Decoding Lower Urinary Tract Signs

And the role of nutrition in their management

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As veterinary professionals, we have the unique ability and responsibility to play a significant role in animal welfare. For many pet owners, there are few things as damaging to the human-animal bond as chronic house soiling or urinary issues. Inappropriate urination is one of the most common causes of owner surrender for both cats and dogs. Cats are 2-6 times and dogs are 2-4 times more likely to be relinquished to a shelter when they are urinating in the home at least weekly. [1] Accurately differentiating between medical and behavioral causes for inappropriate urination as well as strategically selecting our diagnostics and therapies is critical in helping to maintain the human-animal bond.

Lower urinary tract signs (LUTS)

While terms such as feline urologic syndrome (FUS), feline lower urinary tract disease (FLUTD), or lower urinary tract disease (LUTD) may still be in use; many are now using "lower urinary tract signs" (LUTS) to refer to the set of clinical conditions related to inappropriate urine elimination. These clinical signs include hematuria (blood in the urine), pollakiuria (frequent urination), stranguria (straining to urinate), dysuria (painful urination), anuria (no passage of urine), and urination in inappropriate places.[2] The underlying medical conditions resulting in LUTS may be related to the urinary bladder, bladder sphincters, and/or urethra. [2] LUTS are often the result of a combination of genetics, stress and frustration reactions, environment, and medical condition(s). [2] Due to the multifactorial causes and individual animal response, it is essential that we utilize diagnostics and therapeutics strategically in order to prevent misdiagnosis and promote good antimicrobial stewardship when treating LUTS.

Leveraging diagnostics

According to a recent survey of participating veterinarians, as few as 57% of veterinarians performing in-house urinalysis *always* performed a urine sediment.[3] However, it is recommended that a complete urinalysis including dipstick, urine specific gravity, and cytological examination of the sediment be performed in all suspected cases of urinary tract disease. [4] When performing cytological exams, staining dried urinary sediments with a modified Wright-stain is preferred over the use of sediment stains or wet unstained urine samples. Those stained with the modified Wright-stain had significantly improved sensitivity (82.8% vs. 75.9%) and test efficiency (97.7% vs. 57.8%) as compared to wet unstained samples.[5]

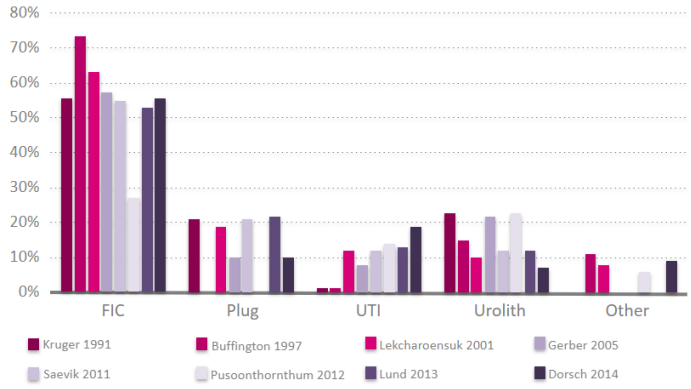
Another benefit to performing a cytological examination of the sediment is the potential detection of crystalluria, a marker of urine saturation and a potential risk factor for both urolith and urethral plug formation. However, while crystalluria is a frequent finding in the urine of both cats and dogs, it does not always predict the presence *or* type of urolithiasis. [6] *In vitro* crystals were found in 11/39 (28%) of animals whose urine was stored at room temperature or refrigerated for 6-24 hours and crystals that have formed *in vitro* do not justify therapy.[7, 8] Furthermore, crystalluria that occurs in individuals with anatomically and functionally normal urinary tracts is typically harmless and does not justify therapeutic intervention. However, when crystalluria can be confirmed in a fresh urine sample by a known stone former, this information may be useful in driving therapeutic management.[8]

Aerobic urine culture plays a critical role in the prevention of misdiagnosis of LUTS and is key to good antimicrobial stewardship. Cystocentesis remains the gold standard for urine collection and samples should either be cultured or refrigerated immediately.[4] Samples collected via cystocentesis and refrigerated immediately for ≤24 hours had a sensitivity of 95% and specificity of 100% compared to cystocentesis samples cultured immediately.[9] In instances where patient demeanor or extenuating circumstances make collection via cystocentesis impossible, voided urine may be used for culture but only when it can be cultured in house immediately or within 4 hours by a diagnostic laboratory. Furthermore, results *must* be interpreted within the veterinary cutoff for significance of bacteriuria of ≥100,000 CFU/mL. [10] Even with the application of these stringent protocols, 4% of voided specimens yielded false positives, 2% yielded false negatives, and 28/94 samples had presumed contamination.[10]

Prevalence of causes of feline LUTS

Prevalence data can be a powerful tool in driving strategic use of diagnostics and therapy. In 1991, Kruger et al published a landmark study investigating the causes of LUTS (referred to as FLUTD at that time) in 141 clinically affected cats.[11] Since this time others have repeated similar studies to further establish the prevalence of causes of feline LUTS. See Figure 1 for a summary of these studies.[12] Feline idiopathic cystitis (FIC) has consistently been the most frequent cause of LUTS followed by urethral plugs, urolithiasis, and much less commonly urinary tract infection.

Figure 1: Prevalence of causes of feline LUTS



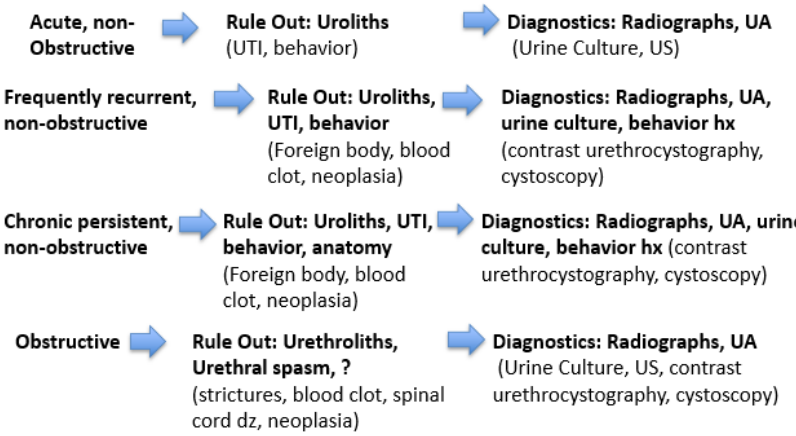
Idiopathic cystitis

Idiopathic cystitis remains a diagnosis of exclusion. Affected individuals likely need to be both susceptible and live in provocative environments. Idiopathic cystitis is likely a result of complex interactions between the urinary bladder, nervous system, adrenal glands, husbandry practices, and the environment.[12] Refer to Table 1 for risk factors. Cats may present with acute, self-limiting non-obstructive disease (80-95%), frequently recurrent, non-obstructive disease (2-15%), chronic persistent, non-obstructive disease (2-15%) or obstructive disease (15-25%). Figure 2 provides a flow chart of suggested diagnostics based on presentation.[13] Symptoms will resolve in 85% of cats within 2-7 days with or without treatment but recurrence is often sporadic and unpredictable.[14]

Table 1: Risk factors for idiopathic cystitis [15, 16]

Unknown?	Nervous disposition
Stress	Low activity level
Low water intake	Environment
Obesity	

Figure 2: Presentation based suggested diagnostics for idiopathic cystitis [13]



**Differentials and diagnostics in bold are the most common and thus most important to rule out whereas those in parentheses are less likely.*

Multimodal environmental modification (MEMO) is the primary therapy for prevention of recurrence of signs of idiopathic cystitis.[14] When done effectively MEMO will create conditions that allow the cat to feel safe and have unrestricted access to species-appropriate novelty, activity, and interactions with other animals and humans.[14] For practical recommendations on implementing MEMO, refer to Table 2 and The Ohio State University College of Veterinary Medicine Indoor Pet Initiative (https://indoorpet.osu.edu). Additional potential therapies for idiopathic cystitis include analgesics such as narcotics (buprenorphine, butorphanol, or fentanyl), NSAIDs, maropitant, or anxiolytic medications. However, these medications should be used judiciously as there is generally a lack of clinical trials and published evidence for their use in cats with idiopathic cystitis.[12, 14]

Table 2: Examples of Multimodal Environmental Modification [12, 14]

Increased water intake	Good litterbox management (cleaning, placement)
Canned foods	Ability to scratch, hide, perch, and play
N+1 Rule: Litterbox, bowls, resting areas	Pheromones

Therapeutic urinary diets are indicated in cases of obstructive idiopathic cystitis but may also be helpful in the treatment of non-obstructive idiopathic cystitis. In a recent clinical trial of 13 shelter cats with suspected FIC, six cats were fed Purina® Pro Plan® Veterinary Diets (PPVD) UR Urinary® St/Ox® feline dry formula and seven cats were fed Hill's® Prescription Diet® c/d® Multicare feline dry formula. Of the cats fed UR, 5 of 6 cats had their hematuria resolve in 28 days in contrast to 6 of 7 cats fed c/d® Multicare who had persistent hematuria for 28 days before their diet was changed to PPVD UR St/Ox®. After the diet change, hematuria resolved for 3 of the 6 cats that had formerly eaten c/d® Multicare.[17]

Urinary tract infections

It is estimated that only 1-2% of cats will have a urinary tract infection (UTI) during their lifetime. Less than 3% of young cats with LUTS will have a UTI, but 40-45% of cats greater than 10 years old will have one.[18] Of cats that develop a UTI, 75-87% will also have a predisposing comorbidity such as an endocrinopathy or chronic kidney disease.[18] This is critical to remember when we are considering antibiotic therapy in cats with LUTS. One retrospective report found 200 out of 333 cats with LUTS were prescribed antibiotic therapy despite an inadequate diagnostic work up in 154 of the cats. Of those cats evaluated in private practice (n=203) only 25% had a urine sediment analysis and 10% had a bacterial culture.[19] Therefore, while UTI is an important source of LUTS in cats older than 10 years (especially

females), it is still very uncommon in young cats and should be confirmed by bacterial cultures in *all* cases. Empirical antibiotic therapy for suspected bacterial cystitis in cats is never recommended.[4, 18]

In contrast to cats, an estimated 14% of dogs will have a UTI during their lifetime.[20] Similar to observations in older cats, more females are affected than males. Infections commonly involve a single agent and *Escherichia coli* is the most frequent isolate causing approximately 50% of all infections.[21] In dogs, urease-producing bacteria (*Staphylococcus pseudintermedius*, *Proteus mirabilis*, or *Klebsiella* spp.) are an important cause of infection-induced struvite urolithiasis. [22]

In 2019, the International Society for Companion Animal Infectious Disease published updated guidelines for the treatment of bacterial urinary tract infections. In this update, they included revisions to terminology and guidelines for the diagnosis and management of bacterial UTIs in dogs and cats including classifications of sporadic bacterial cystitis, recurrent bacterial cystitis, and subclinical bacteriuria. These guidelines can be found on their website: https://iscaid.org/. [4]

Feline urethral plugs

Urethral plugs are the most common cause of urinary tract obstruction in male cats. While they are commonly composed of large quantities of proteinaceous material mixed with crystals, they can occasionally be composed primarily of matrix, tissue, blood cells, or crystalline material. The cause of matrix formation is still incompletely understood and multiple theories exist. [23] In 2007, 92% of uretheral plugs submitted to the Minnesota Urolith Center contained struvite as the primary mineral.[24]

Urolithiasis

In small animals with lower urinary tract signs, urolithiasis is more common in dogs with an estimated occurrence of 33% compared to 15-23% of cats.[25] Over time, the predominant urolith type has varied in both dogs and cats, but calcium oxalate and struvite (magnesium ammonium phosphate) consistently remain the most common mineral types (ranging from 40-50% each) in both species. [24]

Urolithiasis is not a single disease with a single cause. Risk factors (Table 3) often combine to increase the risk of excretory metabolites in the urine to form stones. [24] The complete mechanism of calcium oxalate (CaOx) urolith formation is incompletely understood. Hypercalciuria with or without hypercalcemia is considered to be the primary driver of CaOx urolith formation. Additionally, an autosomal recessive disorder (hereditary calcium oxalate urolithiasis - type 1) has been identified in dogs. Those homozygous for this variant are at risk for calcium oxalate urolith formation. Genetic testing is now available to identify this variant which has been found in English bulldogs and multiple other breeds that are not traditionally identified as being at greatest risk of calcium oxalate urolith formation.[26] Virtually all struvite stones in dogs are secondary to urinary tract infection with urease-producing bacteria, while those in cats are predominantly sterile (~95%).[25]

Table 3: Risk Factors for Urolith Formation [24, 25, 27]

Etiological	***Demographic***	***Environment***
-Infectious -Toxic -Teratogenic agents	-Species -Breed -Age -Gender -Genetic predisposition -Obesity	-Conditions of their habitat -Water and food source -Socioeconomic status -Climate

Two primary methods of urolith management include surgical removal or medical management. While surgical removal was the historical treatment of choice for many, it is rapidly being replaced by minimally invasive techniques. However, in patients with non-dissolvable calculi and clinical signs, surgical intervention is still required if minimally invasive techniques are not possible.[28]

Risk of obstruction from medical dissolution has not been documented in the literature and, at most, is similar to or less than incomplete surgical removal.[28] There is no therapeutic urinary diet that is capable of dissolving calcium oxalate stones in either dogs *or* cats. However, medical dissolution of struvite uroliths should always be recommended unless medications or therapeutic diets cannot be fed, the uroliths are too large or too numerous to be adequately bathed in modified urine, or there is an uncontrollable infection despite appropriate antibiotics and a compliant owner.[28] Appropriate antibiotic administration based on culture and sensitivity is recommended for 2 to 4 weeks past radiographic evidence of complete dissolution of infection-induced struvite stones.[29]

The Benefits of Therapeutic Urinary Diets

Urine contains numerous ions, promoters of crystallization, and inhibitors of crystallization. The interactions of these factors determine if uroliths will form. Relative supersaturation (RSS) utilizes mathematical determinations to assess the crystallization potential of urine and allows estimation of the likely efficacy of therapeutic diets to reduce risk of stone formation in pets.[30] Based on RSS testing, it is possible to minimize the risk of *both* struvite and calcium oxalate urolith formation.

Therapeutic urinary diets are a reliable method of dissolving feline sterile struvite uroliths and aiding in the dissolution of infection-induced struvite uroliths in dogs when combined with appropriate antibiotics. Twelve shelter cats from local humane societies with ≥ 1 episode of LUTS and confirmed uroliths were fed dry PPVD UR Urinary® St/Ox® feline dry formula. By week two, five cats with presumed struvite uroliths achieved complete cystolith dissolution. Furthermore, of the six (three with presumed struvite cystoliths, three with calcium oxalate cystoliths) cats that were available for follow-up radiographs, no evidence of urolith recurrence was found. The authors concluded that feeding PPVD UR Urinary® St/Ox® can successfully dissolve cystoliths that are likely struvite and may lessen the risk of recurrence of struvite and calcium oxalate cystoliths.[31] When combined with appropriate antibiotics, PPVD UR Urinary® Ox/St™ canine formula dry resulted in radiographic dissolution of suspected infection-induced struvite cystoliths in 5/10 dogs within a median of 31 days.[22]

For all mineral types (except infection-induced struvite), feeding diets high in moisture is one of the cornerstones of urolith prevention.[28]. While feeding canned foods is an effective strategy for increasing water consumption (as they typically contain >70% moisture), feeding a canned diet may not be feasible for some dogs and cats. Therapeutic urinary diets can increase urine volume in dogs and cats through supplementation of sodium chloride. One study evaluated the impact of different concentrations of dietary sodium on water intake, urine volume, urine specific gravity, mineral excretion and RSS of calcium oxalate and struvite uroliths in cats. Three diets identical in formulation except for varying concentrations of sodium (0.4%, 0.8%, and 1.2% Na DM) and chloride were fed to 9 healthy cats each for 2 weeks and urine was collected the final 72 hours of each trial. A significant increase in urine volume (ml/kg/day) was noted in cats fed the diet containing 1.2% sodium while producing a urine metastable for calcium oxalate and undersaturated for magnesium ammonium phosphate (struvite).[32]

Some have expressed concerns about the possibility of sodium having adverse effects on renal function or even suggested it may contribute to hypertension. However, multiple studies do not support this concern. In one investigation, twenty-four DSH cats (mean age 7.0 years) were divided into two groups

and fed either the control diet (0.55% sodium DM) or the test diet (1.11% sodium DM) over a six-month period. Various health parameters were monitored, including blood pressure and markers of renal function. The authors concluded that this study provided no evidence of adverse effects associated with increased sodium intake.[33] In another investigation, sixteen cats (mean age 10.1 ± 2.4 years) completed a two-year study where they were divided into two groups and fed either a control diet with 1.0 g sodium/Mcal or a test diet with 3.1 g sodium/Mcal. This study observed *no* significant difference in glomerular filtration rate, blood pressure, creatinine, urea, or phosphate between the two groups. The authors concluded that the results of this two-year study did not support the suggestion that chronic increases in dietary salt intake are harmful to renal function in older cats.[34]

Dogs predisposed to urate urolithiasis may also benefit from a therapeutic diet to help prevent recurrence of their uroliths. Therapeutic diets for prevention of recurrence of urate urolithiasis in dogs should be low-to-moderate in protein and include low purine sources of protein. A 12-week crossover study was performed with 15 client-owned Dalmatians fed Hill's® Prescription Diet® u/d® canine formula (a low protein diet) and Purina® Pro® Plan Veterinary Diets HA Hydrolyzed® Vegetarian canine formula (a moderate protein diet formulated with hydrolyzed soy protein). No difference was observed between diets in 24-hour urine uric acid, allantoin, total purine excretion, or RSS for ammonium urate. The authors concluded that feeding a hydrolyzed soy protein diet may be useful in managing Dalmatians that have formed urate urolithiasis.[35]

Beyond Therapeutic Diets

Veterinarians often recommend strategies such as water fountains, using different types of bowls, adjusting water bowl placement, or even adding flavoring agents to water to encourage pets to increase their water consumption. However, there is very little data to support or refute the efficacy of these interventions and individual preference may drive the effectiveness of these strategies. In a 2010 study, a small number of healthy cats were offered water from a bowl versus a water fountain. In this instance, the drinking fountain did not result in a substantial increase in water consumption or urine dilution.[36] A recent randomized, crossover study measured water intake in healthy laboratory cats offered water in three types of bowls: still, circulating, or free-falling water. Bowl type had no appreciable effects on water intake.[37]

One strategy to increase the liquid intake of cats with LUTS may be to offer nutrient-enriched water with organic osmolytes (glycerin and amino acids), such as Purina® Pro Plan® Veterinary Supplements (PPVS) Hydra Care™. Osmolytes are molecules that are utilized by cells to regulate water movement across osmotic pressure gradients. These organic molecules are different than electrolytes. Thirty-six healthy cats were randomized into three groups of 12, fed PPVD UR Urinary® St/Ox® feline formula and offered either tap water, tap water and nutrient-enriched water Product A, or tap water and nutrient-enriched water Product B. Cats offered either Product A or Product B had significant increases in urine volume and a significant decreases in urine specific gravity when compared to the control group.[38]

Summary

Accurately decoding causes of LUTS is important to animal welfare. Inappropriate urination is a leading cause of pet surrender and euthanasia. As veterinarians, we can leverage diagnostics and therapeutics to avoid misdiagnosing the underlying clinical conditions resulting in LUTS and promote good antibiotic stewardship. While our understanding of urinary health continues to evolve rapidly, therapeutic urinary diets are an essential tool in the treatment of the complex and multifactorial clinical conditions behind LUTS.

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