#### 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.<sup>1-3</sup>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 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 nonobstructive FIC.<sup>4–7</sup> 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.<sup>4–7</sup> Recurrent episodes of acute FIC tend to decrease in frequency and severity as cats become older.<sup>7</sup> 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
1	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 ( <i>P</i> = 0.02) compared with control food
111	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
	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 selflimiting 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 proinflammatory mediators and crystallogenic minerals.
- Increasing urine concentrations of antiinflammatory/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.<sup>1,7</sup> 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.<sup>1,3,7</sup> 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 nonrandomized, open, prospective study.9 Signs of lower urinary tract disease recurred in 11/28 (39%) cats fed the drv 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.<sup>8</sup> 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.<sup>2,5,10</sup> 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.<sup>13</sup> 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.<sup>14-17</sup> 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.<sup>18</sup> 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.<sup>19,20</sup> Studies in cats indicate that consumption of fish oil products results in EPA/DHA incorporation into cell membrane phospholipids in a dose-dependent manner.<sup>21</sup> 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 antiinflammation-resolving inflammatory and eicosanoids is increased.<sup>19</sup> Similarly, vitamin E is a potent antioxidant, which also has antiinflammatory 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 proinflammatory 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.<sup>16</sup> 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.<sup>16</sup> 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.<sup>23</sup>Young to middle-aged, indoor, male or female neutered cats with clinical signs of acute FIC ( $\geq$ 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 multicat 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 drv 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 12month 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  $\geq 2$  clinical signs (hematuria, dysuria, stranguria, pollakiuria and/or periuria). An episode was considered to have resolved when there were two consecutive days with  $\leq 1$  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,

Nutrient amounts Test dry Test wet Control Control (per 100 kcal) dry wet 8.7 Protein (g) 9 10.7 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 81 124 83 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

Table 2Selected nutrient values for test foodcompared with control food

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

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  $\geq 2$  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 catdays) 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.

## 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.<sup>9</sup> In addition, feeding multipurpose therapeutic urinary foods should minimize the risk of struvite crystals combining with inflammatory urinary sediment to form lifethreatening 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.<sup>24</sup>



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, serotoninmodulating 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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