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Feline lower urinary tract disease

Daniëlle A Gunn-Moore*

*Easter Bush Veterinary Centre,
Hospital for Small Animals, Royal
School of Veterinary Studies,
University of Edinburgh, Roslin,
Midlothian, Scotland EH25 9RG,
UK*

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Introduction

The term feline lower urinary tract disease (FLUTD) describes a collection of conditions that can affect the bladder and/or urethra of cats. Unfortunately, since the urinary tract can respond to insult in only a limited numbers of ways, the clinical signs are rarely indicative of a particular disease. While there are many conditions that can result in signs of FLUTD (see below) the vast majority of cases are idiopathic.

Causes of non-obstructive FLUTD

Non-obstructive idiopathic cystitis	65%
Uroliths	15%
Anatomical defects/neoplasia/other	10%
Behavioural problems	<10%
Bacterial infection	<2%

Causes of obstructive FLUTD

Obstructive idiopathic cystitis	29%
Urethral plug	59%
Uroliths	10%
Uroliths+bacterial infection	2%

Cats with FLUTD usually present with signs of dysuria, pollakiuria (increased frequency of urination), haematuria, urethral obstruction, periuria (inappropriate urination), and/or behav-

ioural change (often aggression) and loss of litter-box training.

The annual incidence of FLUTD in British cats is believed to be around 1%. While FLUTD can be seen in cats of any age and sex, it is most frequently seen in middle-aged, over weight, neutered male cats, who take little exercise, use an indoor litter box, have restricted access outside, eat a dry diet, and, typically, live in a multi-animal household. Persian cats appear to be predisposed.

Most cases of non-obstructive FLUTD are self-limiting; usually resolving within 5–10 days. However, most affected cats have episodes of clinical signs, which recur with variable frequency, but generally tend to decrease in frequency and severity over time.

Pathophysiology of FLUTD

FLUTD describes a collection of conditions, rather than a single condition and our understanding of the prevalence and pathophysiology of the many causes of FLUTD has changed radically in the last few years. While historically more interest was placed on the role of bladder stones and crystals, recent evidence has shown that idiopathic cystitis is the most common cause of FLUTD in cats.

Feline idiopathic cystitis (FIC)

In the majority of cases of FLUTD no underlying cause can be found. Research over the last 30 years has failed to find a consistent cause for

Please note that few of the drugs listed in this article are licensed for use in cats. Please refer to the BSAVA Small Animal Formulary for more information and potential side effects.

*Tel.: +44-131-650-7650; fax: +44-131-650-6182. E-mail: danielle.gunn-moore@ed.ac.uk

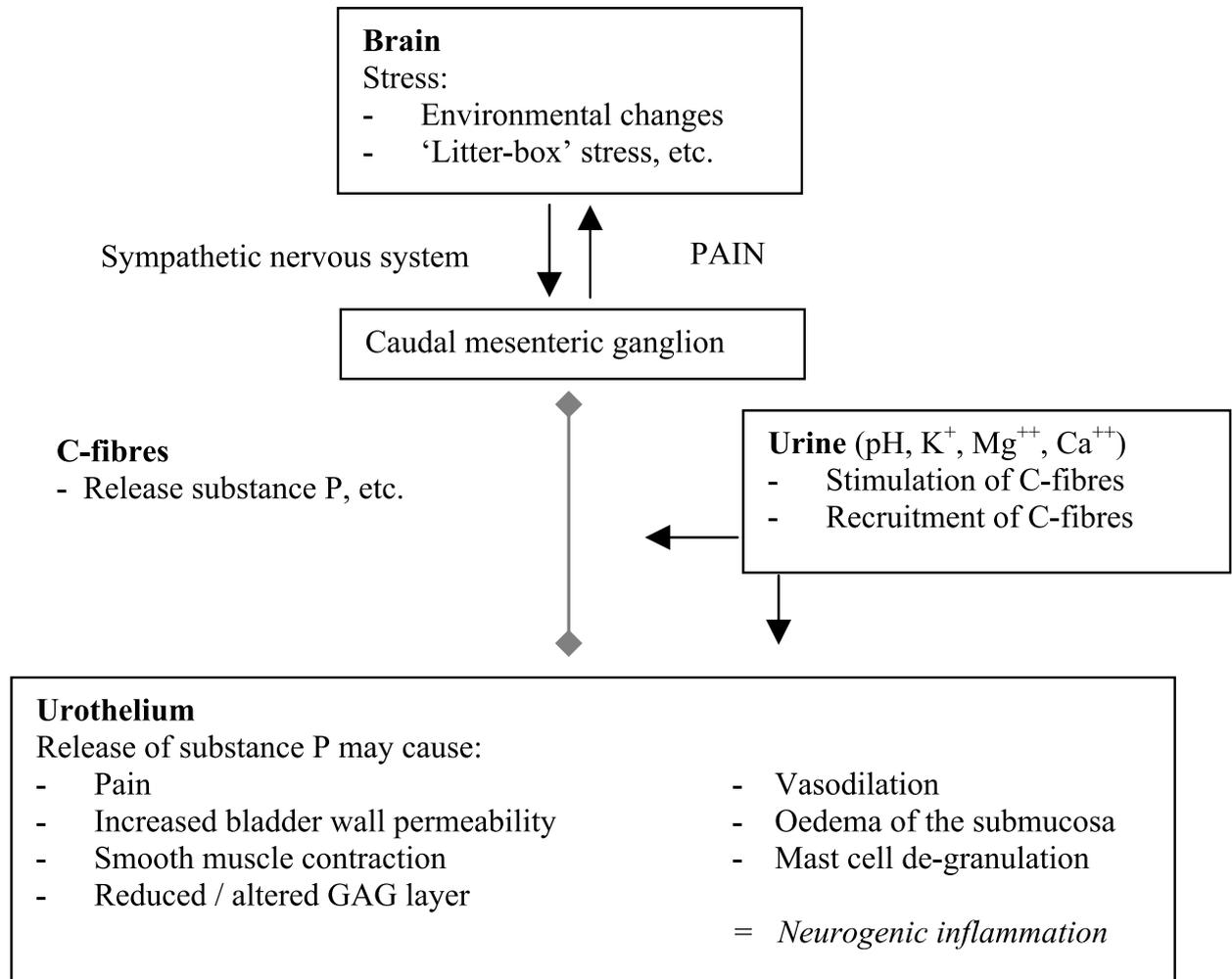


Fig 1. Current hypothesis for neurogenic inflammation in FIC. (Adapted from Buffington CAT, Chew DJ, DiBartola SP (1996) Interstitial cystitis in cats. *Veterinary Clinics of North America*, 26 (2), 317–326.)

the inflammation in these cases. However, a recent hypothesis suggests that FIC may result from alterations in the interaction between the neuronal supply to and from the bladder, the protective glycosaminoglycan (GAG) layer that lines the bladder, and compounds within the urine (see Fig. 1). It has been suggested that FIC may have similarities to an idiopathic, non-malignant, bladder disease of humans, termed 'interstitial cystitis'.

Much of our understanding of FIC has come from studying the histopathology of bladder wall biopsies taken from affected cats. They usually reveal a relatively normal epithelium and muscularis, with submucosal oedema and vasodilation, without obvious inflammatory infiltrate, although large numbers of mast cells are frequently present. Biopsies often reveal increased numbers of pain fibres (C-fibres) and pain receptors (substance P receptors).

It is now known that stimulation of the C-fibres (via central or local triggers) can cause the release of neuropeptides (eg, substance P and others), which can in turn result in pain, vasodilatation of the intramural blood vessels, increased vascular and bladder-wall permeability, oedema of the submucosa, smooth muscle contraction, and mast cell de-granulation. Mast cell de-granulation results in the release of a variety of inflammatory mediators (including histamine, heparin, serotonin, cytokines, and prostaglandins), which can further exacerbate the effects of the C-fibres. Stimulation of C-fibres and the resulting neurogenic inflammation can therefore explain many of the changes recorded in FIC. The nerve endings can be stimulated in response to central triggers (such as 'stress'), or via compounds within the urine (eg, acid pH, potassium, magnesium, and calcium ions). This in turn may result in further recruitment of C-fibres, and intensification of disease.

A thin layer of mucus composed of GAG covers the bladder epithelium. This layer helps to prevent microbes and crystals from sticking to the bladder lining. It has been shown that some cats with FIC have decreased urine concentrations of GAG and increased urinary bladder permeability. This may allow noxious substances within the urine to pass through the urothelium and cause inflammation.

While it appears that neurogenic inflammation may play an important role in the development of the clinical signs of FLUTD, it is unclear whether or not it is as a primary factor, or a secondary event, perhaps triggered by an, as yet, unidentified infectious agent.

Urolithiasis

Urolithiasis is defined as the formation of calculi (uroliths or stones) within the urinary tract. Uroliths can vary in their mineral composition, with struvite and oxalate forms being seen most commonly in cats. Over the last few years much interest has been shown on the design of diets that will aid the dissolution of struvite stones. Unfortunately, while this has resulted in a decline in the incidence of struvite urolithiasis it has resulted in an increase in oxalate urolithiasis.

Urethral plugs

Urethral plugs occur with approximately the same frequency as uroliths. They are of particular importance because they are associated with urethral obstruction. They are composed of varying combinations of a protein-colloid matrix (mucoproteins, albumin, globulin, cells, etc) and crystalline material (most typically struvite). The colloid matrix is believed to 'leak' from the bladder wall as a result of inflammation. The cause of this inflammation may be neurogenic, idiopathic, or secondary to infection, neoplasia, or uroliths. Thick colloid may cause urethral obstruction without evidence of crystalluria. However, where crystalluria is also present, the crystals may become trapped within the matrix, and add to the obstruction. It is therefore usually the colloid that is of primary importance, rather than the presence of crystals per se. While very severe crystalluria may result in urethral obstruction in the absence of colloid matrix, in most cats crystalluria is clinically silent. In fact, most

normal cats develop crystalluria when they are fed many dry cat diets.

Infectious causes

So far, no bacterial, fungal, or viral organisms have been consistently shown to induce FLUTD. However, it is still possible that a very fastidious organism could be involved, and the role of viruses is still being investigated. Bacterial infection is a very rare cause of FLUTD. Where it is seen, it is usually iatrogenic, or secondary to urolithiasis, an anatomical defect, or neoplasia. Older cats, particularly those with concurrent renal failure, have an increased risk of bacterial infection, however, FLUTD is rarely seen in cats of this age-group.

Neoplasia

Transitional cell carcinomas (TCC), adenocarcinoma, leiomyoma, and a number of other tumours may all occur in cat bladders. However, TCC are seen most frequently; either as isolated tumours, or arising secondary to chronic inflammation.

Unifying hypothesis

The different causes of FLUTD may occur individually, or in various interacting combinations (Fig. 2). For example, the formation of urethral plugs may result from concurrent, but not necessarily related, disorders, eg, the simultaneous occurrence of urinary tract inflammation and crystalluria. Obstruction may result from the formation of urethral plugs, from pain or inflammation-induced urethral spasm, or the passage of small uroliths. Although inflammation without crystalluria can result in obstruction with colloid matrix, it more typically causes haematuria and dysuria. While crystalluria is often clinically silent, if severe and persistent, it may predispose to the development of uroliths, and these, in turn can lead to urethral obstruction and bladder inflammation.

Treatment

The key to successful treatment is a correct diagnosis. Where a specific cause can be identified then its treatment can be undertaken. Where no

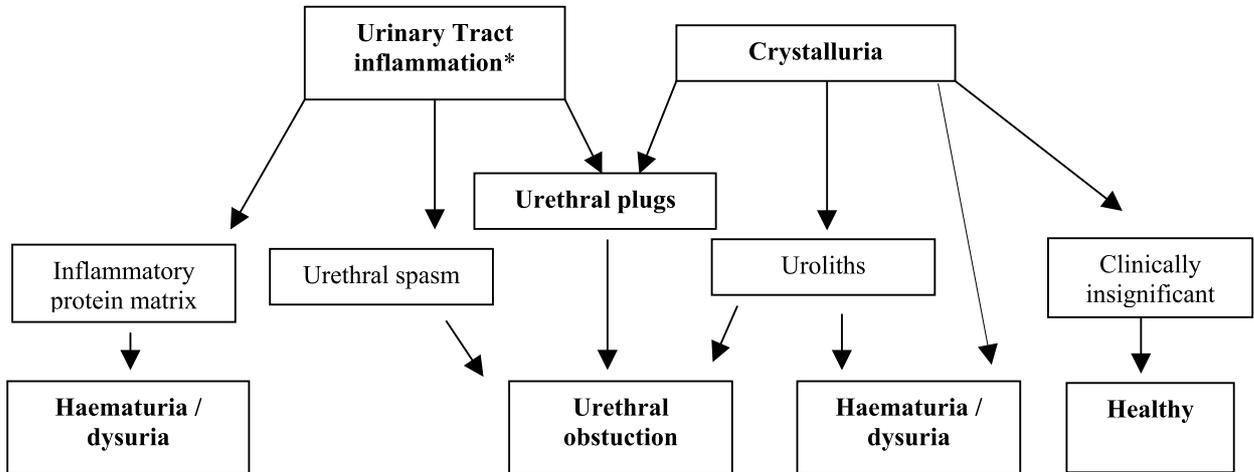


Fig 2. Diagram illustrating how the interaction between urinary tract inflammation and crystalluria can lead to different clinical presentations. (Initial hypothesis from Osborne CA, Kruger JM, Lulich JP, Bartges CA, Polzin DJ, Molitor T, Beauclair, Onffroy (1992) Feline matrix-crystalline urethral plugs: a unifying hypothesis of causes. JSAP, 33, 172–177.) *Urinary tract inflammation may be neurogenic, idiopathic, or secondary to infection, neoplasia, or uroliths.

underlying cause can be identified then the cat should be managed as for FIC.

Treatment of urethral plugs

Urethral plugs consist of protein–colloid matrix and trapped crystals, which have become wedged within the urethra. Initially, the urethra must be unblocked. In the longer term treatment may be aimed at reducing:

- the protein matrix (see section Treatment of FIC);
- the crystals

normal cats commonly produce crystals in their urine, especially when they are fed many of the dry cat foods. The first line of treatment is therefore to change their diet to wet food. Where significant crystalluria persists the nature of the crystals should be assessed and an appropriate prescription diet can be fed (preferably the wet form).

do not feed an acidified diet if the urine is acid and struvite crystals are not a problem. Long-term use of highly acidified diets can result in metabolic acidosis, hypokalaemia, renal damage, and loss of bone density, especially when given to immature cats. They also increase the risk of oxalate urolithiasis.

- urethral spasm (see section Treatment of urethral spasm).

Treatment of bladder stones

While struvite stones may dissolve with dietary manipulation (using the appropriate prescription

diet) oxalate stones need to be surgically removed unless they are small enough to be expelled using 'voiding urohydropropulsion'.

Treatment of bladder diverticula

If a diverticulum does not spontaneously regress with successful management of the underlying cause of the FLUTD then surgical resection is recommended. Resected tissue should be sent for histopathology and routine bacterial culture.

Treatment of bladder TCC

When possible, the treatment of choice for TCC is surgical resection. However, where this is not possible medical options include the use of piroxicam (with which the author has had some moderate success).

- Piroxicam (Feldene™) 0.3 mg/kg PO q48 h

As with other non-steroidal anti-inflammatory drugs (NSAIDs) this can cause gastrointestinal and renal toxicity. It is essential to check urea and creatinine levels before starting treatment, and then monitor them regularly.

Treatment of FIC

Most cases of non-obstructive FLUTD are self-limiting, and usually spontaneously resolve within 5–10 days. However, treatment is recommended because the condition is painful and distressing to the cat, may lead to urethral obstruction, self-traumatization of the perineal

region, and/or long-term behavioural changes, including loss of litter-box training.

Unfortunately, few treatments for FLUTD have been investigated by well-controlled double-blinded experimental studies. Most recommendations are therefore based on uncontrolled clinical observations and personal opinion. Also, since FLUTD is usually self-limiting, many treatments may *appear* to be effective, when they actually have no positive effect. All treatments should therefore be considered with appropriate caution.

As more drugs are tried, the list of those that are either unhelpful, or even harmful, is growing. Treatments that have been critically assessed include *corticosteroids* and *antibiotics*, and neither was found to have a positive effect. A number of drugs should never be given to cats, eg, the urinary tract antiseptic, *methylene blue*, and the urinary tract analgesic, *phenazopyridine*; both of which can result in severe Heinz body anaemia.

The entire list of medications and interventions that have been considered for the treatment of FLUTD is far too extensive to be included in this article. The author has therefore chosen to describe her current approach to the therapeutic management of FIC that is aimed at addressing the factors underlying the disease (see earlier for pathogenesis).

Reduce stress Stress plays a key role in the pathophysiology of FIC. It has been identified as a *flare factor* that can precipitate a recurrence of clinical signs. Identified stressors include living with another cat that they do not like, abrupt changes in diet, environment or weather, overcrowding, owner stress, or the addition to the household of new pets or people. Stress associated with urination can be particularly significant.

- Provide a safe area in which to place the cat's litter box.
- Provide a suitable number of litter boxes with suitable litter. Clean the boxes frequently.
- Reduce overcrowding and bullying. Provide safe escape routes and hiding places.
- Reassure the cat as much as possible.
- Consider the use of Feliway™ (Ceva: synthetic cat facial pheromone believed to reduce feline anxiety).

Create dilute urine Altering the diet most easily modifies the content of urine. Dietary changes can affect urine concentration, volume, pH, and mineral content. While much interest has been placed on altering the urine pH, and the magnesium and calcium content of the urine, it is now believed

that the single most important factor is the rate of water turnover. The aim of dietary manipulation is therefore to increase water turnover and dilute any noxious components within the urine. Rather than altering the contents of a dry diet, it is advisable to feed a wet one.

- Gradually change the diet to wet food.
- Supply free access to water and encourage the cat to drink. Consider offering fish or chicken soup, or using a 'pet water fountain'.
- For discussion of the use of prescription diets where significant crystalluria is present see section 'Treatment of urethral plugs'.

GAG supplements In theory, therapy to replace the GAG layer should be beneficial. It relies on the assumption that exogenous GAG will attach to the defective urothelium and decrease bladder wall permeability. GAGs may also have analgesic and anti-inflammatory effects. These compounds have shown some positive responses in humans with interstitial cystitis and preliminary studies in cats with FIC. From human studies, it appears that there are differences in the relative efficiency of different GAGs in producing positive effects, and the same is likely to be true in cats. It has been suggested that for severely affected cats supplements can be given at higher dose at the time of initial presentation, then reduced to a maintenance level. In cases where oral supplementation is not possible, and repeated visits to the veterinary practice cause distress, Cartrophen™ can be dispensed for home medication.

- *N*-acetyl glucosamine is the precursor of GAG. It can be given as different food supplements. Preference: Cystease™ (Ceva Animal Health) 125 mg per cat PO q24 h.
- Pentosan polysulphate (Cartrophen™; Arthroparm Limited) is a semi-synthetic polymer that is given parenterally, by subcutaneous injection, 3 mg/kg on days 1, 2, 5, and 10, then every 5–10 days.

Possible side effects include prolonged bleeding times, inappetence, and possibly, insulin resistance.

Treatment of urethral spasm Treatment of urethral spasm may reduce the severity of clinical signs in some cats, and may reduce the risk of urethral blockage recurring. Since both smooth and skeletal muscle fibres are responsible for generating urethral tone, it may be beneficial to give drugs to counter this effect. Injectable drugs (eg, ACP) may be given at the time of relieving the

obstruction, after which the author commonly prescribes a 7–14 day course of prazosin and dantrolene. These two drugs can be given together, and longer or intermittent courses may be required in some individuals. The author prefers to wean off these drugs over a few days rather than stopping them suddenly.

- Smooth muscle anti-spasmodics include:
 - Acepromazine (ACP™) 0.05–0.2 mg/kg IV, IM, SC or 1–3 mg/kg PO
 - Prazosin (Hypovase™ 0.5 or 1.0 mg tablets) 0.25–1.0 mg/cat PO q8–12 h
 - Phenoxybenzamine (Dibenyline™ 10 mg capsules*) 0.5–1.0 mg/kg PO q12 h
Give for 5 days before evaluating efficiency.
- Skeletal muscle anti-spasmodics include:
 - Dantrolene (Dantrium™ 25 mg capsules*) 0.5–2.0 mg/kg PO q12 h; (0.5–1.0 mg/kg IV, but very expensive)
Re-encapsulate 1/8–1/4 of the contents of a capsule into empty size 2 or 4 gelatin capsules.

While there have been only a limited number of studies into the use of these drugs in the relief of urethral spasm, prazosin, phenoxybenzamine, and dantrolene have shown most benefit. All smooth muscle relaxants can cause hypotension, and dantrolene may cause liver toxicity.

Tricyclic antidepressants Tricyclic antidepressants have been found to be beneficial in the treatment of some humans with interstitial cystitis, and in a number of cats with FIC, however, there are few well-controlled studies available. These drugs have both behavioural and organic effects. They have anticholinergic (including increasing bladder capacity), anti-inflammatory (including preventing histamine release from mast cells), anti- α adrenergic, analgesic, and antidepressant effects. While long-term administration may be of benefit in some cases of FIC, short-term treatment does not appear to be effective. In cats, tricyclic antidepressants should be used with caution and reserved for those cats with very severe or chronic disease.

- Amitriptyline (Amitriptyline™) 2.5–10 mg/cat PO q24 h (evening)

Side effects include somnolence, urinary retention, and raised liver enzymes. Liver func-

tion should be assessed prior to starting therapy, reassessed 1 month later, then every 6–12 months while the cat is on treatment.

Analgesia and anti-inflammatory drugs

- Analgesia alone may reduce the severity of the clinical signs, but is rarely sufficient. Butorphanol (Torbugesic™), or fentanyl patches (which can be attached to a shaved area on the back of the neck), may show some degree of positive effect.
- Corticosteroids have been shown to be non-effective.
- While NSAIDs have not been investigated for the treatment of FIC they may appear to help in some cases (especially those with TCC or pre-TCC, see above).

Summary of treatment for FIC

It is important to remember that all current treatments for FIC are merely palliative. The best results are gained by instigating a number of changes, ie, reducing stress, feeding a wet diet, possibly replacing GAGs and, if necessary, relieving urethral spasm. In most cases, when tailored to the individual cat, this will reduce or prevent further clinical signs. Tricyclic antidepressants should only be used in very severe recurrent cases.

Where possible, it may help to be proactive. This can be achieved where observant owners are able to notice their cat showing prodromal signs before an episode of FIC becomes clinically obvious. The duration of these signs may vary from a few days to a few hours, and they may include increased perineal and hind-end grooming, or altered behaviour (often seen as inter-cat aggression initiated by the FIC sufferer). These signs probably relate to increasing perineal pain. Making management changes at this time may help to reduce the severity and duration of the episode, ie, further reduce stress (perhaps spray Feliway™), increase fluid intake, and/or give a GAG supplement (or increase its dosage) or (where appropriate) give prazosin. This approach can also be used if a stressful episode is anticipated, (eg, a visit to the vet, a stay in a cattery, builders in the home, etc).