FROM FUS TO PANDORA SYNDROME, PART 1: BACKGROUND AND DIAGNOSIS

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Introduction

Signs referable to the lower urinary tract (LUT) are one of the most common reasons cats in the USA are presented for care to veterinarians. These signs can include variable combinations of dysuria, hematuria, periuria, pollakiuria, and stranguria. Many causes for these clinical signs have been identified; the most common causes appear to include idiopathic disease, urolithiasis, infection, neoplasia, and anatomic abnormalities of the LUT. The name for this group of diseases has gone through several changes over the past 50 years. Osborne, et al.,1,2 have repeatedly recommended replacement of the term “Feline Urologic Syndrome (FUS)”3 with descriptive terms pertaining to the site, causes, and pathophysiologic mechanisms whenever possible to permit the same terminology and approach to diagnosis and treatment used for other species to be used for cats. Unfortunately, their 1984 chapter, subtitled “Feline Lower Urinary Tract Disease with Heterogeneous Causes”, resulted in replacement of one acronym (FUS), with another (FLUTD). Such vague, obsolete, “urocentric” terms have lost their clinical utility as more recent research has provided accurate diagnostic methods for the causes of many if not most of these signs. Moreover, research has demonstrated that these signs also can sometimes reflect a disease elsewhere that is affecting the LUT rather than a problem intrinsic to the LUT itself.4

These findings have revealed that researchers and clinicians now must look beyond the LUT to consider the whole individual when evaluating cats with LUT signs. This change has come in part as the result of studies using cats with severe, recurrent idiopathic LUT signs and variable comorbidities that have demonstrated that these cats provide a naturally occurring disease analog of a chronic pain syndrome in humans called interstitial cystitis (IC).5 As in veterinary medicine, the names to describe this syndrome also are in flux in human medicine, with (also urocentric) suggestions including painful bladder syndrome/IC, bladder pain syndrome/IC, bladder hypersensitivity syndrome, and bladder pain syndrome. Thus, names such as FUS or FLUTD to describe recurrent LUT signs over simplify the problem and focus on the end organ rather than reflecting current understanding of the various causes of these signs. I have proposed use of “Pandora Syndrome” to describe cats with chronic LUT and other clinical signs, for at least two reasons; 1) this term does not identify any specific cause or organ, and 2) it seems to capture the dismay and dispute associated with the identification of so many problems outside the organ of interest of any particular subspecialty.4

Clinical research on IC in humans has expanded to include both genetic6 and epigenetic influences7, to show that comorbid disorders often occur before the onset of LUT signs8, and to document the extent of systemic involvement that occurs in most patients.9 Similar to humans, evidence has accumulated that additional problems outside the LUT commonly are present in cats with chronic LUTS.4 This evidence has led to reconsideration of the cause(s) of the syndrome in these individuals, as well as to considerable debate about the most appropriate nomenclature, diagnostic approach, and treatment recommendations.
Cats can be presented for an initial occurrence of idiopathic LUT signs and may not return for care due to (an often presumed) improvement in the condition, or can return with recurrent LUT signs. Both genders appear to be affected equally. Although FIC can be obstructive or non-obstructive in its presentation, urethral obstruction is far more common in male cats, with no difference reported between intact and castrated males. In addition to genetic and possible early adverse life events, other factors associated with an increased risk for chronic LUT signs have been reported, and include excessive body weight, decreased activity, multiple cat households, indoor housing, and a variety of environmental stressors such as conflict with another cat in the household.

Recent research further complicates the diagnostic challenge, however, because cats may have multiple reasons for their clinical signs as well as other medical and environmental conditions that need to be addressed. For example, some cats with severe, chronic LUT signs seem to have a functional rather than a structural lower urinary tract disorder, and periuria has been found to occur in apparently healthy cats exposed to stressful circumstances.
Recent Research Findings

Infectious disease etiologies

Although microorganisms in the LUT have not been identified as a common cause of (F)IC or associated with chronic LUT signs in the USA, a 2007 study from Norway of 134 cats with a variety of obstructive and non-obstructive causes of LUT signs found a surprisingly high number of cats with bacteriuria exceeding $10^5$ CFU/mL in 44 (33%) cats, and exceeding $10^4$ in 33 (25%), either alone or with variable combinations of crystals and uroliths. These percentages are much greater than those reported from other studies. Interpretation of the general significance of findings from this study is complicated by the proportions of the samples that were obtained from voided midstream (46%) or catheterized urine samples (21%) rather than from the gold standard of cystocentesis (21%; in 10% of cases the method of urine collection was not recorded). In samples cultured on the same day they were collected, bacteria > $10^3$ cfu/ml were isolated from 44 of 118 cats. In 33 of these 44 samples, growth was > $10^4$ cfu/ml and in 20 growth was > $10^5$ cfu/ml. The authors speculated that this higher rate for discovery of UTI in cats with LUT signs might have resulted from differences between cases diagnosed at primary and tertiary care facilities, though geographical differences in occurrence in the development of UTI cannot be excluded. Quantitative growth from midstream voided samples from healthy cats also can be substantial; one study found > $10^3$ cfu/ml in cultures from 55% of males and 40% of females. In human beings, one recent study found evidence of UTI within the past 2 years in 38% of the patients with IC they studied, although they reported that, “... the infection domain was not associated with any increased symptoms.” It also has been speculated that intrinsic abnormalities of the LUT make it more vulnerable to microbial colonization, which could be consistent with the observation of increased risk for bacterial UTI in patients with (F)IC.

The potential role of viruses in FIC also continues to be investigated. The feline caliciviruses, FCV-U1 and FCV-U2, have been the most studied. Feline calicivirus (FCV) viruria has been detected in cats with chronic LUT signs and in cats with upper respiratory infections; however, its etiologic significance has not been determined. Serologic results suggested increased FCV exposure in cats with “FLUTD” compared with controls.

A weak association between seropositivity for Bartonella spp. and FIC also has been reported. What, if any, role these agents play in the etiopathogenesis of chronic LUT signs, or in the systemic manifestations of the syndrome, remains unknown at this time. Lund, et al., recently reported the prevalence of various viral infections in client-owned cats, with clinical signs of FLUTD and 73 healthy control cats, recruited from the Department of Companion Animal Clinical Sciences at the Norwegian School of Veterinary Science from 2006 to 2009. Urine samples were tested for the presence of FCV, feline coronavirus (FCoV) and feline herpesvirus-1 (FHV-1) by polymerase chain reaction. All urinary samples were negative for FCV and FCoV. Only one percent of urines from cats diagnosed with FLUTD were found to be positive for FHV-1, indicating that the viral infections examined were not associated with signs of FLUTD in the study sample.

Bladder and Systemic abnormalities in FIC

A variety of abnormalities have been reported in the urine, bladder and sensory apparatus of cats with chronic LUT signs (reviewed in4). What is far less clear is what role(s) these abnormalities might play in the etiopathogenesis and progression of the syndrome, which are results of it, and which are unrelated “bystander” findings. In humans presenting with chronic LUT signs, urodynamic evaluations often are performed to rule out other LUT diseases, such as overactive bladder, that could account for the clinical signs. Although a decrease in bladder compliance has been reported in cats with FIC, a recent study found no urodynamic evidence for spontaneous bladder contractions (overactive bladder) in female
cats with FIC. However, increased urethral closure pressures were noted in cats with FIC compared to healthy cats, despite a lack of clinical signs at the time the studies were performed, suggesting the possibility of enhanced sympathetic tone. Alterations in autonomic function of the urethra of cats with FIC in vitro previously have been reported. Another recent study reported that the acoustic startle response, a brainstem reflex in response to unexpected loud stimuli, appears to be amplified in cats with FIC. The startle response was greatest and most different in cats with FIC from that of healthy cats during stressful situations, but was still greater in affected than in healthy cats even when adapted to enriched housing conditions.

**Epigenetic Studies**
A range of studies support the concept that the central stress response of patients with (F)IC is unusually sensitive. Recent research suggests that one mechanism underlying the sensitization of the stress response system involves a process called epigenetic modulation of gene expression. Epigenetic modulation of gene expression is a prominent candidate mechanism for the exaggerated stress responsiveness found in cats with FIC because it has been shown to occur in the offspring of pregnant females exposed to stressors, and to result in long term neuroendocrine abnormalities. Importantly, research in both rodents and cats also has demonstrated that effective environmental enrichment can mitigate much of the effect of early life adversity, possibly also by epigenetic modulation of gene expression.

**Comorbidities**
A recent study of healthy cats and cats with FIC found that environmental stressors resulted in increased number of sickness behaviors (e.g., vomiting, lethargy, anorexia) in cats with FIC when the results were controlled for other factors. Furthermore, cats with FIC have variable combinations of co-morbid disorders, such as behavioral, endocrine, cardiovascular, and gastrointestinal (GI) problems. Most human beings with IC also suffer from variable combinations of comorbid disorders that affect a variety of other body systems. That patients with FIC and IC have variable combinations of other comorbid disorders, and the observation that no temporal relationship has been identified among them raises the question of the extent to which a different etiology affects each organ versus the extent to which some common disorder affects all organs, which then respond in their own characteristic ways. Regardless of the eventual explanation(s), the breadth and consistency of these findings makes it imperative that clinicians evaluating cats presented for chronic LUT signs perform a thorough history and physical examination rather than focusing exclusively on the bladder, and obtain a detailed environmental history from owners of all cats with FIC, and for that matter all cats with chronic disease syndromes to avoid missing comorbidities that may suggest the presence of other manifestations of Pandora Syndrome. Some obvious candidates include type-2 diabetes mellitus, asthma, “behavioral inappropriate elimination”, and upper and lower gastrointestinal dysfunction.

**Conclusions**
Clinical and basic science investigations over the past three decades have resulted in a more complex view of chronic LUT signs, both in human beings and domestic cats, challenging the traditional view that the bladder is always the perpetrator of LUT signs, in contrast suggesting that the bladder also can be one victim of a systemic process associated with a sensitized central stress response system. An overarching principle is that LUT signs and a variety of other signs can occur as a consequence of placing a “sensitive cat” into a “provocative” environment. The relationship between the environment and health also is quadratic rather than linear, with both deficient and threatening environments leading to poor health outcomes. With current technology, we have the opportunity to develop collaborative strategies to learn far more about “FUS”, “FLUTD”, “FIC”, “Pandora Syndrome”, or
whatever one’s preferred term is; potentially enough to come up with a truly evidence-based nosology, and treatment(s) based on this understanding.

Finally, one must keep in mind that even presumably healthy cats can develop sickness behaviors related to the LUT when exposed to sufficiently provocative environments, and meeting the environmental needs of all pet cats to ensure their health and well-being is an animal husbandry responsibility we shoulder when we keep them as pets. While the cats studied to date appear to be more sensitive to their surroundings than healthy cats are, they just seem to be further along on a continuum that likely includes all pet cats.

References


