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The terms Feline Urologic Syndrome (FUS) and Feline Lower Urinary Tract Disease (FLUTD) have served as shorthand descriptions for the well-known signs of straining, haematuria, pollakiuria (frequent passage of small amounts of urine) and urination in inappropriate locations (periuria) in cats. There are several differentials for these signs including urolithiasis, urinary tract infections, and primary behavioural abnormalities. When no underlying cause can be found for these signs, cats are diagnosed with feline idiopathic cystitis (FIC).

**PATHOPHYSIOLOGY**

**Changes in the bladder wall**

Histological changes associated with FIC are generally non-specific, and may include an intact or damaged urothelium with submucosal oedema, dilation of submucosal blood vessels with margined neutrophils, submucosal haemorrhage, and sometimes increased mast cell density. Scanning electron microscopy of bladders in cats with FIC revealed patches devoid of superficial epithelial cells (the so called ‘umbrella cells’ of the urothelium) and disruption of tight junctions that worsened after hydro-distension. Based on our experience, no correlation between histology and cystoscopic lesions and clinical signs appears to exist in cats with FIC. In fact, owners have reported complete remission of lower urinary tract signs (LUTS) in cats with FIC, but visualisation of their bladder revealed glomerulations (submucosal petechial haemorrhages) and other abnormalities.

Additional studies in cats with FIC have shown increased leakage of ions across the urothelium and urea leakage in non-hydro-distended bladders. Marked increases in permeability after hydro-distension were also present. We have also documented increased bladder permeability to sodium salicylate in cats with FIC. Furthermore, bladder permeability appeared increased in cats given sodium fluorescein intravenously.

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Changes in autonomic function

Clinical signs of FIC can wax and wane and appear to be exacerbated by stressful circumstances. In previous studies, we found that cats with FIC had a significant increase in tyrosine hydroxylase (TH) immunoreactivity (IR) in the brainstem (locus coeruleus) as well as in the paraventricular nucleus of the hypothalamus. TH is the rate-limiting enzyme of catecholamine synthesis. Chronic stress can increase TH activity in the locus coeruleus (LC), with accompanying increases in autonomic outflow. The increased THIR observed in the LC of cats with FIC may provide a clue to the observation that clinical signs of FIC follow a waxing and waning course, and can be aggravated by environmental stressors. Because of these findings, we evaluated various catecholamines in healthy cats and FIC cats during a moderate stress protocol as well as after a period of environmental enrichment modifications. In these studies, we documented that in the FIC cats norepinephrine (NE) (FIGURE 1), DOPA and other catecholamines are significantly elevated during the initial stress (days 1–8) as compared with healthy cats. As the healthy cats acclimated to the stress, their plasma catecholamine concentrations decreased, whereas cats with FIC demonstrated even higher concentrations of plasma NE, epinephrine and their metabolites. Eventually, NE concentrations in the FIC cats did return to their baseline value during the environmental modification period (day 8–35).

Enhanced stimulus-induced local NE release from the bladder could lead to a functional desensitisation of central alpha-2 adrenoceptors (α-2 AR) in cats with FIC. In the brainstem, α-2 agonists inhibit NE release, whereas in the spinal cord they inhibit transmission of nociceptive input to the brain. To further evaluate this, we tested the functional sensitivity of the α-2 AR in cats with FIC and in healthy cats by evaluating their response to the selective α-2 AR agonist, medetomidine. These studies were carried out under the same protocol that we used to measure catecholamine concentrations. If the post-synaptic α-2 ARs are normal, one would expect a decrease in heart rate and increase in pupil diameter after medetomidine administration. The decline in heart rate following medetomidine administration was significantly greater in healthy cats than in FIC cats, although this difference was attenuated after the environmental enrichment period. The increase in pupil diameter following medetomidine administration was significantly greater in healthy cats as compared with FIC cats. We did not see any significant differences in post-synaptic α-2 AR function when evaluating sedation. Electrical field stimulation studies of bladder strips from FIC cats revealed that atipamezole, an α-2 AR antagonist, did not alter the relaxing effect of NE, further suggesting that α-2 AR’s are down-regulated in this disease.

Changes in adrenal function

In addition to the sympathetic nervous system, abnormalities in the hypothalamic-pituitary-adrenal axis (HPA) have also been observed in cats with FIC. After a high dose (125 μg) of synthetic ACTH was administered, cats with FIC had significantly decreased serum cortisol responses as compared with healthy cats (FIGURE 2). Although no obvious histological abnormalities were identified, the areas consisting of the zona fasciculata and zona reticularis were significantly smaller in sections of glands from cats with FIC than in sections of glands from healthy cats. Therefore, it appears that while the sympathico-neural system is fully activated in this disorder, the HPA axis is not.

It is likely that the pathophysiology of FIC involves complex interactions between several body systems. Abnormalities are not localised just in the bladder, but are present in the nervous, endocrine, and even the cardiovascular system. How these systems communicate and manifest as FIC in some cats, but

![Figure 1. Plasma norepinephrine (NE) concentrations in six cats with FIC and five healthy cats.](https://www.symposiumorganizers.com/NE_concentrations.png)

Plasma NE concentrations were measured during the moderate stressor period (days 1–8) and after environmental enrichment (day 35). Plasma concentrations were significantly increased in FIC cats at all times (P = 0.03).
not in others, remains to be determined. In order to better treat their patients, it is important for clinicians to understand that this syndrome is not just 'a bladder disease' amenable to simple diet or drug therapies.

**APPROACH TO THE PATIENT**

**Diagnostics**

Most cats with FIC are young to middle aged. In as many as 85 per cent of the cats, clinical signs resolve spontaneously within two to three days, with or without treatment. As many as 50 per cent of these cats will have another episode within 12 months, and in one recent study, 39 per cent of cats consuming dry food had one or more recurrent episodes during a 12 month period. 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.

Because FIC is a diagnosis of exclusion, diagnostics should be performed to rule out other causes of LUTS mentioned above. Urolithiasis can occur in approximately 12 to 15 per cent of cats with LUTS, and an abdominal radiograph which includes the entire urinary tract should be performed. Less than two per cent of young (less than 10 years of age) cats have true bacterial cystitis, so urine culture is a low yield test. A quantitative urine culture should be performed in all cats with recurrent LUTS (more than two episodes). The possibility of a urinary tract infection increases with age, with perineal surgery, in the presence of cystic calculi, and with dilute urine.

Contrast studies of the bladder and urethra in cats with FIC are usually unremarkable, though diffuse or asymmetrical thickening of the bladder wall is seen in about 15 per cent of the cases. A contrast cystogram and urethrogram can be helpful to better evaluate the bladder for the presence of non-radiopaque calculi and other lesions such as mass lesions, blood clots, and strictures in those cats with recurrent episodes. If clinical signs continue, despite therapy, an abdominal ultrasound, double contrast cystourethrogram, and/or cystoscopy can be performed to be sure that no other lesions in the lower urinary tract were missed. Contrast studies are especially indicated in elderly cats (more than 10 years of age) where FIC is not as likely to occur.

In those cats with negative findings from radiography and urine cultures, cystoscopy is performed at referral practices when LUTS fails to resolve after standard therapy. This tool allows one to visualise the urethra and bladder at low and high pressures. Small cystic calculi, urachal diverticula, and small polyps all can be visualised. We do not use cystoscopy to 'rule in' FIC, but rather to exclude less common diseases. If none of these are seen, we generally still 'grade' the amount of oedema, glomerulations (FIGURE 3), and debris, that might be suspended in or peeling from in the bladder lumen.

**Treatment of FIC**

The underlying cause of this disorder is unknown, so current treatment recommendations must necessarily be tentative. The current goals of therapy for cats with FIC are not to 'cure' them, but to decrease the severity of their symptoms and to increase their inter-episode intervals, especially for the severely affected cats. Enhanced stress response system activity seems to be central to maintaining the chronic inflammatory process. Any treatment strategy designed to decrease sympathetic nervous system outflow may be important in reducing this inflammation.

When a cat is presented with LUTS, analgesic therapy seems appropriate for the acute management of the disease. Providing analgesia with non-steroidal anti-inflammatory agents such as carprofen and ketoprofen, or butorphanol or more potent opioids such as fentanyl (patches) has been suggested, but no studies to substantiate this have been reported to date, and many drugs are not...
approved for these uses. We believe that breaking the chronic pain-inflammation cycle may be important in the management of at least some cats with severe disease. During acute flare-ups we generally prescribe some form of analgesia such as butorphanol combined with a short-term tranquilizer such as acepromazine.

Multimodal environmental modifications
Based on our previous findings in research cats where catecholamines decreased after environmental modifications, we have evaluated client-owned cats with idiopathic cystitis implementing multimodal environmental modification (MEMO) as the sole management strategy. In this observational study we evaluated 46 client-owned indoor-housed cats with idiopathic cystitis which were diagnosed based on a history of recurrent LUTS with no evidence of urolithiasis or bacterial urinary tract infection. In addition to their usual care, clients were offered recommendations for MEMO based on a detailed environmental history. Cases were followed for 10 months by client contact to determine the effect of MEMO on LUTS and other signs. Significant (p < 0.05) reductions in LUTS, fearfulness, nervousness, signs referable to the respiratory tract, and a trend (p < 0.1) toward reduced aggressive behaviour were identified. These results suggest that MEMO is a promising adjunctive therapy for indoor-housed cats with LUTS.

We follow a staged approach to therapy which begins with client education and MEMO. If a patient relapses, these topics are thoroughly reviewed and additional changes are implemented. In multi-cat households, cats also interact with each other. Unrelated cats housed together in groups appear to spend less time interacting with one another than related ones do. Addressing inter-cat issues can be a very important tactic in the management of this disease. These cats may prefer to have their own separate food and water sources, litter box and resting areas to avoid competition for resources and to permit them to avoid unwanted interactions.

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 the treatment of cats with FIC. There is no known benefit in acidifying the urine or restricting magnesium in cats with FIC. We do encourage increasing water intake, and consumption of a canned food is one way to accomplish this. To avoid the potential stress of being confronted with an unfamiliar diet, we recommend introducing the new canned food alongside the original diet. We reported that LUTS recurred in only 11 per cent of affected cats during one year of feeding the canned formulation of a dietary product designed to result in the production of slightly acidic urine. Recurrence occurred in 39 per cent of cats fed the dry formulation of the same food, suggesting that both constancy and consistency (i.e., increased water intake) may be important, but the reasons for this effect remain to be determined.

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. Feliway® (Ceva® Santé Animale – Libourne, France), a synthetic analogue of this naturally occurring feline facial pheromone, was developed in an effort to decrease anxiety-related behaviours of cats. Although not specifically tested in cats with FIC, 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 FIC patients and their owners. Increased grooming and food intake in hospitalised cats has also been reported with the use of Feliway®.

We have used amitriptyline, a tricyclic antidepressant (TCA), in uncontrolled trials to...
successfully decrease clinical signs of severe, recurrent FIC. Amitriptyline (Elavil®), may provide analgesia by inhibition of NE reuptake at noradrenergic nerve terminals, and possibly due to inhibition of a wide range of nociceptive neurons in the spinal trigeminal nucleus. 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. Improvement in clinical signs was not always accompanied by improvement in the cystoscopic appearance of the bladder.

Clomipramine (Clomicalm® – veterinary label; and Anafranil® – human label) is also a tertiary amine-like amitriptyline, but has more selectivity for blocking the re-uptake of 5-HT. We have prescribed this in recurrent cases of FIC with anecdotal improvements in some patients. Other drugs such as fluoxetine (Prozac®) has been reported to help cats with inappropriate urinations with variable success rate. Fluoxetine was used to help decrease the rate of urine marking after environmental alterations such as litter box hygiene and appropriate cleaning strategies.

We do not recommend amitriptyline for treatment of acute FIC, since it has been shown to have minimal to no benefit in the short-term resolution of signs in cats with FIC. We reserve all the TCAs, as well as the selective serotonin reuptake inhibitors for recurrent, severe cases. These drugs need to be used only after environmental strategies, diet changes (if necessary), and behaviour modifications have failed. Furthermore, it is our opinion that these drugs should then only be used in conjunction with the above-mentioned therapeutic strategies for optimal effects.

REFERENCES

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