ADVANCES IN MANAGEMENT OF

Feline Lower Urinary Tract Disease

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Hill's

ADVANCES IN MANAGEMENT OF FELINE LOWER URINARY TRACT DISEASE:

Efficacy Of Nutritional Struvite Dissolution In Cats

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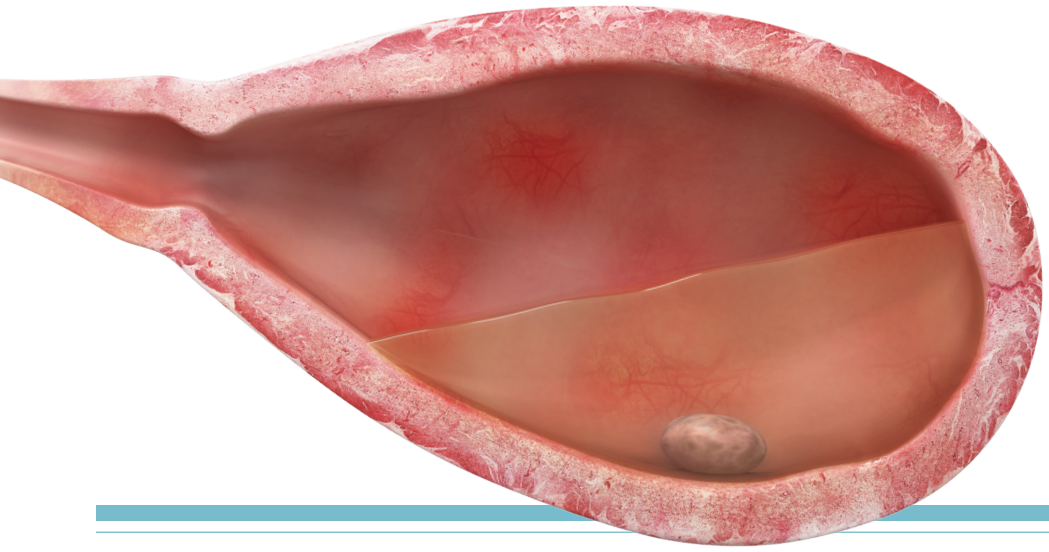
Successful dietary dissolution of a naturally-occurring struvite urolith in a cat was first reported in 1983. Since that time, three additional case series have been published demonstrating the efficacy of prescription foods to dissolve struvite uroliths.[1-3] Despite the unprecedented success associated 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:

1. surgery averts an impending urethral obstruction
2. surgery averts prolonged discomfort during protracted dissolution
3. surgery resolves the problem immediately
4. surgery resolves the clinical signs immediately
5. surgery avoids having to predict mineral composition
6. surgery is more appropriate because it is more successful than nutritional dissolution
7. surgery eliminates the worry of diet acceptance by the patient
8. familiarity with surgical techniques makes it easier for the clinician

The following is a description of our study[4] 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.[5,6] 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.[7] 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 (i.e., buprenorphione).

Cats entering the study were randomly assigned to one of two treatment groups. One group was fed a prevention-dissolution food (i.e., Hill's® Prescription Diet® c/d® Multicare) and the other group was fed a dissolution diet (i.e., Hill's® Prescription Diet® s/d® Feline Dissolution). 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 (grey 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 8-week study. The primary endpoint with respect to treatment (i.e., 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.

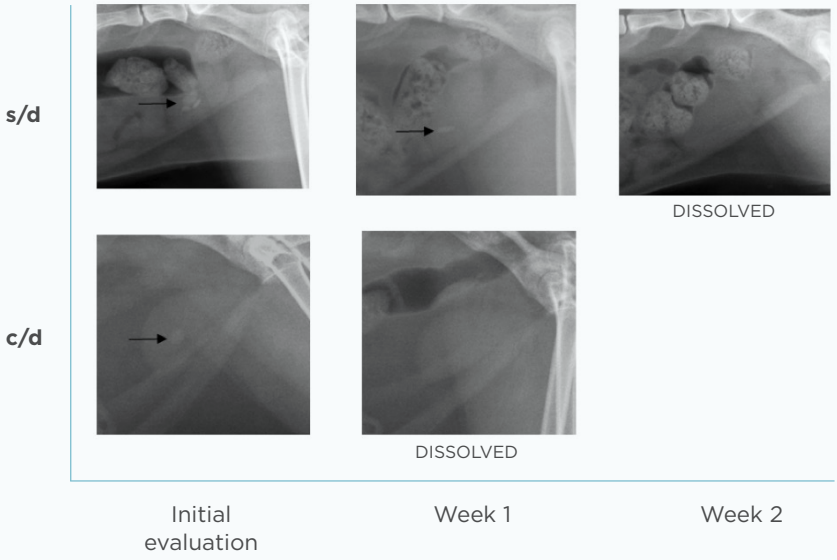
RESULTS AND DISCUSSION

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 (5 male and 11 female) were fed the prevention-dissolution food (Hill's® Prescription Diet® c/d® Multicare) and 16 (2 male and 14 female) were fed the dissolution food (Hill's® Prescription Diet® s/d® Feline Dissolution). 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% assurance over the total

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 Dissolution dry and a 5-year-old female domestic shorthair cat (lower row) whose uroliths were managed with Hill's® Prescription Diet® c/d® Multicare dry. Radiographs were obtained during initial examination and each subsequent week until uroliths were no longer radiographically visible.

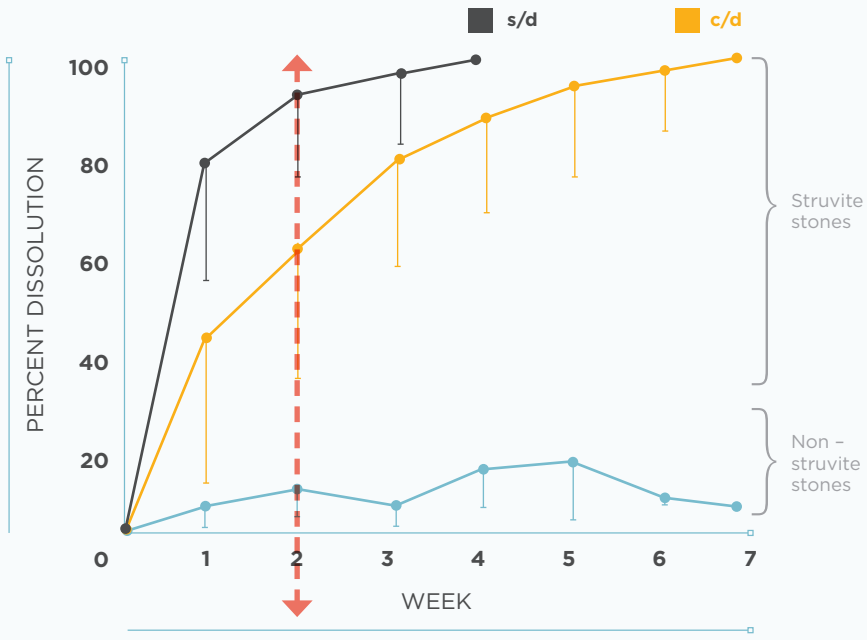


92 treatment weeks (i.e., the cumulative number of surveys completed). At only two rechecks did owners indicate that cats may have eaten less than 95% of the study food. Both of these cats were in the dissolution food group (s/d), and uroliths dissolved in less than 14 days. Adverse events were not observed. Urethral obstruction did not occur in any cat (there were 7 males and 25 females enrolled in the study). Serum biochemistry and CBC values 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 (i.e., uroliths composed of minerals other than struvite; 4 urate and 1 calcium oxalate) were associated with incomplete

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 Dissolution (n=16 [squares]) or Hill's® Prescription Diet® c/d® Multicare (n=16 [circles]) and 5 cats fed 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 2 weeks (dashed line); the point at which struvite stones decreased by 35 to 100% irrespective of which treatment diet was fed. 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.



urolith dissolution. Our results are in agreement with previous studies which also demonstrated successful urolith dissolution.[1-3] This study has several unique strengths. This 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 considered important to encourage water consumption producing less concentrated urine and reducing urinary saturation for struvite. 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 to any other published studies using foods with higher sodium content.[2,3] 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.[8]

In conclusion, both therapeutic foods were 100% successful in dissolving sterile struvite uroliths in cats. Which food to feed should be based on the individual needs of the patient, management conditions of the household, owner's ability to feed the patient in a multi-cat household, and the likelihood that the owner will remain compliant with diet and follow-up recommendations. Use of a prevention-dissolution food (i.e., c/d Multicare) 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 (i.e., s/d Feline Dissolution) 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 latter 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 (e.g., 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 Hill's® Prescription Diet® s/d® Feline Dissolution), uroliths composed of struvite should be approximately 50% (range = 35% to 100%) smaller. 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.[9,10] Some of these adverse surgical associations can be avoided by selecting nutritional urolith dissolution as your primary method of therapy (**TABLE 1**).

TABLE 1

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
EMOTIONALLY DISRUPTIVE HOSPITALIZATION OF PATIENT	Negligible	Major

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 (c/d Multicare) 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, c/d Multicare is a maintenance food for cats.
- Use a dissolution food (s/d Feline Dissolution) when a faster rate of dissolution is optimal for patient well-being (e.g., when other types of nutritional therapy are needed; for example, obesity, inflammatory bowel disease, etc.). No other food on the market dissolves stones faster than 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 cause of urethral obstruction in patients with stones. As stones become smaller dysuria is expected to be less, if not existent.

- A gradual transition to prescription foods was not needed to ensure patient acceptance.
- Dry therapeutic foods, which are more commonly preferred by owners and cats, were 100% effective. Cats in our study readily accepted an abrupt food change.
- 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 (FIC).

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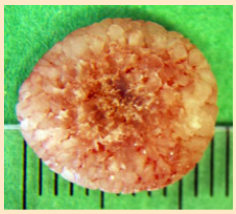
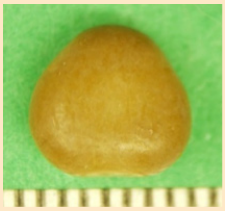
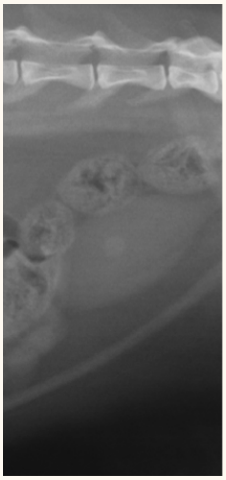
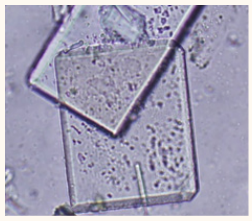
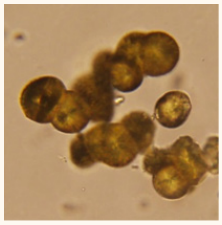
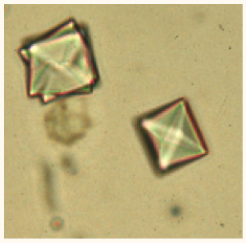
FIGURE 3: EFFICACY OF NUTRITIONAL STRUVITE DISSOLUTION IN CATS

ACCURATELY PREDICTING MINERAL COMPOSITION OF FELINE UROLITHS

	STRUVITE	URATE	CALCIUM OXALATE
PREVALENCE	40 to 50	35 to 45	4 to 6
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 that dissolve in alkalized urine	Double envelope (dipyramidal) of dihydrate salt, rarely picket fence or dumbbell of monohydrate salt
URINE pH	>6 to 6.5	<6 to 6.5	<6 to 6.5

ADVANCES IN MANAGEMENT OF FELINE LOWER URINARY TRACT DISEASE:

Management of Feline Idiopathic Cystitis: Facts, Fads, Fallacies

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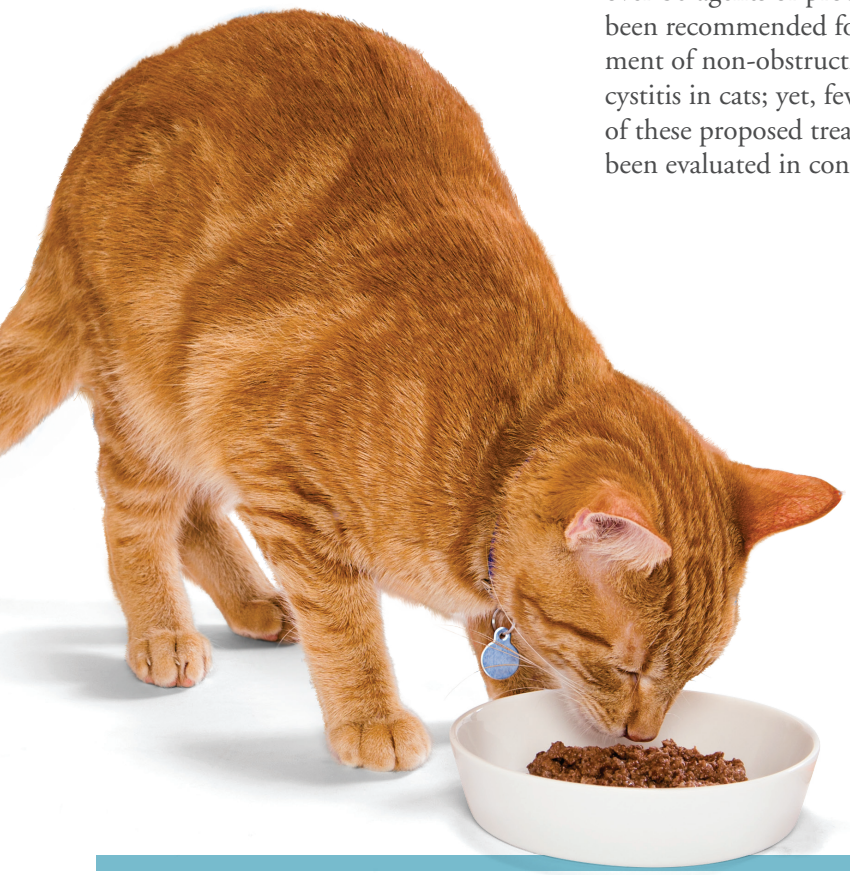

INTRODUCTION

In approximately 65% of non-obstructed male and female cats with naturally occurring lower urinary tract disease, the exact cause(s) of hematuria, dysuria, pollakiuria, stranguria and periuria are still unknown.[1-3] After appropriate diagnostic evaluations, these cats are classified as having idiopathic feline lower urinary tract disease or idiopathic cystitis. In the past decade, over 80 agents or procedures have been recommended for management of non-obstructive idiopathic cystitis in cats; yet, fewer than 10% of these proposed treatments have been evaluated in controlled clinical trials (**TABLE 1**). Debate surrounding the efficacy of various treatments is confounded by the self-limiting nature of clinical signs associated with the majority of cases of idiopathic cystitis. 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 idiopathic cystitis underscores the need for controlled, prospective, double-blinded clinical studies in order to prove the efficacy and safety of various forms of therapy.

WHAT IS THE BIOLOGICAL BEHAVIOR OF IDIOPATHIC CYSTITIS?

Periuria, pollakiuria, stranguria and gross hematuria are the most common clinical signs observed in cats with non-obstructive idiopathic cystitis. Remarkably, these clinical signs subside within 1-7 days without therapy in up to 91% of cats with acute non-obstructive idiopathic cystitis.[4-7] Signs may recur after variable periods of time and again subside without treatment. Approximately 40% to 65% of

TABLE 1

THERAPEUTIC AGENTS OR PROCEDURES advocated by veterinarians for management of non-obstructive feline idiopathic cystitis over a 10-year period from 2003 to 2013 (compiled from the Veterinary Information Network, www.vin.com). Therapies that have been evaluated by controlled clinical trials are indicated by an asterisk (*).

ANTI-INFLAMMATORIES/ ANALGESICS	ANTIDEPRESSANTS/ ANXIOLYTICS	ANTIMICROBICS	MISCELLANEOUS
Prednisolone*	Amitriptyline*	Doxycycline	Parenteral fluids*
Methylprednisolone	Nortriptyline	Enrofloxacin	Furosemide
Dexamethasone	Imipramine	Amoxicillin	Megesterol acetate
Piroxicam	Clomipramine	Amoxicillin/clavulinate	Hydroxyzine
Meloxicam	Fluoxetine	Cefovecin	Cyproheptadine
Ketoprofen	Paroxetine	Chloramphenicol*	Trimeprazine
Carprofen	Diazepam		Cormolyn
Tolfidine	Oxazepam		Arginine
Tepoxalin	Alprazolam		Hydrodistension
Dimethyl sulfoxide	Buspirone		
Zafirlukast			
Montelukast	**ANTISPASMODICS**	**DIETARY MANAGEMENT**	**ALTERNATIVE MEDICINE**
Butorphanol	Propantheline*	Canned diets*	Acupuncture
Buprenorphine	Oxybutynin	Supplemental water	Colloidal silver
Oxymorphone	Aminopentamide	Acidifying diets	Laser therapy
Fentanyl	Atropine	Hypoallergenic diets	Cantharis
Tramadol	Acepromazine	Omega-3 fatty acids	Terebinthia
	Prazosin	Antioxidants	Marshmallow root
	Phenoxybenzamine	L-tryptophan	Parsley root
	Dantrolene	Alpha-casozepine	Uva uris leaf
	Flavoxate		Corn silk
ENVIRONMENTAL MANAGEMENT		**GLYCOSAMINOGLYCANS**	Dandelion
Environmental enrichment		Pentosan polysulfate*	Polyporus mushroom
Litter box management		Glucosamine*	Others
Facial pheromone*		Chondroitin sulfate	
		Polysulfated GAG	
		Hyaluronate	

cats with acute idiopathic cystitis will experience one or more recurrences of signs within one to two years.[4-7] Recurrent episodes of acute idiopathic cystitis tend to decrease in frequency and severity as cats become older.[7] Though recurrent clinical signs in patients with idiopathic cystitis are often assumed to be recurrence of the original disease, recurrent signs may also be the result of a delayed manifestation of the original disease (e.g., spontaneous or iatrogenic urethral stricture), or onset of a different lower urinary tract disease associated with similar clinical signs (e.g., urolithiasis).

We have also encountered a small subset of cats with idiopathic cystitis in which clinical signs persisted for weeks to months or are frequently recurrent. These cats are classified as having chronic idiopathic cystitis. In our experience, less than 15% of cats evaluated because of acute idiopathic cystitis will develop chronic forms of the disease. Whether chronic idiopathic cystitis 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 ARE POTENTIAL SEQUELAE OF IDIOPATHIC CYSTITIS?

Urethral obstruction and formation of vesicourachal diverticuli are potential sequelae of idiopathic cystitis.[2,3,5,8-10] While macroscopic vesicourachal diverticuli are often self-limiting, urethral obstruction is a serious and potentially life-threatening complication. Urethral obstruction in cats with idiopathic cystitis may result from:

1. inflammatory swelling of the urethra
2. urethral muscular spasm
3. reflex dyssynergia
4. intraluminal accumulations of sloughed tissue, inflammatory cells, or red blood cells
5. formation of matrix-crystalline urethral plugs[2,3,5,9,10]

We have hypothesized that formation of matrix-crystalline urethral plugs in cats with idiopathic cystitis occur as a result of cystitis-induced increased inflammatory matrix production in conjunction with a concomitant, but etiologically unrelated, crystalluria.[10] Supporting this hypothesis is the observation of recurrent episodes of non-obstructive hematuria and dysuria, and episodes of plug-induced urethral obstruction in cats with idiopathic cystitis.[9] These observations suggest that male cats with idiopathic cystitis and concomitant crystalluria are at risk for formation of matrix-crystalline urethral plugs and urethral obstruction.

WHAT IS THE ROLE OF NUTRITION IN MANAGEMENT OF IDIOPATHIC CYSTITIS?

OVERVIEW

The goals of treatment of cats with idiopathic cystitis 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 these signs, and the risk for urethral obstruction. Nutritional factors may potentially influence expression of feline idiopathic cystitis (FIC) and its sequela by:

1. decreasing urine concentrations of pro-inflammatory mediators and crystallogenic minerals
2. increasing urine concentrations of anti-inflammatory/pro-resolving mediators and crystallization inhibitors
3. increasing solubility of crystalloids in urine
4. decreasing retention of crystals within the lower urinary tract
5. minimizing potential management- or environment-induced risk factors (e.g., stress)

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

1. thorough diagnostic evaluation to exclude other causes of lower urinary tract disease
2. client education emphasizing the biological behavior of the disease and lack of controlled studies demonstrating efficacy of many proposed therapies
3. consideration of use of pharmacologic agents to reduce the severity and duration of clinical signs

4. strategies to minimize urethral obstruction
5. strategies to minimize risk of recurrences
6. avoidance of iatrogenic disease

We approach treatment of cats with acute idiopathic cystitis 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 idiopathic cystitis typically have concentrated and acidic urine.[1,7] The prevalence and magnitude of crystalluria is variable; however, the prevalence of crystalluria in cats with idiopathic cystitis 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 idiopathic cystitis, 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.[11] 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 idiopathic cystitis was evaluated in a non-randomized, open, prospective study.[12] Signs of lower urinary tract disease recurred in 11 of 28 (39%) cats fed the dry diet, and in 2 of 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.[11]

WHAT IS THE ROLE OF ACIDIFYING MAGNESIUM-RESTRICTED FOODS?

As of yet, there is no known benefit of urine acidification or magnesium restriction in the etiopathogenesis of non-obstructive idiopathic cystitis.[11] However, urethral obstruction is a potentially life-threatening sequela in male cats with idiopathic cystitis that may result from formation of matrix-crystalline urethral plugs.[2,5,9] 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.[10] Over the past three decades, struvite has consistently been the primary mineral component of most urethral plugs, although other mineral types may be encountered.[13] 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 phosphorous concentrations has been reported.[14] 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*.[15,16] 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 idiopathic cystitis. However, clinical studies confirming this hypothesis have not been reported.

WHAT IS THE ROLE "MULTIPURPOSE" URINARY THERAPEUTIC FOODS?

More recently, several so-called feline "multipurpose" urinary therapeutic foods have been developed that are intended to simultaneously manage the combination of risk factors associated with idiopathic cystitis, struvite-, and calcium oxalate-induced lower urinary tract disorders.[15-18] 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 elimination 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 a single food.

Urinary bladder inflammation is a characteristic feature of idiopathic cystitis and urolithiasis.[19] 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.[20,21] Studies in cats indicate that consumption of fish oil products results in EPA/DHA incorporation into cell membrane phospholipids in a dose dependent manner.[22] 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.[20] 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.[21]

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 urinary therapeutic foods.[17] Although dietary omega-3 fatty acids have benefitted people, dogs and cats with a variety of metabolic and chronic inflammatory conditions,[20,22] the specific therapeutic effects of omega-3 fatty acids and vitamin E have not been evaluated in cats with idiopathic cystitis or urolithiasis. Interestingly, consumption of omega-3 fatty acids by people with hypercalciuria and recurrent calcium oxalate urolithiasis was associated with significant reductions in urinary calcium and oxalate excretion.[23] Commercially available feline multipurpose urinary foods vary considerably in their omega-3 and vitamin E content.[17] 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 idiopathic cystitis and urolithiasis.

INVESTIGATING THE ROLE OF NUTRITION IN IDIOPATHIC CYSTITIS: 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 idiopathic cystitis.[24] Young to middle-aged, indoor, male or female neutered cats with clinical signs of acute idiopathic cystitis (≥ 2 lower urinary tract signs 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 lower urinary tract signs. 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 (e.g., 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 (i.e., 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) 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).

The primary endpoint measured was the frequency of recurrent episodes of lower urinary tract signs within 12 months. 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 (e.g., periuria) may be acquired as a result of lower urinary tract diseases and persist despite resolution of the underlying disease, this definition of episode resolution was chosen to minimize potential bias of acquired persistent behaviors on outcome assessments. Once enrolled, lower urinary tract signs (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 one 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 (5m, 6f) were fed the test food and 14 cats (11m, 3f) were fed the control food. Data was analyzed as a binomial proportion of the number of days that an event occurred or the number of episodes of lower urinary tract signs 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 lower urinary tract disease, 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 lower urinary tract signs ($P < 0.05$) 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 lower urinary tract signs was 5/3,904 days (1.28/1,000 cat-days) in the test food group and 47/4,215 days (11.15/1,000 cat-days) in the control food group. This represents an 89% lower overall rate of recurrent episodes of lower urinary tract signs in cats fed the test food consistently compared with the control food group. This is the first study to definitively show that foods of different nutritional profiles impact the expression of lower urinary tract signs in cats with acute idiopathic cystitis.

KEY POINTS FOR APPLYING THE STUDY'S SCIENTIFIC RESULTS TO CLINICAL PATIENTS IN PRACTICE

- Long-term feeding of a multipurpose urinary therapeutic food was associated with a significant reduction in the rate of recurrence of new episodes of lower urinary tract signs in cats with acute idiopathic cystitis compared to feeding a control diet mimicking common grocery brands.
- The basis for the beneficial diet effect was undetermined, but may involve enhanced levels of omega-3 fatty acids and vitamin E.
- The multipurpose urinary food should be fed consistently as the exclusive food to minimize the long-term risk of recurrent episodes of clinical signs of idiopathic cystitis in male and female cats, and the risk of urethral obstruction in male cats.
- The efficacy of the multipurpose urinary food for controlling recurrent signs in cats with chronic idiopathic cystitis was not determined. However, we predict that the multipurpose food would also be of benefit in minimizing recurrence of signs and reducing the risk of urethral obstruction in cats with chronic forms of the disease. Proof of this hypothesis requires further investigations.

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ADVANCES IN MANAGEMENT OF FELINE LOWER URINARY TRACT DISEASE:

When a Clean Litter Box is Not Enough

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CLINICAL IMPORTANCE

Elimination outside of the litter box in unwanted locations remains the number one owner complaint about feline behavior and the number one reason for cat relinquishment.[1] Many treatment strategies are available to keep cats using their litter box or to re-establish good litter box habits.[2] And in many cases, veterinarians in general practice have gotten more adept at helping cat owners with this behavior problem. But, what do you do about situations that do not improve with your tried-and-true treatment options?

DEFINING THE PROBLEM

Feline inappropriate elimination or housesoiling (periuria) can present in one of two ways; either as toileting outside of the litter box — emptying the bladder and/or bowel in some other location or as urine marking, leaving urine on vertical surfaces as a form of social communication. This lecture will discuss elimination outside of the litter box that is not due to urine marking behavior.

MEDICAL AND OTHER FACTORS RELATED TO ELIMINATION PROBLEM BEHAVIORS

Housesoiling can often be precipitated by medical problems; therefore, a good physical examination, urinalysis, culture and imaging studies are essential for all patients that are house soiling.[3] Inappropriate elimination can also be a symptom of other systemic medical abnormalities, such as hyperthyroidism, diabetes mellitus or liver disease. Practitioners should attempt to identify and treat concurrent medical disorders. However, once medical problems are treated or controlled,

learning or other factors may contribute to ongoing housesoiling issues. Multiple studies and papers on feline lower urinary tract disease (FLUTD) and feline idiopathic cystitis (FIC) discuss risk factors,[4] diagnosis[3] and treatment[3] and will not be covered in this *Proceedings* paper.

Beyond the medical issues, social issues, environment, anxiety and stress have all been discussed as related to housesoiling issues in cats.[5] Studies have indicated a correlation between underlying social issues between household cats and urine marking.[6] Medical problems are also influenced by environment and household issues. In 2004, Cameron et al[7] found differences between cats with FIC, their live in control and a control population of cats. Cats with FIC were significantly more likely to be male when compared to live in control and control cats. They also were more likely to live with another cat or live in multi-cat households and more likely to be in conflict with a cat they lived with. Interestingly 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 idiopathic cystitis noting that an increase in stress in FIC affected cats was correlated with return of symptoms.[8] Obviously, the behavioral diagnosis of housesoiling may not be straightforward, but can be influenced by multiple issues both medical and behavioral.[9]

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 (see **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, relationships with the people, opportunities for enrichment, escape and hiding areas, and how cats share the space. 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.[2] Non-litter box use can also be influenced by stress,[4,5] anxiety, and litter box factors such as size, cleanliness and placement. The use of a diagnostic category will help in the formulation of a treatment plan. One major confounding factor in elimination problems in cats is intercat aggression. See **TABLE 1** 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 like one with added carbon. Increased cleaning of litter boxes has shown to be helpful in urine marking.[10]
- 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.
- 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.[11,12] Accommodating these preferences is usually helpful.

TABLE 1.

LITTER BOX USE INFORMATION	
QUESTION	**ANSWER**
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 ☐ Vertically
Is the elimination consistently on one type of material? (wood, carpet, clothing, area rugs)	☐ Yes ☐ No Please list
Does your cat favor one location for elimination outside of the box?	☐ Yes ☐ No Please list them
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
How many elimination spots do you find outside the box daily?	☐ None ☐ 0-1 ☐ 2-4

LITTER BOX INFORMATION	
QUESTION	**ANSWER**
What type of litter box and how many of each type do you provide?	☐ Covered ☐ Small ☐ Uncovered ☐ Medium ☐ Self cleaning ☐ 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 two weeks ☐ Once a month ☐ Never
How often is the litter box replaced with a new one?	☐ Every 6-12 months ☐ Never
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	
QUESTION	**ANSWER**
How many cats including this one are in the home?	☐ One ☐ Two ☐ Three ☐ Four ☐ Five or more
Does this cat get chased, hissed at or growled at by other cats in the home?	☐ Yes ☐ No
Does this cat chase, hiss at 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
Does this cat interact with the people in the house?	☐ Yes ☐ No

ENVIRONMENTAL INFORMATION	
QUESTION	**ANSWER**
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

- If substrate preferences have been identified, offering a choice of 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.
- 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. These can be provided by interactive sessions with owners or by providing toys that are rotated every few days.
- Spread out all resources including food bowls, resting spots, climbing towers, scratching posts and toys.
- Provide food dispensing toys to counteract inactivity, stress and obesity; all of which are linked to FLUTD.
- Keep routine interactions predictable and pleasant. Avoid punishment and other interactions that the cat finds unpleasant.
- Add in pheromones to 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.[13, 14]

THE ELEPHANT IN THE LITTER BOX: FIGHTING BETWEEN HOUSEHOLD CATS

You have done all the right things and the problem still persists, now what? Now it is time to address one of the other causes of housesoiling and marking behavior: the social situation in the home. Fights 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. In all situations, contributory medical factors must be ruled out, identified and treated.

HISTORY TAKING

If you have not already done so, 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. While owners may witness and describe overt aggressive encounters (hissing, growling, chasing and fighting) they may be unskilled at identifying covert aggressive encounters (staring, blocking, stalking). These more covert aggressive actions may result in a cat living in one area of the house to avoid conflict.

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.[16] Additional information should include blocking access to territory but sitting in hallways or doorways, staring, chasing, hissing, growling, biting and attacks. Identify any treatment options already tried and discuss their implementation and effectiveness on the problem behavior. Examination of ongoing behaviors of the cats involved noting signs of anxiety, 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 to you.

Owners may not report chasing and overt aggressive threats such as growling, hissing, biting unless prompted, assuming these things are not contributory to the housesoiling issue. Additionally, threats between cats can be covert, including blocking access to locations, staring or supplanting. Cats showing submission will crouch, turn the ears downward and avoid the situation.[15] In territorial disputes, one cat (the aggressor) will usually chase another (the victim). These chases are accompanied by vocalizations such as hissing, growling and yowling. This may result in one cat living in a restricted area to keep away from the aggressor.

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.

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 housesoiling 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 putting one on either side of the closed door.

Introductions can be accomplished using food or play, and the goal is to associate pleasant things with the presence of each cat. 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.[16,17] Providing elevated perching areas will also allow escape and safety for victims.

The focus is on counterconditioning and desensitization exercises to reintroduce the cats to one another. The goal is to allow the cats to be together without any aggressive behaviors (growling, hissing, chasing, staring, etc.). Introductions are done slowly, using food to facilitate calm, non-anxious behavior (counterconditioning). The cats need to be far apart perhaps with no visual access to each other, so that they are relaxed (desensitization). Each cat is offered a delectable food treat that they will eat; once they have eaten, they are separated again. For safety and control, it is often advisable that each cat wears a harness and leash. Two feedings without the expression of any aggressive or anxious behaviors are done at the same distance before the bowls 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.

If the cats will not eat when they see one another, then it may be possible to get the cats to eat food treats while on opposite sides of a closed door. If the cats will eat at that time, then use non-visual introductions for a few days and then feeding across the room is tried once more.

An additional method of introduction is with the use of a crate. Place one cat in the crate while the other cat is loose in the room. The goal is to allow the cats to become comfortable with the presence (both sight and odor) of one another. Usually it is best to have the aggressor in the cage and the victim to be loose. Use food to help calm the cats and reward the desired behavior. A similar technique using double baby gates or screen doors on doorways to allow the cats to visualize each other without getting too close is effective as well.

DRUG, PHEROMONES AND NUTRACEUTICAL THERAPIES

In many cases of urine spraying and intercat aggression, medication is needed to diminish anxiety that usually underlies these problems. Pharmacological treatment options are detailed in other sources[16] but commonly used medications include fluoxetine, clomipramine and paroxetine. Pheromones (Feliway – Ceva Animal Health) can often calm cats and diminish fear and anxiety. Nutraceuticals like L-theanine (Virbac Animal Health) may also be useful.

PROGNOSIS FOR HOUSESOILING

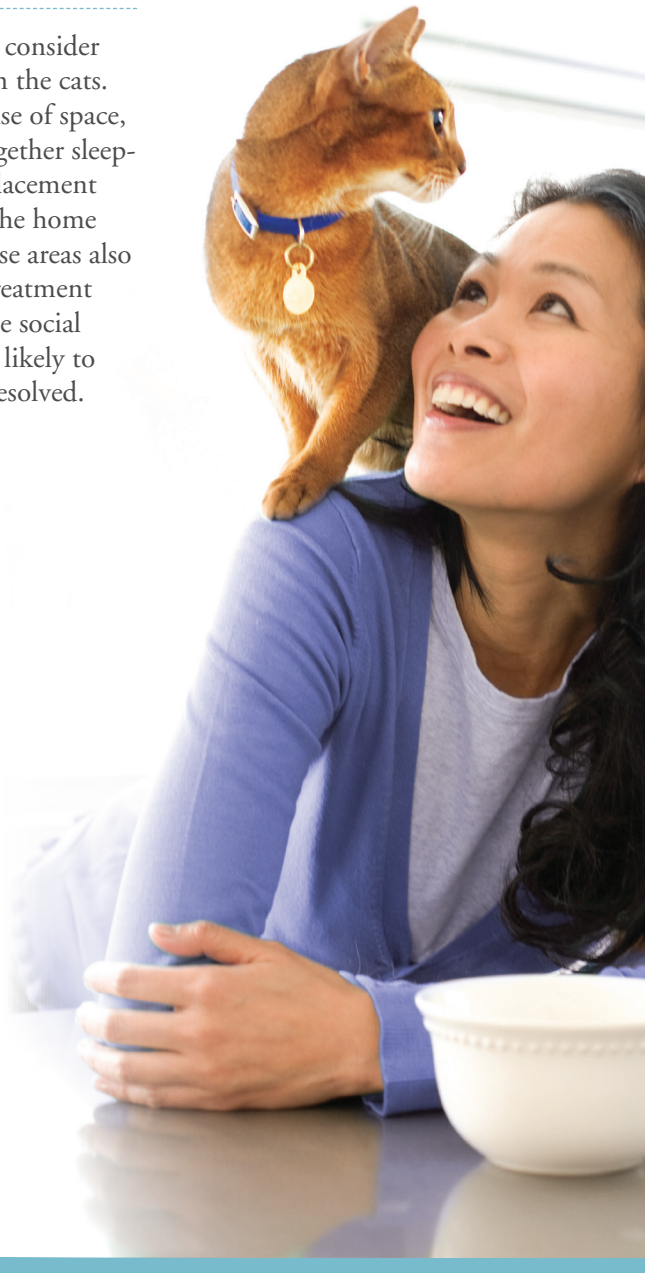
Response to therapy can be quite variable. In some cases, a long-term behavior may be more resistant to change. A study of long-term follow-up of 58 cases for treatment of elimination problems in cats by Marder and Engel demonstrated that 67% (47 cases) showed a 90-100% reduction in frequency of elimination outside of the litter box. Additionally, there was a significant association between caregivers' compliance and outcome.[18] 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 interstitial cystitis 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 significantly greater number of cures than another.[17]

CONCLUSION

In all housesoiling cases, consider the interactions between the cats. 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, housesoiling is likely to continue and remain unresolved.



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