Diagnostic approach to cats with lower urinary tract signs

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Introduction

A combination of findings from history (including details related to behavior, the environment, husbandry practices), physical examination (including all body systems in addition to the lower urinary tract), urinalysis, serum biochemistry, and quantitative urine culture are often needed to establish a definitive diagnosis for the causes of lower urinary tract signs (LUTS). Routine and advanced urinary tract imaging provide pivotal diagnostic anatomical information in cats with recurrent LUTS. Histopathology of urinary bladder or urethral tissue is rarely needed to make a diagnosis except in the instance of neoplasia. Feline idiopathic/interstitial cystitis (FIC) is largely a diagnosis of exclusion of bacterial urinary infection, urolithiasis, and neoplasia. Treatment is dictated by an accurate diagnosis for the causes of LUTS. Figure 1 shows

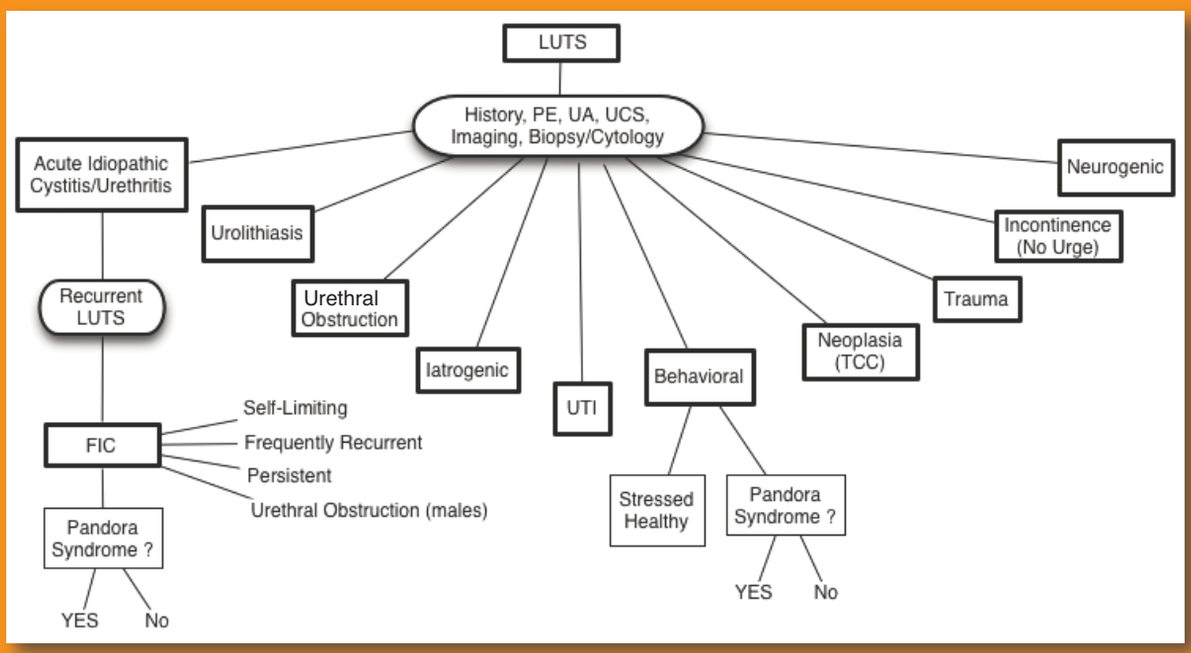

FIGURE 1 Possible causes of LUTS in cats after appropriate diagnostic evaluation. PE = physical examination; UA = urinalysis; UCS = quantitative urine culture (cfu/ml); Imaging = some combination of radiography, contrast urography, ultrsonography and/or uroendoscopy

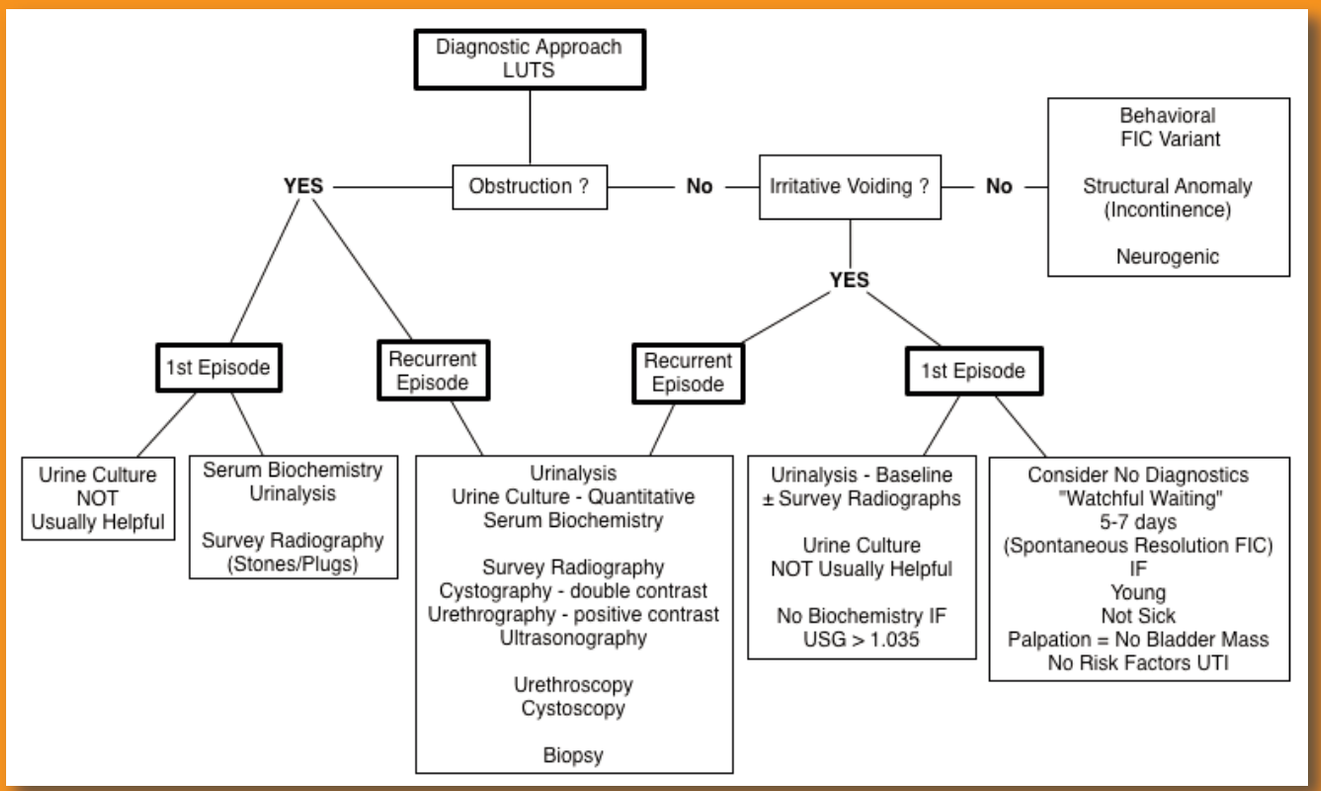

FIGURE 2 A diagnostic approach for cats with lower urinary tract signs (LUTS), emphasizing the distinction between cats with or without urinary obstruction and those with or without irritative voiding. See text for further details as to when specific testing is most helpful and appropriate

the many possible causes of LUTS in cats after appropriate diagnostic evaluation.

History/clinical findings

The signalment, history, and clinical findings provide helpful information to identify the cause of LUTS. Age, breed, gender and neuter status, diet, litter box management, access to the outdoors and other environmental factors are important in the overall assessment of the likelihood for any specific cause of LUTS.

Cats with disorders affecting the lower urinary tract display variable combinations of pollakiuria, stranguria, periuria, dysuria, and/or hematuria. Vocalization such as howling may be observed due to the pain and discomfort associated with LUTS. Urge incontinence is common in obstructive (overflow) and non-obstructive FIC as well as in cats with urolithiasis, urinary tract infection (UTI) and neoplasia. Periuria (urinating in inappropriate locations) unassociated with urgency is common in urinary behavioral disorders, patent urachus, ectopic ureter and neurogenic disorders; it is sometimes the only sign in FIC. These clinical signs are neither specific nor sensitive for any one particular disease.

The most common clinical sign in cats with non-obstructive FIC is periuria, with or without other clinical signs suggesting irritative voiding.[1,2] Clinical signs of FIC often wax and wane and appear to be exacerbated by stressors and deficiencies in the environment.[3–15] The extent and severity of clinical signs will be more severe in cats with complete urethral obstruction from the systemic effects of post-renal azotemia (electrolyte and acid-base derangements along with dehydration).

A detailed collection and analysis of history is necessary to determine behavioral and environmental influences on cats with FIC and behavioral disorders (covered elsewhere in this symposium). Affected cats are often over-reactive to their environment and may display nervous, fearful, defensive or aggressive behaviors and may have a neurotic attachment to their owners.[5,6,12,13,15–18] Vulnerability factors (eg, maternal stress, orphaned, bottle-fed, early neutering) are sometimes identified in this population of affected cats.[15,17,19–21] Stress in the cat's or owner's life should be identified if possible during the history because it can play an important role in initiating and perpetuating clinical signs. Assessment of the cat's living environment as to stressors and deficiencies can provide clues to the diagnosis of FIC and behavioral disorders. There is considerable overlap in the clinical findings between cats that have FIC and those with urinary behavioral problems. Cats that have recovered from FIC (and possibly other causes of LUTS) can continue to display periuria or have bouts of periuria due to acquired behavioral problems, despite resolution of the original cause of LUTS.[22]

Co-morbid conditions and Pandora syndrome

It is important to recognize that cats with FIC (other causes of LUTS have not been specifically studied) often have clinical problems outside the lower

urinary tract.[15,17] These co-morbid disorders are often either not recognized or not considered important due to the clinician's focus on the urinary bladder, urethra and LUTS. The co-morbid conditions frequently encountered are related to the gastrointestinal tract (regurgitation, vomiting of hair or food, soft stool, diarrhea), skin lesions with no fleas (barbering of caudal abdomen), cardiovascular system (heart murmur, gallop rhythm, cardiomyopathy), endocrine system (low adrenal cortical function), behavior problems (frightened, withdrawn, hiding, aggressive, overly attached), obesity, and odontoclastic resorptive dental lesions.[14,23]

Environmental stressors are reported to increase sickness behaviors (lethargy, vomiting, anorexia) more so in cats with FIC compared with healthy cats.[12] Historically, it has been common to focus on history and physical examination related to the LUTS. However, it is essential to obtain the history and physical examination of all organ systems, as well as collection and analysis of a detailed environmental history in all cats with LUTS. A diagnosis of 'Pandora syndrome' applies to those cats that exhibit clinical signs in organ systems in addition to LUTS, waxing and waning of clinical signs associated with stressful events that presumably activate the stress response system, and undergo resolution of the severity of clinical signs following effective environmental enrichment.[15]

Physical examination

Results from physical examination are neither sensitive nor specific for any particular cause of LUTS. For example, the urinary bladder or urethra can be thickened from many different disease processes, as is also true for detection of pain arising from the lower urinary tract. Abdominal palpation frequently fails to detect uroliths and masses in the urinary bladder and urethra, especially in cats that are overweight. An initial first step is to determine if the urinary bladder is large or small at the time of LUTS. It is important to determine if the cat has urethral obstruction at the beginning of the examination because these cats need immediate analysis and treatment that could be life-saving.

Non-obstructive LUTS

In cats with non-obstructive LUTS, a complete physical examination of all other body systems should be performed before focusing on the urinary tract to insure identification of all co-morbid conditions that may be present (described above – Pandora syndrome). The urinary bladder is normal to small in size in cats with any cause of irritative voiding, due to frequent elimination of urine. A thickened and or painful urinary bladder wall may be identified in some cats with chronic FIC, urolithiasis, and neoplasia. Urinary bladder uroliths can sometimes be palpated, especially if there are multiple uroliths that can be rubbed against each other creating a 'crepitant' sensation. It can be difficult to palpate uroliths or masses when the urinary bladder is distended with urine. Inability to palpate the urinary bladder in this population of cats can occur when the urinary bladder is very small or if the cat is obese.

Further diagnostics – clinical laboratory testing and urinary tract imaging

The number of episodes (initial or recurrent) of LUTS the cat has experienced, the severity of the cat's clinical signs, other medical conditions, whether the cat is obstructed or not, and how much money the owner is willing or able to spend all influence the degree of laboratory testing and urinary tract imaging that can be ordered. An exhaustive diagnostic evaluation is not usually necessary in a young otherwise healthy cat experiencing its first episode of FIC as spontaneous remission often occurs within 5–7 days. However, a clinical diagnosis of FIC cannot be made with greater certainty until urolithiasis, bacterial UTI and neoplasia have been excluded as possible causes of clinical signs. More thorough diagnostic evaluation is indicated for all cats that fail to have spontaneous remission of clinical signs within one week or for those with recurrent episodes, urethral obstruction, a history or the presence of other health problems, or in older cats (>8 years of age). Figure 2 details a diagnostic approach to cats with LUTS.

Urinalysis

Findings from urinalysis are useful, but are neither sensitive nor specific for the cause of LUTS. A recent study concluded that the few significant differences in urinalysis results in cats with various causes of LUTS were of limited diagnostic value.[24] All causes of irritative LUTS are characterized by varying amounts of hematuria, proteinuria and pyuria. The classical findings of hematuria and proteinuria in cats with non-obstructive FIC often wax and wane between days and even within the same day.[7,8] Thirty-two of 70 cats with non-obstructive FIC did not have hematuria when measured by disptrip; 32 of these 70 cats had >5 red blood cells (RBC)/high power field (HPF).[2] Consequently, failure to document abnormal findings in a single urine sample does not exclude a diagnosis of FIC. Pyuria is usually identified in cats with LUTS signs associated with UTI. Pyuria, >10 white blood cells (WBC)/HPF, was identified in 77% of cats with obstructive and non-obstructive forms of FIC in a recent report, but many cats in this series were males with recurrent urethral obstruction; the number of male and female cats without obstruction that exhibited pyuria was not detailed. The occurrence of pyuria was significantly higher in male cats with obstruction compared with male cats without obstruction in the same study.[6] Only 2 of 70 cats with non-obstructive FIC were noted to have >5 WBC/HPF in another report.[2]

It is physiologically normal to observe a few struvite or oxalate crystals in urinary sediment, especially when the urine is highly concentrated and if the urine sample has been refrigerated and stored.[25,26] Alkaline urine favors precipitation of struvite crystals and acidic urine favors precipitation of cystine crystals. There is no direct effect of urinary pH on calcium oxalate precipitation in urine and the effect of urinary pH on urate crystals is variable. Crystals in urinary sediment are of no pathological consequence unless the cat is forming a urolith or a urethral plug.

The type of crystalluria may be consistent with

the chemical composition of the patient's urolith but crystalluria is often detected in cats without urolithiasis, can be absent in those with urolithiasis, and the crystal type identified may differ from the chemical composition of the urolith. Struvite crystalluria was identified in 48% of male and female cats in one study, but results were heavily biased from males with urethral obstruction. Struvite crystalluria was greater in male cats with obstruction than in male cats without obstruction (P = 0.051), though cause or effect of the crystalluria was not established. Struvite crystalluria was not associated with hematuria, proteinuria or pyuria but was associated with urinary pH.[6] Struvite crystalluria (rare to few) was observed in only 9 of 70 (six female, three male) cats with non-obstructive FIC in another study.[2] Regardless, the presence of crystals has **NO** known diagnostic impact on non-obstructive forms of FIC and there is no evidence to support that crystals damage a healthy urothelium. If crystals are observed in non-obstuctive FIC, they are usually present in low numbers.[2,7,8,27]

Urine pH by itself does not distinguish amongst the various causes of LUTS in cats and depends on the interaction of many factors including diet, postprandial alkaline tide, stress-induced acute respiratory alkalosis, urease-producing bacteria in UTI and the degree of entry of plasma proteins (pH 7.3–7.4) into urine from the inflammatory process and bleeding. Stress induced by transport to the veterinarian's office has been shown to cause acute respiratory alkalosis and alkaline urine in one cat.[28] Therefore, finding neutral urine pH in cats affected with FIC may not necessarily reflect a failure of the diet to acidify the urine.

In cats with non-obstructive LUTS and urine specific gravity <1.030, some systemic disease (kidney disease, hyperthyroidism, diabetes mellitus) may be present that is interfering with the formation of more concentrated urine. In these instances, diagnostics to exclude polyuric conditions are warranted.

Bacterial urine culture

In urine collected by cystocentesis from young cats with LUTS, quantitative bacterial culture reveals significant growth in <2 % of the samples in most studies from North America.[1,2,29] These university practices included cats largely from first opinion clinics. In a report of cats referred for LUTS, 4.9% had bacterial UTI.[30] In contrast, a study of cats from Norway with a variety of obstructive and non-obstructive causes of LUTS found a surprisingly high number of cats with positive urine cultures (33%).[31] Findings from this study are difficult to interpret since many of the cultures (67%) were from voided midstream or catheterized urine samples rather than collection by cystocentesis. The authors speculated that the higher rate of UTI in cats with LUTS could have resulted from differences between cases diagnosed at primary versus tertiary care facilities, though geographical differences in occurrence of UTI could not be excluded.

Quantitative urine culture is recommended for all cats with recurrent LUTS and for those with disorders that increase risk for UTI. This includes cats with chronic kidney disease, hyperthyroidism, diabetes mellitus, urinary incontinence, perineal urethrostomy, or a history of urethral catheterization within the past 6 months.[30,32–35] In cats older than 10 years of age in one study, UTI was common (>50%), occurring alone or in combination with urolithiasis in those evaluated for signs of urinary urgency.[36–39] Though FIC does not appear to be initiated or maintained by bacterial infection, intrinsic abnormalities of the lower urinary tract in cats with FIC could predispose to microbial colonization, as appears to be true in humans.[40]

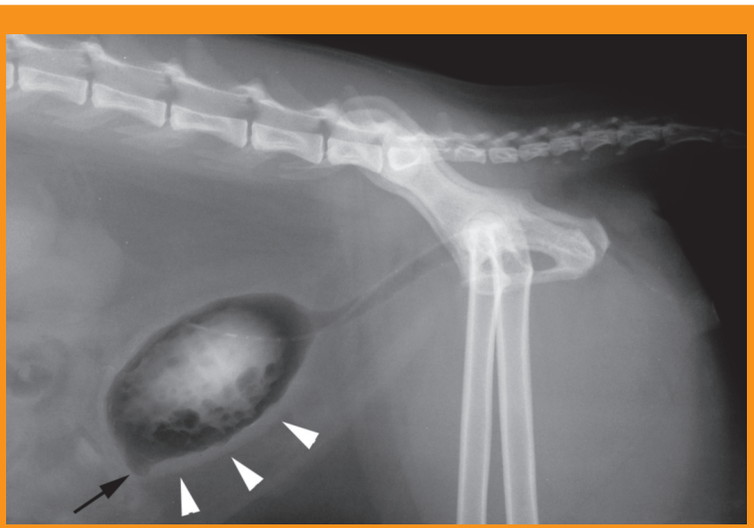

FIGURE 3 Double contrast cystogram of a female cat with non-obstructive FIC. The urinary bladder wall is thickened especially ventrally (white arrowheads). Note the urachal diverticulum (black arrow). Note also multiple irregular filling defects in the central contrast pool likely from blood clots and inflammatory debris. This study excluded any component of urethral obstruction and the presence of radiolucent calculi. The presence of a urachal diverticulum can be identified in some normal cats and can also be acquired transiently in cats with urethral obstruction (this is a female). Anecdotally, surgical removal of a urachal diverticulum lessens the clinical signs of some cats with non-obstructive FIC that do not respond to other treatments

Urinary tract imaging

Urinary tract imaging is recommended for all cats with recurrent LUTS. Survey radiographs are helpful to identify radiodense calculi, most often calcium oxalate or struvite, which are usually observed if ≥2–3 mm in size. In cats with multiple recurrences or persistence of clinical signs, advanced urinary imaging should be pursued when survey radiographs are normal, in order to exclude radiolucent calculi, blood clots, masses, urethral strictures and anatomical defects.

Contrast cystourethrography is normal in about 85% of cats with non-obstructive recurrent FIC.[41,42] Abnormalities that can be identified during double-contrast cystography include focal or diffuse thickening of the urinary bladder wall, permeation of contrast agent into the urinary bladder wall, permeation of contrast through the urinary bladder and into the abdomen and filling defects in the contrast pool (blood clots and cellular debris) (Figure 3). It is important to perform contrast urethrography in male cats that have undergone previous urethral catheterization and now have recurrence of LUTS to identify the presence of acquired urethral stricture or evidence for previous

urethral trauma such as a urethral diverticulum.

Ultrasonography can be useful as a less invasive method of imaging than contrast urethrocystography, though the diagnostic information yielded can be quite different. Wall thickness can be readily measured if the urinary bladder is adequately distended with urine; (overestimation of bladder wall thickness occurs when there is minimal distension with urine (Figure 4). Ultrasonography can document the presence of urinary bladder calculi regardless of their radiodensity if they are of sufficient size (>2 mm) (Figure 5).[43] Ultrasonography of affected and normal cats sometimes reveals highly echogenic acoustic interfaces of both suspended and gravitating particles – the origin of these echogenic particles remains to be determined, but they do not represent crystals in the vast majority of cats among those that we have evaluated. In a recent study, the amount of urinary 'sediment' detected during ultrasonography was not different between male cats with obstructive and non-obstructive FIC and had no relationship to the presence or absence of struvite crystalluria.[6]

Uroendoscopy

Urethrocystoscopy is usually performed to evaluate cats with recurrent LUTS when a diagnosis is not obvious after contrast urography or ultrasongraphy, though cystoscopy can reliably be used instead of contrast cystography in female cats.[44] Urethrocystoscopy allows direct visualization of the urinary bladder and urethral mucosa under magnification and of contents within the lumen (uroliths, foreign body, fronds as a likely indicator of transitional cell carcinoma). Some lesions are visualized with this technique that cannot be detected with contrast urography or ultrasonography. To improve diagnostic accuracy in male cats, urethroscopy is often combined with double contrast cystoscopy. Urethrocystoscopy excels in its ability to document small uroliths, early and advanced neoplastic or polypoid projections from the mucosa, mucosal erosions, foreign bodies, blood clots, urethral stricture, urachal diverticula, hemorrhage, and mucosal vascular changes that commonly characterize cystitis and urethritis. Small urocystoliths and masses that are not visible with radiography or ultrasonography are usually easily detected during cystoscopy. Microscopic examination of tissue samples obtained through the operating port of the rigid scope can be diagnostic for neoplasia, but sometimes are not informative due to their small size. Several specimens from the region of interest should be obtained to increase the chances of differentiating between normal, neoplastic, and inflammatory changes.

In male and female cats with non-obstructive FIC, a varying degree of increased vessel number and tortuosity, edema and glomerulations (submucosal petechial hemorrhages) are often visualized in the urinary bladder (Figure 6). An

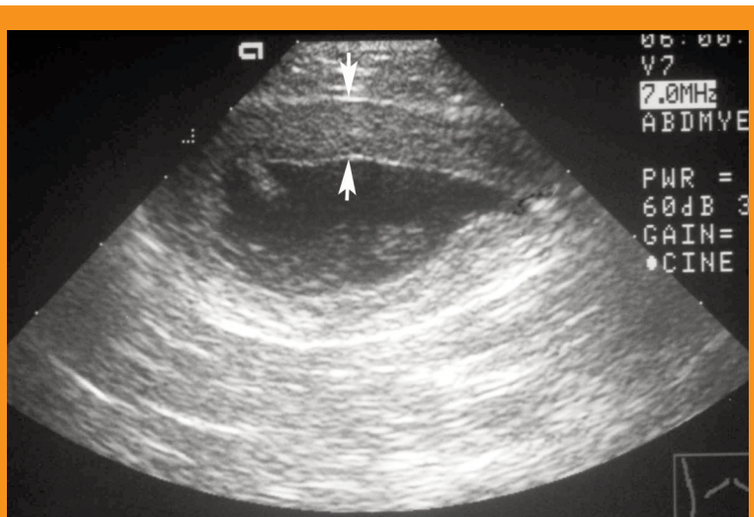

FIGURE 4 Ultrasonographic examination of the urinary bladder from a young female cat with FIC. Note thickening of the urinary bladder wall (between arrowheads). Urinary bladder wall thickness can be overestimated if the urinary bladder is not distended with enough urine. In this instance there is likely enough urine in the bladder lumen to estimate the bladder thickness with reasonable accuracy. Neoplasia (eg, transitional cell carcinoma) is an unlikely diagnosis in this young cat with relatively symmetrical thickening of the bladder wall (the one protrusion into the bladder lumen is likely a blood clot)

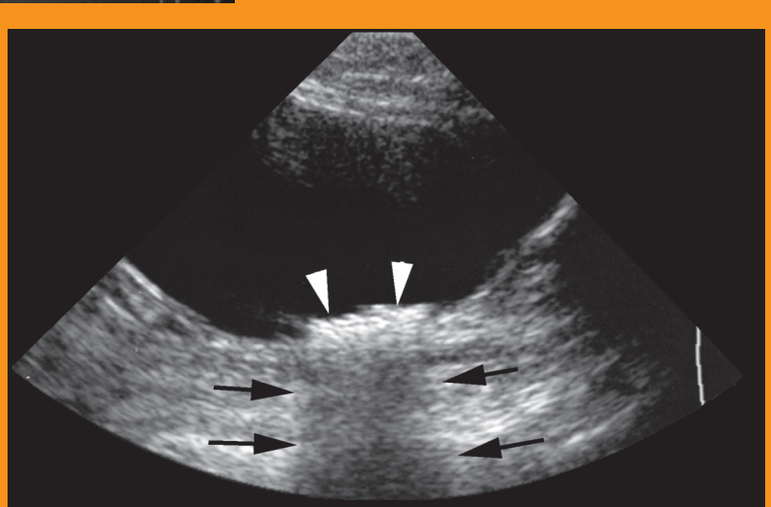

FIGURE 5 Ultrasonographic examination of a male cat with LUTS due to multiple small calculi. Notice the local accumulation of many small hyperechoic round uroliths (arrowheads) with acoustical shadowing below (black arrows)

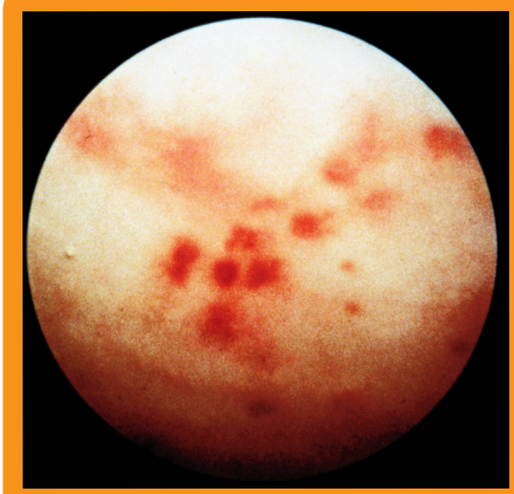

FIGURE 6 Cystoscopic appearance of the urinary bladder from a female cat with severe LUTS due to FIC. Note several submucosal hemorrhages (glomerulations) in the cranial view of the urinary bladder. Also note the absence of the normal pattern of blood vessels, which is obscured by edema of the urinary bladder wall

increase in the number and size of glomerulations often occurs in cats with FIC when higher bladder filling pressures (≥80 cm water) are used during cystoscopy. This finding does not occur in normal urinary bladders and serves as a provocative test for FIC in the absence of other diagnoses (uroliths, UTI, neoplasia). Female cats with FIC rarely have lesions in the urethra whereas urethral lesions (erosions, hemorrhages, glomerulations) are observed in approximately 40% of male cats with non-obstructive FIC.[44] It should be noted that LUTS do not necessarily correlate with the degree or number of cystoscopic abnormalities identified in cats with FIC.[45–47]

Biomarkers

Reliable diagnostic markers for FIC currently are not yet clinically available. 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 cats with FIC. 1-D gel electrophoresis revealed that the urine protein pattern in cats with FIC was significantly different from control cats.[48] Urinary fibronectin was increased in cats with FIC compared with control cats and those with UTI or urolithiasis, and could be 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 differentiation.[48]

Decreased urinary Trefoil factor 2 (TFF2) in cats with FIC compared with control cats 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 FIC.[49]

Three studies in cats have shown decreased glycosaminoglycans (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.[50] In a study by another group, urinary GAG concentration was greatly decreased in cats with FIC when compared with normal adult cats. Chondroitin sulfate comprised the main urinary GAG and was thought to originate from the circulation following filtration by the kidney.[51] Low urinary total GAG was again a finding in the most recent study of FIC.[52] It is unclear whether low urinary GAG in these studies is due to changes in synthesis, metabolism, or urinary bladder permeability. Low GAG concentrations could reflect damage to the urinary bladder surface, resulting in absorption and/or degradation of the endogenous urinary GAGs. We do not yet know whether these

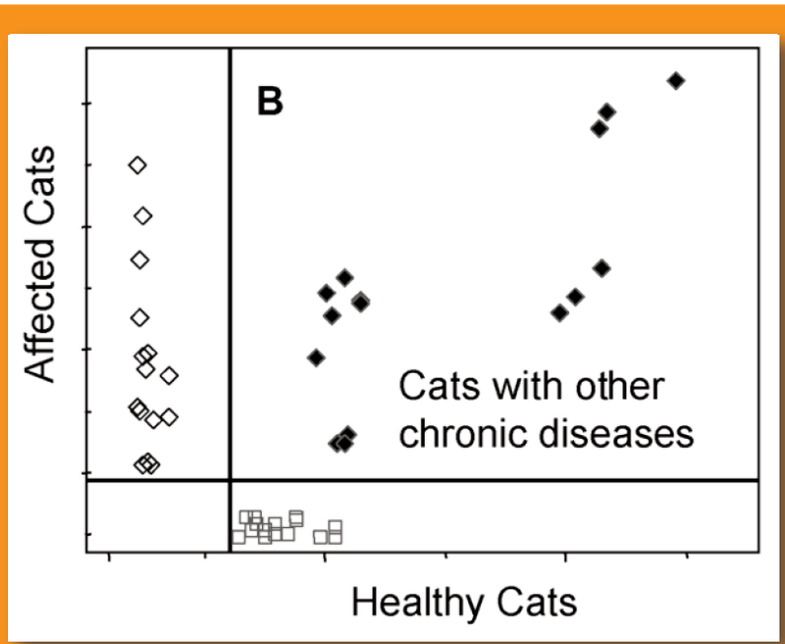

FIGURE 7 Separation of infrared spectra of sera from cats with FIC, healthy cats, and cats with other chronic diseases as evaluated by soft independent modeling by class analogy (SIMCA). Classification required information from the 1500–1800 cm^{-1} spectral region to discriminate these disorders. The internal vertical and horizontal lines represent significant differences (P <0.05) between groups. All groups are significantly different from one another

differences are related to the cause(s) or consequences of the syndrome, neither, or both.

Dried serum films from cats were studied using infrared microspectroscopy and spectra were classified using Soft Independent Modeling by Class Analogy. Cats were classified as healthy or affected with FIC – the condition was predicted in 100% of the cats (Figure 7).[53] Significant differences between healthy and FIC cats were shown in another study using similar methodology when analyzing blood spot cards.[54] Analysis of serum samples using liquid chromatography–mass spectroscopy revealed differences in the concentration of tryptophan and its metabolites between healthy and affected cats in both studies. These results demonstrate the potential utility of infrared microspectroscopy to diagnose FIC; this methodology has been patented.[55]

Summary/key learnings

Though FIC is the most common diagnosis associated with LUTS in young cats, it is important to exclude 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 voiding or not, and how likely stress may be playing a role. In order to determine if LUTS are part of Pandora syndrome, 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 urethrocystoscopy is useful for the exclusion of anatomical defects, radiolucent calculi and proliferative lesions in some cats.

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