Chronic Pelvic Pain & Interstitial Cystitis: Pearls on Diagnosis & Treatment

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Disclosures

- **Research Support**
  - Boston Scientific
  - Abbvie
  - Vodafone

- **Stock Ownership**
  - Mobile ODT

- I will discuss the following off label use and/or investigational use in my presentation:
  - Medications for the treatment of interstitial cystitis: amitriptyline, hydroxyzine, heparin
Chronic Pelvic Pain: A Holistic Approach

- Re-defining the problem
- Simplifying the Differential Diagnosis
- Caring for patients in a busy practice
  - Pearls: History, exam & counseling
- Tools for Diagnosis & Treatment
Chronic Pelvic Pain Psychology

- Acute vs. Chronic Pain¹,²
- “Sick” role
- Drug abuse
- Family impact
- Bio-psychosocial Model

Chronic Pelvic Pain
Differential Diagnosis

- Gynecologic
- Gastrointestinal
- Urologic *
- Musculoskeletal
- Psychogenic
Chronic Pelvic Pain
Psychogenic Causes

- Depression
- Anxiety
- PMS/PMDD

- Feeling
- Enjoyment
- Eating
- Sleeping
Chronic Pelvic Pain
Gastrointestinal Causes

Irritable Bowel Syndrome

Horwitz NEJM 2001;344 (24): 1846-60
Chronic Pelvic Pain
Musculoskeletal Causes

- **Fibromyalgia**
  - Pain
  - Non-restorative sleep
- **Chronic Fatigue syndrome**
- **Trigger points**

Silver, DS, Wallace, DJ. Rheum Dis Clin N Amer. 28(2), 2002
Chronic Pelvic Pain
Gynecologic Causes

- Endometriosis*
- Adenomyosis
- Chronic Pelvic Infection
- Hydrosalpinx
- Leiomyomata uteri
- Adhesions
- Vulvar Vestibulitis (Vulvodynia)*
Chronic Pelvic Pain
Endometriosis

- Why is Severity Not Related to Pain?
- How does Endometriosis Cause Pain?
- How do Treatments Work?

Chonic Pelvic Pain
Anatomy & Terminology

- Nociceptive vs. Neuropathic Pain
- Allodynia vs. Hyperalgesia
- Visceral vs. Somatic Pain
- Convergence or “Cross-talk”
- Central Sensitization

Rogers RM, In Chronic Pelvic Pain: An integrated approach, Saunders 1998
Chronic Pelvic Pain: Could it be Bladder Related?
“The Bladder is in the Pelvis”

Lee Shulman, MD, FACOG
Northwestern University
IC / PBS: A Moving Target

- Inconsistent Nomenclature
- NIDDK criteria for IC research
  - 2/3 of “IC” patients would be missed
- “Official” definition of IC is changing
Chronic Pelvic Pain
Interstitial Cystitis/ BPS

Definition

- **Bladder Pain Syndrome**
  - Pain, Frequency +/- Urgency
  - Without obvious source

- **IC (ICD: 595.1/N-30.10)**
  - PBS with cystoscopic findings

ICS Definitions, 2002
ESSIC - Definitions Of PBS/IC And “Confusable” Disorders, 2005
NIDDK International Frontiers in PBS/IC Symposium, Oct 2006
IC / PBS: Epidemiology

- Prevalence: 1.2 - 9 million people\(^1\)
- \(\approx 8\) physicians before diagnosis\(^2\)
- \(\approx 5 - 7\) years to Diagnosis\(^2\)

\(\text{1. } J\text{ Urol }1999\text{ Feb;161(2):549-52}\)
\(\text{2. NIH-NIDDK IC Database Study } (J\text{ Urol }2000\text{ May;163(5):1434-9}).\)
IC symptoms range from mild to severe and may be attributed to other conditions in the early stages.

- Endometriosis/Vulvodynia “Misdiagnosis”
- Chronic Pelvic Pain (CPP)
- Advanced CPP Syndrome
- UTI “Misdiagnosis”
- Urge/Freq Failed OAB Tx
- Urethral Syndrome
- NIDDK IC
- Advanced IC
Common Causes of Flares

- Perimenstrual
- Sexual intercourse
- Diet / Stress
- Cystitis/vaginitis
- Allergies
The Role of Potassium in the Symptoms of Interstitial Cystitis
The Normal Bladder

- Bladder lumen
- Epithelial cells
- GAG layer/mucus
- Intracellular adhesion molecules
- Extracellular matrix

Slide courtesy of C. Lowell Parsons, MD
Chronic Pelvic Pain: Intervention Strategies

- Efficient Consultation Visits
- Make a Diagnosis of IC
- Effective IC Treatment
Chronic Pelvic Pain: Intervention Strategies

- Acknowledge the pain.
- Review of systems (pelvic)
- Assess psychosocial situation
- Clarify expectations (Good / Bad)
- Put the patient in charge
IC / PBS Diagnosis

History

- PUF Questionnaire
- Describe Pain
- Review of systems

# Pelvic Pain and Urgency/Frequency (PUF) Patient Symptom Scale

Circle the answer that best describes how you feel for each question.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
<th>Bother</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**SYMPTOM SCORE**  (1, 2a, 4a, 5, 6, 7a, 8a)

**BOTHER SCORE**  (2b, 4b, 7b, 8b)

**TOTAL SCORE**  (Symptom Score + Bother Score) =

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-6</td>
</tr>
<tr>
<td>2</td>
<td>0-4</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Never</td>
</tr>
<tr>
<td>5</td>
<td>Never</td>
</tr>
<tr>
<td>6</td>
<td>Never</td>
</tr>
<tr>
<td>7</td>
<td>Never</td>
</tr>
<tr>
<td>8</td>
<td>Never</td>
</tr>
</tbody>
</table>

- **1.** How many times do you void during waking hours?
- **2a.** How many times do you void at night?
- **2b.** If you get up at night to void, to what extent does it usually bother you?
- **3.** Are you currently sexually active? YES _____ NO _____
- **4a.** If you are sexually active, do you now have or have you ever had pain or urgency to urinate during or after sexual intercourse?
- **4b.** Has pain or urgency ever made you avoid sexual intercourse?
- **5.** Do you have pain associated with your bladder or in your pelvis, vagina, lower abdomen, urethra, perineum, testes, or scrotum?
- **6.** Do you still have urgency shortly after urinating?
- **7a.** When you have pain, is it usually—?
- **7b.** How often does your pain bother you?
- **8a.** When you have urgency, is it usually—?
- **8b.** How often does your urgency bother you?
Identifying Patients Is Important
PUF Highlights Voiding Issues

Circle the answer that best describes how you feel for each question.

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6</td>
<td>7-10</td>
<td>11-14</td>
<td>15-19</td>
<td>20+</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. How many times do you void during waking hours?

2. a. How many times do you void at night?
   
   b. If you get up at night to void, to what extent does
Identifying Patients Is Important
PUF Addresses Sexual Activity

Circle the answer that best describes how you feel for each question.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
</table>

3. Are you currently sexually active?
   YES _____   NO_____

4. a. If you are sexually active, do you now have or have you ever had pain or urgency to urinate during or after sexual intercourse?

   b. Has pain or urgency ever made you avoid sexual intercourse?
Identifying Patients Is Important
PUF Highlights Pain Issues

Circle the answer that best describes how you feel for each question.

5. Do you have pain associated with your bladder or in your pelvis, vagina, lower abdomen, urethra, perineum, testes, or scrotum?

6. Do you still have urgency shortly after urinating?

7. a. When you have pain, is it usually—?
   b. How often does your pain bother you?

8. a. When you have urgency, is it usually—?
   b. How often does your urgency bother you?
IC / PBS
Diagnosis

Physical Examination

- Abdominal Wall Tenderness
- Pelvic floor dysfunction
- Bladder tenderness

Abdominal Examination
Musculoskeletal Pain

Physical Examination

- Trigger Point Injections
- CPT: 64425, 64430

Equipment:
- Alcohol pad
- 10 ml syringe
- Lidocaine 1%
- 18 gauge needle
- 25-gauge (1 ½”) needles

Optional Diagnostic Tools

Cystoscopy with hydrodistention¹
   – Findings characteristic of IC

Potassium Sensitivity Test (PST)²-⁴
   – Test for abnormal bladder epithelial permeability

Intravesical anesthetics⁵-⁷

---

382 patients screened with PUF and PST

Results
- PUF score >15  84% positive PST
- PUF score <4  1.8% positive PST

Conclusion
- PUF appears to be a valid tool for detecting IC

Gynecologic Presentation of IC as Detected by Potassium Sensitivity

- 134 Patients Tested in 3 Sites
- 75% had Urologic Symptoms
- 85% had a (+) PST

Gynecologic Diagnosis and Potassium Sensitivity

### Case-Control Study

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>N</th>
<th>PST+ n (%)</th>
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</thead>
<tbody>
<tr>
<td>Pelvic pain</td>
<td>93</td>
<td>71 (76)</td>
</tr>
<tr>
<td>VV</td>
<td>45</td>
<td>37 (82)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>28</td>
<td>25 (89)</td>
</tr>
<tr>
<td>UFS</td>
<td>24</td>
<td>18 (75)</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>22</td>
<td>19 (86)</td>
</tr>
<tr>
<td>UTI (recurrent)</td>
<td>15</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
<td>11 (85)</td>
</tr>
<tr>
<td>IC</td>
<td>4</td>
<td>4 (100)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>244</td>
<td>197 (81)</td>
</tr>
</tbody>
</table>

UFS=urgency/frequency syndrome; VV=vulvovestibulitis/vulvodynia.

## Overall Potassium Sensitivity in Gynecologic Patients

### Case-Control Study

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>PST+ n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>244</td>
<td>197 (81%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Controls</td>
<td>47</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

The Incidence of IC in Patients with Vulvodynia as Detected by the PST

- 121 Patients tested
- 87% with urologic symptoms
- 84% sensitive to intravesical potassium

Protocol URG 101 -105

- A Phase 2a, Biphasic Adaptive Design Randomized, Double-Blind, Placebo-Controlled Multi-Center Single Dose Study to Evaluate the Safety and Effectiveness of URG101 Compared with the Individual Components - Lidocaine and Heparin in Subjects with Interstitial Cystitis/Bladder Pain Syndrome
Interstitial Cystitis Treatment

Overview

- “Self-care”
  - ICA: www.ichelp.com
  - ICN: www.ic-network.com
- Oral medication
- Intravesical therapy
- Hydrodistention
- Surgical management
Overlap of IC & Overactive Bladder (OAB) Symptoms

- Pain
- Wet
- Dry
IC/BPS
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

BASIC ASSESSMENT
- History
- Frequency/Volume Chart
- Post-void residual
- Physical examination

Confirmed or Uncomplicated IC/BPS

- Urinalysis, culture
- Cytology if smoking hx
- Symptom questionnaire
- Pain evaluation

Signs/Symptoms of Complicated IC/BPS

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

Dx Urinary Tract Infection

TREAT & REASSESS

FIRST-LINE TREATMENTS
- General Relaxation/ Stress Management
- Pain Management
- Patient Education
- Self-care/Behavioral Modification

SECOND-LINE TREATMENTS
- Appropriate manual physical therapy techniques
- Oral: amitriptyline, cimetidine, hydroxyzine, PPS
- Intravesical: DMSO, Heparin, Lidocaine
- Pain Management

THIRD-LINE TREATMENTS
- Cystoscopy under anesthesia w/ hydrodistention
- Pain Management
- Tx of Hunner’s lesions if found

FOURTH-LINE TREATMENTS
- Intradetrusor botulinum toxin A
- Neuromodulation
- Pain Management

FIFTH-LINE TREATMENTS
- Cyclosporine A
- Pain Management

SIXTH-LINE TREATMENTS
- Diversion w/ or w/out cystectomy
- Pain Management
- Substitution cystoplasty

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.

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Interstitial Cystitis Treatment

Self Help

- Dietary modification
- Bladder retraining
- Behavior modification
- Physical therapy
- Biofeedback/electrical stimulation
Interstitial Cystitis
Treatment

- Questionnaire-based data suggests:
  - Aggravators:
    - Citrus fruits, tomatoes, vitamin C, artificial sweeteners, coffee, tea, carbonated and alcoholic drinks & spicy foods
  - Relievers:
    - Calcium glycerophosphate (Prelief®) and sodium bicarbonate tend to improve symptoms.

Friedlenader, Shorter, Moldwin, BJU Int 2012; doi:10.1111/j.1464-410X.2011.10860.x
Interstitial Cystitis
Treatment

Oral Therapy

- Pentosan polysulfate
- Antihistamines
- Antidepressants / Neuroleptics
- Anticholinergics
- Urinary analgesics
- Narcotics/pain relievers
Potassium leak into interstitium

Bladder Insult

More injury

Mast cell activation and histamine release

Antihistamine therapy

Activation of C-fibers and release of substance P

Tricyclic therapy

Epithelial Layer Damage

Potassium leak into interstitium

Pentosan polysulfate sodium

Antihistamine therapy

Tricyclic therapy

Multimodality Therapy

Interstitial Cystitis

Slide courtesy of Robert J. Evans, MD
Oral Therapy

Pentosan polysulfate

- 100 mg orally t.i.d.

  - Mechanism of action
    - Strengthen bladder mucosa?
    - Antihistaminic properties?
    - Down regulate pain pathways?
Interstitial Cystitis
Pentosan Polysulfate Sodium

>50% Reduction in Pain After 3 Months


**Percentage of Patients**

- Placebo: 18% (n=74)
- Pentosan polysulfate sodium: 38% (n=74)

P = 0.005
Interstitial Cystitis
Pentosan Polysulfate Sodium

>50% Overall Improvement on PORIS*

*Assessing pain, urgency, frequency, nocturia.
†Completers.
Oral Therapy

*Tricyclic antidepressants*

- Amitriptyline 10 to 75 mg qhs
  - anticholinergic action
  - block reuptake of serotonin + NE
  - antihistaminic properties
Interstitial Cystitis Treatment

Oral Therapy

**Antihistamines**

- Hydroxyzine 10mg - 75mg qhs
  - Stabilize mast cells
  - Sedative

Valium

Starting dose 2-5 milligrams.
After 7-10 days may increase to 10 milligrams
Avg serum levels 0.29 ugm/ml
**Interstitial Cystitis Treatment**

**Intravesical Therapy**

- Silver nitrate 1855
- DMSO 1960s
- Heparin 1963
- Oxychloracine 1955
- BCG* 1955
- Botox

*experimental
The “Therapeutic Cocktail” for IC Patients in Severe Distress or After PST

Intravesical Therapy

- **Heparin** - 40k units\(^2,4,5\)
- **Lidocaine 2%** - 10 ml\(^1,2,3\)
- **NaHCO\(_3\) 8.4%** - 3 ml
- **Sterile H\(_2\)O** - 8 ml

**TECHNIQUE**

- General anesthesia
- 80 cm pressure 2”
- Refill and observe

**MECHANISM**

- Re-epithelialization?
- Mast cell degranulation?
- Neuropraxia?
Interstitial Cystitis Treatment

Surgical

- Neurostimulators
  - implantable (Interstim)
  - Percutaneous (Urgent PC)
- Ablation of ulcers
- Augmentation cystoplasty
- Cystectomy/Urinary diversion
Interstim

- 4 electrodes and extension cable
- Programmable impulse generator
- Sends mild pulses to sacral nerve

http://www.obgmanagement.com
Interstim

- **Urge Incontinence**
  Percent of patients achieving $\geq 50\%$ improvement$^1$

Neurostimulation

- Interstim
- Synergy®
- Restoreadvanced™
- Primeadvanced™
- Urgent PC¹,²

Urol Int. 2007;78(1):58-62
## Interstitial Cystitis
### Clinical & Business Practice

<table>
<thead>
<tr>
<th>Procedure</th>
<th>CPT</th>
<th>RVU/wRVU</th>
<th>Pmt Avg</th>
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</thead>
<tbody>
<tr>
<td>Instillations</td>
<td>51700</td>
<td>2.54/0.88</td>
<td>$129 (x9)</td>
</tr>
<tr>
<td>Ilioinguinal Block</td>
<td>64425</td>
<td>3.51/1.75</td>
<td>$247</td>
</tr>
<tr>
<td>Pudendal Block</td>
<td>64430</td>
<td>4.16/1.46</td>
<td>$239</td>
</tr>
<tr>
<td>PTNS</td>
<td>64566</td>
<td>5.56/0.60</td>
<td>$125 (x12)</td>
</tr>
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</table>
The Mast Cell in Inflammatory Arthritis

- The Future of IC Therapy:
- Tissue specific antihistamines
- Stabilization of mast cells
- Inhibition of mast-cell proteinases
- Use of agents that counter TNF-α

NEJM 348;17 2003
AQX-1125 → SHIP1 Pathway

- PI3K/SHIP1 pathway plays a key role in regulating cell migration and activation
- SHIP 1 is an alternate way of modulating the PI3K pathway
- SHIP1 expression restricted to hematopoietic derived cells - limits off-target toxicity
- SHIP1 activation redirects cellular PI3K signaling, rather than preventing it
- AQX-1125 has clinical potential in multiple inflammatory disorders such as asthma, COPD, pulmonary fibrosis, cystitis, etc.
Potential Targets for Gene Therapy

- Tachykinin NK-1 (SP) receptor
- Protein kinase C-γ isoform
- Cannabinoid receptors
- Vanniloid receptors
- Peripheral sodium channel
- Acetylcholine receptors
Interstitial Cystitis Diagnosis & Treatment Algorithm

Visit 1: 15-30 minutes
- PUF >10, Document Pain symptoms, Review of Systems, Exam
- Direct patient to learning resources

Visit 2: 15-30 minutes
- +/- PST, review disease, initiate therapy
- Diet, medicines, +/- instillations
- Enable patient management of disease

Visit 3: (6-12 weeks later)
- Review progress, adjust therapy
- Further enable patient management of disease

Visit 4-6: (3 months apart)

Chronic Pelvic Pain Summary

- Screen all patients with pelvic pain for IC
- CPP is “Visceral Hypersensitivity”
- Treat the Pain
- Consider Multi-Modality Therapy¹
- You Can Help These Patients!

Questions: kahn.bruce@scrippshealth.org

1. NEJM 352:1324-1334; 2005
Mobile Colposcope – Mobile ODT