Nutrition – a corner stone for management of urinary tract disorders Mini Series

Session Three: The stressed peeing cat – how do we treat feline LUTD?

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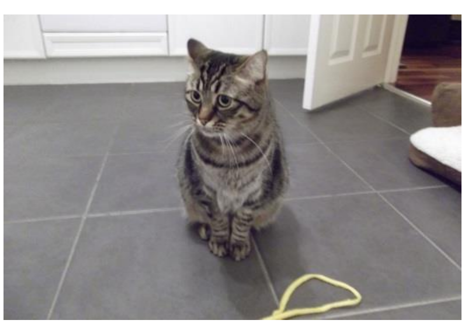

The stressed peeing cat – how do we treat feline LUTD?

The lower urinary tract (LUT) consists of the bladder, urethra and in the male, the prostate. Many lower urinary tract diseases (LUTD) share common clinical signs regardless of cause; it is usually not possible to determine specific aetiologies from the history and clinical signs alone.

Introduction

Lower urinary tract disease (LUTD) includes cystic calculi, urinary tract infections, neoplasia, anatomic defects, behavioural problems, and in cats, feline idiopathic/interstitial cystitis (FIC). In cats, urolithiasis comprises 15 to 23% of LUTD cases, urethral plugs 10 to 21%, anatomic defects up to 11%, bacterial infections 1 to 8% and neoplasia up to 2% (Sparkes 2014).

Bacterial cystitis

Bacterial cystitis is generally uncomplicated and most commonly seen in older female dogs but can also be seen in cats, especially those over 10 yr old. Most uncomplicated bacterial urinary tract infections (UTIs) can be successfully treated with an antibiotic chosen based on culture and sensitivity, used for an adequate duration.

Prevention of recurrent UTI without antibiotics

In over 25% of dogs with recurrent UTIs a cause cannot be identified, so treatment to prevent infection may be warranted (Wood, 2017). One treatment adopted from use in humans is cranberry juice or extract, although a Cochrane review of 24 studies concluded that evidence for preventing UTI in humans is small (Jepson et al., 2012) .Previously it was thought that the urinary acidifying effect of cranberry juice was anti-bacterial; however, cranberry juice does not acidify the urine sufficiently to have this effect (Bartges, 2010). A study on cranberry extract showed decreased *in vitro* adherence of *Escherichia coli* to Madin-Darby canine kidneycells (Chou et al., 2016). An antibacterial effect may occur from proanthocyandins with type A-linkages, an active compound in cranberries which inhibit the binding of P-fimbrae of uropathogens to mannose-like residues on uroepithelial cells (Olby et al., 2017). In dogs with spinal cord injury which are at increased risk of developing bacteriuria due to increased residual urine volume, cranberry extract had no benefit compared to placebo in reducing bacteriuria (Olby et al., 2017). The study results may have been impacted by low numbers (low statistical power); more studies are needed to prove or disprove the efficacy of cranberry juice/extract on preventing UTIs.

The use of D-mannose has been suggested to decrease bacterial adherence by blocking the ability of lectins on type 1 fimbrae to interact with uroepithelial cells. A study in women showed some reduction in reinfection but evidence in dogs and cats is lacking (Kranjčec et al., 2014).

Therapy with glycosaminoglycans (GAGs) could decrease bacterial induced uroepithelial injury by improving the health of the GAG layer within the bladder. Instillation of hyaluronic acid decreased UTI recurrence in humans, but no clinical evidence exists in dogs and cats (Wood, 2017).

In summary, no supplements have been proven to decrease the risk of recurrent UTI, although the studies done have been small or non-existent, so it is possible that these therapies may provide some benefit although it is likely to be small.

Feline Lower Urinary Tract Disease

Feline lower urinary tract disorder (FLUTD) is an important clinical problem in cats and has been rated a top feline health concern by cat owners, preceding dental problems, cancer and feline leukemia virus infection, even though the incidence is likely much lower than some of those. The true incidence (occurrence of new cases) is unknown, but was previously estimated to be approximately 0.85 and 1.5% in USA and UK. The prevalence (proportion of cases in the population) in the USA was reported to be 3% (Sparkes, 2014). A more recent survey of the prevalence of LUTS in cats reported by the owners in the UK was 4.3%, 3.8% and 6.0% at ages 18, 30 and 48 months, respectively (Longstaff et al.2017).

In cats younger than 10 years of age the two most common causes of FLUTD are feline idiopathic cystitis (FIC) and urolithiasis, while in cats older than 10 years of age, bacterial urinary tract infections and urolithiasis are the most common. In cats over 10 years old bacterial infections account for 20 to 50 % of cats with LUTD signs so urine culture should be performed rather than assuming the urine is sterile (Bartges, 2002; Sparkes, 2014). Signs of LUTD in cats under 10 years old without urethral obstruction may be caused by FIC in 55 to 73% of cases (Sparkes, 2014).

Clinical signs

Dysuria, stranguria and pollakiuria almost invariably localise the disease to the LUT and along with haematuria, are the common signs associated with LUTD. In cats, urinating outside the litter box (periuria) can also be a manifestation of cystitis as well as due to management or behaviour problems. Lower urinary tract diseases may or may not affect the patient's general health, and do not cause polyuria, polydipsia or azotaemia unless there is urinary tract obstruction.

Obesity, stress and LUTD

In humans, stress is associated with obesity, though it can be difficult to determine cause and effect between the two. Obesity is thought to possibly be a major contributing factor for LUTS and likely affects the oxidative state.. The expression of oxidative stress markers in bladder tissues were markedly higher in obese mice compared with the lean group. In addition, ROS levels in bladder tissues and serum lipid peroxidation were markedly higher in obese compared with lean mice (Andersson, 2017).

Obesity may also have a direct effect on the bladder and urination. In other species, obese animals exhibit cystometric alterations such as increases in the frequency of voiding and non-voiding contractions In mice which were obese due to genetics (obese B6.V-Lepob/J) there was increased frequency of urination, lower average urine volume and other urinary voiding dysfunctions. Their bladder urothelium was slightly thicker and appears more proliferative. The study's analysis indicated that peritoneal fat strongly correlate with LUTS whereas and other features of obesity moderately correlate with the prevalence of bladder dysfunction (He et al., 2016). Obese prone rats also exhibited urinary retention and impaired detrusor contractility following diet induced obesity, reflected as increased volume threshold, decreased peak micturition pressure, and decreased voiding efficiency compared with non obese rats. The effects of neuromodulation in a novel obese-prone rat model of detrusor underactivity (Gonzalez and Grill, 2017). These findings in rodents may or may not be relevant to FIC.

One half to two thirds of adult cats are overweight or obese. One study showed that overweight and obese cats had a higher prevalence of LUTD, including FIC and urolithiasis, compared to normal weight cats (van de Maeleet. al, 2005).

Pathogenesis of FIC, a highly complex disorder

Cats with FIC have a variable disease course with signs usually resolving in 5 to 7 days, then recurring. This waxing and waning is thought to be associated with events activating the central stress response system (Buffington, 2011). Many affected cats show signs from other organ systems, e.g. the gastrointestinal tract, skin, lung, cardiovascular, central nervous, endocrine, and immune systems. The disease aetiology likely has a neuropathic aspect as well as a local bladder wall disorder.

The bladder smooth and striated muscles and the neurovascular supporting tissues engage in complex neuroendocrine communication with the body and brain to coordinate urination. Bladder neural connections include sensory afferent, central, and somatic, sympathetic, and parasympathetic efferent neurons interacting between the urothelium and the cerebral cortex (Buffington 2011).

Cats with FIC show a denuded uroepithelium with increased permeability and a decreased total glycosaminoglycans layer in the bladder (Buffington, 2011). In a study of urine parameters, urine protein concentration was four times and urine protein to creatinine ratio five times higher in cats with FIC than in normal cats (Panboon et al 2017). Increased serum concentrations of pro-inflammatory cytokines and chemokines are also present in FIC cats (Parys et al 2018).

In addition to uroepithelial bladder abnormalities, urinary changes and altered serum cytokines in FIC, there are alterations in components of acetylcholine synthesis and release. Changes in the nonneuronal cholinergic system may contribute to alterations in cell-to-cell contacts and communication with underlying cells that contributes to changes in sensory function and visceral (bladder) hyperalgesia. Differences in sensory neuron anatomy and physiology are present in FIC cats, suggesting a more widespread abnormality of sensory neuron function. The acoustic startle response, a brainstem reflex motor response to a perceived threat from unexpected auditory stimuli, is increased in FIC cats. Differences in sympathetic nervous system function identified in FIC cats include changes in the brain stem region associated with an important source of noradrenaline. This area is involved in brain functions such as vigilance, arousal, and analgesia and mediates the visceral response to stress. Changes in brainstem help explain the waxing and waning of sign and the aggravation of signs by environment stressors (Buffington, 2011).

Some cats with FIC have abnormalities in the hypothalamic-pituitary-adrenal axis, with decreased serum cortisol secretion and smaller adrenal glands compared with healthy cats. Thus, some of these cats have an excessive sympathetic response to stress, with decreased cortisol response in addition to pathology within the bladder (Buffington 2011).

Risk factors for FIC

Risk factors for FIC include being an indoor cat, young middle age (4-7 years), neutered, and overweight. Other factors may include low activity, using a litter tray, eating a high proportion of dry food, and living with more than one other cat, especially with conflict between the cats. Compared to normal cats, cats with FIC have been described as being more fearful, nervous, having less hunting behaviours, hiding when unknown visitors are in the house and drinking less water (Defauw et al 2011). Episodes are often triggered by stress, e.g. moving house, new cats in the house or neighbourhood, new people in the house, or car rides to the clinic. A case-control study focusing on indoor cats in South Korea showed increased FIC odds ratios for males cv females (odds ratio 2.34), cats not having vantage points to see out (odds ratio 4.64), cats living in an apartment (cv in a house) (odds ratio 2.53), and similar to previous studies, cats cohabiting with other cats compared to those living alone (odds ratio 3.16). Cats using non-clumping litter had 2.62 times the odds compared with those using clumping litter (Kim et al 2017).

Treatment for FIC

FIC generally cannot be cured, though it is often possible to decrease the frequency and severity of episodes. The initial treatment should include analgesics (e.g. buprenorphine) as these episodes are painful. Addressing stress management and diet are among the most important treatments.

Environmental enrichment

A thorough history about feeding and management should be obtained. Resources can be found on line (http://indoorpet.ocu.edu/veterinarians/research/ondex.cfm). Multimodal environmental modification (MEMO) should be adopted to reduce stress, although only one or two changes should be made at a time.

Resources

If possible, provide as many resources as cats plus an additional one. For example, if there are four cats, there should be five litter boxes in different locations, although this can be challenging to place around a house. As non-clumping litter is identified as a risk factor, using a non-scented clumping litter and/or meticulous cleaning of the litter box may help. The litter box should be scooped (at least) daily and washed and refilled very 7 to 10 days. Consider any obstacles to the box access, e.g. location, size, height of entryway. Boxes should be at least 1.5 times the length of the cat (Horwitz, 2014)

If a cat develops a litter box aversion secondary to FIC or experiences an urgency that causes elimination elsewhere, the possibility exists for development of a secondary toileting location or substrate preference (e.g. carpet). To resolve this problem, the preferred inappropriate site should be made less attractive (e.g. by placing double-sided tape or crinkly foil on the surface) or unavailable while the litter box is improved to meet the preferences of the cat. In general it can be helping to remember the ABCs of the Best Box: Accessible, Big, Clean and Clumping Clay (litter) (Nielson, 2012).

Other cat resources include: scratching surfaces, sleeping/resting perches, food and water stations, and opportunities for play and exploration. Each cat should at least have his own food bowl, separate from the water bowl, and both should be away from the litter box. For some cats the stress of having cats within sight when they are eating may be an issue and a private dining place should be found.

The cat should be able to access all resources without competing with other cats. When cats are not compatible, microchip-operated cat flaps in internal doors can offer a means for separate and private access to feeding and litter boxes (Heath 2016). Environmental enrichment should also include resting and hiding places, provision of normal cat behaviours (e.g. scratching, hunting or play-hunting) and a set routine with familiar people.

Synthetic feline facial pheromone therapy (e.g. Feliway®) in the environment has been shown to reduce stress in cats. In a randomized controlled study of 12 cats with FIC, there was a trend for cats exposed to Feliway® to have less severe episodes and fewer recurrences of cystitis (Gunn-Moore 2004).

Inappropriate elimination such as periuria can be very frustrating to owners and can break the pet-family bond. Punishment delivered to the cat upon discovery of a soiled location is not only ineffective, but it may worsen the problem. Owners should be advised to avoid punishing their cat if periuria is observed or discovered. In general, predictable routines and interactions may help reduce stress in the cat as well as addressing litter box and cat competition as mentioned above. The possibility of urinary tract infections contributing to a new onset of periuria should also be considered.

Inter-cat aggression or tension is stressful. Some simple interventions that can improve feline relations include: creating a cat considerate environment with an abundance of resources spread throughout the environment; placing a cat-safe belled collar on aggressor cat(s), and partial or full segregation of the cats. For severe cases, a comprehensive behavioural modification program that includes desensitization and counter-conditioning should be considered (Nielson, 2012)

Feeding management

Cats' normal feeding behaviour includes stalking and hunting prey and eating multiple small meals through the day and night. Feeding a large, highly palatable meal twice day or free choice feeding does not mimic these behaviours and can contribute to weight (fat) gain. There are several food puzzle toys on the market designed for delivery of dry food through toy manipulation. The varying styles may appeal to different cat personalities and hunting styles. Patients on the part of the owner may be needed as it can take some time for some cats to figure out how to use these toys. For owners or cats that do not want to use puzzle toys other options include a food treasure hunt (little allocations of food hidden throughout the home, including on elevated perches), a food toss (toss kibble across the room) or use of a timed automatic feeder (Nielson, 2012) For owners whose cats are waking them up an unsocial hours, an automatic feeder set to go off at those times (e.g. 4:00 am) can be beneficial and may help decrease begging behavious as feeding is not directly associated with the owner. Limiting quantity and increasing frequency of feeding can also improve weight loss success (Russell 2000).

Play and activities

Play time should be scheduled daily when the cat is active and alert. Since cats tend to be most active at dawn and dusk and since most owners are home at those hours, those may make good play periods for the many cats. Cats tend to expend energy in short bursts of high levels of activity (Nielson 2012). The timing of play and the rotation of toys may increase interest in the games. One study found that rotating toys during a play session may spark a renewed interest in play (Hall 2002). Short breaks (5 minutes) between toys seemed to enhance play with second item while prolonged intervals (25 to45 minutes) resulted in a decreased interest in the second toy.

Increasing housing space alone does not change levels of activity. It helps to make the space variable, entertaining and multi-dimensional increases the quality of the space and activity levels. Cats in kennels tend to select elevated perches over the bottom of the kennel and cats prefer upholstered perches over slick surfaced perches, regardless of the height. They prefer resting places that are warm, dry, and protected on two sides and situated in the corners or edges of an enclosure where they can watch without the possibility of being approached from behind. Every household should provide plenty of cat friendly perches. Single cat sized perches may be particularly important in multi-cat households as they may provide a way to gain fairly secure physical separation from other cats. Secure outdoor enclosures or teaching the cat to walk on a leash also add interest and activity to their world (Nielson 2012).

Moisture/Water

Cats with FIC often have concentrated and acidic urine unless they have other disorders. High concentrations of normal and /or abnormal components in urine may be toxic to bladder mucosa of affected cats. The effects of wet and dry forms of an acidifying diet fed to cats with FIC showed signs in 39% fed the dry diet and 11% fed the wet diet. (Lulich 2014). The wet diet lowered the urine specific gravity to 1.032 to 1.041 compared to 1.051 to 1.052 on the dry diet, so if possible, a wet diet should be fed and water intake increased (Markwell et al, 1999). Water intake may be encouraged by daily fresh water and multiple full bowls placed away from food and litter boxes. Some cats prefer running water, e.g. a water fountain. Decreasing the urine SG to <1.035 decreases frequency of the episodes (Gunn-Moore and Shenoy, 2004).

Pain management

FIC episodes are painful for cats and appropriate medications can include opiods such as buprenophrine, butorphanol and/or non steroidal anti-inflammatories (Lulich 2014).

Diet and supplements

Nutritional management should aim to correct the cat's weight and body condition score, decrease pro-inflammatory mediators and cyrstallogenic minerals, decrease solubility of crystalloids, increase anti-inflammatory or pro-resolving mediators, and decrease stress or anxiety.

Weight loss

Weight loss is important for the overweight or obese cat for many health concerns. While overweight body condition is more common in FIC cats than in normal cats, no studies have been done which show that weight loss results in fewer episodes of FIC; however, obesity is associated with a chronic state of inflammation which could exacerbate the urinary signs. Weight loss is beneficial for the cat and will decrease the risk of co-morbidities as well as possibly improving FIC signs. Dealing with stress may improve weight loss success as some cats may eat to deal with stress.

Glycosaminoglycans and Glucosamine

The urinary bladder glycosaminoglycans (GAGs) layer of cats with FIC is thought to be reduced or damaged, and oral provision of glucosamine, the precursor of GAGs, may have some benefit. Studies have not confirmed this in cats, although the studies may have been underpowered as there was a trend to fewer episodes in treated cats (Gunn-Moore and Shenoy, 2004).

Omega 3 fatty acids

The omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are incorporated into cell membranes in a dose dependent fashion, where they replace arachidonic acid. They then synthesize less inflammatory eicosanioids (prostaglandin, leukotrienes, and thromboxanes) than those made from arachadonic acid. They also have anti-inflammatory metabolites, e.g. resolvins and protectins, which function in resolving inflammation and protecting neurons. The effects of EPA and DHA in FIC have not been studied, although they do show efficacy for other inflammatory conditions such as osteoarthritis.

Anti-oxidants

One of the main reactive oxygen species or oxidants is superoxide. Mice with a mutation in the *Immp2 l* gene, which leads to high superoxide ion production showed bladder dysfunction. C-fibre afferent activation is likely involved in lower urinary tract dysfunction such as overactive bladder, and detrusor overactivity was also induced by intravesical administration of the oxidant hydrogen peroxide (H_2O_2) to rats, possibly by activating these capsaicin-sensitive C-fibre afferent pathways. However, while oxidative stress maybe involved in LUT disorders, the clinical relevance of reactive oxygen and nitrogen species (RONS) is still largely unclear (Andersson, 2018).

A struvite prevention diet with lower calcium, phosphorus and added antioxidants (vitamin E and β-carotene) and omega-3 fatty acids resulted in fewer recurrent episodes of clinical sins of FIC compared to cats fed a control diet (Kruger and others, 2015). These results are promising, but again the relevance of specific nutrients is not clear. Marked struvite crystalluria has been associated with LUTD signs in a cat with FIC in a case report, so a decrease in struvite crystals may also have an effect even though crystals are not usually considered pathological without uroliths (Bell and Lulich, 2015).

Stress and anxiety modification with nutrients and dietary ingredients

The two currently used anti-anxiety ingredients for FIC are L-tryptophan and milk protein hydrolysate (MPH). L-tryptophan is an essential amino acid and the precursor of brain serotonin. Increased serotonin is associated with increased sedation and decreased aggression, fearfulness, insomnia and pain sensitivity. In a double-blinded controlled cat study, added L-tryptophan decreased anxiety, stress-related behaviours and house soiling (Pereira 2010). There were also decreased affiliative and exploring behaviours. L-tryptophan can also be metabolised into an anxiogenic neurokynurenine, kynurenric acid, especially in the presence of pro-inflammatory cytokines. Kynurenic acid mat be metabolised into either glutamate (excitatory) or nicotinic acid (anxiolytic) (Beata, 2014).

Milk protein hydrolysates, e.g. alpha-casozepin, have a similar structure to gamma aminobutyric acid (GABA), an inhibitory neurotransmitter which decreases anxiety and stress related disorders. Oral MPH given to cats decreases fearful behaviours and increases contact with people (Beata 2007). A study showed beneficial effects of an alpha-casozepine and L-tryptophan supplemented diet on fear and anxiety in cats placed in an unfamiliar location although fear in the presence of an unfamiliar person was not decreased (Landsburg et al, 2017). A urinary food supplemented with milk protein hydrolysate and L-tryptophan fed for eight weeks to eighteen FIC cats improved FLUTD signs, and emotional and quality of life scores (Meyer and Bečvářová, 2016). Therapeutic diets which combine nutrients or ingredients for anxiety combined with other features (e.g. obesity management, urinary crystals/stones, etc.) exist.

Summary for Treatment of FIC

In summary, feeding a wet food and a food or ingredient to decrease stress have good evidence for decreasing the signs of FIC. Ideally the food would also decrease the risk of uroliths. Anti-oxidant therapy may also help and glucosamine may have some benefit. The use of omega 3 fatty acids has not been studies; however, they do have benefits in other inflammatory conditions. Overweight cats are more at risk and although weight loss has not been studied as a therapy it is recommended due to the risk of co-morbidities of obesity. Pain should be addressed during episodes. Stress management such as sufficient resources including appropriate litter and litter box placement, play and activities to allow for normal behaviours, and decreasing inter-cat difficulties are vital in the management of FIC.

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