

Calcium Oxalate Stones in Cats & Dogs
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Management of Calcium Oxalate Uroliths in Cats and Dogs

Management of CaOx uroliths for dogs and cats is very similar and therefore this section will focus on the management of these stones for both species. There is no dissolution protocol for CaOx uroliths, so removal and quantitative mineral analysis of the stones should be performed if they are growing or causing clinical disease. Less invasive techniques are now available for stone removal including voiding urohydropropulsion, Holmium: YAG laser lithotripsy, basket retrieval through the cystoscope, and laparoscopy with or without the use of the laser. After the CaOx (or any urolith) has been removed, it should be submitted for a complete quantitative crystallographic analysis.

Animal related factors should be addressed initially to ascertain that no intrinsic predisposing problems are present. If serum calcium concentration is elevated, a search should be initiated for underlying causes such as primary hyperparathyroidism, neoplastic processes and idiopathic hypercalcemia in cats.¹ Research in rats suggests that elevated lipids may play a role in CaOx urolith formation² therefore screening animals to evaluate fasted serum triglycerides concentration may be warranted, particularly in breeds prone to hyperlipidemia such as the miniature schnauzer. A baseline urinalysis and urine culture should be performed with special attention given to the evaluation of the urine specific gravity and urine sediment. Urine samples should be analyzed within 60 minutes of collection to minimize temperature- and time-dependent effects on in vitro crystal formation. Presence of crystals observed in stored samples should be reevaluated by analyzing a fresh sample.³

A diet high in moisture is recommended to decrease the urine concentration of mineral precursors. This can be achieved most easily by feeding a canned diet. Alternatively, water can be added to the dry kibble to achieve higher moisture content if the pet will not consume a canned diet, although 85% moisture is difficult to attain using this method. Gradual introduction of the high moisture diet is important to prevent initial diarrhea. In one study⁴ feeding a high moisture diet significantly reduced the relative supersaturation of CaOx in healthy miniature schnauzers. Other studies suggest that dogs that consumed diets highest in moisture were six times less likely to form CaOx uroliths as compared with control dogs.⁵ If the animal does not accept and tolerate an increase in dietary moisture content, attempts can be made to increase voluntary water intake by using drinking fountains, and by adding flavored juices (ham, tuna) or ice cubes to the pet's drinking water. As an initial guideline, a specific gravity of <1.020 for dogs and <1.025 for cats seems reasonable. Urine specific gravity should be monitored at periodic reevaluation until the adequacy of the current strategy is assessed. Urine specific gravity should be evaluated from home samples to gain a better understanding of owner compliance and water intake in the home environment.

The addition of sodium chloride (salt) to the diet is another method of increasing voluntary water intake. Current recommendations for appropriate salt intake in animals with prior CaOx uroliths are controversial, but sodium chloride supplementation has been reported to increase urinary calcium excretion and increase the risk for CaOx uroliths in people.⁶ Caution should be practiced if using dietary salt supplementation to manage lower urinary tract signs, particularly in animals with reduced renal function, cardiac disease or hypertension. After utilizing strategies to increase the moisture content of the diet, if the urine is still too concentrated and /or urine sediment findings

are not ideal, one can try the addition of salt to the diet to increase the urine volume produced daily. A series of studies using healthy dogs showed no effect of added dietary salt on urine calcium or oxalate concentrations⁴ Studies have also shown that increasing the dietary sodium content resulted in a decrease in the CaOx relative supersaturation (RSS) in both miniature schnauzers (a breed predisposed to CaOx urolithiasis) and Labrador retrievers (a breed thought to be at lower risk of CaOx urolithiasis). No increases in urinary calcium concentrations were found in either breed when dietary sodium concentrations as high as 3 grams/1000kcal were fed.¹⁶ No adverse effects of added sodium chloride have been noted in *short term* studies in healthy cats.^{7,8,9}

Several commercially available canine and feline therapeutic diets are marketed as assisting to reduce the recurrence of CaOx uroliths. A diet that is restricted in both calcium and oxalate seems logical for animals prone to CaOx urolithiasis, but no evidence based studies in dogs or cats with naturally occurring disease are available to support or refute this recommendation. Moreover, higher intake of dietary calcium appears to decrease the risk for symptomatic kidney stones in humans. Stevenson, et al, evaluated the effects of dietary calcium and oxalate content when fed to stone forming (Miniature Schnauzers) and normal dogs.¹⁰ The lowest level of dietary calcium and oxalate resulted in the lowest CaOx RSS. The high calcium, low oxalate diet resulted in the highest CaOx RSS, a low calcium diet with increased dietary oxalate also tended to increase CaOx RSS although the results were highly variable. Urinary oxalate increased, although inconsistently, with increased dietary oxalic acid only when dietary calcium was low. In the intestine, non-absorbed dietary calcium is available to form complexes with phosphate, citrate, sulfate and oxalate, in turn preventing their absorption. Thus, the timing of calcium intake with intake of other nutrients may also influence stone formation, and this effect may be different between animals with CaOx urolithiasis and healthy animals. Reducing the dietary content of only one of the CaOx precursors could potentially increase the intestinal absorption and urinary excretion of the other. As with excess calcium, foods rich in oxalate or oxalate precursors should also be avoided. For a list of the oxalate content of foods, please see the Oxalosis and Hyperoxaluria Foundation website: <http://www.ohf.org/diet.html>.

Another nutrient to consider in the dietary management of CaOx urolithiasis is magnesium. Urinary magnesium, as along with urinary citrates and phosphates, are thought to act as inhibitors of CaOx urolith formation and therefore should not be restricted in the diet. Dietary phosphorus should not be excessively restricted because reduced serum phosphorus could result in increased activation of vitamin D₃ to calcitriol by 1- α -hydroxylase in the kidney under the action of PTH and result in increased intestinal absorption of calcium.^{11,12} Avoidance of Vitamin C supplementation is recommended in humans, because it is a metabolic precursor of oxalate. A moderate to slightly increased protein content may also be beneficial to prevent calcium oxalate urolith formation. Recent epidemiologic studies have suggested that increased protein intake may be protective, likely because of protein associated increases in urine volume.¹³ Protein restriction does not seem warranted as a dietary strategy for the management of canine or feline CaOx urolithiasis.

Lastly, as mentioned above dietary fats have been speculated to be involved in CaOx stone formation in rats and humans. Although the pathogenesis of CaOx stone formation in dogs and cats, may differ, it may be prudent to feed dogs with an elevated fasting serum triglyceride concentration and/or pancreatitis a low fat commercially available canned diet (or low fat home cooked diet) with water added to assist with reducing urine specific gravity .

If dietary manipulations are unsuccessful in preventing CaOx urolith recurrence alone, drug therapy may provide additional benefit. Administration of citrate as potassium citrate (Urocit-K®) could be helpful because urinary citrate may act as an inhibitor of calcium oxalate formation. Hypocitraturia may be a risk factor for calcium oxalate stone formation in humans because citrate can become chelated to calcium, forming a more soluble salt than CaOx in the urine. This additive appears beneficial only to humans where citrate excretion is low. The recommended dosage of potassium citrate is 100-150 mg/kg/day for both cats and dogs, but it is unclear if this dosage will actually increase urinary citrate in cats. Dogs generally excrete much less citrate than humans¹⁴ (only about 3% of filtered citrate is excreted by dogs as compared with 10-35% in humans) so what, if any, benefit citrate supplementation has on calcium oxalate formation in this species is, as yet, undetermined.

Hydrochlorothiazide is a diuretic which decreases urine calcium excretion in humans and has been recommended to prevent recurrence of CaOx urolithiasis in dogs. A study in dogs reported that hydrochlorothiazide significantly reduced urine calcium excretion.¹⁵ The hypocalciuric effect of this drug may be negated with augmentation of oral fluid intake. A recent abstract was also published evaluating the effects of hydrochlorothiazide and calcium excretion in healthy cats.¹⁶ The administration of hydrochlorothiazide is contraindicated in cats or dogs with hypercalcemia.

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FELINE IDIOPATHIC CYSTITIS

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Objective: to review the pathophysiology of feline idiopathic cystitis and discuss how these findings relate to current treatment strategies.

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

Pathophysiology:

Research on the bladder of cats with FIC has shown that histological changes are generally nonspecific, and may include an intact or damaged urothelium with submucosal edema, dilation of submucosal blood vessels with marginated neutrophils, submucoal hemorrhage, and sometimes increased mast cell density.¹ Based on our experience, no correlation between histology and cystoscopic lesions and clinical signs appears to exist in cats. Preliminary research evaluating urodynamics in cats with FIC have shown no evidence of overactive bladder and occasional findings of decreased compliance have been noted (unpublished data). Studies evaluating bladder permeability have shown marked increases in permeability after hydrodistention² and increased bladder permeability to sodium salicylate in cats with FIC³ and may be mediated via the sympathetic nervous system. Sympathoneural-epithelial interactions appear to play an important role in permeability. For example, Birder, et al.,⁴ have shown that application of NE to urinary bladder (UB) strips induces release of nitric oxide from UB epithelium. Application of capsaicin results in release of nitric oxide from epithelium as well as nervous tissue in the UB. In light of reports that nitric oxide may increase urothelial permeability^{5,6} these results suggest that some of the sympathetically mediated alterations in permeability may be mediated by NE via this mechanism.

Clinical signs of FIC can wax and wane and appear to be exacerbated by stressful circumstances. In previous studies in cats with FIC, we found they had a significant increase in tyrosine hydroxylase (TH) immunoreactivity in the brainstem (locus coeruleus)⁷ as well as the paraventricular nucleus of the hypothalamus.⁸ TH is the rate-limiting enzyme of catecholamine synthesis. The increased THIR observed in the LC of cats with FIC may provide a clue to the observation that clinical symptoms of FIC follow a waxing and waning course, and can be aggravated by environmental stressors. When evaluating catecholamine concentrations [CCE] in these cats we found plasma DOPA, NE, and DHPG concentrations were significantly increased in FIC cats at all times ($p < 0.05$), no differences between groups were identified in cortisol:creatinine. The marked increment in [DOPA] suggests the possibility of a stress-induced increase in activity of tyrosine hydroxylase (TH), the rate-limiting step in CCE synthesis. In contrast, no effects on urine cortisol:creatinine were identified, suggesting an uncoupling of these two parameters of the stress response

In addition to SNS, we have also found a decreased functional sensitivity of the alpha-2 adrenoceptors (α -2 AR) in cats with FIC.^{9,10} Furthermore, we have identified abnormalities in the hypothalamic-pituitary-adrenal axis (HPA). After a high dose (125 ug) of synthetic ACTH was administered, cats with FIC had significantly decreased serum cortisol responses

compared to healthy cats (figure one).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 from healthy cats. Therefore, it appears that while the sympathoneural system is fully activated in this disorder, the HPA axis is not.

The pathophysiology of FIC is likely involves complex interactions between a number of body systems. Abnormalities are not localized just to the bladder, but are present in the nervous, endocrine, and even cardiovascular systems.¹² How these systems communicate and manifest as FIC in some cats, but not in others remains to be determined. It is important for clinicians to understand that this syndrome is not just a “bladder disease” amenable to simple diet or drug therapies in order to better treat their patients.

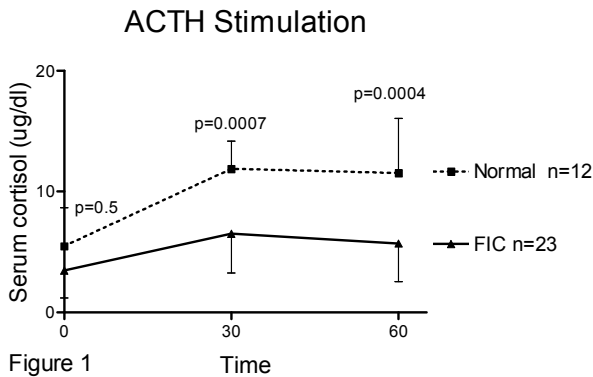


Figure 1

Approach to the Patient Diagnostics

Because FIC is a diagnosis of exclusion, diagnostics should be performed to rule out other causes of LUTS mentioned above. Urolithiasis can occur in approximately 12-15%¹³ of cats with LUTS and an abdominal radiograph which includes the entire urinary tract should be performed. Less than 2% of young (<10 years of age) cats have true bacterial cystitis, so urine culture is a low yield test.^{13,14} Quantitative urine culture should be performed in all cats with recurrent (>2) episodes. The possibility of a urinary tract infection increases with age, perineal surgery, in the presence of cystic calculi, and dilute urine.¹⁵ A contrast cystogram and urethrogram can be helpful to better evaluate for the presence of non-radiopaque calculi and other lesions such as mass lesions, blood clots, and strictures in those cats with recurrent episodes. If clinical signs continue, despite therapy, an abdominal ultrasound, double contrast cystourethrogram, and/or cystoscopy can be performed to be sure no other lesions in the lower urinary tract were missed. Contrast studies are especially indicated in elderly cats (>10 years of age) where FIC is not as likely.

Treatment of FIC

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

When a cat presents with LUTS, analgesic therapy seems appropriate for the acute management of the disease. Providing analgesia with non-steroidal anti-inflammatory agents such as carprofen and ketoprofen, or butorphanol or more potent opioids such as fentanyl (patches) has been suggested, but no studies have been reported to date, and many drugs are not approved for these uses. Breaking the chronic pain-inflammation cycle may be important in the management of at least some cats with severe disease.

Multimodal Environmental Modifications (MEMO)

Based on previous findings where catecholamines decreased after environmental modifications in research cats¹⁶ evaluation of client-owned cats with idiopathic cystitis implementing multimodal environmental modification (MEMO) as the sole management strategy was evaluated. In an observational study we evaluated forty- six client owned indoor-housed

cats with FIC. In addition to their usual care, clients were offered recommendations for MEMO based on a detailed environmental history. Cases were followed for ten months by client contact to determine the effect of MEMO on LUTS and other signs. Significant ($p < 0.05$) reductions in LUTS, fearfulness, nervousness, signs referable to the respiratory tract, and a trend ($p < 0.1$) toward reduced aggressive behavior were identified.¹⁷ These results suggest that MEMO is a promising adjunctive therapy for indoor-housed cats with LUTS.

Following a staged approach to therapy which begins with client education and MEMO seems beneficial in many cats with FIC. If a patient relapses, these topics are thoroughly reviewed and additional changes are implemented. In multi-cat houses, cats also interact with each other. Addressing inter-cat issues seems very important in the management of this disease as well.

Dietary Therapy

Some dietary modifications may reduce the risk of recurrence of LUTS in affected cats. Efforts to acidify the urine using dry foods have no demonstrated value in treatment of cats with FIC. There is no known benefit of acidifying the urine or restricting magnesium in cats with FIC. We do encourage increasing water intake, and consumption of a canned food is one way to accomplish this. It has been reported that LUT signs recurred in only 11% of affected cats during one year of feeding the canned formulation of a dietary product designed to result in production of slightly acidic urine. Recurrence occurred in 39% of cats fed the dry formulation of the same food, suggesting that both constancy and consistency (i.e., increased water intake) may be important, but the reasons for this effect remain to be determined. Suggestions for MEMMO and transitioning diets in cats can be found at the following website: indoorcat.org.

Pheromones and Drug Therapy

Pheromones are fatty acids that seem to transmit highly specific information between animals of the same species. Although the exact mechanisms of action are unknown, pheromones reportedly induce changes in both the limbic system and the hypothalamus that alter the emotional state of the animal.¹⁸ Feliway® (Ceva Sante Animale, Libourne, France), a synthetic analogue of this naturally occurring feline facial pheromone, was developed in an effort to decrease anxiety-related behaviors of cats. Treatment with this pheromone has been reported to reduce the amount of anxiety experienced by cats in unfamiliar circumstances, a response that may be helpful to these patients and their owners. Although a statistically significant difference was not found when Feliway was compared to placebo in cats with FIC, cats that had feliway used in the environment had a trend for fewer bouts of cystitis, and reduced negative behavioral traits.¹⁹ Increased grooming and food intake in hospitalized cats²⁰ also has been reported with the use of Feliway®.

Amitriptyline, (a tricyclic antidepressant (TCA)) has also been reported in uncontrolled trials to successfully decrease clinical signs of severe, recurrent FIC.²¹ Amitriptyline (Elavil®, 2.5-5mg per cat SID), may provide analgesia by inhibition of NE reuptake at noradrenergic nerve terminals,²² and possibly due to inhibition of a wide range of nociceptive neurons in the spinal trigeminal nucleus.²³ Urine retention through anticholinergic effects of the TCA's may result. Findings in a series of cats with severe FIC showed that the clinical signs of some cats were reduced during amitriptyline treatment during a 12- month period.

Clomipramine (Clomicalm®, veterinary label; and Anafranil®, human label) is also a tertiary amine like amitriptyline, but has more selectivity for blocking the reuptake of 5-HT. We have prescribed this in recurrent cases of FIC with anecdotal improvements in some patients. Other drugs such as fluoxetine (Prozac®) has been reported to help cats with inappropriate urinations with variable success rates.²⁴ Fluoxetine was used to help decrease the rate of urine marking after environmental alterations such as litter box hygiene and appropriate cleaning strategies.

Amitriptyline should not be used for acute treatment of FIC since it has been shown to have minimal to no benefit in the short-term resolution of signs in cats with FIC. All TCAs, as well as the selective serotonin reuptake inhibitors should only be considered for recurrent, severe cases. These drugs need to be used only after environmental strategies, diet changes (if necessary), and behavior modifications have failed.

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