Interstitial Cystitis in Cats: How it relates to Human IC

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The Ohio State University  buffington.1@osu.edu
My background

• Commercial angus ranch in CA
• USCG
• UCD ('76, '81, '82, '87!)
• OSU – ’87- present
• Things change…. 
My background

- Commercial angus ranch in CA
- USCG
- UCD ('76, '81, '82, '87!)
- OSU – ’87- present
- Things change…. 
# Introduction to (F)IC

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>P,U,F</td>
<td>P,U,F</td>
</tr>
<tr>
<td><strong>Ulcer</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>~90%</td>
<td>~10%</td>
</tr>
<tr>
<td><strong>Bladder cap.</strong></td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td><strong>Cystectomy</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Cats</strong></td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Classifying Pain

Pain

- Acute
- Chronic

Chronic

- Somatic
- Visceral

Visceral

Nociceptive (Neuro?) (Idio?) pathic
Signs vs. Causes

**Signs**
- Pain
- Urgency
- Frequency
- Blood

**Causes**

- CaOx: 6%
- MAP: 7%
- Behavior: 9%
- Anatomy: 11%
- IC: 63%
- UTI: 2%
- TCC: ?Stone: 63%
(F)IC Diagnosis

**Rule Out**
- Stone
- Behavior
- UTI
- Cancer
- Anatomical defect

**Rule In**
- Bladder Lesions
Saline distention (Mean±SEM)  
(P< 0.05 for Group, <0.001 for Pres.)

- FIC (13 fibers from 7 cats)
- Normal (6 fibers from 2 cats)

Bladder Pressure (cm H₂O)

PPS

Normal Cat  
IC Cat

Deltamethrin  
Naphthyl ac. phosph.

Normal (6 fibers from 2 cats)  
IC (13 fibers from 7 cats)

CAP

Bladder Pressure (cm H₂O)
A naturally occurring model – Interstitial Cystitis in humans

- Multifactorial result of a multimodal cascade of events
- Precipitated by some initiating event
- Propagated by (various) mechanisms

“…this condition is not well understood, generally underdiagnosed, and poorly treated.”

Interstitial cystitis: A chronic pelvic pain syndrome
Nickel, JC Medical Clinics of North America 2004, 88(2)
(F)IC FAQ

- Sudden onset
- Variable severity
- Lesions ≠ symptoms
- Affects both genders
- Waxing and waning signs
- Exacerbated by stressors
- “spontaneous” remission
- No standard (effective) treatment
Is (F)IC a Model for (F)IC?

- **Criteria**
  1. Face Validity
  2. Predictive validity
  3. Construct validity

- **Natural vs. Induced**
  (messy, hard, costly, valid? vs. clean, easy, cheap, valid?)
### Face Validity

#### Patient features

<table>
<thead>
<tr>
<th></th>
<th>Human beings</th>
<th>Cats</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Gender</td>
<td>Females and males</td>
</tr>
<tr>
<td>2</td>
<td>Bladder symptoms</td>
<td>Frequency, urgency, pain</td>
</tr>
<tr>
<td>3</td>
<td>Non-bladder symptoms</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Clinical course</td>
<td>Waxes and wanes</td>
</tr>
<tr>
<td>5</td>
<td>Meet NIDDK criteria</td>
<td>Most</td>
</tr>
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#### Local bladder Abnormalities (AN)

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>6</td>
<td>Petechial hemorrhages</td>
</tr>
<tr>
<td>7</td>
<td>Urothelial Permeability</td>
</tr>
<tr>
<td>8</td>
<td>Tight junction function</td>
</tr>
<tr>
<td>9</td>
<td>Urothelial cell abnormalities</td>
</tr>
<tr>
<td>10</td>
<td>Mast cells</td>
</tr>
<tr>
<td>11</td>
<td>Total GAG excretion</td>
</tr>
<tr>
<td>12</td>
<td>GAG GP-51expression</td>
</tr>
<tr>
<td>13</td>
<td>Vasodil'n and edema w/o infl.</td>
</tr>
<tr>
<td>14</td>
<td>Antiproliferative factor</td>
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#### Sensory AN

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<table>
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<tr>
<td>15</td>
<td>Bladder SP-IR</td>
</tr>
<tr>
<td>16</td>
<td>Sensory neuron AN</td>
</tr>
<tr>
<td>17</td>
<td>Dorsal root ganglia AN</td>
</tr>
<tr>
<td>18</td>
<td>Sacral cord SPIR</td>
</tr>
<tr>
<td>19</td>
<td>Bladder SP receptors</td>
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</table>

#### Central AN

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>20</td>
<td>Response to stress</td>
</tr>
<tr>
<td>21</td>
<td>Startle responsiveness</td>
</tr>
<tr>
<td>22</td>
<td>LC, HT TH &amp; CRF IR</td>
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#### Hormonal AN

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<thead>
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<tr>
<td>23</td>
<td>Adrenocortical</td>
</tr>
<tr>
<td>24</td>
<td>Gonadal</td>
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#### ANS AN

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<tbody>
<tr>
<td>25</td>
<td>Plasma [CCE]</td>
</tr>
<tr>
<td>26</td>
<td>Urine NE excretion</td>
</tr>
<tr>
<td>27</td>
<td>Bladder neuropeptide Y-IR</td>
</tr>
<tr>
<td>28</td>
<td>Bladder TH IR</td>
</tr>
<tr>
<td>29</td>
<td>Bladder NE content</td>
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#### Co-morbid disorders

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<tr>
<td>30</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>31</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>32</td>
<td>Neurological</td>
</tr>
<tr>
<td>33</td>
<td>Psychological/behavioral</td>
</tr>
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#### Response to treatment

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<tbody>
<tr>
<td>34</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>35</td>
<td>Psychological/behavioral</td>
</tr>
</tbody>
</table>
Where is the Problem?

Systemic?

Evidence

- No identifiable organism or toxin
- Inconsistent “GAG” findings
- Lesions ≠ signs
- Ineffectiveness of local therapies
- “Phantom” pain
- Co-morbidity profile & pattern
- Altered SNS/HPA

Caveats

- Inadequately investigated
Could the problem involve the Stress Response System?

- Sensitivity to surroundings
- Comorbid disorders
- Other factors?
The Stress Response System - Healthy

- HT
  - CRF
    - BS
      - SNS
        - CCE, IM
    - AP
      - ACTH
        - ACTH
          - AC
            - Steroids
  - AC
    - Steroids
IC – ↑SNS

- ↑CRF IHC, CSF - C*
- ↑Plasma, CSF NE - C*
- ↓α₂, β₁ -AR – C*
- ↑Bladder NE - C*
- ↑Bladder TH - C&H*
- ↑Urine NE – H*
- ↓Perfusion with filling – H*

* State Dependent

J. Urol. 172;1242-8, 2004
BPS/IC – \(\uparrow\)HPA

- \(\uparrow\)Central CRF* - C
- \(\uparrow\)Plasma ACTH* - C
- \(\downarrow\)AC output* – C, H
- Small Adrenal cortices, esp. F&R - C

* State Dependent
HPa - Histopath

<table>
<thead>
<tr>
<th></th>
<th>FIC</th>
<th>H</th>
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<tbody>
<tr>
<td>Weight (mg)</td>
<td>140</td>
<td>200</td>
</tr>
<tr>
<td>Medulla</td>
<td></td>
<td>=</td>
</tr>
<tr>
<td>Glomerulosa</td>
<td>↓20%</td>
<td></td>
</tr>
<tr>
<td>Fasc. + Retic.</td>
<td>↓40%</td>
<td></td>
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</table>

P=0.004

P=0.07
Not just Cortisol

Measured ACS may be mediators, or markers, of AC function.
HPa Changes - IC

Female IC Patients
P=0.12

Serum Free Cortisol μg/dL

Normal range

Remission (4)
Flare (11)

Female IC Patients
P<0.0001

Serum DHEAS μg/dL

Normal range

Remission (3)
Flare (11)

J. Urol. 172;1242-8, 2004
HPa Changes - CPPS

- ↑ Precursor/Product
- NSD Cortisol
- ↓ Cort r with ↑ pain in pts

Urology 2008;71;261-6
Effect of IC on Acoustic Startle Response

- Brainstem reflexive defensive response to unexpected, loud stimuli.
- ↑ response also seen in other neurovisceral disorders
Effect of IC on Acoustic Startle Response

- Brainstem reflexive defensive response to unexpected, loud stimuli.
- ↑ response also seen in other neurovisceral disorders

13 F IC/PBS patients (age=45.7±3.2) and 16 F controls (age=37.2±3.0, difference ns)
Sickness Behaviors

- Food intake
- Upper GI
- Lower GI
- Bladder
- Epiphora
- Hair & Skin
Predictive Ability

¶↓ Adrenocortical function
  • Cats – 2003
  • Women – 2004
  • Men - 2008

¶↑ Startle responsiveness
  • Cats – 2001
  • Women - 2007

Others ?
How did this occur?

• Distal
  • SNS
  • HPA
• Immune
• Proximal
  • Startle
  • Behavioral
What Determines Activation of the Stress Response System?

Environmental stressors (work, home, neighborhood)

Major life events

Trauma, abuse

Perceived stress (threat, helplessness, vigilance)

Behavioral responses (fight or flight; personal behavior — diet, smoking, drinking, exercise)

Physiologic responses

Adaptation

Allostatic load

Physiol. Rev 2007;87:873-904
Allostatic Load

Other allostatic Illnesses (?)

- Visceral
  - Thoracic
  - Abdominal
  - Pelvic
- Somatic
  - Skin
  - Muscle
  - Bone
- Brain
  - Anxiety
  - PTSD
  - Depression

Eur. J. Pharm. 583;174-85, 2008
Can the SRS affect the bladder?

Urothelial pathophysiological changes in feline interstitial cystitis: a human model

JOHN P. LAVELLE, SUSAN A. MEYERS, W. GIOVANI RUIZ, C. A. TONY BUFFINGTON, MARK L. ZEIDEL, AND GERARD APODACA

Department of Urology, and Laboratory of Epithelial Cell Biology, Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15213; and Ohio State University Veterinary Hospital, Columbus, Ohio 43210-1089

The response of junctional complexes to induced desquamation in mouse bladder urothelium

Peter Veranič*, Kristijan Jezernik

Institute of Cell Biology, Medical Faculty, Lipičeva 2, Ljubljana, Slovenia

Received 16 April 1999; accepted 15 February 2000
Stress & Hematuria

- Remove food
- Collect samples
- New cage, new food
- Repeat sample collection at Day 3 and 8
Mechanism?

Eur. J. Pain 2007;11;756-63
Anes. Clin. NA 2006;24;325-40
Do Cats with FIC have a sensitized SRS?

✓ ↑ SNS/PSNS
✓ ↓ Adrenocortical restraint
✓ ↑ Startle
✓ ↑ Sickness behaviors
How did the SRS become sensitized?

- Bladder disease?
- Genetic influences?
  - Familial clustering
  - Twin concordance
  - Chromosome 13 AN
- Epigenetic influences?
  - Early experiences
Early experience?

- Maternal threat
- SRS products → fetus
- Sensitization of SRS at HT
- ↓ ACTH release
- AC hypoplasia
Int. Factors & Epigenetic Influences
Adding the time dimension?

VULNERABILITY

ENVIRONMENT

EVOLUTION

DEVELOPMENT

Genetic Predisposition

Epigenetic Effects

“Event”

RECOVERY

IFIC

G.I.

SKIN

RESP.

BEHAV.

Tidsskr Nor Laegeforen. 2007;127:3228-31
Int. Factors, Epigenetic. Infl. & Environmental Factors
Environmental factors affecting indoor-housed cats

- Owners
- Other animals
- Intercat Conflict
- Diet
- Toilet
- Scratching objects
- Resting areas
Int. Factors, Epigenetic. Infl. & Environmental Factors

Clinical Threshold
Construct Validity?

good theoretical understanding of the etiopathogenesis of IC

Afferent

Efferent
Effect of Oral PPS on LUTS (given BID on treat before meal)

FISH Index (0-3)
- Frequency
- “Inappropriate urination”
- Straining
- Hematuria
Effect of PPS on LUTS

Outcome

- all groups improved significantly (p<0.001)
- Drug = placebo
Effect of PPS on LUTS –
20 Outcomes

- Client Satisfaction - 80%
  Moderately to highly effective
- Cystoscopy - 71%
  Improved

Bar chart showing outcomes based on PPS mg/kg BW/day:
- 0, 2, 8, 16 mg/kg BW/day

Percentage of outcomes: 0% - 100%
A Follow-up Study
Effect of 10 Months of Treatment
Interpretation

- Results exonerate UB as $1^0$ cause of FIC.
- Although better (and still alive), the cats are not “cured” or “normal”
- Results suggest “top-down” involvement.
Diagnostic Criteria?

- FIC symptoms+
- Vulnerability factors
  - Early adverse experience
  - Environmental instability
- Multiple comorbidities
  - Visceral
  - Somatic
  - Central
- Familial co-aggregation

Construct Validity?
Summary

• (F)IC may be “allostatic illnesses”
• Developmental issues may play a role through EMGEX
• History, context and expectation matter
• Now what?
How to study Chronic pain?

<table>
<thead>
<tr>
<th>Level</th>
<th>Examples</th>
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</thead>
<tbody>
<tr>
<td>Social</td>
<td>Stressors, Conflict</td>
</tr>
<tr>
<td>Behavioral</td>
<td>Personality, Coping</td>
</tr>
<tr>
<td>System</td>
<td>CNS, SRS, Neuroendocrine</td>
</tr>
<tr>
<td>Cellular</td>
<td>Receptors, Ligands</td>
</tr>
<tr>
<td>Molecular</td>
<td>DNA, RNA, etc</td>
</tr>
</tbody>
</table>
Thanks to:


**U Pittsburgh** - C deGroat, G Apodaca, L Birder, M Booth, A Kanai, S Kiss, J Lavelle, S Meyers, J Roppolo, G Somogyi, C Tai, M Zeidel

**Cincinnati VA** – T Geracioti, N Ekhatar, L Bednarik

**NIH** – L Nyberg, K Pacak

**UCD** – J Westropp, and my mentors and professors

Winn, ICA, NIH