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 cystitis
    - 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 cystitis 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 & suprapubic 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 (Acyclovir) 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 immunocompromised 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-inflammatory & 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
• Glomerulations or Hunner's ulcer on cystoscopic examination, and

• Pain associated with the bladder or urinary urgency
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
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 patients
  - 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

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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mode of Action</th>
<th>Results</th>
</tr>
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</table>
| 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

**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