Objectives

- Review the epidemiology and impact of interstitial cystitis/painful bladder syndrome
- Discuss the neuropathophysiology of IC/PBS
- Discuss diagnostic criteria for IC/PBS
- Describe a practical office based approach
- Explore treatment options

Interstitial Cystitis/Bladder Pain Syndrome

- Bladder disorder hallmarked by pelvic pain and/or urinary urgency/frequency
- Prevalence may be as high as 6% in women and 2% in men
- Very high prevalence among women with other "genital" pain syndromes
  - Vulvar dysesthesia: 82%
  - Endometriosis: 86%

Bladder Pain Theories: Glycosaminoglycan Layer
Bladder Pain Theories

- Impaired glycosaminoglycan layer
- Potassium leak
- Activation of C-fibers
- Pain, inflammation

Cystoscopy and Hydrodistension

Bladder Pain Theories

- Only 60% of women with IC/PBS have normal bladder mucosa
- Bladder mucosal lesions characteristically associated with IC are observed in asymptomatic women
  - Blinded study where 5 urologist shown 185 cysto images; could not distinguish asymptomatic women from symptomatic

Etiology IC/PBS

- Local bladder inflammation and lesions of IC can be induced via CNS
  - Pseudorabies virus inoculated into mouse CNS (can not travel retrograde)
  - Central neurogenic inflammation which spreads to shared spinal segments
  - Neurogenic inflammation travels down spinal nerves
  - Mast cell activation in lamina propria
Etiology IC/PBS

• IC/PBS can be an entirely centrally mediated disease in animal models

Neuroanatomy: Sacral Spinal Cord

Large number of afferents and efferents converge over relatively few segments

Etiology IC/PBS

• Signs of systemic immune activation
  – 40% report hypersensitivity/allergy
  – 100 times more likely to have inflammatory bowel disease
  – 30 times more likely to have SLE
  – Sjogren’s syndrome 0.6% general population, 28% in IC/PBS

Etiology IC/PBS

• Bladder
• Other pain condition which induces neurogenic inflammation and pain/inflammation spreads by cross talk in CNS
  – Endometriosis, IBS
• Systemic immune dysfunction
Central Nervous System Plasticity and Chronic Pain

- Dorsal horn reorganization
- Abnormal release neurotransmitters centrally and peripherally
- Up regulation of glutamate receptors
- Membrane re-organization
- Genomic changes
- Autonomic dysfunction
- Loss of descending inhibitory control

Let's Add Depression Into The Mix

- Depression affects neurotransmitters involved in chronic pain
  - e.g. substance P, norepinephrine
- Depression affects inflammatory response
  - Markers of chronic inflammation, such as Interleukin-6, are elevated post-immune challenge in depressed patient but not in controls

Hormonal Factors

- Female predominance in many pain syndromes
- Many pain conditions have cyclic pain
- Cyclic pain DOES NOT imply endometriosis, only that there is a hormonal component

Office Evaluation

- Find the bother factor
  - Pain
  - Voiding dysfunction
- Objective data
  - Voiding diary
  - 24 hours with volumes to discourage retrospect completion
- Record pain scores very visit
FUNCTIONAL PAIN SCALE

<table>
<thead>
<tr>
<th>PAIN SENSATION</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Pain</td>
</tr>
<tr>
<td>1-2-3-4</td>
<td>Functional</td>
</tr>
<tr>
<td>5-6-7</td>
<td>Uncomfortable</td>
</tr>
<tr>
<td>8-9</td>
<td>Severe</td>
</tr>
<tr>
<td>10</td>
<td>Unbearable</td>
</tr>
</tbody>
</table>

The actual feeling of the pain you are experiencing (stabbing, throbbing, ache, burn, tightness)

PHQ-9

Office Evaluation

- PHQ-9
- Functionality
  - What do they do during day
  - Disability
- Locus of control

Office Evaluation

- Quality of pain
- Wake at night with pain or urge or both
- Incontinence
  - Stress or urge
- Exacerbation/remitting factors
- Other pain syndromes
- Hematuria

Myofascial Pain

- Important co-morbidity
- Muscle spasm, myalgias, or both
Musculoskeletal Exam

Pelvic Exam:
- Evidence of other pain syndromes
  - Endometriosis
  - Vulvodynia

Pelvic Exam: Internal

Diagnostics: The Bladder

**KCl test**
- Inexpensive office procedure
- Patients with IC have increased epithelial permeability
- Positive in 80% of women with CPP
- Up to 25% false positive and false negatives may occur
- Painful
- ? May predict response to pentosan polysulfate?

**Cystoscopy hydrodistension**
- Glomerulations, terminal hematuria, ulcers, bladder capacity
- Can miss up to 60% of patients using NIDDK criteria
- 20-30% of patients get therapeutic benefit
- Cystoscopic findings do not correlate with pain
- Ablation of ulcers
- General anesthetic
**Beware of Chart Lore**

- Microbiology of suspected UTIs
- Surgical and cystoscopy
- Pathology reports
- Medications prescribed, filled etc.

**Bladder Pain/Irritative Voiding Symptoms**

<table>
<thead>
<tr>
<th>First Line</th>
<th>Second Line</th>
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<tbody>
<tr>
<td>PT</td>
<td>Adjuvant medications</td>
</tr>
<tr>
<td>Bladder training</td>
<td>Disease specific drugs</td>
</tr>
<tr>
<td>Elimination diets</td>
<td>Intravesical therapy</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Hydrodistension</td>
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<tr>
<td>Pyridium</td>
<td>Percutaneous tibial nerve stimulation</td>
</tr>
<tr>
<td>Prelief</td>
<td></td>
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<tr>
<td>Antispasmodics</td>
<td></td>
</tr>
<tr>
<td>Supplements</td>
<td></td>
</tr>
</tbody>
</table>

**IC: Nonpharmacologic Therapy**

- Elimination diets
  - Avoiding acidic foods, chocolate, alcohol, caffeine, spicy foods, artificial sweeteners, and carbonated beverages
  - Some patients can benefit greatly for both voiding habits and pain; some patients have one or two particular triggers
- Adequate water intake
- Patients can get lists, cookbooks etc from web, such as [www.ica.org](http://www.ica.org)

**IC: OTC Therapy**

- Prelief, pH choice
  - Reduces acid in food
- Azo/Pyridium
  - Bladder analgesic
Physical Therapy

- Biofeedback for urge suppression
- Trigger avoidance
- Body scans
- Treatment of pelvic floor muscle spasm improves pain in 70% of women with IC
- Most effective therapy for OAB

Behavioral Therapy vs Oxybutynin for Urge and Mixed Incontinence

Pentosan Sulfate Sodium

- 100 mg po tid
- 200 mg po bid
- Repair GAG layer
- Heparin analogue
- By 6 months improvement in pain scores may approach 60%
- 84% excreted unchanged in urine

Hormonal Suppression

- Consider if menstrual exacerbation of pain
- Does not imply etiology beyond and effect of estrogen, progesterone, or prostaglandins (or other hormone) on pain
Therapy for OAB

- Anticholinergics
- Antimuscarinics
- 5-HT/NE reuptake inhibitors

Pharmacologic Therapy vs. Behavioral Therapy

- Randomized placebo controlled trial of 197 women over the age of 55 with urge incontinence or mixed urge and stress incontinence
  - Placebo
  - Oxybutynin
  - Behavioral management (trigger avoidance, urge suppression, pelvic floor muscle exercises)


5HT-NE Reuptake inhibitors: Duloxetine

- SNRI
  - Increases stimulation of pudendal motor neurons in the spinal cord at Onuf’s nucleus
  - Rhabdosphincter of the urethra increases tone and resistance in the urethra
- Major side effect is nausea which occurs early in the course of treatment and diminishes with time
- Approved for the treatment of depression (Cymbalta®)

PTNS

- 12 weekly 30 minute sessions with monthly maintenance sessions
- Minimally invasive, well tolerated
- Subjective improvement: 50-64%
- Objective improvement: 33-50%
  - >/= 50% improvement
- CPT 64555
Episodic Therapy: Antispasmodics

- Single agents
  - Belladonna 0.3-1.2 mg qid
  - Hyoscyamine (Levsin) 0.125-0.25 mg qid
  - Clidinium bromide 2.5-5.0 mg qid
  - Glycopyrrolate (Robinul) 1-2 mg tid
  - Dicyclomine (Bentyl) 10-20 mg qid
- Combined sedatives and antispasmodics
  - Clidinium and chlordiazepoxide (Librax) 2.5 and 5.0 mg qid pm
  - Butabarbital and belladonna (Butibel) 15 mg and 1.5 mg qid pm
  - Hyoscyamine, atropine, and phenobarbital (Donnatal) 0.1 mg/0.02 mg/16 mg qid pm

IC: Intravesical Therapy

- Dimethyl sulfoxide (DSMO)
  - FDA approved
- Heparin
- PPS
- Lidocaine
- Sodium hyaluronate (Cystistat)

Adjuvant Medications: TCAs

- Doses lower for pain; start at 10-25 mg gradual escalation, max 100 mg
- Side effects anticholinergic and sedation (caution in elderly)
- Contraindications: narrow angle glaucoma, cardiac conduction problems
- Drug interactions
- Inexpensive and qday dosing
  - Antidepressant action not required
  - Tertiary amines amitriptyline, imipramine
    - More anticholinergic effects, more effective for pain
  - Secondary amines nortriptyline, desipramine

Adjuvant Medications: AEDs

1st Generation
- Carbamazepine
- Phenytoin
- Valproic acid

2nd Generation
- Gabapentin
- Topiramate
- Lamotrigine
- Oxcarbazepine
- Zonisamide
- Levetiracetam

- First Generation
  - Drug interactions
  - Effects on WBC, LFTs
  - Affect cytochrome p450
- Rapid discontinuation can potentiate seizure activity
- Some produce electrolyte disturbances
- Sedation, dizziness most common side effects
- Treat mood disorder
### Botulinum Toxin Therapy

- Cystoscopic guided intravesical injection
- Not FDA approved
- Irreversible ACh blockade
- Doses vary: 100-300 units
- Onset of action 5-7 days
- Duration, ? Unknown, 12 weeks or longer
- Complications
  - Bleeding, UTI, bladder perforation
  - Reflux
  - Retention/high residuals, need for intermittent catheterization

### Neuromodulation

- Exact mechanism of action unknown, but most hypotheses favor modulation of afferent signals
- Patients with IC, or pain in distribution of S3/S4
- Successful percutaneous trial and very careful selection criteria for implantables
- Even with extensive counseling and prolonged trials can have a 20% placebo response rate
- Success for pelvic pain ranges from 30-80%

### Sacral Neuromodulation

![Image of sacral neuromodulation](image)

### Summary

- Many therapies
- Don’t underestimate role of depression
- Return to functioning is a more realistic goal than making a patient pain free
- Integrated approach has best outcome