PANDORA SYNDROME: UPDATES ON IDIOPATHIC/INTERSTITIAL CYSTITIS IN CATS (FIC) **UROLOGY/NEPHROLOGY**

Dennis J. Chew, DVM, DACVIM
Tony Buffington, DVM, PhD, DACVN

The interested reader is referred to three recent reviews for more information on FIC. One article provides a concise general overview,[1] another analyzes an evidence-based medicine approach to treatment and an overview of risk factors,[2] and the third article provides yet another perspective.[3]

What Is Pandora Syndrome?

Is this terminology more helpful than FUS or FLUTD or IC (FIC)? Results of studies over the past 20 years indicate that idiopathic/interstitial cystitis in cats is the result of complex interactions between the bladder, nervous system, adrenal glands, husbandry practices, and the environment in which the cat lives. Many cats with a diagnosis of chronic FIC have lower urinary tract–predominant clinical signs that are part of a larger systemic disorder referred to as "Pandora Syndrome."[3,4] Clinical problems outside the lower urinary tract are common in those with a diagnosis of FIC and include signs related to the GI tract, respiratory system, skin, central nervous system, cardiovascular system, and the immune system. It has been traditional to refer to cats that have obvious LUT signs as those having "feline urological syndrome," "feline lower urinary tract disease," or "feline interstitial cystitis" but this method of naming the disease focuses on the organ with the predominant clinical sign rather than a thorough evaluation of the entire cat and all of its organ systems. A diagnosis of Pandora Syndrome would apply to those cats that exhibit clinical signs in other organ systems (in addition to the LUT), waxing and waning of clinical signs associated with stressful events that presumably activate the stress response system, and undergo resolution of severity of clinical signs following effective environmental enrichment. Currently available evidence suggests that many cases of chronic idiopathic LUT signs presently diagnosed as having FIC actually do have a "Pandora" syndrome. The syndrome might result from early adverse experiences that sensitize the neuraxis to sensory input, increasing the frequency and duration of activation of the stress response system (SRS) when the individual is housed/living in a provocative environment. The chronic wear and tear of persistent activation of the SRS can upregulate the inflammatory response in a variety of tissues including the bladder.

What Are the Different Types of Presentations for Cats with Idiopathic/Interstitial Cystitis?

There are four possible urinary presentations associated with FIC. An acute seemingly self-limiting episode of FIC is thought to be the most common condition presenting to primary care practitioners with an estimated relative prevalence of 80 to 95 percent.[5] However, recurrence is likely if stressful situations become severe enough in the future. Frequently recurrent episodes of clinical signs related to FIC are next in occurrence (2–15%), followed by persistent forms of FIC (2–15%) in which the clinical signs never abate. The fourth possibility is for urethral obstruction to develop in male cats suffering from FIC (15–25%). These 4 types of presentations may represent a spectrum of signs from the same disease process, but this hypothesis has not been tested. Most publications reflect data from cats with frequent recurrences or persistent clinical signs that are presented to university referral practices. Based on our data, a potential fifth category could be healthy cats, especially males, that develop LUT signs when exposed to sufficient stressors.[6]

What Are the Differential Diagnoses for Cats with LUT Signs?

Though FIC is the most common diagnosis associated with LUTS in young cats, it is important to exclude the diagnosis of bacterial UTI and urolithiasis in a population of cats with risk factors. Collection of a detailed history that includes queries regarding environmental issues and husbandry practices is an essential first step in deciding if the LUTS are related to irritative voidings or not, and how likely stress may be playing a role. In order to determine if Pandora Syndrome is part of the LUTS, the history and physical examination must be extended beyond that immediately related to the urinary tract. Quantitative urine culture and survey radiography are recommended in the evaluation of all cats with recurrent LUTS to exclude UTI and radiopaque calculi. Advanced imaging that includes contrast radiography, ultrasonography, and urethra-cystoscopy is useful for the exclusion of anatomical defects, radiolucent calculi, and proliferative lesions in some cats.

Where Are We in Our Understanding of the Pathophysiology of FIC ?

Though all the pieces are not completely understood, the basic centerpiece is one of neurogenic inflammation—this type of inflammation is quite different from the standard kind of inflammation classically involving infiltration of

neutrophils. Increased bladder permeability is an important part of this process, as this allows constituents of urine to gain access to the bladder wall. These compounds stimulate sensory nerve endings to carry excessive pain signals to the brain. The "bottom up" theory emphasizes defects in the bladder wall (GAG and or urothelium that increase permeability) and then over-activation of the noradrenergic nervous system. The "top down" theory emphasizes that stressors from the environment can be potent enough to directly activate the SRS and turn on neurogenic inflammation.[7] Unrestrained outflow of sympathetic nervous system activity characterizes this disease. Excess effects of norepinephrine are known to upregulate a variety of inflammatory processes including that in the bladder. Another piece of the pathophysiology is that cats with FIC appear to have mild adrenal insufficiency based on a blunted increase in cortisol concentration following ACTH stimulation compared to normal cats. The adrenal glands of cats are also smaller than those of normal cats and do not contain histopathologic lesions.[8]

Does MEMO Work?

FIC cats in colony housing have higher levels of circulating catecholamines and their metabolites compared to normal cats, especially when exposed to a stressful environment. A return to lower levels of circulating catecholamines occurred in stressed FIC cats following environmental modification, but this response was less complete and took longer than that which occurred in healthy cats.[9] FIC cats were recently reported to have a heightened response to sensory stimuli when measured by the acoustic startle reflex (ASR) compared to healthy cats.[10] The ASR is a defensive brainstem mediated response to sudden intense stimuli. Environmental enrichment led to a significant decrease in ASR in cats with IC compared to healthy cats. Habituation to new housing prior to environmental enrichment decreased ASR in female but not male cats with FIC.[10] Results of this study add to the concept that management of FIC benefits the cat when the patient's perception of unpredictability in the environment is reduced. Outcome of environmental enrichment and modification was proven beneficial to most FIC cats of a clinical study in which these cats had failed multiple other treatments.[11] In addition to a dramatic increase in the use of the litterbox, there were benefits in behavior and some gastrointestinal signs.

Since GAG Excretion Is Decreased in Active and Quiescent Phases of FIC, Is Glycosaminoglycan (GAG) Treatment Helpful in the Treatment of FIC?

No studies have shown a benefit of GAG therapy over placebo using oral N-acetyl-d-glucosamine,[12] injectable pentosan polysulphate (PPS)[13] or oral PPS.[14,15] In a fourth study, oral N-acetyl-d-glucosamine increased plasma GAG concentrations in cats with IC. Subjective improvements in LUT signs were suggested to occur in those treated with NAG but not those treated with placebo.[16]

Is There a Role for Pheromone Therapy in Treatment of FIC?

Feline facial pheromones (FFP) are commercially available (Feliway®) with the listed indication to decrease urinary spraying and marking. Activation of the sympathetic nervous system is part of the vigilance system that results in urinary spraying and marking and it is thought that these products lower the intensity of sympathetic nervous system output. Since unrestrained output of sympathetic nervous system activity is a central component in neurogenic inflammation that occurs in FIC, it seems reasonable that use of FFP could also be useful for treatment of FIC. In one study of hospitalized healthy and sick cats videography was used to score behavior and food intake of cats in which the cage was pretreated with vehicle placebo or feline facial pheromones.[17] Increased grooming, facial rubbing, interest in food, and walking were found in cats exposed to FFP compared to vehicle. Results of this study suggested that hospitalized cats exposed to FFP were calmer and more comfortable in their cages than cats exposed to vehicle. It has been our observation that some cats are very affected by FFP while in others the effect is minimal to nil. A randomized, double-blinded, placebo-controlled, crossover study was performed in 12 cats (9 of 12 completed the full study) with recurrent FIC, comparing once daily environmental treatment with FFP (Feliway®) or placebo. Treatment was for 2 months, and then switched to the other treatment for the next 2 months.[18] This small number of cats exposed to FFP had fewer mean days displaying signs of cystitis, a reduced number of episodes of cystitis, and fewer negative behavioral traits, but these data did not achieve statistical significance for a difference over placebo treatment of the environment.

How Do We Treat an Acute Episode of LUT Signs for Either Its First Time, or an Infrequently Recurrent Event?

We treat nearly all these FIC cats with a combination of buprenorphine and acepromazine PO for 5 to 7 days. The combination of an analgesic and a tranquilizer with properties that also decrease urethral tone seem like a compassionate and appropriate choice of treatment. It is likely that the tranquilizer reduces the activity of the autonomic nervous system, which is useful in the initial treatment of FIC. We believe that this helps to acutely

decrease clinical signs in cats with acute episodes of FIC or flares of chronic FIC, though this has not been specifically studied. Whether this regimen reduces future episodes of FIC has also not been tested. We take the opportunity at the first visit to discuss with the owners that even a first event of FIC may be associated with recurrence and that there may be steps that can be taken to reduce this likelihood (not yet studied in a prospective way) when environmental enrichment and modification are successfully implemented.

What Analgesic Treatments Should I Consider?
The best approach to analgesia for bladder pain (visceral) has yet to be determined. Butorphanol has been used, but its effects are less long-lived or potent than those of buprenorphine.[19,20] Sustained release formulations of buprenorphine have recently become available that can provide up to 72 hours of therapeutic drug levels for pain relief following a single injection. Fentanyl patches have been used in rare cases in which bladder pain was assessed as severe.

Should I Consider NSAID Treatment to Provide Anti-Inflammatory and Analgesic Effects?
Anecdotal reports of the usefulness of non-steroidal anti-inflammatory drugs (NSAIDs), especially meloxicam and ketoprofen, abound, but no studies of safety or effectiveness are available for review. NSAIDs are not commonly used for treatment of interstitial cystitis in humans. NSAIDs that are licensed for use in cats list indications for preemptive pain management, usually as a single treatment before anesthesia and surgery. Chronic use of NSAIDs in cats can be dangerous due to the possibility for development of acute intrinsic renal failure. This is especially worrisome should the cat become dehydrated for any reason at the time of NSAID administration. The FDA recently required the following statement to be added to the label for meloxicam use in cats: "Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information." Robenacoxib is a long-acting NSAID that has recently become available for use in cats; its effectiveness and safety for use in cats with FIC have yet to be reported to our knowledge.

What Is the Most Important Therapy to Recommend to Owners of Cats with Frequently Recurrent or Persistent Signs of FIC?
There is no simple answer to this question but a key component to a successful outcome is empowering the owner with skills that allow the cat's husbandry to be improved and the environment enriched to a point that decreases the magnitude of the cat's stress response system. We refer you to the Indoor Cat Initiative site that is maintained by Dr. Buffington. This site provides a great number of details and resources that can be considered to implement that will reduce the cat's perception of stress and improve its general sense of well-being while living largely in confined spaces with people (and often with dogs too). Environmental enrichment involves effective resource management, including litter box(es) (type, location, number, substrate, cleaning regimen), food and water (type, location, number), resting areas, opportunities to climb and scratch, interactions with people that are positive, and methods to reduce conflict in the living space with other cats, dogs, and humans.[21–23]

Dietary Treatment of FIC?
Unfortunately, there are no reports on the effect of diet on FIC that have not been funded by commercial pet food companies. An older non-blinded and non-randomized study of feeding canned vs. dry diets of similar formulation (Waltham pH Control® funded by a grant from the Waltham Center for Pet Nutrition) in the treatment of 54 FIC showed a beneficial effect of the canned over the dry product.[24] Fifty-two of 54 cats exhibited more than one episode of LUT signs in the prior 12 months. The study lasted for 12 months, or until signs of recurrence occurred. Signs of LUTD did not recur in 16 of 18 cats fed the canned diet, and 17 of 28 cats fed the dry diet ($P < 0.05$). The recurrence rate in cats being fed the dry food was also reduced compared to the rate encountered in the previous year, but not to the degree of benefit observed in cats consuming the wet formulation. The mean urinary specific gravity was lower in urine from cats fed the canned formulation but the basis for the salutary effect of this particular canned product over the dry formulation was not determined.[24] Other factors that could have influenced results of this study include hedonics (the mouth feel of the food) or the ritual associated with the feeding of canned foods and this effect on cat behaviors. The consumption of dry foods is known as a risk factor for the development of LUT disease in cats on a dose-related basis.[25]

The results of a study of feeding an FIC prevention food (Hill's CD Multicare®—study funded by a grant from Hills Pet Nutrition, Inc.) vs. control food for treatment of acute FIC was recently reported in 25 one- to eight-year-old cats that completed the 12-month study.[26] Compared to the control diet, the prevention food was restricted in

minerals (calcium, phosphorus, magnesium), increased in the antioxidants vitamin E and carotene, and increased in the content of long-chain omega-3 fatty acids provided as eicosapentaenoic acid and docosahexaenoic acid (mostly from fish oil). The feeding of the wet or dry formulation was determined by owner preference. Data were combined from cats eating the wet and dry formulations. There were 5 male and 6 female cats in the prevention diet group. The control diet group included 11 male and 3 female cats. At first glance it appears that a disproportionate number of males were randomly assigned to the control group but this was not considered statistically different between diet groups. There was no difference in USG or urinary pH between diet groups at the start of the study.

The primary outcome variable of the study was the number of recurrent episodes in which a cat had multiple (≥ 2 concurrent) LUT signs within a day (i.e., defined as a multiple-sign day) for the duration of treatment. No difference in episodes of multiple-sign days was found between the two groups (4 of 11 prevention diet vs. 9 of 14 control diet; P = 0.24). One cat fed the control diet had 13 recurrent episodes and another cat had 16 recurrent episodes; these very high numbers of episodes from these 2 cats are far greater than other cats encountered in either diet group and may account for some of the findings reported in this study. Cats fed prevention food had significantly fewer episodes of multiple-sign days per 1,000 cat days compared to cats fed the control food (0.7 vs. 5.4). Episodes/1,000 cat days were lower in cats fed the prevention food for hematuria, dysuria, and stranguria, but not for periuria or pollakiuria. The recurrent event rate for the test diet of this study was similar to the same author's previously reported event rate in untreated cats fed their usual maintenance food of a study 10 years earlier,[27] and to other laboratory and clinical studies, suggesting that the custom manufactured control food might have promoted the reported differences. The mean urine pH across the specific scheduled reevaluations was significantly lower for cats consuming the prevention diet (6.3 ± 0.04) than for cats consuming the control food (6.8 ± 0.06). The urinary specific gravity was slightly lower for cats consuming wet vs. dry formulation of the diets. Four of 11 cats fed the prevention diet in this study were prescribed analgesics compared to 12 of 14 cats fed the control diet, a difference that was significant. The authors concluded that foods they tested appeared to impact mean incidence rates of recurrent LUT signs in cats with FIC. Findings from FIC cats fed diets with stress-reducing compounds have yet to be reported.

References

1. Grauer GF. Current thoughts on pathophysiology & treatment of feline idiopathic cystitis. Today's Veterinary Practice 2013;3.
2. Forrester SD, Towell TL. Feline idiopathic cystitis. The Veterinary clinics of North America 2015;45:783–806.
3. Buffington CAT, Westropp JL, Chew DJ. From FUS to Pandora syndrome: where are we, how did we get here, and where to now? Journal of feline medicine and surgery 2014;16:385–394.
4. Buffington CA. Idiopathic cystitis in domestic cats--beyond the lower urinary tract. Journal of veterinary internal medicine / American College of Veterinary Internal Medicine 2011;25:784–796.
5. Lulich J, Osborne C, Kruger J. What constitutes a diagnosis of feline idiopathic cystitis? ACVIM Forum 2010; Anaheim, CA. p. 630–631.
6. Stella JL, Lord LK, Buffington CA. Sickness behaviors in response to unusual external events in healthy cats and cats with feline interstitial cystitis. Journal of the American Veterinary Medical Association 2011;238:67–73.
7. Westropp JL, Buffington CA. In vivo models of interstitial cystitis. The Journal of urology 2002;167:694–702.
8. Westropp JL, Welk KA, Buffington CA. Small adrenal glands in cats with feline interstitial cystitis. The Journal of urology 2003;170:2494–2497.
9. Westropp JL, Kass PH, Buffington CA. Evaluation of the effects of stress in cats with idiopathic cystitis. American journal of veterinary research 2006;67:731–736.
10. Hague DW, Stella JL, Buffington CA. Effects of interstitial cystitis on the acoustic startle reflex in cats. American journal of veterinary research 2013;74:144–147.
11. Buffington CA, Westropp JL, Chew DJ, Bolus RR. Clinical evaluation of multimodal environmental modification (MEMO) in the management of cats with idiopathic cystitis. Journal of feline medicine and surgery 2006;8:261–268.
12. Gunn-Moore DA, Shenoy CM. Oral glucosamine and the management of feline idiopathic cystitis. Journal of feline medicine and surgery 2004;6:219–225.
13. Wallius BM, Tidholm AE. Use of pentosan polysulphate in cats with idiopathic, non-obstructive lower urinary tract disease: a double-blind, randomised, placebo-controlled trial. Journal of feline medicine and surgery 2009;11:409–412.

14. Chew DJ, Bartges JW, Adams LG, Kruger JM, Buffington CAT. Evaluation of Pentosan Polysulfate Sodium in the Treatment of Feline Interstitial Cystitis: A Randomized, Placebo-Controlled Clinical Trial. J Urology 2011;185:e382 (abstract 952).
15. Chew DJ, Bartges JW, Adams LG, Kruger JM, Buffington CT. Randomized trial of pentosan polysulfate sodium for reatment of feline interstitial (Idiopathic) cystitis Journal of veterinary internal medicine / American College of Veterinary Internal Medicine 2009;23.
16. Panchaphanpong J, Asawakarn T, Pusoonthornthum R. Effects of oral administration of N-acetyl-d-glucosamine on plasma and urine concentrations of glycosaminoglycans in cats with idiopathic cystitis. American journal of veterinary research 2011;72:843–850.
17. Griffith CA, Steigerwald ES, Buffington CA. Effects of a synthetic facial pheromone on behavior of cats. Journal of the American Veterinary Medical Association 2000;217:1154–1156.
18. Gunn-Moore DA, Cameron ME. A pilot study using synthetic feline facial pheromone for the management of feline idiopathic cystitis. Journal of feline medicine and surgery 2004;6:133–138.
19. Warne LN, Beths T, Holm M, Carter JE, Bauquier SH. Evaluation of the perioperative analgesic efficacy of buprenorphine, compared with butorphanol, in cats. Journal of the American Veterinary Medical Association 2014;245:195–202.
20. Steagall PV, Monteiro-Steagall BP, Taylor PM. A review of the studies using buprenorphine in cats. Journal of veterinary internal medicine / American College of Veterinary Internal Medicine 2014;28:762–770.
21. Herron ME. Advances in understanding and treatment of feline inappropriate elimination. Top Companion Anim Med 2010;25:195–202.
22. Herron ME, Buffington CA. Feline focus-environmental enrichment for indoor cats. Compend Contin Educ Vet 2010;32:E1–5.
23. Herron ME, Buffington CA. Environmental enrichment for indoor cats: implementing enrichment. Compend Contin Educ Vet 2012;34:E3.
24. Markwell PJ, Buffington CA, Chew DJ, Kendall MS, Harte JG, DiBartola SP. Clinical evaluation of commercially available urinary acidification diets in the management of idiopathic cystitis in cats. Journal of the American Veterinary Medical Association 1999;214:361–365.
25. Buffington CA. External and internal influences on disease risk in cats. Journal of the American Veterinary Medical Association 2002;220:994–1002.
26. Kruger JM, Lulich JP, MacLeay J, et al. Comparison of foods with differing nutritional profiles for long-term management of acute nonobstructive idiopathic cystitis in cats. Journal of the American Veterinary Medical Association 2015;247:508–517.
27. Kruger JM, Conway TS, Kaneene JB, et al. Randomized controlled trial of the efficacy of short-term amitriptyline administration for treatment of acute, nonobstructive, idiopathic lower urinary tract disease in cats. Journal of the American Veterinary Medical Association 2003;222:749–758.