

## ORIGINAL ARTICLE

# The effect of a therapeutic urinary stress diet on the short-term recurrence of feline idiopathic cystitis

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**Abstract**

The aim of this cohort study was to evaluate the effect of a therapeutic urinary stress diet on recurrent clinical signs of lower urinary tract disease in cats with idiopathic cystitis. The effects of feeding a therapeutic urinary stress diet were compared with feeding a non-therapeutic diet for a duration of 5 weeks. The owners selected themselves which food to feed their cat. Of 31 cats with acute non-obstructive idiopathic cystitis, 17 were fed the test food and 14 the control food. An episode of recurrence was defined as a minimum of one day with at least two clinical signs; i.e. stranguria, periuria, haematuria, dysuria and pollakiuria. The number of cats fed the therapeutic urinary stress diet that had an episode of recurrence (5/17) was significantly lower compared with cats that were fed other commercial diets (11/14). The formulation of the foods fed to the participating cats (dry, moist or a combination of both) was not found significant compared with the recurrence of idiopathic cystitis. Apart from type of diet, no other risk factors affected the short-term recurrence of FIC. A prospective clinical trial is needed to confirm these findings.

**KEYWORDS**

alpha-casozepine, cat, inflammation, l-tryptophan, nutrition, urinary tract

## 1 | INTRODUCTION

Feline lower urinary tract disease (FLUTD) is used to describe any disorder affecting the urinary bladder or urethra in cats. Defined causes of FLUTD are urolithiasis, anatomic defects, bacterial urinary tract infections or neoplasia; but in the majority of cats, the exact cause(s) remains unclear. These cats are classified as having a syndrome called Feline Idiopathic Cystitis (FIC), which is the most common cause of FLUTD (Buffington et al., 1997; Gerber et al., 2005; Kruger et al., 1991; Lekcharoensuk, Osborne, Osborne, & Lulich, 2001). Cats diagnosed with FIC may have a variety of clinical presentations, including urethral obstruction, non-obstructive disease with acute self-limiting episodes, frequently recurring episodes or chronic persistent episodes. The most common clinical signs in cats with FIC

are stranguria, periuria, haematuria, dysuria and pollakiuria (Nelson & Couto, 2014). These clinical signs are however not specific to FIC and may also occur in cats with other causes of FLUTD. Urinalysis of the urine of FIC cats can show a variety of results, but in most cases, the urine is concentrated and acidic. Some cats also show proteinuria and crystalluria (Buffington et al., 1997). However, these urine parameters are a-specific, as they are present in cats with any type of FLUTD. The diagnosis of FIC is therefore based on excluding other causes of FLUTD (Buffington et al., 1997).

In most cases, clinical signs of non-obstructive FIC resolve within 7 days without treatment (Defauw et al., 2011). However, recurrence of clinical signs after variable periods of time is very common. Up to 65% of cats with acute FIC will experience one or more recurrences within one year (Defauw et al., 2011; Dorsch, Zellner, Schulz,

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Sauter-Louis, & Hartmann, 2016; Gunn-Moore & Shenoy, 2004; Kruger et al., 2015; Markwell et al., 1999). In several published studies, the age, reproductive state, body weight, underlying diseases, type of food and environmental stressors have been associated with increased risk for (re)occurrence of FIC (Buffington et al., 1997; Buffington, Westropp, Westropp, Chew, & Bolus, 2006; Cameron, Casey, Casey, Bradshaw, Waran, & Gunn-Moore, 2004; Gerber et al., 2005; Lekcharoensuk et al., 2001).

The main goals of treatment of FIC are to improve quality of life by reducing the severity of clinical signs and prevention of recurrence of clinical signs. The self-limiting nature of clinical signs may explain why there are many different treatment options that have been recommended for cats with FIC (Kruger, Osborne & Lulich, 2009). However, only a few of those options have been scientifically studied using controlled clinical trials. Because of the increased activity of the sympathico-neural system in FIC, therapy is often directed at reducing environmental stressors (Forrester & Towell, 2015). Another important factor of therapy is reducing the noxious substances of urine that irritate the bladder mucosa, which is based on expert opinion and pathophysiological rationale (grade IV evidence) (Forrester & Towell, 2015). To achieve these goals, environmental enrichment, stress reduction, increased water intake and potential drug therapy are currently recommended (Westropp & Buffington, 2004). Of all treatments evaluated in controlled studies, increased water intake by feeding moist food is the only one associated with a significant lower recurrence rate of clinical signs in cats with FIC (Buffington et al., 1997; Gunn-Moore & Shenoy, 2004; Markwell et al., 1999). Therefore, providing moist food and stimulation of water intake should be part of the initial management of FIC patients. Other nutritional factors that might be beneficial in FIC prevention are decreased amounts of crystallogenic minerals, increasing amounts of crystalloid inhibitors, increased amounts of anti-inflammatory mediators such as omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid (EPA and DHA) and dietary management of the urinary pH (Kruger et al., 2015). More recently, a new type of therapeutic urinary food has been produced which does not intend to only prevent the development of crystals, but they also manage the risk factors associated with FIC; these are so-called 'multipurpose' urinary diets. Apart from adaptations to reduce crystal formation, these diets are enriched with alpha-casozepine and L-tryptophan, which have been demonstrated to have some anxiolytic effects (Landsberg, Milgram, Mougeot, Kelly, & Rivera, 2017). A recent study of Kruger et al. (2015) described the effect of consistently feeding a therapeutic urinary food (Hill's Prescription Diet c/d Multicare Feline Dry) on the recurrence of FIC episodes during 12 months compared to a control food. Results showed a significant reduction in recurrence of FIC episodes of 89%. That was the first study reporting a significant impact of nutritional intervention on the long-term recurrence of idiopathic cystitis in cats. The effects of a therapeutic urinary stress diet<sup>1</sup> have since been evaluated in an open trial case series in cats with FIC without a control group (Meyer & Bečvářová, 2016). This study is the first cohort study designed to evaluate the effect of therapeutic urinary stress diet<sup>1</sup> in comparison with control commercial diets, on the short-term recurrence of FIC

in client-owned cats with naturally occurring FIC. The hypothesis is that the therapeutic urinary stress diet<sup>1</sup> will reduce the incidence of short-term recurrence of FIC.

## 2 | MATERIALS AND METHODS

This study took place in veterinary clinics located in the Netherlands from 19-6-2017 to 2-10-2017, with a follow-up period of 5 weeks. During this period, FIC-diagnosed cats over 1 year of age were recruited. From this group, the cats were included in this study when they showed  $\geq 1$  episode of FIC in the past year. An episode is defined as a minimum of one day with at least two clinical signs: stranguria, periuria, haematuria, dysuria and pollakiuria. Only the cats that underwent thorough diagnostic evaluation to exclude other (systemic) disease; i.e. urinalysis, urine culture, radiographs or ultrasound from the abdomen, were included in this study. Prior to enrolment a questionnaire was completed (Appendix S1) and an owned consent form was signed. The cats participating in this research were all from the same breed, the Domestic Shorthair, but differed in age and gender (Table 1). Participating animals were appointed to the test or the control group, depending on the food they received, this was based on the owner's choice. Cats diagnosed with FIC from the test group exclusively received the therapeutic urinary stress diet<sup>1</sup> for this research. The use of a control group of cats consuming other commercial diets ensures that this study is representative for general practice. The animals of the control group were also evaluated with the same diagnostics as the test group, to exclude any other disease and confirm a FIC diagnosis. Finally, participating patients were not allowed to receive any medication during the follow-up period that could potentially suppress clinical signs of FIC. An exception to this criterion was the use of medication to reduce pain in the acute stage of the disease, to make sure that the welfare of the participating animals was not severely affected. The use of meloxicam in a dosage of 0.05 mg/kg once daily with a maximum of 7 days was allowed. This rule of exception applied to the participating animals from both groups. To determine the short-term recurrence of FIC in the participating FIC cats, every cat had to revisit after a period of 5 weeks. During the second visit, patient files were used to whether a patient had an episode of recurrence in the past weeks. An episode of recurrence was defined a day with at least two clinical signs of FIC. For each patient we collected the following data: patient description (the age, reproductive state, weight and breed), clinical signs (all of the clinical signs showed at first presentation of the patient), type of food (dry or moist food or a combination of both), results of urinalysis and recurrence of clinical signs.

### 2.1 | Statistics

Data were tested for normality using the Kolmogorov-Smirnov test in SPSS Statistics 24. Differences in baseline characteristics between groups were tested using a Mann-Whitney *U*-test for non-parametric data (i.e. urine characteristics) and a Chi-square test for normally

**TABLE 1** Baseline characteristics of the cats per group

Variable	Test group n = 17	Control group n = 14	p-value
Age (years)			
1-7	11	9	
>7	6	5	1.00
Gender			
Male	7	6	
Female	10	8	.592
Weight (kg)			
3 to <4.5	9	10	
≥4.5-6	5	4	
≥6-7.5	3	0	.442
Neutered			
Yes	15	12	
No	2	2	1.00
Food formulation			
Dry	7	10	
Moist	3	4	
Combination	7	0	.195
Urine characteristics			
Specific gravity	1.039	1.037	.922
pH	6.3	6.7	.166
Blood	17	13	1.00
Protein (more than trace on dipstick)	15	10	1.00
Microscopic haematuria	14	8	.209
Struvite	1	3	.214
Clinical signs			
Haematuria	9	12	.110
Pollakiuria	12	7	.462
Periuria	3	6	.011
Stranguria	3	5	.027
Dysuria	3	4	.055

distributed data (i.e. clinical signs). For univariate analysis, all the variables included in this study were categorical and coded by 0 or 1. Variables with more than one category were coded accordingly (Table 2). As the age group of 2-7 years is considered a risk factor for FIC, a separate group with cats aged from 2-7 is desirable. Due to the relatively small number of cases in this study, there were no participating cats under the age of two years in the test group and only one cat under the age of two in the control group. As a consequence, the variable age had to be categorized into two categories (i.e. 1-7 and >7 years of age) to be analysed.

The main factor of interest in all analyses was the short-term recurrence of FIC. Associations between the different variables and

**TABLE 2** Names, descriptions and coding of all variables and their categories included in the study as potential risk factors for FIC

Variables	Description	Coding of the variables
Age	Age in years	1-7 >7
Gender	Sex	Male Female
Weight	Weight in kilograms	3-4.5 4.5-6 6-7.5
Neutered	Reproductive state	Yes No
Type of food	Therapeutic urinary diet (Hill's prescription diet c/d Feline Urinary Stress Chicken) or other commercial diet	Hills c/d Urinary Stress Other
Food formulation	Dry food, moist food, or a combination of dry and moist	Dry Combination Moist
Recurrence (dependent)	An episode of FIC in the research period	No

the recurrence of FIC were tested in two stages: first, all the variables were screened using Fisher's exact test. The variables with a p-value of <.05 were considered significant.

Possible associations between independent variables and the recurrence of FIC were screened using a univariate logistic regression.

Because of the small number of cats participating in this study, a multivariable logistic regression to show potential correlation between the variables was not possible. The small sample size also made it impossible to perform statistical analysis on the test and control group regarding the associations between the formulation of the foods fed to the test group and the control group and the recurrence of FIC. These results are presented in a table, without any statistical analysis (i.e. descriptive statistics).

### 3 | RESULTS

At first, 34 cats were eligible for enrolment. One cat from the control group suffered from severe recurrent urethral obstruction and was therefore euthanized before the end of the study. This cat was excluded from analysis. Two cats were diagnosed with FIC but were from a different breed than the Domestic Shorthair (i.e. Abyssinian and Maine Coon cats). To prevent potential bias from a possible predisposition of those breeds on the recurrence of FIC, those cats were excluded from analysis. As a result, a total of 31 cats completed the study and were included in the analysis. These cats were aged

**TABLE 3** Variables screened by univariable analysis with p-values, their distribution of Fisher's exact test, odds ratios (OR) and 95% confidence intervals for 31 cats (16 with an episode of recurrence and 15 without an episode of recurrence) as determined by recurrence of an episode of FIC in cats diagnosed with FIC

Variables	Categories	Recurrence	No recurrence	OR	95% CI	p-value
		(n = 16)	(n = 15)			
		% (n)	% (n)			
Age	1–7	55.0 (11)	45.0 (9)		Ref	.716
	>7	45.5 (5)	54.5 (6)	0.682	(0.156–2.989)	
Gender	Male	61.5 (8)	38.5 (5)		Ref	.473
	Female	44.4 (8)	55.6 (10)	0.500	(0.117–2.139)	
Weight	3–4.5	57.9 (11)	42.1 (8)		Ref	.649
	4.5–6	44.4 (4)	55.6 (5)	0.582	(0.118–2.880)	
	6–7.5	33.3 (1)	66.7 (2)	0.364	(0.028–4.739)	
Neutered	Yes	51.9 (14)	48.1 (13)		Ref	.945
	No	50.0 (2)	50.0 (2)	0.929	(0.114–7.585)	
Type of food	Hills c/d	29.4 (5)	70.6 (12)		Ref	.010
	Other	78.6 (11)	21.4 (3)	8.800	(1.692–45.761)	
Food formulation	Dry	64.7 (11)	35.3 (6)		Ref	.256
	Combination	42.9 (3)	57.1 (4)	0.409	(0.068–2.468)	
	Moist	28.6 (2)	71.4 (5)	0.218	(0.032–1.485)	

**TABLE 4** The number cats who did or did not experienced an episode of recurrence of FIC in the test and the control group, within the different food formulation groups (dry, moist or a combination of both).

Diet	No recurrence	Recurrence	Total
Hill's c/d dry	5	2	7
Hill's c/d moist	3	0	3
Hill's c/d Combination	4	3	7
Total test	12	5	17
Control dry	1	9	10
Control moist	2	2	4
Control Combination	0	0	0
Total control	3	11	14

from 1.7 to 18.7 years, with a mean age of  $6.80 \pm 4.7$  years. Of the 31 cats enrolled in this study, 17 were fed the therapeutic urinary stress diet<sup>1</sup> (test group) and 14 were fed other commercial diets (control group). The most popular control food was Whiskas (the dry form as well as the wet form), representing 64.3% (nine of 14 cats) of all the different control foods the cats participating in this study were fed. When the test food 1 was compared to Whiskas, the test food 1 had an overall higher concentration of omega-3 fatty acids, vitamin E and taurine. Furthermore, feeding the test food resulted in a more acidic urinary pH (between 6.0 and 6.4). The remaining 35.7% of control foods that were fed to the cats from the control group was represented by different commercial adult cat food brands in the Netherlands (e.g. Felix, Albert Heijn, Prins). No significant

differences were found between the test and control groups regarding age, gender, breed, body weight, reproductive state and food formulation (i.e. dry, wet or mixed). A significant difference was found between the test and control group regarding periuria and stranguria (Table 1).

The results of the univariate analysis are shown in Table 3. The type of food (i.e. test or control) was significantly associated with the short-term recurrence of FIC ( $p = .010$ ). The odds of having an episode of recurrence was 8.8 times higher in the control group compared with the test group.

The Odds ratios (ORs) for feeding moist food (0.218) and a combination of moist and dry food (0.409) were lower compared with dry food, but did not reach significance ( $p = .256$ ). None of the three cats from the test group that consumed only moist food experienced an episode of recurrence. There were no cats in the control group that consumed a combination of moist and dry food (Table 4). The OR of the association between the short-term recurrence of FIC and feeding a dry or moist food formulation of the test food was 3.18. The OR of the association between the recurrence of FIC and feeding a dry or moist food in the control group was 6.33.

## 4 | DISCUSSION

This cohort study investigated the effect of a therapeutic urinary stress diet<sup>1</sup> on the short-term recurrence of FIC. The definition of an episode with a minimum of two clinical signs was chosen to prevent potential bias of potential acquired behaviour (such as periuria) as a result of repeated FLUTD. Compared with the control food, feeding the therapeutic urinary stress diet significantly reduced recurrence

rate in cats with FIC in this study. The number of cats which had an episode of recurrence within the follow-up period (5 weeks) was 29.4% (5/17) in the test group and 78.6% (11/14) in the control group. These results are in line with the results previously reported in a controlled clinical trial of Kruger et al. (2015), where 36% (4/11) of the test group cats and 64% (9/14) of the control group cats had an episode of recurrence of FIC within the research period.

The appointment to test or control group was based on the owner's choice of diet, which might have influenced the results based on differences in type of owner.

As no rectal examination or retrograde urethrography was performed, we might have missed cats passing urethral stones.

Age was not significantly associated with the short-term recurrence of idiopathic cystitis in the participating cats of this study. This outcome is contrary to that of Lekcharoensuk et al. (2001), and Hostutler, Chew, Chew, and Dibartola (2005), indicating that cats between two and seven years of age have the highest risk of developing FIC. The cats in this study were aged from 1.7 to 18.7 years, with a mean age of  $6.80 \pm 4.7$  years. As studied before, recurrent episodes of FIC tend to decrease in frequency and severity as cats become older ( $\geq 10$  years) (Dorsch, Remer, Sauter-Louis, & Hartmann, 2014; Hostutler et al., 2005; Kruger et al., 2003). Ten of the 31 cats (32.3%) in this study were older than 10 years of age at the time of first episode of FIC. As a consequence, it is possible that the recurrence rate of FIC is lower than it would have been with more cats representing the category 1–7 years old.

Gender did not affect the recurrence rate of FIC ( $p = .592$ ), which was in agreement with previous studies (Buffington et al., 1997; Kruger et al., 1991). There were a disproportionately large number of neutered cats (27/31) enrolled in this study. Since a previous study has demonstrated that FIC tends to affect intact males and females equally as neutered cats (Defauw et al., 2011), we do not expect any bias by this over-representation of neutered cats. Due to the narrow penile urethra, neutered male cats are predisposed to obstruction with a urolith or urethral plug (Kruger et al., 1991; Lekcharoensuk et al., 2001; Westropp, 2014), which is in agreement with this study, as two cats were presented with the obstructive form of FIC, both of which were neutered males.

According to Cameron et al. (2004) and Defauw et al. (2011), overweight cats are at higher risk for developing FIC. We therefore used body condition score rather than weight, as weight without body condition score can be misleading. Results of this study failed to demonstrate an association between a high body condition score and the recurrence of FIC. This is most likely due to the small number of obese cats (3/31) participating in this study.

Despite significant effects of the therapeutic urinary food on the short-term recurrence of FIC in the cats of this study, the specific food components responsible for the beneficial effect were not determined. Because the foods fed to the cats from the control group all differ in nutritional content, the control food may be a potential confounding factor in this research.

The formulation of the foods was not a significant risk factor for the recurrence of FIC in this study, which is in agreement with previous studies (Cameron et al., 2004; Defauw et al., 2011; Kruger et al.,

2003). However, these findings are contradictory to other studies (Buffington et al., 1997; Gunn-Moore & Shenoy, 2004; Markwell et al., 1999) which suggested that increasing water intake in cats with FIC reduces the recurrence of clinical signs of FIC. The relatively large group of cats that ate a combination of a moist and a dry food ( $n = 7$ , 22.6%), the encouragement of owners to increase their cats water intake and possible shared food bowls from cats in multi-cat households may have resulted in a difference in water intake of participating cats, which could compensate for the lack of wet food. Also, when data were collected from the patient file, it is possible that the patient was not fed exclusively the diet mentioned in the patient file, but was also fed other diets/treats.

The odds of having an episode of recurrence of FIC in cats that received the dry therapeutic urinary stress food<sup>1</sup> is 3.18 times higher compared with the odds of recurrence when fed a moist therapeutic urinary stress food.<sup>1</sup> Moreover, the OR of the association between the recurrence of FIC and feeding a dry or moist food in the control group was 6.33. Although not significant in this study, feeding a moist formulation of any type of food seems to lower the chance of recurrence of FIC, as was also demonstrated by Markwell et al. (1999).

At the time of initial diagnosis, cats in the control group experienced more stranguria and periuria. It might be that the cats in the control group had a higher chance of recurrence compared with the test group.

The fact that no well-accepted diagnostic test for FIC currently exists was another limitation to this study. As a consequence, idiopathic cystitis in cats currently remains a diagnosis of exclusion. In order to rule out other causes of feline cystitis, diagnosis of FIC enquires a thorough diagnostic work-up. Following all the diagnostic procedures needed can be extensive and expensive. During this study, several owners decided not to follow this path mainly for financial reasons, and chose to start symptomatic treatment instead. This is the main reason that the number of participants in this study is relatively small. Another reason for the small sample size could be that not all cats with recurrence returned to the clinic for re-evaluation. Because of the self-limiting nature of FIC (within 7 days without treatment), it is possible that some owners postponed a visit to the vet awaiting resolution of clinical signs without additional treatment.

According to several studies, up to 65% of cats with FIC will experience one or more recurrences within one year (Defauw et al., 2011; Dorsch et al., 2016; Gunn-Moore & Shenoy, 2004; Kruger et al., 2015; Markwell et al., 1999). Results of this study showed an overall recurrence rate of acute FIC of 51.6%. However, the follow-up period was limited to 5 weeks. The study from Dorsch et al. (2016) found that the overall recurrence rate of cats with obstructive FIC within 3 months was 31.5% without treatment. The study of Defauw et al. (2011) analysed the risk factors and clinical presentation of cats with idiopathic cystitis. Results of that study showed that most of the cats had a mean interval between episodes of less than 3 months (51%); only 8% of the cats had a mean episode interval of more than 1 year. Recurrence rates from the study of Markwell et al. (1999) varied between 11% and 39%

within 1 year (depending on whether they were fed a canned or dry diet, respectively). And last, Results from a six month follow-up period Gunn-Moore and Shenoy (2004) showed an episode of recurrence of FIC in 65% of the cats. In conclusion, the duration of time between two episodes can be variable. Therefore, it may be a possibility that with a longer period of the study, more episodes of recurrence could have been seen in the cats in this study.

In the absence of a specific clinical sign for FIC, an episode of recurrence was defined by  $\geq 2$  clinical signs of FLUTD; i.e. stranguria, periuria, haematuria, dysuria and pollakiuria. This was hypothesized to be a more reliable indicator of recurrence and minimized the impact of behavioural factors. For example, persistence of periuria may be caused by behavioural disorders acquired as a result of negative associations with the use of a litter box (Kruger et al., 2015). Additionally, periuria and other LUTD signs are described as non-specific responses to several independent environmental stressors in healthy cats as well as in cats with FIC (Stella, Lord, Lord, & Buffington, 2011). This study considered the variables age, gender, body weight, reproductive state, food formulation and type of food as possible risk factors for the short-term recurrence of FIC. However, apart from type of diet, no other risk factors affected the short-term recurrence of FIC in this study. This study did not evaluate the effects of environmental stressors on the recurrence of idiopathic cystitis in cats. As a result, it is possible that differences in environmental factors and management practices between patients influenced the recurrences of FIC observed in this study.

Further research with a longer follow-up period is necessary to confirm and characterize the specific therapeutic roles of a therapeutic urinary stress diet in the management of FIC.

## 5 | CONCLUSION

Feeding a therapeutic urinary stress diet reduced the short-term (5-week) recurrence of FIC. Apart from type of diet, no other risk factors affected the short-term recurrence of FIC. A prospective clinical trial is needed to confirm these findings.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and

the appropriate ethics review committee approval has been received. The Dutch National Research Council's guidelines for the Care and Use of Laboratory Animals were followed.

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## ENDNOTE

<sup>1</sup> Hill's Prescription Diet c/d™ Feline Urinary Stress Chicken.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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