Non Bacterial Cystitis including Interstitial Cystitis

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Definition

- Catchterm that comprises a variety of medical disorders
  - Nonbacterial infectious (viral, mycobacterial, chlamydial & fungal)
  - Noninfectious (radiation, drug induced, autoimmune)
  - Interstitial cystitis
- All have common symptoms
  - Urgency, frequency, dysuria
  - Occasionally, hematuria, dyspareunia, abdominal cramps and or bladder pain and spasms

Frequency

- Nonbacterial Infectious
  - HSV 1 & 2
  - Adenovirus
  - BK Polyoma virus
  - Chlamydia
  - Mycobacterium Tuberculosis
  - Fungal

Frequency

- Noninfectious cystitis
  - Radiation
  - Drug Induced
    - Chemotherapy
      - Cyclophosphamide
      - Low dose methotrexate
    - Tiaprofenic Acid (Surgam)
  - Autoimmune
      - Sjogren syndrome
      - Systemic lupus erythematosus

Etiology

- Infectious
  - May have acute, subacute or chronic course
  - Viral or Mycobacterial cystits
    - Can involve other organ systems
    - May depend on the degree of host immunosuppression
  - Fungal occur in immunocompromised
- Noninfectious
  - Radiation – Volume, dose & delivery technique
  - SLE & Sjogrens – are said to resemble an interstitial cystits like picture
  - Cyclophosphamide: Metabolite acrolein
  - Tiaprofenic acid: Mechanism unknown

Clinical

- Infectious
  - Symptoms include urgency, frequency & dysuria and occasionally may include hematuria, dyspareunia, abdominal cramps and /or bladder pain and spasm
  - HSV – wide range of symptoms
  - Chlamydia – may have associated mucopurulent cervical or urethral discharge
- Noninfectious
  - Radiation Cystitis Grade 1-3
  - SLE & Sjogrens present mainly as frequency & suprapuic pain
  - Chemical Cystitis – Acute & fulminant but more often delayed and mild

History

- History of Symptoms
- General medical history
  - Diabetes, arthritis, atopic states, autoimmune diseases
  - History of medical treatments for malignancy
  - Drug history- including chronic antibiotic therapy
- Specific medical history
  - Sexual history
  - Travel, immigration etc

Workup

- Infectious
  - Viral infections often difficult to diagnose – PCR
  - Chlamydia – PCR
  - Tuberculosis – Prior exposure Mantoux test, Tissue staining, or PCR
  - Fungal – microscopy of wet smears or histological sections, culture on media, PCR
- Noninfectious
  - Radiation - Obtain relevant history, MSU or cystoscopy
  - Autoimmune – detection of ANA,
    - SLE: anti-(ds) DNA, anti-(Sm) & anti-RNP
    - Sjogrens: Schirmer tear test, anti-Ro, anti-La & lacrimal biopsy
- Imaging Studies
  - Possible imaging tests include ultrasound, CT, IVP or MRI

Management

- Infectious
  - HSV 2
    - Acyclovir (Acyclo-V) 400 mg tds 10 days
    - Valaciclovir (Valtrex) 1000 mg tds 7 days
  - Adenovirus
    - Ganciclovir (Cymevene) protocol related
  - Chlamydia
    - Doxycycline (Doryx) 100 mg bd for 7 days
    - Azithromycin (Zithromax) 1 gm single oral dose
    - Erythromycin 500 mg QID for 7 days
  - Mycobacterium
    - Generally begins with 3-4 agents and varied due to drug sensitivities
  - Fungal
    - If in immunocomprimised with IDC → remove IDC
    - Oral azole antifungal agent Ketoconazole (Nizoral) 200mg daily 2-4 weeks
    - Bladder irrigations amphotericin B 50 mcg/ml for 5 days
    - Consider IV amphotericin B in seriously ill immunosuppressed with disseminated fungal infection

Management

- Noninfectious
  - Radiation
    - Minor bleeding generally self limiting
    - Severe bleeding requires hospitalisation
      - Cystoscopy + clot evacuation +/- diathermy
      - Multitude of other interventions bladder irrigations of various chemicals
      - Ultimately Urinary diversion
  - Chemical
    - Cease Drug
    - Hydration
    - Mesna- synthetic suphydryl compound binds acrolein
    - Aggressive hydration with IV fluids + diuretic
  - Autoimmune
    - Combination of symptomatic relief, anti-inflamatory & immunosuppressive therapy

Interstitial Cystitis

Etiology

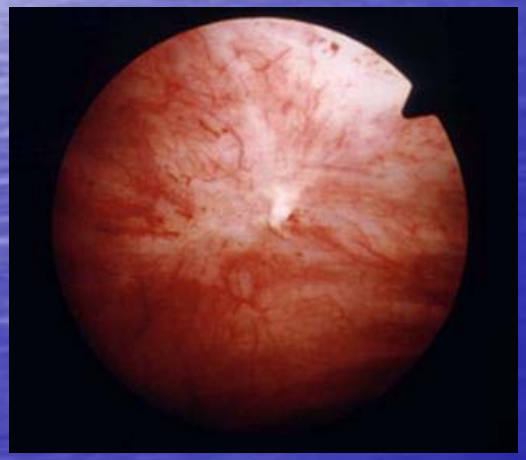
- Infection
- Leaky urothelium
- Immunologic
- Neurogenic inflammation
- Pelvic floor hyperactivity
- Abnormalities of Vanilloid receptors

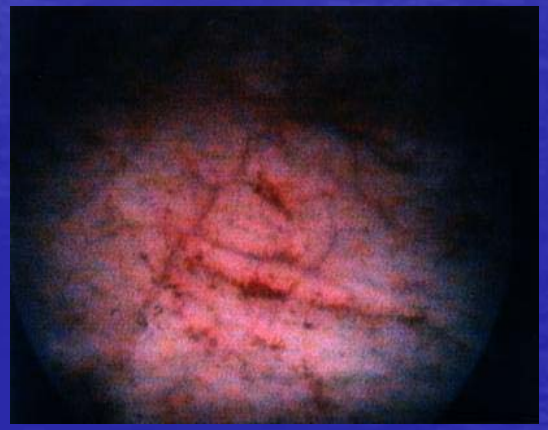
Pathology

- Pathologic diagnosis one of exclusion with no specific or clear criteria
- No specific or diagnostic light microscopic pathologic features by either routine histopathology or immunohistochemistry
- Electron Microscopy has provided new observations

NIDDK Inclusion Criterion

- **Glomerulations or Hunner's ulcer on cystoscopic examination, and**





- **Pain associated with the bladder or urinary urgency**

NIDDK Exclusion Criterion

1. Bladder capacity >350 mL on awake cystometry using either gas or liquid as filling medium
2. Absence of intense urge to void with bladder filled to 100 mL of gas or 150 mL of water during cystometry, using a fill rate of 30-100 mL/min
3. Demonstration of phasic involuntary bladder contractions during cystometry using fill rate described above
4. Duration of symptoms less than 9 months and age <18
5. Absence of nocturia
6. Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics, or antispasmodics (muscle relaxants)
7. Frequency of urination while awake <8 times per day

NIDDK Exclusion Criterion

8. Diagnosis of bacterial cystitis or prostatitis within 3 month period
9. Bladder or lower 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

Current Management of Interstitial Cystitis

- Conservative therapy
  - **Diet**
    - **53-63% can identify acidic fluids or foods incite flair**
      - **Mechanisms for this poorly understood not due to decreased urinary Ph from ingestion (Fisher et al)**
    - **Foods high in arylalkylamines**
      - **Mechanism tryptophan metabolites → Disruption of GAG layer (Kaufman et al)**
    - **Special diet remains a reasonable first line therapy for patients with irritative voiding symptoms**
    - **Tolerable food for IC patients include:-**
      - **Rice, pasta, potatoes, vegetables, chicken, meat, watermelons and grapefruit**

Current Management of Interstitial Cystitis

- Conservative therapy
  - Behavioural therapy
    - 50 – 75% reduction of symptoms in 50% of patient
    - Bladder training with deferment techniques → increase inter-void intervals
  - Treatment of Pelvic Floor Dysfunction
    - Lilius reported 81 % of his IC Patients to have spasm & tenderness of the levator ani musculature
    - Use of trans-rectal Thiele massage, biofeedback & electro-galvanic stimulation

Management – Oral Therapies

DRUG	MODE OF ACTION	RESULTS
Pentosan Polysulphate	GAG replacement	28-32% improvement
Amitriptyline	Anticholinergic, Sedation & Inhibition of Serotonin & NAD reuptake	64-90% response Decrease frequency , nocturia & pain
Hydroxyzine	H1 receptor antagonist → inhibits mast cell activation	30-55% response – effective in atopic individuals
Gabapentin	Unknown	50-63% response – mainly pain relief
Nifedapine	Calcium channel blocker	Up to 75% response – ½ relapse after 4 months
Nalmefiene	Opioid antagonist → Inhibits mast cell degranuation	Up to 59% response
L-Arginine	Substrate for nitric oxide synthase	Up to 33% response
Oxybutynin	Acetylcholine inhibitor	Adjuvant therapy
Tolteridine	Muscarinic receptor antagonist	Adjuvant therapy
Oxycodone	Short acting narcotic	Used to relieve pain while other therapies taking effect
Suplatast Tosilate	Immunoregulatory Drug	71% complete response 14% partial response lasting 1 year

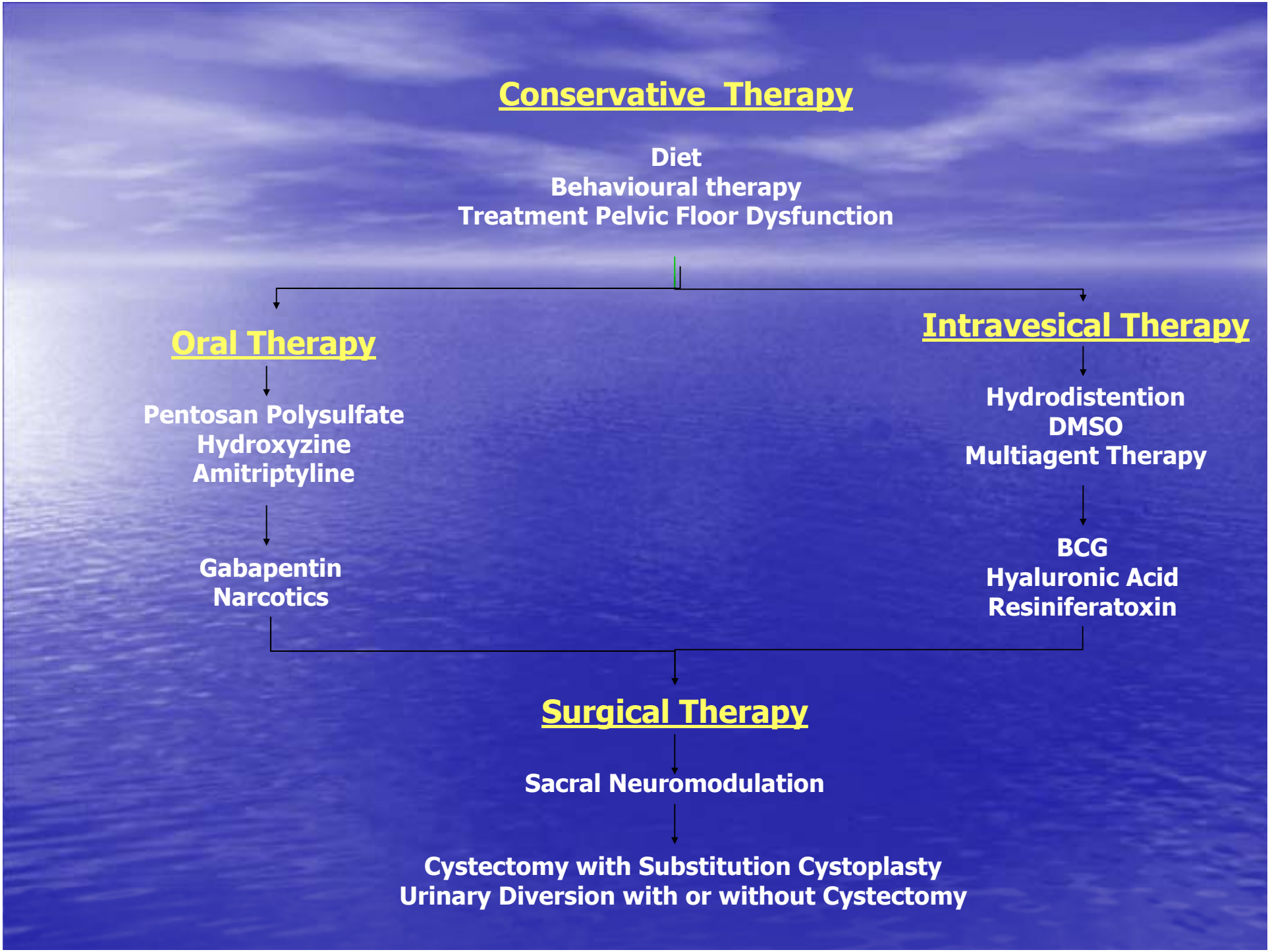
Management – Intravesical Therapies

Therapy	Mode of Action	Results
Hydrodistention	➢Ischaemia of submucosal bladder plexus ➢Widespread mast cell content exhaustion	Dependant on bladder capacity under General Anaesthesia: ➢> 600 mls 12% ➢<600 mls 26% No response > 6 months
DMSO	➢Antiinflammatory ➢Desensitisation / Blockade of afferent nociceptive pathways	➢93% response rate ➢40-52% relapse rate at 24 months ➢93% response to further treatment
BCG	Immune modulator	➢60% response ➢Persistent response in 89% at 27 months
Chlorpactin	Bleach like agent	50-60% response rate of 6 months duration
Hyaluronic Acid	➢GAG replacement ➢Free radical scavenging ➢Immune modulation	56-71% Response rate
Resiniferatoxin	Desensitization of bladder efferents	80% response but short lived
Multiagent therapy	Additive effect of individual agents	92% response rate – mean duration 8 months

Current Management of Interstitial Cystitis

Surgical Therapy

- 10 % disease severe enough for major surgical intervention
- Surgical procedures include:
  - Subtrigonal or supratrigonal cystectomy and substitution cystoplasty
  - Cystectomy with urinary diversion (either ileal conduit, continent diversion or neobladder


Conservative Therapy
Diet
Behavioural therapy
Treatment Pelvic Floor Dysfunction
Oral Therapy
Pentosan Polysulfate
Hydroxyzine
Amitriptyline
Gabapentin
Narcotics
Intravesical Therapy
Hydrodistention
DMSO
Multiagent Therapy
BCG
Hyaluronic Acid
Resiniferatoxin
Surgical Therapy
Sacral Neuromodulation
Cystectomy with Substitution Cystoplasty
Urinary Diversion with or without Cystectomy