Painful bladder syndrome

‘Interstitial cystitis’ first described by Skene in 1887

Complex of voiding symptoms attributable to a functionally reduced bladder capacity

ICS prefers term painful bladder syndrome:

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 (Abrams 2002)

ICS definition emphasises central role for painful bladder filling

Demographics

Incidence estimated at 230 per 100,000 Finnish population (Leppilahti 2005)
Female: male 10:1
Median age 40-50 yrs
Caucasians > blacks

Presentation

Bladder pain, usually accompanied by urgency, frequency, nocturia
Typically subacute development, with relatively rapid deterioration in symptoms, followed by more gradual worsening or plateau
Spectrum of severity from mild urgency-frequency syndrome (no fibrosis, little pain) through to severe bladder pain with decreased bladder capacity (due to fibrosis)

Aetiology

Cats provide reasonable animal model for PBS/IC
Many theories postulated; probably multifactorial
(i) Chronic infection
   Either persistent (minimal evidence to suggest ongoing infection)
   or leading to an autoimmune reaction (raised ANA often seen)
(ii) Reflex sympathetic dystrophy
   Increased sympathetic upregulation in PBS/IC
(iii) Neuroinflammation
   Abnormal neurogenic mechanism leading to upregulation of sensory nerve inputs and ‘neuroinflammation’
(iv) Defective glycosaminoglycan layer
   Popularised by Parsons
   Reduced GAG layer allows leakage of urine into urothelium.
   Toxic molecules (?potassium) within urine then depolarise sensory nerves and muscle, leading to pain and urgency. As potassium is an endogenous waste product, explains lack of inflammation
(v) Antiproliferative factor
   Frizzled 8 protein produced by bladder uroepithelial cells.
   Inhibits heparin binding EGF important for epithelial repair.
   Urinary levels increased in patients with PBS/IC, reduced after hydrodistension. Good sensitivity/specificity for identification of PBS/IC
Pathology
Glomerulations = pinpoint petechial mucosal haemorrhages
Hunner's ulcer = discrete area of mucosal ulceration seen in 6-8% IC cases
Biopsies
Typically show very little evidence of chronic inflammation; occasionally chronic inflammatory cells in lamina propria
Mucosa thin – often only 2-4 cell layers thick (vs. 7-8 normally), but most biopsies performed after hydrodistension artifact
Mast cells seen in ~30% of biopsies. Mast cell degranulation thought to increase epithelial permeability and sensitive nerve endings
Cystectomy specimens
80% have only epithelium, with occasional muscle fibres and BV, with thinning of perivesical fat. Widespread collagenous replacement of bladder wall is not typically a feature

Diagnosis
Interstitial cystitis is a diagnosis of exclusion
Other causes of IC-type voiding symptom complex
Infective
Bacterial, viral, fungal, schistosomal or TB cystitis
Sexually transmitted infections
Inflammatory
Radiation or cyclophosphamide cystitis
Amyloidosis
Neoplastic
CIS, other bladder Ca, urethral cancer
Anatomic Cystocele, urethral obstruction

NIDDK criteria
National Institute for Diabetes, Digestive and Kidney Diseases
Developed criteria for identification of PBS/IC patients in 1998
Used to identify patients for research criteria, not for diagnosis
High specificity but low sensitivity – misses up to 2/3 patients
NIDDK criteria only designed to identify severe group
Inclusion criteria (2)
- Bladder pain or urgency AND
- Glomerulations* or Hunner’s ulcer
Exclusion criteria (18)
- Child < 18 yrs
- Duration < 9 months
- Daytime frequency < 8
- Absence of nocturia
UDS (3)
- Maximum cystometric capacity >350ml
- Absence of urge with bladder filled to 150ml
- Phasic contractions on filling
Infective (5)
- Symptoms relieved by antibiotics/anticholinergics
- Recent confirmed UTI or prostatitis
- TB cystitis
- Active gentital herpes
- Vaginitis
Inflammatory (2)
- Radiation cystitis
- Cyclophosphamide or other chemical cystitis
Neoplastic (2)
- Bladder tumour (benign or malignant)
- Uterine, Cx, vaginal or urethral cancer
Anatomic (2)
- Urethral diverticulum
- Bladder or ureteric calculi

* distension of bladder under anaesthesia at pressure of 80-100cm water for 1-2 minutes. May be repeated x1 before assessment. Glomerulations must be diffuse (in all 4 quadrants) for diagnosis

Investigation
History
- Exclude alternative diagnosis
  IC more common in those with Hx atopy, IBS, fibromyalgia
Vaginal examination
- Tender bladder base anteriorly in >90% (Parsons)
- Urethral diverticulum
- Cystourethrocoele
- Vaginal discharge
Painful bladder syndrome

MSU
Additional urine investigation if TB or schistosomiasis suspected

Cytology
Parsons found no positive cytology in >3000 cases)

Urodynamics
EUA, cystoscopy, diagnostic hydrodistension and bladder biopsy
Bladder biopsy controversial, but finding of mast cells in biopsy may consolidate diagnosis (20% non-ulcer patients; 65% ulcer patients)

Potassium chloride test
0.4M intravesical KCl a/w reproduction of pain
However multiple problems
Supraphysiologic [K+] 10x natural concentration of K+ in urine (40MEq/l)
Poor sensitivity Misses 25% NIDDK patients!
Poor specificity positive in UTI, radiation cystitis, prostatitis, pelvic pain

Urinary antiproliferative factor (APF; Susan Keay, U of Maryland)
94% sensitive (NIDDK positive patients) and 79% specific (Keay 2001) – promising but more studies needed

Management (from Fall 2008: best evidence)
May be conservative, oral, intravesical or surgical

(a) Conservative
   (i) Bladder drill
   (ii) Avoidance of precipitants
       Approximately 50% experience spontaneous temporary remission in symptoms

(b) Oral therapy
   (i) Amitryptylline
       Best study van Ophoven (2004). PC-RCT showing significantly improved symptom score, pain and urgency with self titrated amitryptylline 25-100mg. Follow-up open label study showed 64% response rate at 20 months (mean dose 55mg). Side effects generally drowsiness and other anticholinergic effects
   (ii) Pentosan polysulphate (Elmiron; 150 mg bd)
       Heparinoid polysaccharide
       Overall some benefit identified in RCTs. Largest study Nickel (2005; n=380) showed ~50% response rate at 6 months with 300mg a day. Side effects mild.
   (iii) Cimetidine
       H2 receptor blocker. Best study Thilagarajah 2001; 65% response rate with 400mg bd. Usage limited by side-effects (N+V, diarrhoea, impotence, gynaecomastia, long Q-T interval) and drug interactions (phenytoin, warfarin, theophylline)
   (iii) Hydroxyzine
       H1 histamine receptor antagonist – blocks release of histamine from mast cells
Initial reports of > 90% response with 25-50mg dosage. Only one third of patients respond in PC-RCTs. May be better in subpopulation with pre-existing atopy

(iv) Cyclosporin A
Significantly better when compared in RCT vs. PPS but side effect profile worse

(c) Intravesical therapy

(i) Dimethyl sulphoxide (DMSO)
Chemical solvent believed to have analgesic, anti-inflammatory, collagenolytic and muscle relaxant effects
Best study Perez-Marrero (1988). PC-RCT showing improved symptom score, pain score and UDS data in 93% pts receiving DMSO (? regime/dose get paper) vs. 35% on placebo. High relapse rates of 59%; ? reduced by monthly instillations of intravesical heparin (same group 1993).

(ii) Sodium hyaluronate
Aka. Cystistat
Response rate ~70%

(iii) Chondroitin sulphate

(iv) Pentosan polysulphate

(d) Surgical
No RCTs available to support surgical management of IC

(i) Hydrodistension
Reported 50-60% initial remission rate with Helmstein technique but relapse rate high. Largest trial Glemain 2002 - no placebo group, hydrodistension under epidural for 3 hours a/w 33% efficacy at 1 year. Few centres perform Helmstein due to risk of bladder rupture and necrosis. Short-duration (5 mins ~@ 80-100cm water) hydrodistension reportedly as effective as long-term but effects very short-lived (< 6mo.) has any effect.

(ii) TUR Hunner's ulcer
Peeker 2000 - 90% improvement in Sx following TUR of ulcer, 40% had Sx relief at 3 yrs; Malloy 1994 largest trial of laser fulguration - improved Sx in 33-78% of patients, effects most marked in ulcer group.

(iii) Botox therapy
Promising but unrandomised data so far

(iv) Sacral nerve modulation
Peters et al 2004 (n=34) with permanent implant, > two thirds improved symptom and pain score

(v) Augmentation cystoplasty
Supraretinal cystectomy and enterocystoplasty.
75% pain free; ileocaecal a/w lower ISC than ileal; small capacity (< 250ml) had better functional outcome than larger capacity

(vi) Urinary diversion
Cystectomy and urinary diversion for intractable cases - more effective in patients with capacity < 400 (Lotenfoe 1995).
Urethral syndrome
Signs and symptoms of UTI without positive urine cultures.
More than one study has reported that in patients with signs and symptoms of UTI, negative cultures are found in ~50% (Gallagher 1965; Hamilton-Miller 1994). May represent one of the many causes of irritative LUTS or indeed mild IC. Continued usage of the term urethral syndrome discouraged.