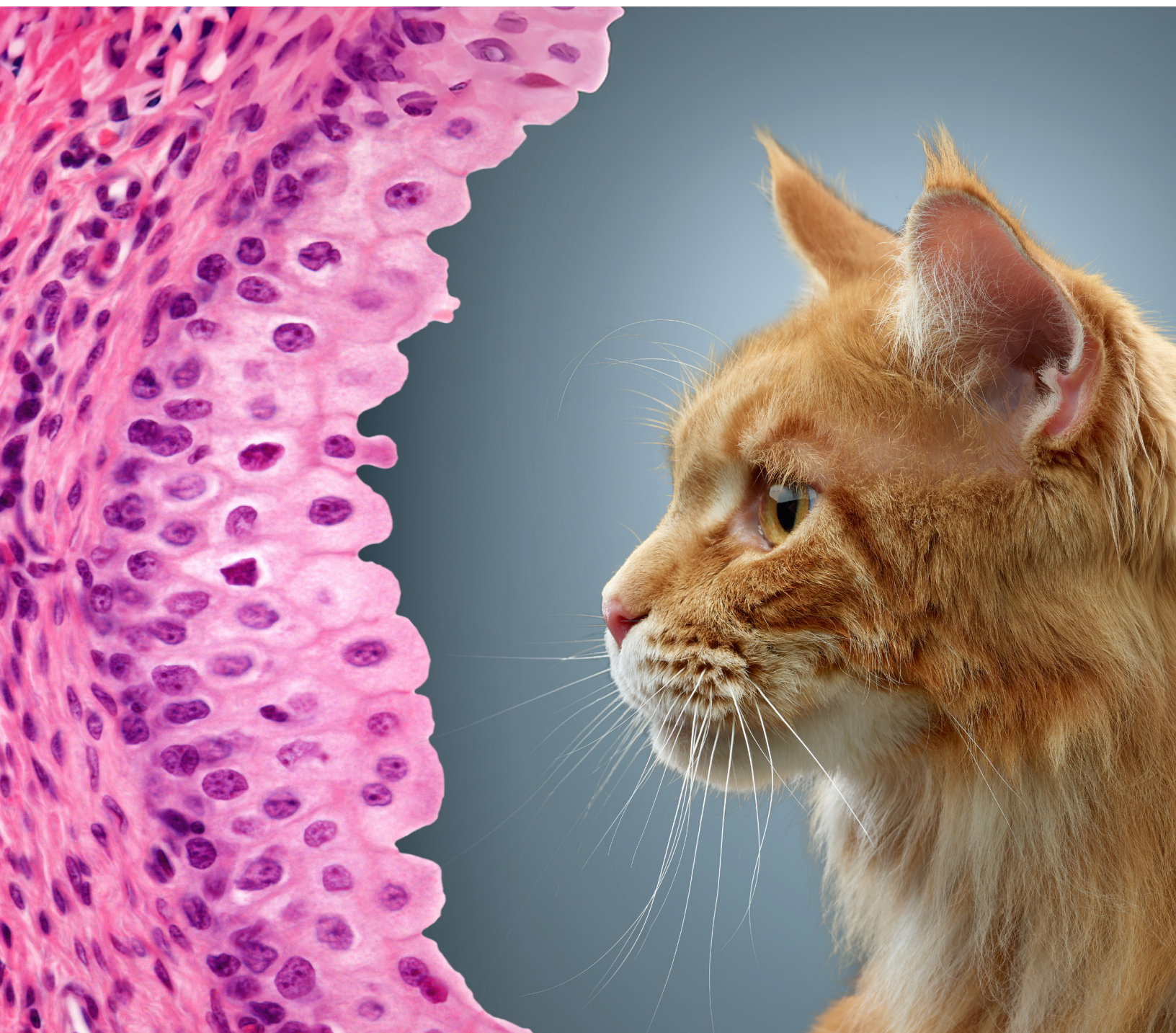


FELINE IDIOPATHIC CYSTITIS: Nutritional Management



FELINE IDIOPATHIC CYSTITIS IS THE MOST COMMON DIAGNOSIS GIVEN TO CATS PRESENTING WITH LOWER URINARY TRACT SIGNS

Feline idiopathic cystitis (FIC) is diagnosed in a cat that has presented with lower urinary tract signs (LUTS) when examination and diagnostics, including urinalysis, urine culture, and imaging, have ruled out other causes. FIC comprises 55–67% of feline lower urinary tract disease cases.¹⁻⁹

FIC is likely to recur,^{3,10-17} which may significantly decrease a cat's quality of life and/or, particularly when inappropriate urination is occurring, may damage the bond between the cat and owner. These concerns may lead to relinquishment of the cat to a shelter or to elective euthanasia.^{3,10,12-14,18-21}

Effective and timely management of FIC is critical. Nutritional intervention can play a key role in the management of idiopathic cystitis.

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CLASSIFICATION & CLINICAL PRESENTATION OF FIC

FIC can be a frustrating disease for veterinarians and cat owners alike. Cats with FIC present with the typical LUTS:

- Pollakiuria – increased frequency of urination.
- Periuria – inappropriate urination, i.e., urinating outside of the litter box.
- Hematuria – blood in the urine.
- Dysuria – difficult and painful urination, often associated with vocalization.
- Stranguria – slow, painful urination; affected cats may strain to urinate.
- Signs of pain on bladder palpation, particularly when obstructed.

FIC may be an obstructive or non-obstructive disease.^{22,23} Some literature has stated that obstructive FIC is less common than non-obstructive.^{22,23} However, other research has reported a higher proportion of obstructive FIC, finding urethral obstruction in 50–60% of cats with FIC.^{1,2,10} Proportions may vary depending on the population evaluated.

Obstruction in FIC may occur due to urethral plugs, urethral muscular spasm, and inflammation, among other causes.^{10,24} One study found 37% of male cats presenting with obstructive FIC had a urethral plug; however, urethral plugs may go undetected if they are dislodged back into the bladder during urinary catheterization.¹⁰

Obstruction typically occurs in male versus female cats due to the narrow diameter of their penile urethra. Surgery (e.g., perineal urethrostomy) may be needed to relieve an obstruction.

Non-obstructive FIC has three clinical presentations: 1) acute, self-limiting, i.e., an episode lasting 5–10 days

(typical duration but may be shorter or longer)^{10,25} before resolving on its own, which is thought to be the most common presentation; 2) frequent recurring incidents, in which signs wax and wane; and 3) persistent occurrence in which clinical signs continue.^{15,22,26-28}

PATHOPHYSIOLOGY OF FIC

The bladder

Although it is not clear if the underlying pathophysiology is identical, FIC appears similar to and is used as a model for bladder pain syndrome (BPS) in people.²⁹ BPS is more common in women than men.

The urothelium, also known as the mucosa, is the bladder wall's innermost layer and is itself composed of a basal, intermediate, and superficial layer.³⁰ In health, an intact urothelium blocks the movement of most substances across it. The urothelium's superficial layer is responsible for this barrier function.

The superficial layer's cells are known as umbrella cells and are linked by tight junctions.³⁰ The umbrella cells also have a luminal glycosaminoglycan (GAG) layer, which appears to serve a protective function. However, the relative contribution of each part of the urothelium's superficial layer (i.e., GAG layer, umbrella cells, tight junctions) to barrier function remains uncertain.

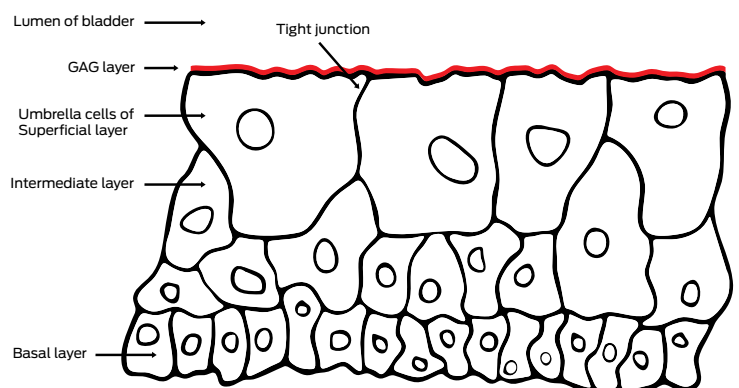


Figure 1:
Components of the uroepithelial layer

Structural and functional damage to the urothelium appears to occur in cats with FIC.^{26,31,32} This may expose sensory neurons in the submucosa to irritating substances in the urine and lead to inflammation and pain.^{26,33} Submucosal petechial hemorrhages and edema may be present. Notably, the severity of lesions does not appear to correspond directly to the degree of clinical signs, as severe clinical signs can occur without significant urothelial damage.

Compromise to the GAG layer is suspected in cats with FIC.^{34,35} It is not clear whether any changes in uroepithelial permeability due to a compromised GAG layer or other part of the superficial layer may contribute to the development of idiopathic cystitis and/or result from it.³⁰

Research showed that urinary levels of GAG, including chondroitin sulfate, the primary GAG in the urine, were decreased relative to healthy adult cats.³⁶⁻³⁸ The mechanism(s) and significance of urinary GAG levels to the GAG layer are not definitively known.

The role of the GAG layer in the pathophysiology of FIC has been further investigated through interventional studies in which GAG “replacements” have been administered, in theory to adhere to and repair the damaged GAG layer and thus help support the bladder mucosal barrier.^{11,14,37,39,40}

The neuroendocrine system

Although FIC is referred to as a cause of LUTS and was initially considered strictly a bladder disease, it is now recognized as a systemic disease associated with abnormalities in the neuroendocrine system in addition to the bladder.³¹ Other body systems may also be involved: A cat with FIC may have one or more comorbidities and may present with various systemic signs, e.g., vomiting, anorexia/hyporexia.^{18,41}

The neuroendocrine component of FIC involves an abnormal response to stress.^{23,26,33,34} In some cats with FIC, the perception of a threat or the presence of chronic stress appears to over-activate the sympathetic nervous system. This affects bladder sensory neurons, catecholamine production, and activity of bladder sensory neurons, pain fibers, neurotransmitters, and receptors, triggering bladder pain and inflammation.

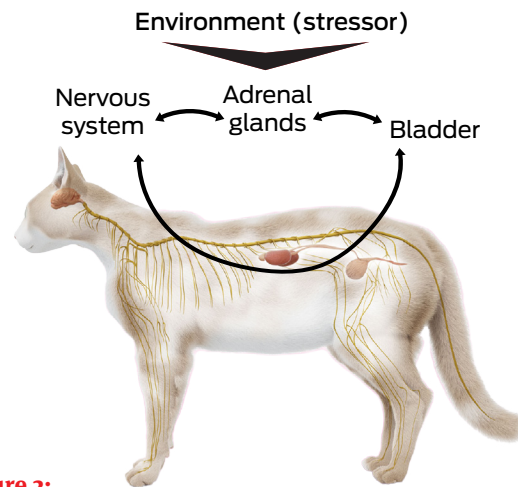


Figure 2:

FIC may result from complex interactions between the nervous system, adrenal glands, bladder, and environment.

The term “Pandora syndrome” has been proposed for a syndrome in cats exhibiting chronic recurrent idiopathic LUTS plus signs of comorbidities when:³⁴

- There is indication of an early adverse event, e.g., a kitten that was orphaned or a pregnant cat in a new home (maternal stressor). Review articles have presented data in multiple species suggesting that maternal stressors, either pre- or postnatally, can alter the developing hypothalamic-pituitary-adrenal (HPA) axis of the fetus or neonate.^{23,34,42} Timing of the stressor in relation to development of the HPA axis affects its impact.
- Clinical signs wax and wane, with appearance of signs associated with a perceived stressor or threat.
- Signs improve with multimodal environmental modification (MEMO) (see further discussion under “Multimodal environmental modification”).

Biomarkers

Researchers are working to identify and validate potential urine and blood biomarkers for cats with FIC, as well as people with BPS.²³ Successful identification of specific and sensitive biomarkers could provide a diagnostic test for FIC as opposed to being a diagnosis of exclusion. Potentially, screening of healthy cats could be employed to identify those at risk so that management could be instituted before clinical signs develop.

RISK FACTORS FOR FIC

As noted above, a stressful event or chronic stress appears to initiate inflammation and signs of FIC in some cats.

One study reported that compared to cats with no history of urinary tract signs, cats with FIC were likely to be more nervous and fearful than housemate cats and to hide from strangers.¹⁰ Owners of nearly 40% of the cats with FIC reported the occurrence of a stressful event in the 3 months before the cat's initial episode.

Research compared cats with LUTS to healthy cats and cats with non-urinary tract disease.⁴¹ Researchers found that the cats with LUTS were more likely to exhibit signs of fear, nervousness, or aggression than the other two groups of cats. Cats with LUTS also showed a significantly greater startle response.

Some research has indicated that living in a multi-pet household increases the risk of FIC, especially when there is conflict between cats and, thus, the potential for chronic stress.^{43,44} Cats without elevated resting places were found to have a 4.64x higher risk of FIC, a risk factor that may be linked to stress.⁴⁴ Genetics may also play a role in susceptibility to stress.³¹

Researchers have identified other risk factors for FIC, including:

- **Sex:** Male cats appear predisposed.^{2,6,9,43,44}
- **Neuter status:** Neutered cats of both sexes are more likely than intact cats to have FIC.⁹
- **Age:** Cats tend to have their first episode of FIC when young to middle-aged.^{1,6,7,9,10} Mean age has been reported as between 2 and 6 years of age.
- **Weight:** Cats with FIC were more likely to be overweight or were significantly heavier than control cats with no history of LUTS.^{10,43,45}

■ **Breed:** Several studies reported that purebred cats were at higher risk.^{9,43} However, other studies have not found a breed predisposition.^{1,5,10}

■ **Activity:** Less active cats¹⁰ or those living indoors⁹ or in an apartment versus a house,⁴⁴ which may link to activity level, have been found to be at higher risk.

The pathophysiology of FIC is very complex and is still being investigated. Based on the contribution of the nervous, endocrine, and immune systems in conjunction with an early adverse event, the environment, genetics, and other risk factors, researchers have suggested that FIC may be triggered when a predisposed cat is placed in a stressful environment.^{10,31,46}

RECURRENCE OF FIC

Similar to other causes of LUTS in cats, FIC is likely to recur, although reported rates of recurrence have varied due to different populations, measures, and follow-up periods.^{3,10-17,23}

Researchers have reported recurrence rates ranging from 24–78% for urinary tract disease signs in cats with FIC.^{3,10,12,14-16} One study found that 80% of recurrent cases recurred within 6 months.¹⁰ In the same study, cats had an average of 5.5 incidents throughout their lifetime.

After resolution of obstructive FIC, research found that 16–36% of affected cats had a recurrent obstruction.^{11,13,16,17}

Since the cause of LUTS may differ between episodes,^{3,47} a thorough examination and relevant diagnostics should be performed each time a cat presents with LUTS.

NUTRITIONAL APPROACH TO FIC

The goals of management for FIC are to:²³

- Shorten the duration of the event.
- Lessen the severity of the episode.
- Lower the risk of obstruction.
- Increase comfort during the episode.
- Reduce the risk of recurrence.

Nutrition and hydration can both play a role in management.

Increased total water intake

Promoting a more dilute urine via increasing water intake is a major goal of management.⁴⁸ In the case of FIC, a more dilute urine contains a lower concentration of compounds that may cause irritation to the bladder lining. A higher urine volume may increase frequency of urination, helping eliminate these substances before they can cause irritation.

To promote water intake, the following strategies may be beneficial:^{49,50}

- **Feeding wet diets or adding water to dry food.**

Cats may have a lower total daily water intake (a lower water to calorie ratio) when eating dry food versus wet food.⁵¹⁻⁵⁴ Studies suggest that dietary moisture levels greater than 70–75% (wet food or dry food with added water) increase total daily water intake and urine volume and decrease urine specific gravity.^{52,54,55}

Feeding a wet therapeutic urinary diet resulted in a recurrence of lower urinary tract signs during a one-year follow-up period in just 11% of cats with FIC versus 39% of cats fed a dry version of the same diet.⁵⁶

- **Feeding a diet with moderately increased levels of sodium (Na) or salt (NaCl).** Research has shown that

feeding cats dry diets with moderately increased levels of Na/NaCl compared to lower Na/NaCl diets for up to 21 days increases voluntary water intake and daily urine volume.^{57,58}

The vast majority of published research in cats, both short- and long-term (from 2 weeks up to prospective research lasting as long as 5 years), has demonstrated that moderately increased levels of salt in diets fed to healthy and aging cats do not adversely affect heart or kidney function or affect blood pressure.⁵⁹⁻⁶⁴

- **Providing a nutrient-enriched flavored water supplement.** Several Purina studies support its benefit:

- In healthy cats fed a dry diet, overall mean free liquid intake was significantly higher for the group offered a nutrient-enriched flavored water supplement (nutrient water) in addition to tap water compared to the group of cats offered tap water only.⁶⁵ In the nutrient water group, nutrient water intake was a mean of 96.6% ± 3% of total daily liquid intake, showing that the increase in free liquid consumption was due to a high nutrient water intake. The increased water intake resulted in production of a significantly higher urine volume and more dilute urine in the nutrient water group.

- Researchers in a second study reported similar findings.⁶⁶ Mean daily free liquid intake and urine volume significantly increased, and urine became significantly more dilute in healthy cats offered nutrient water in addition to tap water, while none of the variables changed significantly in a group of cats offered tap water only.

- **Offering different water sources (i.e., still water, circulating water, free-falling water).** While research has shown that no one source is uniformly superior at encouraging water intake, individual cats did show increases in water intake with either still, circulating, or free-falling water, thus suggesting personal preferences may exist.⁶⁷⁻⁶⁹

- **Providing water in multiple locations around the home.** Water should be located where easily accessible and where cats will not feel threatened while drinking. Providing multiple water bowls around the home may encourage water consumption as well as, in multi-pet households, serve to reduce the risk of resource competition and thereby stress (see “Multimodal environmental modification”).^{33,46}
- **Offering water in different types of bowls, e.g., stainless steel, ceramic, glass, and/or wide bowls** (so that a cat’s whiskers do not touch the sides of the bowl) to determine the cat’s individual preference.

Water should always be clean and fresh.

Therapeutic urinary diets

Research has evaluated the effect of feeding therapeutic urinary diets on resolution of clinical signs in cats with suspected FIC. Five of 6 hematuric cats with suspected FIC fed a Purina therapeutic urinary diet became non-hematuric versus 1 of 7 cats fed a veterinary therapeutic diet from another manufacturer.⁷⁰

Nutritional management of anxiety

Nutritional management of anxious behaviors, as may be associated with stress, has been explored on a limited basis in cats, although not in controlled clinical trials in cats with FIC:

- Purina research showed the proprietary strain of *Bifidobacterium longum* reduced stress and associated behavior in cats.⁷¹
- Other research in cats suggests that alpha-casozepine and L-tryptophan may help reduce anxiety.^{72,73}

MULTIMODAL ENVIRONMENTAL MODIFICATION

Due to the association of FIC with stress, multimodal environmental modification (MEMO) is an important recommendation for cats with FIC.^{32,33,74,75}

MEMO has been defined as “institution of changes in the cat’s environment to attempt to reduce lower urinary tract signs by decreasing the likelihood of activation of the stress response system.”¹⁸ The goal of MEMO is to provide cats with an enriched or “optimized” lower stress environment.^{32,76,77}

Researchers grouped feline environmental needs into five pillars or systems: **nutritional (food and water)**, physical resource (space), elimination (litter boxes and litter), social (social contact), and behavioral (body care and activity).⁷⁶ They noted that providing an enriched environment is important for all cats.

MEMO encompasses:^{32,33,75,76,78}

- Making any changes, e.g., to food, gradually.
- Offering the cat the ability to make choices if the cat desires. During a diet change, presenting the cat with the current food and the new food in two separate bowls allows the cat to choose which diet to eat rather than having the change forced upon them.

Owners should determine whether their cat prefers a particular water source, temperature, and/or receptacle by offering options. A cat may also prefer a particular type of litter box and/or litter.

- Providing ample resources, especially in multi-cat households. “Ample” resources are typically defined as the number of cats in the home plus one of every resource, e.g., litter boxes, food and water bowls, and resting/hiding places. This helps minimize conflict between cats.

Litter boxes should be placed in different locations from food and water bowls. Litter boxes and bowls should be kept clean.

- Locating resources in “safe” areas, where the cat will not feel threatened. It is important to note that this involves an appreciation of what the cat may perceive as a threat regardless of whether it actually is a threat. Providing high towers/perches allows cats to rest where they will not be disturbed, especially but not only useful in households with dogs or small children, and to observe their surroundings.
- Allowing the cat to express natural behaviors, such as predatory and play behavior, e.g., by providing food in food puzzles and/or prey-like toys, and scratching behavior, e.g., by providing scratching posts.
- Making interactions between the owner or other members of the household and the cat positive and predictable. This comprises determining how the cat likes to interact (e.g., playing, being petted or held), what toys the cat enjoys, and how long the cat wishes to interact with family members.

In addition to providing enrichment, toys, play sessions, and puzzle feeders encourage activity, which may help cats maintain ideal body condition.

MEMO should be tailored to the individual cat. Some cats may benefit from intensive management, while less may be needed for other cats.⁷⁵ Working together with the pet owner to develop a MEMO plan is encouraged to help reduce pet owner stress and increase the likelihood of success.⁴⁶

Some research evaluating efficacy of MEMO has been published:

- In an observational study in which a comprehensive individualized MEMO plan was instituted in cats with a history of recurrent FIC, only 28% of cats had further recurrence of LUTS during the follow-up period lasting approximately 10 months.¹⁸ In addition, signs of fear and nervousness and respiratory signs (a sickness behavior suggestive of a comorbidity) significantly lessened.
- In contrast to those results, no benefit in reducing recurrence of LUTS was noted in FIC cats in whom MEMO was instituted compared to FIC cats in whom no environmental modifications were made.³

While the research is limited and results are conflicting, the studies have several limitations. The same environmental modifications (type and number) were not applied for all cats in each study. Cats were in a home environment making the control of other variables not possible. Due to the differences among individual cats in their threshold for stress and causes of stress, research on MEMO is challenging.

Feline idiopathic cystitis is the most common cause of feline lower urinary tract signs and is often recurrent. It may adversely affect a cat’s quality of life, damage the human-animal bond, and lead to relinquishment of the cat or to elective euthanasia. Thus, effective management is crucial. Nutritional intervention, i.e., increasing hydration and feeding therapeutic urinary diets, is a key component of the management of feline idiopathic cystitis.

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