BLADDER PAIN SYNDROME

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Pain Syndromes

- Difficult to define
- Difficult to diagnose
- Difficult to treat
- Difficult for the patient to
  - Accept
  - Understand
  - Cope
  - Live any sort of normal life

Bladder Pain Syndrome

Bladder disorder consisting of a wide variety of symptoms resulting from non-infective inflammation of bladder

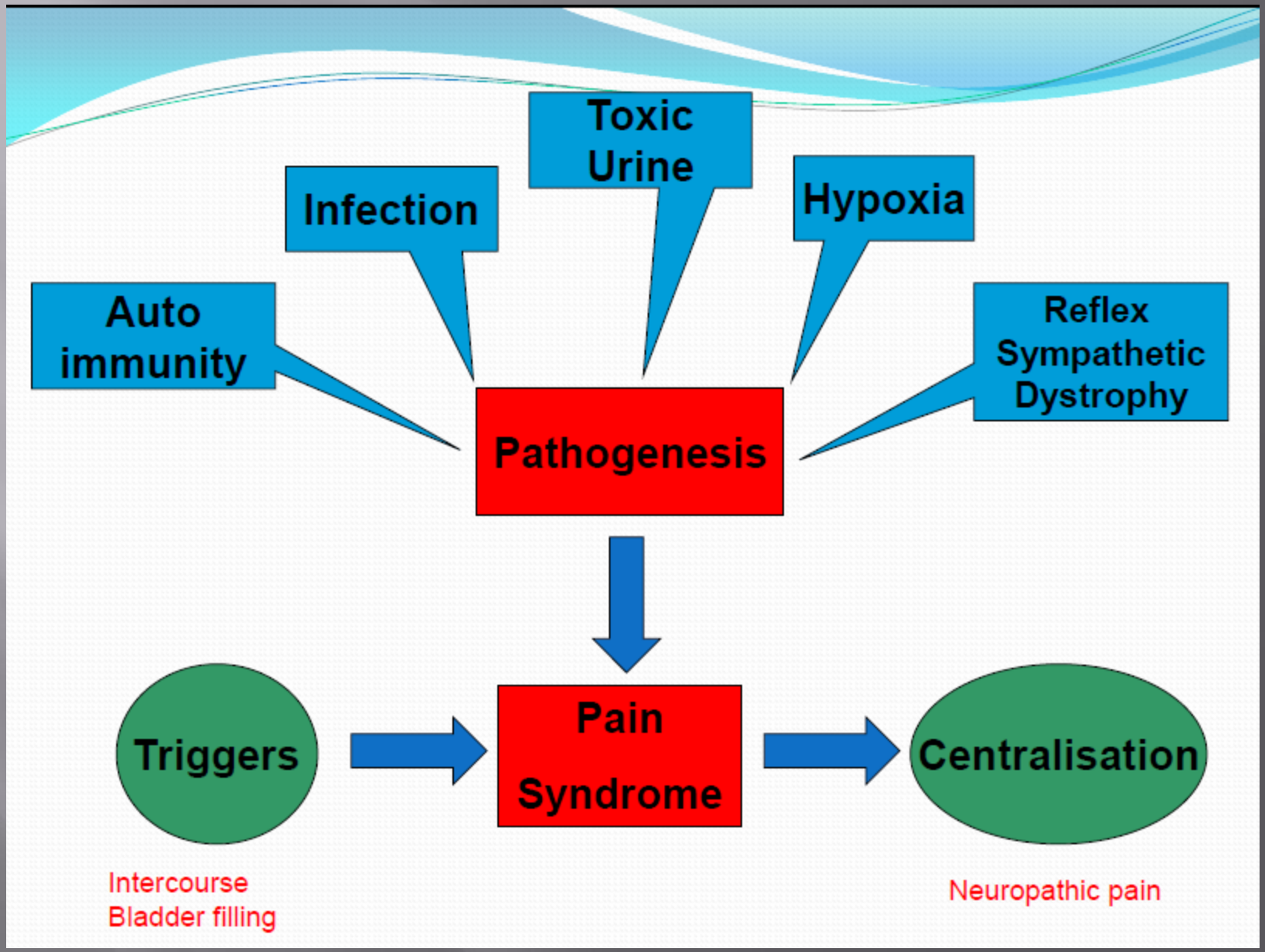
Characterised by pain, urgency, frequency and nocturia

A syndrome is a diagnosis of exclusion

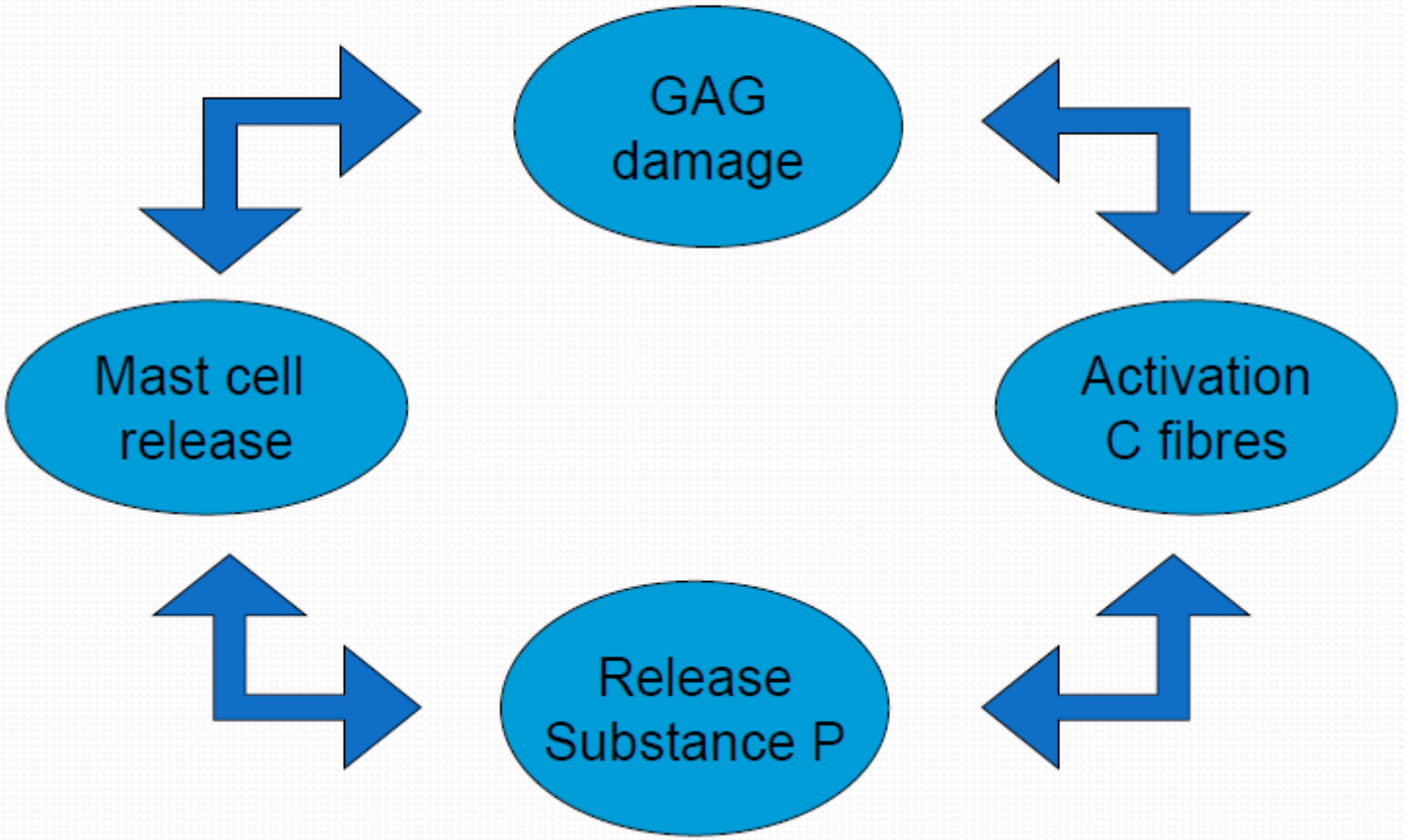
Based on a symptom complex

Common features

- Chronic pain phenotype
- Central Sensitivity Syndromes
- Fibromyalgia, tension headache, Dysmenorrhoea,
- Myafascial pain, Urethral syndrome, IC etc.
- Catastrophizing
- Management of pain > cure


Toxic Urine
Infection
Hypoxia
Auto immunity
Reflex Sympathetic Dystrophy
Pathogenesis
Triggers
Pain Syndrome
Centralisation
Intercourse
Bladder filling
Neuropathic pain

Aetiology of Bladder Pain



Interstitial Cystitis

Historical Prospective

Skene (1887)

- an inflammation that has "destroyed the mucous membrane partly or wholly and extended to the muscular parietes”

Hunner (1915)

- reported on eight women
- with suprapubic pain, frequency, nocturia, and urgency lasting an average of 17 years
- red, bleeding areas he described on the bladder wall came to have the pseudonym "Hunner's ulcer."

Hand (1949)

- first comprehensive paper

Skene AJC: Diseases of the Bladder and Urethra in Women. New York, William Wood, 1887
Hunner GL: A rare type of bladder ulcer in women: Report of cases. Boston Med Surg J 1915;172:660–664
Hand JR: Interstitial cystitis: Report of 223 cases (204 women and 19 men). J Urol 1949;61:291–310

Table 16–1. NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK) DIAGNOSTIC CRITERIA FOR INTERSTITIAL CYSTITIS

To be diagnosed with interstitial cystitis, patients must have either glomerulations on cystoscopic examination or a classic Hunner's ulcer, and they must have either pain associated with the bladder or urinary urgency. An examination for glomerulations should be undertaken after distention of the bladder under anesthesia to 80–100 cm of water pressure for 1 to 2 minutes. The bladder may be distended up to two times before evaluation. The glomerulations must be diffuse—present in at least 3 quadrants of the bladder—and there must be at least 10 glomerulations per quadrant. The glomerulations must not be along the path of the cystoscope (to eliminate artifact from contact instrumentation). The presence of any one of the following may indicate interstitial cystitis:

1. Bladder capacity of greater than 350 cc on awake cystometry using either a gas or liquid filling medium.
2. Absence of an intense urge to void with the bladder filled to 100 cc on cystometry or a maximum cystometric flow rate of 30 to 100 cc/min.
3. The demonstration of phasic involuntary bladder contractions on cystometry, unless [illegible]
4. Duration of symptoms less than 9 months.
5. Absence of nocturia.
6. [illegible] antibacterial agents, urinary antiseptics, anticholinergics, or antispasmodics.
7. A frequency of urination, while awake, of less than 8 times per day.
8. A diagnosis of bacterial cystitis or prostatitis within a 3-month period.
9. Bladder or ureteral calculi.
10. Active genital herpes.
11. Uterine, cervical, vaginal, or urethral cancer.
12. Urethral diverticulum.
13. Cyclophosphamide or any type of chemical cystitis.
14. Tuberculous cystitis.
15. Radiation cystitis.
16. Benign or malignant bladder tumors.
17. Vaginitis.
18. Age less than 18 years.

From Wein A, Hanno PM, et al: Interstitial cystitis: An introduction to the problem. In Hanno PM, Staskin DR, Krane RJ, Wein AJ (eds): Interstitial Cystitis. London, Springer-Verlag, 1990, pp 13–15.

60% of patients deemed to have IC by experienced clinicians would not have met NIDDK research criteria

Associated Conditions

- Irritable Bowel Syndrome 38.6%
- Fibromyalgia 17.7%
- Chronic fatigue syndrome 9.5%
- Worse sleep dysfunction, depression, anxiety, stress and Catastrophizing

Nickel et al, 2010, JUrol; 184, 1358-63 Nickel et al, 2010, JUrol; 183, 167-72

Interstitial Cystitis NIDDK 1987

Pain, Frequency, Urgency, Nocturia

- Max Cystometric Capacity < 350 ml
- No bacterial infection
- No response to ANTIBIOTICS
- At least 18 years old !!!
- Greater than 9/12 history

False positive 10%
False negative 40%
Hanno ICDB 1999

Diagnosis

- Exclusion of serious disease
- Quantification of problem

Voiding diary
Questionnaire

Bladder Pain Syndrome BPS Interstitial Cystitis IC

Basic Assessment

- History and Examination
- Bladder Diary Chart
- Flow Test and Post Void Residual
- Urinalysis/MSU
- Pain Evaluation
- Imaging US/ CT/ MRI

Exclusion of serious disease

Differential diagnosis of pain

- Urological

Bacterial urine infection
STD
Fistula
Stones
Bladder cancer
Radiation cystitis
Bladder endometriosis
TB

- Drugs

Cyclophosphamide
Tiaprofenic acid

- Gynaecological

Endometriosis
Fibroids
PID
Ovarian pathology
Salpingitis
Pelvic adhesions ??

Bowel
Constipation
IBS
IBD
Appendicitis
Hernia

Psychosocial

- Depression
- Sexual Abuse
- Substance Abuse
- Eating Disorder
- School Avoidance
- Need for contraception?

Signs/Symptoms of Complicated BPS/ IC

- Urinary Incontinence/OAB → urodynamics
- Haematuria → CTU + flexi cystoscopy
- GI signs/ symptoms → GI/colorectal referral
- Gynaecological signs/ symptoms → gynae referral / MRI pelvis

Quantification of problem

Questionnaires

Bladder Pain / Interstitial Cystitis Symptom Score (BPIC- SS)

IC Symptom Index (O'Leary Sant)

Generic QOL scores
SF 36
SF 12
EuroQol

Kings Health Questionnaire

Bladder Pain / Interstitial Cystitis Symptom Score (BPIC- SS)

Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) Version 3.0, 23/Sept/10, UK English

Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS)

To be completed by study staff

When answering the following questions, please think about the **PAST 7 DAYS**

	Never	Rarely	Sometimes	Most of the time	Always	SCORE
1. In the past 7 days when you urinated, how often was it because of **pain** in your **bladder**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
2. In the past 7 days, how often did you **still** feel the need to urinate **just after** you urinated?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
3. In the past 7 days, how often did you urinate to **avoid pain** in your **bladder** from **getting worse**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
4. In the past 7 days, how often did you have a feeling of **pressure** in your **bladder**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
5. In the past 7 days, how often did you have **pain** in your **bladder**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	

	Not at all	A little	Somewhat	Moderately	A great deal	
6. In the past 7 days, how **bothered** were you by **frequent urination during the daytime**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
7. In the past 7 days how **bothered** were you by **having to get up** during the **night** to urinate?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	

8. Select the number that best describes your **worst bladder pain** in the past 7 days

No bladder pain										Worst possible bladder pain	
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	

Add the scores for each question together to give a total BPIC-SS score **TOTAL SCORE =**

Total score ranges from 0-38. A total score can only be calculated if ALL questions are completed by the patient

BPIC-SS (GB-eng) 16APR2015 FINAL

Potassium Sensitivity Test
(Parsons et al 1998)

Theory

- Urothelial leakage of potassium
- Predict response to Pentosan Polysulphate

Technique

- Slow INTRAVESICAL infusion
- Slow infusion water plus KCl 15% (20mmol/10ml)
- 60 ml water flush
- Measure strong urgency - stop filling
- Rescue Lignocaine + Heparin instillation

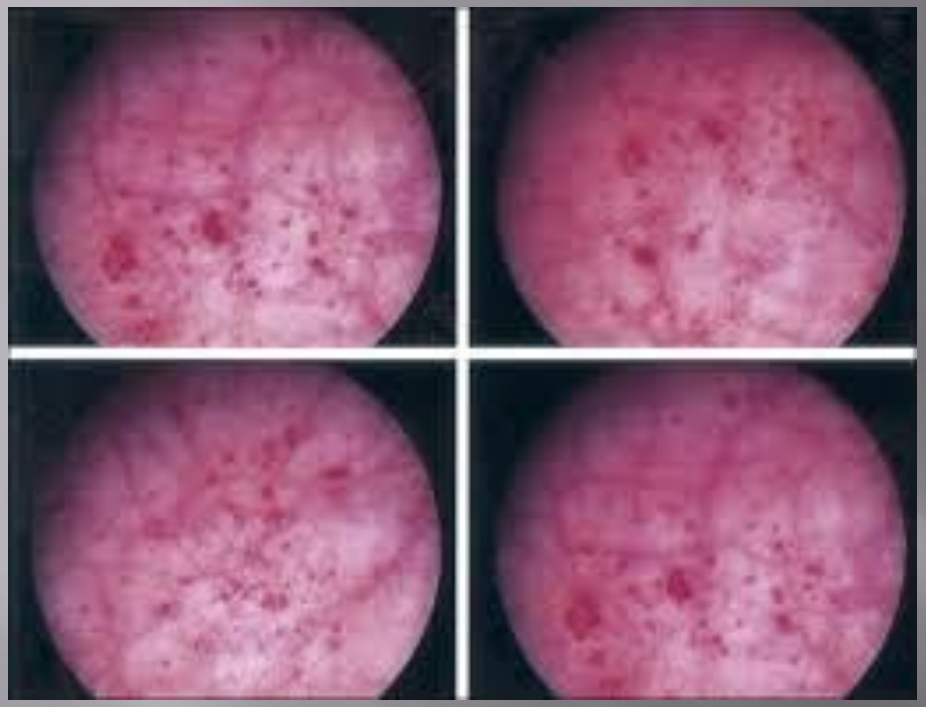
Correlation with IC

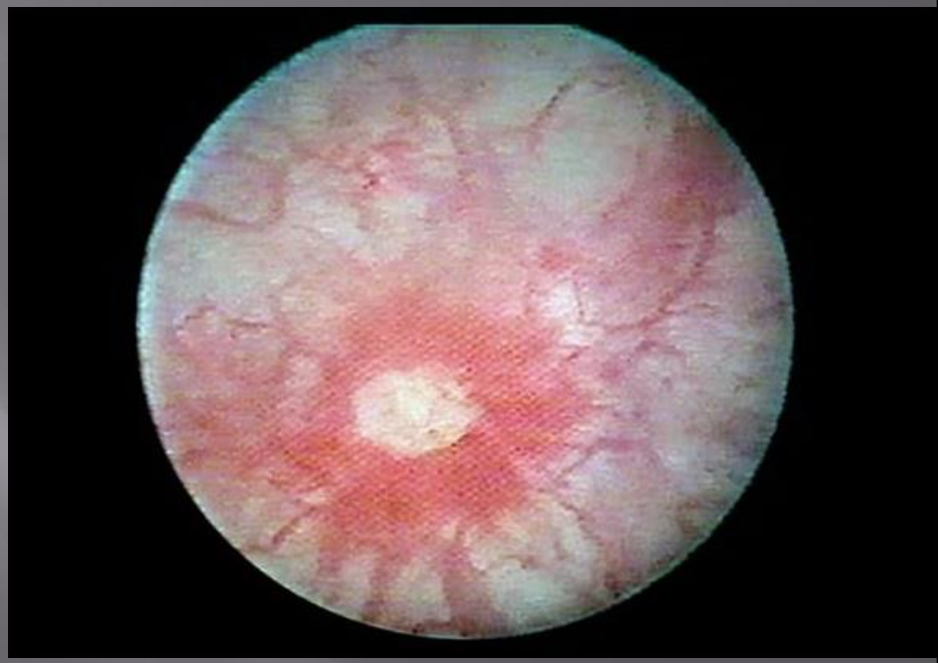
- 5% IC positive
- False positives for DO, Radiation Cystitis, Bacterial cystitis
- Poor discriminating power

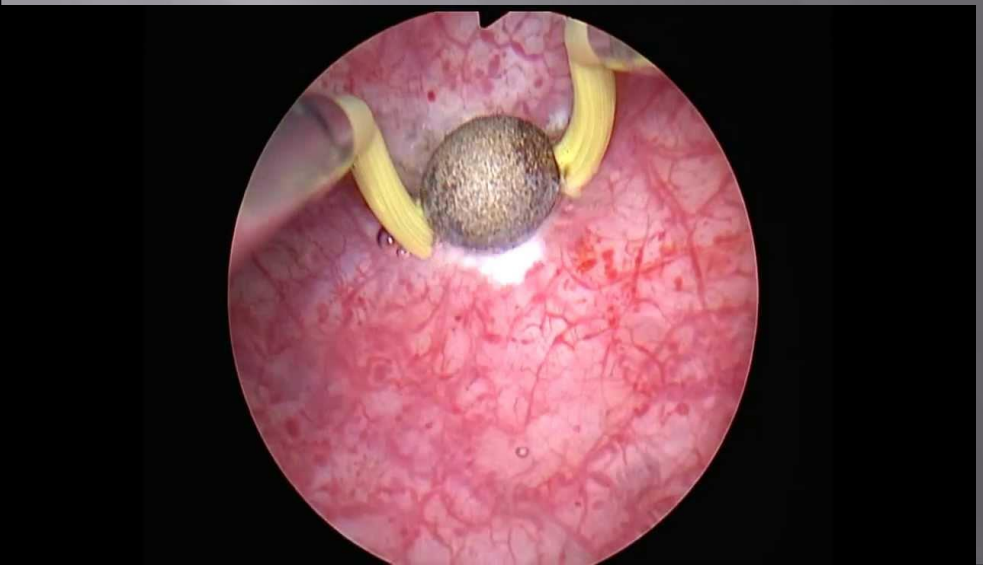
(Mishra 2004)

PBS/UPS/IC Investigations

- Cystoscopy/Cystodistension and Biopsy
  - Cystodistension at 60cmH20 above SP
  - May be therapeutic in 60% for 6-12 months
  - Occasionally worsens
- Ulcers
- Distress under anaesthesia on distension
- Reduced bladder capacity
- Post distension glomerulations
- Biopsy: absence of malignancy +/- presence of increased mast cells in Bx







NIH Criteria Interstitial Cystitis Criteria

Inclusion:

- Hunners Ulcer

Positive:

- Pain on bladder filling relieved by emptying
- Pain (suprapubic, vaginal, urethral, perineal)
- Glomerulations on endoscopy
- Reduced compliance on CMG

NIH Exclusion Criteria Interstitial Cystitis

- Bladder capacity of > 350ml on routine CMG
- > 400ml F/Volume
- Absence of sensory urgency/ IDO on CMG
- Symptoms for < 12 months
- Nocturia < 2/night
- Symptomatic relief by antimicrobials, urinary antiseptics, anticholinergics or antispasmodics
- Awake frequency < 5/12h
- A diagnosis of bacterial cystitis or prostatitis within 3 months
- Bladder or ureteral calculi

NIH Exclusion Criteria Interstitial Cystitis

- Active genital herpes
- Uterine, cervical, vaginal or urethral cancer
- Urethral diverticulum
- Cyclophosphamide or any other chemical cystitis
- TB cystitis
- Radiation cystitis
- Benign or malignant bladder tumours
- Vaginitis
- Age < 18 years

ESSIC Classification
International Society for the Study of BPS

	Cystoscopy with Hydrodistension			
	Not done	Normal	Glomerulations	Hunners Ulcers
Not done	XX	1X	2X	3X
Inconclusive	XB	1B	2B	3B

Treatment

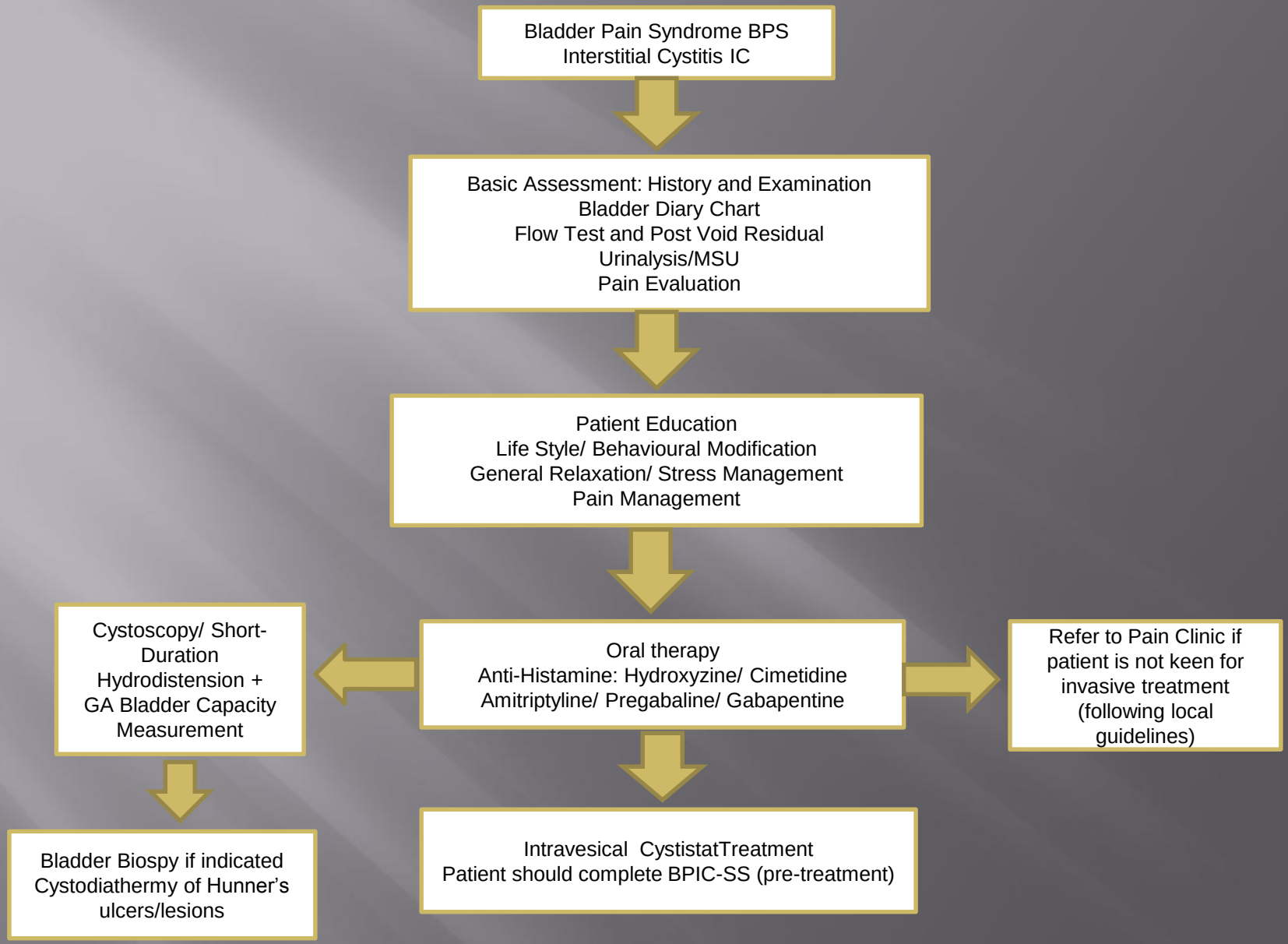
- Patient Education
- Life Style/ Behavioural Modification
- General Relaxation/ Stress Management
- Jointly or Solely by Pain Team / MDT approach
- Simple analgaesics: Paracetamol/NSAID
- Antihistamines: Hydroxizine or cimetidine
- Tricyclic antidepressants: Amitriptyline/Nortriptyline
- Pregabelin OR gabapentin
- Short-term opiates for flare-up
- Pudendal nerve blocks
- Group therapy
- Physical therapy to trigger points

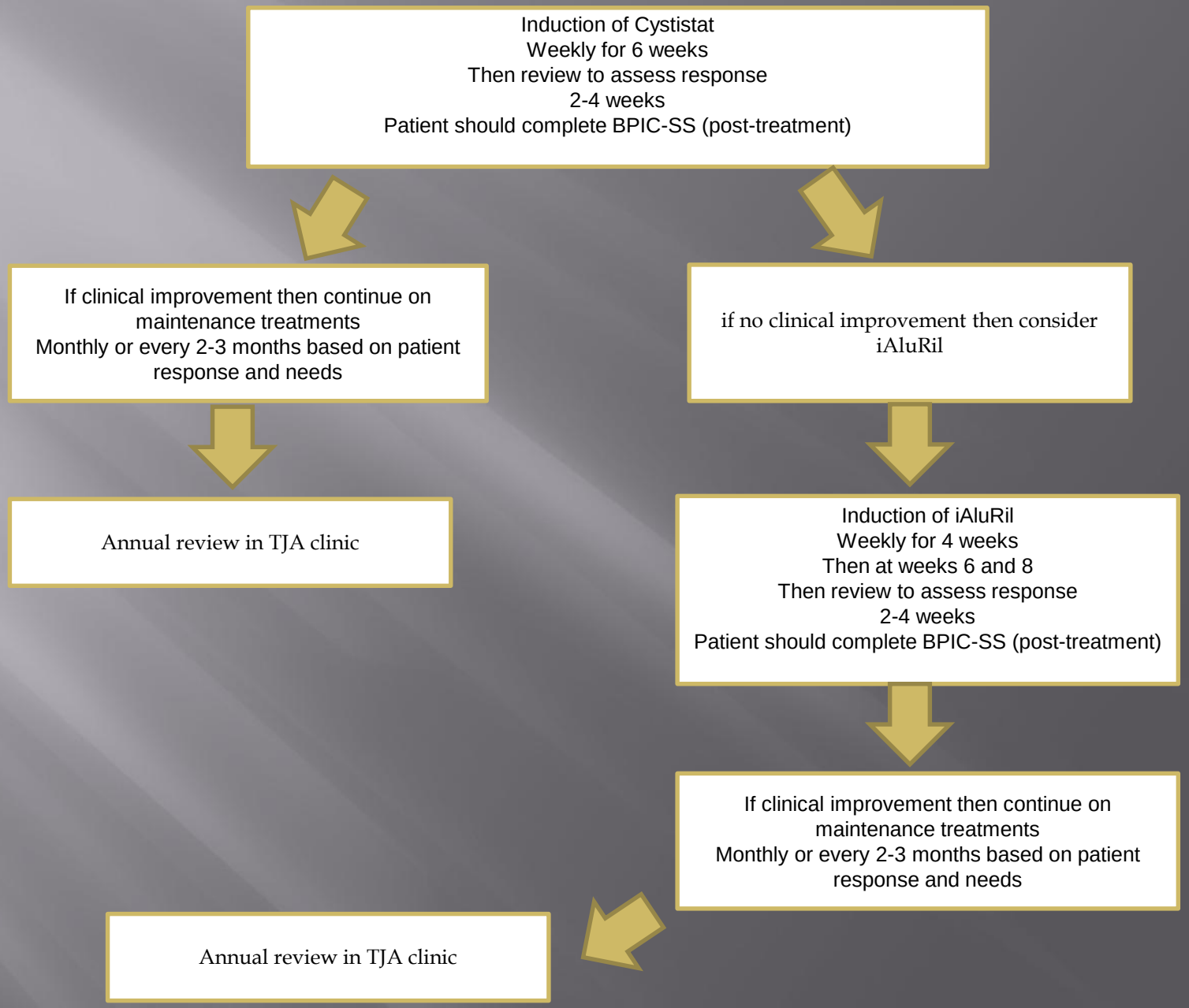
Treatment

- Intravesical instillations (GAG replacement therapy): RIMSO/Cystistat/iAluRil
- Acupuncture
- Botox
- SNM
- pTNS
- Last resort in selected patients: reconstructive surgery after full urological workup with psychiatric assessment

Management

- Endoscopic
- Drugs
- Intravesical Instillations (GAG replacement therapy)
- Other
- Surgery


Bladder Pain Syndrome BPS
Interstitial Cystitis IC
Basic Assessment: History and Examination
Bladder Diary Chart
Flow Test and Post Void Residual
Urinalysis/MSU
Pain Evaluation
Patient Education
Life Style/ Behavioural Modification
General Relaxation/ Stress Management
Pain Management
Oral therapy
Anti-Histamine: Hydroxyzine/ Cimetidine
Amitriptyline/ Pregabaline/ Gabapentine
Cystoscopy/ Short-Duration Hydrodistension + GA Bladder Capacity Measurement
Refer to Pain Clinic if patient is not keen for invasive treatment (following local guidelines)
Bladder Biospy if indicated
Cystodiathermy of Hunner's ulcers/lesions
Intravesical CystistatTreatment
Patient should complete BPIC-SS (pre-treatment)


Induction of Cystistat
Weekly for 6 weeks
Then review to assess response
2-4 weeks
Patient should complete BPIC-SS (post-treatment)
If clinical improvement then continue on maintenance treatments
Monthly or every 2-3 months based on patient response and needs
Annual review in TJA clinic
if no clinical improvement then consider iAluRil
Induction of iAluRil
Weekly for 4 weeks
Then at weeks 6 and 8
Then review to assess response
2-4 weeks
Patient should complete BPIC-SS (post-treatment)
If clinical improvement then continue on maintenance treatments
Monthly or every 2-3 months based on patient response and needs
Annual review in TJA clinic

No Clinical Response to Intravesical Cystistat or iAluRil Treatment

Review in TJA clinic to discuss other treatment options

Last Resort in selected patients
Reconstructive Surgery
After full Urological Workup with Psychiatric Assessment

Signs/Symptoms of Complicated BPS/ IC
Urine Incontinence/OAB
Haematuria
GI signs/ symptoms
Gynaecological signs/ symptoms

Consider:
Specialist Referral to GI/ Gynaecology
Imaging
Urodynamics
Intravsical Botox Treatment
Sacral Neuromodulation

Management Endoscopic

? Bladder distension (Grade 3)

Rationale

- Sensory nerve sprouting, Substance P, upregulation of C fibres
- Submucosal ischaemia

Outcomes

- Dunn 1977 25 patients 64% remission at 2 yr
- Glemain 2002 34 patients. 43% remission at 1 y

? Urethral dilatation (Grade 2)

- RCT Bergmann 1989
- 60 women
- Dilatation 75% subjective improvement
- Tetracycline 50%
- Improved flow

Management Drugs

Analgesics

- Aspirin
- Narcotics
- Fentanyl / Tramadol / MST etc

Antidepressants

Tricyclics

- **Amytryptiline (B)**
- Imipramine

SRIs

Fluoxetine

Anticonvulsants

Gabapentin (C)

Carbamazepine

Muscle relaxants

- Diazepam
- Baclofen

Anti inflammatories

- NSAIDS Ibuprofen / Naproxen

Antihistamines

- **Cimetidine (A)**
- **Hydroxyzine (B)**

Management Drugs

Antibiotics

- Little data
- RCT 50 patients
- Rotational antibiotics in 3/52 cycles
- Improvement 48% antibiotics v 24% placebo
- Pain free 40% antibiotics v 20% placebo

(Warren J Urol 2000 163 1685)

Management Drugs

Cimetidine (Grade A)

- 36 pts in RCT v Placebo
- Reduced symptom scores
- Did not change histological appearance

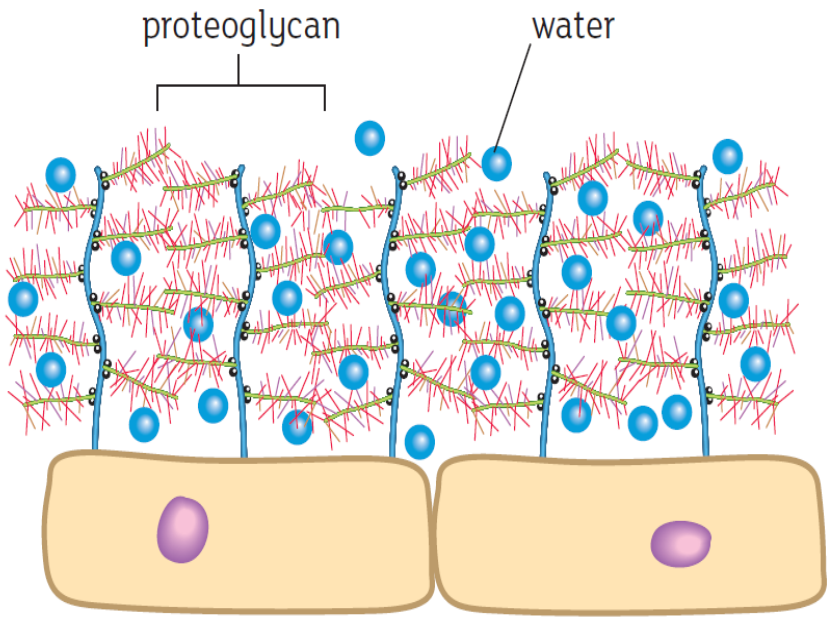
(Thilagarajah BJUI 2001)

Management Drugs

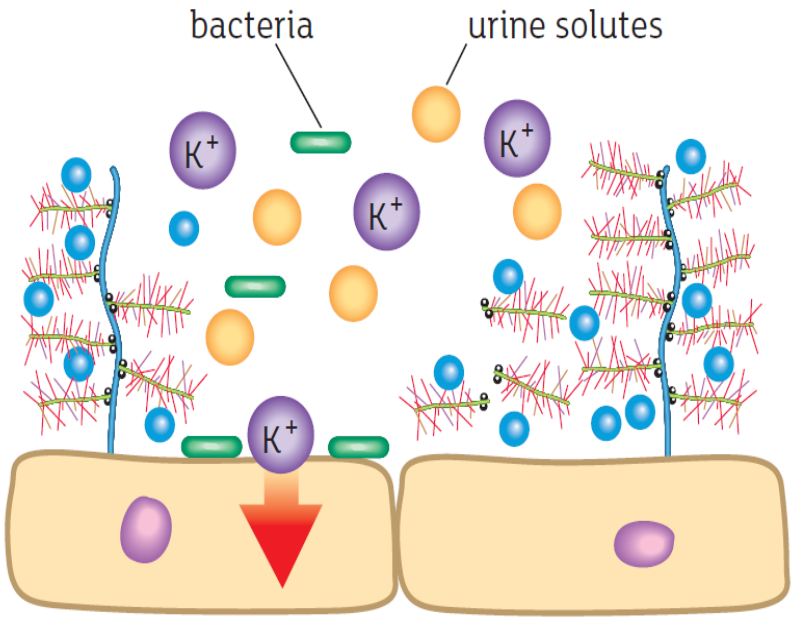
Pentosan Polysulphate (Elmiron)

- 100-200 mg tds orally
- Up to 6 months
- Hair loss and GI symptoms
- Poor bioavailability
- NOT on Formulary/ expensive
- Same outcome as intravesical treatments

GAG replacement therapy



Normal GAG layer



Dysfunctional GAG layer

Damaged urothelium results in increased bacterial adherence and permeability to irritants.

iAluRil®

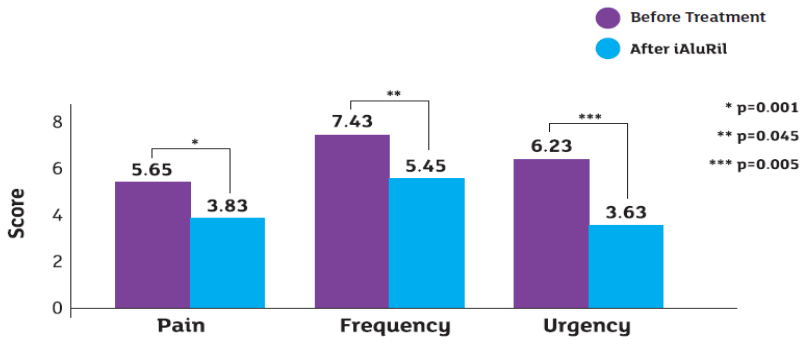
- Combine 2 components of most abundant sulphated GAG molecules in prefilled syringe
  - Chonddoitin sulfate (CS) 1.6% -800mg/50ml
  - Hyaluronic acid (HA) 2% -1g/50ml

- Can treat as well:
  - Recurrent UTIs
  - Radiation induced cystitis
  - Chemical induced cystitis

iAluRil®

Cervigni M et al. 2008 & 2012

VAS

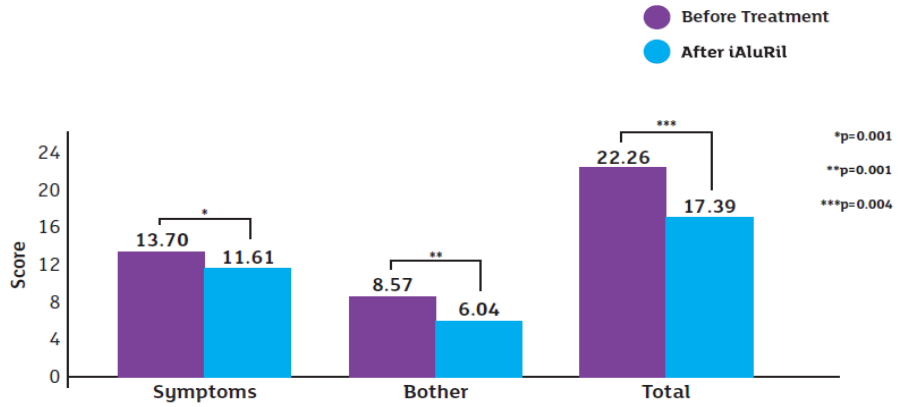


32.2% reduction in pain.

26.6% reduction in urinary frequency.

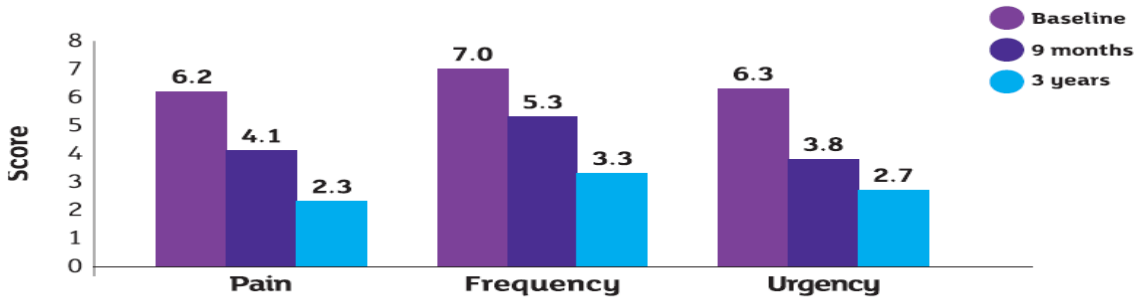
41.7% reduction in urinary urgency.

PUF



21.9% reduction in PUF.

VAS



Management Bladder Instillations

Anti inflammatory

Dimethyl Sulphoxide (DMSO)

Evidence (Grade A)

- 33 pts Cross over trial
- 53% v 18% symptomatic improvement
- Mix with steroids and antihistamine

(Perrez-Marrero 1988)

Management Bladder Instillations

Epithelial Recoating

Pentosan Polysulphate (Grade A)

- RCT n=48
- 32% v 16% improvement (Parsons 1987)
- Metanalysis n = 398
- 16% difference

Heparin self instillation (Grade C)

- 10000 units in 10 ml saline three times per week (Hwang 1997)

Cystistat (Hyaluronic acid) (Grade C)

- RCT n=138
- 50% improvement in Cystistat group
- No significant difference from placebo (Whitmore 2003)

Management Bladder Instillations

Other Instillations

Cocktails

- Lignocaine / Marcaine
- Hydrocortisone
- $NaCO_3$
- Heparin

BCG
EMDA
Vanilloids; Resinoferoxin and Capsaicin and resinaferatoxin
Bioflavinoids
Botox

Bladder treatment assessment form

Date of first treatment:

Patient addressograph

Pre-treatment BPIC-SS completed yes no

Total BPIC-SS score =

Problems during catheterisations yes no

Pain yes no

Bleeding yes no

Difficulty yes no

Others; please specify:

_____

Induction completed yes no

Improved yes no

Date of completetion of induction:_____

Post-induction BPIC-SS completed yes no

BSW questionares completed yes no

Problems post- induction yes no

Pain during catherisations yes no

Bleeding during catherisations yes no

Difficulty during catherisations yes no

UTIs yes no

Haematuria yes no

Others; please specify:

_____

Patient addressograph

Maintenance treatment yes no

Monthly yes no

Every 2 months yes no

(date of change_____)

If frequency of maintainance treatment changed please document the date

Every 3 months yes no

(date of change_____)

Every 4 months yes no

(date of change_____)

Every 5 months yes no

(date of change_____)

Every 6 months or more yes no

(date of change_____)

Annual review in clinic yes no

Clinical improvement continued yes no

Problems following annual review yes no

Pain during catherisations yes no

Bleeding during catherisations yes no

Difficulty during catherisations yes no

UTIs yes no

Haematuria yes no

Others; please specify:

Urethral Pain Syndrome

Pain in urethra?

Symptoms of UTI without evidence of infection?

Urethral syndrome diagnosis

- Response to appropriate antibiotics can be useful diagnostically
- STI screen
- Rule out diverticulum (?MRI)
- Cystoscopy

Management

Avoid antibiotics (unless positive MSU)

K-citrate may help

Amitriptyline

Gabapentin/ Pregabalin

Topical Oestrogen treatment (Vagifem pessaries)

? urethral dilatation

Summary

- BPS/ IC is diagnosis of exclusion
- Can be notoriously hard to diagnose correctly
- Symptoms can remain misunderstood for several years (a survey showed that majority of patients took them > 2yr for diagnosis)
- Accurate patient history is critical
- Treatment is multidisciplinary approach
- Patient education is essential
- Management is step-wise based on predominant symptoms
- Substantial overlap between BPS/IC and other common urological conditions

Any Questions ?????