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## Feline idiopathic cystitis: pathophysiology and management

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Signs of a lower urinary tract disease in cats include variable combinations of frequent attempts to urinate, straining to urinate, urinating in inappropriate places in the house, dysuria and hematuria. These signs are not specific for any one particular disease; they can be seen in cats that have cystic calculi, bacterial urinary tract infections, or neoplasia. In approximately 2/3 of younger-middle aged cats that present with these clinical signs, no definitive diagnosis can be made and therefore this syndrome is called feline idiopathic cystitis (FIC).

**Pathophysiology**

Research on the bladder of cats with FIC has shown that histopathologic changes are generally nonspecific, and may include an intact or damaged urothelium with submucosal edema with minimal cellularity.[1] Clinical signs do not appear to correlate well with histopathologic (or cystoscopic) lesions in most cats. Preliminary research evaluating urodynamics in cats with FIC have shown no evidence of overactive bladder and occasional findings of decreased compliance have been noted (unpublished data). Studies evaluating bladder permeability have shown marked increases in permeability after hydrodistention [2] and may be mediated via the sympathetic nervous system. Sympathoneural-epithelial interactions appear to play an important role in permeability.[3]

Clinical signs of FIC can wax and wane and appear to be exacerbated by stressful circumstances. In previous studies in cats with FIC, we found they had a significant increase in tyrosine hydroxylase (TH) immunoreactivity in the brainstem (locus coerules)[4] as well as the paraventricular nucleus of the hypothalamus.[5] TH is the rate-limiting enzyme of catecholamine synthesis. The increased THIR observed in the LC of cats with FIC may provide a clue to the observation that clinical symptoms of FIC follow a waxing and waning course, and can be aggravated by environmental stressors. When evaluating catecholamine concentrations (CCE) in these cats we found plasma DOPA, NE, and DHPG concentrations were significantly increased in FIC cats at all times ($p<0.05$).[6] In contrast, no effects on urine cortisol:creatinine was identified, suggesting an uncoupling of these two parameters of the stress response.

In addition to the SNS, we have also found a decreased functional sensitivity of the alpha-2 adrenoceptors (α-2 AR) in cats with FIC.[7] Furthermore, we have identified abnormalities in the hypothalamic-pituitary-adrenal axis (HPA). After a high dose (125 µg) of synthetic ACTH was administered, cats with FIC had significantly decreased serum cortisol responses compared to healthy cats.[8] Although no obvious histological abnormalities were identified, the areas consisting of the zonae fasciculata and reticularis were significantly smaller in sections of glands from cats with FIC than from healthy cats. Therefore, it appears that while the sympathoneural system is fully activated in this disorder, the HPA axis is not.

The pathophysiology of FIC likely involves complex interactions between a number of body systems. How these systems communicate and manifest as FIC in some cats, but not in others remains to be determined. It is important for clinicians to understand that this syndrome is not just a 'bladder disease' amenable to simple diet or drug therapies in order to better treat their patients.

**Approach to the Patient**

***Diagnostics***

Because FIC is a diagnosis of exclusion, diagnostics should be performed to rule out other causes of lower urinary tract signs (LUTS) mentioned above. Urolithiasis can occur in approximately 12-15%[9] of cats with LUTS and an abdominal radiograph which includes the entire urinary tract should be performed. Less than 2% of young (<10 years of age) cats have true bacterial cystitis, so urine culture is a low yield test.[10] Quantitative urine culture should be performed in all cats with recurrent (>2) episodes. If clinical signs continue, despite therapy, an abdominal ultrasound, double contrast cystourethrogram, and/or cystoscopy can be performed to be certain no other lesions in the lower urinary tract were missed. Advanced imaging is especially indicated in elderly cats (>10 years of age) where FIC is not as likely.

***Treatment of FIC***

FIC can have a variable outcome. Clinical signs resolve spontaneously in as many as 85% of cats within 2-3 days, with or without treatment. Not all cats with FIC will require intense treatment and environmental modifications described below. As many as 50% of these cats will have another episode within 12 months and 39% recurred in a study of cats consuming dry food.[11] It is not yet possible to predict which cats with FIC will relapse; some cats have multiple recurrences, while clinical signs never resolve in a small population of severely affected

cats.
When a cat presents with LUTS, analgesic therapy seems appropriate for the acute management of the disease. Providing analgesia with non-steroidal anti-inflammatory agents or narcotics such as buprenorphine has been suggested, but no studies have been reported to date, and many drugs are not approved for these uses. The author also uses fentanyl patches, particularly for cats that are difficult to medicate. Breaking the chronic pain-inflammation cycle may be important in the management of at least some cats with severe disease.

***Multimodal environmental modifications (MEMO)***

Based on previous findings where catecholamines decreased after environmental modifications in research cats, evaluation of client-owned cats with FIC implementing multimodal environmental modification (MEMO) as the sole management strategy was evaluated. In an observational study we evaluated forty-six client owned indoor-housed cats with FIC. In addition to their usual care, clients were offered recommendations for MEMO based on a detailed environmental history. Cases were followed for ten months by client contact to determine the effect of MEMO on LUTS and other signs. Significant ($p<0.05$) reductions in LUTS, fearfulness, and nervousness, were identified.[12] These results suggest that MEMO is a promising adjunctive therapy for indoor-housed cats with LUTS.

Following a staged approach to therapy, which begins with client education and MEMO, seems beneficial in many cats with FIC. If a patient relapses, these topics should be thoroughly reviewed and additional changes implemented as needed. In multi-cat houses, cats also interact with each other. Addressing inter-cat issues seems very important in the management of this disease as well. Suggestions for MEMO as well as other helpful links can be found at the following website: www.indoorcat.org

***Dietary therapy***

Some dietary modifications may reduce the risk of recurrence of LUTS in affected cats. Efforts to acidify the urine using dry foods have no demonstrated value in treatment of cats with FIC. Water should be encouraged in the diet, and consumption of a canned food is one way to accomplish this. It has been reported that LUTS recurred in only 11% of affected cats during one year of feeding the canned formulation of a dietary product compared to a recurrence of 39% of cats fed the dry formulation of the same food, suggesting the increased water intake may be beneficial, but the reasons for this effect remain to be determined.[11]

***Pheromones and drug therapy***

Pheromones are fatty acids that seem to transmit highly specific information between animals of the same species. Although the exact mechanisms of action are unknown, pheromones reportedly induce changes in both the limbic system and the hypothalamus that alter the emotional state of the animal.[13] Feliway® (Ceva Sante Animale, Libourne, France), a synthetic analogue of this naturally occurring feline facial pheromone, was developed in an effort to decrease anxiety-related behaviors of cats. Treatment with this pheromone has been reported to reduce the amount of anxiety experienced by cats in unfamiliar circumstances, a response that may be helpful to these patients and their owners. Feliway was compared to placebo in cats with FIC; cats that had Feliway used in the environment had a trend for fewer bouts of cystitis, and reduced negative behavioural traits.[14]

Amitriptyline (a tricyclic antidepressant (TCA)) has been reported in uncontrolled trials to successfully decrease clinical signs of severe, recurrent FIC.[15] Amitriptyline (Elavil®, 2.5-5 mg per cat SID), may provide analgesia by inhibition of NE reuptake at noradrenergic nerve terminals.[16] Urine retention through anticholinergic effects of the TCAs may result. Findings in a series of cats with severe FIC showed that the clinical signs of some cats were reduced during amitriptyline treatment during a 12- month period.

Clomipramine (Clomicalm®, veterinary label; and Anafranil®, human label) is also a tertiary amine like amitriptyline, but has more selectivity for blocking the reuptake of 5-HT. The author has prescribed this in recurrent cases of FIC with anecdotal improvements in some patients. Other drugs such as fluoxetine (Prozac®) have been reported to help cats with inappropriate urinations with variable success rates.[17] Fluoxetine was used to help decrease the rate of urine marking after environmental alterations. The TCAs should not be used for acute treatment of FIC since it has been shown to have minimal to no benefit in the short-term resolution of signs in cats with FIC. All TCAs, as well as the selective serotonin reuptake inhibitors should only be considered for recurrent, severe cases.

**References**

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*The complete list of references is available from the author*