Feline idiopathic cystitis:
Epidemiology, risk factors and pathogenesis

Andy Sparkes
BVetMed PhD DipECVIM MRCVS
Veterinary Director,
International Cat Care and International Society of Feline Medicine, UK

Epidemiology of feline idiopathic cystitis

Feline lower urinary tract disease (FLUTD) is a common syndrome in veterinary practice. In 1999, from a study of 52 private veterinary practices in the United States, Lund et al[1] reported that cats with a diagnosis of cystitis or feline urological syndrome together represented approximately 3% of all feline cases presented to those clinics during four non-consecutive month-long periods in 1995. In this study, FLUTD was also one of the top 10 most common disorders reported in cats. Similarly, Kirk et al[2] reported a prevalence of 4.6% in a cross-sectional study of clinics in North America, and in a study from the United Kingdom (UK) Adams and Dean,[3] the prevalence of FLUTD in cats in general practice was reported to be 3.3%. In a study of cats with veterinary insurance in Sweden,[4] disorders affecting the lower urinary tract were reported to represent 13% of claims during the period of 1999—2006 and to be the third most common cause of morbidity — it was noted though that this figure was not entirely representative as insurance did not cover elective dental procedures and that low-cost diagnoses were also under-represented in the database (ie, the data was skewed to more expensive procedures that would have prompted an insurance claim). Examination of the Veterinary Medical Database of 13 North American teaching hospitals in between 1980 and 1997[5] also revealed a prevalence (proportional morbidity rate) of FLUTD of 8% of cats evaluated. These data, together with others and with clinical experience, all confirm that FLUTD is a common syndrome in small animal practice.

A number of different identifiable causes of FLUTD are recognised, and these include bacterial cystitis, urolithiasis, urethral strictures, urethral plugs, trauma and neoplasia. Where appropriate investigations fail to identify a specific cause, a diagnosis of feline idiopathic cystitis (FIC) is made. In most studies, FIC in fact makes up the majority of cases of FLUTD and appears to be the single most common diagnosis. Whether FIC represents a single disease entity or a syndrome with multiple (as yet unidentified) causes still remains to be determined.

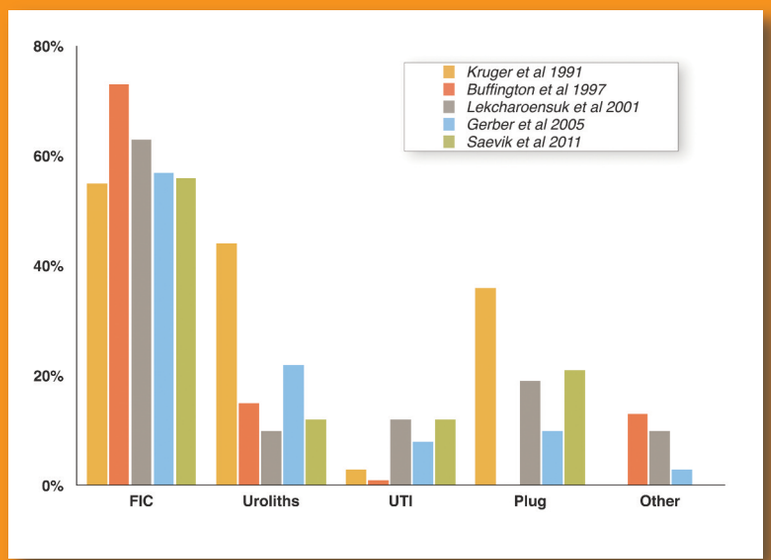

FIGURE 1 Prevalence of different causes of FLUTD in five published studies from North America and Europe
FIC = feline idiopathic cystitis;
UTI = bacterial urinary tract infection;
Plug = urethral plug or urethral obstruction
Other

Some of the studies that have evaluated groups of cats with FLUTD and identified the different underlying causes in those groups are shown in Figure 1. These studies have found that FIC accounted for between 55% and 73% of the cases seen.[5–9] Feline idiopathic cystitis thus represents the single most common cause of signs of FLUTD.

Risk factors for FIC

Some studies have evaluated risk factors for the development of FLUTD in general in cats, but such studies are of limited value as they do not discriminate the underlying cause of the FLUTD signs. Nevertheless, from a very large case-control study in North America, Lekcharoensuk et al[5] reported that Persian, Manx and Himalayan cats had an increased risk of developing FLUTD and Siamese cats had a reduced risk. Further, middle aged (4–7 years old) and neutered cats were identified as being at higher risk, along with overweight cats. In a New Zealand study, risk factors identified for FLUTD included low activity levels, use of a litter tray, restriction indoors, a high number of rainy days in the preceding month and stress (such as moving house or another cat in the house).[10] The feeding of a high proportion of dry food in the diet has also been identified as a risk factor in cats with lower urinary tract signs (LUTS) in some studies,[7,9] but not others.[11,12]

In terms of FIC, a breed predisposition has not been identified.[5,9] FIC is seen over a wide age range of cats (eg, 1–15 years) with Lekcharoensuk et al reporting a somewhat higher risk in cats between 2 and 7 years old[5] and others reporting the average age of affected cats to be around 5–6 years old.[7,9] Two European studies have noted a higher proportion of male than female cats affected with FIC[7,9] and a trend towards this was also evident in one large study from North America[5] where intact females were reported to have a lower risk.

In at least two studies, the feeding of dry cat food has been associated with an increased risk of FIC specifically[6,7] but again, further work is needed to substantiate these observations and to determine whether there is a causal association.

Two studies have looked specifically at certain risk factors for the development of FIC.[11,12] In one of those studies[11] which was conducted in Scotland, cats with FIC were compared with unaffected cats in the same household (where present) and with a control population of cats. That study found that cats with FIC were significantly more likely to be male, long-haired and overweight than both the control population and compared with other cats in the household. Compared with cats in the control population, those with FIC were also significantly more likely to:

- Have access to a litter box
- Live with at least one other cat
- Be in conflict with a cat in the same house

Diet, age and indoor/outdoor access were not identified as a risk factors, but there was a tendency for more pedigree cats (and especially Persians) to be affected with FIC.

In the second report,[12] a retrospective case-control study was performed in Belgium, involving 64 cats with FIC. The following factors were found to be significantly associated with the 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
- Having less access to an outdoor environment

Diet and breed were not identified as risk factors

in this study.

While epidemiological studies are very valuable for identifying potential factors associated with the development of disease, a causal relationship cannot be established with these studies and thus care is necessary in their interpretation. Nevertheless, the results of these studies do show some intriguing findings and can be interpreted as being supportive of the hypothesis that environmental stress may be a factor in the development of FIC in at least some cats although the identification of other risk factors in at least some studies (eg, diet and/or water intake) suggests other factors may also be involved.

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.[13]

Nevertheless, in a number of different studies, both local bladder abnormalities and/or neuro-hormonal 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.

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.[14–16] The quantity of urinary GAGs is assumed to reflect the quantity of GAGs that line the mucosal surface of the bladder where they form an important protective function. Bladder mucosal GAGs help prevent adherence of bacteria and crystals to the epithelial surface, and importantly also form a barrier between urine itself and the underlying epithelium.

The main GAG in cat urine has been found to be chondroitin sulphate, with appreciable quantities of dermatan sulphate, and also some heparin suphate.[15] The fact that urinary concentrations of these GAGs in cats with FIC are significantly reduced appears well established (see Figure 2), but the precise relationship to the development of disease remains to be determined. Nevertheless, it is possible that deficiencies in this mucopolysaccharide layer that overlies the bladder epithelium may contribute to damage, ulceration and increased permeability of the underlying epithelium (as has also been observed in FIC cases) and to submucosal haemorrhage.[14,17–19]

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, galaectin-7, I-FABP, fibronectin, and trefoil factor 2.[20–23]
- Mucosal muscarinic receptors have been reported to have increased sensitivity in cats with FIC,[24] which could potentially enhance smooth muscle spontaneous contraction, although evidence of an overactive bladder has not been found in association with FIC.[25]
- Increased bladder tissue concentrations of norepinephrine,[26] and an increase in maximum urethral pressures and urethral closure pressures in affected cats.[25]
- Histological changes in the bladder wall including oedema, haemorrhage, vasodilation, occasionally ulceration, and a variable increase in the number of mast cells.[27,28]
- 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.[29–34]

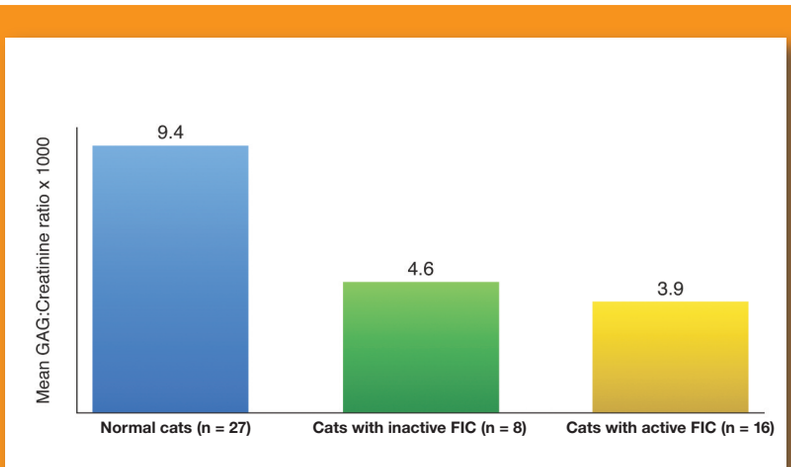

FIGURE 2 Urine GAG:creatinine ratio (x1000) in three groups of cats (from Buffington et al 1996[14]). Mean urine GAG:creatinine ratios were significantly reduced (*P* = 0.0001) in cats with FIC compared with normal cats

Neuro-hormonal abnormalities in the pathogenesis of FIC

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 dihydroxylphenylalanine in FIC cats compared with normal cats, but without a concomitant increase in cortisol or adrenocorticotrophic hormone (ACTH).[19,35]
- 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.[36]
- 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.[37]
- Differences in responses to the α_2-adrenergic agent medetomidine in FIC cats compared with normal cats.[38]

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 supressed adrenocortical responses.

Presence of other diseases in cats with FIC

If, as studies suggest, FIC is not a disease limited to the urinary bladder but is rather a condition characterised (at least in part) by underlying neuro-hormonal abnormalities and an abnormal response to stress, it would be surprising if FIC was the only manifestation of disease in affected cats.

Published data does in fact suggest that cats with FIC may have other manifestations of disease as well. In addition to showing signs of nervousness or fearfulness (indicators of increased stress – see under Risk Factors for FIC), affected cats may also show gastrointestinal, respiratory, dermatological and behavioural signs.[39–42]

Conclusions

While further well-designed studies are needed to provide better data on the epidemiology, risk factors and pathogenesis of FIC, current data provides some intriguing insights. While the pathogenesis of FIC is far from understood, and whether this is a single disease or a syndrome with different underlying causes still needs to be determined, current evidence shows some strong similarities between FIC and interstitial cystitis in humans and suggests a complex underlying disease mechanism.

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