Scientific Proceedings
Hill's Global Symposium on Feline Lower Urinary Tract Health

Prague, 23rd - 24th April 2014

Think inside the box

Hill's

Global Symposium

Prague 2014

Introduction

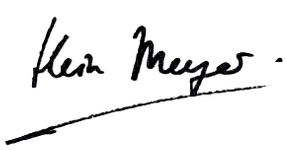
We are pleased to present the Proceedings for the Hill's Global Symposium on Feline Lower Urinary Tract Health: 'Think inside the box', taking place in Prague, Czech Republic from 23–24 April 2014. This Symposium follows the series of Hill's Global Symposia which are dedicated to increasing knowledge, and stimulating research and career development on subjects important to the veterinary profession. This year's Hill's Symposium is exciting as internationally recognized leaders in the field of disorders that affect the lower urinary tract of cats and bladder pain syndrome meet to present the most comprehensive and up-to-date information regarding lower urinary tract problems in cats and people during a day and half scientific programme.

Feline lower urinary tract signs are rated a top feline health concern by cat owners. The most common causes behind this syndrome are feline idiopathic cystitis (FIC) and urolithiasis. The management possibilities for FIC, which is a recurring and frustrating condition, are limited and the clinicians' goals consist of decreasing severity of signs, minimizing pain and increasing the inter-episode intervals.

We are extremely proud to present new research findings that demonstrate a crucial role of food in the management of FIC. While dietetic modifications appropriate for the management of some mineral types are currently available, new scientific evidence of their efficacy is emerging and will be presented during the Symposium programme as well. Furthermore, research in the area of dietary ingredients for the management of stress and anxiety, which play a role in the development of FIC, will be discussed.

As we continue our commitment to advance the field of feline clinical nutrition, we wish to express our sincere gratitude to all the speakers who support our mission in the management of cats with disorders affecting the lower urinary tract. We anticipate that you will find these Proceedings informative and you leave the Symposium enriched with clinical updates relevant to your work and professional interests.

Sincerely,



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Working in partnership

Cats are now the most popular pets worldwide, and their importance simply cannot be ignored. Since 1996 the International Society for Feline Medicine (ISFM), the veterinary division of the not-for-profit organisation International Cat Care, has been working hard and developing resources to help veterinarians everywhere who treat cats in their clinics. The Society has developed many new approaches to making information on cats digestible, practical and state of the art. From the innovative *Journal of Feline Medicine and Surgery* with its alternating monthly classic (research based) and clinical practice (practical reviews) issues, to its lively annual congresses, it provides a balanced and targeted tool for practitioners. The Society also realises that treating cats is as much of an art as a science – an understanding of their behaviour, their needs, how stress can affect health, and how correct handling and attitude within veterinary practice and in communication with cat owners can have a huge effect on how successful working with feline patients can be. ISFM's ground-breaking Cat Friendly Clinic project is now a global movement, and growing numbers of clinics are finding that altering the way they deal with cats

The ISFM/Hill's Award for outstanding contributions to feline medicine came as a lovely birthday surprise for Dr Susan Little when it was presented to her at ISFM's World Feline Veterinary Congress in Barcelona last June. From left, Claire Bessant, Chief Executive ISFM, Susan Little, Iveta Bečvářová and Todd Towell of Hill's Pet Nutrition

can have very positive outcomes in cat health, both preventive and reactive, with practice personnel and in bonding clients.

ISFM sets out to be inclusive and welcoming – its organisers and its members care about cats and want to share their knowledge – this results in relaxed, friendly and fun European and Asia Pacific conferences every year and a growing enthusiasm for making things better. Hill's has worked with and supported ISFM since the very first (small and tentative) two-day conference in Stockholm, 12 years ago and the society is very proud of this association with its Founding Sponsor. The European congress has grown and developed, going from strength to strength, with over 600 attendees in Barcelona last year from 37 different countries, and the inclusion of masterclasses, simultaneous translations, poster sessions, pre-congress days and fun social events. This year the conference is in Riga (www.icatcare.org/learn/vets for more details).

Hill's has partnered with ISFM in recognising the growing importance of the cat (working together towards better feline veterinary care) and the need to share high quality knowledge and treatments in an approachable and practical manner. The relationship has been very successful both at the European Congress and at ISFM's pre-congress feline study day at BSAVA Congress which is an ever popular sell-out for practitioners. Hill's will also sponsor ISFM at its pre-congress feline day at SEVC in September this year for a day focusing on lower urinary tract disease.

ISFM membership has many tangible benefits, from the *Journal of Feline Medicine and Surgery* to an active member forum (where a great many cases are discussed between practitioners and leading experts in a friendly and non-judgemental atmosphere), to member rates for great conferences and CPD. For a full list go to www.icatcare.org/learn/vets.

We would love to welcome you as an ISFM member to enjoy learning more about cats, to share information with others and to join our growing international community of vets who care about cats.

ISFM feline events sponsored by Hill's in 2014:

- ISFM pre-congress feline day, BSAVA congress, UK, April 2
- ISFM European Congress, Riga, Latvia, June 19—22
- Pre-congress day SEVC, Barcelona, Spain, October 16

Claire Bessant
BSc
Chief Executive, International Cat Care

ISFM and Hill's working together towards better feline veterinary care

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ISFM European Feline Veterinary Congress

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Feline idiopathic cystitis:
Epidemiology, risk factors and pathogenesis

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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.

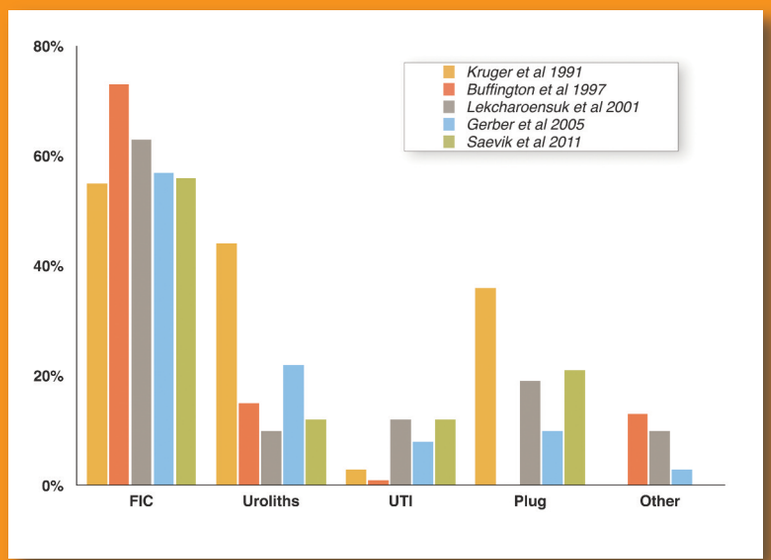

FIGURE 1 Prevalence of different causes of FLUTD in five published studies from North America and Europe
FIC = feline idiopathic cystitis;
UTI = bacterial urinary tract infection;
Plug = urethral plug or urethral obstruction
Other

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]

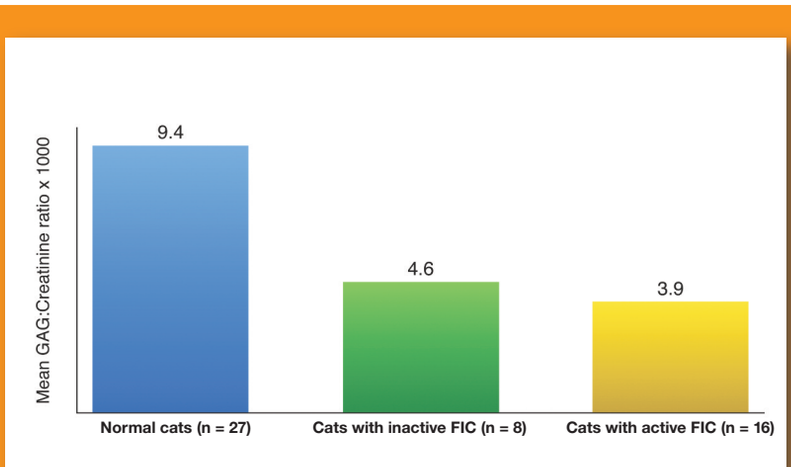

FIGURE 2 Urine GAG:creatinine ratio (x1000) in three groups of cats (from Buffington et al 1996[14]). Mean urine GAG:creatinine ratios were significantly reduced (*P* = 0.0001) in cats with FIC compared with normal cats

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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Role of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system in the pathogenesis of feline idiopathic cystitis

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Abnormalities in the sympathetic nervous system as well as the hypothalamic-pituitary-adrenal axis have been reported in cats with feline idiopathic cystitis (FIC). Tyrosine hydroxylase (TH) is the rate-limiting enzyme of catecholamine synthesis. A significant increase in TH immunoreactivity has been identified in the locus coeruleus (LC) (Figure 1), an area of the brainstem that is rich in alpha adrenergic receptors and is the origin of the descending excitatory pathway to the urinary bladder; it is the most important source of norepinephrine (NE) in the feline central nervous system.[1,2] Furthermore, TH was also increased in the paraventricular nucleus of the hypothalamus in cats with FIC.[3] The increased TH immunoreactivity observed in the LC of cats with FIC may provide a clue to the observation that clinical signs of FIC in cats follow a waxing and waning course and can be aggravated by environmental stressors.[4,5]

In addition to increased LC activity, we have reported that cats with FIC also have increased plasma NE concentrations.[4,5] When evaluating various catecholamines (CCE) in both healthy cats and cats with FIC during a period of mild stress (cats were moved from their regular vivarium to a room with new cages, food, and change of external environment), we noted increased plasma and cerebrospinal fluid (CSF) concentrations of CCE and their metabolites. We found that plasma concentrations of dihydroxyphenylalanine (DOPA), NE, and

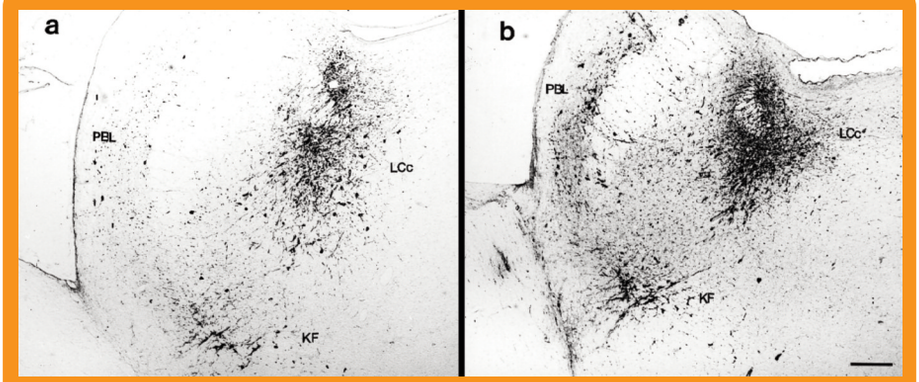

FIGURE 1 Photomicrographs of coronal sections of locus coeruleus of normal cat (a) and a cat with FIC (b), immunostained for tyrosine hydroxylase. Note increased staining density in locus coeruleus complex, parabrachial lateral (PBL) and Kolliker-Fuse (KF) nuclei of cat with FIC compared with normal cat. Scale bar: 20 pm. (From Reche AJ and Buffington CAT. Increased tyrosine hydroxylase immunoreactivity in the locus coeruleus in cats with feline interstitial cystitis. *J Urol* 1998; 159: 1045–1048)

its metabolite dihydroxyphenylglycol (DHPG), were significantly increased in FIC cats at all times during this stress protocol compared with healthy cats. Furthermore, as the healthy cats acclimated to the stress, their plasma CCE concentrations decreased, whereas even higher concentrations of plasma NE, epinephrine and their metabolites were demonstrated in cats with FIC.[4] The marked increment in DOPA concentrations suggests the possibility of a stress-induced increase in activity of TH, the rate-limiting step in CCE synthesis. In contrast, no effects on urine cortisol:creatinine was identified, suggesting an uncoupling of these two stress parameters. Plasma CCE concentrations did begin to return to baseline values after environmental enrichment strategies were employed, suggesting this therapeutic intervention may be beneficial for cats with FIC.

The acoustic startle response, a brainstem reflex in response to unexpected loud stimuli, is amplified in cats with FIC. This reflex in cats with FIC is greatest and most different from that of healthy cats during stressful situations, but is still greater in cats with FIC compared with healthy cats, even when adapted to enriched housing conditions.[6]

Enhanced stimulus-induced local NE release from the urinary bladder, could lead to a functional desensitization of the central alpha-2 adrenoceptors (α-2 AR) in cats with FIC.[7,8] In the brainstem (particularly the area of the LC), α-2 agonists inhibit NE release, whereas in the spinal cord they inhibit transmission of nociceptive input to the brain.[9] By evaluating the response of FIC cats to the selective α-2 AR agonist, medetomidine, both in vivo and in vitro studies have documented a functional desensitization of α-2 AR in affected cats.[7,8]

In addition to the sympathetic nervous system, abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis have also been observed in cats with FIC. Administration of ovine corticotropin releasing factor resulted in significant increases in adrenocorticotropic hormone (ACTH), but not cortisol.[10] Administration of synthetic ACTH (125 µg) to cats with FIC resulted in significantly decreased serum cortisol responses compared with healthy cats.[11] 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 in glands from healthy cats, while the area of the zona glomerulosa was significantly larger (Figure 2). Therefore, it appears that while the sympathoneural system is fully activated in this disorder, the HPA axis is not.

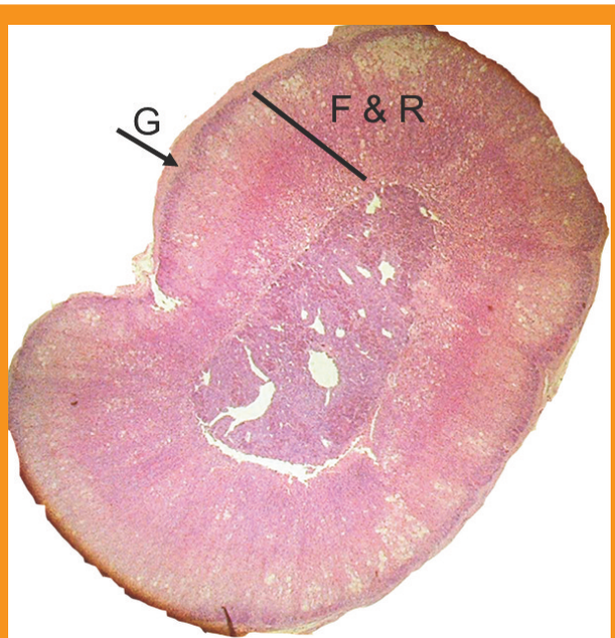

Figure 2 Histopathologic cross-section of an adrenal gland from a cat with FIC. Cats with FIC had adrenal glands with a significantly smaller zonae fasciculata and reticularis (F, R) (83% ± 2% vs 87% ± 4%, *P* = 0.03) and larger zona glomerulosa (G) (17% ± 2% vs 13% ± 3%, *P* = 0.02). No other histopathologic changes were reported

Summary

The pathophysiology of FIC likely involves complex interactions between a number of body systems. Abnormalities are not just localized to the urinary bladder, and cats can often present with various other comorbidities. In order to better treat these patients, it is important for clinicians to understand that this syndrome is not just a 'bladder disease' amenable to simple dietary or drug therapies.

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Feline uroliths and urethral plugs: Epidemiology, risk factors and pathogenesis

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Introduction

Urolithiasis is a common cause of morbidity in cats and affects both the upper and lower urinary tract. Mineral composition of feline uroliths is primarily struvite (magnesium ammonium phosphate hexahydrate) or calcium oxalate; together this represents approximately 90% of submitted feline uroliths globally (Figure 1). Less common are purine, cystine, xanthine, calcium phosphate, silica and mixed composition uroliths. Over the past 25 years mineral composition has changed in response to nutrition and the environment. Epidemiologic studies describe feline demographic and risk factors to help identify underlying mechanisms of urolith formation, which help enable optimal treatment and prevention strategies.

Prevalence

Few studies have evaluated the overall prevalence of uroliths in cats and there are no published studies of longitudinal trends. Previous estimates of the incidence of lower urinary tract disease (LUTD) in the United States and United Kingdom indicated uroliths affect 0.85 to 1.0% of cats per year.[1] Yet, the proportion of cats presenting for treatment to veterinary hospitals ranges from 1 to 6%.[1]

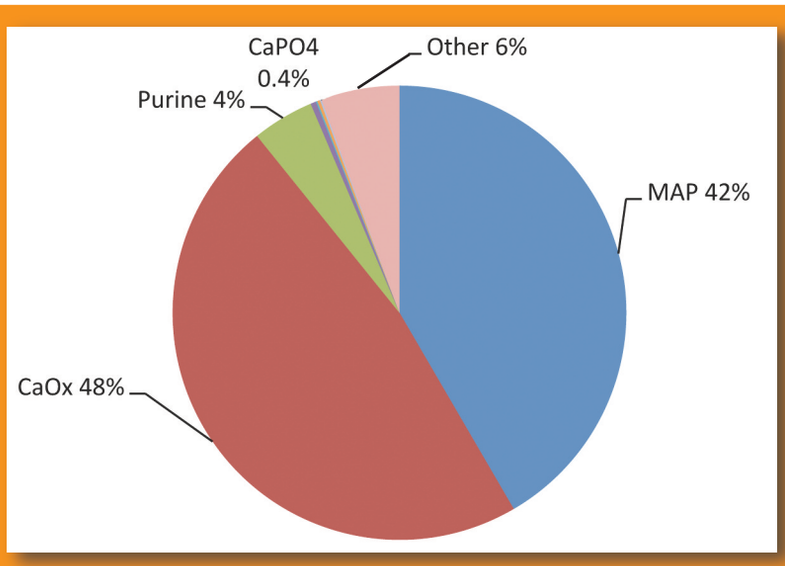

FIGURE 1 Average mineral composition of feline uroliths reported for 5 global regions. MAP = magnesium ammonium phosphate or struvite; CaPO4 = calcium phosphate, CaOx = calcium oxalate) (see Table 1 for additional details)

Table 1 Mineral composition of feline uroliths reported in the USA, Canada, and Europe

Site (year)	Minnesota[10] (2007)	California[7] (1984–2004)	Canada[11] (2008)	UK[12] (2002–2010)	Benelux[13] (2004)
Mineral composition	**% of total feline urolith submission**				
Struvite	48.6	37.8	42.1	47.7	32
Calcium oxalate	40.8	46.1	49.3	40.7/30.6	61
Purines	4.9	8.4	4.7	0.95	~3
Calcium phosphate	0.3	0.4	0.7	< 0.1	
Cystine	<0.1	0.1	<0.1	0.2	
Silica	<0.1	0.4	<0.1	< 0.1	
Xanthine	<0.1	0.1	0.1	0.2	
Other	5.1	6.7	2.98	< 10.3	4

Results of a cross-sectional study characterized the prevalence of urinary tract disease in 15,226 cats seen at private veterinary practices in the United States.[2] The combined prevalence of upper and lower urinary tract disease was 6.6%, and LUTD was diagnosed in 4.6% of all cats. Urolithiasis affected only 0.3% of this private practice population or 6.6% of cats with LUTD; this proportion is much lower than the prevalence reported in other studies. In a prospective clinical study conducted at the University of Minnesota, 143 untreated cats with hematuria, dysuria, urethral obstruction, or a combination of these signs were evaluated; 32 (22.4%) had urethral plugs, 30 (21%) had urolithiasis, and two (1.4%) had UTI.[3] In other studies the proportion of cats with LUTD related to uroliths varied from 11.8–22%.[4–6] Uroliths primarily are found in the lower urinary tract (93%), but may occur in all areas of the urinary tract. Cannon[7] reported the site prevalence of calcium oxalate uroliths as: 73% urinary bladder, 7.3% ureters, 4.3% kidneys, 13% urethra and 2% voided. Upper urinary tract uroliths, though less common than urocystoliths, have emerged as an important association with acute and chronic kidney disease over the past two decades.[8] While struvite is most commonly associated with urethral plugs, feline ureteroliths are reported to contain calcium oxalate 98% of the time.[9]

Urolith composition has changed dramatically over the past three decades. Sequential data from the Minnesota Urolith Center and the GV Ling Urinary Stone Analysis Laboratory (University of California at Davis) indicate calcium oxalate uroliths represented less than 5% of feline urolith submissions before 1987 and over 50% of the submissions in 1999.[7,10] While there is some variation in the proportion of struvite and calcium oxalate uroliths among laboratories and between regions, calcium oxalate now represents one of the most common mineral components found in feline uroliths across the globe (Table 1).

The rapid increase in prevalence of feline calcium oxalate uroliths may be multifocal, but is temporally associated with the 1980s trend to modify feline diets to reduce the risk of uroliths, urethral plugs and urinary obstruction associated

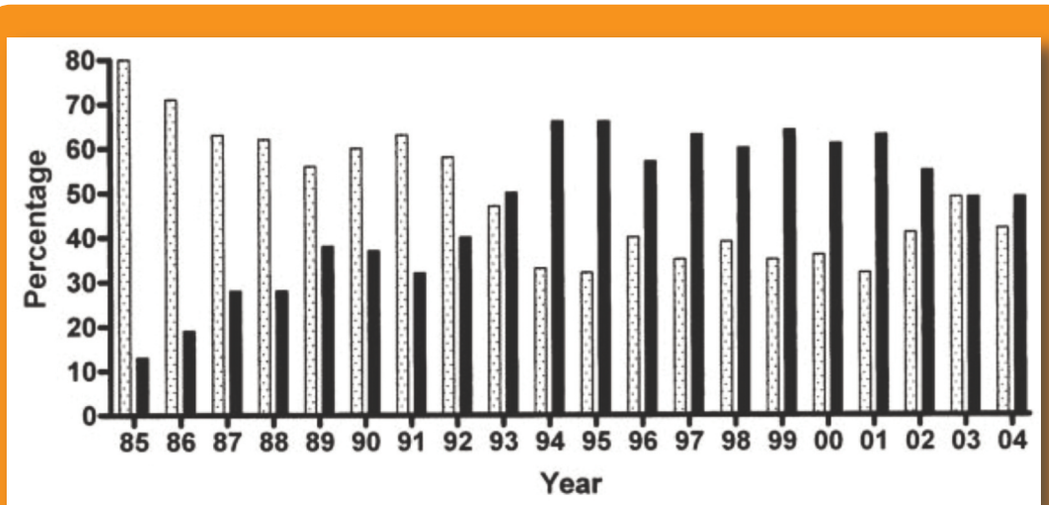

FIGURE 2 Percentage of feline calcium oxalate (black bars) and struvite (white bars) uroliths submitted to the GV.Ling Urinary Stone Analysis Laboratory at the University of California at Davis. (From Cannon AB et al. Evaluation of trends in urolith composition in cats: 5230 cases (1985–2004). *J Am Vet Med Assoc* 2007; 231: 570–576)

with struvite crystals. Dietary acidification and mineral restriction was broadly adopted and has been implicated as a risk factor in the proportional increase of calcium oxalate and decrease in struvite uroliths. Since 2002, the occurrence of calcium oxalate uroliths appears to have plateaued and even declined.[7,10] Calcium oxalate uroliths represent 40.8% of submissions and struvite uroliths rose to 48.6% of uroliths analyzed at the Minnesota Urolith Center, while the GV Ling Urinary Stone Analysis Laboratory (University of California at Davis) reported 44% struvite and 40% calcium oxalate between the period of 2002 and 2004 (Figure 2).[10] It is possible that moderation of dietary acidification may be the reason for the change.

The proportion of cats with lower urinary tract signs attributed to urethral obstruction varies from 18–58% and crystalline-matrix plugs account for approximately 21–60% of obstructions.[4,14] A 2002 report from the Minnesota Urolith Center noted that the prevalence of urethral obstruction had declined from 1.9–0.7% from 1980 to 1999 and that the percentage of obstructions related to plugs or urethroliths declined from 49–23% over that same period.[15] Urethral plugs are composed of at least 45–50% matrix and variable amounts of mineral; although 100% matrix plugs are commonly observed.[16] Despite the frequency of calcium oxalate uroliths, struvite has consistently remained the most common mineral identified in feline urethral plugs over the past 25 years. Of plugs submitted for quantitative analysis, the crystalline component has consistently been greater than 81% struvite (Table 2).[16–18]

Epidemiology and risk factors for disease

While epidemiologic studies suggest the etiology of feline urolithiasis and urethral plugs is multi-factorial, there is strong evidence that nutritional factors, genetics and environmental factors influence disease expression and mineral content of feline uroliths.

Non-dietary factors associated with the occurrence of uroliths include: age, breed, gender, reproductive status, body composition, housing, and potentially stress. Nutritional risk factors associated with uroliths include diet-induced urinary pH alterations, feeding method, food form, food variety, dietary supplements and water intake. Data supporting individual nutrients as sole risk factors are less robust and are specific to individual urolith types. Reported risk factors vary across studies and confound the interpretation of significance of the epidemiological evidence.

TABLE 2 Mineral composition of urethral plugs at the Minnesota Urolith Center (MUC) and the Canadian Veterinary Urolith Center (CVUC)

	MUC (1981–2007)	MUC (2007)	CVUC (1998–2003)
Mineral composition	**% of urethral plugs submitted**		
Struvite	83.5	91.5	81.1
Matrix	11.5	6.5	4.5
Calcium oxalate	0.9	1.0	6.6
Calcium phosphate	0.6	0.4	NR
Purines	0.1	0	NR
Other	3.4	0.6	NR

Calcium oxalate uroliths

Age Uroliths from all causes tend to occur in older cats; mean age across several studies is 7.0–7.6 years of age.[9,19–22] Cats ≥7 years but ≤10 years of age are reported to be 67 times more likely to develop calcium oxalate while struvite is more common in younger cats, both in Germany and the United Kingdom.[12,20–21]

Breed Results from early epidemiologic studies evaluating risk factors for calcium oxalate uroliths found domestic shorthair, domestic long hair, Persian and Himalayan breeds were at highest risk.[19–22] The Persian and Himalayan breeds were 5.5 to 8 times more likely to develop uroliths than non-Persian breeds.[19–21] In a study evaluating 1573 feline uroliths within Europe, European Shorthair 64.3% and purebred cats (Persian 15.2%, British shorthair 3.9%, Chartreaux 1.7%, Maine Coon 1.5%, Siamese 1.1%) were at highest risk.[20] A similar distribution of purebred cats (British Shorthair, Exotic Shorthair, Foreign Shorthair, Havana Brown, Himalayan, Persian, Ragdoll, and Scottish Fold cats) within the United States at risk of developing calcium oxalate uroliths has been reported.[21]

Gender Most studies report fairly similar gender distribution for most urolith types with a slight gender bias toward male cats. Regional variation in gender risk has been described and may explain contrasting reports.[19] Males are at 1.5 times the risk for calcium oxalate uroliths compared with females,[21–22] while female cats appear more at risk for struvite.[12–21] The biologic relevance of this difference has not been recognized except for male cats, who are at risk for urinary obstruction.

Neutering Neutering appears to be a significant risk factor across all uroliths types with 81.8% of cats presenting with urolithiasis having been surgically altered.[21]

Metabolic factors Kidney disease is commonly associated with calcium oxalate uroliths, particularly of the upper urinary tract.[7,10] The mechanism may be due to metabolic acidosis, which promotes hypercalciuria secondary to increased bone turn over and increased serum ionized calcium concentration, or altered calcium excretion at the level of the kidney.

Hypercalcemia is associated with an increased risk of calcium oxalate urolith formation; in cats with calcium oxalate uroliths, hypercalcemia was observed in 35% of the cases.[23] Conversely, in cats with idiopathic hypercalcemia, uroliths developed in 35% of the affected cats.[24] When severe, hypercalcemia results in increased urinary fractional excretion of calcium and hypercalciuria. Interestingly, epidemiological studies indicate a protective effect of increased dietary calcium.[21] Yet,

feeding studies evaluating the effect of a therapeutic food on calcium oxalate risk in urolith-forming cats, support the benefit of controlled dietary calcium intake in reducing hypercalcemia.[25] Obesity results in a three-fold increase in risk for calcium oxalate urolithiasis.[21] The link of urolith formation to obesity has been suggested to be associated with a number of factors: decreased mobility and urine retention, inflammation and oxidative stress, or is a marker for increased mineral intake. Regardless, attention to body composition should be considered when managing risk-reduction in urolith prevention protocols.

Environment Assessment of environmental factors are limited. Both descriptive and epidemiological data supports increased risk for cats housed indoor-only (odds ratio 3.0) which has been associated with other comorbidities (ie, obesity and stress). Water source has not been defined as a risk factor although most cats are provided water from municipal sources, complicating adequate study design and power.

Nutritional factors

The impact of diet on the risk of feline calcium oxalate urolith occurrence has been evaluated in detail by Lekcharoensuk.[26] Cats with calcium oxalate uroliths were most commonly fed foods with lower levels of protein, calcium, phosphorus, potassium and moisture and highly acidified to induce acidic urinary pH (5.99–6.15). A decreased risk was observed in cats fed moderate calcium, and increased phosphorus and magnesium.

Water All studies support the benefit of increased moisture intake in reducing urolith risk. Increased water intake and urine dilution reduces the activity product of calcium oxalate and reduces risk for urolith formation by three-fold.[23,26] Strategies for increasing water intake include feeding high moisture foods, high protein diets, increased water availability or appeal, and stimulating thirst through the addition of dietary salt. All strategies increase water intake to variable degrees and appear safe in healthy cats. Contraindications exist for the use of salt and high-protein foods in cats with kidney disease, a viewpoint that may not be shared by all.

Urine pH Significant aciduria (urine pH <6.2) is a risk factor for calcium oxalate formation. Acidic urine alters several steps in the pathogenesis of urolithiasis from increasing mineral precursors to decreasing crystal inhibitors. All studies evaluating the role of diet on urinary acidification find a strong association with diet-related urinary acidification and calcium oxalate urolithiasis. In one study, cats fed acidifying diets or urinary acidifiers had a 5–20 times increased risk for developing calcium oxalate uroliths; the strongest association identified.[19] Other reports describe up to a three-fold increase in urolith risk with the lowest urine pH.[23,26]

Calcium It is important to recognize that the reported relationship of dietary calcium to urolith risk appears bimodal, suggesting a dual role for calcium in calcium oxalate formation. This dual risk for high and low levels of calcium intake has been reported in people. Low dietary calcium intake may increase the availability of intestinal oxalate uptake thereby increasing urinary oxalate excretion. Dietary calcium is known to complex with intestinal oxalate and promote fecal calcium oxalate excretion in the gut, thereby reducing urinary calcium and oxalate concentrations. At very high calcium intakes, increased calcium absorption may increase urinary excretion and calcium oxalate risk, although calcium uptake is well regulated in normal cats.[27]

Urolith inhibitors In addition to the effect of intraluminal calcium as an inhibitor of intestinal oxalate absorption, urinary inhibitors of calcium oxalate crystal formation include magnesium, pyrophosphate, potassium and citrate. The association of lower dietary phosphorus, potassium and magnesium with increased calcium oxalate risk has a logical association. The role of diet acidification and the impact on inhibitor urine concentration and function will be discussed elsewhere.

Oxalate There is little information about the nutritional risk of dietary oxalate. Oxalate is found in various vegetable products and is also a byproduct of endogenous ascorbate (vitamin C) metabolism. Over supplementation of vitamin C and fiber are known to increase oxalate intake in other species. Fiber is not significantly associated with oxalate uroliths[26] and modest vitamin C inclusion in feline diets does not increase urinary oxalate concentrations in healthy cats.[28] Investigation into the role of oxalate metabolizing gut microflora (*Oxalobacter formigenes*) is ongoing, but specific risk factors for uroliths are undefined.[29]

Protein Low protein diets (<8 g/100 kcal) were associated with an increased risk of calcium oxalate uroliths in epidemiologic studies.[26] High-protein meals have been reported to alter mineral excretion, increase water intake, increase urine volume, lower urinary oxalate and acidify urine in healthy cats.[30,31] While urine dilution and reduced oxalate could aid in urolith prevention, urine acidification may oppose such benefit. Feeding trials have resulted in minimal impact of high-protein foods on calcium oxalate activity product compared with moderate-protein diets when urine pH is controlled (Kirk, unpublished data).

Struvite Uroliths

Age Sterile struvite uroliths form typically in cats between 1 and 10 years of age and are more common in younger cats compared to cats with calcium oxalate uroliths (6.6 vs 7.6 years).[12,20] Risk for struvite urolith formation decreases after approximately 6 to 8 years of age in cats.[21]

Breed factors Chartreux, Domestic Shorthair, Foreign Shorthair, Himalayan, Oriental Shorthair, and Ragdoll cats have an increased risk of developing struvite uroliths. Himalayan and Persian cats had 2.6 times increased risk of developing struvite uroliths and seem to be prone to both struvite and calcium oxalate urolith formation.[21,23]

Gender Female cats are at higher risk for sterile struvite uroliths compared to males and in comparison to other urolith types.[12.21] While male

cats are at risk for urethral plugs, of which struvite is the major crystalline component, they are 30% less likely to develop struvite uroliths.[21]

Neuter status Neutered cats represented 91% of cats presenting with struvite uroliths compared to 9% who are intact.

Environment Housing cats indoors is associated with two times the risk for struvite development compared to outdoor cats. Obesity and stress have been associated with increased risk of struvite uroliths, similar to calcium oxalate.[21]

Nutritional factors

Diets high in magnesium, phosphorus and protein, combined with alkaline urine pH have been associated with struvite risk for over 30 years. Other nutrients associated with increased risk include calcium, chloride, sodium and fiber.

Water Increasing moisture in the diet could help struvite urolith prevention and dissolution; however, this has not been critically evaluated. Oddly, epidemiological studies did not find a significant protective effect of foods high in moisture, which is likely explained by the primary role of urine pH and mineral control in sterile struvite prevention.[26] Foods high in fiber are recognized to increase risk of uroliths by approximately two-fold in epidemiologic studies as well as clinical observations. The increased struvite risk could be due to the hygroscopic nature of fibers in the gut and a subsequent reduction in urine volume.

Urine pH The relationship between urinary pH and struvite solubility is well established and the basis for the effective medical dissolution of struvite uroliths. Urine pH values from 6.5 to 6.9 are associated with two times the risk for sterile struvite urolith development compared with urine with a pH <6.[15]

Protein Consumption of high dietary protein in healthy cats increased water intake and urine volume, increased urine acidification and reduced struvite activity product.[30] However, in studies by Lekcharoensuk, no risk reduction was noted with increased protein.[26] The potential for increased phosphorus intake from protein consumption to negate benefits may explain the lack of benefit noted in other studies.

Magnesium Diets high in magnesium (0.36 to 1.40 mg of magnesium/kcal) were 3.7 times as likely to be associated with struvite uroliths compared with cats fed low magnesium (0.09 to 0.18 mg/kcal) foods.[26] Urinary magnesium excretion reflects dietary intake when body stores are replete. Increased magnesium intake has been shown to increase feline struvite formation.

Phosphorus Like magnesium, phosphorus is a major component of struvite and increased intake results in increased urinary phosphorus excretion and supersaturation with a key calculogenic substrate. Increased dietary phosphorus increases struvite risk by 3.5–4.4-fold at levels above 1.76 mg of phosphorus/kcal.[26]

Miscellaneous nutrients Other nutrients associated with struvite risk are increased intake of calcium (3 odds radio; OR), chloride (2 OR) and sodium (4 OR). Alterations in mineral metabolism or excretion and casual association with other stone-forming minerals (eg, sodium phosphate, calcium phosphate etc.) may explain these epidemiologic associations.[26]

Urate uroliths

Age Cats developing urate uroliths were at greatest risk between 4 and 7 years of age (mean age 6.2 years) with over 50 times greater risk of developing urate uroliths than cats less than 1 year of age.[32]

Breed factors Cats developing urate uroliths were most often purebreds with Bengal, Berman, Egyptian Mau, European Shorthair, Havana Brown, Ocicat, Oriental, Ragdoll, Rex Snowshoe and Sphinx at increased risk. American Shorthair, Himalayan, Manx and Persian breeds were protected.[32]

Gender Most studies report fairly similar gender distribution for urolith types with a slight gender bias toward male cats. Males have 1.1 times the risk as females for urate uroliths.[32]

Neutering Neutering or castration appears to be a significant risk factor for uroliths with 81.8% being surgically altered. Compared with surgically unaltered cats, the risk of developing urate uroliths was 12 times greater in neutered cats.[32]

Metabolic Urate stones in cats are often associated with portocaval anomalies.

Nutritional factors Specific nutritional factors have not been associated with urate risk in cats although decreased dietary protein and urinary alkalization are suggested for prevention.

Urethral plugs

Age In a study of 77 European cats with lower urinary tract disease, urethral plugs occurred in 10% of the cases.[6] Ages ranged from 2–11 years with a mean age of 4 years. In the US, the greatest risk was in those cats 4–6 years of age with an odds ratio of 2.9.[33]

Breed Domestic Shorthair, Norwegian Forest, Persian and Siamese are reported to have increased risk of urethral plugs.[6,14]

Gender As expected, all cats with urethral plugs were male, with 92% being neutered and 8% intact.[8]

Metabolic Primary metabolic abnormalities associated with urethral obstruction are uncommon, aside from those secondary to acute urethral obstruction. Obesity has been reported as a possible risk factor, and a larger proportion of cats reported by Gerber were overweight (mean 5.7 kg; range 4.5–7.2 kg) compared to cats with urinary tract infections.

Housing Indoor housing appears to be a common risk factor for urethral plugs. Of eight cats described with plugs, 75% were housed exclusively

indoors.[6] This finding is consistent with the risk of idiopathic LUTD, in general.

Nutrition Nutritional factors are similar to those for cats with struvite disease, and cats with urethral plugs are more commonly fed a major proportion of their diet as dry foods or dry food exclusively.[6]

Pathogenesis – urolith formation

Overview Urolith formation, dissolution, and prevention involves complex physical processes. Major factors include:

- Supersaturation resulting in crystal formation.
- Effects of inhibitors of crystallization and inhibitors of crystal aggregation and growth.
- Crystalloid complexors.
- Effects of promoters of crystal aggregation and growth.
- Effects of non-crystalline matrix.[34,35]

Concept of urine saturation Urolith formation is associated with two complementary but separate phases: initiation and growth. It appears that initiating events are not the same for all types of uroliths. In addition, factors that initiate urolith formation may be different from those that allow it to grow. The initial step in formation of a urolith is formation of a crystal nidus (or crystal embryo). This phase of initiation of a urolith formation, called nucleation, is dependent on supersaturation of urine with calculogenic crystalloids. The degree of urine supersaturation may be influenced by the magnitude of renal excretion of the crystalloid, urine pH, and/or crystallization inhibitors or promoters in urine. Non-crystalline proteinaceous matrix substances may also play a role in nucleation in some instances.

Nucleation has been classified as homogeneous or heterogeneous. Homogeneous nucleation occurs spontaneously in highly supersaturated urine in the absence of foreign substances; therefore, the nidus is composed of identical crystalloids. Heterogeneous nucleation is catalyzed by foreign material such as suture material, indwelling catheters, tissue debris, crystal embryos of different composition, and so on (Figure 3). Urine contains many impurities that might promote heterogeneous nucleation and initiate crystal formation at a concentration of crystalloids below the formation concentration. These substances may be thought of as facilitators or potential facilitators of crystallization. Any crystal type may be a potential nidus for nucleation of another crystal type. A greater degree of supersaturation (that is, a higher formation product) is required for homogeneous nucleation than for heterogeneous nucleation (Figure 4). Once nucleation has occurred, however, crystal growth can occur at any degree of supersaturation (even at metastability).

Further growth of the crystal nidus is dependent on:

- Its ability to remain in the lumen of the urinary system.
- The degree and duration of supersaturation of urine with crystalloids identical to or different from that in the nidus.
- Physical characteristics of the crystal nidus. If they are compatible with other crystalloid, crystals may align themselves and grow on the surface of others. This is called epitaxial growth and may represent a heterogeneous form of nucleation, and may account for mixed and compound uroliths.

An important driving force behind urolith formation is saturation state of urine with lithogenic substances (Figure 4). When a solution such as urine is saturated, it refers to the maximal amount of a substance, such as calcium oxalate, that can be completely dissolved. This point is termed the thermodynamic solubility product. When calcium oxalate is present in urine at a concentration less than the solubility point, the urine is undersaturated with calcium oxalate and it completely dissociates and dissolves. When calcium oxalate is present in urine at a concentration that is equal to the solubility point, the urine is saturated with calcium oxalate and calcium oxalate may begin to precipitate. When calcium oxalate is present in urine at a concentration above the solubility point, the urine is supersaturated with calcium oxalate and calcium oxalate precipitates.

Urine contains ions and proteins that interact and/or complex with calcium and oxalic acid so as to allow them to remain in solution. This explains why calcium and oxalic acid in urine do not normally precipitate to form calcium oxalate

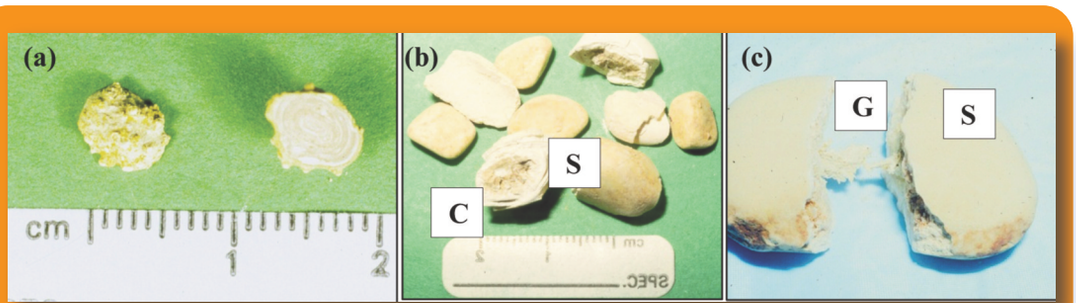

FIGURE 3 Example of (a) homogeneous nucleation and (b and c) heterogeneous nucleation. (a) Ammonium urate urolith removed from a 3-year-old, intact male, English Bulldog. Note the laminations. (b) Compound urolith removed from a 4-year-old, spayed female Toy Poodle. The outer layers are composed of infection-induced struvite (S) around a calcium oxalate nidus (c). (C) Infection-induced struvite urolith removed from a 2-year-old, spayed female Miniature Schnauzer. The urolith (S) formed around a piece of fibrous material (gauze sponge, G), inadvertently left behind at a previous cystotomy for urolith removal

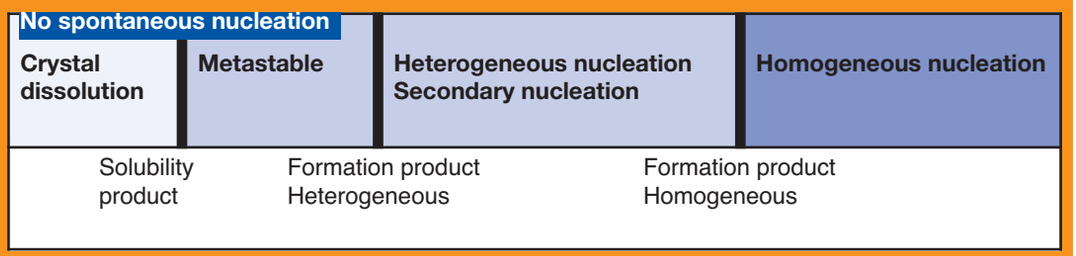

FIGURE 4 States of urinary saturation

crystals. Urine is normally supersaturated with respect to calcium and oxalic acid. But energy is required to maintain this state of calcium and oxalic acid solubility, and, therefore, the urine must constantly 'struggle' to maintain calcium and oxalic acid in solution. Thus, urine is described as being metastable. The metastable region refers to the degree of supersaturation of a crystalloid that lies between the solubility product and the formation product. Metastability applies to those solutions (such as urine) that have the capacity to retain more of a compound in solution than would be predicted by knowledge of its true solubility in water. A metastable solution is thermodynamically unstable, but does not contain enough energy to initiate crystal formation. However, if crystals are already present, they may grow.

If the concentration of calcium and oxalic acid is increased, a threshold is eventually reached at which urine cannot hold more calcium and oxalic acid in solution. The urine concentration at which this occurs is the formation point of calcium oxalate. Above the thermodynamic formation product, urine is oversaturated and unstable with respect to calcium and oxalic acid. Thus, calcium oxalate crystals will precipitate, grow in size, and aggregate together.

Urine is a complex solution containing a variety of substances that can inhibit or promote crystal formation and growth.[36–44] Inhibitors include molecules that reduce calcium oxalate and calcium phosphate supersaturation. Some inhibitors (eg, citrate, magnesium, pyrophosphate) form soluble salts with calcium, oxalic acid or phosphate, and thereby reduce the quantity of calcium, oxalate or phosphate available for precipitation. Other inhibitors (eg, nephrocalcin, uropontin, glycosaminoglycans, Tamm-Horsfall glycoprotein, other inert ions) interfere with the ability of calcium and oxalic acid to combine, and thereby minimize crystal formation and growth. Also, glycosaminoglycans act as protectors by preventing adherence of crystals to the urinary tract mucosa.

Summary

Uroliths are a common cause of feline morbidity. Prevalence patterns are globally similar with struvite and calcium oxalate representing over 90% of all urolith types, and changes in prevalence mirrored in many regions. Despite variability across studies and urolith composition, several key risk factors appear common. Shorthair, Himalayan and Persian breeds are consistently reported within high risk for urolithiasis, although purebred cats as a whole seem more proportionally affected. Most cats developing urolithiasis are middle aged with a mean age of 7, although cats with struvite and urate are somewhat younger. Being neutered and housed indoors are risk factors for major urolith types with gender distribution varying by urolith composition and region. Urethral plugs are consistently found in male cats. Nutritional risk factors common to all uroliths are low water intake and the diet-regulated urinary pH. Dietary protein, fat and mineral content may influence urolith risk, but the relative risks reported in epidemiologic studies are less robust. Use of epidemiological findings coupled with a strong understanding of the pathophysiological process will help direct future research and evidence-based treatment and prevention.

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Diagnostic approach to cats with lower urinary tract signs

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Introduction

A combination of findings from history (including details related to behavior, the environment, husbandry practices), physical examination (including all body systems in addition to the lower urinary tract), urinalysis, serum biochemistry, and quantitative urine culture are often needed to establish a definitive diagnosis for the causes of lower urinary tract signs (LUTS). Routine and advanced urinary tract imaging provide pivotal diagnostic anatomical information in cats with recurrent LUTS. Histopathology of urinary bladder or urethral tissue is rarely needed to make a diagnosis except in the instance of neoplasia. Feline idiopathic/interstitial cystitis (FIC) is largely a diagnosis of exclusion of bacterial urinary infection, urolithiasis, and neoplasia. Treatment is dictated by an accurate diagnosis for the causes of LUTS. Figure 1 shows

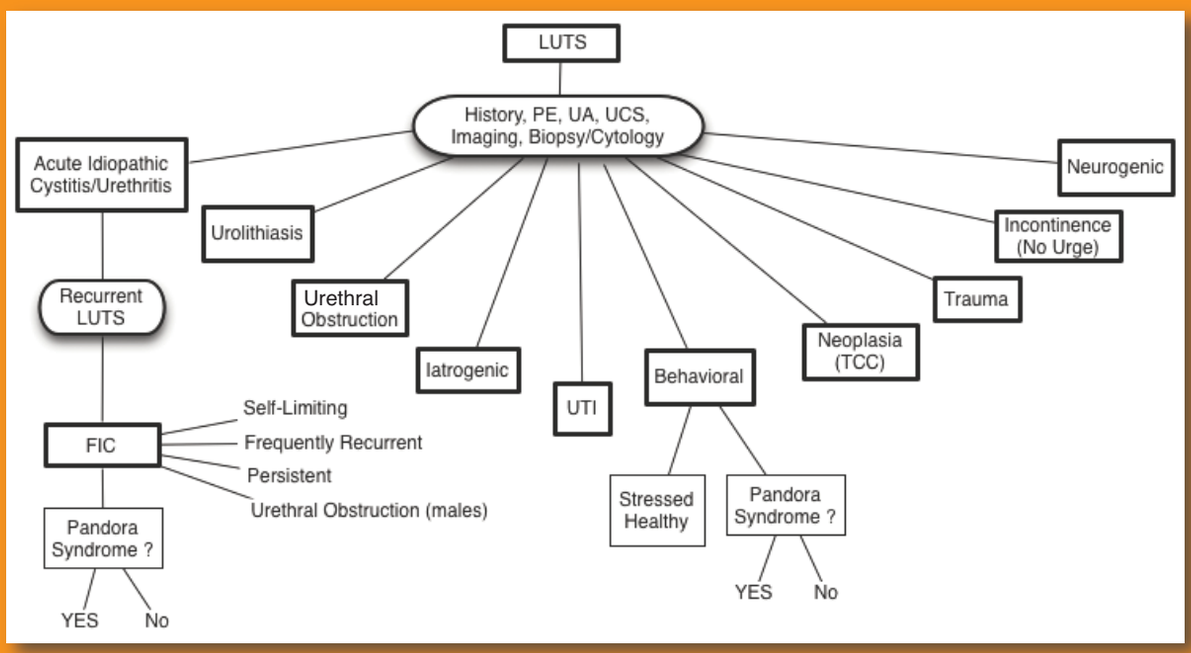

FIGURE 1 Possible causes of LUTS in cats after appropriate diagnostic evaluation. PE = physical examination; UA = urinalysis; UCS = quantitative urine culture (cfu/ml); Imaging = some combination of radiography, contrast urography, ultrsonography and/or uroendoscopy

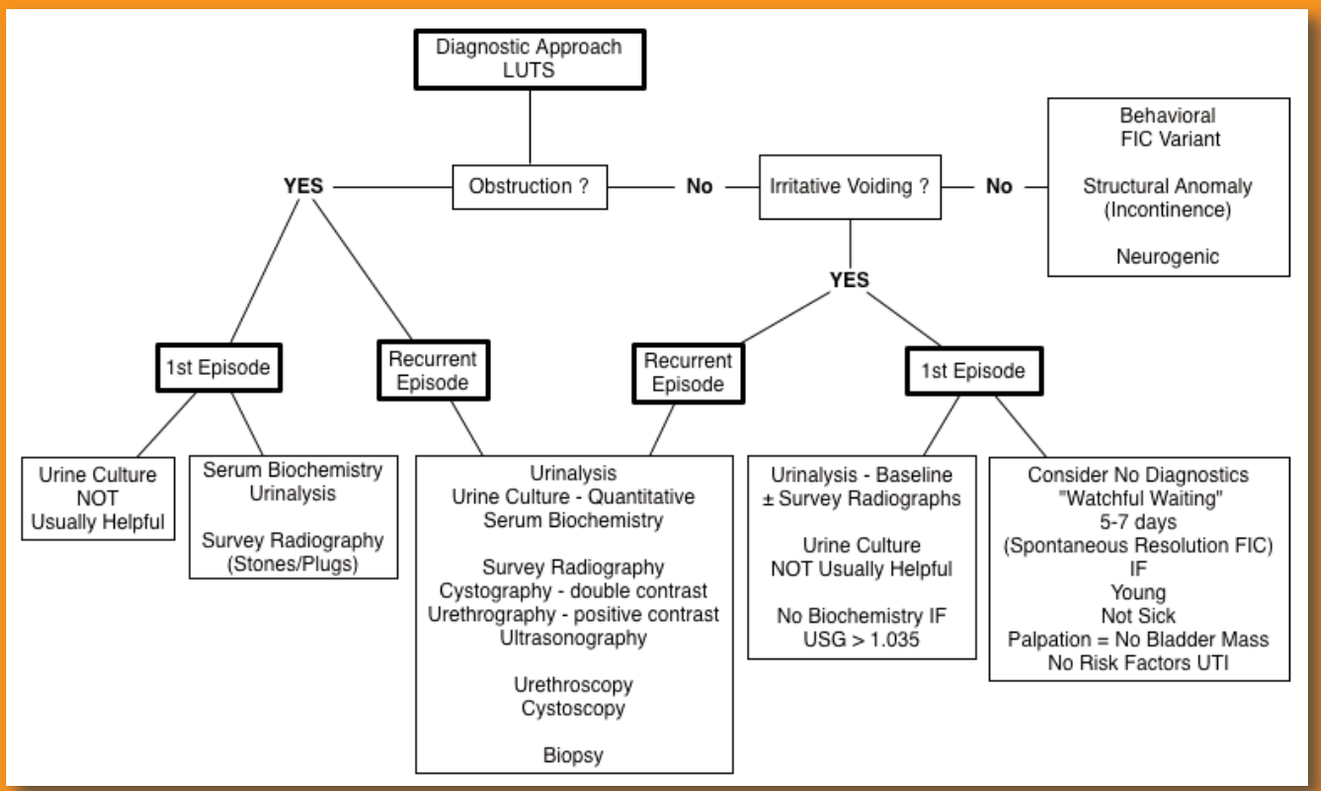

FIGURE 2 A diagnostic approach for cats with lower urinary tract signs (LUTS), emphasizing the distinction between cats with or without urinary obstruction and those with or without irritative voiding. See text for further details as to when specific testing is most helpful and appropriate

the many possible causes of LUTS in cats after appropriate diagnostic evaluation.

History/clinical findings

The signalment, history, and clinical findings provide helpful information to identify the cause of LUTS. Age, breed, gender and neuter status, diet, litter box management, access to the outdoors and other environmental factors are important in the overall assessment of the likelihood for any specific cause of LUTS.

Cats with disorders affecting the lower urinary tract display variable combinations of pollakiuria, stranguria, periuria, dysuria, and/or hematuria. Vocalization such as howling may be observed due to the pain and discomfort associated with LUTS. Urge incontinence is common in obstructive (overflow) and non-obstructive FIC as well as in cats with urolithiasis, urinary tract infection (UTI) and neoplasia. Periuria (urinating in inappropriate locations) unassociated with urgency is common in urinary behavioral disorders, patent urachus, ectopic ureter and neurogenic disorders; it is sometimes the only sign in FIC. These clinical signs are neither specific nor sensitive for any one particular disease.

The most common clinical sign in cats with non-obstructive FIC is periuria, with or without other clinical signs suggesting irritative voiding.[1,2] Clinical signs of FIC often wax and wane and appear to be exacerbated by stressors and deficiencies in the environment.[3–15] The extent and severity of clinical signs will be more severe in cats with complete urethral obstruction from the systemic effects of post-renal azotemia (electrolyte and acid-base derangements along with dehydration).

A detailed collection and analysis of history is necessary to determine behavioral and environmental influences on cats with FIC and behavioral disorders (covered elsewhere in this symposium). Affected cats are often over-reactive to their environment and may display nervous, fearful, defensive or aggressive behaviors and may have a neurotic attachment to their owners.[5,6,12,13,15–18] Vulnerability factors (eg, maternal stress, orphaned, bottle-fed, early neutering) are sometimes identified in this population of affected cats.[15,17,19–21] Stress in the cat's or owner's life should be identified if possible during the history because it can play an important role in initiating and perpetuating clinical signs. Assessment of the cat's living environment as to stressors and deficiencies can provide clues to the diagnosis of FIC and behavioral disorders. There is considerable overlap in the clinical findings between cats that have FIC and those with urinary behavioral problems. Cats that have recovered from FIC (and possibly other causes of LUTS) can continue to display periuria or have bouts of periuria due to acquired behavioral problems, despite resolution of the original cause of LUTS.[22]

Co-morbid conditions and Pandora syndrome

It is important to recognize that cats with FIC (other causes of LUTS have not been specifically studied) often have clinical problems outside the lower

urinary tract.[15,17] These co-morbid disorders are often either not recognized or not considered important due to the clinician's focus on the urinary bladder, urethra and LUTS. The co-morbid conditions frequently encountered are related to the gastrointestinal tract (regurgitation, vomiting of hair or food, soft stool, diarrhea), skin lesions with no fleas (barbering of caudal abdomen), cardiovascular system (heart murmur, gallop rhythm, cardiomyopathy), endocrine system (low adrenal cortical function), behavior problems (frightened, withdrawn, hiding, aggressive, overly attached), obesity, and odontoclastic resorptive dental lesions.[14,23]

Environmental stressors are reported to increase sickness behaviors (lethargy, vomiting, anorexia) more so in cats with FIC compared with healthy cats.[12] Historically, it has been common to focus on history and physical examination related to the LUTS. However, it is essential to obtain the history and physical examination of all organ systems, as well as collection and analysis of a detailed environmental history in all cats with LUTS. A diagnosis of 'Pandora syndrome' applies to those cats that exhibit clinical signs in organ systems in addition to LUTS, waxing and waning of clinical signs associated with stressful events that presumably activate the stress response system, and undergo resolution of the severity of clinical signs following effective environmental enrichment.[15]

Physical examination

Results from physical examination are neither sensitive nor specific for any particular cause of LUTS. For example, the urinary bladder or urethra can be thickened from many different disease processes, as is also true for detection of pain arising from the lower urinary tract. Abdominal palpation frequently fails to detect uroliths and masses in the urinary bladder and urethra, especially in cats that are overweight. An initial first step is to determine if the urinary bladder is large or small at the time of LUTS. It is important to determine if the cat has urethral obstruction at the beginning of the examination because these cats need immediate analysis and treatment that could be life-saving.

Non-obstructive LUTS

In cats with non-obstructive LUTS, a complete physical examination of all other body systems should be performed before focusing on the urinary tract to insure identification of all co-morbid conditions that may be present (described above – Pandora syndrome). The urinary bladder is normal to small in size in cats with any cause of irritative voiding, due to frequent elimination of urine. A thickened and or painful urinary bladder wall may be identified in some cats with chronic FIC, urolithiasis, and neoplasia. Urinary bladder uroliths can sometimes be palpated, especially if there are multiple uroliths that can be rubbed against each other creating a 'crepitant' sensation. It can be difficult to palpate uroliths or masses when the urinary bladder is distended with urine. Inability to palpate the urinary bladder in this population of cats can occur when the urinary bladder is very small or if the cat is obese.

Further diagnostics – clinical laboratory testing and urinary tract imaging

The number of episodes (initial or recurrent) of LUTS the cat has experienced, the severity of the cat's clinical signs, other medical conditions, whether the cat is obstructed or not, and how much money the owner is willing or able to spend all influence the degree of laboratory testing and urinary tract imaging that can be ordered. An exhaustive diagnostic evaluation is not usually necessary in a young otherwise healthy cat experiencing its first episode of FIC as spontaneous remission often occurs within 5–7 days. However, a clinical diagnosis of FIC cannot be made with greater certainty until urolithiasis, bacterial UTI and neoplasia have been excluded as possible causes of clinical signs. More thorough diagnostic evaluation is indicated for all cats that fail to have spontaneous remission of clinical signs within one week or for those with recurrent episodes, urethral obstruction, a history or the presence of other health problems, or in older cats (>8 years of age). Figure 2 details a diagnostic approach to cats with LUTS.

Urinalysis

Findings from urinalysis are useful, but are neither sensitive nor specific for the cause of LUTS. A recent study concluded that the few significant differences in urinalysis results in cats with various causes of LUTS were of limited diagnostic value.[24] All causes of irritative LUTS are characterized by varying amounts of hematuria, proteinuria and pyuria. The classical findings of hematuria and proteinuria in cats with non-obstructive FIC often wax and wane between days and even within the same day.[7,8] Thirty-two of 70 cats with non-obstructive FIC did not have hematuria when measured by disptrip; 32 of these 70 cats had >5 red blood cells (RBC)/high power field (HPF).[2] Consequently, failure to document abnormal findings in a single urine sample does not exclude a diagnosis of FIC. Pyuria is usually identified in cats with LUTS signs associated with UTI. Pyuria, >10 white blood cells (WBC)/HPF, was identified in 77% of cats with obstructive and non-obstructive forms of FIC in a recent report, but many cats in this series were males with recurrent urethral obstruction; the number of male and female cats without obstruction that exhibited pyuria was not detailed. The occurrence of pyuria was significantly higher in male cats with obstruction compared with male cats without obstruction in the same study.[6] Only 2 of 70 cats with non-obstructive FIC were noted to have >5 WBC/HPF in another report.[2]

It is physiologically normal to observe a few struvite or oxalate crystals in urinary sediment, especially when the urine is highly concentrated and if the urine sample has been refrigerated and stored.[25,26] Alkaline urine favors precipitation of struvite crystals and acidic urine favors precipitation of cystine crystals. There is no direct effect of urinary pH on calcium oxalate precipitation in urine and the effect of urinary pH on urate crystals is variable. Crystals in urinary sediment are of no pathological consequence unless the cat is forming a urolith or a urethral plug.

The type of crystalluria may be consistent with

the chemical composition of the patient's urolith but crystalluria is often detected in cats without urolithiasis, can be absent in those with urolithiasis, and the crystal type identified may differ from the chemical composition of the urolith. Struvite crystalluria was identified in 48% of male and female cats in one study, but results were heavily biased from males with urethral obstruction. Struvite crystalluria was greater in male cats with obstruction than in male cats without obstruction (P = 0.051), though cause or effect of the crystalluria was not established. Struvite crystalluria was not associated with hematuria, proteinuria or pyuria but was associated with urinary pH.[6] Struvite crystalluria (rare to few) was observed in only 9 of 70 (six female, three male) cats with non-obstructive FIC in another study.[2] Regardless, the presence of crystals has **NO** known diagnostic impact on non-obstructive forms of FIC and there is no evidence to support that crystals damage a healthy urothelium. If crystals are observed in non-obstuctive FIC, they are usually present in low numbers.[2,7,8,27]

Urine pH by itself does not distinguish amongst the various causes of LUTS in cats and depends on the interaction of many factors including diet, postprandial alkaline tide, stress-induced acute respiratory alkalosis, urease-producing bacteria in UTI and the degree of entry of plasma proteins (pH 7.3–7.4) into urine from the inflammatory process and bleeding. Stress induced by transport to the veterinarian's office has been shown to cause acute respiratory alkalosis and alkaline urine in one cat.[28] Therefore, finding neutral urine pH in cats affected with FIC may not necessarily reflect a failure of the diet to acidify the urine.

In cats with non-obstructive LUTS and urine specific gravity <1.030, some systemic disease (kidney disease, hyperthyroidism, diabetes mellitus) may be present that is interfering with the formation of more concentrated urine. In these instances, diagnostics to exclude polyuric conditions are warranted.

Bacterial urine culture

In urine collected by cystocentesis from young cats with LUTS, quantitative bacterial culture reveals significant growth in <2 % of the samples in most studies from North America.[1,2,29] These university practices included cats largely from first opinion clinics. In a report of cats referred for LUTS, 4.9% had bacterial UTI.[30] In contrast, a study of cats from Norway with a variety of obstructive and non-obstructive causes of LUTS found a surprisingly high number of cats with positive urine cultures (33%).[31] Findings from this study are difficult to interpret since many of the cultures (67%) were from voided midstream or catheterized urine samples rather than collection by cystocentesis. The authors speculated that the higher rate of UTI in cats with LUTS could have resulted from differences between cases diagnosed at primary versus tertiary care facilities, though geographical differences in occurrence of UTI could not be excluded.

Quantitative urine culture is recommended for all cats with recurrent LUTS and for those with disorders that increase risk for UTI. This includes cats with chronic kidney disease, hyperthyroidism, diabetes mellitus, urinary incontinence, perineal urethrostomy, or a history of urethral catheterization within the past 6 months.[30,32–35] In cats older than 10 years of age in one study, UTI was common (>50%), occurring alone or in combination with urolithiasis in those evaluated for signs of urinary urgency.[36–39] Though FIC does not appear to be initiated or maintained by bacterial infection, intrinsic abnormalities of the lower urinary tract in cats with FIC could predispose to microbial colonization, as appears to be true in humans.[40]

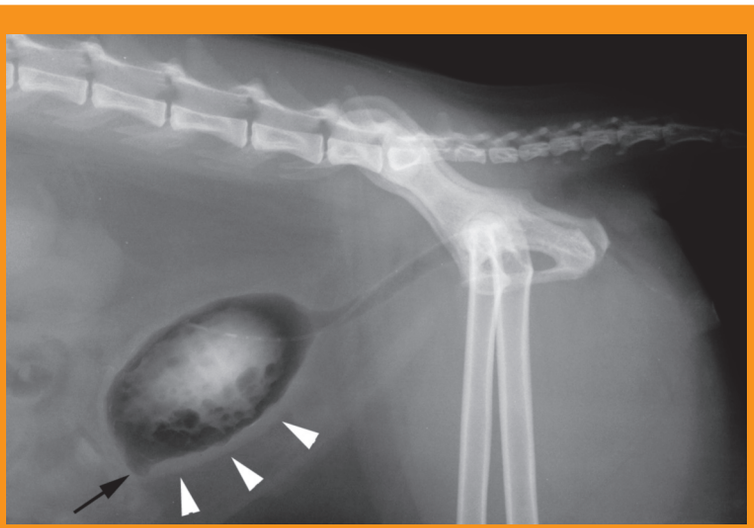

FIGURE 3 Double contrast cystogram of a female cat with non-obstructive FIC. The urinary bladder wall is thickened especially ventrally (white arrowheads). Note the urachal diverticulum (black arrow). Note also multiple irregular filling defects in the central contrast pool likely from blood clots and inflammatory debris. This study excluded any component of urethral obstruction and the presence of radiolucent calculi. The presence of a urachal diverticulum can be identified in some normal cats and can also be acquired transiently in cats with urethral obstruction (this is a female). Anecdotally, surgical removal of a urachal diverticulum lessens the clinical signs of some cats with non-obstructive FIC that do not respond to other treatments

Urinary tract imaging

Urinary tract imaging is recommended for all cats with recurrent LUTS. Survey radiographs are helpful to identify radiodense calculi, most often calcium oxalate or struvite, which are usually observed if ≥2–3 mm in size. In cats with multiple recurrences or persistence of clinical signs, advanced urinary imaging should be pursued when survey radiographs are normal, in order to exclude radiolucent calculi, blood clots, masses, urethral strictures and anatomical defects.

Contrast cystourethrography is normal in about 85% of cats with non-obstructive recurrent FIC.[41,42] Abnormalities that can be identified during double-contrast cystography include focal or diffuse thickening of the urinary bladder wall, permeation of contrast agent into the urinary bladder wall, permeation of contrast through the urinary bladder and into the abdomen and filling defects in the contrast pool (blood clots and cellular debris) (Figure 3). It is important to perform contrast urethrography in male cats that have undergone previous urethral catheterization and now have recurrence of LUTS to identify the presence of acquired urethral stricture or evidence for previous

urethral trauma such as a urethral diverticulum.

Ultrasonography can be useful as a less invasive method of imaging than contrast urethrocystography, though the diagnostic information yielded can be quite different. Wall thickness can be readily measured if the urinary bladder is adequately distended with urine; (overestimation of bladder wall thickness occurs when there is minimal distension with urine (Figure 4). Ultrasonography can document the presence of urinary bladder calculi regardless of their radiodensity if they are of sufficient size (>2 mm) (Figure 5).[43] Ultrasonography of affected and normal cats sometimes reveals highly echogenic acoustic interfaces of both suspended and gravitating particles – the origin of these echogenic particles remains to be determined, but they do not represent crystals in the vast majority of cats among those that we have evaluated. In a recent study, the amount of urinary 'sediment' detected during ultrasonography was not different between male cats with obstructive and non-obstructive FIC and had no relationship to the presence or absence of struvite crystalluria.[6]

Uroendoscopy

Urethrocystoscopy is usually performed to evaluate cats with recurrent LUTS when a diagnosis is not obvious after contrast urography or ultrasongraphy, though cystoscopy can reliably be used instead of contrast cystography in female cats.[44] Urethrocystoscopy allows direct visualization of the urinary bladder and urethral mucosa under magnification and of contents within the lumen (uroliths, foreign body, fronds as a likely indicator of transitional cell carcinoma). Some lesions are visualized with this technique that cannot be detected with contrast urography or ultrasonography. To improve diagnostic accuracy in male cats, urethroscopy is often combined with double contrast cystoscopy. Urethrocystoscopy excels in its ability to document small uroliths, early and advanced neoplastic or polypoid projections from the mucosa, mucosal erosions, foreign bodies, blood clots, urethral stricture, urachal diverticula, hemorrhage, and mucosal vascular changes that commonly characterize cystitis and urethritis. Small urocystoliths and masses that are not visible with radiography or ultrasonography are usually easily detected during cystoscopy. Microscopic examination of tissue samples obtained through the operating port of the rigid scope can be diagnostic for neoplasia, but sometimes are not informative due to their small size. Several specimens from the region of interest should be obtained to increase the chances of differentiating between normal, neoplastic, and inflammatory changes.

In male and female cats with non-obstructive FIC, a varying degree of increased vessel number and tortuosity, edema and glomerulations (submucosal petechial hemorrhages) are often visualized in the urinary bladder (Figure 6). An

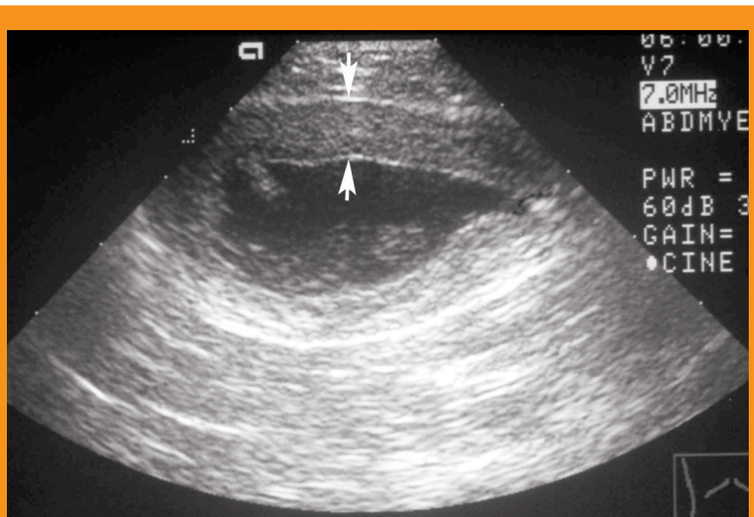

FIGURE 4 Ultrasonographic examination of the urinary bladder from a young female cat with FIC. Note thickening of the urinary bladder wall (between arrowheads). Urinary bladder wall thickness can be overestimated if the urinary bladder is not distended with enough urine. In this instance there is likely enough urine in the bladder lumen to estimate the bladder thickness with reasonable accuracy. Neoplasia (eg, transitional cell carcinoma) is an unlikely diagnosis in this young cat with relatively symmetrical thickening of the bladder wall (the one protrusion into the bladder lumen is likely a blood clot)

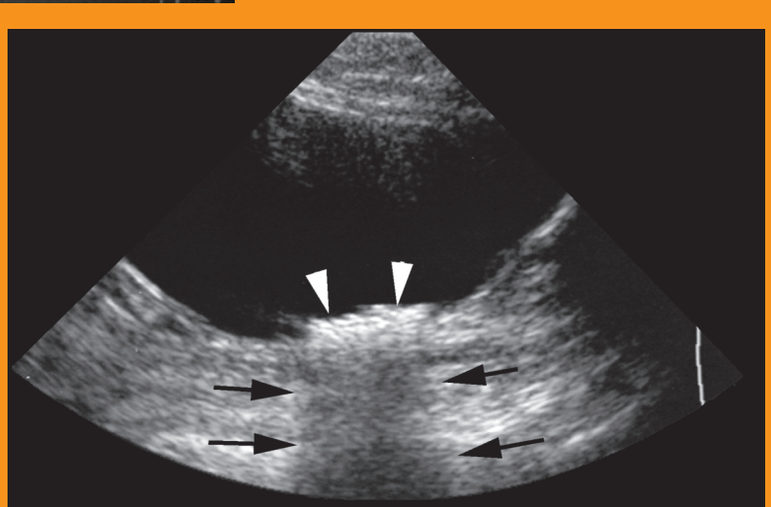

FIGURE 5 Ultrasonographic examination of a male cat with LUTS due to multiple small calculi. Notice the local accumulation of many small hyperechoic round uroliths (arrowheads) with acoustical shadowing below (black arrows)

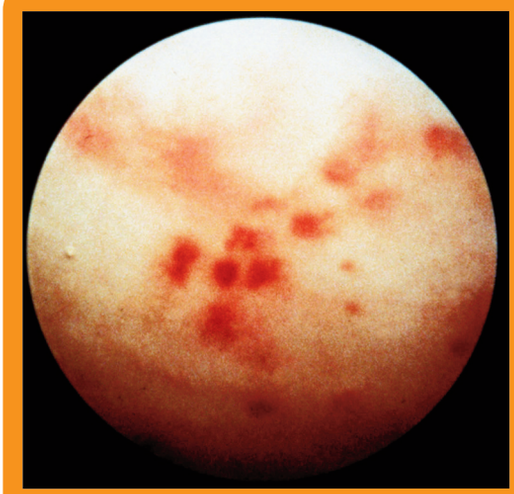

FIGURE 6 Cystoscopic appearance of the urinary bladder from a female cat with severe LUTS due to FIC. Note several submucosal hemorrhages (glomerulations) in the cranial view of the urinary bladder. Also note the absence of the normal pattern of blood vessels, which is obscured by edema of the urinary bladder wall

increase in the number and size of glomerulations often occurs in cats with FIC when higher bladder filling pressures (≥80 cm water) are used during cystoscopy. This finding does not occur in normal urinary bladders and serves as a provocative test for FIC in the absence of other diagnoses (uroliths, UTI, neoplasia). Female cats with FIC rarely have lesions in the urethra whereas urethral lesions (erosions, hemorrhages, glomerulations) are observed in approximately 40% of male cats with non-obstructive FIC.[44] It should be noted that LUTS do not necessarily correlate with the degree or number of cystoscopic abnormalities identified in cats with FIC.[45–47]

Biomarkers

Reliable diagnostic markers for FIC currently are not yet clinically available. Urinary levels of antiproliferative factor, heparin-binding epidermal growth-like factor, and epidermal growth factor distinguish human patients with interstitial cystitis from healthy controls, but have not been investigated in cats with FIC. 1-D gel electrophoresis revealed that the urine protein pattern in cats with FIC was significantly different from control cats.[48] Urinary fibronectin was increased in cats with FIC compared with control cats and those with UTI or urolithiasis, and could be considered as a biomarker for FIC. It could also be important in the pathophysiology of this disease as fibronectin is important in cell adhesion, migration, growth and differentiation.[48]

Decreased urinary Trefoil factor 2 (TFF2) in cats with FIC compared with control cats was demonstrated using quantification of Western Blot signal intensities and immunohistochemistry. A decreased ability to repair the urothelium could result from a deficiency of TFF2, so this could be operative in the pathophysiology of FIC as well as serving as a biomarker for FIC.[49]

Three studies in cats have shown decreased glycosaminoglycans (GAG) excretion in cats with FIC. An early study showed reduced urinary total GAG in both random and 24-hour urine samples for those with FIC.[50] In a study by another group, urinary GAG concentration was greatly decreased in cats with FIC when compared with normal adult cats. Chondroitin sulfate comprised the main urinary GAG and was thought to originate from the circulation following filtration by the kidney.[51] Low urinary total GAG was again a finding in the most recent study of FIC.[52] It is unclear whether low urinary GAG in these studies is due to changes in synthesis, metabolism, or urinary bladder permeability. Low GAG concentrations could reflect damage to the urinary bladder surface, resulting in absorption and/or degradation of the endogenous urinary GAGs. We do not yet know whether these

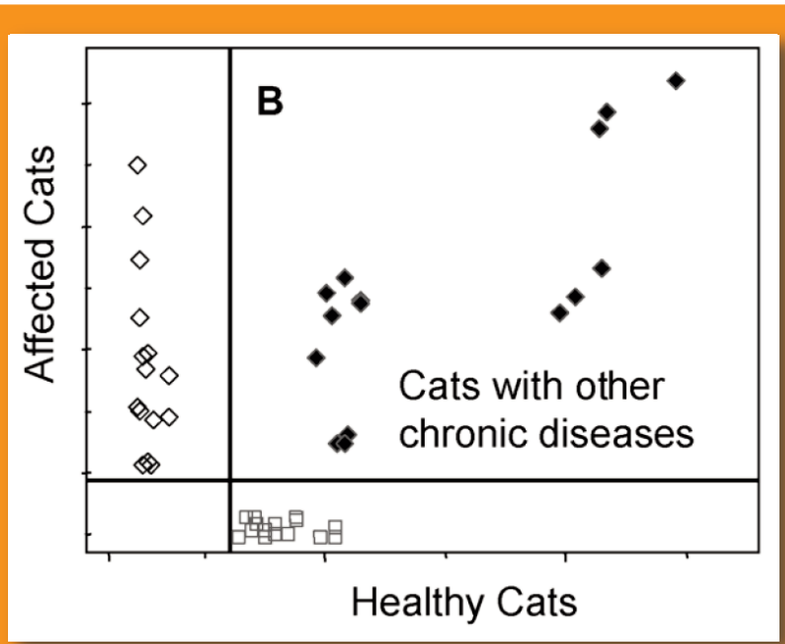

FIGURE 7 Separation of infrared spectra of sera from cats with FIC, healthy cats, and cats with other chronic diseases as evaluated by soft independent modeling by class analogy (SIMCA). Classification required information from the 1500–1800 cm^{-1} spectral region to discriminate these disorders. The internal vertical and horizontal lines represent significant differences (P <0.05) between groups. All groups are significantly different from one another

differences are related to the cause(s) or consequences of the syndrome, neither, or both.

Dried serum films from cats were studied using infrared microspectroscopy and spectra were classified using Soft Independent Modeling by Class Analogy. Cats were classified as healthy or affected with FIC – the condition was predicted in 100% of the cats (Figure 7).[53] Significant differences between healthy and FIC cats were shown in another study using similar methodology when analyzing blood spot cards.[54] Analysis of serum samples using liquid chromatography–mass spectroscopy revealed differences in the concentration of tryptophan and its metabolites between healthy and affected cats in both studies. These results demonstrate the potential utility of infrared microspectroscopy to diagnose FIC; this methodology has been patented.[55]

Summary/key learnings

Though FIC is the most common diagnosis associated with LUTS in young cats, it is important to exclude bacterial UTI and urolithiasis in a population of cats with risk factors. Collection of a detailed history that includes queries regarding environmental issues and husbandry practices is an essential first step in deciding if the LUTS are related to irritative voiding or not, and how likely stress may be playing a role. In order to determine if LUTS are part of Pandora syndrome, the history and physical examination must be extended beyond that immediately related to the urinary tract. Quantitative urine culture and survey radiography are recommended in the evaluation of all cats with recurrent LUTS to exclude UTI and radiopaque calculi. Advanced imaging that includes contrast radiography, ultrasonography and urethrocystoscopy is useful for the exclusion of anatomical defects, radiolucent calculi and proliferative lesions in some cats.

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Feline idiopathic cystitis:
Evidence-based management

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Initial management

Feline idiopathic cystitis (FIC) can be obstructive or non-obstructive in its presentation. There is little evidence to recommend a specific protocol for relieving obstruction in cats; smaller studies have shown no significant beneficial effects from administration of intravesical lidocaine[1] or glycosaminoglycans (GAG).[2] Urethral pressures have been reported to be increased in female cats with FIC compared with healthy cats, even when clinical signs were not overtly present.[3] Therefore, there may be justification for administration of alpha antagonists, such as prazosin or phenoxybenzamine, in some cats with idiopathic urethral obstruction, but these drugs have not been formally investigated in male cats to prove or refute this statement. Pain appears to be a prominent feature of this disease and analgesics should be administered to help control these clinical signs. Once the cat has been stabilized, management is similar to the non-obstructed FIC cat, which can include analgesics, addressing the environmental needs of the cat, and possibly dietary and pharmacologic interventions.

While some cases of presumed FIC may appear to resolve quickly and not recur, the clinician should be aware that the patient's environmental needs are likely not being met and these issues should be addressed (see below). In addition to environmental alterations, analgesic therapy for initial management of lower urinary tract signs (LUTS) has been described with anecdotal success. As pain appears to be a clinical sign in cats with FIC, providing analgesia with narcotics such as oral buprenorphine (0.01 mg/kg transmucosal, squirted in the mouth PO q8–12h), butorphanol (0.2 mg/kg subcutaneously [SC] or PO q8–12h) or a fentanyl patch can be used, depending on the severity of the pain. Non-steroidal anti-inflammatory drugs (NSAIDs) have also been described for this disease, with variable results. To the author's knowledge, the only oral NSAID approved in the United States for use in cats is robenacoxib, and its use in FIC has not been described. Because of the risk for dehydration-associated reductions in blood flow to the kidneys and the potential for

acute kidney injury, these medications might increase the risk for adverse outcomes. Furthermore, they have not been found to benefit patients with interstitial cystitis/painful bladder syndrome (IC/PBS), an analogous disease in human beings, and are not routinely recommended. Unfortunately, evidence based data are lacking regarding these treatment options for the initial signs of FIC. It has been reported that many cats with LUTS do not have bacterial urinary tract infections,[4] therefore antimicrobials should only be administered if there is confirmation of a positive urine culture.

Chronic management

Environmental alterations

No cure is currently available for cats with FIC; treatment options are aimed at clinical recovery, keeping the cat's clinical signs to a minimum, and increasing the disease-free intervals. Environmental stressors have been reported to exacerbate clinical signs of FIC. In cats with severe FIC, increased concentrations of circulating catecholamines have been reported compared with control cats during a period of mild stress.[5,6] These catecholamines returned to baseline after periods of environmental enrichment. A recent study of healthy cats and cats with FIC found that environmental stressors resulted in increased number of sickness behaviors (eg, vomiting, lethargy, anorexia) in cats with FIC when the results were controlled for other factors.[7] Due to these studies, environmental enrichment has been investigated in client-owned cats with FIC. In a non-placebo controlled trial, 46 client-owned cats with FIC were evaluated and multimodal environmental modifications (MEMO) therapy was found to be successful in most cats with FIC followed over a 1-year period.[8] Placebo controlled trials are difficult when evaluating cats with FIC due to the waxing and waning nature of the disease as well as the numerous variables that one encounters in a home environment.

MEMO therapy involves obtaining a thorough environmental history, including but not limited to the topics presented in Table 1. A detailed client history form, as well as additional client and veterinarian resources can be found online at http://indoorpet.osu.edu/veterinarians/research/index.cfm. Furthermore, guidelines for meeting the environmental needs of cats has also recently been published by the *Journal of Feline Medicine and Surgery* and International Society for Feline Medicine working group.[9] After the diagnosis of FIC is made, a thorough environmental history, as well as notation of all other co-morbidities present, needs to be obtained so the clinician (and/or staff member) can begin to tailor a plan to address all the needs of each individual cat. It is helpful to establish a veterinary technician/nurse-based program, in which a staff member works with these pet owners and patients as often as necessary to ensure the cat's problems are thoroughly explained to the owners so they understand the disease process enough to feel comfortable with managing their cat's disease.

The client should complete the questionnaire for all cats in the household and the clinician can then review the list and identify issues that may be contributing to the cat's clinical signs, including any inter-cat conflict that may be present in multi-cat households. After the questionnaire has been completed, the veterinary technician/nurse can review it with the client and agree on helpful modifications.[10,11] The author suggests recommending only one or two changes to the client initially so as not to overwhelm them or the cat. Meeting the environmental needs of the cat does not have to involve a large expense for clients (Figures 1a and b). Key resources to consider include water, food, litter boxes, interaction with humans and other animals (for some cats) and hiding/resting areas. It is important to make certain that proper litter box hygiene is followed and provide a structured MEMO plan.

Table 1 Questionnaire to ascertain if the environmental needs of the cat are being met

1. Where was the cat obtained?
2. Number of cats in the household
   - Is intercat conflict an issue?
   - Number and type of other pets
   - Number of family members
3. Size and type of the household dwelling
4. Litter pans
   - Number?
   - How often are they cleaned?
   - How often are they changed?
   - Location in the house?
   - Type of litter used?
   - Depth of litter preferred by the cat?
5. Feeding
   - Type of food (including brand, canned versus dry)?
   - Location of bowls?
   - Food preferences?
   - Is competition for food present in the household?
6. Play and rest activity
   - Preferred toys?
   - Space in house available for play?
   - Preferred type of play?
7. Indoor or outdoor housing status?
8. Resting or hiding areas preferred?
9. Changes in household
10. Behavioral concerns
    - Aggression
    - Fear
    - Nervousness
    - Separation anxiety
11. Other sickness behaviors or co-morbid diseases present?

Diet

Up to 90% of humans with IC/PBS report sensitivities to a wide variety of foods; however, these data were formulated primarily from questionnaire–based surveys.[12,13] Sensitivities reported in humans include such foods as citrus fruits, alcohol, vitamin C and artificial sweeteners;

FIGURE 1 Examples of inexpensive environmental enrichment for cats. Proper resting (a) and hiding (b) areas for cats are important to provide a 'safe' area for all cats in the household. Environmental needs of the cat should be addressed for all cats in the household and clinicians also need to address inter-cat conflict if present. (Images courtesy of Dr Hazel Carney)

whereas, calcium glycerophosphate and sodium bicarbonate tended to improve clinical symptoms. Unfortunately, a specific diet does not alleviate symptoms for all IC/PBS patients; furthermore, dietary recommendations are confusing for clinicians if all the potential co-morbidities often encountered with IC are taken into consideration.[14,15] For some human patients, tailored elimination diets are considered when developing a therapeutic plan.

Cats with FIC also have a variable combination of co-morbid disorders[8,16–19] such as behavioral, endocrine, cardiovascular and gastrointestinal (GI) problems. Due to these findings, it is advised that the clinician complete a thorough physical examination as well as a detailed environmental history for cats suspected of FIC, and not focus entirely on the urinary bladder. That patients with FIC (and IC) have variable combinations of other co-morbid disorders raises the question as to why some cats present with primarily LUTS as their main clinical feature. However, all co-morbidities and the effect of diet must be considered when making recommendations for cats with FIC. Therefore, if the clinician is considering dietary changes for cats with FIC, a tailored approach to altering the cat's diet is advised.

To date there are no published studies to support that acidified diets are beneficial in the management of chronic FIC; anecdotal evidence suggests that beverages that acidify the urine in human patients with IC/PBS can exacerbate clinical symptoms (http://www.ichelp.org/). There is also no evidence to support consuming a diet that produces urine with primarily an alkaline urinary pH benefits humans with IC/PBS. In cats, if pronounced struvite crystalluria is present in an obstructed male cat, a diet formulated for struvite dissolution may be warranted to help prevent recurrent urethral obstructions. Finally, obesity may be a risk factor for FIC, and implementing an obesity therapy program may be of benefit.[20] All the cat's needs and concurrent diseases, if present, must be taken into consideration when making dietary and environmental recommendations.

Dietary moisture

An older study evaluating the recurrence of LUTS in cats with FIC that were fed a canned or dry formulation of the same diet revealed a significant reduction in the clinical signs in those cats consuming the canned food.[21] Increasing water intake by feeding canned food — or other methods, such as broths or automatic water dispensers[22] — may or may not be beneficial for cats with FIC. Some hypothesize that added water might help dilute the potential 'noxious' stimulants in the urine such as urea and potassium chloride. Potassium chloride has been used as a diagnostic probe for IC/PBS in human beings,[23] and it has been speculated, but never demonstrated, that the urine potassium concentration plays a role in the pathophysiology of IC/PBS. For some cats, canned food or added dietary moisture in the forms described above may serve as a form of environmental enrichment (eg, increased contact with humans who provide the food on differences in mouth feel/texture for the cat), which might have a positive impact on the cat's clinical signs.

Pheromones

Pheromones are chemical substances that transmit highly specific information among animals of the same species. Although the exact mechanisms of action are unknown, pheromones reportedly induce changes in the limbic system and hypothalamus that alter the emotional state of the animal. Feliway (Ceva Animal Health, St Louis) is the synthetic F3 fraction of the naturally occurring feline facial pheromone. Treatment with this pheromone has been reported to reduce the amount of anxiety experienced by cats in unfamiliar circumstances, a response that may or may not[24] be helpful for FIC cats and others that experience anxiety-related problems.[25] In a pilot study evaluating Feliway in cats with FIC, a decrease in the number of days they exhibited clinical signs was reported, although this finding was not significant ($P = 0.06$).[26] Feliway can be purchased as a spray formulation or a room diffuser. The spray can be used in areas such as where the litter pan is kept, or sprayed in carriers 10 to 15 minutes prior to car transport. Room diffusers can be placed in designated rooms for cats and may help decrease anxiety and clinical signs of FIC.[9]

Drug therapy

A variety of drugs have been tried in cats with FIC (Table 2), but prospective, randomized, properly masked, placebo-controlled studies are lacking to confirm their clinical efficacy. If MEMO (and possibly pheromone) therapy fails to control signs,

Table 2 Drug therapy for chronic feline idiopathic cystitis*

Drug	Class/action	Dosage	Potential side effects
Amitriptyline	Tricyclic antidepressant	2.5–5 mg/cat q12–24h	Sedation Lethargy Urine retention
Buspirone	Non-benzodiazepine anxiolytic	2.5–5.0 mg/cat q12h	Sedation
Clomipramine	Tricyclic antidepressant	0.25–0.5 mg/kg q24h	Sedation Lethargy Urine retention
Fluoxetine	Serotonin reuptake inhibitor	1mg/kg PO, q24h	Gastrointestinal upset
Glycosamino-glycans	May coat urinary bladder lining and protect uroepithelium from noxious substances	50 mg/cat PO, q12–24h (Elmiron)	Rarely gastrointestinal upset

*Controlled clinical studies evaluating use of these drugs are limited

the medications listed in Table 2 can be considered. These drugs should not be used for cats on initial presentation for care of LUTS; they should be considered only for cats after their environmental needs have been addressed, and should not be discontinued abruptly.

Amitriptyline (2.5–7.5mg/cat PO q 24h), a tricyclic antidepressant (TCA), was evaluated in an open, non-placebo controlled trial and appeared to help clinical signs in some cats with severe, refractory FIC.[27] This drug, or possibly clomipramine, another TCA (0.25–0.5mg/kg PO q24h), may need to be administered for at least one week or longer before a beneficial effect may be noted. If no improvements are noted, or medicating the cat is too stressful (for owner or cat), these drugs should be gradually discontinued over 1 to 2 weeks. Side effects of the TCAs can include sedation, lethargy, weight gain and urine retention. Due to the possibility of urine retention, it is advised to monitor the cat for urolithiasis if clinical signs re-develop after receiving this class of drugs for an extended period of time. Fluoxetine (1 mg/kg PO q24h) is a selective serotonin reuptake inhibitor (SSRI) and has been shown to decrease signs of urine marking in cats; however, its effects in cats with FIC have not be described.[28] This drug should also not be abruptly discontinued. Side effects of the SSRI's can include behavior changes such as anxiety, and sleep disturbances. Many drugs used for FIC are considered 'off-label'and owner consent should be obtained prior to therapy.

Pentosan polysulfate sodium is a semi-synthetic carbohydrate derivative similar to GAGs that is also approved for humans with IC. A multi-centered, placebo-controlled, masked study in cats reported no significant differences when comparing pentosan polysulfate sodium with placebo.[29] However, all groups had clinical benefit, suggesting a strong 'placebo' effect. All medication was provided to the cat in a food treat; the authors of this study hypothesized that improving the interaction and environmental needs of the cat may inadvertently have contributed to the positive outcomes noted in all groups. Similar findings were reported in two other studies evaluating GAG replacers in cats with FIC.[30,31]

Summary

The clinician and client must understand that FIC is not limited to abnormalities solely of the urinary bladder. Because FIC can be a chronic condition in some cats, excellent client communication in conjunction with MEMO therapy, and possibly pharmacologic agents, may be beneficial for managing chronic FIC. Some cats may retain their underlying predisposition for this disorder and, if exposed to a significant stressor, clinical signs can recur. Early intervention can be important and research in both rodents[32] and cats[5,8] has demonstrated that effective environmental enrichment might mitigate much of the effects of early life adversity. Analgesics can be used short-term if the cat is presented with recurrent clinical signs. Continual work with the owner and cat can yield positive results, and encouragement to reinforce these behaviors during successes can be beneficial, as is the case with any chronic medical condition.

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L-tryptophan and alpha-casozepine: What is the evidence?

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Introduction

Since the introduction of a therapeutic food for improving the lives of pets with kidney disease, much attention has focused on the role of nutrition for disease management in companion animals. The benefits of nutritional management for a variety of disorders, including kidney disease, heart disease and allergic dermatitis are well understood. There is now growing interest in the effects of nutrients on behavior in pets, including anxiety and stress-related disorders. While there may not be a consensus on the role of nutrition for managing behavioral disorders, everyone probably agrees that companion animals today frequently experience stressful situations. Helping alleviate stress and anxiety by providing foods that contain specific nutrients with proven anti-anxiety benefits offers a novel approach for behavioral management.

As for other therapeutic options, it is important to consider the available evidence supporting effectiveness of nutritional management or dietary supplements. The best evidence is provided by results of randomized, controlled clinical studies in pets with naturally occurring disease – if a treatment is effective in this situation, it is likely to be effective for your clinical patients. Fortunately, nutritional management with L-tryptophan (L-Trp) and alpha-casozepine (A-Cas) is supported by clinical studies in dogs and cats. This is especially beneficial for cats, where daily administration of treatments can be potentially difficult or even stressful. If food can provide the necessary supplement to decrease anxiety and stress, this makes it easier for the cat and the owner, and likely increases compliance. This article provides an evidence-based review of the effect of dietary ingredients, L-Trp and A-Cas, on modifying anxiety and stress-related behaviors in companion animals, with a primary focus on cats.

Metabolism of tryptophan

Serotonin modulates mood and emotion in animals and human beings; many drugs (eg, fluoxetine) exert their effects by selectively inhibiting reuptake of serotonin at the synaptic cleft. Tryptophan is an amino acid that serves as a precursor for the synthesis of serotonin, one of the major neurotransmitters in

the brain. Serotonin cannot cross the blood-brain-barrier to enter the central nervous system; however, tryptophan and 5-hydroxytryptophan are able to cross via a carrier protein. Tryptophan competes with other large neutral amino acids for transport via this carrier protein; in human beings, it has been shown that increasing the amount of dietary L-Trp (relative to other large neutral amino acids) facilitates transport of more L-Trp into the central nervous system where it is available for serotonin synthesis.[1,2]

Another forgotten but important component of L-Trp metabolism involves the kynurenine pathway. In most species, 95% of the intake of L-Trp goes into the kynurenine pathway, and only 5% enters the serotonin pathway (Figure 1). This is important because metabolites of these two pathways have different behavioral consequences. This has been extensively studied for decades and the outcome provides useful information related to management of anxiety and stress.[3] It has been demonstrated that excitatory neurokynurenines, particularly KYN, have anxiogenic activity in standard animal models, whereas other neurokynurenines have an anxiolytic pharmacological profile.

Another consideration is that species differences exist; it is known that cats have a different enzymatic system[4] with the major activity of picolinic carboxylase conducting to favor the existence of PICA, and glutamate, respectively an anxiolytic and an excitatory compound (Figure 2).[5] Two enzymes, tryptophan 2,3-dioxygenase 6 (TDO) and indoleamine 2,3 dioxygenase (IDO), play a major role at the beginning of tryptophan metabolism and appear to be capable of changing the ratio between the serotonin pathway and the kynurenine pathway and are affected by inflammatory states.

Pro-inflammatory cytokines are linked to many behavioral or psychiatric diseases in animals and human beings.[7–10] They also are known to increase IDO and are capable of increased activity in the kynurenine pathway. Feline stressors (eg, those

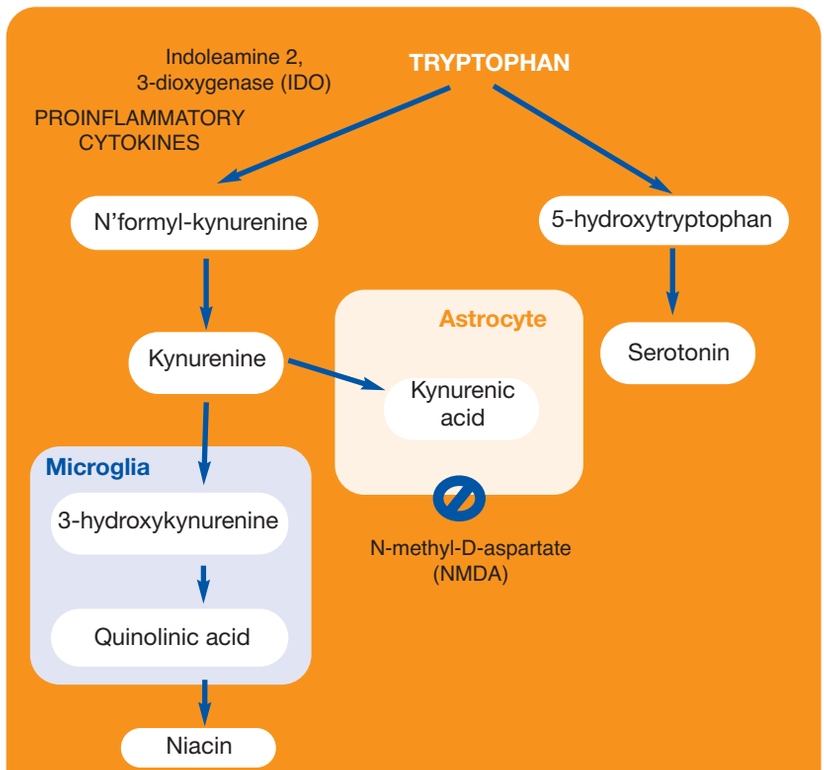

FIGURE 1 Tryptophan is an amino acid that serves as a precursor for synthesis of serotonin, a neurotransmitter than affects mood and anxiety. Tryptophan also may enter the kynurenine pathway resulting in production of neurokynurenines that have either anxiogenic activity or anxiolytic effects. Chronic stress can increase the level of pro-inflammatory cytokines, and lead to anxious pathological states that could be linked with a shift in tryptophan metabolism

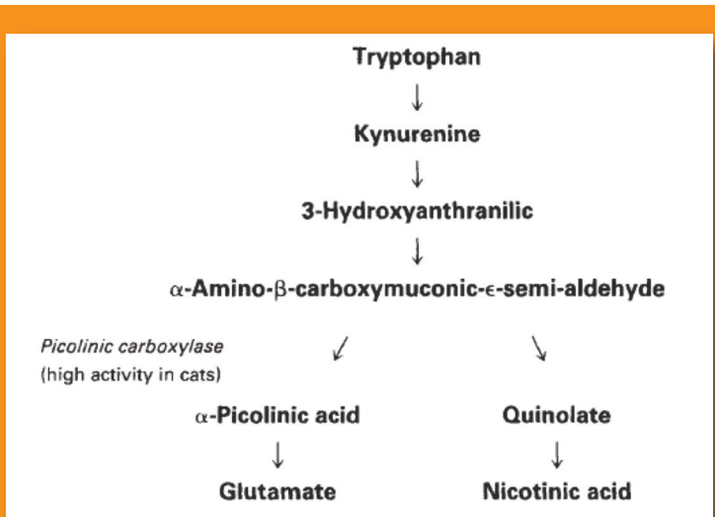

FIGURE 2 Species differences exist regarding metabolism of tryptophan; cats have high activity of picolinic carboxylase, which favors formation of picolinic acid (anxiolytic), and subsequently glutamate (excitatory compound)

associated with unusual events) can increase the level of pro-inflammatory cytokines.[11] As a result, chronic stress can lead to anxious pathological states and this could be linked with a shift in tryptophan metabolism. In cats with feline immunodeficiency virus infection, the level of pro-inflammatory cytokines is high; this is one example where increases in metabolism via the kynurenine pathway has been demonstrated.[12]

Effect of L-tryptophan on stress-related disorders

As a precursor of serotonin, L-trp supplementation has been investigated as a possible way of regulating serotonin concentrations in the brain. The use of tryptophan supplementation is based on the fact that low levels of serotonin have been found for some behavioral conditions such as aggression, pointing out the role of this monoamine neurotransmitter. Tryptophan supplementation has been evaluated for its effects in dogs with aggression (dominance or territorial) or hyperactivity.[13,14] The best results occurred in dogs with territorial aggression when fed a lower protein diet supplemented with L-Trp. The worst results occurred in dogs with dominance aggression when fed a high-protein diet without L-Trp supplementation; however, the effect was not statistically significant.

Studies with L-Trp have also been conducted in dogs and cats to evaluate efficacy for managing stress-related behaviors.[15,16] Pereira et al presented

findings from two placebo-controlled studies including either working dogs or multi-housed cats. In both studies, there was a 2-week period of habituation, followed by 4 weeks without L-Trp, and then 8 weeks with L-Trp supplementation. In the canine study, there was a statistically significant decrease in barking (P <0.05) and staring (P <0.01). The authors concluded that L-Trp supplementation decreased signs of anxiety and improved animal welfare. In the study of multi-housed cats (a known cause of stress for cats), there were a greater number of statistically significant differences between L-trp supplementation and treatment with placebo (Table 1). The authors concluded that *'These results suggest that L-Trp supplementation had an effect in changing the frequency of the stress-related behaviors, decreasing anxiety signals. As the L-Trp supplementation reduces some of the cat's anxiety signs, we conclude that this effect improves their welfare.'* While it is clear that the decrease of some agonistic (fighting) behaviors, house-soiling and scratching are consistent with a decrease of anxiety, the meaning of decreased affiliative, exploring and sustaining behaviors is unclear.

L-Tryptophan appears to be a putative useful option for triggering effects on serotonin-linked behavioral disorders; however, further studies are needed to better understand what happens long-term in stressful conditions. Also, as previously discussed, there are species differences regarding effects of tryptophan and it is important to consider these when evaluating or recommending L-Trp supplementation. For example, in horses, low doses of tryptophan (relative to those contained in commercial preparations) appear to cause mild excitement, whereas high doses reduce endurance capacity.[17] In cats, today, too few things are known about the specificities of tryptophan metabolism, including the possible shift to the kynurenine pathway to be sure of the efficacy.

Effect of alpha-casozepine on anxiety

Cow's milk has long been considered a beverage with natural 'tranquilizing' properties and previous research has confirmed an impact of peptides present in milk.[18] This overall calming effect was observed in babies, and researchers hypothesized that a natural component in the milk was created via digestion (tryptic hydrolysis) by the gastrointestinal tract of babies. Trypsin is more active in the digestive tract of infants whereas pepsin is primarily responsible for protein digestion in adults. α-S_1 casein is one of the major proteins in cows' milk and studies have demonstrated that peptides derived from this milk protein have strong biological effects.[19–21] Researchers from a dairy company first identified a decapeptide, obtained via tryptic hydrolysis, whose spatial structure was analyzed and found to be responsible for the anxiolytic activity.[22,23]

Initial studies in multiple species

As for many other compounds, A-Cas was first tested in classic studies in rats to confirm anxiolytic activity. The conditioned defensive burying paradigm is one of the most classical tests to screen drugs for their potential anxiolytic activity.

Table 1 Signs affected by L-tryptophan supplementation for multi-housed cats (Pereira[15])

Signs (All decreased)	*P* value
Stereotypies	<0.01
Vocalization	>0.05
Agonistic behaviors	<0.01
Affiliative behaviors	<0.01
Exploring	<0.01
Sustaining behavior	<0.01
House soiling, scratching, agonistic interactions within the group	<0.05

Rats are known to bury aversive stimuli and this has been confirmed as an indicator of anxiety.[24] Administration of anxiolytic agents prevents or decreases this conditioned defensive burying response in rats. This test is sensitive because it allows discrimination between anxiolytic effects and effects on general activity. Alpha-casozepine has shown as much efficacy against anxiety as the gold-standard reference molecule, diazepam. Interestingly, A-Cas has not been associated with increased aggression nor loss of working memory, both side effects that may occur with benzodiazepines.[25] Similar results have also been found with the elevated-plus maze paradigm, another standard test to evaluate putative anxiolytic effects of drugs.[26] Human volunteers have been tested[27–29] with positive results and two trials have been successfully conducted in dogs, one of which has been published in an international peer-reviewed journal.[30]

Evaluation of alpha-casozepine in cats

One multi-center, randomized, double-blinded, placebo-controlled clinical trial has been conducted in Europe to evaluate the anxiolytic effects of A-Cas in cats.[31] Cats were selected from general or specialist practices and investigators had to confirm that cats were not subject to inadequate living conditions. A scale validated by the investigators (all veterinary behaviorist surgeons) was used to evaluate cats included in the study (Table 2).

A total of 34 cats were randomly assigned to receive either A-Cas (15 mg/kg) or placebo once daily for 56 days. Practitioners were allowed to implement classical behavior modifications. Three items were evaluated:

- Overall score.
- The number of items quoted 0.
- The owner's evaluation of the improvement.

To be assessed as a success, three requirements were needed:

- Overall score equal or superior to 16.
- Number of items quoted 0 had to equal 0.
- Owner's evaluation mark equal or superior to 6 (out of 10).

Of all cats evaluated, 14 were judged to have a successful outcome and 10 of these were in the A-Cas group; this was a statistically significant difference (Chi-square test, 1 df, P = 0.02) (Table 3).

Table 2 Scale used to evaluate anxiety in cats at baseline and during/after treatment with either alpha-casozepine or placebo for 56 days

	Contact tolerance with familiars
0	Can't be touched
1	Only short contacts and when the cat initiates it
2	Does not stand by long, provoked or spontaneous, contacts
3	Variable acceptation and seeking of contacts
4	The cat regularly seeks for and accepts contacts – seldom refuses
5	Easily manipulated
	Contact tolerance with non-familiars
0	Systematically disappears or is aggressive
1	Comes to observe but can't be touched
2	Initiates contact after a while but does not accept to be touched
3	Initiates contact after a while and accepts to be touched
4	Accepts non familiars excepts precise categories or individuals
5	Tolerant, friendly and playful with non-familiar as with familiars
	Aggression
0	Hurtful aggression with familiar and non-familiar
1	Hurtful aggression with familiar and non-familiar except one person
2	Possible but infrequent hurtful aggression
3	Threats – without fleeing
4	Threats and flees
5	Never aggressive
	Other fears
0	Frightened by the littlest noise or any new stimulus
1	Difficult exploration, numerous frightening stimuli
2	Fearful but explores after a while
3	Frightened by some precise stimuli
4	Seldom frightened – Calms down quickly
5	Never afraid
	Organic signs
0	Systematic stress-related autonomic signs (± displacement activities)
1	Frequent stress-related autonomic signs (± displacement activities)
2	Displacement activities with severe consequences (± autonomic signs)
3	Displacement activities with medium consequences (± autonomic signs)
4	Displacement activities with mild consequences (without autonomic signs)
5	Nothing

Detailed results are summarized in Table 4. This study provides evidence for the efficacy of this product in the management of anxiety in cats, including those in socially stressful conditions. These results confirm the clinical impression of investigators based on testimonials from customers.

Nutritional management of stress

Stress is a normal part of life; however, it may contribute to anxious behavior and it appears to play a key role in the pathogenesis of some diseases such as feline idiopathic cystitis (FIC). Methods to decrease anxiety and stress (eg, environmental enrichment, pheromones, dietary supplements, therapeutic foods with ingredients to help manage stress) are an important component

Table 3 Summary of treatment outcome for 34 cats that received either alpha-casozepine (n = 17) or placebo (n = 17) for 56 days to manage anxiety

	Alpha-Casozepine	Placebo
Successes	10	3
Failures	7	13

Table 4 Summary of results on different items for 34 cats that received either alpha-casozepine (n = 17) or placebo (n = 17) for 56 days to manage anxiety

	Score	Number 0	Evaluation	Familiar humans	Non-familiar humans	Fears	Autonomic signs	Aggressions
Mann Whitney U test	<0.01**	0.04*	0.09 t	0.04*	0.03*	0.09 t	0.16 NS	0.70 NS

t = trend; NS = not significant

of multimodal management for cats with FIC. Use of dietary supplements or therapeutic foods may be helpful; however, it is important to keep some key points in mind:

- The amount of nutrient/ingredient provided on a daily basis should be similar to the minimal requirements that have been established.
- Interactions between the different nutrients/ingredients in the diet need to be studied to determine if there are synergistic, or at least neutral, effects.
- The way the food is provided to the patient may be of major importance because ingredients or nutrients need to achieve a certain threshold to exert a beneficial effect. For example, if food is provided ad libitum and the pet eats multiple small meals throughout the day, as many cats do, is it possible to achieve a therapeutic threshold?

Answers to all these questions require clinical studies with the final product showing that the expected efficacy is present.

Conclusions

Behavioral disorders and stress-related medical conditions can greatly affect the lives of pets today, especially cats. Diets can be useful for managing these situations, and are particularly helpful for cats, a species that may experience additional stress associated with daily administration of any treatment. We continue to learn more about the efficacy of different nutrients and dietary ingredients, and this provides veterinarians with an additional approach to manage anxiety and stress-related behaviors in cats.

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Bladder pain syndrome/interstitial cystitis:
Current therapeutic perspectives

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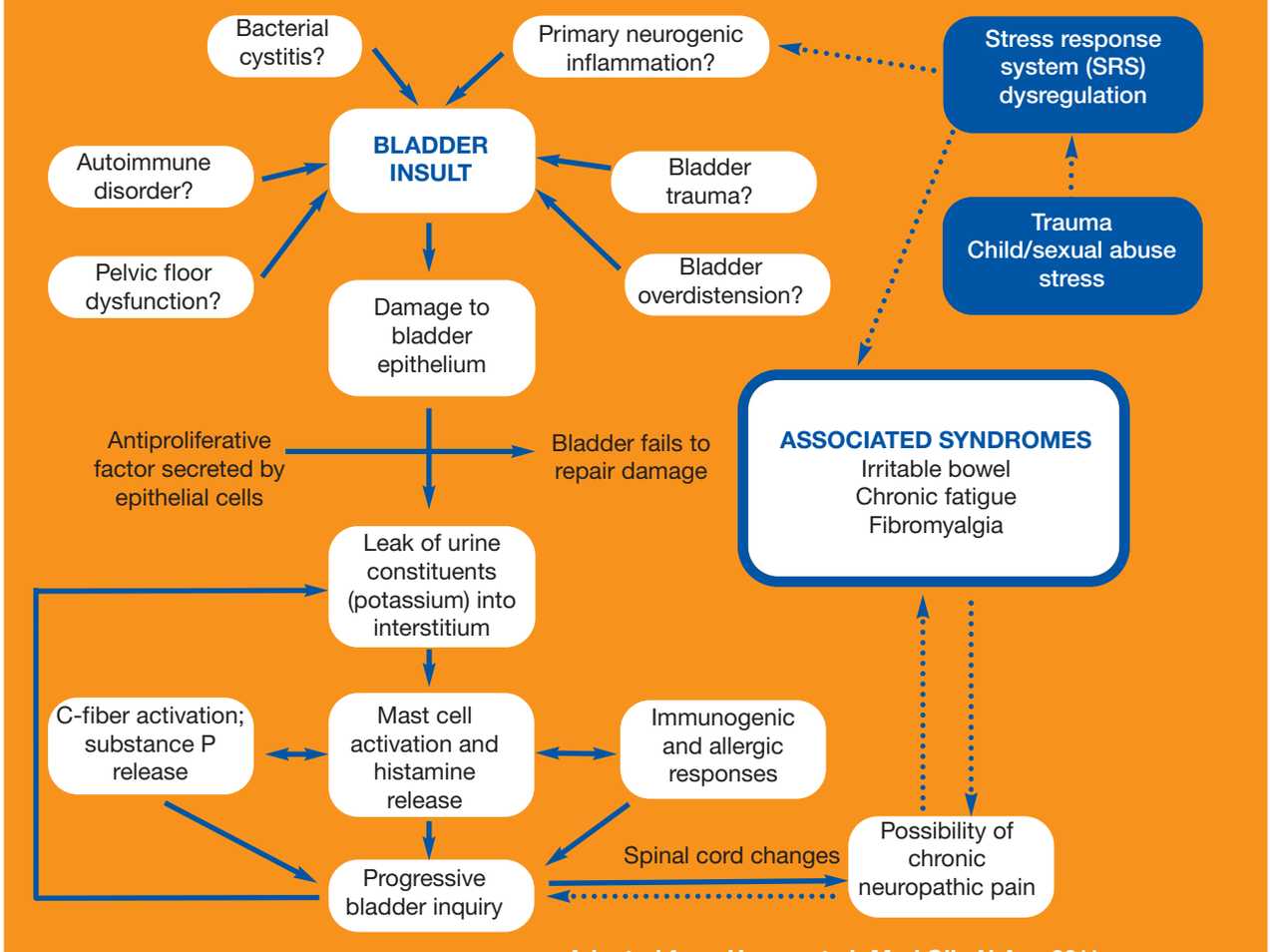
Bladder pain syndrome/interstitial cystitis (BPS/IC) is a debilitating chronic disease of unknown etiology characterized by pain, pressure or discomfort perceived to be related to the bladder, accompanied by at least one other urinary symptom. Confusable diseases must be excluded. The presence of other organ symptoms as well as cognitive, behavioral, emotional and sexual symptoms, should be addressed.[1] The case for BPS/IC as being part of a larger functional systemic disorder is increasingly supported by the fact that BPS patients often present with varying non-bladder syndromes, namely irritable bowel syndrome, fibromyalgia, vulvodynia, chronic fatigue syndrome, migraine,

FIGURE 1 Bladder pain-syndrome (BPS) – pathophysiology



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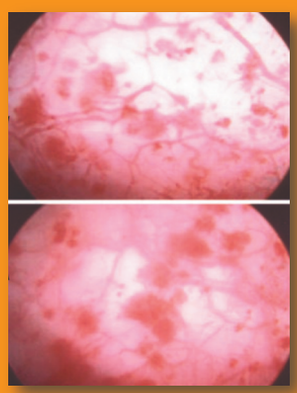

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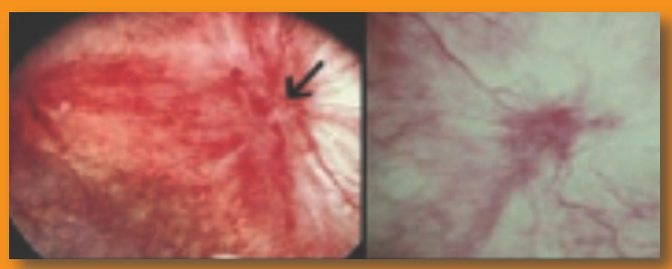
Johansson et Fall, *J Urol* 1990



Hunner's lesion (arrow)
Marinkovic et al, *BMJ* 1990

FIGURE 2 Bladder cystoscopic findings in BPS

panic disorder and social anxiety disorder.[2,3] Furthermore epidemiological studies have shown a high prevalence of child abuse, sexual and other, in BPS/IC patients.[4] Various studies have shown high urinary and plasma adrenaline levels and functional alteration of sympathetic autonomic function.[5] Patients with IC present with increased heart rate at baseline and throughout mental stress challenge in laboratory studies and have increased startle reflex.[6,7] They also have significant increase of symptoms with daily stressors.[8] Experimental studies in murine models have shown that sustained epinephrine administration induces bladder wall alterations similar to those found in BPS/IC patients.[5] Taken together these data point even more to the possibility that BPS/IC or part of

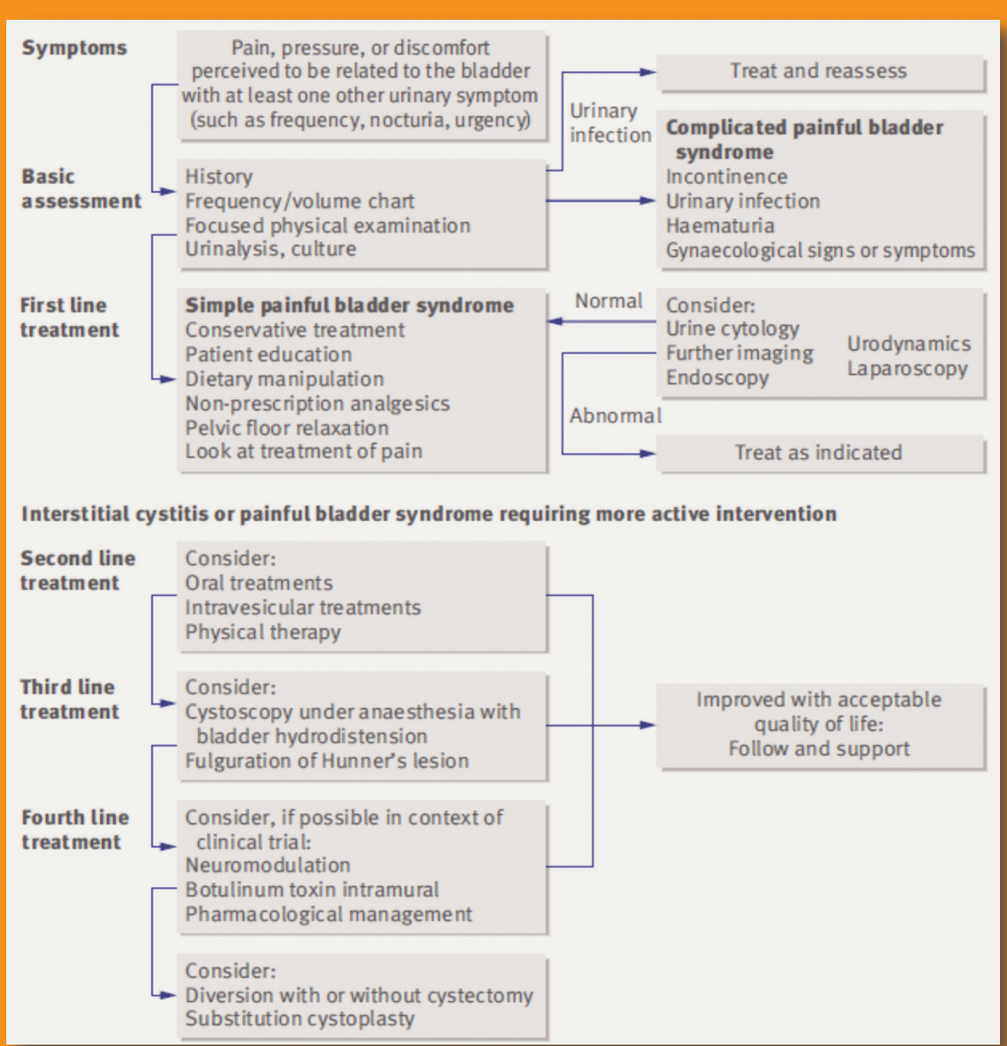
FIGURE 3 Treatment algorithm for BPS

What patients are like is important:

- Depression
- Anxiety
- Panic attacks
- Catastrophizing
- Functional systemic non-bladder syndromes (FSS)

What patients eat is important:

- Coffee, tea,
- Soda,
- Alcoholic beverages,
- Citrus fruits and juices,
- Artificial sweeteners,
- Hot pepper



Adapted from Marinkovic et al, *BMJ* 2009

it might be an aspect of a broader systemic disease where the stress response system (SRS) alteration, plays an important role (Figure 1). Despite this, most research up to now has centered on the bladder as the site of a putative initial insult that triggers a reaction whereby bladder epithelium would become leaky. This would lead to an inflammatory process in the bladder wall, generating inflammation and pain (Figure 2). Eventually, in prone individuals, neuroplasticity of pain circuits would lead to chronic pain. Treatment is not well defined and is still under intense investigation. Most patients are initially controlled with general measures: counselling, avoidance of some comestibles (caffeine, alcohol, chocolate, tea, spicy food), stress alleviating activities and over the counter analgesics on demand. Mainstays of oral therapies are empirical due to lack of knowledge on etiology of this disease. The few oral drugs that showed efficacy in placebo controlled trials are amitriptyline, pentosan polysulfate sodium, hydroxyzine and cyclosporine A (Figure 3 and Table 1). As for intravesical treatments reasonable evidence is available for dimethyl sulfoxide (Table 2) and resection of visible Hunner's lesions. Neuromodulation and reconstructive surgery can also be recommended in selected cases (Table 3). Further studies into the causes and mechanisms of the disease are paramount for the development of effective treatments. Foreseeable therapeutic objectives will likely include oral blockade of sensory nerve receptors, immune system modulation, peripheral nerve fiber inactivation/desensitization, anti-proliferative factor blockade and pain gene therapy.[9] However, identification of BPS/IC phenotypic subgroups

Table 1 BPS oral treatments

Treatment	LE	GR	Comment
Analgesics	2b	C	Indications limited to cases awaiting further treatment
Corticosteroids	3	C	Corticosteroids not recommended as long-term treatment
Hydroxyzine	1b	A	Standard treatment, even though limited efficacy shown in RCT
Cimentidine	1b	B	Insufficient data
Amitriptyline	1b	A	Standard treatment
Sodium pentosanpolysulphate	1a	A	Standard treatment. Data contradictory
Antibiotics	1b	A	Limited role in the treatment of IC
Prostaglandins	3	C	Insufficient data on IC, adverse effects
L-arginine	1b	C	Effect in IC uncertain
Cyclosporin	1b	A	RCT: superior to PPS but more adverse effects
Duloxetin	2b	C	No effect, tolerability poor
Oxybutynin/tolterodine	3	C	Limited indication in IC
Gabapentin	3	C	Preliminary data so far
Suplatast tosilate	3	C	Preliminary data so far
Quercetin	3	C	Preliminary data so far

Table 2 BPS intravesical treatments

Treatment	LE	GR	Comment
Intravesical anaesthesia	3	C	
Intravesical PPS	1b	A	
Intravesical heparin	3	C	
Intravesical hyaluronic acid	2b	B	
Intravesical chondroitin sulphate	2b	B	
Intravesical DMSO	1b	A	
Intravesical Bacillus Calmette Guerin	1b	Not recommended	
Intravesical clorpactin	3	Not recommended	Obsolete
Intravesical vanilloids	1b	C	Data contradictory

LE = level of evidence: GR = grade of recommendation

Tables 1 and 2: Fall M, Baranowski AP, Elneil S, et al. *Eur Urol* 2010

Table 3 BPS interventional procedures

BPS interventional treatments

- Hydrodistension
- Neuromodulation
- Transurethral resection of Hunner's lesion
- Major surgery

Procedure	LE	Recommendation
Hydrodistension	3	C
Ulcer resection, fulguration	3	C
Cystolysis	3	-A (not recommended)
Sympathetic deinervation	3	-A (not recommended)
Parasympathetic deinervation	4	-A (not recommended)
Cystoplasty	3	C
Urinary diversion ± cystectomy	3	C

Hanno P, Lin A, Nordling, et al. *Neurourol Urodvn* 2010

should help delineate individualized treatment which will be aimed at the disease and its multiple manifestations rather than at bladder focused complaints. Patient classification can rely on subtyping (eg, according to International Society for the Study of BPS criteria) and or be based on clinical criteria such as forwarded by Nickel et al.[10] In the latter classification, Urinary, Psychological, Organ specific, Infection, Neurological/systemic disorders and Tenderness in muscles (UPOINT)[10] domains are evaluated and approached in an integrated manner (Figure 4). This means that complaints not bladder related but equally damaging to patient well being are systematically sought and classified and patients treated for the entire clinical picture they present with. Stemming from UPOINT phenotyping, the future will see evaluation and treatment of BPS/IC become increasingly multidisciplinary. Co-existing bladder diseases like infection or others causing lower urinary tract symptoms, non-bladder syndromes, as well abuse/traumatic events will be systematically evaluated. Treatment will evolve from an organ (bladder) centered approach to a new paradigm where psychological and psychiatric support, physical therapy, management of infection, and the treatment of non-bladder regional and distant pain complaints will be readily available to the BPS/IC patient along with the traditional end organ approach.

FIGURE 4 BPS clinical phenotyping and comprehensive multidisciplinary treatment

Urinary Urgency Frequency Dysuria	U
Psychosocial Depression Maladaptive coping mechanisms Social interaction problems	P
Organ specific Pain with bladder cycle Glomerulations/Hunners' ulcers Inflammation in biopsy specimen	O
Infection Significant bacteriuria that worsens symptoms and improves with antibiotic treatment	I
Neurologic/systemic conditions Irritable bowel syndrome Fibromyalgia Chronic fatigue syndrome Vulvodynia Any other condition that suggested neuropathy or neural upregulation	N
Tenderness of skeletal muscles Tenderness or pain in pelvic or abdominal muscles and ligaments	T

Adapted from Nickels et al, *J Urol* 2009; 182: 155–160

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Stress and anxiety in cats:
Effect on litter box use

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Clinical importance

Elimination outside of the litter box in unwanted locations has been a frequent owner complaint about feline behavior for over 25 years[1,2] and the number one reason for cat relinquishment.[3] Many treatment strategies are available to keep cats using their litter box or to re-establish litter box usage habits.[4] Although veterinarians in general practice have become more adept at helping cat owners with this behavior problem, many patients seem resistant to treatment. In these cases it is likely that stress and anxiety from a variety of factors, and perhaps even medical disease, are contributing to non-litter box use. For the best resolution of the problem and to keep cats in their homes, all contributing factors must be identified and addressed.

Defining the problem

Feline inappropriate elimination or house soiling (periuria) can present in one of two ways: (1) toileting outside of the litter box — emptying the bladder and/or bowel in some other location or (2) marking — leaving urine on vertical surfaces as a form of social communication. House soiling can occur for a variety of reasons, which are discussed below. Cats generally utilize urine marking as a form of feline communication — to mark territory, organize themselves spatially from other cats when they are anxious and to advertise sexual availability.

Urine marking usually occurs in a standing posture and although it is often cited that smaller amounts of urine are voided, this may not always be the case. Cats that mark with urine usually continue to utilize the litter box for emptying the bladder and bowel. Two studies have examined the presence of disease in cats that urine mark. One study of 34 cats found evidence of abnormalities in 13 (38%), ranging from renal calculi, cystic calculi, bacterial urinary tract infections and/or crystalluria (struvite was the most common crystal identified).[5] Another study compared urine-marking cats with a control group of non-marking cats and found that bacteriuria, hematuria, proteinuria, crystalluria, and casts were found with equal frequency in both groups.[6] Based on these two studies, the presence of disease as a factor in urine marking

is not clear. This article will focus on elimination outside of the litter box that is not urine marking behavior, although techniques to diminish stress and anxiety are likely to help with urine marking behavior as well.

Medical and other factors related to elimination problem behaviors

House soiling can often be precipitated by medical problems; therefore a good physical examination, urinalysis, urine culture and imaging studies are essential for all patients that are house soiling.[7] Inappropriate elimination can also be a sign of other systemic medical abnormalities such as hyperthyroidism, diabetes mellitus or hepatic disease. Practitioners should attempt to identify and treat all concurrent medical disorders. However, once medical problems are treated or controlled, learning of other factors may contribute to ongoing house soiling issues and of course both may co-exist in the same patient. Other articles provide detailed information about disorders that cause LUTS, including risk factors, diagnosis and treatment.[7–8]

Beyond the medical disorders, other contributing causes such as social issues, environment, anxiety and stress have all been discussed as related to non-litter box usage in cats.[9] Studies have indicated a correlation between underlying social issues and urine marking in household cats.[10] Medical problems are also influenced by environment and household issues. In 2004 Cameron et al[11] found differences between cats with feline idiopathic cystitis (FIC), their live-in control cat, and a control population of cats. Cats with FIC were significantly more likely to be male compared with live-in control and the external control cats. They also were more likely to live with another cat or live in multi-cat households and were more likely to be in conflict with another cat in the household. In the same study, cats in the control group who lived with another cat were more likely to spray and urine mark. Others have looked at the effects of stress in cats with FIC and noted that increased stress in cats with FIC was correlated with return of LUTS.[12] Obviously the behavioral diagnosis of house soiling may not be straightforward but can be influenced by multiple issues, both medical and behavioral.[13] However, cats that have no change in urination frequency, quantity and characteristics of the urine are more likely to have a behavior problem. Therefore, questions targeting the frequency of urination, size of urine clumps (if using clumping litter material) and perhaps color of the urine can help establish if medical issues are concurrent with behavioral problems.[14]

Feline inappropriate elimination

All cats depositing urine or stool outside of the litter box need a complete behavioral evaluation. The systematic gathering of information is most efficiently accomplished utilizing a pre-printed history form (Table 1). History taking information points should include information on the elimination problem itself: duration, type of elimination deposited outside of the box, location and material/substrate. Litter box information on type of litter, rate of cleaning, location and number must be established. Household information can yield significant information on sources of possible stress and anxiety and should include number of cats and other pets, relationship with the people, opportunity for enrichment, escape and hiding areas and how cats share the space. Additionally, owners should be queried about any changes in environment, schedule, visitors and other possible unusual events as these have been implicated in the occurrence of 'sickness behaviors' which can include non-litter box use.[15] Naturally all previous treatment attempts, behavioral, medical and pharmacological must be discussed and evaluated.

Diagnosis

Diagnostic categories for feline inappropriate elimination include location preference, substrate preference, litter aversion, location aversion and marking.[3] Non-litter box use can also be influenced by stress,[8,9] anxiety and litter box factors such as size, cleanliness and placement. The use of accepted diagnostic categories will help in the formulation of a treatment plan. One major confounding factor of elimination problems in cats is living in a multiple cat home or experiencing episodes of intercat aggression. See Table 2 for information on differentiation of diagnostic categories.

Conventional litter centered treatment options

- Improving litter box cleanliness: scoop box daily, empty, wash and refill every 7–10 days. Utilize a good odor control clumping litter, perhaps one with added carbon.[17] Increased cleaning of litter boxes has shown to be helpful in urine marking as well.[16]
- Consider any obstacles to good box access: location, size, height of sides, etc. Ideally, the room should have more than one entry/access point to limit confrontations and increase the ability of escape. Boxes should be at least 1.5 times the length of the cat.
- It is absolutely essential to provide enough litter boxes: rule of thumb, one box per cat plus one. The boxes must be in multiple locations to allow all cats to have access to an elimination location that is near where they spend the majority of their time. Several litter boxes in just one location is only one toileting area and is often not sufficient when problems arise.
- Research has indicated that when given a choice, cats prefer clumping litter materials to clay materials and larger size boxes.[17,18] Accommodating these preferences is usually helpful.
- If substrate preferences have been identified, offering a choice of different materials in several different boxes may find the option that best suits the cat.
- If location preferences are evident in the history, providing a litter box in the new location may resolve the problem. Usually this box is left in place until litter box use has been re-established and other ancillary issues resolved. At that time if desired it may be possible to slowly move the box back to another location. If intercat aggression has forced the cat to choose another location it may not be possible

Table 1 History taking is best taken using a preprinted form

Question	Answer
Litter box use information	
How long has the cat been soiling outside of the litter box?	Less than 3 months ☐ More than 3 months ☐ Six months or longer ☐
What waste material is found outside the litter box?	Urine ☐ Stool ☐ Both ☐
Where is urine deposited outside the litter box?	Horizontally (floor) ☐ Vertically (wall) ☐
Is the elimination consistently on one type of material? (wood, carpet, clothing, area rugs)	Yes ☐ No ☐ Please list all
Does your cat favor one location for elimination outside of the box?	Yes ☐ No ☐ Please list all
Does your cat ever use the litter box?	Yes ☐ No ☐
How many urine spots do you find daily in the litter box?	None ☐ 0—1 ☐ 2—4 ☐ >4 ☐
How many elimination spots do you find outside the box daily?	None ☐ 0—1 ☐ 2—4 ☐ >4 ☐
Litter box information	
What type of litter box and how many of each type do you provide?	Covered ☐ Uncovered ☐ Self cleaning ☐ Small ☐ Medium ☐ Large ☐
Are the litter boxes all in the same room?	Yes ☐ No ☐
What type of litter material is provided?	Scented ☐ Unscented ☐ Clumping ☐ Crystal ☐ Paper ☐ Plain clay ☐ Pine ☐ Wheat ☐ Other ☐
How often is the litter box scooped clear of waste material?	Multiple times daily ☐ Once daily ☐ Every other day ☐ Twice weekly ☐ Once weekly or less ☐
How often is the litter box emptied, washed and refilled?	Once a week ☐ Once every 2 weeks ☐ Once a month ☐ Never ☐ Other – please indicate ☐
How many litter boxes are there in the home?	1—2 ☐ 2—3 ☐ 4 or more ☐
Are litter boxes all in one location?	Yes ☐ No ☐
Social information	
How many cats including this one are in the home?	One ☐ Two ☐ Three ☐ Four ☐ Five or more ☐
Does this cat get chased, hissed or growled at by other cats in the home?	Yes ☐ No ☐
Does this cat chase, hiss or growl at other cats in the home?	Yes ☐ No ☐
How often does this cat appear in all rooms in the house?	Daily ☐ Occasionally ☐ Rarely ☐ Never see her/him at all ☐
Does this cat spend all its time in just one room?	Yes ☐ No ☐
Is this cat interactive with the people in the house?	Yes ☐ No ☐
Environmental information	
How many food bowls are available in the home?	1—2 ☐ 2—3 ☐ 4 or more ☐
Are food bowls all in one location?	Yes ☐ No ☐
How many climbing towers are available?	None ☐ 1—2 ☐ 2—3 ☐ 4 or more ☐
Is there daily playtime with this cat?	Yes ☐ No ☐
Are food dispensing and foraging toys provided	Yes ☐ No ☐

Table 2 A cat may have more than one diagnositic category; for example, a litter aversion and a substrate preference

	Location aversion	Litter aversion	Substrate preference	Location preference	Marking
Location of elimination	Elimination in multiple sites other than the litter box	Elimination near but not in litter box may perch on litter box edge	Elimination always on same material other than litter	Elimination usually in one spot, area or room other than where litter box is located	Elimination usually on vertical surfaces; occasionally on horizontal ones
Relations between cats in the same house or cats outside	Possible social conflicts between cats; negative association or inability to access location	Unlikely to be related to social problems within the house	Unlikely to be related to social problems within the house but may develop because of it	Cat restricted to one area due to social conflicts with other cats. No or limited litter box access	Often related to social conflicts within the house. May also be related to cats outdoors
Use of the litter box	Cat rarely seen using the litter box	May use litter box for one type of elimination and not other	May use litter box for one type of elimination and not other	May use the litter box some of the time	Usually continues to use the litter box

to remove the box until that primary problem, aggression is resolved.
- Try to make soiled areas aversive so the cat will not go back to them. Options include covering the area with plastic, blocking access into the area, and cleaning the areas well with a good enzymatic cleaning material.

Enrichment and enhancing daily life and welfare

- Increase positive interactions with owners through play and enrichment activities. Cats like a variety of play items especially those that are light and move easily. Providing toys that are rotated every few days can provide play opportunities alone or as interactive sessions with owners.
- Spread out all resources including food bowls, resting spots, and climbing towers, scratching posts and toys.
- Provide food-dispensing toys to counteract inactivity, stress and obesity — all of which are linked to FIC.
- Keep routine interactions predictable and pleasant. Avoid punishment and other interactions that the cat finds unpleasant.
- Adding in pheromones may help create a calmer environment. Feliway (Ceva Animal Health) is a synthetic copy of the facial pheromone in cats and has been shown to reduce stress in cats with FIC and in other situations.[19,20]

Fighting between household cats an important source of stress

Many times cat owners realize that they need to have cleaner, more accessible litter boxes and increase enrichment in the home and are willing to make these changes. But often when multiple cats live together pet owners do not realize the additional stress that the social environment, especially aggressive interactions, can create. Aggressive interactions can occur between cats that have lived together for some time perhaps due to a change in social status or a traumatic event. Fights may be the sequel to redirected aggressive behavior, perhaps due to outdoor cats or another anxiety-producing event. Aggression may occur with the introduction of another cat, or due to illness or social changes within the home. Fear, anxiety and territorial responses all contribute to intercat aggression within a household.

Additional history points

Owners may not report chasing and overt aggressive threats such as growling, hissing, or biting unless prompted, and may assume these events are not contributory to the house soiling issue.

- Collect information regarding the daily routine, pet-owner interactions and how resources are allocated within the home.
- Query the owner to help you identify all participants in any aggressive encounters no matter how brief or seemingly benign.
- Ask about obvious aggressive interactions, hissing, growling, chasing and fighting and covert aggressive encounters, which include staring, blocking and stalking.
- Identify where all cats spend their time, covert aggressive actions may result in a cat living in one area of the house to avoid conflict.
- Ask for video of the cats when relaxed and at other times.

Detailed descriptions of several selected aggressive episodes will help to identify triggers, participants, owner responses and possible treatment options. Attempting to identify all aggressive behaviors, facial expressions and body postures can be difficult but can be facilitated by using pictures.[21] Cats showing submission will crouch, turn their ears downward and avoid the situation.[22] Cats may chase one another

accompanied by vocalizations such as hissing, growling and yowling. However, threats between cats can be covert, including blocking access to locations and staring or supplanting, which can be just as stressful, but unidentified by owners. Identify any treatment options already tried and discuss their implementation and effectiveness on the problem behavior. Discussion of the ongoing behaviors of the cats involved, noting signs of anxiety and fear and defensive behaviors (hiding, inappetence, lack of evidence of grooming) can determine the effect of treatment and resolution of these signs. Litter box usage by all cats should be noted; often social issues contribute to non-litter box usage or urine marking behaviors of other cats besides the one presented as the patient.

Diagnosis

After a behavioral history is taken, attempt to reach a diagnosis. Common diagnostic categories include territorial aggression, social status aggression, redirected aggression, fear related aggression, defensive aggression, offensive aggression, irritable aggression and intermale aggression (Table 3, case study).

Treatment options

Within a multiple cat household, there should be multiple litter boxes, food bowls, water bowls and resting areas. These should not be clustered together, but spread throughout the environment with awareness of how the various cats access the space available to them. Some cats may only have access to certain household areas and if resources are not within those areas, anxiety and house soiling may result.

In order to create harmony, it may be necessary to keep fighting cats separated unless supervised or using structured introductions. When separated, do not allow persistent aggression such as hissing or growling at the barrier; create a neutral zone if needed. Perhaps encourage play through the door by tying two toys together with string and put one on either side of the closed door.

FIGURE 1 Feeding cats on opposite sides of a gate

Introductions can be accomplished using food or play and the goal is to associate pleasant things with the presence of each cat (Figure 1). It also might be helpful for the aggressor to wear an approved cat collar with a large bell that will forewarn the victim of their approach allowing the victim to escape.[21,23] Providing elevated perching areas will also allow escape and safety for victims. Naturally, any intervention can increase rather than decrease anxiety and therefore the use of any treatment modality should be evaluated in each individual situation.

The focus is on counter conditioning and desensitization exercises to re-introduce the cats to one another. The goal is to allow the cats to be

Table 3 Case history

Patient	Emily F (sp) DSH 8 year. Four other cats in home: Chippy M (n) 8 years , Winston M (n) 7 years, Alice F (sp) 6 years, Kitten F (sp) 5 years Emily lives on the couch, rarely ventures elsewhere in the home
Behavioral complaint	Emily: Elimination outside of the litter box for 5–6 years
Significant historical information	Litter boxes and food bowls clustered in one area and poorly maintained Chippy urine marks and attacks Emily daily
Intervention for problem elimination	Diagnostic evaluation to identify any contributory medical problems Determine if substrate preference was a diagnostic consideration Create a new safe place for Emily with all necessary resources
Intervention for resources	Give Emily resources in her own room Spread out other litter boxes Clean boxes daily, wash, empty and refill weekly Food bowls spread throughout the environment
Intervention for Chippy and urine marking	Separate Chippy and Emily: give each a territory Resource distribution
Resolution	Emily: Within 10 days separate territories resulted in consistent litter box usage Chippy: Marked decrease in urine marking from daily to once weekly

together without any aggressive behaviors (growling, hissing, chasing, staring, etc). Counterconditioning is accomplished by associating food with calm and relaxed behaviors preferably in a neutral setting prior to any introductions. Desensitization occurs by creating a distance gradient that allows the cats to be in proximity to one another without anxiety as evidenced by their willingness to continue to eat the delectable treat or food offered. The cats initially may need to be far apart perhaps without seeing each other or relaxation and eating may not occur.

Depending on the baseline aggression and anxiety of each cat, these introductions may need to be on either side of a closed door, in a large open area at least 10—15 feet (3—5 m) apart or by utilizing cat carriers for each cat. If cats are introduced when not confined in any way, it is often advisable that each cat wears a harness and leash for safety and control. Two feedings without the expression of any aggressive or anxious behaviors are done at the same distance before the bowls or carriers are moved closer together. Clients should be cautioned that this is a slow process and not to rush. Allowing the cats to interact in an aggressive manner sets the program back and makes resolution more difficult.

This type of behavioral program may be difficult to implement and for owners to execute therefore for severe cases of intercat aggression a consultation with a board certified veterinary behaviorist may be necessary. In USA, diplomates and additional information about treating behavior cases can be found at dacvb.org, and in Europe the European College of Animal Welfare and Behavioural Medicine is found at www.ecawbm.com. More information is also available at veterinary sites such as Veterinary Information Network where members can ask about behavior cases and interface with boarded veterinary behaviorists.

Drug, pheromones and nutraceutical therapies

In many cases of urine spraying and inter cat aggression medication is needed to diminish anxiety that usually underlies these problems. Pharmacological treatment options are detailed in other sources[21] but commonly used medications include fluoxetine, clomipramine and paroxetine. Pheromones (Feliway; Ceva Animal Health) can often calm cats and diminish fear and anxiety; however, meta-analyses of the effectiveness of pheromonal therapies have reached conflicting conclusions.[24,25] Nutraceuticals like L-theanine (Virbac Animal Health), Zylkene (Vetoquinol) may also be useful but limited evidence of effectiveness is available.[26,27]

Prognosis for house soiling

Response to therapy can be quite variable. In some cases, a long-term behavior (12—18 months or more) may be more resistant to change. A study of long-term follow-up of 58 cases for treatment of elimination problems in cats by Marder and Engel demonstrated that 67% (47 cases) showed a 90—100% reduction in frequency of elimination outside of the litter box. Additionally, there was a significant association between caregivers' compliance and outcome.[28] Follow-up with owners is important to assess progress and help them follow a treatment plan. In cases that are resistant to therapy, medical complications such as FIC and uroliths may be factors and ongoing social factors in the home may undermine resolution.

Prognosis for intercat aggression

A retrospective study of 48 cases of intercat aggression found that 30 cases reported themselves as cured while 18 did not. No one treatment resulted in a significant greater number of cures than another.[23] If intercat aggression is creating stress and anxiety that can result in FIC, then treatment for the aggression may lessen relapses of the disorder.

Conclusions

In all house-soiling cases consider the interactions between the cats and possible sources of stress. Questions targeting the use of space, which cats spend time together sleeping and grooming and placement of resources throughout the home will help determine if these areas also must be targeted in the treatment plan. Without treating the social problems, house soiling is likely to continue and remain unresolved.

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A randomized, controlled clinical trial evaluating the effect of a therapeutic urinary food for feline idiopathic cystitis

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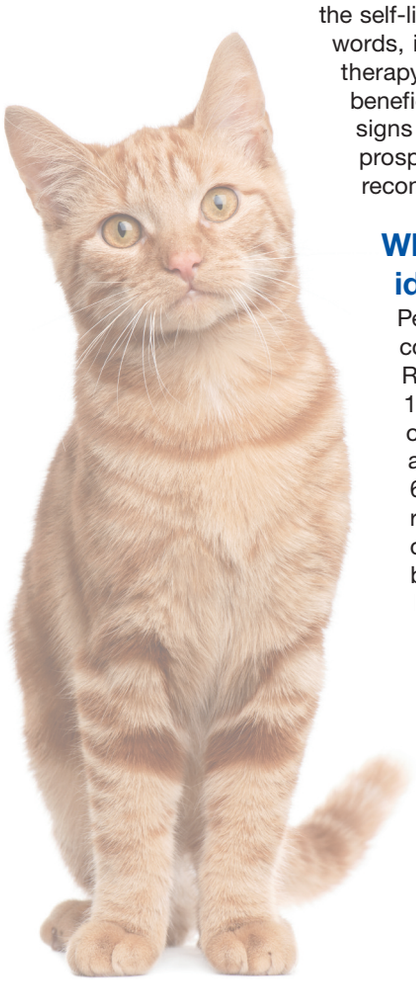
In approximately 65% of non-obstructed cats with naturally occurring lower urinary tract disease, the exact cause(s) of dysuria, pollakiuria, stranguria, periuria, and hematuria after appropriate diagnostic evaluation remain(s) unknown.[1–3] These cats are classified as having idiopathic feline lower urinary tract disease or feline idiopathic cystitis (FIC). In the past decade, over 80 agents or procedures have been recommended for management of non-obstructive FIC in cats. Yet, few treatments have been evaluated in controlled clinical trials. Debate surrounding the treatment efficacy is confounded by the self-limiting nature of clinical signs in the majority of cases. In other words, in most cases clinical signs resolve in 7 days with or without therapy. In this setting, any form of therapy might appear to be beneficial as long as it is not harmful. The self-limiting nature of clinical signs in many cats with FIC emphasizes the need for controlled, prospective, double-blinded clinical studies in order to prove that recommended treatments are effective (Table 1).



What is the biological behavior of feline idiopathic cystitis?

Periuria, pollakiuria, stranguria and gross hematuria are the most common clinical signs observed in cats with non-obstructive FIC. Remarkably, these lower urinary tract signs (LUTS) subside within 1–7 days without therapy in up to 91% of cats with acute non-obstructive FIC.[4–7] Signs may recur after variable periods of time and again subside without treatment. Approximately 40% to 65% of cats with acute FIC will experience one or more recurrences of signs within 1 to 2 years.[4–7] Recurrent episodes of acute FIC tend to decrease in frequency and severity as cats become older.[7] Though recurrent clinical signs in patients with FIC are often assumed to be recurrence of the original disease, recurrent signs may also be the onset of a different lower urinary tract disorder (eg, urolithiasis, infection, inappropriate behavioral urination).

Table 1 Grade of evidence and description of several studies evaluating treatment for feline idiopathic cystitis (FIC)

Evidence grade	Treatment recommendation	Study and outcome
I	Therapeutic food (Hill's Prescription Diet c/d Multicare) reduces recurrent episodes of FIC	Randomization = Yes Blinding identity of treatment groups to care providers = Yes Treatment = Canned or dry c/d Multicare Control = Composite of average grocery store brand n = 25 client cats with acute episode of FIC (original n = 31) Duration = 1 year Monitoring = Owner-daily recording; hospital visits 1, 3, 6, 9, 12 months Outcome = 89% reduction in recurrent episodes (P = 0.02) compared with control food
III	Environmental enrichment (abundant resources and enhanced interactions) and stress reduction decrease signs of FIC	Randomization = No Blinding identity of treatment groups to care providers = No Treatment = Multimodal environmental enrichment Control = None n = 46 client cats with 2 clinical bouts in past 10 months (original n = 73) Duration = 10 months Monitoring = Telephone or electronic mail Outcome = 72% (33/46) had no recurrence of LUTS (P = 0.0001), but without a control, we cannot determine if this is better than no therapy or a placebo
III	Canned therapeutic food reduces proportion of cats with recurrence FIC signs compared to dry therapeutic food	Randomization = No Blinding identify of treatment groups to care providers = No Treatments = Waltham Feline Control pHormula dry or canned Control = Yes n = 46 client cats with initial or recurrent episode of FIC (original n = 54) Duration =1 year Monitoring = Hospital visits at 0.5, 4, 6, 12 months, and telephone updates monthly Outcome = 89% of cats fed canned food did not experience recurrent lower urinary tract signs compared with 61% fed the dry food (P = 0.04)

Environmental enrichment = abundant resources (litter pans, food, resting places) and enhanced interactions
Stress reduction = reduced conflict and gradual changes
Waltham Feline Control pHormula reformulated/renamed Royal Canin Feline Urinary SO

We have also encountered a small subset of cats with FIC in which clinical signs persisted for weeks to months or are frequently recurrent. These cats are classified as having chronic FIC. In our experience, less than 15% of cats evaluated because of acute FIC will develop chronic forms of the disease. Whether chronic FIC represents one extreme in the spectrum of clinical manifestations associated with similar etiologic factors, or whether it represents an entirely different mechanism of disease than that associated with acute self-limiting idiopathic disease is unknown.

What is the role of nutrition in management of FIC?

The goals for treatment of cats with FIC are to improve the quality of life for affected cats and their caregivers by reducing the duration and severity of clinical signs, the rate of recurrence of clinical signs, and the risk for urethral obstruction. Nutritional factors may potentially influence expression of FIC and its sequelae by:

- Decreasing urine concentrations of pro-inflammatory mediators and crystallogenic minerals.
- Increasing urine concentrations of anti-inflammatory/pro-resolving mediators and crystallization inhibitors.
- Increasing solubility of crystalloids in urine.
- Decreasing retention of crystals within the lower urinary tract.
- Minimizing potential management- or environmentally-induced risk factors such as stress.

Specific recommendations for management of cats with acute and chronic FIC should ideally be based on results of controlled clinical trials that document efficacy and safety of therapeutic agents and modalities. Management of cats with non-obstructive FIC should encompass:

- Diagnostic evaluation to exclude other causes of LUTS.
- Client education emphasizing the biological behavior of the disease and lack of controlled studies demonstrating efficacy of many proposed therapies.
- Consideration of use of pharmacologic agents to reduce the severity and duration of clinical signs.
- Strategies to minimize urethral obstruction.
- Strategies to minimize risk of recurrences.
- Avoidance of iatrogenic disease.

We approach treatment of cats with acute FIC by emphasizing client understanding of the disease, administering short-term analgesic therapy to reduce severity of clinical signs and improving litter box use, and minimizing the risk of recurrences through the use of long-term nutritional and environment management strategies.

What is the role of moisture?

Unless complicated by other illness, cats with FIC typically have concentrated and acidic urine.[1,7] The prevalence and magnitude of crystalluria is variable; however, the prevalence of crystalluria in cats with FIC does not differ significantly from that of unaffected cats.[1,3,7] While crystalluria, per se, does not appear to be a risk factor for non-obstructive FIC, it has been hypothesized that high concentrations of normal and/or abnormal components in urine may be toxic to urinary bladder tissues in affected cats.[8] The comparative effects of wet and dry forms of a diet designed to lower urine pH on the frequency of recurrence signs in cats with FIC was evaluated in a non-randomized, open, prospective study.[9] Signs of lower urinary tract disease recurred in 11/28 (39%) cats fed the dry diet, and in 2/18 (11%) cats fed the moist diet. Although the basis for the beneficial response associated with the canned diet was not determined, cats consuming the moist diet had a significantly lower urine specific gravity (range 1.032 to 1.041) than those consuming the dry diet (range 1.051 to 1.052). Based on these observations and until other randomized controlled studies are available, we routinely recommend increasing dietary water intake by feeding moist food or by use of other strategies designed to increase water consumption.[8]

Role of acidifying foods with controlled amounts of magnesium?

As of yet, there is no known benefit of urine acidification or magnesium restriction in the etiopathogenesis of non-obstructive FIC.[8] However, urethral obstruction is a potentially life-threatening sequel in male cats with FIC, and it may result from formation of matrix-crystalline urethral plugs.[2,5,10] Because insoluble microscopic crystals appear to be an integral part of many matrix-crystalline urethral plugs, using medical protocols to prevent crystal formation in patients at risk for urethral obstruction is logical.[11] Over the past three decades, struvite has consistently been the primary mineral component of most urethral plugs, although other mineral types may be encountered.[12] Successful prevention of recurrent urethral obstruction caused by struvite-containing urethral plugs using a struvite calculolytic diet to reduce urine pH and urine magnesium and phosphorus concentrations has been reported.[13] More recent studies indicate that acidifying, low-magnesium maintenance diets formulated to promote formation of urine with struvite relative supersaturation (RSS) values of <1 effectively dissolve struvite uroliths in vivo.[14,15] Presumably, these diets would also be of benefit in reducing struvite crystalluria and the risk of struvite-induced urethral plug formation in male cats with FIC. However, clinical studies confirming this hypothesis have not been reported.

What is the role of 'multipurpose' urinary therapeutic foods?

More recently, several feline 'multipurpose' therapeutic urinary foods have been developed that are intended to simultaneously manage the combination of risk factors associated with FIC, struvite disease (uroliths and plugs), and calcium oxalate uroliths.[14–17] Multipurpose foods have the advantage of allowing long-term feeding of a single maintenance diet to manage risk factors for lower urinary tract disorders that may occur at different lifestages. In addition, use of a multipurpose food for dissolution and prevention of struvite uroliths eliminates the need to transition cats to a different maintenance food following dissolution. Multipurpose foods may also foster greater owner compliance by allowing for the convenience of feeding all healthy cats in a household the same food.

Urinary bladder inflammation is a characteristic feature of FIC and urolithiasis.[18] Long-chain omega-3 (n-3) polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and antioxidants, such as vitamin E, are potent anti-inflammatory agents.[19,20] Studies in cats indicate that consumption of fish oil products results in EPA/DHA incorporation into cell membrane phospholipids in a dose-dependent manner.[21] By shifting the substrate for eicosanoid biosynthesis from arachidonic acid to EPA and DHA, synthesis of pro-inflammatory eicosanoids via the cyclo-oxygenase (COX) and lipoxygenase (LOX) pathways is decreased and production of anti-inflammatory and inflammation-resolving eicosanoids is increased.[19] Similarly, vitamin E is a potent antioxidant, which also has anti-inflammatory properties. Oxidative stress and increased free radical-induced peroxidation of cell membrane phospholipids may cause tissue injury by impairing cell membrane functions and inducing inflammation through the generation of pro-inflammatory cytokines and prostaglandins.[20]

Omega-3 fatty acids and vitamin E have been advocated for management of inflammatory lower urinary tract disorders of cats and are frequently included in commercial multipurpose therapeutic urinary foods.[16] Although dietary omega-3 fatty acids have benefitted people, and dogs and cats with a variety of metabolic and chronic inflammatory conditions,[19,21] the specific therapeutic effects of omega-3 fatty acids and vitamin E have not been evaluated in cats with FIC or urolithiasis. Interestingly, consumption of omega-3 fatty acids (EPA and DHA) by people with hypercalciuria and recurrent calcium oxalate urolithiasis was associated with significant reductions in urinary calcium and oxalate excretion.[22] Commercially available feline multipurpose urinary foods vary considerably in their omega-3 and vitamin E content.[16] Additional studies are needed to better define the optimal therapeutic dose range of omega-3 fatty acids and vitamin E, and to evaluate the safety and efficacy of feline multipurpose urinary foods for long-term management of FIC and urolithiasis.

Investigating the role of nutrition in FIC: a controlled clinical trial

We have recently completed a prospective, randomized, double-masked study evaluating the efficacy and safety of a multipurpose therapeutic urinary food, enriched with omega-3 fatty acids (EPA and DHA) and antioxidants, for the long-term management of acute FIC.[23] Young to middle-aged, indoor, male or female neutered cats with clinical signs of acute FIC (≥2 LUTS in the past week) were recruited for the study at Michigan State University and the University of Minnesota. A thorough, diagnostic evaluation was performed to exclude

systemic illnesses and other causes of LUTS. Cats were excluded from the study if they lived in multi-cat households (>2 cats) and owners could not comply with feeding exclusively the test or control foods; had recently consumed urolith dissolution foods; had been treated with any drug or supplement that could potentially affect diagnostic evaluation or expression of clinical signs (eg, antimicrobics, antihistamines, antidepressants, anti-inflammatories, glycosaminoglycans or nutritional supplements).

Owners could choose whether they wanted to offer wet or dry food exclusively and then cats were assigned randomly to either the test or control food groups. Investigators and pet owners were masked to treatment groups for the duration of the 12-month study. The test food was a commercially available multipurpose urinary therapeutic food (ie, Hill's Prescription Diet c/d Multicare). The control food was custom manufactured and was formulated to meet or exceed Association of American Feed Control Officials (AAFCO) nutrient requirements for adult cats. The mineral concentrations and target urine pH of the control food were designed to mimic common grocery brands. Compared with the test food, the control food contained substantially lower concentrations of antioxidants and omega-3 fatty acids (EPA and DHA) (Table 2).

The primary endpoint measured was the frequency of recurrent episodes of LUTS within 12 months. The beginning of a recurrent episode was defined as an initial day with ≥2 clinical signs (hematuria, dysuria, stranguria, pollakiuria and/or periuria). An episode was considered to have resolved when there were two consecutive days with ≤1 clinical sign. Because certain behaviors (eg, periuria) may be acquired as a result of lower urinary tract diseases and persist despite resolution of the underlying cause, this definition of episode resolution was chosen to minimize potential bias of acquired persistent behaviors on outcome assessments. Once enrolled, LUTS (periuria, stranguria, hematuria and pollakiuria), daily food consumption, environmental changes, additional treatments, and any other signs of illness were documented daily by the owner for a period of 1 year. Owners were instructed to return to the veterinary hospital should a recurrence of clinical signs occur and also for scheduled rechecks at 1, 3, 6, 9 and 12 months.

Twenty-five cats ranging in age from 1 to 9 years were included in the study. Eleven cats (five males, six females) were fed the test food and 14 cats (11 males, three females) were fed the control food. Data were analyzed as a binomial proportion of the number of days that an event occurred or the number of episodes of LUTS out of the total number of days a cat was in the study for a factorial arrangement of two diets and two formulations. Both study groups were similar with regard to age, sex, body condition score, food preference, residence, prior episodes of LUTS, and prior treatment with therapeutic foods. Cats consuming the test food had a significantly lower proportion of total days with ≥2 clinical signs and total episodes of LUTS (P <0.05) with 4/11 (36%) test food group cats and 9/14 (64%) control food group cats exhibiting ≥ 2 clinical signs on at least one occasion during the 12-month study. The rate of recurrent episodes of LUTS was 5/3904 days (1.28/1000 cat-days) in the test food group and 47/4215 days (11.15/1000 cat-days) in the control food group. This represents an 89% lower overall rate of recurrent episodes of LUTS in cats fed the test food consistently compared with the control food group (Figure 1). This is the first study to definitively show that foods of different nutritional profiles impact the expression of LUTS in cats with acute FIC.

Table 2 Selected nutrient values for test food compared with control food

Nutrient amounts (per 100 kcal)	Test dry	Test wet	Control dry	Control wet
Protein (g)	9	10.7	8.7	11
Calcium (mg)	176	217	346	310
Phosphorus (mg)	182	209	291	289
Magnesium (mg)	17	19.5	29.4	25.4
Sodium (mg)	83	83	81	124
Vitamin E (IU)	24	30	1	3
Omega-3 EPA (mg)	53	65	4.6	10.5
Omega-3 DHA (mg)	36	44	2.7	10.5
n6:n3 ratio	5.1	6.3	21.5	17.6
Target urine pH	6.2–6.4	6.2–6.4	6.6–7.0	6.6–7.0

Test food (Hill's Prescription Diet c/d Multicare); Control food (single composite food)

Evidence-based treatment recommendations for FIC

- Based on the evidence, feed a therapeutic multi-purpose, urinary-tract food (ie, Hill's Prescription Diet c/d Multicare) to reduce recurrence of clinical signs; it has the highest evidence (Grade 1) of all treatments for effectively managing painful episodes of LUTS in cats with FIC. Evidence also suggests that both dry and canned foods are effective; however, in a separate study with other foods, canned food was more effective than the dry formulation.[9] In addition, feeding multipurpose therapeutic urinary foods should minimize the risk of struvite crystals combining with inflammatory urinary sediment to form life-threatening urethral plugs.
- Based on our understanding of the biology and pathophysiology of disease, implement environmental enrichment (ie, abundant resources and enhanced interactions) and stress reduction (eg, www.indoorpet.osu.edu; www.icatcare.org; www.catvets.com).
- Because we are a compassionate profession, administer medication to reduce pain during acute episodes of LUTS. Studies evaluating analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) have not been reported; current management includes opioid analgesics (butorphanol or buprenorphine) and/or NSAIDS (eg, meloxicam, piroxicam). In one study, prednisolone (1 mg/kg q12h) was no more effective than a placebo.[24]

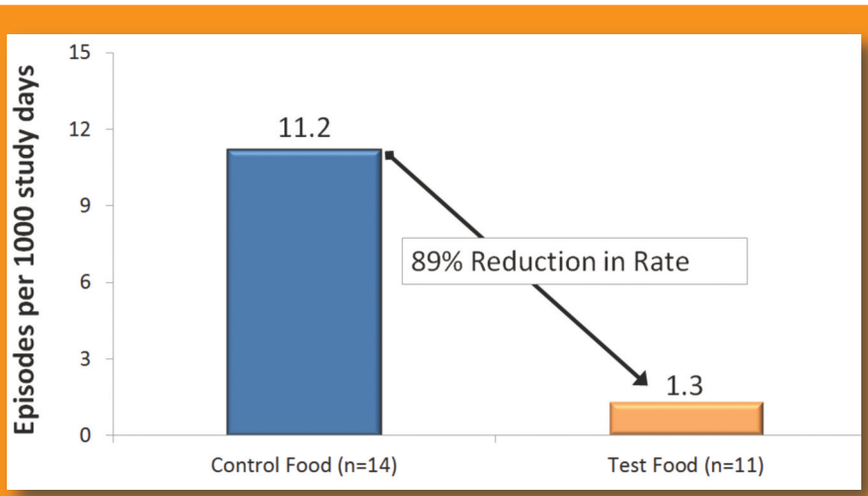


FIGURE 1 In a 12-month clinical study, cats consistently fed test food (Hill's Prescription Diet c/d Multicare (n = 11) had a significantly lower proportion of total days with episodes of FIC signs (*P* <0.05) compared with cats fed a control food (n = 14)

- Glycosaminoglycans, pheromones, serotonin-modulating drugs, antibiotics, fluid therapy, salt supplementation, etc, were either no better than a placebo or have not been evaluated, but can be considered in difficult, highly recurrent or chronic cases of FIC.
- Remember that chronic cases should have more extensive diagnostic evaluations (eg, contrast urethrocystography) to rule out more probable diseases (eg, urethral stricture, radiolucent uroliths) versus assuming a recurrence of FIC signs.

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Urine pH, urine saturation and feline uroliths:
What we know (and don't)

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Formation of uroliths is not a disease, but rather a complication of several disorders.[1] Some disorders can be identified and corrected (such as infection-induced struvite urolith formation), some can be identified but not corrected (such as hyperuricosuria that occurs in Dalmatians that form ammonium urate uroliths), while for others the underlying etiopathogenesis is not known (such as calcium oxalate urolith formation in many cats). A common denominator of these disorders is that they can from time to time create oversaturation of urine with one or more crystal precursors resulting in formation of crystals. In order to develop rational and effective approaches to treatment, abnormalities that promote urolith formation must be identified with the goal of eliminating or modifying them. It is important, therefore, to understand several basic concepts associated with urolithiasis.

What we know and what we don't

Medical dissolution of certain types of uroliths is achieved by inducing a state of undersaturation with respect to the calculogenic minerals. Medical prevention is achieved by inducing a state of undersaturation or low- to mid-metastability as long as there is no mechanism for heterogeneous nucleation present. Urinary supersaturation with calculogenic minerals represents an increased risk towards urolith formation and is required for urolith formation, but other factors are important.

Various factors involved with urolith formation may be evaluated by:

- Epidemiological studies performed at urolith centers and designed to identify risk and protective factors.
- Measuring urine concentrations of calculogenic substances.
- Evaluating the influence of urine pH on crystal formation.
- Measuring the degree of undersaturation, supersaturation, and/or oversaturation of urine with crystallogenic substances.

Determination of urinary biochemical parameters and urinary saturation can only be done in patients that are 'stone free' because active urolith disease results in depletion of calculogenic compounds in urine that alters results.[2]

Urinary mineral concentrations

Measurement of urinary mineral concentrations is helpful in identifying animals that excrete large quantities and/or abnormal types of calculogenic substances. However, the concentration of a mineral is influenced by many variables including dietary consumption, intestinal absorption, endogenous production, renal excretion, and urine volume. Because many variables are involved, measurement of urine concentration of minerals per se is not a reliable index of whether or not uroliths will form.

Urinary pH

The influence of urine pH on canine and feline urolith formation, particularly those composed of struvite and calcium oxalate, has received considerable attention.[3–9] Urine pH may have a profound effect on excretion and solubility of minerals.[10,11] Struvite solubility increases substantially in acidic urine and markedly decreases in alkaline urine.[12] In a study comparing a struvite dissolution diet and a struvite preventative diet, a lower urinary pH was associated with more rapid dissolution of sterile struvite uroliths in cats.[13] Urine pH has also been shown to influence calcium oxalate formation in cats with calcium oxalate being more soluble in alkaluria when compared with aciduria.[14] Potassium bicarbonate administration to cats induces alkaluria, increased urinary potassium excretion and decreased calcium excretion in cats.[15] Urine pH also influences inhibitors of uroliths, especially calcium oxalate formation. Feeding an alkaluria-inducing 'oxalate preventative diet' is associated with increased urinary glycosaminoglycan excretion in cats, which decreases risk of urolith formation.[16] Inducing a neutral to alkaline urine pH in cats is associated with increased excretion of citrate and potassium and decreased calcium excretion, and more importantly decreases urinary saturation for calcium oxalate.[14] While urine pH influences urolith formation it does not provide a reliable index of urolith formation, but indicates increased or decreased risk in combination with other factors.

Mineral supersaturation in urine

Although results of epidemiologic studies and measurement of urinary mineral concentrations and urine pH are often helpful in diagnosis and management of stone disease, they are insensitive tests. Because supersaturation of urine with stone-forming substances is necessary for stones to form, measurement of urine saturation with minerals is a more accurate means of assessing risk of stone formation. An emphasis of urolithiasis research is evaluation of crystallization methods as urolith formation is preceded and advanced with crystal formation.

'Crystallization is a physical chemical process involving a change of state from solution to solid. The supersaturation, which is a measure of the chemical energy available for this process, is a crucial factor and governs all aspects of crystallization such as nucleation, growth, and aggregation. As the reaction proceeds, the supersation will decline (unless replenished) and this in turn will impact upon the kinetic behavior of the crystallization process. While the physical chemistry and kinetics are always important, the process of stone formation takes place in a biological environment.' – JP Kavanagh, 2006[17]

In addition to various techniques developed to evaluate crystallization, several 'risk formulae' have been proposed to evaluate propensity for urolith recurrence (primarily for calcium oxalate) in human patients,[18] although debate exists as to the utility of these formulae.[19] These include: urinary calcium-to-magnesium ratio, urinary calcium-to-citrate ratio, saturation-inhibition index, 24-hour urine quotients [(calcium x oxalate/magnesium x creatinine) and (calcium x oxalate/magnesium x creatinine x inhibition of calcium oxalate crystal growth in dilute urine)], probability index and the ion-activity product index.[18]

Supersaturation

In solution chemistry, the difference in chemical potential of two states ($\Delta\mu$) is dependent on the activities of the crystallizing salt in the supersaturated solution (a) and in the solution when it has come to equilibrium (a_{eq}):

$$\Delta\mu = RT\ln(a/a_{eq})$$

where R is the universal gas constant and T is the absolute temperature (Kelvin). The activity of the crystallizing salt is represented by the activity product (AP) for that salt where the activities of the ions comprising that salt are multiplied. The term 'activity' of a mineral is an index of the likelihood that the mineral will combine with other substances in urine, and is determined by multiplying the concentration of the ion by the activity coefficient for similarly charged molecules. For example, the activity of calcium is determined by multiplying the concentration of calcium in solution (molarity) by the activity coefficient for a doubly charged molecule since calcium carries a '2+' charge. The 'activity' of a mineral is dependent on several factors including the:

- Urine concentration of that mineral
- Urine concentrations of other substances such as sodium, potassium, calcium, etc
- Quantity and functional state of non-mineral or non-measured mineral inhibitors and promoters of crystal formation, growth and aggregation
- Urine pH
- Temperature of urine

Growth of crystals may occur through enlargement of existing crystals by direct incorporation of solution species into the solid crystal lattice or by aggregation of crystals. Aggregation can also result in enlargement of the crystal mass, and occurs through the net result of crystals colliding and either dispersing or consolidating, with the outcome being dependent on an efficiency factor. As consolidation is achieved by crystal bridges that fuse the lattice structures of individual crystals, aggregation also is dependent on supersaturation.[20,21]

Relative supersaturation

Determining the relative supersaturation of a urolith-forming substance in a patient's urine is one technique used to assess risk of urolith formation.[22,23] Relative supersaturation (RSS) is determined by measuring urine concentrations of several analytes including ammonium, calcium, chloride, citrate, hydrogen (pH), magnesium, oxalate, phosphate, potassium, and sodium (and possibly cystine, sulfate, uric acid and other compounds), in urine. These values are then entered into a computer program (EQUIL or SUPERSAT), which calculates the activity coefficients for the various ions and combines the relevant ion concentrations and activity coefficients to produce the activity product (AP). For example, the AP of calcium oxalate is calculated as the mathematical product of the activity of calcium and activity of oxalic acid. The AP for each urolith-forming compound is divided by its known thermodynamic solubility product (SP) and the resultant RSS produced.

RSS = ion AP of the patient's urine / ion SP

Relative supersaturation is related to the energy available for crystal nucleation and growth; however, RSS values are limited by the fact that the

thermodynamic solubility products used for these calculations have not been measured in the patient's urine. It is probable that different macromolecules, including inhibitors and promoters of crystal formation, growth, and aggregation, in the patient's urine have a pronounced influence on free ion concentrations. By using calculations measured in urine from healthy human beings, RSS may overestimate SPs and APs of different minerals, and thus tend to underestimate the risk of urolith formation. Another technical problem in evaluating dogs and cats is that the computer program used to calculate RSS involves comparison of the pet's urine values to standardized values based on the composition of human urine.

Activity product ratios

Activity product ratios (APR) also are designed to express the degree of supersaturation of solutions with calculogenic minerals. APRs are obtained by calculating the ion AP in the patient's urine samples before and after equilibrium with various seed crystals such as calcium oxalate.

$$\text{APR} = \frac{\text{ion AP of patient's urine before incubation with seed crystals}}{\text{ion AP of patient's urine after incubation with seed crystals}}$$

In determining the APR, the patient's urine is incubated with preformed seed crystals composed of pure urolith-forming mineral of interest (for example, calcium oxalate). Following incubation for 48-hours with the seed crystals, the urine concentration of the same analytes are measured. The post-incubation concentrations of analytes are then used to calculate a 'post-incubation' AP. Dividing the 'pre-incubation' AP by the 'post-incubation' AP gives the APR for that patient's urine sample.

An exact measurement of supersaturation is not obtained by determining APR, but the method provides useful information about the relative increase or decrease of the ion AP in the patient's urine that result from seed crystal growth or seed crystal dissolution. An APR less than one represents undersaturation of urine with the mineral being evaluated. An APR equal to one represents saturation of the patient's urine sample. An APR value >1 indicates that the patient's urine sample is supersaturated.

Activity product ratios can be calculated for any calculogenic mineral as long as pure seed crystals for that type of mineral are available. Use of APR methodology will not eliminate errors associated with the effect of unknown factors such as crystallization inhibitors or promoters on ion activities; however, since the same urine sample obtained from the patient is analyzed before and then after equilibration with seed crystals (such as calcium oxalate), the same type of error occurs in evaluation of both analyses and therefore the errors cancel. Whereas calculation of RSS can overestimate supersaturation, saturation, and undersaturation, the APR method overestimates undersaturation, underestimates supersaturation, and correctly measures saturation, provided that a sufficient amount of seed crystals have been used. One limitation of APR determination is the assumption that urine has reached the SP for the salt following 48 hours of incubation, which has been shown to be a false assumption in some cases.[24] Urine may not reach true equilibrium saturation level, particularly when coming from a supersaturated level, presumably due to presence of various inhibitors of crystal growth that slow down the approach to equilibrium. In this instance, when the true RSS is measured following 48 hours of seed incubation, the AP achieved at that point may be two to three times higher than the thermodynamic solubility product. The APR calculated at this point, therefore, systematically underestimates the actual level of supersaturation since the denominator (AP/SP) is too large. The opposite may occur when the urine is undersaturated.

Other measures of urine saturation

There are other techniques for estimating urine saturation in addition to RSS and APR such as the Bonn-Risk Index and Joint Expert Speciation System (JESS). These are used in human beings and could have potential for veterinary patients.

Use of urinary saturation testing

Limited studies utilizing urine saturation testing have been performed in veterinary medicine, particularly in animals that have formed uroliths. Despite the number of studies, very few have been performed in dogs or cats that are urolith-formers and no studies exist that compares estimates of urinary saturation with recurrence rates of uroliths. In cats, calcium oxalate urolith formation typically occurs when urinary RSS for calcium oxalate is greater than 12; the metastable zone lies between an RSS value for calcium oxalate of 1 and approximately 12.[25] Sterile struvite urolith formation in cats typically occurs when urinary RSS for struvite is greater than 2.5; the metastable zone lies between a RSS value for struvite of 1 and approximately 2.5.[25] Urinary supersaturation represents a risk for urolith formation, but as in human beings, there is overlap in values between urolith-forming animals and healthy, non-urolith-forming animals;[26,27] therefore, other factors are important. Use of urinary saturation studies can provide further information as to mechanisms of urolith formation, screening of animals at risk for urolith formation, and monitoring efficacy of urolith management.

Clinical application to dogs and cats

So what does all of this mean? There are several factors to keep in mind:

- Urinary saturation is the most important, but not the only, driving force for crystallization and urolith formation.
- Several methods exist for estimating urinary saturation; however, none of them adequately describe what is occurring naturally in the biological system (urinary tract).
- Determination of RSS and APR values, while used to estimate urinary saturation, give different results and information. Determination of RSS is a valuable and reasonably reliable technique for estimating urinary saturation; however, it (a) is heavily influenced by concentration of analytes measured, which, in turn, is influenced by urine volume, and (b) it does not account for urinary constituents that are not measured including the influence of inhibitors. Because it is influenced by urine volume, methods designed to increase urine volume (eg, feeding canned foods, administration

of diuretics, and stimulating water consumption by increased levels of dietary sodium) would be expected to lower the RSS; however, clinical studies in urolith-forming dogs and cats are lacking.[28–33] Determining APR values do not give an exact estimation of the supersaturation; however, because a patient's urine is used pre- and post-incubation with seed crystals, this technique does account for unmeasured urinary constituents and the influence of inhibitors.

- Medical dissolution of uroliths is accomplished by inducing a state of undersaturation of urine (below the solubility product) with the minerals that formed the uroliths.
- Medical prevention of uroliths is accomplished by inducing a state of undersaturation of urine or at least a state of saturation at the lower end of the metastability limit.
- Despite use of estimates of urinary saturation, there are no published studies in urolith-forming dogs and cats that validate their prediction of urolith recurrence. Until that time, these techniques are useful for formulating diets, but await recurrence data for validation.
- Means to decrease urinary saturation include increasing urine volume ('dilution is the solution to pollution') thereby decreasing the concentrations of calculogenic substances and decreasing dietary intake of calculogenic substances. Despite these measures, they do not guarantee prevention of urolith recurrence in all patients demonstrating that urolith formation is a complex process and many questions remain unanswered.

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Managing a cat with lower urinary tract signs:
A case report

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Introduction

Lower urinary tract signs (LUTS) are a common problem in pet cat populations around the world. There have been major recent advances in our understanding of the underlying problems that produce the painful and distressing signs that are typical of disorders affecting the lower urinary tract of cats and this improved understanding will allow us to adopt improved approaches to the prevention, investigation and management of these conditions. Nevertheless for cats, owners and veterinary healthcare teams around the world, LUTS remain a substantial cause of distress and frustration. This short case report illustrates some of the practical difficulties that can arise when dealing with this condition in day to day practice, but offers practical solutions that can help improve the lives of affected cats and their owners.

Case report

Sooty, a 9-year-old neutered female domestic shorthair cat, presented with a recent history of LUTS (Figure 1).

Background information

Sooty had been adopted by her current owners (Mr and Mrs B and their son and daughter) about 1 year previously and she was the only pet in their household. She had been overweight when she was adopted but Mrs B had controlled her

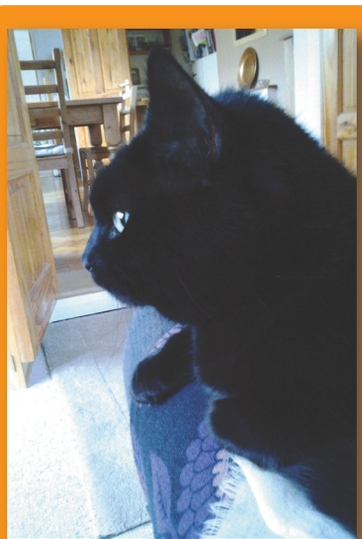

FIGURE 1 Sooty, a 9-year-old, neutered female

FIGURE 2 Overgroomed ventrum of the patient causing loss of fur

food intake and had successfully reduced her weight. Sooty was a generally healthy cat but she persistently over-groomed her ventrum causing loss of fur but not breaking the skin (Figure 2). She had free access to the outdoors but chose to spend most of her time indoors and she was fed a mixture of wet and dry proprietary cat foods.

Presenting problem – for Sooty

Approximately 4 weeks prior to presentation Sooty had started urinating in her litter tray more frequently than usual and was also urinating outside of her litter tray about once a day. On some occasions she was seen straining unproductively to urinate, while at other times she was producing urine in variable amounts, sometimes with visible blood discoloration. Her habitual overgrooming of her ventrum had now also extended to include her perineum and her hind-feet. There were no changes in her appetite or thirst and she showed no other signs of ill-health.

Presenting problem – for Sooty's owners

Throughout the previous year Sooty had always been a clean, 'low maintenance' cat who socialized well with the family and had become a much loved pet. However, for the past 4 weeks she had been urinating around the house on towels, beds and carpets – the extra burden of laundry and cleaning was tiring and despite best efforts there was an all-pervading aroma of cat urine around the house. Sooty was being shut out of some of her favourite rooms, eg, the younger son's bedroom, because she might urinate on his bed. Keeping doors shut all the time was proving difficult to live with, and being denied access to certain rooms was distressing to Sooty and this in turn was distressing to her owners. They were acutely aware that Sooty was showing signs of pain when urinating which worried them and was upsetting to watch, and the overgrooming was causing progressive alopecia of the hind-end which spoiled Sooty's normally sleek good looks, and was a permanent visual indication that Sooty was not well.

Mrs B had presented Sooty to another local veterinary practice and a suspected diagnosis of 'idiopathic cystitis' lead to treatment with meloxicam. The treatment was was well tolerated and Sooty took the medication on her food without complaint, but despite good compliance there was no improvement in Sooty's signs and behaviour. Her owners were worried that Sooty had something 'seriously wrong' with her, or that this might be a 'habit' that she had developed and that if it continued they might not be able to keep her. In the face of lack of improvement, the owners decided to seek another opinion and presented Sooty at the Oxford Cat Clinic.

Physical examination and initial investigation

On presentation Sooty was bright, inquisitive and interactive and she was in good body and coat condition (weight 4.2 kg, body condition score 3/5). Her urinary bladder was empty and while there were no gross abnormalities on palpation she did appear to be uncomfortable during this part of the examination. There were no other substantial findings other than the self-induced alopecia of the ventral abdomen and hind-feet.

Differential diagnosis

The likely causes of inappropriate urination and LUTS in an otherwise apparently healthy cat were ranked in approximate order of likeliness based on the history and physical examination:

Differential diagnosis	Quite likely	Likely	Maybe	Less likely	Quite unlikely
Urolithiasis	✔				
Feline idiopathic cystitis		✔			
Bacterial urinary tract infection			✔		
Neoplasia				✔	
Primary behavioural/ 'being naughty'					✔

Plan

The most direct, minimally invasive and cost effective plan to narrow down the differential list would involve:

- Collecting a sample of urine by cystocentesis for complete urinalysis including specific gravity, dip-stick evaluation, urine sediment examination, and quantitative bacterial culture
- Ultrasound examination of the bladder looking for evidence of urolithiasis, neoplasia, diffuse thickening of the bladder wall, etc.

However, since neither of these procedures could be done at the time of presentation a modified plan was for the owner to collect a urine sample using non-absorbent litter in her litter tray and bring it to the clinic the next day for urinalysis.

Urinalysis: voided, stored sample

- Appearance: bright yellow translucent sample
- Specific gravity: >1.050
- Dip-stick analysis: glucose negative, pH 8.0, blood +++, protein ++
- Sediment: frequent red blood cells, some struvite crystals, occasional white blood cells, no bacteria seen.

The high urine specific gravity and lack of glucosuria suggested that bacterial urinary tract infection was less likely, so the modified differential diagnosis list was now:

Differential diagnosis	Quite likely	Likely	Maybe	Less likely	Quite unlikely
Urolithiasis	✔				
Feline idiopathic cystitis		✔			
Bacterial urinary tract infection					✔
Neoplasia				✔	
Primary behavioural/ 'being naughty'					✔

New plan

Sooty met the inclusion criteria for a small scale pre-launch open-label acceptance study looking at in-clinic feeding experience with a new therapeutic urinary food (Hill's Prescription Diet c/d Urinary Stress). Her owner agreed to enroll her in the

TABLE 1 Emotional scale for Sooty

	0	1	2	3	4	5
Contact tolerance with familiar people	Can't be touched	Allows only short contact with humans when the cat initiates it	Does not tolerate long, provoked or spontaneous contact	Variable acceptance and seeking of contact	The cat regularly seeks and accepts contact – seldom refuses	Easily manipulated
Contact tolerance with non-familiar people	Disappears or is aggressive in the presence of people	Comes to observe but cannot be touched	Initiates contact after a while but does not accept being touched	Initiates contact after a while and accepts being touched	Accepts most, but not all human contact	Tolerant, friendly and playful with non-familiar and familiar people
Aggression	Aggressive to familiar and non-familiar people, causing injury	Aggressive to familiar and non-familiar people, except for one person, causing injury	Possible but infrequent aggression that causes injury	Threatens without fleeing	Threatens and flees	Never aggressive
Other fears	Frightened by the slightest noise or any new stimulus	Unwilling to explore; responds in a fearful way to numerous stimuli	Exhibits fearful behaviour, but explores after a while	Frightened only by specific, known stimuli	Seldom frightened – calms down quickly	Never afraid

feeding experience and we arranged to start this food at the earliest available out-patient opportunity while also recommending an in-patient visit for abdominal ultrasound and repeat urinalysis on a fresh urine sample collected by cystocentesis.

The feeding experience

Feeding experience design: A non-blinded, non-controlled feeding experience of client-owned cats with signs compatible with a clinical diagnosis of 'feline idiopathic cystitis' (FIC).

- Inclusion criteria: Cats showing LUTS within the last 2 weeks, excluding those known to have uroliths, plugs, bacterial infections, other less common causes of LUTS, and true behavioural problems.
- Exclusion criteria:
  - Major systemic diseases that could affect the stress levels of these patients.
  - Treatments and/or supplements that could affect stress hormones, behavior, or LUTS such as corticosteroids, NSAIDs, antidepressants, antibiotics, pheromones, etc.
- Feeding experience period: 60 days on the food with no other measures/treatments besides environmental enrichment (ie, no pheromones, nutraceuticals or other treatments such as NSAIDs, antidepressants, antibiotics, etc, that are used for cats with LUTS).

Evaluations:

- Consultation (V0)
  - Full history and physical examination
  - Baseline 'Cat Emotional Scale', food preferences, FLUTD scale
  - Morning voided urine sample collected at home: standard urinalysis, cortisol/creatinine ratio.
- Telephone owner follow-up (2 weeks) (T1)
  - Cat emotional scale, taste perception, FLUTD scale
- Consultation (4 weeks) (V1) = as V0
- Telephone owner follow-up (6 weeks) (T2) = as T1
- TConsultation (8 weeks) (V2) = as V0

Starting the feeding experience

Sooty was presented at 9 am the next morning for V0: on physical examination her bladder was again empty.

Her baseline emotional scale per owner is indicated by red circles on the Table 1.

Her owner's assessment of Sooty's FLUTD scale were:

	No presence 0	Minimal presence 1	2	Medium presence 3	4	Severe presence 5
Frequent visits to the litter box					✔	
Signs of pain or difficulty during urination				✔		
Urinating at inappropriate places						✔
Red discoloration of the urine			✔			
Straining				✔		
Over-grooming						✔

Recommended alterations to her environment included:

- Litter tray(s): Sooty had always used a covered litter tray and there had been no recent changes to its site or the substrate (non-fragranced, clumping, clay-based). Recommendation: Provide an additional litter tray in a separate area of the house.
- Food and water bowls: Sooty had one food bowl and one water bowl, both sited quite close to the litter tray. Recommendation: Move both bowls further from the litter tray and provide an additional water bowl in a separate area of the house.
- Resting places: Currently excluded from some of her favourite resting sites (due to inappropriate urination). Recommendation: Allow access to favourite sites. Clean any areas of urine soiling thoroughly using detergent and an enzymatic odour eliminator.
- Interaction/playing: Sooty had a number of toys and enjoyed playing with the children. Recommendation: Increase quality time spent with owners and increase play.

Mrs B was provided with a supply of both wet and dry 'feeding experience food' (Hill's Prescription Diet c/d Urinary Stress) with instructions to transition Sooty to the new food over a 7 day period and to let us know if Sooty was not accepting the food; if the LUTS deteriorated further; or if any new signs developed. An in-patient appointment for ultrasound and urinalysis was booked for 5 days time (being the earliest date the owner could manage) and a follow up telephone interview (T1) was scheduled for 2 weeks time.

Outcome

Mrs B was keen to start dietary and environmental modifications and to make progress rapidly – she instituted all the recommended changes but with some trepidation regarding allowing Sooty free access to all areas. Sooty ate the food well (see Figure 3), and in view of this and to try to expedite response to dietary management, Mrs B elected not to transition gradually to the new food, but rather to achieve the change in 2 days.

FIGURE 3 Sooty ate the new food (Hill's Prescription Diet c/d Feline Urinary Stress) well

Sooty showed an immediate and marked change in her condition from the time that Mrs B started to feed the new food. There were no further episodes of inappropriate urination, visits to the litter tray settled to normal (Sooty continued to use the familiar tray, disregarding the new tray although it remained available to her) and Mrs B was not aware of any further episodes of haematuria. She cancelled the planned in-patient appointment and at the 2-week follow-up interview reported complete resolution of all LUTS with no relapses. Her assessment of Sooty's emotional scale was unchanged, but the FLUTD Scale was now:

	No presence 0	Minimal presence 1	2	Medium presence 3	4	Severe presence 5
Frequent visits to the litter box	✔					
Signs of pain or difficulty during urination	✔					
Urinating at inappropriate places	✔					
Red discoloration of the urine	✔					
Straining	✔					
Over-grooming				✔		

This remarkable and rapid response to dietary and environmental modification was maintained throughout the subsequent weeks.

- Was Sooty suffering a particularly prolonged episode of FIC or struvite disease, or both, which was resolved by the therapeutic urinary food? We don't know.
- Was the apparent response to diet genuine, or was it co-incidental? Again we don't know.

Nevertheless:

- Was the cat happy? Yes
- Were the owners happy? Yes
- Was the veterinary healthcare team happy? Yes
- Was it a good outcome? Absolutely!

Role of nutrition in endogenous oxalate metabolism in cats

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Introduction

Over the past 30 years, a progressive increase in calcium-oxalate (CaOx) urolith prevalence is seen in domestic cats diagnosed with urolithiasis.[1,2] This increase appears to have occurred since dietary modifications were introduced to address magnesium ammonium phosphate urolithiasis, although a solid scientific basis for this argument is lacking. Current non-invasive strategies based on nutrition are not able to reliably prevent CaOx urolithiasis and such strategies may partly be limited by incomplete knowledge regarding the pathogenesis of this multifactorial condition.

Several risk factors have been identified for CaOx urolithiasis in cats. As for animal related factors, cats with an increasing age (7–10 years) show the highest predisposition in developing CaOx uroliths.[3] Also, male cats seem to be more affected, and 95% of cats with CaOx urolithiasis are neutered.[3]

Hypercalcemia is thought to play an important role in the pathophysiology as well. In cats suffering from CaOx urolithiasis, mild hypercalcemia (11.1 to 13.5 mg/dl) was reported in 35% of the cases.[4] Although animal related factors may play a role in CaOx formation, the short time span in which the progressive increase in prevalence took place, may suggest a significant influence of nutritional factors. Any nutritional factor that is able to influence urinary concentrations of calcium (Ca) and oxalate may play a role in CaOx urolith formation.

Figure 1 displays a schematic model of dietary risk factors that are likely to increase urinary Ca or oxalate concentrations.

Dietary factors influencing urinary Ca concentration

For decades, the general consensus existed that a restricted dietary Ca intake would reduce the chance of CaOx urolith formation by reducing the urinary Ca excretion.[6] However, recent literature in humans and dogs indicate a possible advantage of an increased dietary Ca content.[7,8] This is thought to be related to complexation between dietary Ca and oxalate in the intestinal tract, making dietary oxalate less available for absorption. In support of this, a case control study by Lekcharoensuk et al[6] indicated that consuming diets with a

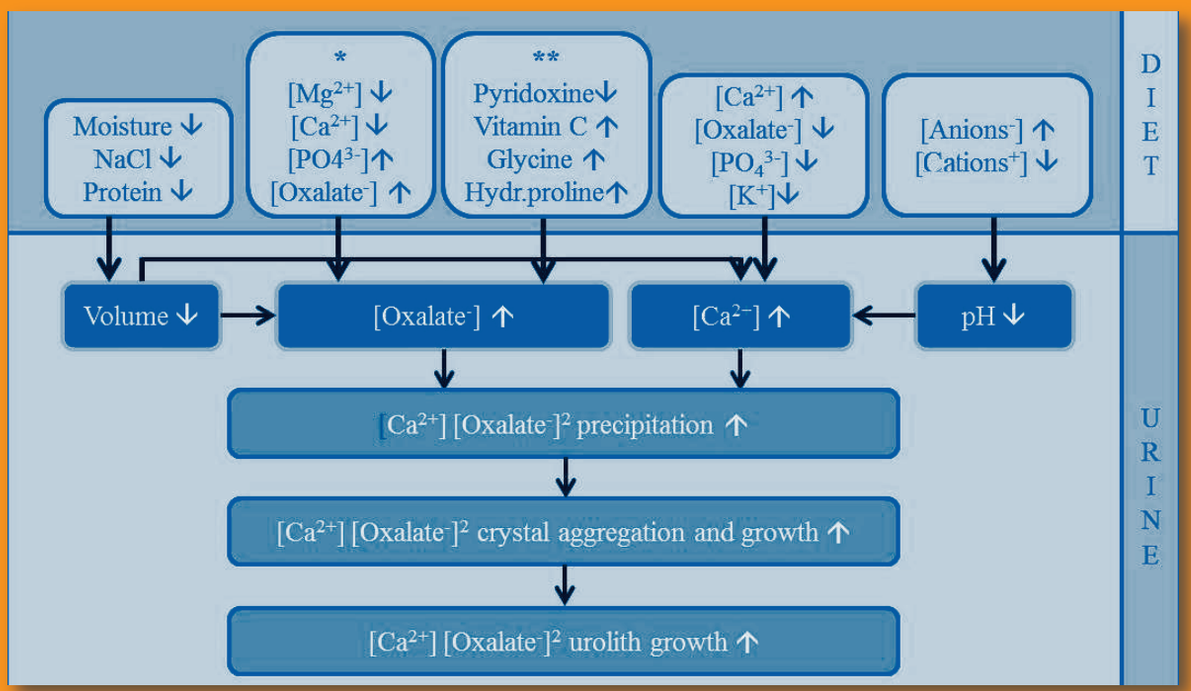

FIGURE 1 Schematic model of the influence of diet on urinary calcium and oxalate concentrations.
*** Dietary factors affecting exogenous oxalate.**
**** Dietary factors affecting endogenous oxalate synthesis.**
Modified from Dijcker et al[5]

relatively low amount of Ca (0.23–0.49 g/MJ) was associated with a higher risk for developing CaOx uroliths compared to diets with higher amounts of Ca (>0.49 g/MJ).

Low dietary intake of phosphate (P) may be related to an increased urinary Ca excretion in cats.[9] The rationale behind this finding may be a higher Ca availability in the gastrointestinal tract due to a reduced complexation with P. This is in agreement with the finding of Lekcharoensuk et al[6] that feeding diets with a low P content (0.2–0.4 g/MJ) showed an increased risk for CaOx urolithiasis compared to diets with a moderate P content (0.66–0.76 g/MJ). That same case-control study revealed that diets with a relatively high potassium (K) content (0.5–0.75 g/MJ) were less as half as likely (OR 0.45) to develop CaOx urolliths compared to cats that were fed diets with relatively low K content (0.23–0.38 g/MJ). A possible explanation for this effect may be the alkalizing effect of K salts, leading to a higher urinary pH, since a decrease in urinary pH is associated with an increase in urinary Ca excretion in cats.[10]

Dietary factors influencing exogenous urinary oxalate (Uox) concentration

Today's dry petfoods generally contain a relatively high amount of dietary oxalate, derived from bran concentrates and cereals. In 252 commercially available dry petfoods for cats the oxalate content was found to range between 3.1 and 117.9 mg/MJ, with a mean oxalate content of 27.2 mg/MJ.[11] The average daily intake of oxalate (7 mg/kg BW/day) compared to human daily oxalate intake (2—3 mg/kg BW/day)[12] can thus be considered high.

A high intake of dietary oxalate is a known factor that may increase Uox concentration. However, the amount of oxalate absorbed depends greatly on the availability of free oxalate in the gut. Research has shown that other dietary factors, like dietary Ca and magnesium content significantly affect the availability of oxalate for absorption. Both minerals can directly interact with oxalate, resulting in a lower free oxalate concentration in the gut.[13] The question remains whether dietary oxalate significantly contributes to Uox excretion in cats. In a recent study by Dijcker et al,[14] it was shown that increasing the oxalate intake from 13 to 93 mg/100g dry matter (corresponding with ± 15 mg/kg BW/day) did not affect Uox excretion. It was estimated that the intestinal absorption of supplemented oxalate was only 5.9 ± 5.24% and contributed for 0.78% to oxalates excreted in the urine. It was suggested that the relatively high Ca content of feline diets in general will lower the amount of free oxalate available for absorption, making the contribution of exogenous oxalate to Uox negligible.

Dietary factors influencing endogenous Uox concentration

Endogenous biosynthesis of oxalate mainly occurs in the liver, and is highly dependent on the glyoxylate content in the hepatocytes.[15] A schematic overview of the metabolic pathway of glyoxylate is given in Figure 2. Any glyoxylate that is not reduced to glycolate or transaminated to glycine is oxidized to oxalate, which is a metabolic 'end-waste product'. A key-enzyme in oxalate metabolism is alanine:glyoxylate aminotransferase 1 (AGT1), which converts glyoxylate into glycine. An essential co-factor for this enzyme is pyridoxine (Vitamin B6). A deficiency in pyridoxine has shown to significantly increase Uox excretion in kittens.[16]

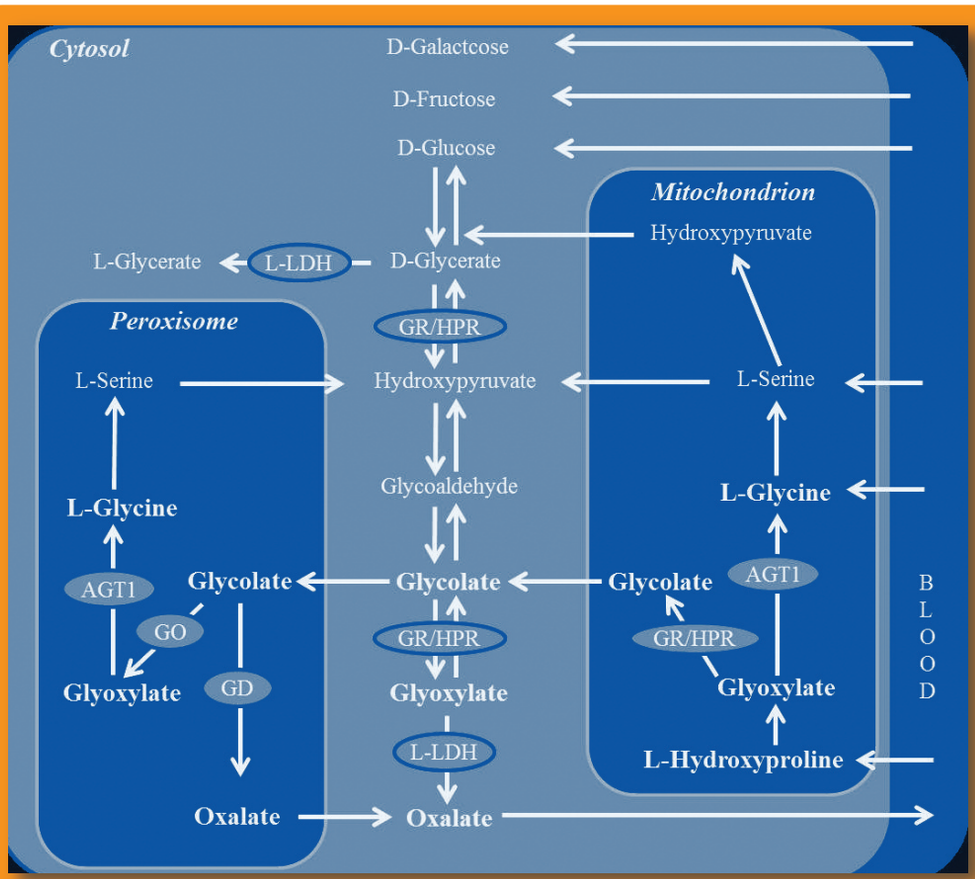

FIGURE 2 Schematic representation of de novo oxalate synthesis via glyoxylate metabolism in the hepatocyte. AGT-1 = alanine:glyoxylate aminotransferase; GD = glycolate dehydrogenase; GO = glycolate oxidase; GR/HPR = glyoxylate reductase/hydroxypyruvate reductase; L-LDH = L-lactate dehydrogenase. Modified from Dijcker et al[5]

AGT1 is both localized in mitochondrion and peroxisome, which reflects its dual physiological function, namely detoxification in peroxisomes and aiding gluconeogenesis in the mitochondrion.[17] Intra-peroxisomal detoxification of glyoxylate is essential in herbivores, since their diet is rich in glycolate and carbohydrates. To prevent oxidation of cytosolic glyoxylate to oxalate by L-lactate dehydrogenase (L-LDH, Figure 2), a high activity of AGT1 in the peroxisomes is needed. In contrast, carnivores naturally consume little glycolate and carbohydrates, which makes glyoxylate detoxification in the peroxisomes redundant. The high amount of animal protein in the natural diet of cats would clearly favor contribution of gluconeogenesis in the mitochondrion. This physiological difference between herbivores and carnivores is clearly expressed in the spatial localization between the different species. In carnivores AGT1 is mainly present in mitochondria, while in herbivores and humans AGT1 is predominantly located in the peroxisomes.[17]

The glyoxylate content in the hepatocyte is dependent in certain dietary precursors. In rats, it was shown that an increased intake of sugars (ie, glucose, fructose, galactose, xylose) and certain amino acids (hydroxyproline, glycine, serine) contributes to endogenous production of oxalate.[18–20] Based on the predominantly mitochondrial localization of AGT1 in cats, Dijcker et al[21] hypothesized that a high carbohydrate intake in this carnivorous species might induce endogenous oxalate synthesis and thereby affecting Uox excretion. To test their hypothesis, a randomized controlled trial was conducted in which 12 cats were fed three diets in a latin square design, only differing in macronutrient profile (high protein, high carbohydrate and high fat). It was found that, although the Uox concentration was significantly lower when the high protein diet was fed, net Uox excretion (mmol/kg BW0.75) was unaffected by a change in macronutrient profile. It was concluded that the activity of AGT1 in the peroxisomes was apparently sufficient for the removal of sugar-derived glyoxylate. Interestingly, Zentek et al,[22] in a study investigating the influence of dietary protein quality (horse meat, collagen tissue and soy isolate) and quantity (high or low protein) on Uox excretion, found the highest oxalate excretion when feeding the high and low protein diet formulated with collagen tissue, with an inverse relationship between Uox excretion and protein intake. The outcome of the Zentek's study is not in agreement with the data found by Dijcker.[21] This may be attributed to the protein sources used in the two

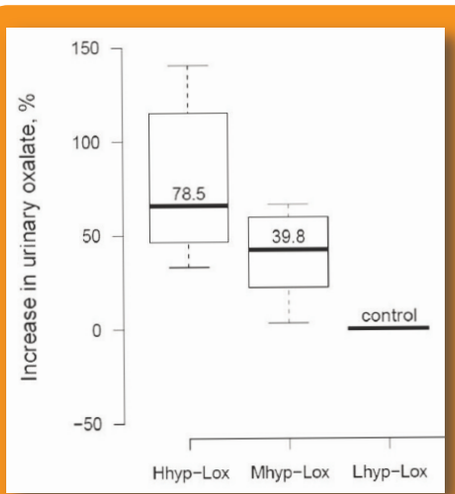

Figure 3 Box plot of the increase in urinary oxalate excretion in adult cats fed a low oxalate diet with low (Lhyp-Lox), moderate (Mhyp-Lox) and high (Hhyp-Lox) hydroxyproline. The box is representing values within 25th and 75th percentile. Whiskers extend to minimum and maximum values. Modified from Dijcker et al[14]

different studies. In the study of Dijcker, casein was used as a protein source, which is known to have no apparent effect on Uox excretion in cats. In the study of Zentek, collagen tissue was used as a protein source, generally rich in the amino acid hydroxyproline (hyp). In humans, rats and mice it was shown that significant amounts of endogenously synthesized oxalate is derived from hyp.[20,23,24] In another study by Dijcker et al[14] it was tested if hyp also influences endogenous oxalate metabolism in the carnivorous cat. For this purpose eight female cats were fed a diet low in oxalate (13 mg/100g DM) and low, medium or high in hyp (0.2, 2.0 and 3.8 g/100g DM, respectively) in a 48-day study with a latin square design. Increasing hyp intake resulted in an increased Uox excretion (P <0.0001) (Figure 3) and in a significant linear dose-response equation:

$$\text{Uox (mg/day)} = 5.622 + 2.097 * \text{hyp intake/day} \quad (r^2 = 0.56).$$

Based on the outcome of this study it was suggested by the authors that use of hyp-containing protein sources (like collagen tissue) should be minimized in CaOx preventative diets until their effect on Uox excretion is determined.

Conclusions

Nutrition seems to be able to influence formation of CaOx uroliths in cats, mainly by exerting an effect on Uox excretion. Urinary oxalate is largely derived from endogenous synthesis, as recent research has shown that exogenous oxalate marginally contributes to Uox excretion in cats. AGT1 is a key enzyme in endogenous oxalate metabolism. A nutritional deficiency in its co-factor vitamin B6 has shown to significantly increase Uox excretion. Protein source rather than protein content may be related to changes in endogenous oxalate synthesis, with hyp being a potent substrate in the formation of endogenous oxalate in cats.

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Efficacy of nutritional management of struvite uroliths in cats

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Introduction

Successful dietary dissolution of a naturally-occurring struvite urolith in a cat was first reported in 1983.[1] Since that time, three additional case series have been published demonstrating the efficacy of therapeutic foods to dissolve struvite uroliths.[2–4] Despite the unprecedented success associated with dietary dissolution, struvite remains one of the most common uroliths submitted to laboratories for quantitative analysis, an indication that invasive urolith extraction is often selected for many cats in which non-invasive nutritional dissolution would have resolved disease with overwhelming success and little or no risk.

Reasons for rationalizing urolith extraction over nutritional dissolution have not been evaluated; however, the following factors are likely involved in maintaining some misconceptions of the benefits of surgery over nutritional dissolution:

- Surgery averts an impending urethral obstruction
- Surgery averts prolonged discomfort during protracted dissolution
- Surgery resolves the problem immediately.
- Surgery resolves the clinical signs immediately
- Surgery avoids having to predict mineral composition
- Surgery is more appropriate because it is more successful than nutritional dissolution.
- Surgery eliminates worry about diet acceptance by the patient
- Familiarity with surgical techniques makes it easier for the clinician.

The following is a description of our study[5] emphasizing the ease and appropriateness of nutritional dissolution in addition to the reduced costs of effective care for clients.

Study objectives and design

Our study was designed to evaluate efficacy, safety, and speed with which two therapeutic foods dissolve sterile struvite uroliths in cats. To test these hypotheses, cats with naturally-occurring urocystoliths participated in a prospective, multicenter, double-masked, randomized, controlled, clinical trial. These client-owned cats were enrolled following validated client consent. Cats were included if survey abdominal radiography supported a diagnosis of struvite urocystoliths (moderately radiopaque, round or discoid stones with a smooth to slightly irregular contour) and were found to be otherwise healthy based on results of the physical examination, survey abdominal radiography, urinalysis, urine culture, serum biochemical profile and complete blood cell count. Survey radiography was selected over ultrasonography as the method of diagnosis because although ultrasonography is more sensitive at detecting the presence of uroliths, ultrasonography does not provide accurate information about urolith radiopacity or shape which are helpful when predicting urolith composition.[6,7] In addition, results of a recent in-vitro study indicated that uroliths measured by survey radiography more accurately reflected actual urolith size compared to uroliths measured by ultrasonography.[8]

Cats were excluded if they had nephroliths, urethroliths, urethral obstruction, or urinary tract infection at the time of initial evaluation. In addition, cats had to be free of significant diseases of the skin, heart, liver, eyes or kidneys. Cats were excluded if they were receiving medications or diets to manage lower urinary tract diseases except for the administration of medication to reduce pain (ie, buprenorphine).

Cats entering the study were randomly assigned to one of two treatment groups. One group was fed a prevention-dissolution food (ie, Hill's Prescription Diet c/d Multicare Feline) and the other group was fed a dissolution food (ie, Hill's Prescription Diet s/d Feline). In addition to patient randomization, the clinical care team and clients were masked as to which food the cat was assigned to eat. To achieve masking, both foods were identical in appearance, form (dry kibble), and packaging. Treatment foods were distinguished by a color coded square (gray or peach) on the front cover of each sealed package of food; and each was manufactured, analyzed for its nutrient content, and packaged with its appropriate color code prior to shipment to the clinical study centers. Food was dispensed at the end of the first patient appointment. A suggested daily quantity of food to maintain the cat's current body weight was calculated, and owners were advised to feed the assigned food exclusively to maintain body condition. Treatment foods were to start immediately without a gradual transition. To improve feeding compliance, sufficient study food was dispensed to feed all clinically healthy cats in the same household.

This was an eight-week study and the primary

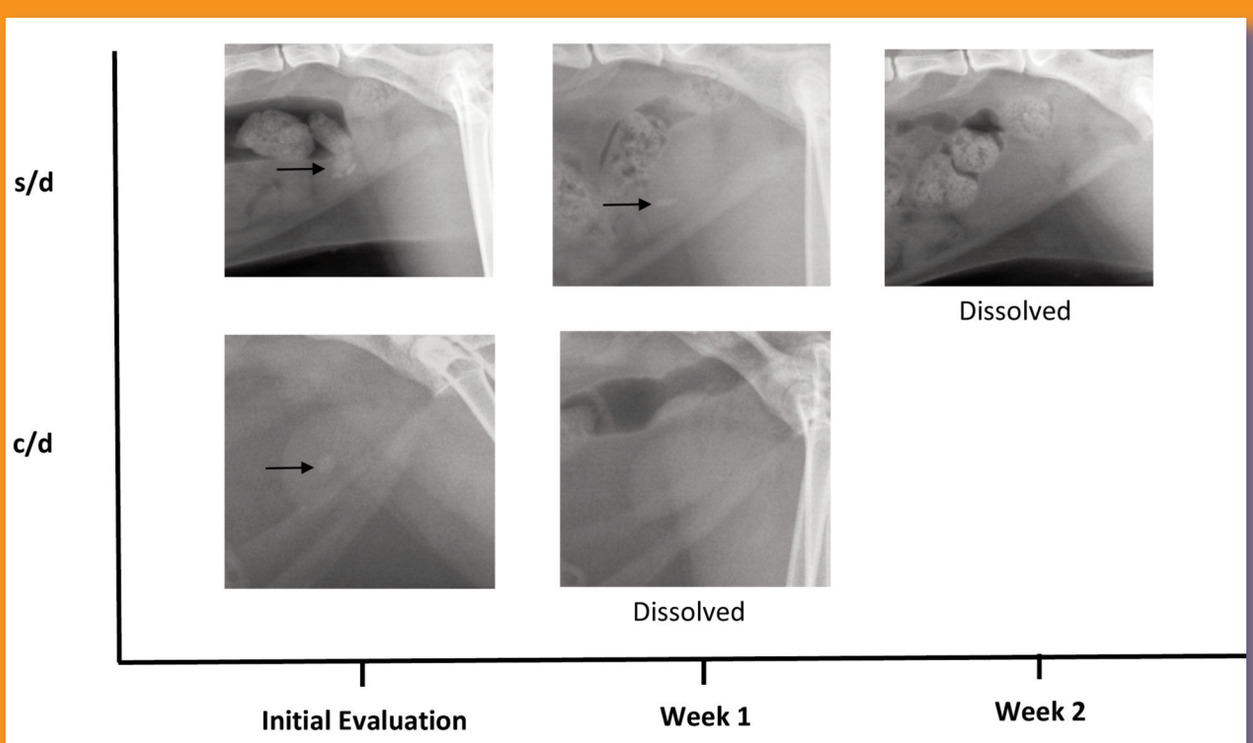


FIGURE 1 Right lateral radiographic images of the caudal aspect of the abdomens of a 5-year-old male domestic shorthair cat (top row) whose uroliths were managed with Hill's Prescription Diet s/d Feline dry (s/d) and a 5-year-old female domestic shorthair cat (lower row) whose uroliths were managed with Hill's Prescription Diet c/d Multicare Feline dry (c/d). Radiographs were obtained during initial examination and each subsequent week until uroliths were no longer radiographically visible

endpoint with respect to treatment (ie, food) efficacy was time to urolith dissolution. To determine dissolution time, cats were evaluated weekly with a physical examination, survey abdominal radiographs, and a complete urinalysis including urine pH determined by meter. Survey abdominal radiographs were digitally acquired. All radiographic images were assessed by board-certified radiologists without their knowledge as to the cat's group assignment. The time for urolith dissolution was the number of days from initial group assignment to the radiologist's assessment that uroliths were no longer radiographically visible. Cats, whose uroliths were unaffected by treatment were withdrawn from the study; their owners were offered urolith removal for no additional cost. Removed uroliths were quantitatively analyzed for their mineral composition. Cats with undissolved uroliths composed of struvite were categorized as treatment failures. Cats with undissolved uroliths not composed of struvite were categorized as diagnostic failures.

Results and discussion

Thirty-seven cats were included in the study; on the basis of laboratory tests, all cats were considered healthy, other than the presence of urocystoliths. In five cats, uroliths did not dissolve. These uroliths were surgically removed and quantitatively analyzed for their mineral composition; no undissolved uroliths were composed of struvite. In four cats persistent uroliths were composed of 100% ammonium urate and in one cat the urolith was 100% calcium oxalate. These five cats were excluded from further evaluation of the foods because they were classified as diagnostic failures.

In the remaining 32 cases; 16 (five male and 11 female) were fed the prevention-dissolution food (Hill's Prescription Diet c/d Multicare Feline) and 16 (two male and 14 female) were fed the dissolution food (Hill's Prescription Diet s/d Feline). Complete urolith dissolution was achieved in all of these 32 cats (Figure 1) with presumed struvite urocystoliths (Figure 2). Mean dissolution times between treatments were significantly different (P = 0.002); the prevention-dissolution food dissolved uroliths in 27.0 ± 2.6 (range = 7 to 52) days and the dissolution food dissolved uroliths in 13.0 ± 2.6 (range = 6 to 28) days. The time for urolith size to decrease by 50% was 1.75 ± 0.27 weeks for the prevention-dissolution food and 0.69 ± 0.1 weeks for the dissolution food. Owners indicated that cats strictly consumed the study food with 99 ± 6% (mode, 100%; range, 55% to 100%) assurance over the total 92 treatment weeks (ie, the cumulative number of surveys completed). At only two rechecks did owners indicate that cats may have eaten less than 95% of the study food. Both of these cats were in the dissolution food group (ie, Hill's Prescription Diet s/d), and uroliths dissolved in less than 14 days. Adverse events were not observed and urethral obstruction did not occur in any cat (there were seven males and 25 females enrolled in the study). Results of serum biochemistry and CBC remained within their normal ranges during treatment and did not change from pretreatment values.

Results of this study indicate that dietary dissolution is an effective, safe and rapid method of eradicating sterile struvite uroliths from the urinary bladders of cats. Only diagnostic failures (ie, uroliths composed of minerals other than struvite, including four urate and one calcium oxalate) were associated with incomplete urolith dissolution. Our results are in agreement with previous studies that also demonstrated successful urolith dissolution.[2–4] Guidelines are available to help predict urolith mineral composition based on results of diagnostic imaging and urinalysis fndings (Table 1).

This study has several unique strengths. It is the first multicenter, double-masked, randomized, controlled, clinical trial evaluating nutritional dissolution of sterile struvite uroliths. This is also the first study measuring urine pH with a pH meter. Sodium levels exceeding 1.1% of the food on a dry matter basis have been recommended to encourage water consumption producing less concentrated urine and reducing urinary saturation for struvite.[4] The foods evaluated in this study contained less than half that sodium recommendation and were as effective. In fact, in our study, the dissolution food had the shortest mean dissolution time compared with any other published studies using foods with higher sodium content.[3,4] This observation is consistent with reports in healthy cats in which diets with 0.4% to 1.2% sodium on a dry matter basis had no effect on relative supersaturation and activity product ratios for urine struvite, even though urine volume significantly increased with the high-sodium food.[9]

In conclusion, both therapeutic foods were 100% successful in dissolving sterile struvite

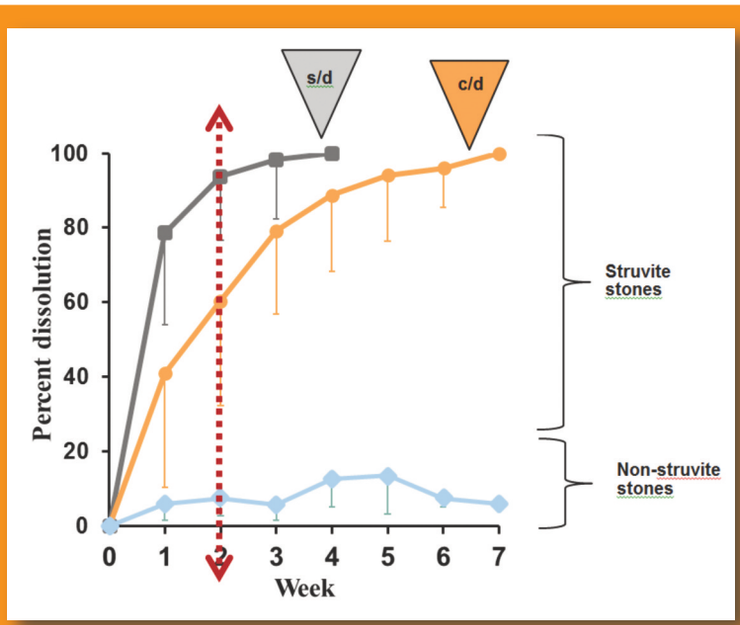
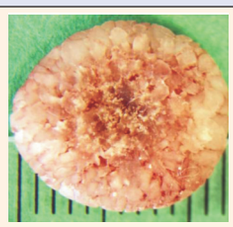
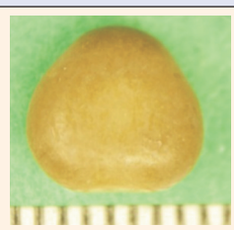
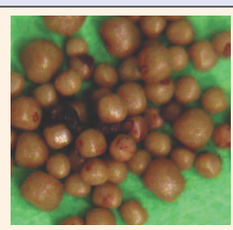
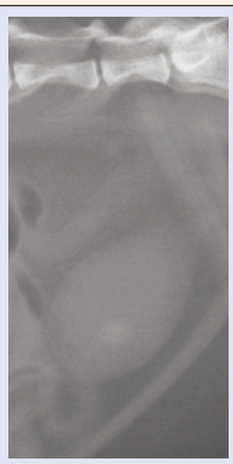
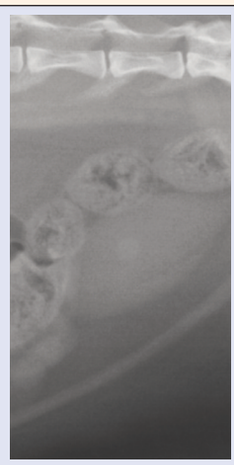
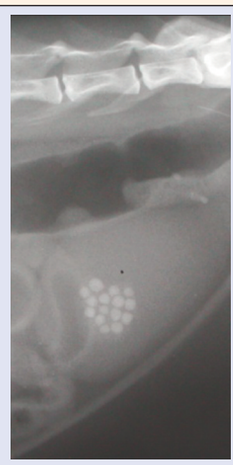
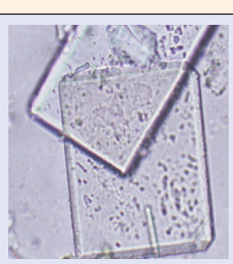
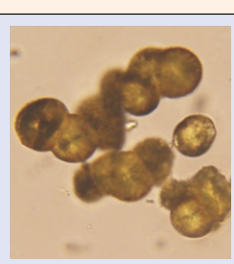
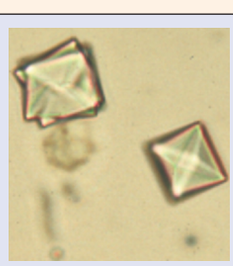


Figure 2 Percentage stone dissolution (mean and SD) by week for cats with struvite uroliths that were treated with either Hill's Prescription Diet s/d Feline (s/d) (n = 16 [squares] or Hill's Prescription Diet c/d Multicare Feline (c/d) (n = 16 [circles]) and five cats fed food either food that had uroliths not composed of struvite (100% ammonium urate (n = 4) or 100% calcium oxalate (n = 1). All cats (n = 32) whose stones were struvite dissolved. Of interest is the observation at two weeks (dashed line); the point at which struvite stones decreased by 35 to 100% irrespective of which treatment diet was feed. Stones that were not struvite had minimal change. Evidence of a marked reduction in stone size at this therapeutic midpoint can be used to support a diagnosis of struvite, and the decision to continue nutritional dissolution therapy

Table 1 Predicting mineral composition of feline uroliths based on radiographic findings and urinalysis

	Struvite	Urate	Calcium oxalate
Prevalence (%)	40 to 50	35 to 45	4 to 6
Physical appearance			
Radiographic appearance			
Radiographic density	Moderately radio-opaque	Usually radiolucent; however, larger uroliths are moderately radio-opaque	Usually very radio-opaque Monohydrate salts have smooth edges; dihydrate salts have irregular sharp edges
Radiographic contour	Smooth to slightly rough edges	Smooth to rough edges	Monohydrate salts have smooth edges; dihydrate salts have irregular sharp edges
Radiographic number	Usually < 3 to 5	Usually <3	Usually > 3 to 5
Microscopic crystalluria			
Description of microscopic crystalluria	Pyramidal to low square	Spherules or amorphous crystals that dissolve in alkaline urine	Double envelope (dipyramidal) of dihyddrate salt, rarely picket fence or dumbbell of monohydrate salt
Urine pH	> 6 to 6.5	< 6 to 6.5	< 6 to 6.5

uroliths in cats. Food selection should be based on individual needs of the patient, management conditions of the household, owners' ability to feed the patient in a multicat household, and the likelihood that owners will remain compliant with diet and follow-up recommendations. Use of a prevention-dissolution food (ie, Hill's Prescription Diet c/d Multicare Feline) eliminates the need to transition cats from a dissolution food to a different long-term maintenance food for prevention, and allows for the convenience of feeding all healthy adult cats in a household a single food. Use of a dissolution food (ie, Hill's Prescription Diet s/d Feline) may be advantageous in situations where a faster rate of dissolution is optimal for patient well-being or when a different food is indicated for

long-term dietary management of other health problems. In the later circumstance, uroliths can be rapidly dissolved with a dissolution food and then the cat transitioned to a food more suitable for treatment of its other health conditions (eg, obesity, inflammatory bowel disease, renal disease, etc). Irrespective of the food selected, we recommend repeating radiographic imaging in two weeks after initiating therapy. At this therapeutic midpoint, our results indicated that when feeding these foods (Hill's Prescription Diet c/d Multicare or s/d), uroliths composed of struvite should be approximately 50% (range = 35% to 100%) smaller (Figure 2). If urolith size has changed minimally, consider the possibility that the owner or patient is not compliant with dietary recommendations, or that uroliths are composed of minerals other than sterile struvite.

Cystotomy remains a common method of urolith removal, and while major complications are rare, minor ones are common.[10,11] Some of these adverse surgical associations can be avoided by selecting nutritional urolith dissolution as your primary method of therapy (Table 2).

Table 2 Benefits of nutritional dissolution compared to surgical urolith extraction

	Nutritional dissolution	Surgical extraction
Efficacy	100%	80%
Cost	Relatively inexpensive	Relatively expensive
Anesthetic risks	None	Potential
Resolution of clinical signs	6–28 days	3–19 days
Potential for suture nidus contributing to recurrence	None	Possible

Key points for applying the study's scientific results to clinical patients in practice

- Medical dissolution of uroliths is safe, effective, cost-effective, rapid and the compassionate choice. Surgical urolith removal may contribute to recurrence by increasing the chance of suture nidus of recurrent stones.
- Use of a prevention-dissolution food (Hill's Prescription Diet c/d Multicare Feline) eliminates the need to transition cats to a long-term prevention food and allows for the convenience of feeding all healthy cats in the same household the same food. In addition to managing struvite related diseases, Hill's Prescription Diet c/d Multicare is a maintenance food for cats.
- Use a dissolution food (Hill's Prescription Diet s/d Feline) when a faster rate of dissolution is optimal for patient well-being (eg, when other types of nutritional therapy are needed; for example, obesity, inflammatory bowel disease, etc). No other food on the market has been shown to dissolve stones faster than Hill's Prescription Diet s/d.
- Urethral obstruction, although possible, was not observed in this or previous studies, and is therefore an unlikely complication of dietary dissolution. Dysuria is a common sign of urethral obstruction in patients with stones. As stones become smaller dysuria is expected to be less, if not existent.
- A gradual transition to therapeutic foods was not needed to ensure patient acceptance. Cats in our study readily accepted an abrupt food change.
- Dry therapeutic foods, which are more commonly preferred by owners and cats, were 100% effective.
- Therapeutic prevention-dissolution foods should be safe and effective for managing other struvite-related disease; for example, minimizing urethral re-obstruction following urethral plug removal, or eliminating struvite crystals in cats with crystal-associated dysuria and inappropriate urination of unknown cause (eg, feline idiopathic cystitis).

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Common diagnostic and treatment pitfalls in cats with uroliths

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Uroliths in cats may be associated with clinical signs (stranguria, pollakiuria, hematuria, periuria or a combination of these) or they may be documented as an incidental finding in some cats. Diagnostic evaluation is indicated to estimate mineral composition of the uroliths and confirm their location, which helps guide treatment recommendations. This article reviews some of the common diagnostic and treatment pitfalls for cats with uroliths.

Urinalysis

For cats with suspected or confirmed uroliths, a baseline urinalysis including sediment examination is advised and urine should be evaluated within 60 minutes of collection to minimize temperature and time-dependent effects on in vitro crystal formation.[1] Studies evaluating urine pH in cats indicate that measurements obtained by a pH meter provide the most accurate results and samples collected at home may also be used.[2] Results of the urinalysis and sediment examination are not specific for urolithiasis in the cat, and must be considered together with all clinical and diagnostic findings. For example, the presence of struvite or calcium oxalate (CaOx) crystals in the urine does not always indicate the presence of uroliths,[3] and may be an incidental finding, or in vitro artifact.[1] Furthermore, crystal type does not always correlate well with urolith type; this means that cats with one crystal type may have uroliths of another mineral type.[4] In addition, cats with uroliths may have no urine crystals identified on sediment examination.

Urate crystalluria in cats might warrant further diagnostics, such as imaging studies and measurement of fasting and post-prandial serum bile acids. The diagnostics selected for a cat with suspected urate uroliths are variable and depend on the cat's age, clinical signs present (including those suggestive for a portosystemic shunt), the presence or absence of abnormalities on a complete blood count and serum biochemical panel, as well as the number of episodes of urate urolithiasis. Cystine crystals are rare in cats and if present, imaging studies are warranted to evaluate for the presence or absence of cystine uroliths.

In addition to being part of the diagnostic evaluation, urinalysis can be helpful for monitoring the effects of the prescribed treatment regimen in patients with urolithiasis. Monitoring the specific gravity is a good parameter to evaluate the cat's moisture intake; anecdotal evidence suggests a urine specific gravity continually <1.025 may help prevent recurrent episodes of urolithiasis; however, this needs further study.

Imaging studies

Abdominal radiographs are very helpful in cats with suspected uroliths and they should be performed in cats with lower urinary tract signs as well as those with azotemia. It is important to perform imaging studies in cats with azotemia to evaluate the patient for lower as well as upper tract urolithiasis (see below). Although ultrasound examination may be more sensitive for detection of uroliths, radiography provides accurate results of size, shape and radiopacity of the urolith.[5] Knowing the radiopacity and shape of the urolith can aid in identification of the mineral composition prior to removal.[6] CaOx- and struvite-containing calculi are radiopaque and, if present, can often be visualized on plain abdominal radiography. It is important that the entire urinary tract be included in this image, so as not to miss calculi in the urethra (Figure 1) or ureters (Figure 2). Struvite uroliths often occur as single, large, elliptical mineral opacities in the urinary bladder, whereas, CaOx often occurs as multiple uroliths and can have distinct 'jagged edges.' Placing a wooden paddle in the area of the urinary bladder and applying gentle compression can help delineate details in this area.

In one retrospective study, urate uroliths (ammonium hydrogen urate) were often identified in cats when evaluating plain abdominal radiographs, even though they were not as radiodense as struvite or CaOx.[4] However, there was a small percentage of cases where the urolith was identified only by ultrasonography and not radiographically.[4] Therefore, radiography as well as ultrasonography should be considered when evaluating cats suspected of urolithiasis. Contrast cystourethrograms can be performed for patients suspected of urolithiasis and this study is excellent for evaluating the urethra of male cats. Advanced imaging techniques such as contrast computed tomography (CT) or cystoscopy usually are not necessary for the identification of uroliths in cats. However, removal of small cystic calculi identified during the cystoscopic procedure may be accomplished by performing Ho:YAG laser lithotripsy and/or basket retrieval through the cystoscope in selected cases.

Ureterolithiasis

The sensitivity of survey abdominal radiography for the diagnosis of ureterolithiasis in cats is 81%.[7] CaOx-containing ureteral calculi are the most common uroliths identified in the upper urinary tract of cats[8] and are most readily identified in the retroperitoneal area on the lateral radiographic projection. Visibility on lateral radiographs alone can lead to difficulty in determining which ureter is involved or whether one or both ureters are affected. Therefore, abdominal ultrasonography is recommended for cats suspected of having ureteroliths; it has a sensitivity of 77%. Although this is lower than plain radiography, ultrasonography can help delineate which ureter is obstructed and the severity of hydronephrosis and hydroureter, if it exists. A combination of survey radiography and ultrasonography has a sensitivity of 90% for the diagnosis of ureterolithiasis, so it is the preferred approach. In subacute ureteral obstructions, ureteral and pelvic dilation may not have yet developed, so it is critical to consider ureteral obstruction as a differential diagnosis in appropriate cases, even when dilation is not present. Additional imaging modalities, such as antegrade pyelography or CT

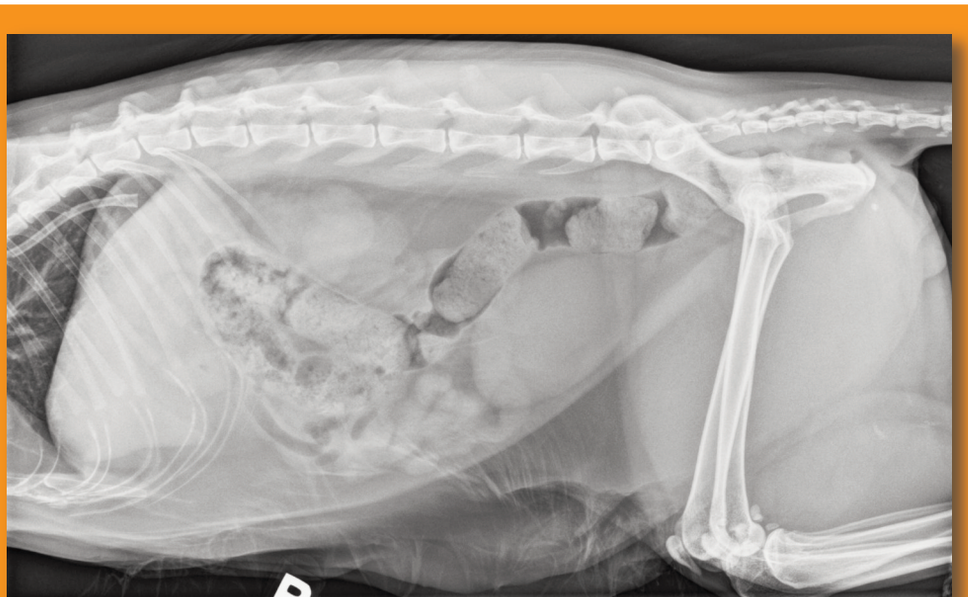

FIGURE 1 Lateral radiographic projection of a middle-aged male castrated cat illustrating the importance of including the entire urinary tract in the field of view. A small radiopaque urethrolith was visible on the radiograph but was not detected using ultrasound

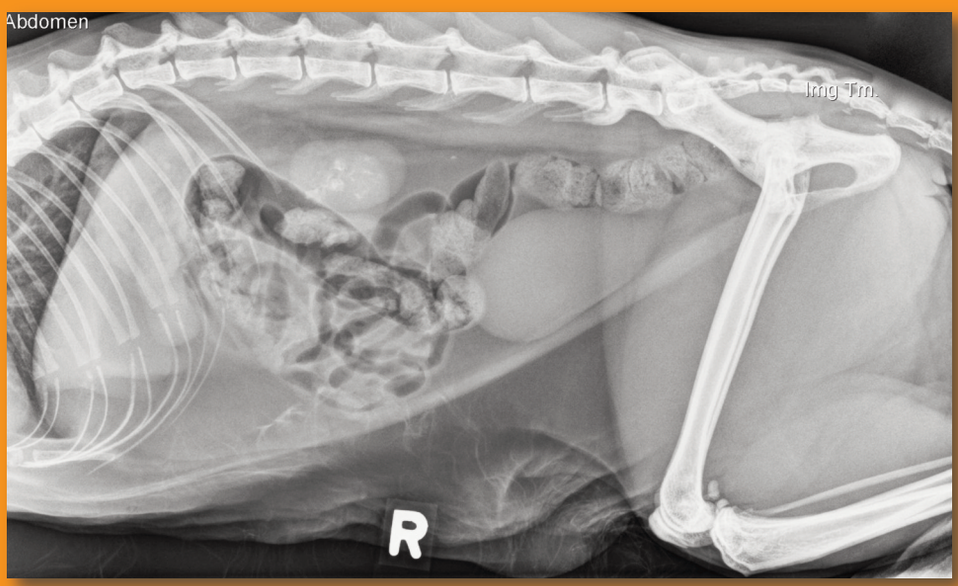

Figure 2 This lateral radiographic projection shows significant renal mineralization as well as a ureterolith. An enema should be performed in this cat to fully evaluate the retroperitoneal area as well as ultrasonography to ascertain if ureteral obstruction is present or not

may be indicated to identify calculi that are not apparent on survey radiography or ultrasonograms. Researchers evaluating imaging techniques in humans[9] reported that CT scan, using the bone window, provided the greatest in vitro accuracy from which actual stone measurements can be estimated; however, the craniocaudal diameter measurement was overestimated. Furthermore, using the soft tissue window overestimated urolith size. Data from our institution confirms that CT (plain or contrast enhanced) did not significantly improve the diagnostic performance for detection of ureteral obstruction in cats.[10]

Therapeutic considerations for feline urolithiasis

It is important to obtain radiographs (or other imaging studies appropriate for the urolith type) prior to recovering the cat from anesthesia to be certain all the uroliths have been removed during the procedure (eg, surgery, voiding urohyrdropropulsion, ureterotomy). Small uroliths can be inadvertently missed. Furthermore, periodic monitoring may allow the clinician to visualize recurrence of uroliths when they are small enough to be removed by minimally invasive procedures. The clinician must also keep in mind that struvite cystouroliths (eg, single elliptical calculus, urinary pH persistently >6.8) can be successfully dissolved with dietary therapy,[11,12] and surgery can be avoided.

When managing ureterolithiasis, conservative non-dietary medical management can be considered, because these are most often comprised of 100% CaOx and no dissolution protocol exists. Therefore, therapies consisting of intravenous fluid diuresis with administration of the diuretic mannitol, with or without other drugs such as alpha antagonists, can be tried. During conservative management it is crucial to critically evaluate patient stability and fluid status. Cats should be monitored by serial measurements of serum creatinine and blood urea nitrogen (BUN) concentrations, and these are often the most sensitive indicators that the obstruction has improved or progressed. It is important to remember that if significant intrinsic renal damage has occurred, passage of the ureteral obstruction does not always lead to immediate improvement in azotemia; in cases with significant kidney disease prior to obstruction, azotemia may persist. Serial radiography and ultrasonography can be useful in monitoring the success of medical management for ureterolithiasis. It has also been reported that uroliths can spontaneously move retrograde back into the renal pelvis rather than passing into the urinary bladder.[13] For cats that have significant increases in BUN, serum creatinine or potassium, or fluid overload at the time of initial examination, more aggressive intervention such as a ureteral stent placement or subcutaneous ureteral bypass surgery is recommended to relieve the obstruction and hopefully preserve renal function.

Summary

The key diagnostic tests for detecting urolithiasis in feline patients are often complementary. Each can help provide essential data including urine composition, presence and location of uroliths and their mineral composition, and consequences that can result from this disease (eg, ureteral obstruction, hydronephrosis). The diagnostic test chosen for each individual patient depends on the number of episodes of clinical signs, owner finances, and availability of equipment. In many cats, plain radiography is a non-invasive, cost effective means for identifying both upper and lower urinary tract uroliths. Keeping in mind the various minerals present within feline uroliths (and their radiopacity) is important when choosing the best therapeutic option for each cat.

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Use of urohydropropulsion, cystoscopy and lithotripsy to manage feline urolithiasis

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Determining the need for urolith removal and effective therapies depends on the effects of the urolith on the patient (asymptomatic, recurrent infection, dysuria, or urinary obstruction), the physical characteristics of the urolith (mineral composition, size, contour, and location), and the familiarity of procedures and availability of equipment to the veterinarian. For example, with additional training and newer technologies (cystoscopy, basket retrieval, and lithotripsy), surgical removal of uroliths is becoming less desirable for both the patient and client (Table 1).

Table1 Methods for urolith removal

	Method	Suitable application	Considerations
Least invasive	**Medical dissolution**	Sterile struvite and infection-induced struvite uroliths are quickly dissolved with special foods and medication at a fraction of the cost of surgery. For more information visit us urolithcenter.org (activate the recommendations tab on the left for a list of therapeutic recommendations based on urolith type)	Sterile struvite uroliths dissolve within weeks. Infection-induced struvite uroliths may take 1–2 months to dissolve. Nephroliths require longer dissolution times than urocystoliths. Urethral obstruction is uncommon during dissolution
	Voiding urohydro-propulsion	To evacuate small to moderate size (≤4 mm) urocystoliths of any composition in female cats. Uroliths with an irregular contour may need to be smaller	Not suitable for male cats, including males with a perineal urethrostomy. Not suitable in cats with an active urinary tract infection. Not suitable for cats with urethral obstruction If the cat has many (> 5) irregular larger (> 3 mm) uroliths, consider basket retrieval. Not suitable for cats that have recently undergone urinary bladder surgery
Most invasive	**Urolith basket retrieval**	To evacuate small to moderate size (≤ 4 mm) urocystoliths of any composition in female cats. Uroliths with an irregular contour may need to be smaller	Performed during cystoscopy. Not suitable for male cats, including males with a perineal urethrostomy. Not suitable for cats with a urethral obstruction

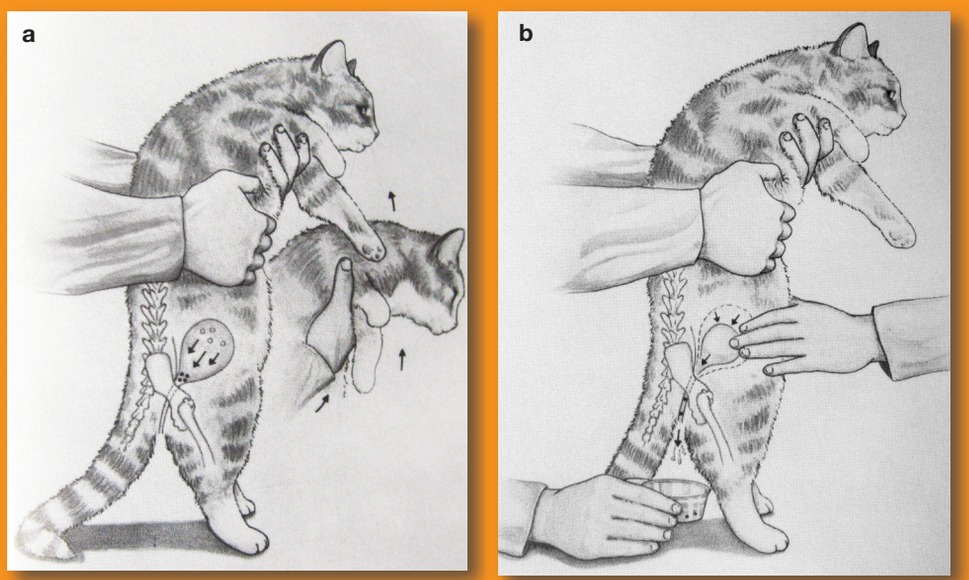


FIGURE 1 (a) To remove urocystoliths by voiding urohydropropulsion the patient is positioned so that the longitudinal axis of the vertebral column is approximately vertical. As a result uroliths move from the ventral portion of the urinary bladder to the urinary bladder neck. (b) To expel urocystoliths, voiding is induced by applying steady digital pressure to the urinary bladder

Voiding urohydropropulsion

Twenty years ago at the University of Minnesota, we developed an innovative technique to remove urocystoliths, called voiding urohydropropulsion (Table 2).[1] By taking advantage of the effect of gravity on urolith position in the urinary bladder and dilation of the urethral lumen during the voiding phase of micturition, this simple technique allowed uroliths to be rapidly flushed out of the urinary bladder (Figures 1 and 2). This procedure is ideal for eliminating recurrent uroliths in patients that are routinely monitored. Detecting recurrent uroliths early, prior to them causing clinical signs, usually indicates that they are small enough to easily void and that the bladder wall is sufficiently healthy to easily accommodate forceful manual expression. Below is a list of important considerations to ensure successful urolith removal:

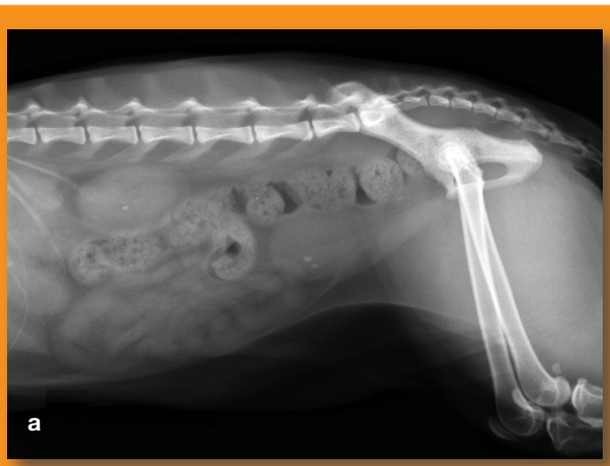
- Choose the right patient. Voiding urohydropropulsion works well in female cats with small urocystoliths (< 4 mm).[1] The urethra in male cats is too narrow to accommodate passage of the uroliths once the diagnosis is made.
- Don't assume that a light plane of anesthesia is sufficient to relax the urethra; full anesthesia beyond the depth necessary to perform an abdominal celiotomy should be utilized.
- This procedure is not suitable for managing uroliths in the urethra. Therefore, using only ultrasound to diagnose uroliths is inadequate to avoid performing voiding urohydropropulsion in cats with urethroliths.[2]
- This procedure is not suitable for managing patients with urethral obstruction or recent urinary bladder surgery; the integrity of the urinary bladder wall has been compromised and may not accommodate safe bladder expression.
- Select cats based on urolith size and your level skill. If you have never performed voiding urohydropropulsion, select cats with smaller (≤3 mm), smooth uroliths, and prepare for cystotomy in case of an adverse event. You should not be concerned about uroliths becoming lodged in the urethra during urinary bladder expression because they are easily flushed back into the urinary bladder for surgical removal.[3]

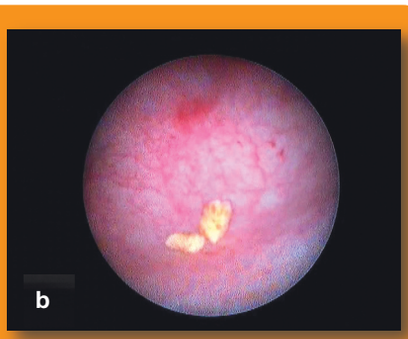
FIGURE 2 To facilitate repositioning of uroliths into the trigone and urinary bladder access for manual expression, the anesthetized cat is supported under the forelegs and positioned such that the patient's back rests against the chest of the holder. Alternatively, the cat can be placed in a V trough, the cat is held secure as the head of the V trough is tilted upward

Basket removal of urocystoliths

Specially-designed baskets are used to remove urocystoliths during cystoscopic evaluation of the urinary bladder (Figure 3). These very slim baskets are inserted through the biopsy channel in the cystoscope. After the urolith is visualized, an opened basket is placed around the urolith and once it is captured, the basket is closed. The urolith is positioned close to the end of the cystoscope, and the urolith and cystoscope are slowly pulled through the urethra as water is flushed to maintain urethra dilation. The process is repeated until all the uroliths have been removed. Urolith diameter and contour are important factors permitting passage of uroliths through the urethra. Below is a list of important considerations to ensure successful urolith removal.

- Choose the right patient. Basket removal of uroliths works well in female cats with smaller uroliths (Table 1). However, the urethral lumen in male cats is too narrow to accommodate





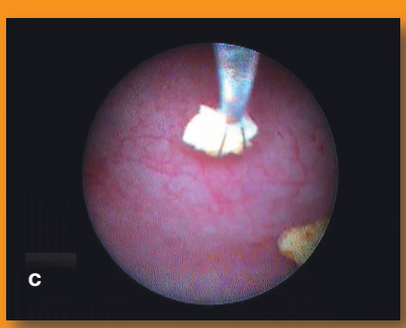


Figure 3 (a) Right lateral radiographic image of the caudal aspect of the abdomen of a 7-year-old female Bengal cat with dysuria obtained during initial examination. Two radio-opaque structures in the urinary bladder measuring 3.7 mm and 2.5 mm in diameter are consistent with a diagnosis of urocystolithiasis. A third structure (2.7 mm) of similar density in the right kidney was consistent with a diagnosis of nephrolithiasis. (b) Cystoscopy performed following general anesthesia of the cat confirmed two urocystoliths in the urinary bladder. (c) A urolith removal basket inserted through the working channel of the cystoscope retrieved the uroliths, permitting their removal through the lumen of the urethra. (d) Retrieved urocystoliths were composed of 100% calcium oxalate

passage of suitable cystoscopes to retrieve uroliths.

- Don't assume that a light plane of anesthesia is sufficient to relax the urethra; full anesthesia beyond the level necessary to perform an abdominal celiotomy is desired.[4,5] This is especially important because the feline urinary bladder is easily traumatized, possibly causing moderate hematuria that minimizes cystoscopic visibility.
- This procedure is not ideal for managing patients with urethral uroliths or urethral obstruction. Uroliths lodged in the urethra are likely too large to be pulled through the narrower portions of the distal urethra.
- Small uroliths inadvertently left during a recent cystotomy are easily removed by basket retrieval; integrity of the urinary bladder wall is sufficient to accommodate cystoscopy but concurrent hemorrhage may minimize cystoscopic visualization.

Laser lithotripsy

The term lithotripsy is derived from the Greek words 'lith' meaning stone, and 'tripsis' meaning to crush. A lithotriptor is a device for crushing or disintegrating uroliths. Extracorporeal shock wave lithotripsy is commonly utilized to fragment uroliths in the upper urinary tract, whereas intracorporeal lithotripsy is commonly used to fragment uroliths in the lower urinary tract via urethrocystoscopy. Although several forms of energy (ultrasonic, ballistic, electrohydraulic, and laser) can fragment uroliths, not all energy forms are suitable for use in companion animals. For example, the probes for ultrasonic lithotripsy are too large to pass through the operating channel of cystoscopes commonly used for cats. When treating humans, the safety and efficacy of electrohydraulic lithotripsy was inferior to Holmium:YAG laser lithotripsy.[6] Because of the versatility and safety of the Holmium:YAG laser, it has become the author's treatment modality of choice for intracorporeal fragmentation of urocystoliths. The Holmium:YAG laser is a thermal device that delivers light energy to the urolith through a special flexible glass (quartz) fiber that is less than a millimeter in diameter. The laser creates a super-heated bubble at the fiber tip. To accurately aim the laser, the quartz fiber is inserted through the biopsy channel of the cystoscope. The tip of the fiber is touching the urolith when the laser is activated. As the laser energy is absorbed by the water in the urolith; the water rapidly expands fragmenting the urolith. This photo-thermal effect is confined to a small space of approximately 1–2 mm in diameter, and therefore does not damage the urinary bladder wall.

Table 2 Steps for performing voiding urohydropropulsion

1 **Anesthetize the patient**	The type of anesthesia selected may vary based on patient considerations. A common mistake is assuming that only a minimal depth of anesthesia is needed. In our experience, the depth of anesthesia needed to perform voiding urohydropropulsion is greater than that needed for routine surgery. Consider the addition of short-acting anesthetics (eg, Propofol, 0.5–1 mg/kg IV) 30 seconds prior to urinary bladder expression, or lumbar epidural anesthesia (0.1–0.2 ml/kg of 2% lidocaine without epinephrine) to facilitate urethral relaxation. Avoid anesthetic drugs likely to increase urethral tone (eg, dexmedetomidine and other adrenergic receptor agonists)
2 **Attach a 3-way stopcock to the end of an 8 Fr urinary catheter and insert catheter into urethra**	The three-way stopcock facilitates control of the volume of fluid entering the urinary bladder and containment of fluid once the urinary bladder is full
3 **Fill the urinary bladder**	Sterile physiologic solutions (lactated Ringer's solution, normal saline) are injected through a transurethral catheter to distend the urinary bladder. If fluid is expelled prematurely around the catheter prior to adequate urinary bladder filling, the vulva and/or urethra can be gently occluded using your thumb and first finger. Placement of additional fluid may not be needed
4 **Position the patient such that the spine is approximately vertical**	Repositioning the patient allows uroliths to accumulate at the neck of the urinary bladder facilitating their expulsion. Anatomically, the urethra does not become vertical until the caudal spine is 20 to 25 degrees anterior of vertical, but this may not be clinically important
5 **Agitate the bladder**	Gently agitating the urinary bladder left and right is performed to dislodge uroliths that may be loosely adhered to the urinary bladder mucosa
6 **Remove the urinary catheter**	
7 **Express the urinary bladder**	Apply steady digital pressure to the urinary bladder to induce urination. Once voiding begins, the urinary bladder is more vigorously compressed. Compress the urinary bladder dorsally and cranially (toward the back and head of the patient). Movement of the urinary bladder caudally toward the pelvis may cause the urethra to kink preventing maximal urethral dilation
8 **Repeat steps 2 through 7**	The urinary bladder is flushed repeatedly until no uroliths are expelled
9 **Medical imaging**	Imaging provides an appropriate method of assessing successful expulsion of uroliths. To enhance detection of remaining small uroliths consider a double-contrast cystography (only the lateral view is needed)

Not all cats are suitable candidates for laser lithotripsy. Below is a list of important considerations to insure successful urolith removal.

- Choose the right patient. This procedure works well in female cats (Table 2). The urethra of male cats is too narrow to accommodate passage of suitable cystoscopes to fragment uroliths using laser lithotripsy.
- Don't assume that a light plane of anesthesia is sufficient to relax the urethra; full anesthesia beyond the level necessary to perform an abdominal celiotomy is desired.
- This procedure is ideal for managing female cats with urethral uroliths or urethral obstruction. Uroliths lodged in the urethra are held in place which facilitates rapid laser targeting and fragmentation.
- Laser lithotripsy is well suited for managing uroliths inadvertently left in the urinary bladder following a cystotomy and therefore, avoids additional surgical incisions.
- Patients with very large uroliths or a large number of uroliths may require longer anesthetic periods to complete removal; therefore, cats with this clinical picture may be better managed with standard surgical urolith removal.

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