Interstitial Cystitis: An Update
What is the Bottom Line??

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“I have no idea what this diagnosis is (or means), what causes it, nor what the best management method is”
anon (me)

The Evolution of a Definition
IC has had sequential definitions

NIDDK criteria are too restrictive and exclude too many pts (Hanno PM, J Urol 1999)

Painful Bladder Syndrome –PBS as defined by the ICS (Abrams P, NUU 2002):
  suprapubic pain with bladder filling
  increased urinary frequency and urgency (nocturia)
  absence of definable pathology

What is the patient group?

OAB Dry
Pelvic Pain No LUTS
Demographics
9/10 patients are female
Age of onset is middle decades (40’s)
- Strong correlation with childhood voiding dysfunction (Hx of recurrent UTI’s)
- Persistence of childhood voiding dysfunction
- Occurrence post pelvic surgery
- Discreet relationship to UTI
- Constellation of associated symptoms

Associated Symptoms
- Low back pain
- Fibromyalgia
- Headache
- Migraine syndromes
- Bowel dysfunction
- Irritable Bowel Syndrome
- Depression
- Neurologic Disease
- Reflex Sympathetic Dystrophy
- At least 30% concordance

Natural History
- Significant short-term symptomatic variability
- Unknown long term course
- Relapsing / Remitting
- Exacerbated by
  - UTI
  - Ingestant foods or drinks
  - Cyclic or menstrual association
  - Stress (omnipotent / omnipresent)

Goals of Evaluation
- Reasonable
  - Assess relationship of symptoms to lower urinary tract
  - Exclude the excludable

No definitive diagnostic (nor exclusionary) tests
- Ergo: Do not definitively diagnose
Differential Diagnosis

- UTI
- Carcinoma
- Neurogenic Disease (MS)
- Obstruction
- Prior toxin exposure (XRT)
- Anatomic lesion (ie urethral diverticulum)
- Etc
- Etc

What must be done

- History
- Physical examination (include focused examination)
  - Pelvic examination in women
  - Digital rectal examination in men
  - Assessment of pelvic floor
- Urinalysis
- Urine culture

What else do I Do

- Cytology (risk factors)
- Symptom index
  - VAS
  - O’Leary, Sant
- Voiding log/diary
- Cystoscopy (usually at time of hydrodistention)
- Urodynamics

Symptom Scores

- Not diagnostic due to lack of specificity
- Quantify bother
  - At baseline
  - Post therapy
- Scores most commonly used
  - ICSI/ICPI (O’Leary MP, Urology sup 5A 1997)
  - PUF score (Parsons CL, Urology 2002)
Voiding Diary

*Time /volume chart (possibly with urge scale)*

*Best is 1 day (Mazurick CA, J Urol 2000)*

*Why*
- Exclude polyuria
- Establish baseline
- Component of physiotherapy

Role of Cystoscopy/Hydrodistention

*At best uncertain*
- Not a diagnostic test
- Possible treatment (35% symptom improvement)

*Utility*
- Exclude malicious lesions (with biopsy if indicated)
- Identify focal mucosal lesions (ie “ulcers”*
Caveats with Cystoscopy
Anesthetic capacity indicative of functional "reserve"
- Loss of capacity correlates with defunctionalization
- Profound loss (< 200cc) consider diversion

Presence of ulcers (est 10% of PBS population)
- Possible role or fulguration or other thermotherapy

Should Biopsy Be Performed?
Not necessary for diagnosis
No pathologic finding correlates with syndrome
- Mast cells have no predictive value
- Mucosal denudation associated with ulcers
- Non-specific inflammatory infiltrate
- Vascular deficiency
- Role of hypoxia

What Does an Ulcer Mean?
Seen usually in older patients
Different pathophysiology
Associated with:
- Decreased bladder capacity
- Increased inflammation on biopsy
- Respond to thermotherapy
  - Laser fulguration (Rofeim O, J Urol 2001)
  - TUR resection (Peeker R, Int Urogyn J 2000)

Optional Investigations
- Urodynamics
- Potassium sensitivity test
- Pelvic imaging (usually ultrasound)
Urodynamics in IC

- Problematic testing methodology in this population
- Abnormal sensation
  - Urge at $\leq 150$ cc
  - Capacity $\leq 350$ cc
- Compliance abnormalities imply possible Detrusor Overactivity
- Exclusionary by NIDDK
- However many patients have this finding

Potassium Sensitivity Testing

- Uncertain role
- No longer considered a standard diagnostic test
- Not sensitive; about 25% of IC pts are neg
- Not specific; positive in other disorders
- Not recommended by consensus conferences
  - Hanno P, Int Urogyn J 2005
  - Van der Merwe J, Eur Urol Today 2006
  - Parsons CL, J Urol 1998

Antiproliferative Factor (APF)*

- Peptide structure – noted in IC patients
- Epithelial growth inhibitor
- No screening test yet available

- Keay SK, PNAS 2004 and Zhang CO, J Urol 2005

Flexible Algorithm

- Allows treatment to be individualized
- Links diagnosis to required work-up
- Unique patient oriented approach
- Evidence basis is largely lacking
Principles of Therapy

*No unified approach*
- Initiate simple RX
- Often sequential therapy is needed
- Combination therapy if a cornerstone
- Changes often necessary
- Cognizance of “flare” phenomenon

*Include pain management*

IC/PBS Treatment Principles (cont.)

*High degree of emotional overlay*
- Anger/hostility
- Perceived lack of motivation on the part of prior providers

*Exacerbations and stress association*

*Consider additional in-clinic support*

Conservative Therapy

*Dietary changes*
- Restricted diet
- Urinary alkalinization

*Bladder re-training*

*Adjunctive Rx (e.g. heat, ice, exercise, stress reduction)*
**Diet Considerations**

ICA diet is highly restrictive
Individualize
Usual offenders are acidic products

Alkalinize

Unique patients affected by unique irritants

**Conservative Treatments**

Heat, ice, exercises (results vary among patients)

Stress reduction

ICA is a great resource:
Phone: 800-HELP-ICA
Web site: www.ichelp.org
Email: icamail@ichelp.org

**Complementary Therapy**

Multiple options
Aloe vera
Quercitin (Katske F, Tech Urol 2001)
Chondroitin sulfate
Glucosamine (Theoharides TC, Int J Immunopath Pharm 2005)
Methylsulfonylmethane (DMSO$_2$)

Controlled data lacking
Some data for hyaluronic acid

**Diagnosis / Hydrodistention**

↓

Multimodal oral therapy / stepped if possible

↓

Multimodal intravesical therapy

↓

Salvage therapies
**Treatment**

*Multimodal oral therapy*
- Antihistamines
- Anticholinergics
- Systemic Analgesic – not narcotic
- Local analgesics
  - ? Surface restorative agent

**Rx IC Treatments**

*FDA approved to treat IC*
- Intravesical 50% DMSO
- Oral pentosanpolysulfate

*Off-label use, better than placebo:*
- Cimetidine
- Amitriptyline

**Not Proven In Controlled Trials**

*Commonly used, off-label for IC*
- Oral hydroxyzine
- Intravesical heparin and “cocktails”

*Investigational, off label use for IC*
- Montelukast
- Calcium channel blockers
- Gabapentin
- Immunosuppression

**Pentosanpolysulfate (PPS)**

*FDA approved*

*Mechanisms of action:*
- Replace deficient bladder glycoconjugates
- Bind and inactivate pro-inflammatory urine components (Sadhukhan PC, J Urol 2002)
- Inhibit mast cell histamine release (Chiang G, J Urol 2000)
- Various anti-inflammatory effects
Dosing and Side Effects

100 mg tid; dose escalation ineffective (300 tid)
(Nickel JC, Urology 2005)

3-6 months needed for maximum benefit

Side effects:
- Nausea/diarrhea
- Alopecia
- Weak Anticoagulant activity
- Liver enzyme abnormalities

Placebo-Controlled Trials of PPS

PPS better than placebo:
- Parsons CL, J Urol 1987
- Mulholland SG, Urology 1990
- Parsons CL, J Urol 1993

PPS not significantly better:
- Holm-Bentzen M, J Urol 1987
- Sant GR, J Urol 2003

Multimodal Use

4 arms (response rates in parentheses):
- PPS and hydroxyzine (40%)
- PPS and placebo (23%)
- Placebo and hydroxyzine (28%)
- Two placebos (13%)

Combining arms to compare PPS vs. no PPS:
- 18% if no PPS
- 34% if PPS (p=0.064)

Amitriptyline

Evidence mostly open label (van Ophoven A, J Urol 2004)

Possible mechanisms:
- $H_1$ receptor blocker
- Anticholinergic
- Sedation (improves sleep/nocturia)
- Decreased nociception in CNS
Clinical Use of Amitriptyline

Usual dose: 25-75 mg po qHS
Ways to improve morning lethargy:
  - Start with 10 mg and increase gradually
  - Consider nocturnal use
Side effects:
  - Constipation
  - Palpitations, tachycardia (Caution in elderly)
  - Weight gain

Randomized Trial of Cimetidine for Painful Bladder Disease

36 patients with chronic inflammation on biopsy
No symptom changes in placebo group
Cimetidine group improved in:
  - Suprapubic pain (p=0.009)
  - Nocturia (p=0.006)
  - Total symptom score (p<0.001)

Cimetidine for Painful Bladder

Randomized study included only patients with bladder inflammation on biopsy, so same good results may not apply to other patients

Mechanisms unknown but may include:
  - Anti-inflammatory (H₂ receptors on T cells)
  - Stabilize mast cells (bind to H₂ receptors)

Hydroxyzine: Proposed Mechanisms

H₁ receptor blocker
Inhibits mast cell secretion and activation
  - Theoharides TC, Urology sup 5A, 1997
Sedative effect improves sleep, nocturia
Hydroxyzine: Clinical Trial Results

Effective in an open-label trial
(Theoharides TC, Urology suppl 5A, 1997)

Randomized trial (Sant GR, J Urol 2003)
- Hydroxyzine, PPS, both or placebo
- 20% responded if no hydroxyzine
- 31% responded if hydroxyzine
  (p=0.26)

Clinical Use of Hydroxyzine

Start with 10 mg qHS, increase gradually:
- Ideally to 50 mg
- Lower dose if 50 not tolerable
- Up to 100 if 50 not effective

Symptom relief can take 2-3 months
Sedation is the only significant side effect, good for nocturia

Intravesical Therapy

DMSO cocktail
- Bicarbonate
- Heparin
- Lidocaine
- Hydrocortisone

BCG

RTX

DMSO

Superior in two controlled trials
Saline placebo (Perez-Marrero R, J Urol 1988)
BCG (Peeker R, J Urol 2000)

Proposed mechanisms of action in IC*
- Analgesic, altered bladder innervation
- Free radical scavenger, anti-inflammatory
- Collagen dissolution

*1988 study and Rossberger J, Scan J Urol Nep 2005
Timetable for DMSO Treatments

Start with 6 weekly treatments

Maintenance
  Variable time tables from weeks to months
  Preferential to minimize exposure

Yearly ophthalmologic exam (risk of cataracts)

Extremely surface active agent

DMSO Cocktails

Comparator evidence lacking

Cocktail formulations:
  40 mg methylprednisolone + 5000 u heparin
  (Ghoneim GM, World J Urol 1993)
  100 mg hydrocortisone, 5000 u heparin, 50 ml NaHCO₃
  (Parkin J, Urology sup 5A, 1997)
  10 mg triamcinolone, 10,000 u heparin, 44 ml NaHCO₃
  (Pontari M, Urology sup 5A, 1997)

Other Cocktail Mixtures

  20 ml 0.5% bupivacaine
  100 mg hydrocortisone
  10,000 u heparin
  80 mg gentamicin
  40-50 ml NaHCO₃ (add this last)

Parsons CL, Urology 2005
  8 ml 1% lidocaine (use 2% if 1% fails)
  3 ml 8.4% NaHCO₃
  40,000 u heparin

Heparin

Glycoconjugate replacement

Effects include:
(Cassuto J Acta Anes Scand 2006)
  inhibit complement activation
  enhance barrier function of endothelium
  inhibit leukocyte migration
  reduce reactive oxygen metabolites
  inhibit pro-inflammatory cytokines
  inhibit eosinophil cationic proteins
**Intravesical Heparin for IC**

First use: 20,000 u q day at first, less often in remission (Parsons CL, Urology sup 5A, 1997)

Now: usually used as part of an intravesical “cocktail” with some or all of the following:
- local anesthetic
- sodium bicarbonate
- steroid

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**Intravesical Instillation**

Small catheter (10-12 Fr)

2% lidocaine jelly

Use viscous or liquid anesthetic agent

Short dwell time (15-20 minutes maximum)

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**Salvage Therapy**

*Alternative pharmacotherapies*

- Neuromodulation
  - Acupuncture
  - Interstim

- Bladder replacement
  - Only for failure of bladder storage

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**Investigational Treatments**

- Montelukast
- Gabapentin
- Immunosuppression
Open-Label Trial of Montelukast (Leukotriene Receptor Blocker)

10 IC patients with mast cells on bladder biopsy*

Significant improvements in:
- Pain score (47 to 20, p=0.006)
- Day voids (17.4 to 12, p=0.009)
- Nocturia (4.5 to 2.8, p=0.019)

(Bouchelouche K, J Urol 2001)

Gabapentin

Role in neuropathic pain
- Diabetic neuropathy (Backonja M)
- Post-herpetic neuralgia (Rowbotham M)

Possible role in PBS

Effective in small open-label trials

Systemic Steroids

Early studies had variable results and many side effects, so essentially abandoned

In two recent open-label trials with ulcer type IC, approx 50% with response
- Soucy F, J Urol 2005
- Hosseini A, J Urol 2004
  (bladder nitric oxide decreased in responders)

Cyclosporine A

23 patients who met NIDDK criteria
  all failed hydrodil (most had other Tx also)
  mean age 61 (minimum 49)

Results:
- 20 of 23 pain-free
- Significantly improved frequency and awake bladder capacity

Sairanen J, J Urol 2004
Sacral Nerve Stimulation

*Not approved for PBS*

*Anecdotal effect for “urgency-frequency”*

*Outcomes best for urinary symptoms*

*NOT FOR PAIN*

Sacral Nerve Stimulation References

**Percutaneous trials**
- Maher CF, J Urol 2001
- Chai TC, Urology 2000
- Whitmore KE, Int Urogynecol J 2003

**Long-term studies**
- Comiter CV, J Urol 2003
- Peters KM, BJU International 2004
- Elhilali MM, Urology 2005

Surgical Intervention

*Rarely indicated*

*Cystectomy and orthotopic bladder: controversial*

*Do not to Augmentation cystoplasty*

*Cystectomy and ileal loop is best (only for defunctionalized capacity)*