State of the Art Diagnosis and Management of Interstitial Cystitis/ Painful Bladder Syndrome

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Appearance of Bladder on Cystoscopy and Hydrodistension

Normal Bladder
Interstitial Cystitis Bladder

Clinical Presentation
- Urinary Frequency
- Urinary Urgency
- Pelvic pain
  - Worse with bladder filling
  - Worse with intercourse
- Symptoms worse with stress
- Failed antibiotic therapy
- Failed anticholinergic therapy
- Bowel dysfunction
- Fibromyalgia
- Allergies
- Food sensitivities

Glomerulations
Not Pathomonomic for IC
- Furuya, 2007 AUA. Men
- Patients with “classic” IC symptoms and normal hydrodistension—What does that mean?

Definitions of IC/PBS
- Ulcerative IC is defined as symptoms of urinary frequency and/or urgency and pelvic pain with documentation of an ulcerative lesion in the bladder on cystoscopic evaluation. (only in 5-10% of the IC cases)

Hunner's Ulcer

**Definitions of IC/PBS**

Non ulcerative IC/PBS as defined by the International Continence Society (ICS) is the complaint of suprapubic pain related to bladder filling accompanied by other symptoms, such as increased daytime and nighttime frequency in the absence of proven urinary infection or other obvious pathology.


**ESSIC terminology for IC**

- European Society for the Study of IC/PBS (ESSIC) uses the name "bladder pain syndrome" = BPS
- They have developed a specific diagnostic grid based on the results of biopsy and cystoscopy with hydrodistension.
- In the US, concerns with this terminology was R/T billing/reimbursement issues for pts and the need for biopsy/cysto/hydrodistention for diagnosis

**ESSIC Classification**

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Cystoscopy with hydrodistention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

- Biopsy: glomerulations grade 2–3.
- Cystoscopy: glomerulations grade 2–3.
- Cystoscopy: glomerulations grade 2–3.
- Cystoscopy: glomerulations grade 2–3.
- Cystoscopy: glomerulations grade 2–3.
- Cystoscopy: glomerulations grade 2–3.

**Diagnosis**

- Rule out other infections or abnormalities
- Remember: No single definitive diagnostic measure for IC exists
- Patient history with urgency, frequency, and pelvic/bladder pain is key. The PUF questionnaire & ICSI may be helpful, but are not diagnostic.
- Cystoscopy with hydrodistention may help to confirm the diagnosis

**Differential Diagnosis**

- Recurrent UTI
- Urethral Stricture
- Carcinoma In Situ of the Bladder
- Bladder and/or Prostate Cancer
- BPH
- Neurogenic Bladder
- Vulvodynia
- Detrusor instability, OAB
- Pelvic Floor Dysfunction
- TB, Schistosomiasis
- Endometriosis
- Fibromyalgia

- Endometriosis
- Fibromyalgia
**IC: Theories of Pathogenesis**

- Mucosal barrier glycosaminoglycans (GAG) deficiency
- Mast cell activation
- Neurogenic inflammation
- Autoimmune Disease
- Pelvic Floor Dysfunction

**Role of GAG Layer in IC: Defective Urothelial Barrier**

**Role of Mast Cells in IC**

- Located predominantly in the detrusor layer and, to a lesser extent, in the lamina propria and the bladder epithelium
- Absence does not exclude diagnosis of IC
- Current stains underestimate mast cell number
- May justify use of antihistamines in treating IC

**Vicious Cycle of IC & Pelvic Pain**

**Chronic Pelvic Pain**

- 1 out of 9 women in the U.S has CPP
- More than 700,000 of these women have IC

**IC & Pelvic Floor Dysfunction**

- Approximately 70% of patients with IC have pelvic floor dysfunction
- Levator ani muscle myalgia can be a source of chronic pelvic pain.
Evidence for Central Up-Regulation

- Visceral pain syndrome (ie: IBS)
- The limbic system (modulates emotions and pain) is involved. Tested by UCLA using the startle blink reflex (SBR).
- 6 IC pts and 19 controls were tested by actual or anticipated electrical bladder stimulation.
- IC pts had significantly greater SBRs during non-imminent threat periods than controls. Likewise in anxiety and PTSD pts. On "High alert".

Stress Response-IC/PBS

- University of Iowa studies demonstrated IC/PBS patients had increased urgency and bladder pain in response to stress.
- IC/PBS patients exhibit abnormalities in their hypothalamic-pituitary-adrenal axis that alter their response to stress leading to neural upregulation and increased symptoms.

Translation:

- The brain pathway that responds to stress and releases hormone-like chemicals in our bodies is altered in people with IC/PBS.
- This causes the nerves to "flare" more easily, and bladder symptoms increase.

Basic Science Research

- In mice, cystitis induced pelvic pain. Interestingly, lidocaine instilled into the bladder or colon or both resolved this pelvic pain.
- This model supports the idea of neural cross-talk and also that the bladder is more vulnerable to this effect. One idea is that neuronal cross-talk is unidirectional.

Syndrome:

(syn-drnm; noun)
1. A group of symptoms that collectively indicate or characterize a disease, psychological disorder, or other abnormal condition.
Prevalence of Abuse

- 1 out of 6 women were either sexually or physically abused during their childhood.4

- Beaumont’s mailed survey study (2005) found that 36.9% of women with IC reported being abused vs. 22.4% of the controls. This was a significant difference (p=0.0).

Methodology of WISH Study

- Women with IC and pelvic pain were seen by a certified Women’s Health NP in the Beaumont Women’s Initiative for Pelvic Pain and Sexual Health (WISH) program.

- A comprehensive history and pelvic exam were done, including a levator pain assessment based on a patient-reported VAS (0-10) with the exam.

Results

Abuse:

- 55% of these women had been abused physically, sexually or emotionally.

- Mean number of years from onset of abuse to IC diagnosis = 24.4 years.

<table>
<thead>
<tr>
<th>Age at 1st Abuse</th>
<th>Child &lt; 14</th>
<th>Ages 14-19</th>
<th>Adult &gt; 20</th>
<th>Ongoing abuse &lt; age 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>59%</td>
<td>12%</td>
<td>29%</td>
<td>24%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Types of Abuse</th>
<th>Sexual</th>
<th>Physical</th>
<th>Emotional</th>
<th>Domestic Violence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>42%</td>
<td>45%</td>
<td>48%</td>
<td>39%</td>
</tr>
</tbody>
</table>
Conclusions

- Abuse appears to be more common in women with IC who have levator pain than those without levator pain (55% vs 36.9%).
- The pelvic floor may be a significant source of pain in women with IC.

WISH Data—Pelvic Surgeries

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number (%)</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime Pelvic Surgeries</td>
<td>64/87 (99%)</td>
<td>4.4 (range 0-21)</td>
</tr>
<tr>
<td>3 or more pelvic surg</td>
<td>20/87 (23%)</td>
<td></td>
</tr>
<tr>
<td>2 pelvic surgeries</td>
<td>15/87 (20.7%)</td>
<td></td>
</tr>
<tr>
<td>1 pelvic surgery</td>
<td>2/87 (31%)</td>
<td></td>
</tr>
<tr>
<td>Pelvic surg before dx</td>
<td>87/150 (53%)</td>
<td></td>
</tr>
<tr>
<td>Pelvic surg same yr as dx</td>
<td>13/150 (8%)</td>
<td></td>
</tr>
<tr>
<td>Pelvic surg after dx</td>
<td>50/150 (33%)</td>
<td></td>
</tr>
</tbody>
</table>

Prevalence of Sexual Dysfunction

43% WISH Program IC Pts

Clinical Exam Data

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total N=77</th>
<th>Number (%)</th>
<th>Pelvic surgeries*</th>
<th>Vulvar Pain Score averaged at 3 sites*</th>
<th>Pelvic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginism</td>
<td>45 (58.4%)</td>
<td>5.1</td>
<td>3.96</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Yes Vaginism</td>
<td>32 (41.6%)</td>
<td>3.2</td>
<td>.26</td>
<td>3.7</td>
<td></td>
</tr>
</tbody>
</table>

Adulthood

- % had streeme
- % with low of pain nites
- % with pain nites
Physical Exam is Very Important

- Abdominal exam to rule-out mass, inflammation
- Pelvic exam:
  - Vaginal pH, vaginal culture
  - Palpate urethra, r/o diverticulum
  - Assess prolapse
  - Consider postvoid residual
  - Determine trigonal tenderness
  - Palpate levator muscle complex
    - Assess degree of pain
    - Referred pain
    - Muscle spasticity
    - Trigger points
- Rectal exam
  - Prostate tenderness—in men
  - Levator tenderness

Palpation of Levator Muscles

Pelvic Floor Muscles

Arteries and Nerves of Perineum
Pelvic Floor—Urinary Symptoms

- More Frequency, Urgency, Pain
- Increased PFD needed to suppress Urgency/Frequency
- Slow relaxation, Hesitant, Painful Voiding

Source: UPPCRN PT Protocol V.1.0 Sept 2006

A Multidisciplinary Team Approach

- Patient
  - Urologists
  - NP/PAs/Nurses
  - Psychologists
  - Acupuncturists
  - Pain Clinics
  - Gynecologists/Primary Care
  - Physical Therapists
  - Nutritionists
  - Rheumatologists

IC/PBS Diagnosis & Treatment Algorithm

- IC/PBS symptoms
- Rule out other causes
- Educate: diet, stress, PT, FAD, yoga, acupuncture
- Follow up and support
- Referrals to ICA, CR, pelvic pain, or vulvodynia (non-bladder) organ
- Cystoscopy with Hydrodistention
- Chk for Ulcers, cancer
- Ulcerative IC—cauterize Ulcers and follow up
- IC/PBS: Continue PT, CBT, Neuromodulation
- Meds, intravesical txs, Pain clinic referral, research trial
- Follow up and support
- Referrals to ICA, ICN, pelvic pain, or vulvodynia (non-bladder) groups

Oral Meds Used for IC/PBS

<table>
<thead>
<tr>
<th>Drug</th>
<th>RCT?</th>
<th>% Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamine</td>
<td>Yes</td>
<td>42%</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Yes</td>
<td>48%</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>No</td>
<td>90%</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Yes</td>
<td>31%</td>
</tr>
<tr>
<td>Sodium pentosan polysulfate</td>
<td>Yes</td>
<td>33%</td>
</tr>
<tr>
<td>Quercetin</td>
<td>No</td>
<td>92%</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Yes</td>
<td>65%</td>
</tr>
</tbody>
</table>


DMSO (dimethylsulfoxide)
- One of only two drugs for IC/PBS approved by the Food and Drug Administration (FDA).
- Believed to be anti-inflammatory, analgesic and a bladder relaxant.
- IC symptoms may exacerbate for a few days following treatment, then improve.
- DMSO penetrates the bladder wall, and gives rise to the garlic-like taste and odor apparent for up to 72 hours after treatment.

Lidocaine
- used for pain, usually in combination with other drugs in a bladder instillation cocktail.
- There have been reports of improved absorption using alkalinized lidocaine and also with the use of electromotive drug administration (EMDA).

**Heparin**
- Believed to have an anti-inflammatory effect on the surface of the bladder wall.
- It may temporarily repair the GAG layer.
- It can take 2-3 months before it produces any effect.
- Can be used alone or in cocktails.

**Sodium hyaluronate (hyaluronic acid)**
- Is one of the naturally occurring substances in the glycosaminoglycan or GAG layer of the bladder wall.
- Believed to temporarily repair the damaged GAG layer.
- Reported to be well tolerated.
- Cystistat® has been approved for the temporary replacement of the GAG layer in the bladder and is commercially available in about 20 countries.

**Pentosan polysulfate sodium**
- Intravesical PPS along with oral med.
- Randomized, double blind study.
- 41 women with IC. 15% with ulcers.
- All on oral PPS bid; ½ with placebo (30ml saline) instillation, ½ with 400mg (2 caps) mixed with 30ml sterile ni buffered saline. Instillations 2x/wk.
  *Note: other meds/txs not mentioned as stable*
- **Results:** IC-SIPI decreased 46% in tx gr. At wk 12.
  - At wk 18 QOL in tx gr vs. placebo.
  - But frequency significant in placebo gr vs. tx gr.
- At wk 18 the proportion of “responders” was comparable in both groups

**Physical Therapy**
- Should be performed by a physical therapist specially trained in pelvic floor dysfunction related to these symptoms.
- Involves internal and external therapy.
- Biofeedback
- Very successful in improving symptoms pelvic pain, dyspareunia, urgency, frequency

**Randomized Multicenter Pilot Trial Shows Benefit of Manual Physical Therapies in the Treatment of Chronic Pelvic Pain**
MP FitzGerald,1,2 RU Anderson,2 CK Payne,2 J Potts,3 KM Peters,4 JQ Clemens,5

1 Loyola University Medical Center, IL 2 Stanford University School of Medicine, CA 3 Cleveland Clinic Foundation, OH 4 William Beaumont Hospital, MI 5 The University of Michigan Medical Center, MI

Dr. Clemens conducted this research while at Northwestern University.

**results**
- 126 patients with UCPPS were approached for study participation
- 68 (54%) agreed to participate and 47 were randomized
- 23 (49%) men (22 CP/CPPS) and 24 (51%) women (IC/PBS)
- All patients identified as eligible by their study physician were considered eligible by the study physical therapist
- Forty-four (94%) patients completed the study, with 2 patients withdrawing from the GTM treatment arm and 1 withdrawal from MPT treatment arm.
results

<table>
<thead>
<tr>
<th></th>
<th>GTM</th>
<th>MTP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Randomized</td>
<td>24</td>
<td>23</td>
<td>47</td>
</tr>
<tr>
<td>Total (p=0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>5 (21%)</td>
<td>13 (57%)</td>
<td>18 (38%)</td>
</tr>
<tr>
<td>Non-responders</td>
<td>19 (79%)</td>
<td>10 (43%)</td>
<td>29 (62%)</td>
</tr>
</tbody>
</table>

Female (p=0.02)

<table>
<thead>
<tr>
<th></th>
<th>GTM</th>
<th>MTP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>6 (55%)</td>
<td>4 (33%)</td>
<td>10 (45%)</td>
</tr>
<tr>
<td>Non-responders</td>
<td>13 (21%)</td>
<td>6 (55%)</td>
<td>23 (45%)</td>
</tr>
</tbody>
</table>

Male (p=0.45)

<table>
<thead>
<tr>
<th></th>
<th>GTM</th>
<th>MTP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>3 (8%)</td>
<td>8 (67%)</td>
<td>11 (57%)</td>
</tr>
<tr>
<td>Non-responders</td>
<td>10 (20%)</td>
<td>4 (33%)</td>
<td>14 (43%)</td>
</tr>
</tbody>
</table>

summary

- Such a trial was feasible
- Manual therapies were acceptable to patients
- Therapists were able to adhere to standardized treatment protocols
- Patients randomized to receive internal and external MTM had more favorable outcomes than those receiving GMT

conclusion

- Our initial encouraging results suggest that myofascial physical therapy methods offer meaningful clinical benefit to patients with UCPPS
- Further validation of the efficacy of MPT is needed, by studying a larger group of patients treated by a greater number of therapists in a greater number of centers.

Interferential Stimulation

- Interferential stimulators use a fixed carrier frequency of 4,000 Hz per second and a second adjustable frequency of 4,001-4,400 Hz per second to impact large muscle fibers where the current intersects.
- Interferential Stimulation differs from TENS because it allows a deeper penetration of the tissue with more comfort (compliance) and increased circulation.
- These frequencies interfere with the transmission of pain messages at the spinal cord level.
- This deep tissue penetration can be adjusted to stimulate parasympathetic nerve fibers for increased blood flow.

Pelvic Floor Stretching Exercise

Behavioral Therapy

- Guided Imagery
- Cognitive behavioral therapy
- Stress Reduction
- Increase water intake (dilute the urine)
- Dietary modifications
- Yoga/meditation
Sacral Neuromodulation for the Treatment of Refractory Interstitial Cystitis

Effects of Sacral Neuromodulation on the Central Nervous System

- PET scans of the brain done with sacral neuromodulation stimulation.
- The perigenual anterior cingulate cortex, pons and hippocampus areas responded to stimulation felt by pt.
- With high stimulation, there was increased activity in the left dorsal ant. cingulate cortex. This suggests less pain inhibition due to the decreased activity in this brain area.

Reproduced with permission from Dr. KM Peters

Percutaneous Tibial Nerve Stimulation (PTNS)

- PTNS is a type of Neuromodulation used to treat urgency and frequency of urination.
- Scientific studies show that 2 out of 3 individuals treated with PTNS see a reduction in their symptoms.
- PTNS may work even when other therapies have failed.

Bladder function is regulated by nerves at the base of the spine – the sacral nerve plexus

With PTNS, an impulse is sent along the tibial nerve to the sacral nerves

Benefits of PTNS

- Non-surgical/cost effective
- Low risk
- Covered by many insurances
- No need to stop/change medications during treatment.
- More than half of the people using PTNS had improved urgency or frequency of both.
- 2007 research* showed that the # of mast cells decreased in rats with IC w/ tibial nerve electrical stimulation. More research is needed.


What new research is being done?

**AUA 2008 Research Presentation**

**Benefit of Manual PT for CPP**
- Randomized, multicenter NIH funded
- 45 pts had either internal and external PT or a full body Western massage by the PT.
- CPP pts (M & F) <3 yrs with + levator pain
- 10 weekly 1 hour sessions given

**Results**: 57% of PT group vs 21% massage had a positive response.

**Limitations**: lack of power, massage not done by certified massage therapist, no blinding.

Peters KM et al. UPPCRN group. AUA 2008, Plenary session.

**AUA 2008 Research Presentation**

**Effects of Different Enkephalin Treatments on Bladder Pain:**
- Female rats with induced bladder pain
- Enkephalin given systemically (it’s a specific-type of opioid receptor agonist)
- HSV-mediated gene transfer with the precursor of enkephalin was also used.

**Results**: Both methods decreased bladder pain in rats
- These therapies targeting bladder afferent pathways be useful in humans with IC, and lack systemic effects.


**AUA 2008 Research Presentation**

**Intravesical Alkalized Lidocaine (PSD597)**
- Offers immediate and sustained relief from the symptoms of IC/PBS
- Multicenter (19), RCT, double-blind
- 99 women, 3 men with IC from US and Canada
- Daily instillation: PSD597 or placebo for 5 consecutive days.
- In alkalized lidocaine instillation
  - Use lidocaine solution 1st, followed by sodium bicarbonate solution. Creates non-ionic bioavailable lidocaine.

**Results**: 30% responders with drug; 10% placebo

Nickel JC, Wyllie MG, Henry RA. AUA 2008 podium session 5--#180

**AUA 2008 Research Presentation**

**Pharmacokinetics of Liposomes after Intravesical Administration**
- Liposomes are phospholipid bubbles filled with water, adhering to a surface.
- Liposomes stay put in the bladder for 24 hrs.
- Safe
- May act by coating the bladder lining, thus decreasing irritative symptoms.


**2008 SUFU Updates on IC/PBS**
Childhood voiding dysfunction (CVD) is related to pelvic disorders in adult women.

- 344 twin sisters surveyed.
- Results: a significant association exists between DVD and UI in adults.
- Those with CVD had worse scores on questionnaires assessing: PFD, depression, IC/PBS, sexual function.


Pilot study of Acupuncture for IC

- 7 newly diagnosed women w/ IC/PBS (sx >9 mos).
- Acupuncture q wk x 12 wks w/ e-stim.
- Questionnaires done pre- post-treatment.
- Results: 19% improved QOL; ICSI-PI improved @ 22%; freq., urge, pain improved (UDI-6), no significant improvement in sexual function.


Botox Update

- Results are variable.
- Botox for IC/PBS improved sx in 9/13 pts after intravesical treatment for a mean of 4 mos.
- Botox 200 units give to 10 IC/PBS pts at Cleveland Clinic did not show any significant change in objective or subjective outcomes.


Botox

- 15 pts study done in Italy—reported in 2008 that Botox A is effective for in the short-term (3-5 mos). Without additional Botox, symptoms recurred.
- Note: *9/15 subjects had impaired detrusor contractility 1 month after BTX. 3 subjects had to self-cath due to high post-vd residuals—1 continued to self-cath for 5 mos.


Botulinum toxin A (Botox)

- injected into bladder wall and trigone at 26 sites
- 83% pts improved: day freq ↓ 50%
- urgency ↓ 43%; pain ↓ 81%; nocturia ↓ 75%.
- 2 pts had temporary hematuria
- 3 had residuals =100ml
- 1 man had retention

At 6 mos. 24% had pain recur and had Botox again

The majority of IC/PBS is probably not related only to the bladder because:

- IC/PBS pts used guided imagery 2x/day x 8 wks. Results: Significantly less pain and urgency. 45% GRA responders in our RCT.
- Neuromodulation helps decrease frequency, urgency and oftentimes pain.
- Physical therapy can improve s/sx.
- Oral/intravesical agents do not work on everyone with IC/PBS—they should if it’s a GAG layer issue only.

**Liposomes**

- Dr. Chancellor’s team is working with liposomes, a capsule type of delivery system that can be used for medications to improve efficacy and absorption into the bladder.
- Liposomes alone decreased urinary frequency induced by KCL. They may enhance the urothelium’s barrier.

**EMDA—Electromotive drug administration**

- Facilitates the transport of water soluble drugs by the use of an electrical current.
- Oxybutynin, local anesthetics have been administered intravesically using EMDA.
- Side effect: Transient skin erythema at abd. electrode site. No fatal effects.

**Miniaturo™-I**

- Electrostimulator from Israel used now for stress or urge incontinence.
- Placed subcutaneously in the pubic area, with a lead placed adjacent to the urethral sphincter.
- A low electrical charge stimulates the muscle and nerve to perform their natural function.
- The programmer allows individual patients’ parameters to be set or modified remotely.
- Each patient can turn the Miniaturo on and off, using a personal safety magnet.

**NIH—MAPP grant**

- Multi-disciplinary Approach to the study of Chronic Pelvic Pain Research Network.
- Starting in 2008—multi-center
- IC/PBS-men and women, fibromyalgia, IBS, CFS (may include vulvodynia, migraines)
- All proposals include epidemiology, phenotyping, basic science components.
So, exactly what is IC? PBS? BPS?

65 years later..... We still don’t know!!

Resources/Referrals
- Interstitial cystitis association: www.ichelp.org
- Interstitial cystitis network: www.ic-network.com
- American Psychological Association www.apa.org
- International Painful Bladder Foundation: http://www.painful-bladder.org
- For Pelvic Pain: www.pelvicpain.org
- For Vulvodynia: www.nva.org or www.vulvapainfoundation.org
- www.urgodtoday.com for a summary of current research
- www.clinicaltrials.gov for current research studies

Beaumont Women’s Initiative for Pelvic Pain and Sexual Health
The WISH Program
Interstitial Cystitis/PBS
Pelvic Pain
Guided Imagery
Vulvodynia
Female Sexual Function
Research
248-551-3565
in the Detroit area, in Michigan