 94% of patients and sustained relief after two weeks in 80%

2. Hyaluronic acid and chondroitin sulphate are described to repair defects in the GAG layer

3. Intravesical heparin Symptomatic improvement was reported in 80% of BPS patients

4. Intravesical heparin plus dorsal tibial nerve
Other treatments

1. **Hyperbaric oxygen** (HBO) has a moderate effect on a small subgroup of BPS patients
   Disadvantages include high cost, limited availability of treatment sites, and time-consuming treatment
   - **Treatments of limited value for BPS**

2. **Cimetidine**

3. There is limited data to suggest that cimetidine improves symptoms of BPS in the short-term **Prostaglandins**
   - Misoprostol is a prostaglandin that regulates various immunological cascades. The incidence of adverse drug effects was 64%.

4. **L-Arginine**
   - Oral treatment with the nitric oxide (NO) synthase substrate L-arginine decreases BPS-related symptoms.
   - Nitric oxide is elevated in patients with BPS. However, others have not demonstrated symptomatic relief or changes in NO production after treatment
Bladder distension n’ more

bladder hydrodistension is a common treatment for BPS, the scientific justification is scarce

1. Hydrodistension and Botulinum toxin type A
   symptomatic improvement, effective and long-lasting as 87%
   AUA guidelines panel has recently upgraded BTX-A treatment from fifth to a fourth line treatment

2. Transurethral resection (TUR), coagulation and laser

3. Open Surgery for BPS

4. Pudendal Neuralgia and surgery

2. Neuromodulation sacral neuromodulation (SNM) vs. pudendal nerve stimulation (PNS), showed an overall 59% improvement in symptoms with PNS vs. 44% with SNM)
Current pharmacologic approaches

• **Tanezumab, Fulranumab**, human monoclonal antibodies (NGF inhibition) produced a significant reduction in average daily pain.

• **Anti-TNF therapeutics Adalimumab** have been successful and changed the management of autoimmune diseases such as rheumatoid arthritis. It has a high selectivity and affinity for TNF and reduces TNF-induced inflammatory responses.

• **Aqx-1125**, a modulator of immune/inflammatory processes & p2x3 receptor antagonists.

• **Reduction of sympathetic overactivity and stress** selective α1A-AR inhibition can improve both functional and morphological changes.

• **Intravesical liposomes**
EAU algorithm

- **Classic**
  - TUR / Laser
  - Inadequate Response

- **BPS/IC**
  - Pain related to the urinary bladder accompanied by at least one other urinary symptom
  - Detailed history, ICSI Score
  - Micturition chart
  - Cystometrography
  - Cystoscopy with hydrodistension under anaesthesia, biopsy (ESSIC-type indication)

- **Nonulcer**
  - Noninvasive therapy
    - Oral agents, TENS
    - Complementary treatments
    - Inadequate Response
    - Intravesical therapy
      - PPS, Hyaluronic Acid, Chondroitin Sulphate, DMSO, EMDA
      - Inadequate Response
        - Pain Team
          - Multimodal Pain Therapy
          - Inadequate Response
            - Experimental: Botox
              - Sacral neuromodulation
              - Complementary treatments

- Ultima (I) ratio:
  - Consider surgical resection for refractory debilitating symptoms in late-stage ulcerative disease / small capacity bladders (experienced surgeons only)
Vicious Cycle of IC

Bladder Insult

Potassium Leak into Interstitium

Epithelial Layer Dysfunction

 Activation of C-fibers and Release of Substance P

Mast Cell Activation and Histamine Release

More Injury
Conclusions

• Chronic Pelvic Pain requires patience, understanding and collaboration from both patient and physician
• Obtaining a thorough history is key to accurate diagnosis and effective treatment
• HL disease is pathologically and clinically distinct from NHL in IC/BPS/hypersensitive bladder patients
• Diagnosis is often multifactorial – may affect more than one pelvic organ
• All guidelines apply the fundamental principle of using the most conservative therapies
• Physical, pharmacological and surgical therapies are reserved for patients where previous therapies failed
Literature & Further reading

- EAU Guidelines on Chronic Pelvic Pain 2018
- Painful Bladder Syndrome (including interstitial cystitis) ICS committee 21
- The American College of Obstetricians and Gynecologists
- CUA guideline: Diagnosis and treatment of interstitial cystitis/ bladder pain syndrome
- *National Kidney and Urologic Diseases Information Clearinghouse*
- Pathomechanism of Interstitial Cystitis/Bladder Pain Syndrome and Mapping the Heterogeneity of Disease Int Neurourol J 2016;20 Suppl 2:S95-104
- Pbs/ic questionnaire survey for urologists International Painful Bladder Foundation
- Variations in bladder pain syndrome/interstitial cystitis (IC) definitions, pathogenesis, diagnostics and treatment: a systematic review and evaluation of national and international guidelines *International Urogynecology Journal* 22 April 2019
- Pathophysiology of interstitial cystitis International *Journal of Urology* - Wiley Online Library 30 May 2019