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FLUTD: Insights and Updates

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Feline Lower Urinary Tract Disease (FLUTD) is an umbrella term that covers a number of maladies associated with the feline urinary system as well as stress and pain processing in cats with Feline Idiopathic (Interstitial) Cystitis (FIC). The incidence of lower urinary tract (LUT) signs in cats ranges from 1 to 5% of the total feline population. With an estimated 220 million owned cats worldwide, approximately 11 million cats are impacted by this disease. Fifty percent of those 11 million cats go on to develop a urethral obstruction.

Terminology and History

Lower urinary tract signs (hematuria, pollakiuria, periuria, and strainguria) were previously dubbed FLUTD or Feline Urologic Syndrome (FUS). They were thought to be caused by inappropriate diet composition, containing too much magnesium, resulting in struvite (magnesium-ammonium-phosphate) stone formation. Struvite stones were suspected to be the primary cause of FLUTD in cats at the time. When diet modifications were prescribed to reduce magnesium levels and acidify urine, no fewer cats suffered from LUT signs. We only succeeded in shifting to a higher percentage of calcium oxalate stones. It was also realized at this time that many cats suffering from LUT signs had no evidence of stones.

In the 1990s, Dr. Tony Buffington and colleagues began NIH-funded studies in cats with LUT signs as a model for chronic pelvic pain syndrome, or interstitial cystitis in humans. After being admitted to the enriched cat colony, they started to notice that many of the cats (with previously diagnosed intractable lower urinary tract signs) had resolution of their signs. There was a paradigm shift, and we started to consider that there may be some other underlying issue or condition affecting the bladder rather than this being a primary disease of the bladder and LUT. In humans with interstitial cystitis, they began a more comprehensive investigation into other disorders beyond the bladder and started to develop phrases such as “medically unexplained syndrome,” “bodily distress syndrome,” or “central sensitivity syndrome.” Buffington and colleagues coined the term “Pandora syndrome” to describe a similar condition in cats.

Feline LUT signs can be caused by interstitial cystitis, urethral plugs, urethral spasms, stricture, or neoplasia. Interstitial cystitis is the leading cause of LUT signs in cats. It can result from bladder stones, crystalluria, and infection or may be deemed idiopathic once other causes have been excluded.

Feline Idiopathic Cystitis (Pandora Syndrome) is defined as a “chronic, sterile inflammatory condition of the urinary bladder resulting from complex interactions between the urinary bladder, nervous system, adrenal glands, and the environment.”

Pathophysiology

When looking at the complex pathophysiology, it’s helpful to separate bladder and urethra from the nervous system. Looking at the nervous system of cats with signs and symptoms consistent with FIC, we see a sensitization and upregulation of the stress response, which is then mostly notably manifested in the urinary bladder and urethra. Cats

with FIC were found to have upregulated larger sensory neurons in the dorsal horn and tended to secrete high levels of norepinephrine compared to normal cats. These cats appear to have an exaggerated acoustic startle response that increases under stressful conditions. Compared to controls, they also appear to have desensitized alpha-2 receptors in the central nervous system. This results in less inhibition of norepinephrine and increased levels of stress hormones within the body. Lastly, FIC cats have less inhibition of nociception transmission, which causes increases in pain transmission.

So, these cats have a chronically activated central stress response system (CSRS) that can be made worse by intermittent or daily perceived threats in an environment where the cat has little control to escape these threats or modify its behavior in response to them. It is unknown if there is a specific genetic or epigenetic link in these cats or whether there is a specific environmental response and/or change to the CSRS from a previous environment early in life.

In the bladder, we can see a disruption in the glycosaminoglycan (GAG) layer (also seen in women with interstitial cystitis). The disruption of the GAG layer allows for leakage of urine and its contents, which begets more inflammation and more leakage. Additionally, C fibers (non-myelinated pain-conducting fibers) in the bladder wall become activated, causing increased pain. Substance P (an important neurotransmitter associated with pain, anxiety, and depression in humans) is released. The damaged uroepithelium increases mast cell inflammation and more backleak of urine contents. The cat starts to feel systemically ill and may stop eating and drinking, concentrating the urine and its contents further and enhancing the cycle of inflammation and pain.

Other causes of LUT signs in cats include urinary tract infections, urolithiasis, neoplasia, and stricture.

Epidemiology

The incidence of LUT signs is approximately 1 to 5% of the total feline population, and about 50% of those cats develop a urethral obstruction. We tend to see this condition mostly in young indoor, and overweight male cats fed more dry food than canned food. An anxious or nervous personality may be appreciated and may be exacerbated if these cats are living in a multi-cat household where inter-cat conflict can increase stress in the home.

Diagnosis

It is important to obtain as detailed of a history as possible in these cats, including where and how the cat was obtained, as well as information on the human family dynamic and/or new or chronic stressors. A definitive diagnosis of “Pandora Syndrome” is not easily obtained. A tentative diagnosis can be made based on ruling out other causes (listed above) of LUT signs (stranguria, periuria, dysuria, pollakiuria, hematuria, etc.) and identifying early adverse life experiences, comorbidities, waxing, and waning signs. Largely, the diagnosis can be assumed if the patient responds favorably to Multimodal Environmental MOdification (MEMO), which will be described in more detail below.

Cats who have progressed to urethral obstruction often have a large, turgid, painful bladder that cannot be expressed. Owners may describe their cats as going in and out of the litter box without producing any urine. Passing even small drops of urine makes full urethral obstruction less likely. Vitals can be normal in blocked cats. Cats with LUT that present with signs of hypothermia, bradycardia, and obtundation almost certainly have an obstruction. ECG and blood work may also help you to determine if the patient is blocked. Bradycardia with absent P waves, tented T waves, and wide QRS complexes indicate hyperkalemia, which can be confirmed on lab work. Azotemia and hyperlactatemia may also be present.

Emergency Treatment of the Blocked Cat

- Analgesia (methadone 0.2 mg/kg IM), +/- gabapentin 10-20 mg/kg PO if amenable to oral administration
- Management of hyperkalemia
    - IV 10% calcium gluconate 0.5 mL/kg diluted 1:5 with 0.9% NaCl administered over 10 minutes with ECG monitoring
        - Cardioprotective by increasing the threshold potential
    - Regular insulin: 1 unit IV followed by 50% dextrose: 0.5 mL/kg diluted 1:2 IV over a couple of minutes
        - Drives intracellular movement of K+
        - Ideally, check blood glucose prior to administration of insulin
        - Dextrose given to prevent hypoglycemia as well
    - IV fluid bolus (5-10 mL/kg) of any isotonic crystalloid over about 10-15 minutes
        - Increases GFR and dilutes K+
    - Unblock the cat
- Sedation
    - Additional opioids (methadone 0.1-0.2 mg/kg IV)
    - Benzodiazepines (midazolam 0.15 mg/kg IV)
    - Propofol (2-4 mg/kg) vs Alfaxalone (1-2 mg/kg) titrating to effect
    - Occasionally requires epidural and/or general anesthesia
    - In severely obtunded and critically ill cats, sedation may not be required and is not recommended
- Unblocking
    - Supplies
        - Sterile gloves, lubricant, and saline flush
        - Unblocking catheter
            - Polypropylene (Tom Cat – open end)
            - Olive-tipped
            - Peripheral 22 g IV catheter
            - Polyvinyl (Red Rubber)
            - Polytetrafluoroethylene (PTFE – Teflon coated) (Slippery Sam)
            - Stylet-reinforced
        - Macro extension set (primed with sterile saline)
    - Process
        - Dorsal recumbency with hind limbs extended cranially
        - Gentle clip and clean of the area
        - Push prepuce back into the body with your non-dominant hand, exposing the penis
        - Gentle grasp the penile frenulum and extend the penis caudally, parallel to the spine
        - Insert lubricated tip into the penis
        - Assistant flushes in pulsating manner as you advance the catheter
    - Placement of indwelling
        - I prefer 3.5 – 5 Fr red rubber urinary catheter
        - 3.5 Fr may decrease risk of short-term recurrence in one study
        - 5 Fr may be needed if there is substantial grit and debris in the bladder
    - To flush or not to flush?
        - No studies that show risk or benefit of flushing
        - I tend to empty and flush the bladder if there is gross hematuria or debris in the urine
    - When to remove?
        - Should remain in place for at least 24 hours
        - Longer catheterization was associated with lower risk of recurrent obstructive event
        - Longer than 24 hours does not show benefit
        - Remove once urine is grossly clear and non-hemorrhagic

        - Conflicting studies
        - ALWAYS flush the urinary catheter with sterile saline as you are removing it to prevent debris from being dragged into the urethra
- Post-Unblocking Treatment
    - Intravenous fluids
    - Quantify ins and outs every 4 hours, adjusting IVF rate as needed
    - If there is a deficit of urine output compared to volume of fluids delivered, especially if the patient is azotemic, I would recommend increasing the fluid rate every 4 hours until urine output matching fluid input and then start to decrease again every 4 hours
    - Analgesia (buprenorphine 0.02 mg/kg IV q8h)
    - Urethral anti-spasmodics (prazosin, phenoxybenzamine, and acepromazine)
        - Alpha receptor antagonists
        - Cause smooth muscle relaxation
        - Distal portion of feline urethra is skeletal muscle – so pharmacologically, these do not make sense
        - Evidence is lacking
    - Cerenia
        - Substance P (NK-1) receptor antagonist – vomiting center of the brain (antiemesis) and within the central nervous system (may mediate pathophysiology of pain, mast cell inflammation, and anxiety)
        - 1 mg/kg IV q24h
        - 1-2 mg/kg PO q24

Nonobstructive FIC and post-obstructive chronic FIC management

Multimodal environmental modification (MEMO), based on research by Dr. Tony Buffington and colleagues, is paramount in managing these cases. Nearly all cats in his study showed improved clinical signs after implementing MEMO guidelines. To remain successful, owners must be engaged in caring for their cat for these environmental modifications.

Many diets are currently marked for stress and urinary issues, but their effectiveness has yet to be evaluated, and for many cats, their symptoms can be managed without a diet change. There is good evidence to support incorporating more canned food into a cat's diet, with the goal being more water consumption overall and a urine-specific gravity of <1.035. If a diet change is elected, it is important to wait until the cat feels generally well and give the cat options. Once the cat has indicated its preferred food, slowly, over the course of several days to weeks, implement the change.

Within the cat's home environment, it is important to identify and decrease areas of perceived (cat's perception) threat and increase their perception of control. These cats should have free, unobstructed access to resources such as food, water, litter box, affection, play, and rest. The 1+1 rule for litter boxes can be applied to all pertinent resources. For every one cat in the home, add one additional resource/space. Cats need multiple places of refuge, areas to climb, hide, and rest, and places to eat, play, and scratch without fear. Cats seem to prioritize social interaction with their owner over food and toys.

Cats should be allowed to eat in a quiet, solitary location. Some cats benefit from mimicking natural hunting behaviors. Food puzzles or hiding food around the house can encourage some of this natural behavior. Litter boxes should also be placed in a safe, quiet, and solitary location, free from the hustle and bustle of the home. Owners may also need to consider both litter and litter box type along with location. Cats enjoy novelty, so determining a cat's play behavior preferences and rotating different activities can be helpful to keep these cats engaged. Playtime and space should be free from other animals, especially dogs or younger cats, who may like to dominate the play session. Addressing these environmental modifications may also help to decrease inter-cat conflict within the home.

Prevention

Aside from MEMO, pharmaceutical intervention may also help to limit the clinical signs and symptoms associated with Pandora Syndrome. Pain management for acute flare-ups is important but may not prevent progression to urethral obstruction. While there is no specific data to support a particular pain management protocol, I tend to discharge UO patients with 0.02 mg/kg buprenorphine sublingually every 8 to 12 hours as well as 10 to 20 mg/kg gabapentin every 8 to 12 hours. I do not use steroids or non-steroidal anti-inflammatories as evidence is lacking, and side effects are a significant risk. Amitriptyline can be prescribed if MEMO is ineffective. However, this is not something I recommend starting for acute episodes of FIC.

What's New?

- Radiation Therapy

Dr. Allison Kendall, out of NC State, is researching the effectiveness of single-low-dose radiation therapy (RT). Her current study (in 2023 at the time of this article's publication) is a proof-of-concept, safety pilot study. They are looking to see if cats experience a decreased rate and time to re-obstruction, as well as how clinical signs of FIC change following RT. Fifteen male cats with FIC and/or a history of, or active UO were selected for the study. They tried to find cats with chronic recurrent signs of FIC or UO that had failed environmental and medical management. These cats had to be otherwise healthy and have a confirmed diagnosis of FIC. Cats with previous perineal urethrostomy were excluded. Diagnostics, including a CBC, Chemistry, UA, blood pressure, urine culture, and some form of abdominal imaging (radiographs or abdominal ultrasound), were required to rule out other causes of LUT signs. Owners were instructed not to change anything about their current FIC management for at least 12 months following RT. Cats received a single dose of 6 Gy to the entire urinary tract, and most cats were able to go home the same day, minimizing stress in the hospital. As of October 2023, 15 cats had been treated. The first cat was treated in 2021, and the last cat was treated in late 2023. All 15 cats showed clinical improvement in their signs, and none had a UO episode. One cat was treated a second time after a recurrence of clinical signs about five months following the first RT treatment. Thirteen of the cats did not had a single LUT sign since treatment (based on owner reports). Minimal to no side effects from the RT were documented. Next, they plan to do a large blinded controlled clinical trial in both male and female cats and have control cats.

- FIP stones

In an August 2023 report out of the Minnesota Urolith Center, they report the submission of three atypical stones. These stones were all from cats less than one year of age and all from North and South America. When asked about their medical histories, it was reported that all three cats had been diagnosed with FIP and were all treated with either Remdesivir or its metabolite GS441524.

Most urinary stones contain high levels of phosphorus, calcium, and magnesium. These stones contained high levels of nitrogen, carbon, and oxygen. The infrared spectrographic pattern between the stones and these antivirals was identical. Following administration, GS441524 is primarily eliminated in the urine. Due to this medication's limited water solubility, it very easily forms stones within the bladder. So, if you are seeing cats with LUT signs who have been treated for FIP, it might be a good idea to perform abdominal imaging sooner rather than later.

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