Learning objectives:
1. To understand the role of neurogenic inflammation in the genesis of lower urinary tract signs in feline idiopathic/interstitial cystitis and to further understand that the bladder is more a victim than the perpetrator of these signs (Pandora Syndrome).
2. To be able to employ diagnostic strategies that easily allow the clinician to differential true bacterial urinary infection from urolithiasis and idiopathic cystitis.
3. To appreciate that true bacterial UTI is exceedingly uncommon in otherwise healthy cats less than 10 years old.
4. To understand the role of diet, water intake, and optimal litterbox management in the treatment of FIC.
5. To gain an appreciation that successful implementation of environmental modification and enrichment results in successful outcomes in most cats WITHOUT need for drugs.
6. To understand how to use TCA such as amitriptyline in select cases in which environmental modification is not effective at first.

What is Pandora Syndrome?

Is this terminology more helpful than FUS or FLUTD or IC?

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. A recent review emphasizes that many cats with a diagnosis of FIC have lower urinary tract- predominant clinical signs that are part of a larger systemic disorder referred to as “Pandora Syndrome”. 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.

Are there 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% (Lulich ACVIM Forum Proceedings Anaheim 2010) – recurrence is likely if stressful situations become severe enough in the future. Frequently recurrent episodes of clinical signs related to FIC is next in occurrence
(2 to 15%), followed by persistent forms of FIC (2 to 15%) in which the clinical signs never abate. The fourth possibility is for urethral obstruction to develop in male cats suffering from FIC (15 to 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.

Is it true that bacteria are once again in the forefront of thought for causing signs of LUTD in cats?

The frequency of UTI in reports of young cats with LUT signs is quite low (often reported at less than 2%) in most studies. Idiopathic/interstitial cystitis accounts for 60 to 70% of diagnoses in cats presenting for some form of urinary urgency. In cats older than 10 years, UTI was quite common (>50%) in those evaluated for signs of urinary urgency in one study (Bartges J: Lower urinary tract diseases in geriatric cats, Proceedings of the ACVIM, Lake Buena Vista, Fla., 1997, 322–324); idiopathic cystitis accounted for only 5% of cases in this group of cats.

A study in 2007 of cats from Norway with a variety of obstructive and non-obstructive causes of LUT signs found a surprisingly high number of cats with positive urine culture in large quantitative growth, far more so than in other reports. Findings from this study are difficult to interpret since many of the cultures were from voided midstream (46%) or catheterized urine samples (21%) rather than from the gold standard of cystocentesis (21%); in 10% the method of urine collection was not recorded. 44 of 118 samples cultured on the same day isolated bacteria > 10^3 cfu/ml. In 33 of these 44 samples, growth was > 10^4 cfu/ml and in 20 growth was > 10^5 cfu/ml. Quantitative growth from midstream voided samples from healthy cats is sometimes substantial as was shown in 55% of males and 40% of females that grew > 10^3 cfu/ml in another study (Lees 1984).

UTI does occur in special populations of cats. This includes cats that have been previously catheterized or have had a perineal urethrostomy surgery. Chronic kidney disease (CKD), hyperthyroidism, and/or diabetes mellitus all increase the risk for cats to acquire a true bacterial UTI, though clinical signs of UTI may not be present (asymptomatic bacteriuria). In a report comparing 155 cats with UTI to 186 cats without UTI, significant risk factors to acquire UTI were identified for cats with urinary incontinence, transurethral procedures, gastrointestinal diseases, decreased body weight, and decreased urine specific gravity. 35.5% of cats in this study had no clinical signs associated with their UTI (asymptomatic bacteriuria). UTI in this study was defined as any growth from samples collected by cystocentesis and > 10^3 cfu/ml from samples collected by urethral catheterization. Decreased urinary specific gravity was not identified as a risk for UTI in cats of another study.

In a study of 42 female and 44 male cats with CKD undergoing routine urine culture surveillance, positive urine cultures in samples collected by cystocentesis were identified 31 times from 25 cats over a period up to 3 year of their CKD. Eighteen of the 25 cats (72%) were classified as having occult UTI. Eighty-seven percent of cats with positive urine cultures were found to have active urinary sediment. Increasing age was a significant risk factor to acquire occult UTI in female CKD cats. The presence of UTI was not associated with the severity of azotemia or survival.

Is there a new blood test that can be used to diagnose FIC?

Reliable diagnostic markers for interstitial cystitis (IC) currently are not yet clinically available. Dried serum films from cats were studied using infrared microspectroscopy (IRM) and spectra
were classified using Soft Independent Modeling by Class Analogy (SIMCA)⁷. Cats were classified as healthy or affected with IC – the condition was predicted in 100% of the cats. Analysis of cat samples using liquid chromatography–mass spectroscopy revealed differences in the concentration of tryptophan and its metabolites between healthy and affected cats. These results demonstrate the potential utility of infrared microspectroscopy to diagnose IC.

Figure 1. Spectra from domestic cat serum from FIC, healthy, and subjects with chronic disorders other than FIC Rubio-Diaz 2009.

In a similar study extending this extraction and analytic technology to blood spots, 22 healthy cats were differentiated from 20 cats with idiopathic cystitis when dried blood spot cards were analyzed by infrared microspectroscopy. Differences were again in the region related to metabolites of tryptophan⁸.

Based on the success in the above proof of concept studies using dried serum and dried blood spots in normal cats, FIC cats, and cats with non-urinary chronic disorders, a new study of cats is underway that includes cats with chronic LUT signs due to a variety of disorders (stones, tumor, UTI, behavioral, anatomical, obstruction). Results of this study will determine if this method can distinguish FIC from other LUTD disorders. A single drop of blood is placed onto the dot area on the card and allowed to dry for at least 4 hours. The card is then stored in specially provided low gas permeable ziplock bags (regular grocery store bags are NOT adequate). Storage for a few days in the refrigerator is acceptable before shipping. The samples must be accompanied by a completed history of clinical signs, physical exam findings, and results from urinalysis, urine culture, and imaging that the cat may have had performed and your clinical diagnosis.

Are there other biomarkers for FIC?

None are presently available for clinical use. Urinary levels of antiproliferative factor, heparin-binding epidermal growth-like factor, and epidermal growth factor distinguish human patients with interstitial cystitis from healthy controls, but have not been investigated in FIC. 1-D gelelectrophoresis revealed that the urine protein pattern in cats with idiopathic cystitis was significantly different from control cats. Urinary fibronectin was increased in cats with idiopathic cystitis compared to control cats and those with UTI or urolithiasis, and could considered as a biomarker for FIC. It could also be important in the pathophysiology of this disease as fibronectin is important in cell adhesion, migration, growth, and differentiation⁹.

Decreased urinary Trefoil factor 2 (TFF2) in cats with FIC compared to control was demonstrated using quantification of Western blot signal intensities and immunohistochemistry. A decreased ability to repair the urothelium could result from a deficiency of TFF2, so this could be operative in the pathophysiology of FIC as well as serving as a biomarker for FIC¹⁰.
Three studies in cats have shown decreased glycosaminoglycan (GAG) excretion in cats with FIC. An early study showed reduced urinary total GAG in both random and 24-hour urine samples for those with FIC 11. In a study by another group, urinary glycosaminoglycan concentration was greatly decreased in animals with idiopathic cystitis when compared to normal adult cats. Chondroitin sulfate comprised the main urinary GAG and was thought to originate from the circulation following filtration by the kidney 12. Low urinary total GAG was again a finding in the most recent study of FIC 13. It is unclear whether low urinary GAG in these studies is due to changes in synthesis, metabolism, or bladder permeability. Low glycosaminoglycan levels could reflect damage to the bladder surface, resulting in absorption and/or degradation of the endogenous urinary glycosaminoglycans.

We do not yet know whether these differences are related to the cause(s) or consequences of the syndrome, neither, or both.

Can you summarize where we are 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 increase in bladder permeability likely involves changes in the GAG layer and the integrity of the structure and function of the urothelium. The stress response system (SRS) becomes activated but is not adequately terminated by release of cortisol as it is in normal cats. 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. Infiltration with mast cells is important in some cats with FIC – degranulation of mast cells then contributes to the inflammatory process (vasodilation, edema, diapedesis of RBC, recruitment of sensory nerves with NGF). Local axon reflexes within the bladder wall can result in vasodilation directly, degranulation of mast cells, and detrusor muscle contractions. Certain constituents of urine that gain access to the bladder wall are more potent stimulators of pain than others; absence of some substances in urine can magnify the pain response. 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 14. 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 15. One explanation proposes that these small hypofunctioning adrenal glands are the result of a maternal perception of threat from the environment that is transmitted to the fetus from hormones that cross the placenta to effect the development of the fetal adrenal gland at a critical time for its development. 16. It should be emphasized that only adrenocortical steroid measured was that of cortisol, and that many other adrenocorticosteroids have the potential to also be deficient 17, but this has not yet been studied in cats. Cats with idiopathic cystitis do not appear to experience long-term benefit from current glucocorticoid therapy regimens. The same in utero developmental story just described could also account for a fetal stress response that has been programmed toward enhanced vigilance that would then be manifested after birth by an intense SRS output when the cat faces provocateurs. 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. 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. 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. 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. Urodynamic evaluation of female cats with FIC revealed no finding of spontaneous detrusor muscle contraction that can occur in overactive bladder (OAB) further separating FIC from OAB. Consequently, drugs that target detrusor muscle contraction do not appear warranted in cats with FIC. High maximal urethral closure pressure (MUCP) was documented in female cats with FIC of the same study, suggesting that alpha-1 adrenoceptor antagonists, alpha-2 agonists, or skeletal muscle relaxants could potentially be useful treatment but this has yet to be studied.

Since GAG excretion is decreased in active and quiescent phases of FIC, is glycosaminoglycan (GAG) treatment helpful in the treatment of FIC?

Three studies have employed glycosaminoglycan (GAG) as treatment for FIC, none of which were able to show a benefit over control. In the first study, 40 cats with recurrent idiopathic cystitis were treated with either 125 mg N-acetyl glucosamine or a placebo by mouth daily for six months. No significant differences were observed using the owner assessment of the mean health score, the average monthly clinical score, or the average number of days with clinical signs. Both groups improved over the course of the study, possibly due to salutary effects from dietary change initiated at the start of the study. In a second study of 18 cats, injectable pentosan polysulphate (PPS) was compared to control injections in cats with non-obstructive idiopathic cystitis. Subcutaneous injections of PPS were given at 3mg/kg on days 1, 2, 5, and 10. Clinical signs were not different between treatment groups when evaluated on day 5, 10, 14, and then 2, 6, and 12 months. A multicenter study involved 4 universities comparing BID oral PPS to placebo as treatment in 107 cats with interstitial cystitis. Enrolled cats had at least two episodes of LUTS within the past six months, cystoscopic findings of glomerulations, and absence of an alternative diagnosis. Cats were randomly assigned to 0.0 (vehicle placebo), 2.0, 8.0 or 16.0 mg/kg PPS orally twice daily for 26 weeks. No statistically significant differences were observed between any of the groups based on the owner's evaluation of clinical signs or overall improvement in cystoscopic score. A statistically significant decrease in friability score on cystoscopy was observed at the 16.0 mg/kg dose. Clinical improvement occurred in most cats (owner reported scores decreased by 75% in all groups), regardless of the dose of PPS administration or changes in cystoscopic appearance of the bladder. It is likely that accidental environmental enrichment occurred during this study which could account for the improvement scores in all cats overall. In a 4th study, N-acetyl-d-glucosamine (NAG) at 250 mg PO once daily significantly increased plasma GAG concentrations in cats with IC after 21 days of treatment. Subjective improvements in LUT signs were suggested to occur in those treated with NAG but not those treated with placebo.

Is there a role for pheromonotherapy 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 pre-treated with vehicle placebo or feline facial pheromones\textsuperscript{25}. 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 \textsuperscript{26}. 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 this data did not achieve statistical significance for a difference over placebo treatment of the environment.

**Is there a role for amitriptyline or other tricyclic anti-depressant (or analgesic) TCA for the treatment of FIC?**

In some cases YES. The need for this kind of therapy has dramatically lessened since we as a profession have become much more successful at implementing environmental modification, which usually works well without need for chronic drug therapy. We do prescribe amitriptyline for its beneficial effects for cats with FIC that have frequent recurrences or persistent LUT signs AFTER the client’s best efforts to implement environmental enrichment have failed to improve the cat’s clinical signs. This type of therapy should NOT be undertaken for an initial episode of FIC or a “flare” of signs that occur infrequently. We sometimes prescribe amitriptyline for cats owned by clients that are considering euthanasia for their cat with FIC – this can sometimes allow the client to see early benefits while implementing environmental enrichment. Maximal beneficial effects of TCA, if any, often require weeks to months to be observed and in general should not be abruptly discontinued (so called “abrupt withdrawal syndrome”). Treatment series of FIC with amitriptyline has been reported 3 times, 1 study of chronic FIC (frequently recurrent or persistent signs) and 2 of acute bouts of FIC. In the chronic study, 15 cats were enrolled with FIC that failed to respond to other treatments; no placebo group was treated. Amitriptyline treatment (10 mg PO every 24 hours in the evening) successfully decreased clinical signs of severe recurrent FIC in 9 of 15 cats treated for 12 months (11 of 15 cats for the first 6 months). Somnolence, weight gain, decreased grooming, and transient cystic calculi were observed during treatment in some cats. Despite clinical improvement, cystoscopic abnormalities persisted in all cats at the 6- and 12-month evaluations \textsuperscript{27}. In one short term study, 31 untreated male and female cats with acute (<14 days signs), nonobstructive, idiopathic lower urinary tract disease were enrolled in a placebo controlled study. Cats were hospitalized and treated with 5mg amitriptyline or a placebo daily for 7 days and then treatment discontinued. Clinical signs and hematuria resolved similarly in both groups of treated cats by day 8. Cats were evaluated in the clinic 1 month later and by questions over the telephone 6, 12, and 24 months after treatment. Clinical signs recurred faster and more frequently (10.5 vs. 2.4 events/1,000 days) in the amitriptyline treated cats, a finding likely attributable to the abrupt withdrawal of amitriptyline treatments after 7 days- there was no difference in recurrence when the first 21 days were excluded from the analysis \textsuperscript{28}. In another short term study of FIC, amitriptyline at 10 mg once daily per os (11) or placebo (13) was given for 7 days by owners at home. All cats were also treated with amoxicillin BID for 7 days. The severity of clinical signs was assessed at days 0, 7, and 14 – no significant difference was found between amitriptyline and placebo treated cats of this study\textsuperscript{29}.

**How do we treat an acute episode of LUT signs for either its first time, or an infrequently recurrent event?**

We treat nearly all FIC cats of this type 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 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 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 30-32. Outcome of environmental enrichment and modification was proven beneficial to most FIC cats of a study in which they had failed multiple other treatments 33. In addition to a dramatic increase in the use of the litterbox, there were benefits in behavior and some gastrointestinal signs.

**Is there anything new regarding dietary treatment of FIC?**

A non-blinded and non-randomized study of feeding canned vs. dry diets of similar formulation (Waltham pH Control®) in the treatment of 54 FIC showed a beneficial effect of the canned over the dry product 34. 52 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 34. 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 35. The results of a test food vs control food as treatment of FIC was recently reported as an abstract in 31 cats over 12 months. The test food contained more anti-oxidants and omega-3 dietary oil than the control food as the main difference. The feeding of the wet or dry formulation was determined by owner preference. The number of episodes for LUT signs and days exhibiting LUT signs (1.3 vs. 10.3 events/1000 days) were fewer in cats fed the test food of this study. Outcome was the same during the feeding of either the wet or dry formulations of the test food36. The event rate for the test diet was not significantly different from the same author’s previously reported event rate in untreated cats 28; the basis for the effect of the control or test formulations in this study was not determined.
How important are non-specific therapeutic responses in treatment of FIC?
Nonspecific therapeutic responses might occur during treatment of cats with FIC, possibly by altering their perception of their surroundings as part of a placebo-response. The effectiveness of environmental enrichment suggests that pharmacological or other therapeutic interventions face an important barrier to demonstrate efficacy in the presence of the large therapeutic response to this approach in cats with the syndrome.
Figure 2. **Neurogenic inflammation as it affects the urinary bladder in interstitial cystitis.** Sensory neurons (C-Fiber) seem to play a central role in transmission of action potentials via the dorsal root ganglia (DRG) to the spinal cord (SC) and brain. These signals may be perceived as painful by the brain. Sensory fibers also can propagate a local axon reflex without transmission of an axon potential. The axon reflex results in release of peptide neurotransmitters such as substance P (SP) by the nerve endings. Interaction of SP with receptors on vessel walls results in vascular leakage, which can be augmented by SP-induced release of histamine by mast cells. These actions may give rise to the submucosal petechial hemorrhages (glomerulations) observed at cystoscopy. Receptors for SP also occur on smooth muscle, which when activated stimulate muscle contraction. Also shown are the urothelium (epithelium) and the overlying glycosaminoglycan (GAG) layer adjacent to the bladder lumen. Damage or malfunction of either or both of these layers may permit constituents of the urine, such as protons, potassium ions, or hyperosmolar (>2,000 mOsm/L) fluid to activate the sensory fibers. The effects of stress on sensory fibers may be related to descending efferent sympathetic (SNS) signals stimulating the DRG and inducing peripheral release of neuropeptides. Local release of neurotransmitters by bladder sympathetic fibers also could stimulate sensory fibers. Another factor probably involved in chronic, neurogenic inflammation of the bladder, but not shown, is local and systemic release of nerve growth factors, which may promote sensory fiber terminal sprouting to increase the size of sensory fiber receptive fields.
Figure 3. **Imbalanced neuroendocrine system of cats with idiopathic cystitis.** Excitatory sympathetic nervous system (SNS) outflow is inadequately restrained by cortisol and other adrenocortical steroids. This enhanced activity can increase tissue permeability, resulting in increased sensory afferent activity. Feedback inhibition at the level of the anterior pituitary and hypothalamus also is reduced, which tends to perpetuate corticotrophin releasing factor (CRF) output. Neurosteroid production by the adrenal cortex, which generally enhances central nervous system (CNS) inhibitory tone during chronic stress, also may be reduced. The bold solid arrows indicate stimulation, and the dotted arrows indicate. Line thickness is intended to indicate intensity of the signal.

Figure 4: A Normal bladder. Urine is repelled by the normal uroepithelium of the bladder and the glycosaminoglycan (GAG) layer. B: Chronic FIC showing increased bladder permeability. The GAG layer (1) or the GAG layer and the uroepithelium (2) have been damaged, allowing urine to permeate the bladder wall. Increased permeability in chronic FIC cats has been demonstrated even when cats were not showing signs of active inflammation. Infiltration with mast cells and increased numbers of sensory nerve fibers are a result (2).
Figure 5. What do WE Do? Step-wise approach to treatment of cats with idiopathic lower urinary tract signs. More diagnostics should be performed when cats fail to spontaneously clear of their initial lower urinary tract signs and when signs recur to ensure that the diagnosis is really idiopathic lower urinary tract disease. Properly controlled clinical trials may provide better approaches to treatment in the future, but this is what we do in the interim.

**Lower Urinary Tract Signs**

Minimum database: Urinalysis + Abdominal x-ray if signs >7 days
Urinary history (vertical vs horizontal periuria? Irritative voidings?)
Detailed environmental history

Provide analgesia/antispasmodics for “flare” : Acepromazine + Buprenorphine

“Watchful” waiting - spontaneous resolution
Client education -
“From the cat’s point of view”
Litter box management
• Unscented litter / texture / depth
• Preferences / aversion
• Location / ventilation / access to box
• Increased cleaning frequency
Clean up and eliminate “accident” odors

**Signs recur or persist?**

+ Consistent diet (canned = best)
  + Increased water intake
  + Stress reduction

**Signs recur or persist?**

+ Facial pheromones
+ More water intake dynamics
+ More stress reduction
Extended database:
  Urine culture
  Contrast radiography
  Ultrasonography

**Signs recur or persist?**

+ Amitriptyline (?)
+ GAG (?)
+ More stress /
  behavioral modification
+ More or greater analgesia
Cystoscopy (?)
Repeat MDB
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 are useful for the exclusion of anatomical defects, radiolucent calculi, and proliferative lesions in some cats.
Figure 7. Likelihood for Diagnosis of LUT Signs

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Figure 7. A diagnostic approach for cats with LUTS, emphasizing the distinction between those cats that are obstructed or not, and cats that do or do not have irritative voiding. See text for further details as to when specific testing is most helpful and appropriate.
Table 1: Drugs used in the management of FIC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Indications</th>
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<th>Potential adverse effects</th>
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<tr>
<td>Butorphanol (Torbugesic®)</td>
<td>Synthetic partial opioid agonist</td>
<td>Analgesia, acute episode</td>
<td>0.2-0.4 mg/kg q8h PO or SC</td>
<td>Sedation</td>
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<td>Buprenorphine (Buprenex®)</td>
<td>Synthetic partial opioid agonist</td>
<td>Analgesia, acute episode</td>
<td>0.01-0.02 mg/kg q12h to q8h PO or SC</td>
<td>Sedation</td>
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<td>Acepromazine (PromAce®)</td>
<td>Phenothiazine derivative</td>
<td>Sedation, anti-spasmodic</td>
<td>0.05 mg/kg q8h SC</td>
<td>Sedation, hypotension</td>
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<td>Fentanyl (Duragesic®)</td>
<td>Opioid agonist</td>
<td>Analgesia, acute episode</td>
<td>25 μg/hr</td>
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<td>Prazosin (Minipress®)</td>
<td>α1-adrenoceptor antagonist</td>
<td>Anti-spasmodic</td>
<td>0.5 mg per cat q12h PO</td>
<td>Sedation, hypotension</td>
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<tr>
<td>Phenoxybenzamine (Dibenzyline®)</td>
<td>α1-adrenoceptor antagonist</td>
<td>Anti-spasmodic</td>
<td>2.5 mg per cat q12h PO</td>
<td>Sedation, hypotension</td>
</tr>
</tbody>
</table>

**Acute therapy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Indications</th>
<th>Dosage</th>
<th>Potential adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (Elavil®)</td>
<td>Tricyclic antidepressant</td>
<td>FIC</td>
<td>5 to 12.5 mg per cat q24h PO</td>
<td>Sedation, anti-cholinergic effects, weight gain, urine retention, urolith formation</td>
</tr>
<tr>
<td>Clomipramine (Clomicalm®, Anafranil®)</td>
<td>Tricyclic antidepressant</td>
<td>FIC, urine spraying</td>
<td>0.5 mg/kg q24h PO</td>
<td>Sedation, anti-cholinergic effects</td>
</tr>
<tr>
<td>Buspirone (BuSpar®)</td>
<td>Non-benzodiazepine anxiolytic</td>
<td>FIC, urine spraying, anxiety</td>
<td>2.5 to 5.0 mg per cat q12h PO</td>
<td>Rare: sedation, other neurologic effects</td>
</tr>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td>Selective serotonin reuptake inhibitor</td>
<td>FIC, urine spraying</td>
<td>1 mg/kg q24h PO</td>
<td>Rare: decreased food intake, vomiting, lethargy</td>
</tr>
<tr>
<td>Pentosan polysulfate sodium (Elmiron®)</td>
<td>Glycosaminoglycan (GAG) supplement</td>
<td>FIC</td>
<td>50 mg per cat q12h PO</td>
<td>Rare: vomiting, diarrhea</td>
</tr>
<tr>
<td>F3 fraction of feline facial pheromones (Feliway®)</td>
<td>Synthetic pheromone</td>
<td>Anxiety, FIC</td>
<td>1 spray in affected area q24h or room diffuser</td>
<td>None reported</td>
</tr>
</tbody>
</table>

**Chronic therapy**
“Pearls” Pandora Syndrome – aka Feline Interstitial/Idiopathic Cystitis (FIC)
1. Signs of urinary urgency during FIC may be expressions of a systemic disease created by a highly active outflow (unrestrained) from the sympathetic nervous system in response to stressors (provocateurs).
2. When multi-modal environmental modification (including environmental enrichment) is effectively implemented, treatment with drugs is RARELY NEEDED.
3. Stress up-regulates the inflammatory potential of several organs, including the bladder.
4. Bacterial urinary infections (UTI) are rarely identified in cats with signs of lower urinary tract disease, unless they have specific risk factors (U-cath within last 6 months, perineal urethrostomy, dilute urine – CKD, diabetes mellitus, hyperthyroidism).
5. The term “Pandora Syndrome” should help to remind the clinician that LUT signs may be part of a bigger picture that involves other organ systems.
6. We advocate the use of analgesia (buprenorphine) during acute episodes of FIC.
7. We use tranquilization with acepromazine in combination with buprenorphine in most of our cases of non-obstructive episodes.
8. On occasion, the use of amitriptyline can be useful in the treatment of FIC.
9. The use of GAG (glycosaminoglycan) supplementation has failed to show an effect superior to placebo in several studies of FIC treatment.
10. The use of feline facial pheromones has not been shown to be superior to placebo in the treatment of FIC.
11. The feeding of as much wet food as possible in the diet is advocated by some for its protective effect on the recurrence of the signs of FIC, and may be helpful as long as it does not result in additional threat to the cat.
12. There is no indication for surgery in non-obstructive FIC.
13. When surgery is performed in patients with FIC, obtain a full thickness bladder biopsy to allow evaluation of mast cells with special stains (toluidine blue).
14. Sometimes a so-called “placebo” treatment actually can have a positive effect between the cat, the owner, and the environment such that a positive outcome is achieved.
15. In most cases, antibiotic treatment does not have a role in the treatment of FIC.
16. Treatment of FIC with glucocorticosteroids has not shown an effect greater than that of placebo in limited study.
17. Chronic treatment of FIC with NSAIDs is NOT ADVOCATED due to the high sensitivity of the cat to sustain renal injury with this class of drugs, especially if there is any tendency toward dehydration.

References


