INTERSTITIAL CYSTITIS/ PAINFUL BLADDER SYNDROME: Advances in Diagnosis and Management

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Outline

- Definition
- Epidemiology
- Etiology
- Diagnosis
- Evidence Based Management
Definition

- 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.


Epidemiology

- Considerable variability among studies regarding incidence and prevalence
- First population based study in Helsinky (1975):
  - Prevalence in women 18.1 / 100,000
  - Both sexes 10.6 / 100,000
  - Incidence in females 1.2 per 100,000
More recent studies suggest...

- Prevalence likely higher
- 197 women per 100,000 population (from physician-assigned diagnosis) (Clemens et al, 2005)
- 450 women per 100,000 population (from validated symptom questionnaire) (Roberts, 2003)
- 865 women per 100,000 population (from patient self-report)
- roughly 236,000 to > 1 million American women

EPIDEMIOLOGY

- Prevalence estimates per 100,000
  - United States: 35-24,000
  - Netherlands: 7
  - Finland: 10.6-450
  - Japan: 1.2
- Female to male ratio = 5:1
- Economic cost of disease ~ $427 million

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ETIOLOGY

- Likely multifactorial
- Many theories

Role of infection

- Little data to support the role of infectious etiology
- Bacterial cystitis may be the first step leading to a low level inflammatory response
- Unlikely that active infection is involved in the ongoing pathological process or that antibiotics have a role in treatment
Immune/neuroimmune mechanisms

- Excessive release of sensory nerve neurotransmitters and mast cell inflammatory mediators → propagation of symptoms
- Inflammation → altered nerve growth factor content → morphological changes in sensory and motor neurons → long-term symptoms after inflammation subsides.

Role of Mast Cells

- Histamine release in tissue causes pain, hyperemia and fibrosis
- A high number of activated mast cells have been seen in the bladder of patients with PBS/IC
- Could contribute to failure of epithelialization of the bladder surface following injury by 2 potential mechanisms:
  1) inhibition of epithelial cell replication
  2) interference with epithelial cell spreading, thus resulting in the leaky epithelium found in some cases.
Leaky Epithelium

• GAG layer functions as a permeability and anti-adherence barrier
• Patients with IC have a lower excretion of urinary uronic acid and GAGS than normals, possibly due to a leaky transitional epithelium that might be absorbing these substances to surfaces.
• Increased mucosal permeability is non-specific and a consequence of bladder inflammation

Neurogenic inflammation

• Activation of sensory nerves → neuropeptides such as substance P, neurokinin A → neurogenic inflammation.
Consolidating theories

Nervous system and IC

- Repetitious activation of C fibers results in a progressive build-up of the magnitude of the electrical response recorded in the second order dorsal horn neurons.
- “wind-up” phenomenon
- persistent NMDA receptor activation cause spinal cord cells to undergo trophic changes, and the pain resulting from subsequent stimulation becomes exaggerated and prolonged.
DIAGNOSIS

• Diagnostic approaches vary widely
• No general agreement on a diagnostic algorithm
• Heavy reliance on other aspects of the NIDDK criteria

NIDDK criteria

• Based on consensus among a group of researchers who wanted to define strict, homogenous criteria for patient recruitment into research trials
• Not meant to define the disease, but rather to ensure comparability between that groups of patients research studies
NIDDK Criteria

To be diagnosed with interstitial cystitis, patients must have either glomerulations on cystoscopic examination or a classic Hunner 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 to 100 cm H2O for 1 to 2 minutes. The bladder may be distended up to two times before evaluation. The glomerulations must be diffuse and present in at least three 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 excludes a diagnosis of interstitial cystitis:

1. Bladder capacity of greater than 350 mL 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 mL of gas or 150 mL of liquid filling medium
3. The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate just described
4. Duration of symptoms less than 9 months
5. Absence of nocturia
6. Symptoms relieved by antimicrobial agents, urinary antiseptic agents, anticholinergic agents, or antispasmodic agents
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. Actino genital herpes
11. Uterine, cervical, vaginal, or urethral cancer
12. Urethral diverticulum
13. Cystocele, rectocele, or any type of chemical cystitis
14. Tuberculous cystitis
15. Radiation cystitis
16. Benign or malignant bladder tumors
17. Vaginitis
18. Age younger than 18 years

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NIDDK Criteria - Criticisms

- ICDB study accumulated data on 424 pt with IC.
- Entry criteria were much more symptom driven than those promulgated for research studies
- Fully 90% of expert clinicians agreed that patients diagnosed with IC by those criteria in the ICDB indeed had the disorder.
- 60% of patients deemed to have IC by these experienced clinicians would not have met NIDDK research criteria.
NIDDK Criteria - Criticisms

- More recent studies challenge the need for cystoscopy for diagnosis.
- 39-60% of patients have minimal reduction in capacity, minimal or scant glomerulations, and no consistent urine marker or bladder biopsy findings.
- 8.7% of patients in the IC database had normal cystoscopy.
- Glomerulations are not specific for IC and may be just a response to distention after a prolonged period of under filling rather than a pathological process.
- Pts. with symptoms of less than 9 months duration could still have IC.

Pathology

- Way to exclude other diagnoses.
- No pathognomonic picture.
- No consistent findings.
- Great variation within the same patients.
- Pathologic findings.
Associations among Pathologic Features and Patient Symptoms

Night-Time Frequency
- Mast cell count in lamina propria on tryptase stain
- Complete loss of urothelium
- Granulation tissue in lamina propria
- Vascular density in lamina propria

Urinary Urgency
- Percentage of submucosal granulation tissue

Urinary Pain
- Percentage of mucosa denuded of urothelium
- Percentage of submucosal hemorrhage

KCL Test
- Comparing the sensory nerve provocative ability of sodium versus potassium using a 0.4 M KCl solution
- Pain and provocation of symptoms constitutes a positive test.
- Not valid for diagnosis of IC (Chambers et al, 1999)
- A 36% false-positive rate in asymptomatic men (Yilmaz et al, 2004)
KCL test (continued)

- Up to 25% of patients meeting the NIDDK criteria will have a negative KCl test (Parsons et al, 1998)
- May be positive in overactive bladder, radiation cystitis and urinary tract infection

How does one make the diagnosis?

Three consensus panels concluded that the diagnosis is suspected on the basis of history, physical examination, and laboratory tests, including negative urinalysis, negative urine culture, negative cytology, and possibly cystoscopy findings.

Antiproliferative Factor

- Frizzled-related peptide growth inhibitor
- Produced by the urothelium of patients with IC.
- Found in bladder urine but not in renal pelvic urine
- High APF has been linked to IC patients with many racial backgrounds


Antiproliferative Factor

- APF seems to have role in increasing cell permeability
- induces reversible inhibition of HB-EGF production and normal bladder epithelial cell proliferation

Antiproliferative Factor

• Sensitivity and specificity of increased APF activity in IC has been postulated to be 94 and 95%
• Could be used to gauge response to treatment – improvement in APF activity noted after hydrodistention and neuromodulation.


Prevalence of urine antiproliferative factor activity in interstitial cystitis patients and control groups

Groups No. Pos/Total
No. (%) No. (%)
Pts: Interstitial cystitis 206/219 (94)
Controls:
Asymptomatic 10/113 (9)
Overactive bladder 2/32 (6)
Bacterial cystitis 7/56 (12)
Microscopic hematuria 2/19 (10)
Stress incontinence 1/10 (10)
Neurogenic bladder 0/11 (0)
Benign prostatic hyperplasia 1/14 (7)
Nonbacterial prostatitis 1/16 (6)
Vulvovaginitis 0/12 (0)
Miscellaneous 1/16 (6)

Symptoms

- urinary urgency (57-98%)
- daytime frequency (84-97%)
- pain (66-94%)
- nocturia (44-90%)
- pain with voiding/dysuria (71-98%)
- suprapubic pain (39-71%)
- perineal pain (25-56%)
- patient sensation of bladder spasms (50-74%)
- pubic pressure (60-71%)
- dyspareunia (46-80%)
- Depression (55-67%)


Clinical Symptom Scales

- Three published PBS/IC symptom questionnaires:
  - University of Wisconsin IC Scale,
  - O'Leary-Sant IC Symptom Index and IC problem Index,
  - Pelvic Pain and Urgency/Frequency (PUF) Scale.
The University of Wisconsin IC Scale

• Includes seven PBS/IC symptom items
• captures severity of symptom expression
• IC patients do NOT score higher than controls (Porru et al, 2005)
• Addresses some QOL issues
• Easy to implement
• Not validated for identification or diagnosis of PBS/IC

O'Leary-Sant IC Symptom Index

• subjected to test-retest reliability analysis
• validated by administration to IC patients and asymptomatic controls
• centered on three questions related to urgency/frequency and one on bladder-associated pain
Pelvic Pain and Urgency/Frequency (PUF) Scale

- Includes questions that directly reflect a wide variety of the symptoms
- One third of the questions address pelvic pain
- A large study utilizing the PUF questionnaire has concluded that up to 23% of American females have PBS/IC (Parsons et al, 2002a)
- Face validity and utility in question.
THERAPY

- Conservative
- Hydrodistention
- Oral therapy
- Intravesicle therapy
- Neuromodulation
- Surgery

Conservative Approach

- A single trial with empirical course of antibiotics maybe warranted
- Doxycycline has been reported to have an efficacy of up to 70% in relieving / improving symptoms in a prospective cohort analysis (Burkhard et al, 2004)
- Repeat courses of antibiotics not recommended in absence of negative cultures.
Conservative Approach

- Patient education and empowerment
- Timed voiding and behavioral modification therapy
- Stress reduction, exercise, warm tub baths (No RCT evidence)

Dietary Modifications

- Elaborate dietary restrictions are unsupported by any literature.
- Anecdotal association of IC with many acidic foods.
- The only placebo-controlled dietary study, while small, failed to demonstrate a relationship between diet and symptoms (Fisher et al, 1993).
Hydrodistention

- Perform an initial cystoscopic examination
- Obtain urine for cytology
- Distend the bladder for 1 to 2 minutes at a pressure of 80 cm H2O.
- Bladder is emptied and then refilled
- A look for glomerulations or ulceration.
- A therapeutic hydraulic distension follows for another 8 minutes.

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Hydrodistention

- Therapeutic responses in patients with a bladder capacity under anesthesia of less than 600 cc were excellent in 26% and fair in 29% compared to 12% excellent and 43% fair in patients with larger bladder capacities.
- Most favorable responses were extremely brief, with the exceptional patient noting improvement for 6 months.

Hydrodistention

- Allows for “staging” of the disease, giving the clinician some idea of the capacity with which conservative therapies may work.
- A capacity with the patient under anaesthesia of less than 200 cc would not bode well for the likelihood of success of medical therapy
- Allows for identification of Hunner’s ulcers.

Oral Therapy

- Tricyclic antidepressants
- Antihistamines
- Sodium Pentosan Polysulfate
- Analgesics
Oral Therapy

Table 10-11: Some Oral Medications That Have Been Used for Treatment of PBS/IC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Randomized Control Trial % Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibiotic regimens</td>
<td>Yes</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>No</td>
</tr>
<tr>
<td>Benzydamine</td>
<td>Yes</td>
</tr>
<tr>
<td>Chloroquine derivatives</td>
<td>No</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Yes</td>
</tr>
<tr>
<td>Cortisone and other steroids</td>
<td>No</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>No</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>No</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>No</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Yes</td>
</tr>
<tr>
<td>L-Arginine</td>
<td>Yes</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>No</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>No</td>
</tr>
<tr>
<td>Montelukast</td>
<td>No</td>
</tr>
<tr>
<td>Nalmefene</td>
<td>Yes</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>No</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>No</td>
</tr>
<tr>
<td>Phenazopyridine</td>
<td>No</td>
</tr>
<tr>
<td>Quercetin</td>
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</tr>
<tr>
<td>Sodium pentosan polysulfate</td>
<td>Yes</td>
</tr>
<tr>
<td>Suplatast tosylate</td>
<td>Yes</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>No</td>
</tr>
</tbody>
</table>

AUA Update Series, Lesson 9: Volume 25, 2006

Tricyclic Antidepressants

- Amitriptyline has been the staple of oral therapy
- Mechanism of action:
  - central and peripheral anticholinergic actions
  - block the active transport system in the presynaptic nerve ending that is responsible for the reuptake of the released amine neurotransmitters serotonin and noradrenaline
  - sedatives, an action that occurs presumably on a central basis but perhaps is related to their antihistaminic properties
Amitriptyline

- RCT, intent to treat
- N = 50 (44 women, 6 men)
- Methods:
  - randomized to amitriptyline (25) versus placebo (25)
  - prospectively treated for 4 months with a self-titration protocol that allowed them to escalate drug dosage in 25 mg increments in 1 week-intervals (maximum dosage 100 mg).
  - **primary outcome parameter**: change from baseline in the O’Leary-Sant IC symptom and problem index
  - **secondary outcome parameters**: functional bladder capacity and frequency (48-hour voiding log), and intensity of pain and urgency (visual analog scales)
• statistically significant change in the symptom score

• statistically significant improvement of pain and urgency intensity compared with placebo

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amitriptyline</th>
<th>Placebo</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean score ± SD</td>
<td>-3.6 ± 3.4</td>
<td>-3.3 ± 3.3</td>
<td>0.385</td>
</tr>
<tr>
<td>Mean pain intensity ± SD (mm on VAS)</td>
<td>-31.3 ± 26.1</td>
<td>-6.3 ± 12.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean urgency intensity ± SD (mm on VAS)</td>
<td>-40.9 ± 23.5</td>
<td>-4.1 ± 12.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean 24-hr frequency ± SD</td>
<td>-2.3 ± 3.1</td>
<td>-1.4 ± 3.1</td>
<td>0.063</td>
</tr>
<tr>
<td>Mean functional bother value ± SD (m/L)</td>
<td>10.0 ± 6.82</td>
<td>-7.7 ± 47.5</td>
<td>0.083</td>
</tr>
</tbody>
</table>

Amitriptyline...

• Anticholinergic side effects were reported by all except 2 patients in the amitriptyline group (92%) and by 5 patients in the placebo group (21%).

• Mouth dryness was the most frequent side effect reported in the amitriptyline group (79%).

- Prospective cohort analysis
- N= 94
- Methods = patients stratified in 2 groups:
  - IC with NIDDK
  - IC without NIDDK (characteristic symptoms)
- Mean Follow up = 19 months
- Results: response rate = 64% (60 patients).
- Mean dose = 55 mg (range 12.5 to 150)
- Side effects in 79 patients (84%) (dry mouth 79%, weight gain 59%).
- Therapeutic result was excellent or good in 43 (46%).
- Dropout rate = 31% (29 patients)
- Non response to treatment was the primary reason for dropout in all cases, while side effects contributed to dropout in 25 (86%).

**Antihistamines**

- Stems from mast cell theory of IC
- In some uncontrolled studies, hydroxyzine showed symptomatic improvement by up to 30%.
- No significant response to hydroxyzine was found in an NIDDK placebo-controlled trial (*Sant et al, 2003*).
- Cimetidine, an H2 antagonist, showed efficacy in double blind, placebo controlled trial. (*Thilagarajah et al, 2001*)
Sodium Pentosan Polysulfate

- Its use stems from an attempt to correct a defect in the epithelial permeability barrier, the GAG layer, of the bladder.
- A heparin analogue available in an oral formulation.
- 3% to 6% excreted into the urine.
- Contradictory reports of efficacy in literature.

Two placebo controlled multicenter trials in the United States were published.

In the initial study overall improvement of greater than 25% was reported by 28% of the PPS treated group versus 13% in the placebo group. (Mullholand et al, 1990)

In the latter study the respective figures were 32% on drug versus 16% on placebo. (Parsons et al, 1993)


Sodium Pentosan Polysulfate

- A recent NIDDK study looking at PPS and hydroxyzine, alone and in combination, compared to placebo failed to show a statistically significant response to either medication.


Cyclosporine Versus Pentosan Polysulfate

- Randomized comparative study
- N = of 64 IC patients diagnosed by NIDDK criteria
- Methods: randomized in a 1:1 ratio to cyclosporine A (Sandimmun Neoral®) or to pentosan polysulfate sodium (bene-Arzneimittel GmbH, Munich, Germany) treatment for 6 months.
- Endpoints: daily micturation frequency, voided volume, number of nocturia episodes, O’Leary-Sant symptom and problem indexes, visual analogue scale for pain and subjective global response assessment.
- Results:
  - CyA was found to be superior on all parameters at 6 months.
  - More adverse events noted in the cyclosporine arm.

Intravesicle Therapy

- remains a mainstay of treatment in the therapeutic armamentarium of IC

DMSO

- Mainstay of intravesicle treatment

- Pharmacologic properties:
  - membrane penetration
  - enhanced drug absorption
  - anti-inflammatory action
  - analgesic action
  - collagen dissolution
  - muscle relaxation
  - mast cell histamine release
DMSO

- Success rate of up to 70% noted in prospective studies done in 1970’s
- Most patients ultimately required re-treatment or further therapy with other modalities
- Patients with bladder instability do not respond

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Heparin

Mechanism of action:
- Mimic the activity of the bladder's own mucopolysaccharide lining
- Anti-inflammatory effects
- Inhibit fibroblast proliferation, angiogenesis, and smooth muscle cell proliferation.
Heparin

- No systemic absorption
- Some SMALL case series showing symptomatic improvement (Parsons, 2000) (Kuo, 2001)
- Unproven by any placebo-controlled trial.

BCG

- Unclear mechanism of action
- Immunologic and/or anti-inflammatory mechanisms have been postulated (Peters et al, 1999)
- Early small RCT showed high response rate of 60% compared with a 27% placebo response (Peters et al, 1997).
- Recent large RCT fails to show high response rate.
A RANDOMIZED CONTROLLED TRIAL OF INTRAVESICAL BACILLUS CALMETTE-GUERIN FOR TREATMENT RE-REFRACTORY INTERSTITIAL CYSTITIS

ROBERT MAYER,² KATHLEEN JOY PROPER,³ KENNETH M. PETTES,³ CHRISTOPHER K. PAYNE,² YAYEI ZHANG, DAVID BURKS, DANIEL J. CULBIN, ANASTASIOS DIORNO, PHILIP HANNON, J. RICHARD LANDIS,¹ ROSEMARY RODGAN, EDWARD M. MESSING,³ J. AUGUST NICKEL,⁴ GRANNUM B. KANG, JOHN WARREN, ALAN J. WEIN,¹ JOHN W. KUSEK, LEROY M. NYBERG, HARRIS E. FOSTER,§

AND THE INTERSTITIAL CYSTITIS CLINICAL TRIALS GROUP

From the University of Rochester, Rochester, New York (RWM, JMK); University of Pennsylvania, Philadelphia, Pennsylvania (GBP, YH, JLH, EM, KMW); William Beaumont Hospital, Royal Oak, Michigan (AYD, AZA); Stanford University, Stanford, California (CKO); Henry Ford Hospital, Detroit, Michigan (DB); Oklahoma University Health Sciences Center, Oklahoma City, Oklahoma (DMC); Queens University, Kingston, Ontario (KSN); Saint-Vincent Infirmary, New York, New York (GGB); University of Maryland, Baltimore (JWK); National Institutes of Diabetes and Digestive and Kidney Diseases, National Institute of Health, Bethesda, Maryland (JWK, LMK), and Yale University, New Haven, Connecticut (HEP)

• RCT
• N = 265
• Participants were randomized to intravesical BCG or intravesical placebo, and received up to 6 instillations within 6 to 10 weeks.
• F/U 24-28 WKS
• Primary outcome: patient reported global response assessment
• Secondary outcomes: 24-hour voiding diary, pain, urgency, validated IC symptom indexes and adverse events
RESULTS

- Response rates for the primary outcome were 12% for placebo and 21% for BCG (p 0.062). No statistical significance reached.

- Small improvements were observed for all secondary outcomes, some more so with BCG, but these differences were of borderline statistical significance.

- Although a large number of adverse events were reported in the BCG arm, there was no statistically significant difference between the treatment arms in overall adverse event rates.

Conclusion

- Intravesical BCG therapy was reasonably well tolerated but not more effective than placebo in this population of patients with moderate to severe IC.
Table 10-12: Some Intravesical Medications That Have Been Used for Treatment of PBS/IC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Randomized Controlled Trial</th>
<th>% Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver nitrate</td>
<td>No</td>
<td>60%</td>
</tr>
<tr>
<td>Chlorapte WC-90</td>
<td>No</td>
<td>60%</td>
</tr>
<tr>
<td>Dimethylsulfoxide</td>
<td>Yes</td>
<td>70%</td>
</tr>
<tr>
<td>Bacillus</td>
<td>Yes</td>
<td>No proven efficacy</td>
</tr>
<tr>
<td>Calmette-Guerin</td>
<td>Yes</td>
<td>No proven efficacy</td>
</tr>
<tr>
<td>Resiniferatoxin</td>
<td>Yes</td>
<td>No proven efficacy</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Yes</td>
<td>No proven efficacy</td>
</tr>
<tr>
<td>Heparin</td>
<td>No</td>
<td>60%</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>No</td>
<td>33%</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>No</td>
<td>65%</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>No</td>
<td>No demonstrated efficacy</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>No</td>
<td>Efficacy suggested</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>No</td>
<td>Anecdotal efficacy</td>
</tr>
<tr>
<td>Pentosan polysulfate</td>
<td>Yes</td>
<td>40%</td>
</tr>
</tbody>
</table>

Neuromodulation

- relieves pain by stimulating myelinated afferents to activate segmental inhibitory circuits
- patients who do best with this treatment modality are those who have identifiable pain and dysfunction in the pelvic muscles
Neuromodulation – the process

- Trial stimulation performed with a percutaneous temporary electrode for a 3 to 4-day temporary stimulation period to assess efficacy.
- S3 nerve is most frequently used.
- A wire electrode is inserted into the foramen and connected to an external pulse generator.
- If the trial is successful, the patient would be considered for implantation of a permanent neural prosthesis.
- More recently, a staged procedure has supplanted the traditional percutaneous approach, as the response to stimulation can be better assessed with more accurate lead placement and stability than through the more hit or miss percutaneous lead placement.

Neuromodulation – evidence

- No RCT evidence.
- A decrease in antiproliferative factor activity and normalization of HB-EGF levels in patients with successful test stimulation (Chai et al, 2000a).
- In a prospective study of 27 refractory patients, implantation of sacral nerve root stimulator showed improvements in urinary frequency, voided volumes, nocturia and pain after a mean follow up of 14 months (Commite, 2003).
- Sacral neuromodulation can decrease narcotic requirements significantly in refractory PBS/IC (Peters et al, 2004).
Surgical therapy

- Reserved for motivated and well-informed patients in the category of extremely severe, unresponsive disease, a group which comprises fewer than 10%.
- Aimed at increasing the functional capacity of the bladder or diverting the urinary stream.
- Augmentation (substitution) cystoplasty and urinary diversion with or without cystectomy have been used as a last resort with good results in select patients.
CONCLUSIONS

- Interstitial cystitis is much more common than what was initially thought.
- Once confirmed by other centers, APF may prove to be a useful marker in diagnosis of IC.
- Multiple effective treatment options are available.
- A step wise approach to management should be used.

Thank-you