Urine Agony: Feline Lower Urinary Tract Disease
Joe Bartges, DVM, PhD, DACVIM, DACVN
Cornell University Veterinary Specialists, Stamford, CT, USA
Prevalence of lower urinary tract disease is more common in cats between 1 and 10 years of age; whereas in dogs, the prevalence increases with advancing age. In cats greater than 10 years of age, bacterial urinary tract infection is most common. In young cats, idiopathic lower urinary tract disease occurs most commonly. Urinary tract infections and urolithiasis has been discussed previously in this conference; therefore, this discussion will focus on feline idiopathic cystitis (FIC).

**WHAT IS THE PATHOGENESIS OF FIC?**
By definition, FIC is an idiopathic disease and therefore the underlying cause is unknown. As noted earlier, it is entirely possible (and perhaps even probable) that FIC is not a single entity, but rather a syndrome that may have more than one underlying cause. This, for example, is evident in the ongoing search for a potential viral role in some cases of FIC. Nevertheless, in a number of different studies, both local bladder abnormalities and/or neurohormonal changes have been observed in at least a proportion of cats affected by FIC. While these changes are hard to interpret, and again it can be difficult to differentiate cause from effect (and sometimes even incidental observation), they do support the concept of complex underlying abnormalities and predispositions that may contribute to the development of FIC.

There are several proposed local bladder abnormalities in the pathogenesis of FIC. Studies in cats with idiopathic cystitis have shown that as in humans with interstitial cystitis, there is a decreased concentration of glycosaminoglycans (GAGs) in the urine of affected cats. Other local bladder factors have also been identified that may have a role to play in the pathogenesis of FIC. These include: an altered tissue or and/or urine concentration of inflammatory or other bioactive molecules such as complement c4a, thioredoxin, NF-κB p65, galactin-7, I-FABP, fibronectin, and trefoil factor 2; mucosal muscarinic receptors have been reported to have increased sensitivity in cats with FIC, which could potentially enhance smooth muscle spontaneous contraction, although evidence of an overactive bladder has not been found in association with FIC; increased bladder tissue concentrations of norepinephrine and an increase in maximum urethral pressures and urethral closure pressures in affected cats; histological changes in the bladder wall including oedema, haemorrhage, vasodilation, occasionally ulceration, and a variable increase in the number of mast cells; there is evidence to support the presence of neurogenic inflammation and mediators of pain and inflammation in the bladder, with evidence of increased expression of transmitters such as ATP and nitric oxide, altered expression of purinergic receptors, increased numbers of substance P containing neurons, increased expression of high affinity substance P...
receptors, and increased excitability of afferent bladder neurons, with evidence that urothelial cells themselves may be involved in the process.

As in humans with interstitial cystitis, a number of neuro-hormonal abnormalities have been detected in cats with FIC that might have a role to play in the pathogenesis of the condition. These observations include: an increase in plasma norepinephrine and dihydroxyphenylalanine in FIC cats compared with normal cats, but without a concomitant increase in cortisol or adrenocorticotrophic hormone (ACTH); an increase in tyrosine hydroxylase immunoreactivity in the locus coeruleus of the brain of cats with FIC (during apparent quiescent periods), further supporting a role for increased sympathetic activity in cats with FIC; potential adrenal insufficiency in cats with FIC evidenced by significantly reduced responses to ACTH compared with healthy cats, and reduced volume of their adrenal glands; differences in responses to the α2-adrenergic agent medetomidine in FIC cats compared with normal cats. Collectively, these findings (although performed in a limited number of cats) lend support to the fact that FIC appears to be associated with a stress response in many cats, but also suggests an uncoupling of the normal stress responses with increased sympathetic stimulation but suppressed adrenocortical responses.

**Clinical Signs of Lower Urinary Tract Disease**

Causes of lower urinary tract disease in cats present with similar clinical signs including, but not limited to pollakiuria, hematuria, stranguria, and inappropriate urination.

**What Are Risk Factors For FIC?**

Data from studies are conflicting for the most part. Some studies show a higher risk in males while others show no gender predisposition. Most studies do not show a breed predilection; however, one study did show a predisposition in long-haired cats. In another study, the following factors were found to be associated with development of FIC: being more fearful than other cats in the same household, being more nervous than other cats in the household, having a lower water intake, partaking in less hunting activity, having lower activity levels, using a litter box, moving house, hiding when unknown visitors are in the house, having a higher body condition score, and having less access to an outdoor environment. Additionally, it is not uncommon for cats with FIC to have one or more other chronic diseases such as inflammatory bowel disease, respiratory disease, and behavioral disorders.

**Diagnostic Testing with Lower Urinary Tract Signs**

CBC and biochemical analysis are normal unless urethral obstruction is present. Urinalysis reveals hematuria; however, pyuria and bacteriuria may be present with UTI. Urine culture is negative unless UTI is present. Abdominal radiography and ultrasonography may be normal unless uroliths are present. In cats with FIC, cystoscopy reveals small pin-point hemorrhages called glomerulations and bladder wall biopsy often reveals submucosal edema, mucosal ulceration, possible submucosal inflammation, and possible fibrosis. FIC is a diagnosis of exclusion.

**Treatment of Lower Urinary Tract Disease**

**Urethral Obstruction**

Urethral obstruction may occur from uroliths or urethral plugs. Matrix-crystalline urethral plugs are found only in male cats and approximately 84% of matrix-crystalline plugs contain a mineral component with struvite being the most common mineral present. Uroliths have been discussed previously. Urethral obstruction results in dehydration, azotemia, metabolic acidosis, hyperphosphatemia, hyperkalemia, and eventually death. Treatment involves rehydration, relieving the urethral obstruction, and managing hyperkalemia. After relieving urethral obstruction, an indwelling urinary catheter may be required. If inserted, use a closed collection system, do not administer antimicrobial agents, and do administer urethral relaxants (alpha adrenergic blockers).
Non-Obstructive Idiopathic Lower Urinary Tract Disease
There have been dozens of proposed treatments for cats with lower urinary tract disease; very few have undergone evaluation in a randomized controlled clinical trial.

Antimicrobial Agents
The role of microbial agents in feline lower urinary tract disease is controversial. In young adult cats evaluated at university referral hospitals, the incidence of bacterial urinary tract infection is 1% or less; however, approximately 1 in 3 cats seen at primary care facilities in Norway had bacterial urinary tract infection. Furthermore, older adult cats are more likely to have a bacterial urinary tract infection and as many as 50% of older cats with lower urinary tract signs have a bacterial urinary tract infection. Unless a UTI is present, administration of an antimicrobial agent is not warranted.

Urinary Tract Antiseptics and Analgesics
Methenamine and methylene blue are not indicated in cats as they may induce metabolic acidosis and Heinz body anemia. Phenazopyridine is an over the counter preparation available for use by women with recurrent vaginitis/cystitis that causes Heinz body anemia in cats.

Smooth Muscle and Skeletal Muscle Relaxants
Many cats with FIC have urge incontinence and inappropriate urination. Propantheline, an anticholinergic agent, minimizes force and frequency of uncontrolled detrusor contractions and may be beneficial in some cats; however, one study did not document a benefit. Phenoxybenzamine and prazosin are sympatholytic agents that decrease urethral tone and spasm and may help some cats. Cats with FIC have been found to have a dysregulation in their stress response with an increase in sympathetic autonomic nervous tone and a decreased hypothalamic-pituitary-adrenal response. Prazosin has more systemic effects than phenoxybenzamine and, therefore, may have benefit in cats with FIC to decrease the increased sympathetic nervous system activation. Diazepam and dantrolene are skeletal muscle relaxants that may decrease tone and spasm of the distal urethra.

Anti-Inflammatory and Analgesic Agents
Glucocorticoids have been used to decrease inflammation; however, studies have shown no benefit in cats with FIC. They are contraindicated in cats with urethral obstruction or those that have indwelling urinary catheters because they increase risk of UTI. Nonsteroidal anti-inflammatory drugs (NSAID) may decrease inflammation and pain; however, they are contraindicated with azotemia and dehydration. Buprenorphine and Torbugesic do not have anti-inflammatory properties, but do decrease pain and appear to make cats with FIC more comfortable.

Amitriptyline
Amitriptyline is a tricyclic antidepressant that may have analgesic properties, stabilize mast cells, and decrease inflammation. In one uncontrolled study, 9 of 15 cats with idiopathic lower urinary tract disease improved with amitriptyline. One controlled study of cats with active lower urinary tract disease showed no benefit and cats receiving amitriptyline had a higher incidence of recurrence of lower urinary tract signs. The goal is to find a dose that will have a calming effect.

Glycosaminoglycans (GAGs)
Cats with FIC have decreased concentrations of GAGs in their urine. GAGs may have a protectant role at the mucosal-urine interface. Two controlled studies, failed to show a difference in clinical signs between a GAG and placebo in cats with idiopathic lower urinary tract disease. There is one pilot study of intravesical instillation of a GAG (A-CYST) in cats presenting with urethral obstruction that showed reduction in repeated urethral obstruction (0% recurrence in GAG treated cats versus 43% in placebo treated cats); however, it was not statistically different.

Dietary Modification
In cats with matrix-crystalline plugs or with struvite crystalluria, feeding a struvite preventative diet may have some benefit. In one study of cats with idiopathic lower urinary tract disease, cats fed a canned diet had fewer recurrences than those fed a dry diet. In a more recent randomized controlled clinical trial, cats
with FIC had an 89% reduction in recurrences when fed a diet enriched with omega-3 fatty acids and anti-oxidants also containing L-tryptophan and alpha-casozepine.

**Maropitant**

Maropitant is used as an anti-emetic because it is a neurokinin inhibitor. It has been suggested that may aid in treating cats with FIC by reducing spasticity; however, no studies have been performed to validate this hypothesis.

**Stress Reduction and Multi-Modal Environmental Modification (MEMO)**

The role of stress in eliciting clinical signs in cats predisposed to FIC is well documented. Decreasing stress by modifying environment may be beneficial. Cats do not respond to force, are territorial, and like to be in control of their environment. Minimizing stress and conflict may help some cats with FIC. Litter boxes and food should be away from noise and distractions. Cats like to climb, hide, scratch, and hunt; therefore, vertical and horizontal space should be provided. One food dish, water bowl, and litter pan should be available for each cat in the household with one additional of each. Additional information can be found at the Indoor Cat Initiative: https://indoorpet.osu.edu <VIN editor: link updated May 1, 2015>. Additionally, the ‘urinary stress’ diet that was shown to decrease recurrences by 89% is formulated to not only be anti-inflammatory but to also have a calming effect.

**Clomipramine and Fluoxetine**

These drugs are used for urine spraying / marking behavior. They appear to modify behavior may have some analgesic effects.

**Pheromones**

Feline facial pheromones may calm a cat; however, in one study of cats with FIC, no benefit was found.

**HOW DO I TREAT CATS WITH LOWER URINARY TRACT DISEASE?**

**Young Cat, First Episode**

- Urethral obstruction
  - Unobstruct
  - Radiographs, UA (other lab work?)
  - Indwelling catheter?
  - Torbugesic?
  - Diet change (likely)?
  - Antibiotics (peri-catheterizationMEMO?)
  - If persists or recurs, diagnostics
  - Urinalysis (minimum)
  - MEMO
  - Torbugesic?
  - Diet change? Likely - usually stones or plugs)
  - If persists or recurs
    - Do additional diagnostics
    - Diet?
    - Amitriptyline?
    - Glycosaminoglycans?

**Old Cat, First Episode**

- Urethral obstruction
  - Unobstruct
  - Radiographs, UA (other lab work?)
  - Indwelling catheter?
  - Torbugesic?
  - Diet change (likely) - stones or plug?
  - Others?
o Antibiotics (peri-catheterization)
o If persists or recurs - diagnostics
o No urethral obstruction
o Diagnostics
o MEMO
o Torbugesic?
o Diet change? Likely - urolithiasis - calcium oxalate)
o If persists or recurs
  ▪ Do additional diagnostics
  ▪ Torbugesic as needed
  ▪ Diet?
  ▪ Amitriptyline?
  ▪ Glycosaminoglycans?

REFERENCES