Hill's
Transforming Lives

CLINICAL EVIDENCE REPORT

Managing the most common causes of feline lower urinary tract disease with nutrition

The nutrition of Hill's Prescription Diet c/d Multicare, Hill's Prescription Diet c/d Multicare Stress and Hill's Prescription Diet c/d Multicare Stress + Metabolic effectively manages the most common causes of lower urinary tract signs in cats.

- **Reduces the rate of recurrent feline idiopathic cystitis (FIC) signs by 89%**
- **Safely and effectively dissolves struvite uroliths in as early as 7 days (average = 27 days) and reduces risk of recurrence**
- **Helps manage risk for urethral plugs, which often are associated with FIC and struvite crystalluria**
- **Significantly lowers the likelihood for calcium oxalate to precipitate in urine**

Feline lower urinary tract disease (FLUTD) is a common challenge managed in clinical practice and can have important consequences on the pet-family bond. Inappropriate elimination, a frequent feline lower urinary tract sign, is a top reason for relinquishment of cats to shelters[1]. The most common causes of feline LUTD include FIC, which is responsible for approximately two-thirds of cases, followed by uroliths and urethral plugs[2]. Struvite and calcium oxalate are the most common uroliths in cats and urethral plugs are almost always composed of struvite[3]. Urethral obstruction is very common in male cats with urethral plugs and frequently occurs in cats with FIC[4-7].

Being overweight or obese is associated with a 3-fold increase in prevalence of FLUTD in cats[8]. Current evidence suggests that stress also plays an important role in the pathogenesis of FIC, and it has been shown that reducing stress by environmental enrichment significantly decreases the clinical signs of FIC[9]. Nutritional intervention has been shown to effectively manage body weight[10-12], reduce recurrence of FLUTD in cats[13-18] and reduce signs of stress in cats[14].

Feline Idiopathic Cystitis

- **Of the available management options for FIC, Hill's Prescription Diet c/d Multicare has the best evidence (published Grade 1 clinical study) for decreasing the rate of recurrent episodes of FIC signs[13,19].**
- **Feeding c/d Multicare was associated with an 89% reduction in the rate of recurrent FIC signs compared with cats fed a control food in a 1-year study[13].**
- **Cats with FIC that were fed c/d Multicare had a significantly lower ($P<0.05$) proportion of days with LUTS compared with cats fed a control food[13].**
- **Significantly fewer ($P = 0.02$) cats with FIC required analgesics for pain management when fed c/d Multicare (35%) compared with cats fed a control food (86%)[13].**

Effects of nutritional management of cats with FIC were evaluated in a controlled, double-blinded 1-year clinical study[13]. Owners chose to feed either moist or dry food exclusively for the duration of the study and cats were assigned to either the test food group (n=11) and were fed c/d Multicare, or the control group (n=14). The control food was an experimental food designed to mimic the nutrient profile of popular selling grocery brand cat foods. Compared with the test food, the control food contained substantially lower concentrations of omega-3 fatty acids from fish oil and antioxidants. The same protocol for environmental enrichment (including litter box management) was recommended for all cats (test and control food groups) and owners were able to request, and/or veterinarians could prescribe, opioid analgesic medication to manage cats' pain as needed.

Owners were instructed to monitor for presence of five clinical signs (dysuria, hematuria, periuria, pollakiuria, stranguria) and record their observations daily. The primary endpoint was the number of recurrent episodes in which a cat had multiple (≥ 2 concurrent) LUTS within a day (defined as multiple-sign day). Further, multiple sign days that were contiguous or that were separated by no more than 24 hours with a single sign were considered a single episode. Episodes were considered to have concluded when there were two or more days with 1 or 0 clinical signs. Secondary endpoints were the number of recurrent episodes of a single LUTS. Mean incidence rate was calculated as the proportion of the number of recurrent episodes of clinical signs out of the total number of days a cat was in the study. There was no statistical difference in recurrence of LUTS between cats eating dry versus moist food, therefore, data from cats in the dry and moist food groups were combined and comparisons were made between nutritional profiles (test food versus control food).

There were no significant differences between groups regarding major stressors reported over the course of the study (e.g., changes in number of people or pets, moving, remodelling, visitors, or pet sitters during owner absences), availability of window perches and scratching posts, increased number of litter boxes, or change in litter box type or location. The overall mean urine specific gravity for cats fed the test food (1.052 ± 0.015) was not significantly different compared with the control food group (1.049 ± 0.015). The median time of study enrollment was 364 days (range, 187 to 400 days) for cats fed test food and 352 days (range, 47 to 370 days) for cats fed control food. The mean ± SD time of enrollment for cats fed control food (301 ± 115 days) was significantly (P = 0.03) shorter than that of cats fed test food (355 ± 58 days); in total, 3,904 cat days were analysed for the test food group (11 cats) and 4,215 days for the control food group (14 cats).

Key Findings

- **The overall incidence rates for recurrent episodes of multiple-sign days were 1.3 episodes/1,000 cat-days for cats fed test food and 11.2 episodes/1,000 cat-days for cats fed control food, representing an 89% decrease in the rate of recurrent FIC signs in cats eating c/d Multicare (Figure 1)[13].**
- **Cats with FIC fed c/d Multicare had a significantly lower mean incidence rate for multiple sign days (P=0.01) (Figure 1)[13].**
- **A significantly (P = 0.04) lower proportion of cats fed c/d Multicare (18%, 2/11) had stranguria compared with cats fed control food (64%, 9/14)[13].**
- **Mean incidence rates of individual signs for haematuria (P=0.01), dysuria (P=0.02), and stranguria (P=0.01) were significantly lower in cats fed c/d Multicare compared with control food[13].**
- **Opioid analgesics were dispensed during the study to a significantly (P = 0.02) greater proportion of cats fed control food (86%, 12/14) than cats fed c/d Multicare (35%, 4/11) (Figure 2)[13].**

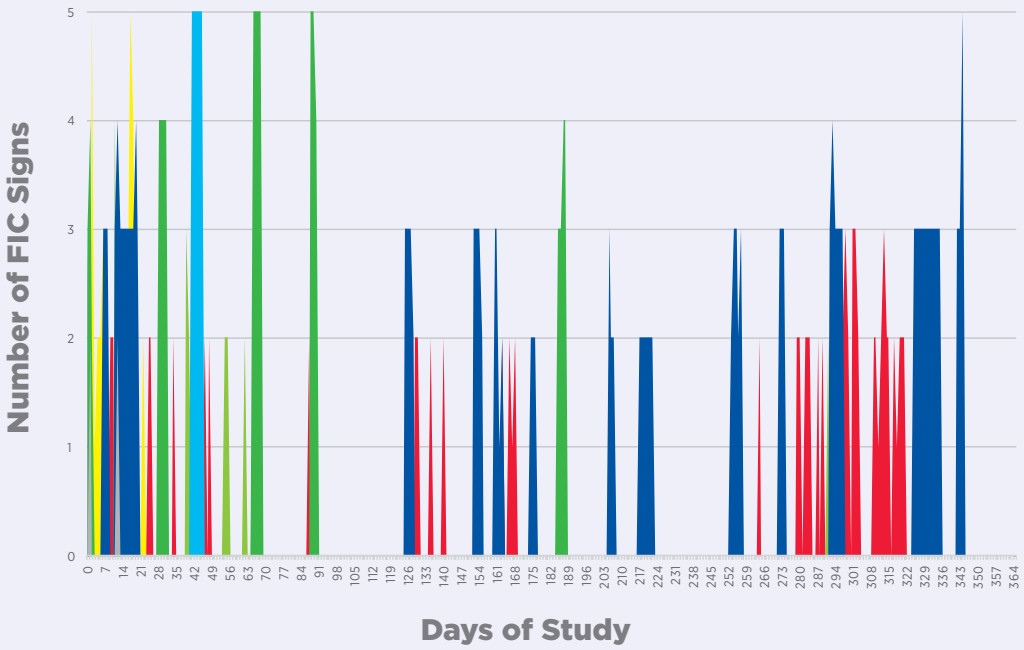

Figure 1a. There was a total of 47 episodes of FIC signs in 9 of 14 cats eating the control food for 1 year, representing an overall incident rate (47 episodes/4215 study days) of 11.2 episodes per 1000 study days. The number of FIC signs observed on each day is indicated on the vertical axis and the duration of each episode is shown on the horizontal axis. The episodes for each cat are represented by different colours.

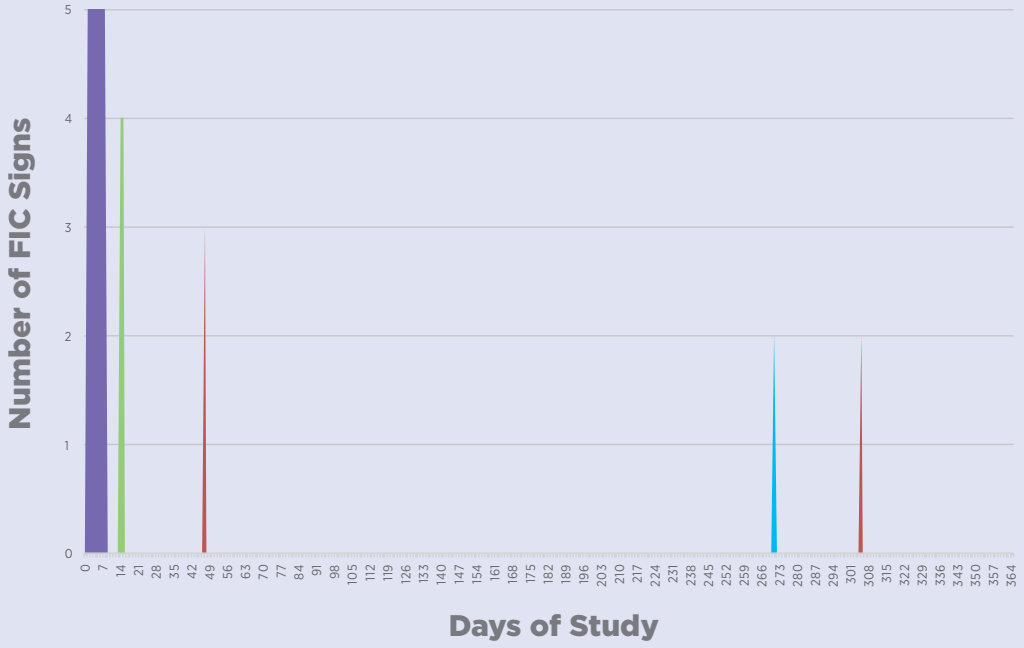

Figure 1b. There was a total of 5 episodes of FIC signs in 4 of 11 cats eating c/d Multicare for 1 year, representing an overall incident rate (5 episodes/3904 study days for 4 cats) of 1.3 episodes per 1000 study days.
Cats with FIC fed c/d Multicare had a significantly lower mean incidence rate for multiple sign days compared with the control group (P=0.01).

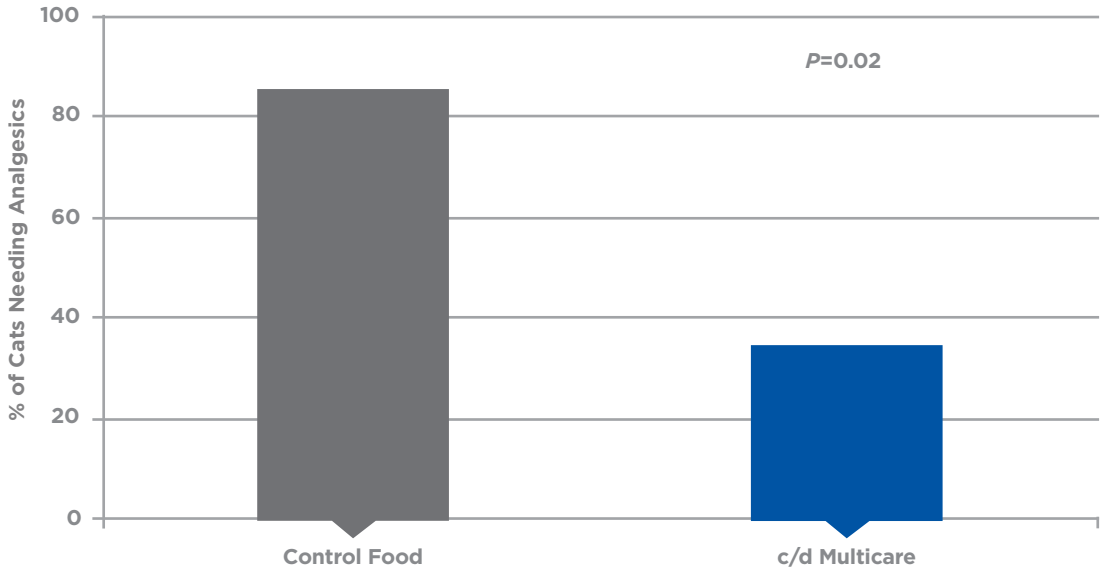

Figure 2. Opioid analgesics were dispensed during the study to a significantly greater proportion of cats fed control food (86%, 12/14) compared with cats fed the test food, Prescription Diet c/d Multicare (35%, 4/11).

Nutritional Management of Stress

- **Cats with FIC that were fed c/d Multicare Stress had a significant reduction in LUTD signs and improved emotional scores and quality of life as perceived by owners (P < 0.05)[14].**
- **Feeding cats diagnosed with FIC c/d Multicare Stress significantly reduced short-term recurrence of FIC compared to feeding non-therapeutic, owner's choice control foods[15].**
- **Oral supplementation with milk protein hydrolysate and L-tryptophan, an essential amino acid, have been reported to have positive effects on alleviating anxiety and stress-related behaviours in various species including cats[20-23] and may, therefore, aid in the management of FIC.**

Stress is postulated to play an important role in the development of FIC, and stress reduction is recommended as a key component of multimodal management for these cats[9]. Milk protein hydrolysate and L-tryptophan have been shown to decrease anxiety and stress-related behavioural signs[20-23] and may be helpful for cats with FIC. Milk protein hydrolysate (such as casein hydrolysate, which is formed by trypsin hydrolysis) has been associated with significant alleviation of stress in models of anxiety in rodents and people. The exact mechanism of these anxiolytic effects is unknown but may be mediated through the gamma amino butyric acid (GABA)/benzodiazepine receptor complex[21]. L-tryptophan is the precursor for serotonin synthesis. Serotonin cannot cross the blood brain barrier so it is important to have an adequate dietary supply of L-tryptophan for serotonin synthesis in the brain. Serotonin in the central nervous system is generally regarded to influence mood, satiety, cognition, and learning ability. Increased concentrations of serotonin have been associated with a feeling of happiness and decreased anxiety in people and animal models [20].

Study 1[14] – A blinded, uncontrolled study of 10 cats with FIC was conducted to evaluate the effects of c/d Multicare Stress. Cats (mean age 5.9 years) were diagnosed with FIC by ruling out other causes of FLUTD. Cats with other major diseases and/or receiving medical treatment that could affect their stress levels were excluded from the study. A thorough history was taken related to dietary intake and environmental enrichment of the cat. After enrolment, the cats were transitioned to c/d Multicare Stress dry and/or pouches at home. Advice was given as to how to improve the environment following a protocol described by Buffington et al[24]. Cat emotional scores, quality of life, and LUTS scores were recorded at enrolment and during clinic visits after four and eight weeks. Taste perception of the new food was recorded during repeat visits. These data were also recorded during telephone interviews by the practice at two and six weeks after enrolment.

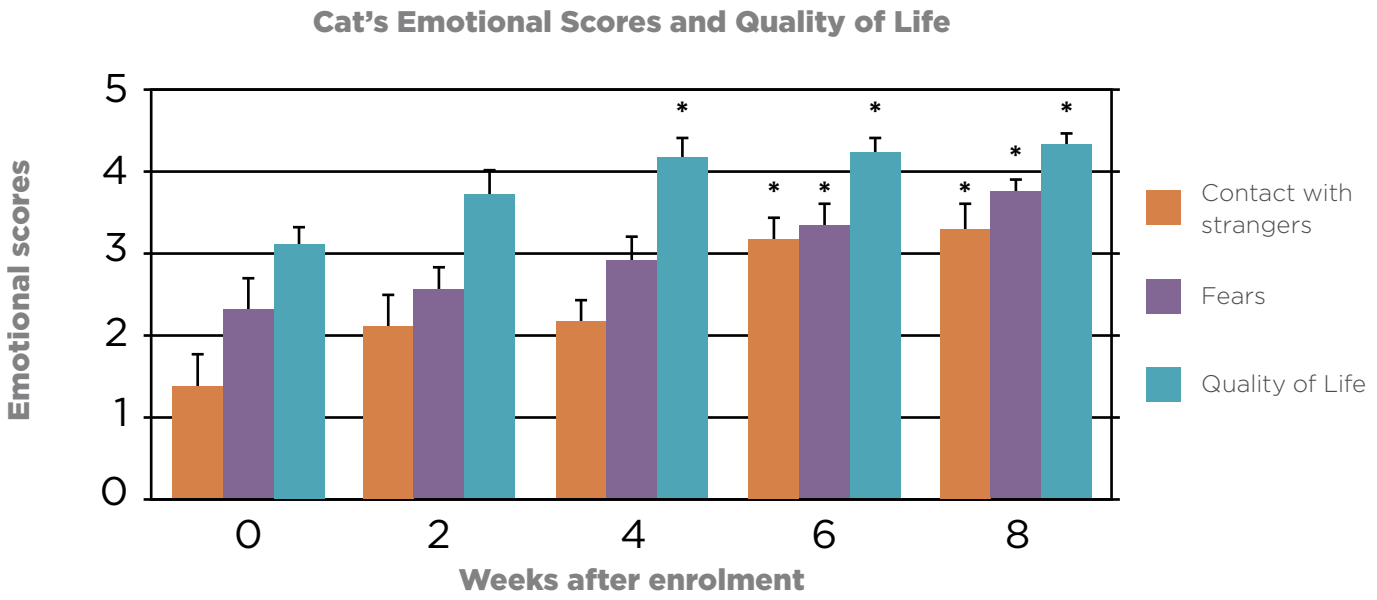

Figure 3. Cat Emotional Scores and Quality of Life (mean ± SEM) in 10cats with FICat week 0 (enrolment), 2, 4, 6 and 8.

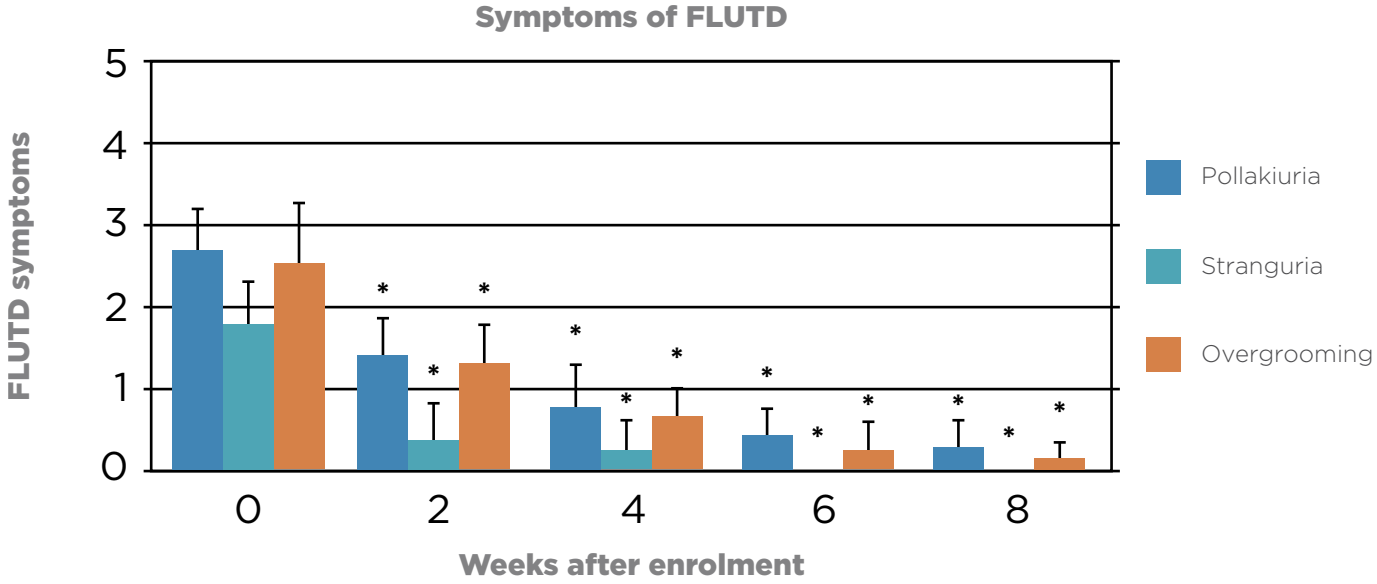

Figure 4. FLUTD Scores (mean ± SEM) in 10cats with FIC at week 0 (enrolment), 2, 4, 6 and 8.

Taste perception of both the dry and wet formulas was rated as excellent throughout the study. Emotional scores and quality of life, as perceived by the owner, improved significantly **(Figure 3)**. LUTS also improved significantly as rated by the owners **(Figure 4)**.

Study 2[15] – Thirty-one cats diagnosed with acute non-obstructive FIC were enrolled in this study to evaluate the short-term effect of diet on recurrent feline LUTS. For a 5-week period, 17 cats were fed c/d Multicare Stress and 14 cats were fed a non-therapeutic commercial food that the owner selected. Cats with a minimum of 2 LUTS (e.g., dysuria, haematuria, periuria, pollakiuria, stranguria) for a duration of at least one day were considered to have a recurrent FIC episode. Cats fed c/d Multicare Stress had a significantly lower rate of recurrence (5/17) compared to cats that were fed owner's choice foods (11/14).

Struvite Uroliths and Urethral Plugs

- **Nutritional dissolution of feline struvite uroliths is quick, safe, and effective and is now the standard of care for these patients[18]**
- **Nutritional management dissolves struvite uroliths in as little as 7 days (mean = 27 days for c/d Multicare)[16]**
- **Within 2 weeks of feeding c/d Multicare to cats with struvite uroliths, an average 50% reduction in urolith size occurs (Figure 3)[16]**
- **Long-term feeding of c/d Multicare significantly reduces occurrence of struvite crystalluria and risk for forming struvite uroliths and plugs[17]**

Struvite Urolith Dissolution

Based on the 2016 ACVIM Consensus Guidelines, nutritional dissolution is now the standard of care for managing cats with struvite uroliths[18]. It is highly effective and avoids risks and complications of anaesthesia and surgery including suture-induced urolith recurrence[18,25]. Surgical removal of uroliths is not 100% effective; 14 to 20% of cats and dogs undergoing cystotomy in a veterinary teaching hospital had incomplete urolith removal in three studies[26-28]. Although some believe nutritional dissolution may increase risk for urethral obstruction in male cats, this has not been reported.

In a prospective, multicentre, randomised clinical trial, 21 cats with presumed sterile struvite uroliths were randomly assigned to be fed Hill's Prescription Diet c/d Multicare (dry).[16] Diagnostic evaluation was performed at baseline and weekly until radiographic disappearance of uroliths. A total of 16 cats had complete urolith dissolution and mean time (± SD) to observe a 50% reduction in urolith size was 1.75 ± 0.27 weeks for cats fed c/d Multicare **(Figure 5)**. Mean time for complete urolith dissolution for cats fed c/d Multicare was 27 ± 2.6 days (range of 7 to 52 days). Adverse events, including urinary tract obstruction, were not observed in any cats during the study.

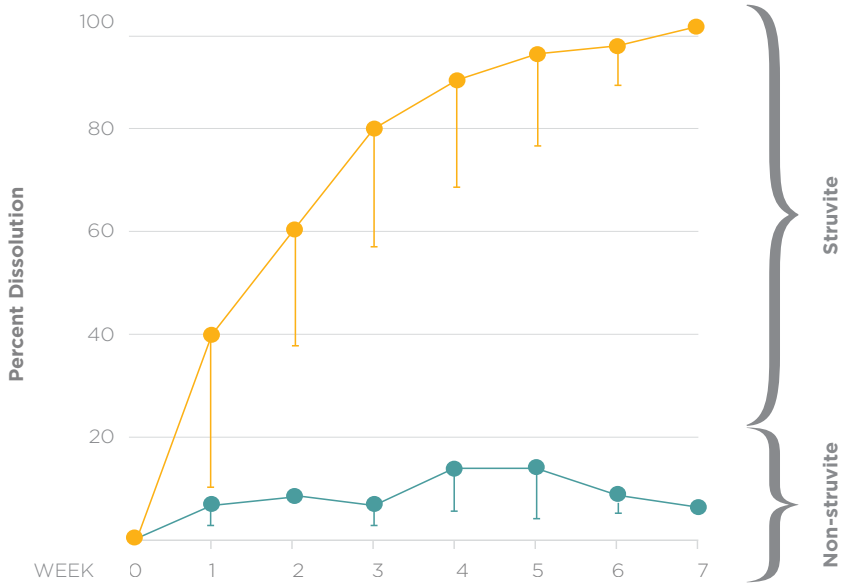

Figure 5. Percent urolith dissolution (mean ± SD) by week for cats that were fed Hill's Prescription Diet c/d Multicare Feline with struvite uroliths (n=16), ammonium urate uroliths (n=4), or calcium oxalate uroliths (n=1). Note that at 2 weeks, struvite uroliths were (on average) > 50% or more dissolved whereas non-struvite uroliths had minimal change. Evidence of a marked reduction (at least 50% compared with baseline) in urolith size by 2 weeks can be used to support a diagnosis of struvite uroliths, and the decision to continue nutritional dissolution therapy.

Decreasing Risk for Struvite Urolith & Urethral Plug Recurrence

Therapeutic foods with low magnesium and phosphorus that acidify urine (pH ≤ 6.4) are recommended to decrease recurrence of sterile struvite uroliths and urethral plugs in cats [3,18]. Effects of feeding c/d Multicare were evaluated in a 2-year, randomised, controlled, double-blinded clinical study of cats with struvite uroliths[17]. Cats were assigned to receive either test food (n=19), c/d Multicare, or control food (n=18) with a nutritional profile similar to the top five selling grocery food brands in the US. The test food contained decreased magnesium and phosphorus compared with the control food, and had a target urine pH of 6.2-6.4 (versus 6.6-6.8 for the control food). During the study, four control food cats (22%) and one test food cat (5 %) had recurrence of struvite uroliths. The relative risk of forming a urolith was 4.2 times higher when cats were fed control food, and struvite relative supersaturation was 2.97 times higher in control cats (P=0.004). There was also a significant month-diet interaction such that struvite crystalluria increased over time in the control food group and declined in cats eating c/d Multicare **(Figure 6)[17].**

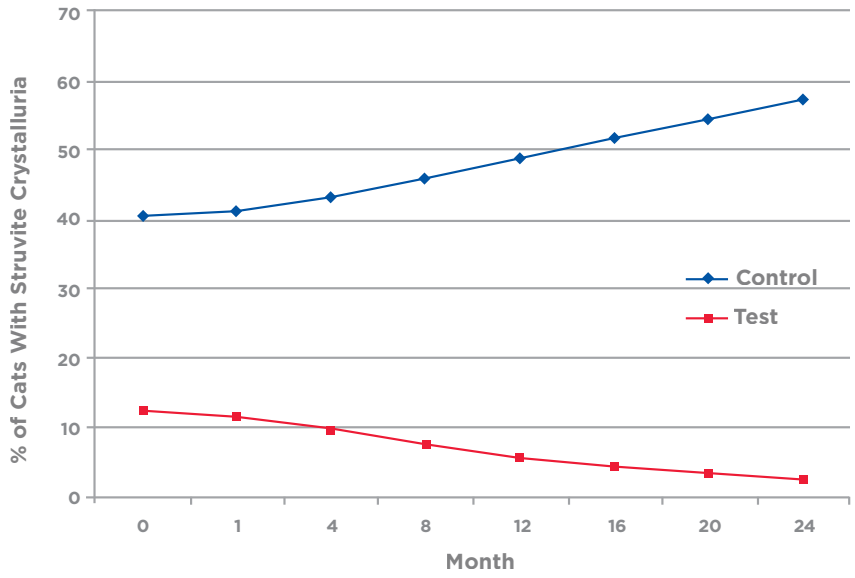

Figure 6. During the 2-year study the % of cats with struvite crystalluria increased to over 50% in the control food group and decreased to less than 10% in cats eating Prescription Diet c/d Multicare (test group); the difference between groups was significant (P= 0.0456).

Nutritional Management of Weight

- **Cats in a controlled environment fed Metabolic had a mean weight loss of 11% in 60 days [10].**
- **In typical households under normal management conditions, 81% of cats safely lost weight in two months at a rate of 0.5% per week [11].**
- **Weight loss was achieved in client-owned cats fed Metabolic in spite of higher than recommended caloric intake[12].**
- **Cats in a controlled environment fed Metabolic for weight maintenance continued to lose significant amounts of fat mass and gain an average of 4.4% lean body mass without a change in overall body weight [10].**

Study 1[10] – Twenty overweight or obese cats in a controlled environment were enrolled and assigned to a test food containing the nutrition found in Metabolic. Overweight was defined by a body condition score (BCS) of ≥4/5 and > 30% body fat as determined by dual-energy X-ray absorptiometry (DEXA). Cats were initially fed at least 0.8*RER (resting energy requirement) of estimated ideal body weight. All cats were weighed weekly with food intake monitored daily and adjusted every two weeks if necessary to target a safe rate of weight loss (0.5–1.0% body weight/week)[29]. Cats continued the weight loss regimen until they had reached an ideal body condition or four months, whichever occurred first, followed by a 4-month weight maintenance period. During weight maintenance, they were fed sufficient calories to maintain the body weight achieved at the end of the weight loss period. DEXA analysis was performed monthly throughout the study.

Significant weight loss was observed after 60 days on the weight loss regimen. Cats safely exceeded the recommended weight loss of 0.5–1.0% of body weight, with the average being 1.25% per week. In addition, during the weight maintenance phase of the study, cats consumed more calories than colony controls to maintain body weight, thus resisting weight regain. DEXA analysis during the weight maintenance period revealed that cats continued to lose significant amounts of fat mass while adding significant amounts of lean mass without a change in overall weight **(Figure 9)**.

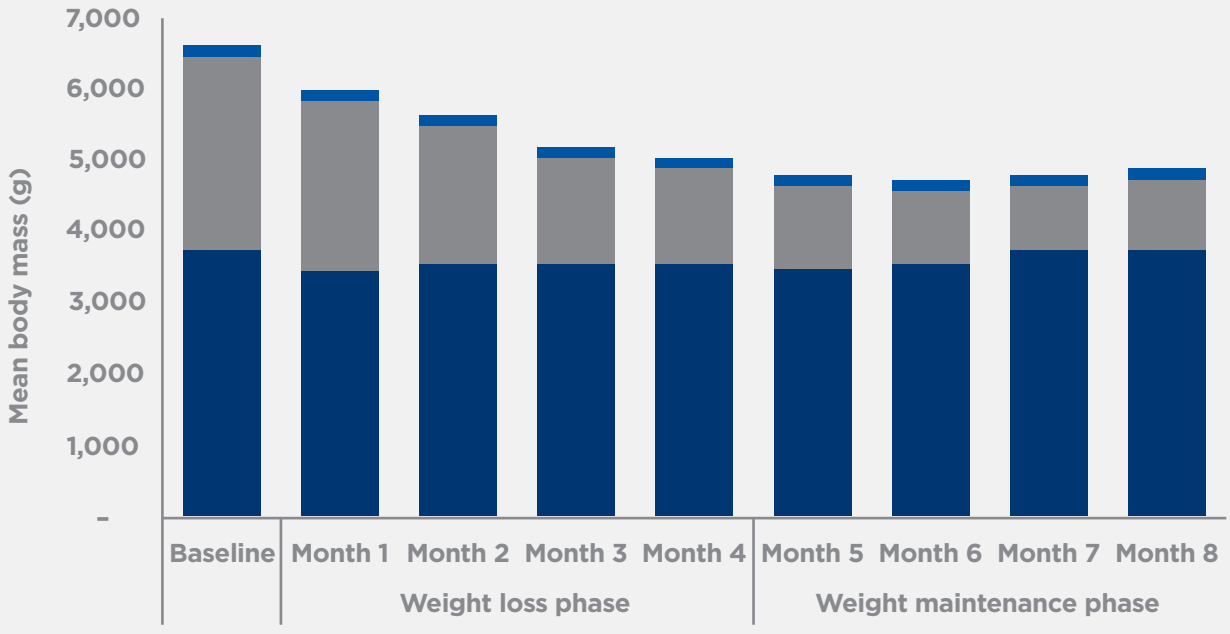

Figure 9. Mean body mass for 20 overweight or obese cats fed Metabolic. Lean body mass (dark green bars), body fat mass (light green bars), and bone mass (green bars) were determined monthly by DEXA.

Study 2[11] – This study assessed the effectiveness of Metabolic in client-owned cats (n=155, mean age 6.7 years) with a BCS ≥4/5. Cats were fed at 0.8*RER of estimated ideal body weight and the amount was not changed throughout the study. Body weight was recorded at the start of the study and after 1 and 2 months. In typical households under normal management conditions (i.e., no change in lifestyle or activity level), 81% of cats lost weight in 2 months at an average rate of 0.5% per week. Owners agreed that Metabolic is an easy way for pets to lose weight, keeps their pet full and satisfied, and the majority would recommend it to a friend with an overweight pet.

Study 3[12] – This clinical trial in 132 overweight or obese client-owned cats confirmed the effectiveness of Metabolic for achieving weight loss in an in-home setting. Eighty-three percent of the cats lost weight over 6 months, with an average weight loss of 11.0% at a rate of 0.45% per week. The majority of cats lost weight in spite of 79% of them consuming a higher than recommended caloric intake for weight loss (0.8*RER). Quality of life scores, specifically for perceived levels of energy and happiness, significantly improved over time as reported by owners, while begging behaviour and changes in appetite remained unchanged throughout the study.

Weight and stress are postulated to play an important role in the development of FIC. In addition, excessive nutrients such as magnesium or phosphorus also contribute to urolithiasis. Managing the most difficult and complex FLUTD cases is made simple with one comprehensive product containing clinically proven nutrition: c/d Multicare Stress+Metabolic (**Figure 10)**.

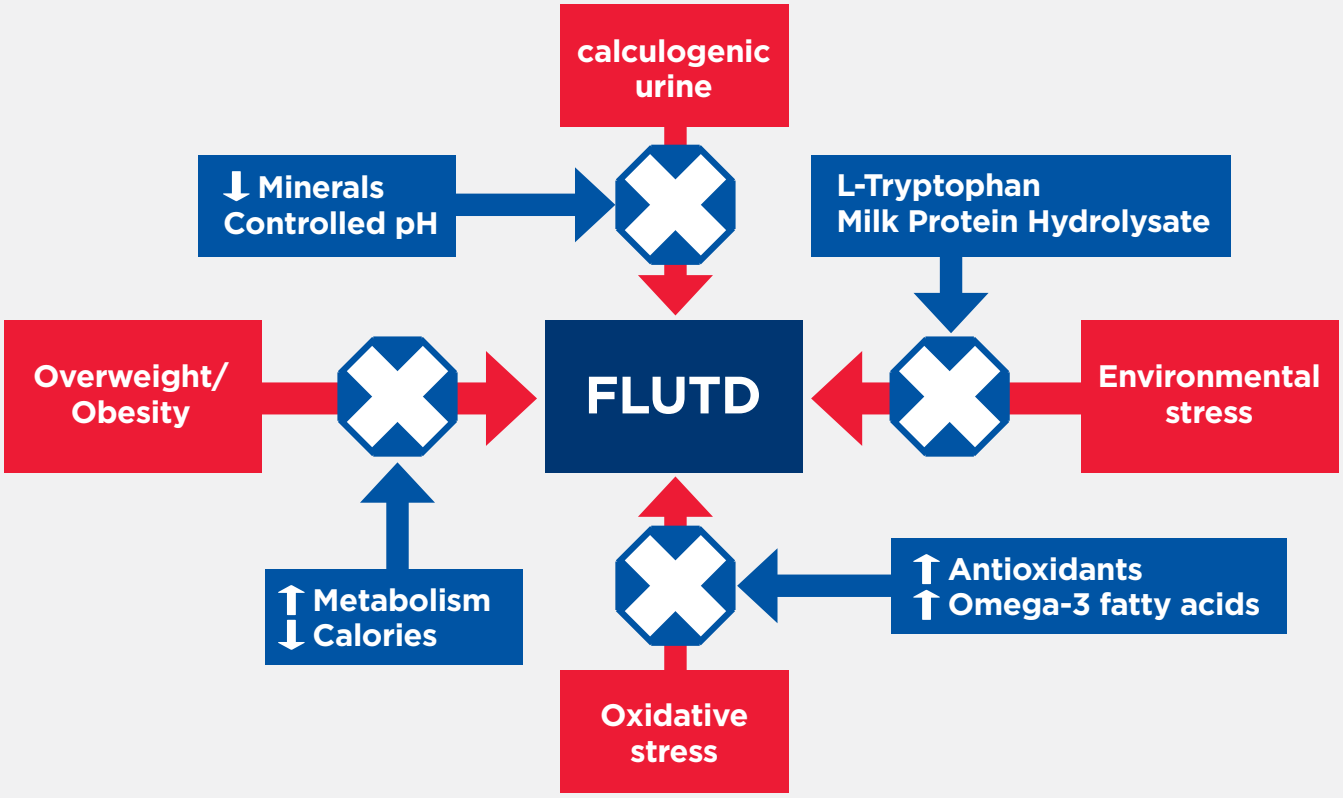

Figure 10. Prescription Diet c/d Multicare Stress + Metabolic contains four distinct nutritional technologies to help manage overweight/ obesity (synergistic blend of ingredients), stress (L-tryptophan and milk protein hydrolysate, calculogenic urine (controlled minerals and urine pH) and oxidative stress (antioxidants).

Summary

Results of clinical studies support that the nutrition of Hill's Prescription Diet c/d Multicare, Hill's Prescription Diet c/d Multicare Stress, and Hill's Prescription Diet c/d Multicare Stress+Metabolic effectively manages the most common causes of lower urinary tract signs in cats[13-17]. Consistent feeding results in:

- **Significantly lower rate of recurrent episodes of FIC signs and requests for pain management[13]**
- **Safe, quick, and effective dissolution of struvite uroliths[16]**
- **Significantly decreased occurrence of struvite crystalluria and therefore decreased risk for recurrence of struvite uroliths and urethral plugs[17]**
- **Significantly improved emotional scores and quality of life as perceived by owners[14] (c/d Multicare Stress and c/d Multicare Stress+Metabolic)**
- **Safe and effective weight loss and weight maintenance[10-12] (c/d Multicare Stress+Metabolic)**

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