LUTS in Cats - From FUS To Pandora Syndrome

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Plan

1. Introduction, background, diagnosis
2. Treatment – acute, chronic
3. Follow-up & prognosis
4. Conclusions
Lower Urinary Tract Signs (LUTS) - common in cats

Top 10 Feline VP Insurance Claims – 2013

1. Bladder/urinary tract
2. Periodontitis/Dental disease
3. Chronic kidney disease
4. Excessive thyroid hormone
5. Upset stomach/Vomiting
6. Diabetes
7. Diarrhea/Intestinal upset
8. Lymphoma
9. Upper respiratory virus
10. Skin allergies
Signs

- Frequency
- Inappropriate
- Straining
- Hematuria
LUTS ~ 100 years of History

- 1920s – Environment, diet, weight
- 1950s – ↑Ash (mineral)
- 1970s – ↑Mg, infection, ↓H₂O, *environment*
- 1980s – ↑Alkali
- 1990s - “Interstitial Cystitis (IC)”
We Need YOU!

If you have a client who might donate an IC cat they intend to euthanize, please call 614-292-7987
The “Brick” Model

Outside influences cause disease

Diet
Infestation
Infection
Injury
Introduction

There is alteration in expression of components of the nonneuronal acetylcholine machinery in FIC esophageal epithelium as well as bladder urothelium.”

Nervous System

Saline distention (Mean±SEM) (P < 0.05 for Group, <0.001 for Pres.)

Bladder Pressure (cm H₂O)

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

PPS

Nervous System

FIC (13 fibers from 7 cats)
Normal (6 fibers from 2 cats)
Acoustic Startle Responses

Acoustic Startle

mV (log10)

Healthy (n=11)
FIC (n=16)

Pre
Post

Enrichment

A large object is dropped by someone 300 miles away.
Chelimsky et al., compared the structural integrity of the autonomic nervous system (ANS) in IC and control females using CV response to deep breathing, Valsalva maneuver, 30 min head up tilt & sudomotor test.

**Results** The two groups did not differ, except for elevated average peak heart rate at baseline (supine; p = 0.06) for IC subjects prior to a tilt test.

**Conclusions** - No structural ANS abnormalities were found in IC subjects. Higher baseline HR supports the concept of functional rather than structural ANS changes, such as an abnormality of sympathetic/parasympathetic balance that will require further evaluation.
Fig. 1 Mean peak heart rate data at baseline (interval 0) and during the first, second, and third 10-min blocks (intervals 1, 2, and 3, respectively) of the upright tilt. a Slopes of post-baseline trends for healthy controls and subjects with IC/BPS. Data are mean peak heart rate ± SE. b Raw mean peak HR data points for each group at their respective intervals.
Autonomic Alterations - Functional

Nervous System

[Graph showing HF-HRV for different groups: HC, MPP, IC/BPS + MPP, IC/BPS]

[Graph showing HF HRV for different groups: H-HF, FC-HF]
Table 3
Results of paired t-tests of physiologic measures. Bold type indicates significant results at $P < 0.05$ level. FIC = feline interstitial cystitis; B = baseline; S = stress; SD = standard deviation; N = number of cats analyzed.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Units</th>
<th>Reference range</th>
<th>Healthy Baseline Mean ± SD</th>
<th>Healthy Stress Mean ± SD</th>
<th>B v S P-value</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte</td>
<td>($x 10^9$/L)</td>
<td>4.0–14.5</td>
<td>8.1 ± 1.7</td>
<td>7.84 ± 1.49</td>
<td>0.62</td>
<td>10</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>($x 10^9$/L)</td>
<td>3.0–9.2</td>
<td>2.9 ± 0.74</td>
<td>2.86 ± 1.02</td>
<td>0.98</td>
<td>10</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>($x 10^9$/L)</td>
<td>0.9–3.9</td>
<td>4.25 ± 1.79</td>
<td>4.24 ± 1.18</td>
<td>0.98</td>
<td>10</td>
</tr>
<tr>
<td>N: L</td>
<td></td>
<td></td>
<td>1.71 ± 1.25</td>
<td>1.71 ± 0.94</td>
<td>0.99</td>
<td>10</td>
</tr>
<tr>
<td>IL-1β</td>
<td></td>
<td></td>
<td>0.8 ± 0.28</td>
<td>0.67 ± 0.46</td>
<td>0.28</td>
<td>10</td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td></td>
<td>1.51 ± 0.86</td>
<td>0.85 ± 0.49</td>
<td>0.04*</td>
<td>9</td>
</tr>
<tr>
<td>TNF-α</td>
<td></td>
<td></td>
<td>0.6 ± 0.48</td>
<td>0.62 ± 0.52</td>
<td>0.47</td>
<td>10</td>
</tr>
<tr>
<td>Cortisol</td>
<td>(ng/ml)</td>
<td>1.0–13.5</td>
<td>5.6 ± 3.3</td>
<td>5.26 ± 2.87</td>
<td>0.72</td>
<td>10</td>
</tr>
</tbody>
</table>

* Indicates a statistically significant decrease from baseline.
** Outliers removed from data set (Healthy N = 10, FIC N = 18).
*** Removed for missing data.

Table 4
Expression of serum interleukin-1β, interleukin-6, tumor necrosis factor-α, and interleukin-8 in patients with interstitial cystitis/bladder pain syndrome and control patients [55].

<table>
<thead>
<tr>
<th>Controls (n = 26)</th>
<th>IC/BPS (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F:16 M:10</td>
<td>F:26 M:4</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32.4 ± 1.56 (22–55)</td>
<td>50.6 ± 2.68 (24–86)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-1β (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.64 ± 0.47 (0.00–6.08)</td>
<td>6.45 ± 0.71 (2.77–23.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.79 ± 0.21 (0.00–3.67)</td>
<td>1.52 ± 0.24 (0.00–6.14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.91 ± 0.17 (0.00–4.64)</td>
<td>2.63 ± 0.60 (0.62–13.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-8 (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.45 ± 0.21 (0.00–4.09)</td>
<td>3.23 ± 0.48 (0.00–15.08)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Mean ± standard error (range).
IC/BPS = interstitial cystitis/bladder pain syndrome; IL = interleukin; TNF = tumor necrosis factor.
Inflammation (salivary cort) correlated with pain

**Fig. 1.** Means and standard deviations of diurnal salivary cortisol concentrations in interstitial cystitis/bladder pain syndrome (IC/BPS) participants and healthy controls. Natural log-transformed values are back transformed. *Significant time-by-group interaction in repeated-measures analysis of variance (F$_{2,06}$ = 4.414, $P$ = .016).

**Fig. 2.** Means and standard deviations of Genitourinary Pain Index (GUPI) pain frequency item for interstitial cystitis/bladder pain syndrome (IC/BPS) participants grouped by median split of cortisol slope and Toll-like receptor 4 (TLR-4) inflammation response.
1. Nonspecific clinical and behavioral signs such as vomiting, diarrhea, decreased food and water intake, fever, lethargy, somnolence, enhanced pain-like behaviors, and decreased activity, grooming, and social interactions. Seen in all species.

2. Can occur in response to:
   a. Infection
   b. Inflammation
   c. **Threat**
SB - by system

% of total SB

- Affected (20)
- Control (12)

Sickness Behavior:
- Upper GI
- Not eating
- Not using box
- Skin
- No elimination
- Avoidance
- Lower GI
- Other
- LUT's
Effect of Stress on SB

Average # SB's/week

P=0.0005

P=0.0001

H-C
H-Stress
FIC-C
FIC-Stress
Endocrine System

**Figure 1.** Mean serum cortisol response ± SD to 125 μg synthetic ACTH administered intramuscularly was significantly less in cats with P/C than in healthy cats (2-way repeated measures ANOVA p < 0.05). Tukey-Kramer post hoc tests were used to compare groups at each time point.

**Table 3. Adrenocortical function in women with IC**

<table>
<thead>
<tr>
<th></th>
<th>Flare</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>44 ± 7.8</td>
<td>51 ± 18</td>
</tr>
<tr>
<td>Mean body mass index ± SD</td>
<td>26 ± 6</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>Free cortisol:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (μg/dl)</td>
<td>0.55 ± 0.14</td>
<td>1.06 ± 0.48</td>
</tr>
<tr>
<td>No. pts</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>DHEAS:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (μg/dl)</td>
<td>49 ± 16</td>
<td>219 ± 52</td>
</tr>
<tr>
<td>No. pts</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

**Figure 2.** Adrenal gland weight as percent of cat body weight. Weight of adrenal glands in cats with P/C was significantly less than that in healthy cats (p < 0.0001). Horizontal lines indicate mean.
Endocrine System

--Diagram on the page shows the Endocrine System, focusing on the synthesis of hormones, starting from cholesterol through various intermediates such as pregnenolone, progesterone, androgenic hormones, and finally to mineralocorticoids.

**Figure 1.** Normal pathways and adrenocortical biochemical abnormalities in men with CP/CPPS. First step in adrenal steroid synthesis is combination of acetyl coenzyme A and squalene to form cholesterol, which is then converted into pregnenolone. Enclosed area contains core steroidogenic pathway used by adrenal glands and gonads. 21 = 21-hydroxylase (CYP21A2, P450c21); DHEA = dehydroepiandrosterone; DHEAS = DHEA sulfate.

**KEY**
- Increased hormone concentration
- Decreased hormone concentration
- No difference between cases and controls
- Concentration not measured

- Core steroidogenic pathway used by adrenal glands and gonads
- Glucocorticoid synthetic pathway
- Mineralocorticoid synthetic pathway
- Sex steroid synthetic pathway
Small Adrenal Glands

- Weight (mg): FIC 140, H 200
- Medulla
- Glomerulosa: ↓20% P=0.07
- Fasc. + Retic.: ↓40% P=0.004
Do LUTS come first?

- Neurological
- Immune
- Sickness Behaviors
  - Somatic
    - Gastrointestinal
    - Skin
    - Cardiovascular
    - Respiratory
  - Central
    - Fear
    - Anxiety
    - Attached
- Endocrine – adrenal abnormalities
Synthesis

Anes. Clin. NA 2006;24;325-40

Early life environments epigenetically shape stress responses later in life in both rodents and humans.*

*Gräff J et al. Physiol Rev 2011;91:603-649
Epigenetics

Genetics – genes you have
Epigenetics - genes you use

Sculpted by environment
Epigenetic Processes

LUTS +

- Systemic pathology
- Co-morbidity
- Order of onset
- EAE
- Epigenetics
- Environment
Synthesis - PS

VULNERABILITY/RESILIENCE

ENVIRONMENT

EVOLOLUTION

DEVELOPMENT

Genetic Predisposition

Epigenetic Effects

FIC

G.I.

RECOVERY

SKIN

RESP.

BEHAV.
LUTS Diagnosis

- Acute Idiopathic Cystitis/Urethritis
  - Recurrent LUTS
    - FIC
      - Pandora Syndrome?
        - YES
        - No
      - Self-Limiting
      - Frequently Recurrent
      - Persistent
      - Urethral Obstruction (males)

- Urolithiasis
- Urethral Obstruction
- Iatrogenic
- UTI
- Behavioral
  - Stressed Healthy
  - Pandora Syndrome?
    - YES
    - No

- Neurogenic
- Incontinence (No Urge)
- Trauma
- Neoplasia (TCC)
- Trauma
- Iatrogenic
- Self-Limiting
- Frequently Recurrent
- Persistent
- Urethral Obstruction (males)
LUTS Diagnosis

External World

Brain

Immune
- Acute Idiopathic Cystitis/Urethritis
  - Recurrent LUTS
    - FIC
      - Pandora Syndrome?
        - YES
        - NO

Endocrine
- Urolithiasis
- Urethral Obstruction
- Iatrogenic
- UTI
- Stressed
  - Healthy
- Pandor Syndrome?
  - YES
  - NO

Autonomic
- Neurogenic
- Incontinence (No Urge)
- Trauma
- Neoplasia (TCC)
- Self-Limiting
- Frequently Recurrent
- Persistent
- Urethral Obstruction (males)
- Behavioral
LUTS ~ 100 years of History

- **1920s** – Environment, diet, weight
- **1950s** – ↑Ash (mineral)
- **1970s** – ↑Mg, infection, ↓H₂O, environment
- **1980s** – ↑Alkali
- **1990s** – “Interstitial Cystitis (IC)”
- **2000s** – Comorbidities, Early adverse experience, DOHaD, epigenetics, environment
- **2010** – Pandora Syndrome (?)
- **2010s** – more research!
Environmental effects on Cats; not just LUTS

- CaOx stones
- FORL
- Obesity
- Type 2 DM
- Behavior
- Others?
Conclusions

1. Take a thorough history (Look beyond the organ!)
2. Pandora Syndrome Ho:
   a. Not just “FIC” (?)
   b. Not just cats
   c. Currently testing it
Questions?
Comments?
Approach to Therapy

**Acute**
- Environment
- Analgesia

**Chronic**
- Client
- Environment
- Cat
Cats in cages are...

- Captive
- Dependent
  - Food & water
  - Elimination
  - Safety
- Scared
Chronic Treatment

• Treating the Client
• Treating the Environment “Multimodal Environmental Modification (MEMO)”
• Treating the Cat
Communicating with Clients about chronic care

- Clients expect us to “find it & fix it”.
- We expect: “one ill, one pill & one bill”.

Treating the Client
Treating the Client

Chronic care is a little Different….

• Manage vs. Cure
• Clients do the work
• We can help
Communication Goals

- ↓ anxiety
- ↑ trust
- Empathize
- Educate
- Enlist
## “Expert” vs. “Coaching” approaches

<table>
<thead>
<tr>
<th>Expert</th>
<th>Coach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treats patients</td>
<td>Helps clients help themselves</td>
</tr>
<tr>
<td>Tells clients what to do</td>
<td>Builds motivation, confidence, and engagement</td>
</tr>
<tr>
<td>Relies on expert skills and knowledge</td>
<td>Relies on client self-awareness and insights</td>
</tr>
<tr>
<td>Strives to have all the answers</td>
<td>Strives to help clients find their own answers</td>
</tr>
<tr>
<td>Focuses on the problem</td>
<td>Focuses on what is working well</td>
</tr>
<tr>
<td>Dictates</td>
<td>Collaborates</td>
</tr>
</tbody>
</table>
Where Are We?

Environment
Health

Barren
Chaotic

Good
Poor

Treating the Environment
Environmental Enrichment Resources and References

Converging evidence from a variety of studies (available below) suggests that idiopathic cystitis (IC) in some cats is more likely to be a systemic disorder affecting the bladder than an intrinsic bladder disease. In these patients, IC may be more comparable to the effects on the bladder of diabetes or spinal cord injury than of a urinary tract infection or bladder tumor. That the clinical signs of all these (and other) conditions are similar may be related more to the limited number of responses the bladder is capable of mounting than to the location of the insult.

Cats with IC seem to have variably severe involvement of their stress response system (internal factors), and are exposed to a range of environmental stimuli (external factors). Given the current state of our knowledge, we have limited capacity to treat the internal factors, and so have focused on modification of external factors pending development of drugs to modulate the activity or output of the stress response system.

Although many indoor housed cats appear to accommodate to a wide range of surroundings, the neuroendocrine abnormalities in the cats we treat do not seem to permit them the adaptive capacity that healthy cats have. Moreover, since external factors have been shown to unmask susceptibility to many common chronic diseases in cats, we recommend environmental enrichment as preventative health care for all cats, just as we recommend appropriate vaccination and provision of satisfactory nutrition.

You will need Adobe Reader to download and view PDF documents.

Forms and Documents

- Our current indoor evaluation form in English & French
- How to set up a low-stress cage for a cat
- Environmental Enrichment for Confined Cats

Optimal housing and handling of cats

Learning to safely house and handle cats in cages improves the experience for both the cats and the caretaker. This training will help you better understand cats and how they interact with their cages, their environment and the humans they encounter. Click HERE to begin the interactive training.
Multimodal Environmental MODification:

**Goals:** – to help clients:

1. Understand how they contribute to their cat’s health and wellbeing
2. Manage their cat’s environment
3. Improve the cat’s pControl/pThreat (& activation of stress response system).
Multimodal Environmental MEdification:

Methods:
1. Client education
2. Environmental Enrichment
   a. Resources – food, water, litter box, toys
   b. Interactions
      i. Other cats
      ii. Other animals
      iii. Humans
An Indoor Cat Resource ✔ List

✔ Understanding

✔ Safety

✔ Choice
  ✔ Food & Water
  ✔ Toilet
  ✔ Interactions

✔ Stimulation
Understanding – How cats learn

+ Reinforcement
  • Praise
  • Treats
  • Praise

+ Punishment
  • Sticky tape
  • Aluminum foil
  • Carpet runner
  • Citrus scent
  • Yelling
  • Hitting
An Indoor Cat Resource ✓ List

✓ Understanding

☐ Safety
An Indoor Cat Resource ✓ List

✓ Understanding

☐ Safety
Outdoor access?
An Indoor Cat Resource ✔ List

✔ Understanding

✔ Safety

☐ Choice
  ☐ Food & Water
Food

- Cat – appropriate food for
  ✓ life stage
  ✓ BCS
- Diet
  ✓ Satisfactory
  ✓ Agreeable to owner
    AND cat
- Feeding – safe & enriched
Recent Diet Study

12 Month Study

Dry & Canned Combined Both “enriched”

Dramatic difference Between test Foods

No “enriched” or “usual care” control groups
Recent Diet Study

Dramatic difference between test foods; NSD between “vet test” and “usual care” (or other studies)
What Cats Need

Water
An Indoor Cat Resource ✓ List

✓ Understanding
✓ Safety
✓ Choice
✓ Food & Water
✓ Toilet
An Indoor Cat Resource ✔ List

- ✔ Understanding
- ✔ Safety
- ✔ Choice
  - ✔ Food & Water
  - ✔ Toilet
- ❏ Interactions
An Indoor Cat Resource ✓ List

✓ Understanding
✓ Safety
✓ Choice
  ✓ Food & Water
  ✓ Toilet
  ✓ Interactions
✓ Stimulation

I'm bored.

Amuse me.
An Indoor Cat Resource ✔ List

✔ Understanding
✔ Safety
✔ Choice
  ✔ Food & Water
  ✔ Toilet
  ✔ Interactions
✔ Stimulation – C & S
What Cats Need

Your results may vary…

ZIGGY...
by Tom Wilson & Tom II

SOMEBODY’S BEEN SCRATCHING THE FURNITURE AGAIN... AND I KNOW WHO IT IS!!

DON'T GIVE THAT INNOCENT LOOK! ALL THESE SCRATCH MARKS ARE EXACTLY YOUR HEIGHT!!

THAT'S WHY I GOT YOU THIS SCRATCHING POST! USE THIS FOR YOUR SCRATCHIN' FOR NOW ON!

SCRATCH SCRATCHITY SCRATCH SCRATCH SCRATCH SCRATCH
An Indoor Cat Resource ✔ List

✔ Understanding
✔ Safety
✔ Choice
  ✔ Food & Water
  ✔ Toilet
  ✔ Interactions
✔ Stimulation
Drug Therapy

Amitriptyline: “alt to euth”
NSAIDS: Be careful about hydration & kidney.
No benefit (NB) in humans; cats?.
Glucocorticoids - NB.
Antispasmodics (Valium, propantheline): NB
Antiadrenergics (phenoxybenzamine, prazosin, clonidine, etc.) - NB
Chronic Therapy

Other Drugs - NB

- Antibiotics
- Anti SP
- Elmiron

Other Tx - ??

- “alternative”?
- “complementary”?
Chronic Therapy

Research findings

• Laboratory
• Clinical
  • RCT
  • Observational
Sickness Behaviors

JAVMA 2011;238:67-73
Randomized, Placebo-Controlled Clinical Trial of Pentosan Polysulfate (PPS) for Treatment of Recurrent LUTS

ACVIM Forum 2009

Dennis J. Chew, DVM, Dipl ACVIM
Joseph W. Bartges, DVM, PhD, Dipl ACVIM
Larry G. Adams, DVM, PhD, Dipl ACVIM
John W. Kruger, DVM PhD, Dipl ACVIM
C.A. Tony Buffington, DVM, PhD, Dipl ACVN
Methods

- 107 cats with history of recurrent LUTS
- DX based on LUT evaluation including cystoscopy pre & post treatment
- Randomized to 0, 2, 8, 16 mg/kg PPS given BID on treat by owner
- Weekly 0-3 owner rating of LUTS – frequency, not using box, straining, hematuria, and vocalization for 26 weeks
Results – LUTS – 83%↓

Clinical - RCT

Total LUTS Score

8.1±0.5

1.4±0.7
Ten months of MEMO

The endogenous pharmacotherapy of MEMO

Environmental enrichment

Mediators

Up-regulation

- IGF-I
- BDNF
- Intracellular kinases (e.g., PKA)
- CREB
- Histone acetylation
- Synaptic receptors (e.g., NMDA)
- Neuronal adhesion molecules
- Neurotransmitter release (e.g., serotonin)

Effects

- Enhanced brain plasticity
- Faster brain development
- Brain repair
- Phenotypic rescue of intellectual disability
- Improved aging brain health

Down-regulation

- DNA methylation
- Inhibition/Excitation
- Extracellular matrix components
- β-amyloid

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Sale A et al. Physiol Rev 2014;94:189-234
Prognosis –

- Cat
- Client
- Environment
1. Chronic LUTS common in confined cats
2. Many cats also have other problems as well
3. Pandora Syndrome may explain some cases
4. Responsive to MEMO
5. Benefit from ongoing (chronic) care approach
Conclusions

- Cats *can* thrive indoors –
  - *Because changing context*
  - *Changes expectation*
  - *Which changes history!*

- Enrichment needs vary
  - Provide choice
  - Positive feedback

- Promotes health & wellbeing *for both!*
Questions?
Comments?