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

Session Two: Can't pee? Dietary management of urolithiasis – when and how can it help?

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Urinary tract diseases are among the main reasons for consultations in veterinary clinics and hospitals. It can affect pets of any age, breed and gender. Among the diseases that affect the urinary tract, urolithiasis is the second largest cause of clinical signs compatible with lower urinary tract disease causing of about 20% of cases.

Uroliths (also called calculi or stones) are organized polycrystalline concretions within the urinary tract. The bulk (90-95% by weight) of most uroliths is composed of crystalloid material, with the remainder consisting of non-crystalloid proteins, the organic matrix. The most common location for urolith formation is the bladder lumen, although uroliths may also occur within the renal pelvis, the ureters or the urethra.

Uroliths are classified based on the type of mineral present in their composition so quantitative and qualitative analyzes are relevant for therapeutic decisions. Pets with urolithiasis can be asymptomatic or show nonspecific clinical signs, making the diagnosis difficult and a urine analysis essential. Risk factors include dietary, metabolic, genetic and infectious causes, as well as factors that affect the chance of development of uroliths such as breed, age, sex, age range, obesity, sedentary lifestyle, geographic region and climate (da Rosa Gomes et al., 2018).

In cats about half the uroliths are struvite, composed predominantly of the crystalloid form of magnesium ammonium phosphate hexahydrate, and about half are calcium oxalate. These two uroliths have each been predominant over the last few decades, with the predominant one changing back and forth (Cannon et al 2007; Kirk 2014; Gerber et al 2016). Other less common feline uroliths include urates, cystine, calcium phosphate, xanthine, solidified blood, and uroliths composed of a mixture of one or more crystalloids.

Struvite uroliths are the most common type in dogs although calcium oxalate uroliths accounts for 42 to 45% of canine uroliths. Most struvite uroliths in dogs are caused by a urinary tract infection (UTI) with a urease-producing microorganism. *Staphylococcus* spp. are the most common microbes causing struvite urolithiasis, followed by *Proteus spp*. Other less common urease-producing bacteria that cause struvite urolithiasis include *Pseudomonas spp., Klebsiella spp., Corynebacterium urealyticum, Enterococcus, Streptococcus*, *and Ureaplasma/Mycoplasma spp*. Sterile struvite urolithiasis is rare in dogs but does occur.Urease increases the ammonium and bicarbonate ions in urine, resulting in an increase in urine pH. Increased urine pH results in a change in the ionization state of phosphorus to the trivalent form. Supersaturation with ammonium ions promotes struvite formation, while the bicarbonate ions alkalinise the urine. Interestingly, struvite uroliths associated with UTI tend to be more radiodense than struvite uroliths that form in sterile urine.

Unlike in dogs, most struvite uroliths in cats occur in sterile urine, although a urine culture to ensure the urine is sterile should be performed, especially in cats over 10 years of age. Struvite uroliths in cats may be associated with infection, especially when caused by bacteria that produce urease, such as *Staphylococcus,* and *Proteus* ssp.

In addition to uroliths, cats may present with a urethral obstruction from crystalline-matrix plugs which are composed of 45-100% matrix and variable amounts of mineral. The most common mineral in plugs is struvite (Kirk 2014).

In one study, domestic cats had significantly less calcium oxalate stones compared to British Shorthair, Persian or Himalayan cats (Gerber et. al 2016; Lekcharoensulet al., 2000), but any breed may be affected. Obesity is also more common in affected cats (Van de Maele et. al 2005).

Overall, uroliths tend to occur in older cats (mean 7.6 yearsold), and cats between 7.0 and 10.0 are at the most risk of calcium oxalate, with struvite uroliths more common in younger cats. Female and male cats

are generally about equally affected with stones, although calcium oxalates and urates are more common in males and struvites more common in females (Kirk 2014, Gerber et al 2016; Lekcharensuk et al., 2000; Rogers et al., 2011; Picavet et al., 2007; Houston et al., 2003) .

Nephroliths

Nephroliths form with the same disorders or under the same conditions that increase the risk of urolith formation elsewhere in the urinary tract. Dog breeds that are predisposed to lower urinary tract uroliths of different mineral composition are also at risk for nephroliths. A significant increase in the occurrence of nephroliths has occurred in cats over the last several years (Ross, 2013, Bartges 2012).

Nephroliths are most commonly composed of calcium oxalate. Calcium oxalate nephroliths account for >70% of canine nephroliths and 70-90% of feline nephroliths (Ross, 2013, Bartges, 2012). Nephroliths of other mineral types (e.g. xanthine, silica, cystine, urate) are isolated less often.

Nephroliths can (but don't always) cause urinary obstruction at the level of the kidney, or they can travel into the ureter and cause ureteral obstruction. Nephroliths may serve as a nidus for infection and lead to pyelonephritis. Chronic haematuria and pain can also occur with nephrolithiasis.

Nephroliths are found with increasing frequency in cats with kidney disease; however, a causal relationship has not been established. It is controversial as to whether the presence of nephroliths, without concurrent ureteral obstruction, leads to progression of chronic kidney disease (CKD). In one study of 14 cats with CKD (7 with nephroliths, 7 without nephroliths), no association was noted between nephrolithiasis and the rate of disease progression, incidence of uremic crisis, or death (Ross et al., 2007). However, another study compared 43 cats with nephrolithiasis to 21 geriatric, healthy control cats. The mean lifespan for cats with nephrolithiasis was 3 years shorter than the mean lifespan of control cats, suggesting that nephrolithiasis has an adverse effect on overall mortality rate (Hall et al., 2017)

Struvite uroliths

Dissolution

The ACVIM Small Animal Consensus Recommendations on the Treatment and Prevention of Uroliths in Dogs and Cats recommends that struvite uroliths should be medically dissolved unless appropriate foods or medications are contraindicated, the pet will not eat them, if the stone cannot be adequately bathed in modified urine, e.g. due to a urinary obstruction of a large bladder stone occupying nearly all of the bladder, or there is an uncontrollable infection despite good management (Lulich et al., 2016). A risk of urethral obstruction by using medical dissolution rather than surgery has not been reported, and cystotomy with bladder sutures has been reported to increase the risk of inducing urolith reoccurance (Lulich et al., 2016; (Appel et al., 2008). A failure to remove all uroliths via cystotomy has also been reported in 5 of 20 cats (Lulich et al., 2013). In one study, persistent cystotomy site thickening was present up to 3 months after cystotomy for urolithiasis in dogs, and 11 of 18 dogs had reoccurrence of hyperechoic foci within the bladder (median time to first detection, 17 days after surgery (Mariano, et al., 2018).

Most struvite uroliths can be dissolved in less than 2 to 5 weeks (Lulich et. al 2013; Houston et. al, 2004) and dietary dissolution is considered safe as well as effective. Medical treatment consists of antibiotic therapy when appropriate and dietary modification with a calculoytic diet. The diet should be low in magnesium and phosphorus and result in an acidic urine. In one study comparing two dissolution diets, the diet which produced the lower mean urine pH (6.12 +/- 0.1 vs 6.34+/- 0.1, by pH meter) resulted in a shorter time to complete urolith dissolution (Lulich et al., 2013). Only if the diet fed is not designed to

acidify the urineshould oral urinary acidifierssuch as methionine be considered. Some diets for urolith dissolution contain increased sodium (e.g>1.2 % dry mater basis [DMB]) to encourage water consumption and decreased urine concentration, although in the study by Lulich et al. (2013) the diets resulting in successful urolith dissolution contained 0.41% and 0.34% sodium on a DMB.

Therapeutic response may be monitored by urinanalysis (and culture if infection has been diagnosed) and abdominal radiographs. Radiographs should be taken 2 weeks after the initiation of treatment, at which time the urolith size should have decreased by 50%.

Removal of a urolith located in the bladder, ideally by a non-invasive method, is indicated if a reduction in urolith size is not detected despite the clearance of infection, good owner compliance with dietary and medical management, and the production of acidic urine. Cystotomy is not the first recommendation; however, it may be necessary in some cases. Where the stone has not dissolved, it is likely that the stone is either not struvite or has a mixed mineral composition. Urate stones can look similar to struvite stones radiographically, as moderately radiopaque, smooth, round to ovoid stones.

Prevention of reoccurrence of struvite uroliths
It is recommended that a therapeutic maintenance diet with low magnesium and phosphorus which acidifies urine is fed to prevent reoccurrence of struvite uroliths. The goal is to have the urine pH <6.5 (Lulich et al., 2016). Some dissolution diets are not formulated for long term (e.g. >2-3 months) maintenance feeding as they are likely very low in magnesium, phosphorus and possibly calcium. These very restricted and highly acidifying diets should also not be fed to growing puppies or kittens or dogs or cats with chronic kidney disease. If an infection has been present, the urine should be cultured monthly for 2-3 months.

<u>Calcium Oxalate Uroliths</u>
Pathogenesis
Calcium oxalates are they are usually located within the bladder, but may also be found in the kidneys and ureters. For these uroliths to form, the urine must be supersaturated with calcium. Factors involved in the pathogenesis of calcium oxalate urolithiasis in cats are not completely understood but involve urine supersaturation with calcium and oxalate. The following factors likely play a role in formation:

- Increased dietary intake of oxalate, such as in bran concentrates and cereals, although absorption and oxaluria depends on availability of free (unbound) oxalate in the gut (Plantinga 2014). A study has shown that increasing oxalate intake from 13 to 93 mg/100 g DM did not affect urinary oxalate excretion but resulted in an increase in faecal oxalate output.
- Increases in endogenous urinary oxalate excretion can be caused by increasing dietary hydroproline intake. Thus, the protein source rather than amount may influence the formation of endogenous oxalate, as the amino acid hydroxyproline is a substrate for oxalate (Plantinga 2014)
- Dietary calcium and magnesium affect oxalate absorption. For years calcium restriction was suggested to decrease the amount of urinary calcium. More recent research shows that increased calcium may complex with oxalate in the intestine and decrease absorption and urinary excretion.A study of dietary factors and the occurrence of feline calcium oxalate uroliths showed diets with higher calcium (>0.49g/MJ) resulted in a lower risk of calcium oxalate uroliths than ones with lower (0.23 to 0.49 g/MJ)(Lekcharoensuk et al., 2001). Another study on the effects of increasing dietary calcium on excretion showed an increase in faecal calcium excretion but little effect on urinary excretion in healthy cats (Paβlack et al., 2016).

- Metabolism of vitamin C, glycine, and glyoxylate can increase production and excretion of oxalate. Endogenous production of oxalate depends on the glycooxalate content of the liver (Plantinga 2014). Vitamin B6 (pyridoxine) is a co-factor in oxalate metabolism and a deficiency in pyridoxine has been shown to increase urine oxalate in kittens (Bai et al., 1989).

- Hypercalciuria may result from hypercalcemia. Mild hypercalcaemia (11.1 to 13.5 mg/dl or 2.78 to 3.38 mol/l) has been reported in 35% of cases (Osborne et al., 1996). Ionized calcium concentrations should be measured in cats with calcium oxalate uroliths.

- Low dietary phosphorus intake may also be related to increased urinary calcium excretion due to decreased enteric binding (Lekcharoensuk et al., 2001; Pastour et al., 1995).

- Decreased concentrations of calcium oxalate crystallization inhibitors (eg, citrate, magnesium, nephrocalcin, and osteopontin) may contribute to calcium oxalate urolith formation. Nephrocalcin reduces the tendency of calcium oxalate crystals to grow or aggregate. Other potential inhibitors include citrate, glycosaminoglycans, Tamm-Horsfall proteins, and osteopontine.

- The solubility of calcium oxalate crystals is not directly influenced by urine pH within the physiologic range, but acidosis may increase the amount of calcium released from the bones to buffer the acid, resulting in hypercalciuria.

- Increased water intake and decreased urine concentration decreases the risk of urolithiasis in as formation of more dilute urine lowers the risk of supersaturation.

Treatment

Calcium oxalate uroliths are not amendable to medical or nutritional treatment. In pets without clinical signs with urocystotiliths (bladder uroliths) too large to pass into the urethra, current recommendations are to monitor clinical signs and with imaging. In pets with clinical signs, urocystoliths small enough to pass through the urethra should be removed by voiding hydropropulsion, basket retrieval or other nonsurgical extraction. Only nephroliths causing a clinical problem, e.g. outflow obstruction, recurrent infection, or pain, require treatment and this should be attempted by minimally invasive procedures.

Prevention

Decreasing the risk of reoccurrence includes decreasing hypercalcuria by treatment of underlying cause of hypercalcaemia such as idiopathic hypercalcemia or excess dietary vitamin D.

Other preventative measures include decreases the risk factors as mentioned above. Increasing water intake with high moisture foods (>75% water) is recommended. Some cats will eat dry food with water added to it if feeding a canned food is not possible. Cats often don't increase their total fluid intake adequately on a dry diet. In one study total fluid intake was significantly increased when cats were fed a 73.3 % moisture diet (145 ml, or 30 ml/kg body weight per day) compared with a dry diet of 6.3 % and cats fed the 73.3 % moisture diet had a more dilute urine (Buckley et al., 2011). Formation a urine with a specific gravity of <1.030 is the goal of treatment.

The diet should not result in a urine pH less than 6.25 as this is associated with an increase in calcium oxalate formulation.

Studies on the effects of the amounts of dietary protein are controversial. One study indicated a beneficial effect for high dietary protein diets by increasing water intake (Hashimoto et al., 1995) and another

showing an increased renal calcium and oxalate excretion with higher dietary protein (Paßlack et al., 2014). A recent article concluded that a high protein canned diet might not be a specific risk factor for CaOx urolith formation, at least in cats. In this study, protein quality had a minor, but significant impact on urine composition (Paßlack et al., 2018).

High salt diets have been recommended to increase the urine volume and decrease urine concentration. These may increase the total amount of calcium excreted, but decrease the calcium concentration (saturation) due to the more dilute urine. The ACVIM Consensus recommendations are that feeding a high sodium (>375 mg/100 kcal) dry diet should not be a recommended substitute for high moisture foods. High sodium foods increase urinary water excretion; however, the effects may not be long term. Increased dietary salt was suggested as an alternative in cases where owners declined to feed high-moisture foods.

Other recommended dietary modifications include, with adequate but not excessive phosphorus, magnesium and potassium. Potassium citrate is recommended as an alkalinizing salt and urinary undersaturation with calcium oxalate has been reported to be achieved by inducing alkaluria. Potassium citrate also promotes urinary excretion of the calcium ion chelator, citrate which may decrease urinary calcium.

Adapting a maintenance diet to decrease the reoccurrence of calcium oxalate uroliths is difficult; using commercial diets formulated for this is recommended. In one study of 10 cats with calcium oxalate urolithiasis feeding a urolith prevention diet also increased the urine concentration of glycosaminoglycans, which are glycoprotein inhibitors of growth and aggregation of calcium oxalate crystals (Lulich et al., 2012)

Probiotics may play a role in management of calcium oxalate uroliths in the future. Manipulation of the gut microbiome with *Oxalobacter formigenes* or some strains of *Lactobacillus acidophilus*may decrease intestinal oxalate by degrading it, and correspondingly decrease intestinal oxalate absorption and renal excretion (Mittal and Kumar 2004; Weese et al.,2004). In vivo studies are needed to determine whether probiotics can decrease urine oxalate concentrations and reduce risk of urolith recurrence in dogs and cats with a history of calcium oxalate urolithiasis.

Urate

Urate uroliths account for approximately 5-8% of all uroliths retrieved from dogs and cats.Urate uroliths are comprised of uric acid and its various salts. Ammonium urate is the most common primary salt found in urate stones, accounting for approximately 86% of all urate uroliths. Cats over 4 but less than 7 years of age had the highest odds and were 51 times as likely to develop urate uroliths as were cats < 1 year of age (Dear et al., 2014).

Urate urolithiasis occurs when urine is supersaturated with uric acid and its related salts. Uric acid is formed by purine degradation. Purines are nitrogen-containing compounds that are a component of some nucleotides. Sources of purines in cats include diet (especially organ meats and seafood) and endogenous cell turnover. Purines are degraded to hypoxanthine which is oxidized to xanthine by xanthine oxidase. Xanthine is further oxidized to uric acidby xanthine oxidase. Uric acid in the plasma is normally converted to allantoin by hepatic uricase, so allantoin is ordinarily the end product of purine metabolism. Allantoin is more soluble in urine than uric acid. In patients with urate urolithiasis, uric acid is the final product of purine metabolism, which leads to hyperuricemia and hyperuricosuria. Uric acid excreted in the urine is less soluble and can crystallize with various cations to form urate salts. Hyperuricosuria, concentrated urine and acidic urine are the main factors in urate urolith formation.

Etiology

Protosytemic shunts (PSS) and other liver disorders are often associated with non-Dalmation dogs with urate urolithiasis.Portosystemic shunts occur less often in cats and are not a common cause of urate urolithiasis in this species.Patients with hepatic dysfunction can be at increased risk for forming urate uroliths due to their decreased ability to convert ammonia to urea and to convert uric acid to allantoin. The incidence of urate urolithiasis is highest in dogs with portosystemic shunts (PSS) compared to other forms of hepatic dysfunction. In one study of 95 dogs with extrahepatic PSS, 35.8% had uroliths and 16/17 uroliths analyzed were ammonium urate (Caporali et al., 2015).

In dogs, a genetic abnormality has been identified in the dalmatian, English bulldog, black Russian terrier, and Australian shepherd that reduce the transport of uric acid into hepatocytes, resulting in decreased conversion of uric acid to allantoin and increased excretion of uric acid in the urine (Karmi et al., 2010). A similar genetic defect is not known to occur in the cat.

Treatment

Medical dissolution is recommended; if a PSS is present it should be addressed first as dissolution may not be possible with untreated liver disease. If a urinary obstruction is present, the obstruction must be relieved before medical management is attempted.Physical removal should also be considered when medical dissolution therapy fails and for unacceptable clinical signs associated with urolithiasis. Voiding urohydropropulsion, cystoscopic retrieval via a basket (female cats), laser lithotripsy (female cats), extracorporeal shock wave lithotripsy is generally recommended as non-invasive methods of stone removal and preferred to surgery although cystotomy, ureterotomy, or urethrotomy may be necessary in some cases. Retrograde urohydropropulsion involves flushing uroliths from the urethra into the urinary bladder where they may be dissolved medically.

Dietary management/prevention

The goal of dietary modification is to decreases urinary excretion of uric acid and ammonium ions; alkalinize the urine; and increases urine volume. Protein restriction is the main requirement for dissolving urate uroliths. Protein restriction reduces the intake of purines; decreases uric acid excretion in the urine; and promotes renal medullary washout. Fish and organ meats are highest in purine content. Eggs, vegetable proteins, and dairy products are lower in purine content, except cats require protein from meat, fish or poultry. Unfortunately, no commercial, low-protein diets for cats are marketed for urate dissolution. Veterinary therapeutic diets formulated for kidney disease or hydrolysed soy protein containing diets are often used. This is a logical approach; however, evidence of the effectiveness has not been published. To prevent recurrence of urate stones, a diet that is lower in protein compared to the previous diet is often recommended, meaning a good dietary history is mandatory. Feeding canned food or adding water to the diet (>75% moisture) should help to increase urine volume and decrease urine concentration. The goal is a urine specific gravity below 1.030.

Urinary alkalinizing agents such as potassium citratemay help. While the solubility of ammonium urate plateaus at pH>7.2, in vitro dissolution occurred at a high rate at pH >8.0. This study used uroliths from dolphins, and as it would be difficult to achieve this urine pH in cats, the target is usually urine pH of 7.0-7.5, although the efficacy is not well reported (Argrade et al., 2013). Therapeutic diets for kidney disease are also usually formulated to be alkalinizing although the target pH may not reach the target of even 7.0.

Allopurinol is a xanthine oxidase inhibitor that is used to help dissolve urate uroliths in dogs but its benefit in cats is unknown. Allopurinol is used in conjunction with dietary modification and should not be given to patients with PSS.

Cystine uroliths

Pathophysiology

Cystine is a sulfur-containing amino acid consisting of two cysteine molecules bound by a disulfide bond. Cystinuria occurs when a defect is present in carrier proteins responsible for proximal renal tubular reabsorption of cystine (and often other bibasic amino acids, e.g. ornithine, lysine and arginine) which leads to increased levels of cystine in the urine. Cystinuria is an inherited defect and a mutation of the SLC3A1 gene that leads to defective amino acid transport has been described in one cat (Mizukami et al., 2015).

Cystine is relatively insoluble in urine; however, not all patients with cystinuria develop urolithiasis. Cystine uroliths are more common in middle aged to older cats and Siamese appear to be at slightly higher risk.

Prevention and Management

Few controlled studies have been published on prevention strategies in dogs, and as cystine uroliths are quite uncommon in cats they will be even more difficult to do. Therapy will need to be monitored and adjusted as needed. Removal may require non-invasive methods as described for other stones. The recurrence rate is high after removal.

Dietary modification can be used to reduce urine cystine concentration and increase solubility of cystine in urine. Feeding a low protein, low sodium diet leads to formation of alkaline urine and can help reduce cystine urine excretion, although the amounts of protein and sodium restriction have not been determined. Feeding a prescription renal diet may help to prevent recurrence of cystine uroliths. Methionine is a sulfur containing amino acid which is a precursor to cystine so the diet should not be excessive in methionine, which is present in many animal proteins and some plants (e.g. nuts, tofu, wheat).

Feeding a canned diet is also encouraged to increase water consumption and decrease urine concentration. Target urine specific gravity is (again) <1.030.

The solubility of cystine increases greatly when urine pH is >7.2 and the target pH is about 7.5. If dietary therapy alone is insufficient to maintain an alkaline urine, potassium citrate at 50-75 mg/kg PO q 12 hours should be considered. Sodium bicarbonate is not recommended as dietary sodium can increase cystine excretion in the urine. 2-mercatopropionylglycine (2-MPG, Tiopronin) is not tolerated well in cats, so is not used. In male dogs, some forms of cystinuria is improved by neutering; this has not been investigated in cats (and un-neutered owned males are less common than with dogs). If a breeding tom cat did have cystinuria, neutering would be advised to prevent the genetic transmission.

Summary of Urolith Types and Treatment

Stone	Radiodensity	Medical dissolution	Target urine pH to decrease risk	Target urine specific gravity to decrease risk	Dietary factors to decrease risk of reoccurrence
Struvite	Radiodense	Recommended (treat urinary tract infection if present	6.0-6.4	<1.030	Low magnesium, low phosphorus, acidify urine
Calcium oxalate	Radiodense	Not possible	>6.2	<1.030	Add potassium citrate to increase urine pH and chelate calcium ions
Cystine	Faint to moderate	May not be possible	>7.5	<1.030	Add potassium citrate. Low protein, low methionine, adequate carnitine
Urate	Variable radiodensity from lucent to moderate radiodensity	Treat liver disease; dissolution may be possible	>7.2	<1.030	Decrease protein and purines

References and Recommended Reading

Appel SL, Houston DM, Moore AEP,Weese JS. (2010) Feline urate urolithiasis. Can Vet J; 51(5):493-496.

Appel SL, Lefebvre SL, Houston DM et al.(2008) Evaluation of risk factors associated with suture-nidus cystoliths in dogs and cat: 176 cases (1999-2006) Am Vet Med Assoc;233:1889-1895.

Albasan H, Osborne CA, Lulich JP, Lekcharoensuk C. (2012) Risk factors for urate uroliths in cats. J Am Vet Med Assoc; 240(7):842-7.

Argade S, Smith CR, Shaw T, et al. (2013) Solubility of ammonium acid urate nephroliths from bottlenose dolphins (Tursiops truncates) J Zoo Wildl Med;44:853-858.

Bai SC, Sampson DA, Morris JG et al. (1989) Vitamin B-6 requirement of growing kittens. J Nutr;119:1020-1017.

Bartges J: (2012) When Two Are Not Better: Feline Chronic Kidney Disease and Nephroureterolithiasis. ACVIM 2012.

Bartges J (2010) Nutraceuticals for the management of urinary tract infections: effect of cranberry extract. Conference Proceedings, Western Veterinary Conference. Las Vegas, Nevada, February, 2010.

Bartges JW, Kirk CA, Cox SK, Moyers TD (2013) Influence of acidifying or alkalinizing diets on bone mineral density and urine relative supersaturation with calcium oxalate and struvite in healthy cats. Am J Vet Res;74(10):1347-1352.

Buckley CMF, Hawthorne A, Colyer A, Stevenson AE. (2011) Effect of dietary water intake on urinary output, specific gravity and relative supersaturation for calcium oxalate and struvite in the cat. Br J Nutr ;106 Suppl 1(0):S128-130.

Cannon AB, Westropp JL, Ruby AL, et al. (2007) Evaluation of trends in urolith composition in cats: 5230 cases (1985-2004) J Am Vet Med Assoc;213:570-576.

Caporali EHG, Phillips H, Underwood L, Selmic LE (2015) Risk factors for urolithiasis in dogs with congenital extrahepatic portosystemic shunts: 95 cases (1999-2013). J Am Vet Med Assoc; 246(5):530-6. DOI: 10.2460/javma.246.5.530

Chew D and Buffington C. (2014) Diagnostic approach to cats with lower urinary tract signs. Hill's Global Symposium, Prague 23-24 April 2014, pp 23-30.

Cho JG, Gebhart CJ, Furrow E, Lulich JP. (2015) Assessment of in vitro oxalate degradation by *Lactobacillus* species cultured from veterinary probiotics. Am J Vet Res;76(9):801-6.

Chou, H-I, Chen K-S, Wang H-C, et al. (2016) Effects of cranberry extract on prevention of urinary tract infection in dogs and on adhesion of *Escherichia coli* to Madin-Darby canine kidney cells. Am J Vet Res 77(4):421-427.

da Rosa Gomes V, Ariza PC, Borges NC, et al. (2018) · Risk factors associated with feline urolithiasis. Vet Res Commun ;42(1):87-94.

Dear JD, Shiraki R, Ruby AL, et al. (2011) Feline urate urolithiasis: a retrospective study of 159 cases. J Feline Med Surg; 13 (10): 725-32.

Djicker JC, Hagen-Plantinga EA, Thomas DG et al. (2014) The effect of dietary hydroxyproline and dietary oxalate on urinary oxalate excretion in cats. J Anim Sci; 92(2):577-84.

Gerber B, Brandenberger-Schenk F, Rothenanger E, Müller C.(2016) [Uroliths of cats in Switzerland from 2002 to 2009] UrolithenbeiKatzen in der Schweiz von 2002 bis 2009.Schweiz Arch Tierheilkd.;158(10):711-716.

Gunn-Moore D. (2003) Lower urinary tract disease in older cats. Vet Times;33:12-14.

Hagen-Plantinga E. (2014) Role of nutrition in endogenous oxalate metabolism in cats. Hill's Global Symposium, Prague 23-24 April 2014. Pp 69-72.

Hall JA, Yerramilli M, Obare E, et al. (2017) Serum concentrations of symmetric dimethylarginine and creatinine in cats with kidney stones. PLoS One; 12 (4): e0174854.

Hashimoto M Funaba M, Abe M. Ohshima S. (1995) Dietary protein levels affect water intake and urinary excretion of magnesium and phosphorus in laboratory cats. Exp Anim 44;293-299.

Houston DM, Moore AE, Favrin MG Hoff B. (2003) Feline urethral plugs and bladder uroliths: a review of 5484 submissions 1998-2003. Can Vet J;44:974-977.

Houston DM, Rinkardt NE, Hilton J. Evaluation of the efficacy of a commercial diet in the dissolution of feline struvite bladder uroliths. Vet Ther Fall 2004;5:187-201.

Jepson RG, Williams G, Craig JC. (2012) Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev 10(0):CD001321. DOI: 10.1002/14651858.CD001321.pub5

Karmi N, Safra N, Young A, Danika L Bannasch DA. (2010) Validation of a urine test and characterization of the putative genetic mutation for hyperuricosuria in Bulldogs and Black Russian Terriers. Am J Vet Res ;71(8):909-14. DOI: 10.2460/ajvr.71.8.909

Kirk CA. (2014) Feline uroliths and urethral plugs: epidemiology, risk factors and pathogenesis. Hill's Global Symposium, Prague 23-24 April 2014, pp15-22.

Lekcharoensuk C, Lulich JP, Osborne CA, et al. Association between patient-related factors and risk of calcium oxalate and magnesium ammonium phosphate urolithiasis in cats. J Am Vet Med Assoc 2000;217:520-525.

Lekcharoensuk C, Osborne CA, Lulich JP, et al. (2001) Association between dietary factors and calcium oxalate and magnesium ammonium phosphate urolithiasis in cats. J Am Vet Med Assoc; 219(9):1228-1237.

Lekcharoensuk C, Osborne CA, Lulich JP, et al. (2005) Trends in the frequency of calcium oxalate uroliths in the upper urinary tract of cats. J Am Anim Hosp Assoc;41:39-46.

Lulich JP, Berent AC, Adams LG, et al. (2016) ACVIM small animal consensus recommendations on the treatment and prevention of uroliths in dogs and cats. J Vet Intern Med;30:1564-1574.

Lulich JP, Kruger JM MacLeay JM et al. (2013) Efficacy of two commercially available, low-magnesium , urine-acidifying dry foods for the dissolution of struvite uroliths in cats. J Am Vet Med Assoc;243(8):1147-1153.

Lulich JP, Osborne CA, Carvalho M, Nakagawa Y. (2012) Effects of a urolith prevention diet on urine compositions of glycosaminoglycans, Tamm-Horsfall glycoprotein, and nephrocalcin in cats with calcium oxalate urolithiasis. Am J Vet Res;73(3):447-51.

Mariano AD, Penninck DG, Sutherland-Smith J, Kudej RK (2018) Ultrasonographic evaluation of the canine urinary bladder following cystotomy for treatment of urolithiasis. J Am Vet Med Assoc;252(9):1090-1096. DOI: 10.2460/javma.252.9.1090

Martinez-Ruzafa I, Kruger JM, Miller R et al. (2012) Clinical features and risk factors for development of urinary tract infections in cats. J Feline Med Surg;14:729-740.

McClain HM, Barsanti JA, Bartges JW. (1999) Hypercalcemia and calcium oxalate urolithiasis in cats: a report of five cases. J Am Anim Hosp Assoc;35(4):297-301.

Midkiff AM, Chew DJ, Randolph JF, et al. (2000) Idiopathic hypercalcemia in cats. J Vet Intern Med;14:619-626.

Mittal RD, Kumar R. (2004) Gut-inhabiting bacterium *Oxalobacterformigenes*: role in calcium oxalate urolithiasis. J Endourol;18:418-424.

Mizukami K, Raj K, Giger U. (2015) Feline cystinuria caused by a missense mutation in the SLC3A1 gene. J Vet Intern Med; 29(1):120-125.

Osborne CA, Lulich JP, Humchai R et al.(1996) Feline urolithiasis. Etiology and pathophysiology. Vet Clin North Am Small AnimPract; 26(2):217-32.

Paßlack,N, Burmeier H, Brenten T et al. (2014) Relevance of dietary protein concentration and quality as risk factors for the formation of calcium oxalate stones in cats. J Nutr Sci; 3: e51. Published online 2014 Nov 7. doi: 10.1017/jns.2014.13

Paßlack N, Kohn B, Doherr MG, Zentek J. (2018**)** Influence of protein concentration and quality in a canned diet on urine composition, apparent nutrient digestibility and energy supply in adult cats**.** *BMC Veterinary Research* **14**:225-237.

Paβlack N, Schmiedchen B, Raila J et al. (2016)Impact of increasing dietary calcium levels on calcium excretion and vitamin D metabolites in the blood of healthy adult cats. PLoS One DOI:10.137/journal. Pone.0149190:1-19.

Pastour FJ, Van T, Klooster AT, et al. (1995) Increasing phosphorus intake reduces urinary concentration of magnesium and calcium in adult ovarectomized cats. J Nutr; 125:1334-1341.

Picavet P Detileux J, Verschuren S. et al. (2007) Analysis of 4495 canine and feline uroliths in the Benelux. A retrospective study: 1994-2004. J AnimPhysiolAnimNutr (Berl); 91(5-6):247-51.

Rogers KD, Jones B, Roberts L, et al . (2011) Composition of uroliths in small domestic animals in the United Kingdom. Vet J; 188:228-230

Ross L: Managing Nephro- and Ureterolithiasis in Cats. (2013) Central Veterinary Conference 2013.

Ross SJ, Osborne CA, Lekcharoensuk C, et al. (2007) A case-control study of the effects of nephrolithiasis in cats with chronic kidney disease. J Am Vet Med Assoc; 230 (12): 1854-9.

Rutland BE (2015) Bladder matters: The approach and management of chronic cystitis in dogs and cats. Conference Proceedings: Ontario VMA Conf & Trade Show: Ontario VMA 2015.

Van de Maele I, Depuydt D, Daminetet S. (2005) Retrospective study of 53 cats with lower urinary tract disease (LUTD) J Small Anim Pract ;46(12): 29-34.

Weese JS, Weese HE, Yuricek L, Rousseau J. (2004) Oxalate degradation by intestinal lactic acid bacteria in dogs and cats. Vet Microbiol;101(3):161-6.

Wood MW (2017) Lower urinary tract disorders. In Textbook of Veterinary Internal Medicine. Eds. Ettinger SJ, Feldman EC, and Côte E. Elsevier, St Louis, Missouri, pp 1992-1995.