



Nutrition and Lower Urinary Tract Disease in Cats

Joseph W. Bartges, DVM, PhD*, Claudia A. Kirk, DVM, PhD

Department of Small Animal Clinical Sciences, Veterinary Teaching Hospital,
College of Veterinary Medicine, The University of Tennessee, Knoxville, TN 37996–4544, USA

INCIDENCE

Lower urinary tract disease occurs commonly in cats, but the incidence is unknown. Previous estimates of the incidence in the United States and United Kingdom have been 0.85% to 1.0% per year [1,2]. These estimates were based on the presence of clinical signs only, and therefore did not consider actual diagnoses. The proportional morbidity rate, defined as the frequency with which cases are seen at veterinary hospitals, has been reported to be 10% [3], although 1% to 6% is more commonly reported [3,4]. In a cross-sectional study of 15,226 cats examined at 52 private practices, cats were likely to be examined because of renal disease, cystitis, feline urologic syndrome, and inappetence [5].

FELINE LOWER URINARY TRACT DISEASE

Any disorder of the lower urinary tract may cause signs of lower urinary tract disease. In two prospective studies, 1 of 143 cats [6] and 1 of 109 cats [7] with lower urinary tract disease, idiopathic cystitis was diagnosed most commonly (Fig. 1). In a retrospective study performed at the University of Georgia and University of Tennessee of 110 cats older than 10 years of age with lower urinary tract disease, bacterial cystitis was diagnosed most commonly [8]. Thus, causes of lower urinary tract disease seem to be different in cats of different ages, although clinical signs are similar.

IDIOPATHIC CYSTITIS

The most common cause of lower urinary tract disease in cats younger than 10 years of age is idiopathic cystitis. Idiopathic cystitis is characterized by signs of lower urinary tract disease (hematuria, stranguria, pollakiuria, and inappropriate urination) without identifiable cause(s) for the clinical signs. Often, the clinical signs resolve in 3 to 7 days; however, recurrence is variable and unpredictable. Because no specific cause has been identified, no specific treatment is available that works consistently in all cats.

*Corresponding author. E-mail address: jbartges@utk.edu (J.W. Bartges).

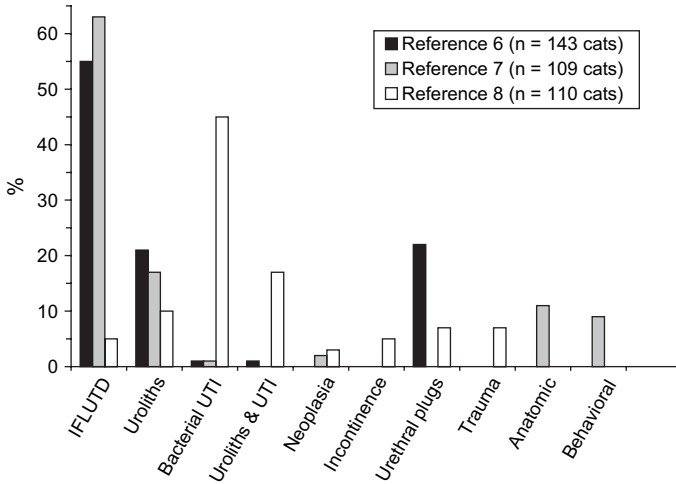


Fig. 1. Percentage of cats evaluated with lower urinary tract disease in two prospective [6,7] and one retrospective [8] studies. Cats in the retrospective study were older than 10 years of age.

The role of a canned diet in managing cats with idiopathic cystitis has been evaluated in two studies. In one nonrandomized prospective study of cats with idiopathic cystitis, recurrence of clinical signs occurred in 11% of cats consuming a canned food when compared with 39% of cats consuming a dry food [9]. The diets evaluated in this study were acidifying and formulated to prevent struvite crystalluria and urolithiasis. In another study, clinical improvement and decreased recurrence of clinical signs in cats with idiopathic cystitis were associated with the owners feeding canned foods [10]. Results of these studies have resulted in the recommendation to feed canned food to cats with idiopathic cystitis; however, these studies were not randomized controlled trials. Furthermore, specific dietary ingredients have not been evaluated in cats with idiopathic cystitis.

CRYSTAL-RELATED LOWER URINARY TRACT DISEASE

Of the various causes of feline lower urinary tract disease, crystal-related disease accounts for 15% to 45% of cases. There are many minerals that may precipitate in the urinary tract to form crystals and stones; however, more than 90% of uroliths from cats are composed of struvite (magnesium ammonium phosphate hexahydrate) or calcium oxalate monohydrate or dihydrate (Fig. 2). Struvite is the most common mineral observed to occur in matrix-crystalline urethral plugs (Fig. 3).

Urolith and matrix-crystalline plug formation involves complex physiochemical processes. Major factors include (1) urine supersaturation resulting in crystal formation (nucleation); (2) effect of inhibitors of mineral nucleation, crystal

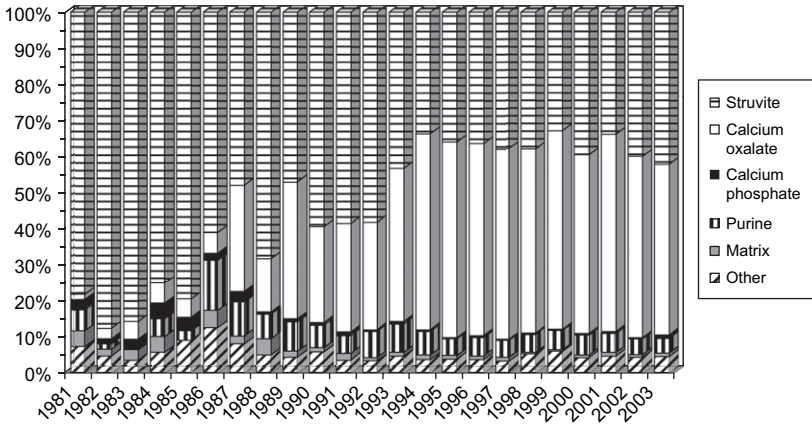


Fig. 2. Mineral composition of 55,418 uroliths retrieved from cats and analyzed at the Minnesota Urolith Center between 1981 and 2003. (From Kirk CA, Bartges JW. Dietary considerations for calcium oxalate urolithiasis. In: August JR, editor. Consultations in feline medicine, vol. 5. St. Louis (MO): Elsevier; 2005. p. 425; with permission.)

aggregation, and crystal growth; (3) crystalloid complexors; (4) effects of promoters of crystal aggregation and growth; (5) effects of noncrystalline matrix; (6) and urine retention or slowed transit for the process to occur [11,12]. Urethral matrix-crystalline plugs have only been identified in male cats and may represent an intermediate phase between lower urinary tract inflammation without crystals and urolith formation [13]. The most important driving force

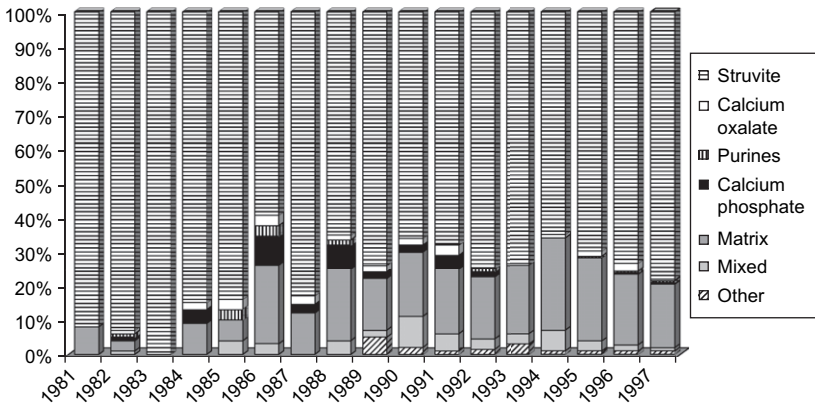


Fig. 3. Mineral composition of 1901 matrix-crystalline urethral plugs retrieved from male cats and analyzed at the Minnesota Urolith Center between 1981 and 1997. (From Osborne CA, Lulich JP, Albansan H, et al. Mineral composition of feline uroliths and urethral plugs: current status. In: Managing urolithiasis in cats: recent updates and practice guidelines. Topeka (KS): Hill's Pet Nutrition Inc.; 2003. p. 26; with permission.)

behind urolith formation is urinary supersaturation with calculogenic substances [14]; however, as mentioned previously, other factors are important. The goal of urinary crystal-related disease is to promote a reduced state of urinary saturation.

Urolithiasis

Calcium oxalate

Calcium oxalate urolith formation occurs when urine is oversaturated with calcium and oxalate [14]. In addition to these alterations in activities of ions, large-molecular-weight proteins occurring in urine, such as nephrocalcin, uropontin, and Tamm-Horsfall mucoprotein, influence calcium oxalate formation [15]. We have a limited understanding of the role of these macromolecular and ionic inhibitors of calcium oxalate formation in cats. Certain metabolic factors are known to increase the risk of calcium oxalate urolith formation in several species, including cats. Medical and nutritional strategies for stone prevention have focused on amelioration of these factors.

Hypercalcemia is associated with an increased risk of calcium oxalate urolith formation. In cats with calcium oxalate uroliths, hypercalcemia was observed in 35% of the cases [16]. Conversely, uroliths developed in 35% of cats with idiopathic hypercalcemia [17]. Hypercalcemia results in increased calcium fractional excretion and hypercalciuria when severe.

Hypercalciuria is a significant risk factor but not necessarily the cause of calcium oxalate urolith formation in human beings, dogs, and cats [18]. Hypercalciuria can result from excessive intestinal absorption of calcium (gastrointestinal [GI] hyperabsorption), impaired renal reabsorption of calcium (renal leak), or excessive skeletal mobilization of calcium (resorptive) [12]. In Miniature Schnauzers, GI hyperabsorption seems to occur most commonly, although renal leak hypercalciuria has also been observed [19]. Hypercalciuria has not been well defined in normocalcemic cats with calcium oxalate uroliths but is thought to occur.

Metabolic acidosis promotes hypercalciuria by promoting bone turnover (release of calcium with buffers from bone); increasing serum ionized calcium concentration, resulting in increased urinary calcium excretion; and decreased renal tubular reabsorption of calcium. Consumption of diets supplemented with the urinary acidifier ammonium chloride by cats has been associated with increased urinary calcium excretion [20]. Significant aciduria (urine pH <6.2) may represent a risk factor for calcium oxalate formation because of acidemia and hypercalciuria. In addition, acidic urine alters the function and concentration of crystal inhibitors. Low urine pH decreases the urinary citrate concentration by increasing renal proximal tubular citrate reabsorption. Acidic urine is known to impair the function of macromolecular protein inhibitors.

Inhibitors, such as citrate, magnesium, and pyrophosphate, form soluble salts with calcium or oxalic acid and reduce the availability of calcium or oxalic acid for precipitation. Other inhibitors, such as Tamm-Horsfall glycoprotein and nephrocalcin, interfere with the ability of calcium and oxalic acid to combine, minimizing crystal formation, aggregation, and growth.

Oxalic acid is a metabolic end product of ascorbic acid (vitamin C) and several amino acids, such as glycine and serine, derived from dietary sources. Oxalic acid forms soluble salts with sodium and potassium ions but a relatively insoluble salt with calcium ions. Therefore, any increased urinary concentration of oxalic acid may promote calcium oxalate formation. Dietary increases of oxalate and vitamin B₆ deficiency are known factors increasing urinary oxalate. Hyperoxaluria has been observed experimentally in kittens consuming vitamin B₆-deficient diets [11] but has not been associated with naturally occurring calcium oxalate urolith formation. Genetic anomalies may increase urine oxalic acid concentration. Hyperoxaluria has also been recognized in a group of related cats with reduced quantities of hepatic D-glycerate dehydrogenase, an enzyme involved in the metabolism of oxalic acid precursors (primary hyperoxaluria type II) [21]. Hyperoxaluria has also been associated with defective peroxisomal alanine/glyoxylate aminotransferase activity (primary hyperoxaluria type I) and intestinal disease in human beings (enteric hyperoxaluria). These have not been evaluated in cats.

Decreased urine volume results in increased calcium and oxalic acid saturation and an increased risk for urolith formation. Cats can achieve urine specific gravities in excess of 1.065, indicating a marked ability to produce concentrated urine. Many cats affected with calcium oxalate uroliths have a urine specific gravity greater than 1.040 unless there is some impairment of renal function or concentrating ability [18].

Detection of calcium oxalate crystals indicates that urine is supersaturated with calcium oxalate and, if persistent, represents an increased risk for calcium oxalate urolith formation. Calcium oxalate crystalluria is present in less than 50% of feline cases at the time of diagnosis of urolithiasis, however [18].

Medical protocols that promote dissolution of calcium oxalate uroliths are not currently available; therefore, uroliths must be removed physically, surgically or by voiding urohydropropulsion [22].

Nutritional or medical protocols should be considered to minimize urolith recurrence or prevent further growth of uroliths remaining in the urinary tract. A significant number of cats develop recurrent uroliths within 2 years of their initial episode if prevention protocols are not initiated [23]. If possible, metabolic factors known to increase calcium oxalate risk should be corrected or minimized. Goals of dietary prevention include (1) reducing urine calcium and oxalate concentration, (2) promoting high concentrations and activity of urolith inhibitors, (3) reducing urine acidity, and (4) promoting dilute urine.

Increasing urine volume is a mainstay of preventative therapy for calcium oxalate urolithiasis in human beings. By increasing water intake, urinary concentrations of calculogenic minerals are reduced. In addition, larger urine volumes typically increase urine transit time and voiding frequency, thereby reducing retention time for crystal formation and growth. Feeding cats a canned food is the most practical means of increasing water intake and lowering calcium oxalate urine saturation. The goal is to dilute urine to a specific gravity of 1.030 or lower [24]. Flavoring water, enhancing water access, and adding

water to dry foods may be used in cats that refuse to eat canned foods. Sodium chloride should not routinely be added to the diet in an effort to stimulate thirst. Although cats increase water intake and dilute urine in response to salt, the consequence of high-sodium foods in cats prone to oxalate uroliths is unknown. Increased dietary sodium may increase urinary calcium excretion and can contribute to ongoing renal damage in cats with marginal renal function [24].

The solubility of calcium oxalate in urine is minimally influenced by pH; however, epidemiologic studies consistently identify acidifying diets among the most prominent risk factors for calcium oxalate urolithiasis [25–27]. Persistent aciduria may be associated with low-grade metabolic acidosis, which promotes bone mobilization and increases urinary calcium excretion. In a case series of five cats with hypercalcemia and calcium oxalate uroliths, discontinuation of acidifying diets or urinary acidifiers was associated with normalization of the serum calcium concentration [26]. Furthermore, aciduria promotes hypocitraturia and functional impairment of endogenous urolith inhibitors. Thus, feeding an acidifying diet or administering urinary acidifiers to cats at risk for calcium oxalate is contraindicated. A target urine pH of 6.6 to 7.5 is suggested in cats at risk for recurrence of calcium oxalate uroliths [24].

Although reduction of urine calcium and oxalic acid concentrations by restriction of dietary calcium and oxalic acid seems logical, it is not without risk. Reducing consumption of only one of these constituents may increase availability and intestinal absorption of the other, resulting in increased urinary excretion. Conversely, increasing dietary calcium levels in normal cats contributes directly to an increased urine calcium concentration. Because epidemiologic data in cats suggest that marked dietary calcium restriction increases urolith risk, moderate levels of dietary calcium are advised in nonhypercalcemic cats [24].

Urinary oxalate is derived from the endogenous metabolism of oxalate precursors (ie, glycine, ascorbic acid) and dietary oxalic acid. Most pet food ingredients are low in oxalic acid, with the exception of vegetables, legumes, and several vegetable-based fermentable fibers (ie, beet pulp, soybean fiber). Dietary oxalic acid concentrations in foods for cats should be reduced to the lowest possible level. Suggested levels are less than 20 mg of oxalic acid per 100 g of food (dry matter basis) [25].

Excess intake of vitamin C, a metabolic oxalate precursor, should similarly be avoided [24]. Although normal dietary vitamin C levels are not considered a risk in human beings, extremely small increases in urinary oxalate are a concern in urolith formers. Because cats do not have a dietary vitamin C requirement, supplementation should be avoided in foods fed to cats at risk for calcium oxalate uroliths. Cranberry concentrate tablets are also contraindicated. They provide mild acidification and are high in oxalate as well as vitamin C [28].

Potassium citrate is often included in diets designed for calcium oxalate prevention. In urine, citric acid combines with calcium to form soluble complexes,

thereby reducing the ionic calcium concentration. Citric acid also directly inhibits nucleation of calcium and oxalate crystals. When oxidized within the tricarboxylic acid cycle, supplemental citrate results in urine alkalization because of the production of bicarbonate. The metabolic alkalization increases endogenous renal citrate excretion and reduces calcium absorption and urinary excretion [24]. Commercial products that add citrate but continue to acidify the urine ($\text{pH} < 6.5$) negate the benefit of citrate therapy.

Consumption of high levels of sodium may augment renal calcium excretion in human beings. Recent studies in healthy cats did not find increased urine calcium excretion in response to high dietary salt intake [24]. In cats with marginal renal function and increased calciuria, sodium exacerbated calcium excretion. No studies have evaluated the effect of sodium in cats prone to calcium oxalate stones. Epidemiologic evidence suggests that low dietary sodium levels in cat foods increase the risk for calcium oxalate urolithiasis [29]. Nonetheless, when fed a food lower in sodium, cats with naturally occurring calcium oxalate uroliths excreted less urine calcium [23]. Until further data are available, orally administered sodium chloride or loop diuretics, which promote renal sodium excretion, for diuresis should be used cautiously and with careful monitoring because they may increase the risk of calcium oxalate urolith formation in some patients. Recommended levels of sodium in foods for cats predisposed to calcium oxalate formation are between 0.3% and 0.5% sodium on a dry matter basis.

Dietary phosphorus should not be restricted in cats with calcium oxalate urolithiasis. Low dietary phosphorus is a risk factor for calcium oxalate urolith formation in cats [29]. Reduction in dietary phosphorus may be associated with activation of vitamin D, which, in turn, promotes intestinal calcium absorption and hypercalciuria. Additionally, phosphate status determines pyrophosphate urinary concentrations, an inhibitor of calcium oxalate urolith formation in human beings and rodents. If calcium oxalate urolithiasis is associated with hypophosphatemia and normal calcium concentration, oral phosphorus supplementation may be considered. Caution should be used, however, because excessive dietary phosphorus may predispose to formation of calcium phosphate uroliths. Whether this occurs in cats is unknown. Phosphorus levels in the foods for cats predisposed to calcium oxalate formation should not be excessive. Levels from 0.5% to 0.8% have been recommended [24].

Urinary magnesium forms complexes with oxalic acid, reducing the amount of oxalic acid available to form calcium oxalate. Studies in cats associate low dietary magnesium with calcium oxalate risk [26,27,29–32]. In human beings, supplemental magnesium has been used to minimize the recurrence of calcium oxalate uroliths; however, supplemental magnesium may increase the risk of struvite formation in cats. At this time, the risks and benefits of magnesium supplementation to cats with calcium oxalate urolithiasis have not been evaluated, and it is not advised. It seems logical that magnesium should not be highly restricted in diets that are consumed by cats with calcium oxalate urolithiasis. Many diets that claim to benefit feline “urinary tract health” are

reduced in magnesium and promote urinary acidification. These foods are designed for struvite prevention and are not appropriate for cats at risk for calcium oxalate urolithiasis. Prudent levels of dietary magnesium are from 0.08% to 0.10% dry matter, or approximately 20 mg of magnesium per 100 kcal [24,29].

Consumption of high amounts of animal protein by human beings is associated with an increased risk of calcium oxalate formation. Dietary protein of animal origin may increase urinary calcium and oxalic acid excretion, decrease urinary citrate excretion, and promote bone mobilization to buffer the acid intake from metabolism of animal proteins. A case-control study showed that higher protein concentration in cat foods seemed to be protective against calcium oxalate uroliths, however [29]. Protein levels between 8 and 9 g of protein per 100 kcal seemed most protective. Although several coassociations (eg, higher protein in canned foods) might explain this finding, cats are obligatory carnivores and dietary protein restriction in the management of calcium oxalate urolithiasis is not advised.

Excessive levels of vitamin D (which promotes intestinal absorption of calcium) and vitamin C (which is a precursor of oxalic acid) should be avoided. Diets with vitamin D levels between 500 and 2000 IU/kg should suffice. As discussed previously, vitamin C is an oxalate precursor as well as a weak urinary acidifier. Both features may increase the likelihood of urolith recurrence.

The diet should be adequately fortified with vitamin B₆ because vitamin B₆ deficiency promotes endogenous production and subsequent urinary excretion of oxalic acid [33]. There is no evidence that providing increased vitamin B₆ beyond meeting the nutritional requirement provides a benefit in cats. Because most commercial diets designed for cats are well fortified with vitamin B₆, it is unlikely that additional supplementation is beneficial, except in homemade diets. Regardless, vitamin B₆ is reasonably safe and sometimes provided to cats with persistent calcium oxalate crystalluria or frequent recurrences.

Increased dietary fiber intake is associated with a decreasing risk of calcium oxalate recurrence in some human beings but not in cats unless they are hypercalcemic. Certain types of fiber (soy or rice bran) decrease calcium absorption from the GI tract, which may decrease urinary calcium excretion. Also, higher fiber diets tend to be less acidifying. In five cats with idiopathic hypercalcemia and calcium oxalate uroliths, feeding a high-fiber diet with supplemental potassium citrate resulted in normalization of serum calcium concentrations [34]; however, the efficacy of increased fiber intake is unproved at this time.

Although the relation of obesity to urolith formation is not understood, it remains a consistent risk factor in all studies to date. Restricting food intake to obtain an ideal weight and body condition is encouraged.

Cats that are meal fed, on average, have a more alkaline urinary pH, controlled food intake for obesity prevention, and a lower risk of calcium oxalate urolith formation. This method of feeding is also the preferred choice for canned foods. This is a relatively simple step that owners can take to improve preventative measures.

At the time of writing, there are three therapeutic foods that are formulated and marketed for the prevention of calcium oxalate uroliths in cats (Table 1). These diets contain potassium citrate (as an alkalinizing agent and a source of citrate) and are designed to induce a higher urine pH compared with standard foods or are designed to promote a significant increase in water intake. Consumption of Prescription Diet Feline x/d (Hill's Pet Nutrition, Topeka, Kansas) and Urinary SO (Royal Canin, St. Charles, Missouri) by healthy cats results in

Table 1

Comparison of diets formulated for prevention of calcium oxalate urolithiasis in cats

Component	x/d dry ^a	x/d canned ^a	pH/O dry ^b	pH/O canned ^b	S/O dry ^c	S/O canned ^c
Moisture As fed (%)	8	76	10	78	7	79
Protein						
As fed (%)	31.3	10.5	32.4	10.6	32.2	8.5
Dry matter (%)	34.0	42.9	36.0	48.3	34.6	40.5
G/100 kcal ME	8.3	8.8	7.7	9.2	7.8	8.3
Fat						
As fed (%)	15.3	4.8	16.5	6.9	17.5	9.1
Dry matter (%)	16.6	19.6	18.3	31.2	18.0	43.1
G/100 kcal ME	4.1	4.0	3.9	5.9	4.2	8.8
Fiber						
As fed (%)	0.8	0.6	1.7	0.2	3.0	0.51
Dry matter (%)	0.9	2.4	1.9	1.0	3.2	2.4
G/100 kcal ME	0.2	0.5	0.4	0.2	0.7	0.5
Sodium						
As fed (%)	0.33	0.09	0.44	0.11	1.3	0.2
Dry matter (%)	0.36	0.37	0.49	0.5	1.4	1.0
G/100 kcal ME	0.09	0.08	0.10	0.10	0.32	0.20
Calcium						
As fed (%)	0.70	0.17	1.01	0.27	1.0	0.21
Dry matter (%)	0.76	0.69	1.12	1.23	1.1	1.0
G/100 kcal ME	0.19	0.14	0.24	0.23	0.24	0.20
Phosphorus						
As fed (%)	0.61	0.13	0.87	0.20	0.8	0.28
Dry matter (%)	0.66	0.53	0.97	0.91	0.86	1.33
G/100 kcal ME	0.16	0.11	0.21	0.17	0.19	0.27
Magnesium						
As fed (%)	0.07	0.02	0.08	0.02	0.07	0.02
Dry matter (%)	0.08	0.08	0.09	0.14	0.08	0.09
G/100 kcal ME	0.02	0.02	0.02	0.02	0.02	0.02

Dry matter indicates percentage of nutrient in product after moisture is removed. G/100 kcal ME indicates intake for every 100 kcal of metabolizable energy consumed.

^aPrescription Diet Feline x/d: nutrient information for diets as of November 2004; manufactured by Hill's Pet Nutrition, (Topeka, Kansas).

^bModerate pH/O/Feline: nutrient information for diets as of July 2003; manufactured by Iams Company (Dayton, Ohio).

^cUrinary S/O: nutrient information for diets as of November 2004; manufactured by Royal Canin (St. Charles, Missouri).

From Kirk CA, Bartges JW. Dietary considerations for calcium oxalate urolithiasis. In: August JR, editor. Consultations in feline medicine, vol. 5. St. Louis (MO): Elsevier; 2005. p. 431.

low urine saturation with calcium oxalate. Clinical trials using Prescription Diet Feline x/d in cats with naturally occurring calcium oxalate urolithiasis reduced calcium oxalate supersaturation by 59% [23]. The reduction in calcium oxalate formation production seemed to be a function of its ability to lower urine calcium. We have had some success in reducing mild hypercalcemia in certain calcium oxalate urolith-forming cats by feeding a high-fiber diet (Prescription Diet Feline w/d; Hill's Pet Nutrition) and administering potassium citrate.

Struvite

Struvite is another name for crystals or uroliths composed of magnesium ammonium phosphate hexahydrate. The chemical composition of struvite is $Mg^{2+} NH_4^+ PO_4 [3-] \cdot 6H_2O$. For uroliths to form, urine must be oversaturated with respect to the minerals that precipitate to form that type of urolith. For struvite uroliths to form, urine must be oversaturated with magnesium, ammonium, and phosphate ions. Urinary oversaturation with struvite may occur as a consequence of a urinary tract infection with a urease-producing microbe (infection-induced struvite) or without the presence of a urinary tract infection (sterile struvite) in cats [35].

Sterile struvite. Sterile struvite uroliths typically form in cats between 1 and 10 years of age. The risk for struvite urolith formation decreases after approximately 6 to 8 years of age in cats [32]. They occur with equal frequency in male and female cats. Sterile struvite uroliths form because of dietary composition as well as innate risks for urolith formation. Experimentally, magnesium phosphate and struvite uroliths formed in healthy cats consuming calculogenic diets containing 0.15% to 1.0% magnesium (dry matter basis) [36–38]. These data are difficult to interpret, however, because the amount of magnesium consumption by cats in these studies may be different than that by cats consuming commercial diets and spontaneously forming sterile struvite uroliths because of differences in caloric density, palatability, and digestibility [39]. The influence of magnesium on struvite formation depends on urine pH [40] and the influence of ions, minerals, and other components in urine [41]. Alkaluria is associated with an increased risk for struvite formation [42,43]. In a clinical study including 20 cats with naturally occurring struvite urocystoliths and no detectable bacterial urinary tract infection, the mean urinary pH at the time of diagnosis was 6.9 ± 0.4 [35]. An additional factor is water intake and urine volume. Consumption of increased quantities of water may result in lowering concentrations of calculogenic substances in urine, thus decreasing the risk of urolith formation [44]. Consumption of small quantities of food frequently rather than one or two large meals per day is associated with the production of more acidic urine and a lesser degree of struvite crystalluria by cats [45,46].

Sterile struvite uroliths can be dissolved by feeding a diet that is restricted in magnesium, phosphorous, and protein and that induces aciduria relative to maintenance adult cat foods [35]. In a clinical study including 22 cats with sterile struvite urocystoliths, urocystoliths dissolved in 20 cats in a mean of 36.2 ± 26.6 days (range: 14–141 days) [35]. The cats were fed a high-moisture (canned)

calorically dense diet containing 0.058% magnesium (dry matter basis) and increased sodium chloride (0.79% dry matter basis). The diet (Prescription Diet Feline s/d; Hill's Pet Nutrition) induced a urine pH of approximately 6.0.

Prevention of sterile struvite uroliths involves inducing a urine pH less than approximately 6.8; increasing urine volume; and decreasing excretion of magnesium, ammonium, and phosphorous. There are many diets available that are formulated to be "struvite preventative."

Infection-induced struvite. Infection-induced struvite uroliths occur more commonly in cats less than 1 year and greater than 10 years of age. There is no published information on gender predilection for infection-induced struvite uroliths in cats. Infection induced-struvite uroliths form because of an infection with a urease-producing microbe in a fashion similar to that in dogs and human beings [38]. In this situation, dietary composition is not important, because the production of the enzyme urease by the microbial organism is the driving force behind struvite urolith formation.

Infection-induced struvite uroliths can be dissolved by feeding a "struvite dissolution" diet and administering an appropriate antimicrobial agent based on bacteriologic culture and sensitivity testing. The average dissolution time for infection-induced struvite uroliths was 79 days (range: 64–92 days) in three cats reported on in a study [35]. It is important that the cat receives an appropriate antimicrobial agent during the entire time of medical dissolution, because bacteria become trapped in the matrix of the urolith and are released into urine as the urolith dissolves. If therapeutic levels of an appropriate antimicrobial agent are not present in urine, an infection may recur and dissolution ceases.

Prevention of infection-induced struvite does not require feeding a special diet, because the infection causes these struvite uroliths to form. It involves preventing a bacterial urinary tract infection from recurring and treating bacterial infections as they arise. Dietary manipulation does not prevent infection-induced struvite uroliths from recurring, because diet does not prevent the recurrence of a bacterial urinary tract infection.

Purines

Uric acid is one of several biodegradation products of purine nucleotide metabolism [47]. In most dogs and cats, allantoin is the major metabolic end product; it is the most soluble of the purine metabolic products excreted in urine. Purine accounted for approximately 5% to 8% of feline uroliths submitted to the Minnesota Urolith Center from 1981 to 2002: 64 (0.14%) were composed of xanthine and the rest were composed of urate. Ammonium urate is the monobasic ammonium salt of uric acid, and it is the most common form of naturally occurring purine uroliths observed to occur in dogs and cats [48]. Other naturally occurring purine uroliths include sodium urate, sodium calcium urate, potassium urate, uric acid dihydrate, and xanthine.

Urate. Urate uroliths have been observed in several breeds of cats; male cats seem to be affected as frequently as female cats. Most urate uroliths occur in

cats younger than 4 years of age. Urate uroliths may occur as a consequence of liver disease, specifically a portal vascular anomaly, or without the presence of liver disease, termed *idiopathic urate urolithiasis*. Urate uroliths occurring in association with portal vascular anomalies are most commonly composed of ammonium urate and are often diagnosed in cats younger than 1 year of age.

Apparently, there have been few studies of the biologic behavior of ammonium urate uroliths in dogs with portal vascular anomalies [49–52] and none in cats. It is logical to hypothesize that elimination of hyperuricemia and reduction of urine ammonium concentration after surgical correction of anomalous shunts would result in spontaneous dissolution of uroliths composed primarily of ammonium urate. Appropriate clinical studies are needed to prove or disprove this hypothesis. We have occasionally been successful in medically dissolving urate uroliths in dogs with portal vascular anomalies but have not attempted dissolution in cats with ammonium urate uroliths and portal vascular anomalies. Additional clinical studies are needed to evaluate the relative value of calculolytic diets, allopurinol, or alkalinization of urine in dissolving ammonium urate uroliths in cats with portal vascular anomalies. The pharmacokinetics and efficacy of allopurinol may be altered in cats with portal vascular anomalies, because biotransformation of this drug, which has a short half-life, to oxypurinol, which has a longer half-life, requires adequate hepatic function. Xanthine uroliths have been observed to form in dogs with portal vascular anomalies given allopurinol; therefore, allopurinol had an effect on xanthine oxidase conversion of xanthine to uric acid.

Although no studies have been performed evaluating the efficacy or safety of medical dissolution of urate uroliths in cats with idiopathic urate urolithiasis, we have successfully dissolved urate uroliths in cats using a low-protein diet (Prescription Diet k/d; Hill's Pet Products) and allopurinol (7.5 mg/kg administered orally every 12 hours). Until further studies are performed to confirm the safety and efficacy of medical dissolution, surgical removal remains the treatment of choice for urate uroliths in cats. Prevention of urate urolith recurrence in cats has been greater than 90% successful when using a protein-restricted alkalinizing diet (Prescription Diet k/d).

Xanthine. Xanthine uroliths retrieved and analyzed from cats contain pure xanthine, although a few contain small quantities of uric acid. Of 64 cats that formed xanthine uroliths in one report [53], none of the cats had been treated with the xanthine oxidase inhibitor, allopurinol. Sixty-one xanthine uroliths were obtained from the lower urinary tract, whereas xanthine uroliths from 3 cats came from the upper urinary tract. Xanthine uroliths occurred in 30 neutered and 8 nonneutered male cats and in 25 neutered female cats (the gender of 1 cat was not specified). The mean age of the cats at the time of diagnosis of xanthine uroliths was 2.8 ± 2.3 years (range: 4 months to 10 years). Eight of the 64 cats were less than 1 year of age. Urinary uric acid excretion was similar between 8 xanthine urolith-forming cats and healthy cats (2.09 ± 0.8 mg/kg/d versus 1.46 ± 0.56 mg/kg/d); however, urinary xanthine excretion ($2.46 \pm$

1.17 mg/kg/d) and urinary hypoxanthine excretion (0.65 ± 0.17 mg/kg/d) were higher (neither are detectable in urine from healthy cats).

No medical dissolution protocol for feline xanthine uroliths exists. Prevention involves feeding a protein-restricted alkalinizing diet. Without preventative measures, xanthine uroliths often recur within 3 to 12 months after removal. In 10 cats consuming the protein-restricted alkalinizing diet and followed for at least 2 years, only 1 has had a recurrence.

Cystine

Cystine accounts for less than 1% of feline uroliths. Cystine uroliths occur with equal frequency in male and female cats. The mean age at diagnosis of cats with cystine uroliths is 4.1 years (range: 10 months to 11 years) [39]. Most cats affected with cystine uroliths are domestic short-hair cats.

Cystine uroliths occur when urine is oversaturated with cystine. Cystine is a disulfide-containing amino acid that is normally filtered and reabsorbed by proximal renal tubular cells. Therefore, cystinuria occurs when there is a defect in proximal renal tubular absorption and must be present for cystine uroliths to form. Evaluation of urine amino acid profiles from four cats with cystine uroliths revealed increased concentrations of the amino acids cystine, arginine, lysine, and ornithine [39,54].

Medical protocols exist for dissolution of cystine uroliths in dogs using thiol-containing drugs, such as N-(2-mercaptopropionyl)-glycine (2-MPG), with or without dietary modification [55] or urinary alkalinization. Reducing dietary protein has the potential of minimizing the formation of cystine uroliths by decreasing intake and excretion of sulfur-containing amino acids and by decreasing renal medullary tonicity, resulting in a larger urine volume. Many feline protein-restricted diets are formulated for use with renal failure and have an added advantage of containing a urinary alkalinizing agent. Solubility of cystine increases exponentially when the urine pH is greater than 7.2 [56]. If necessary or if dietary modification cannot be implemented, potassium citrate may be administered to induce alkaluria. Although thiol-containing drugs are used in dogs and human beings, their use has not been evaluated adequately in cats.

Matrix-Crystalline Urethral Plugs

Urethral matrix-crystalline plugs occur in approximately 20% of male cats younger than 10 years of age that are presented with obstructive lower urinary tract disease [6]. Urethral plugs have only been observed to occur in male cats. They are composed of at least 45% to 50% matrix and variable amounts of mineral; they may be composed entirely of matrix [57]. Struvite is the most common mineral found in urethral plugs. Multiple factors are thought to be associated with urethral plug formation. If a mineral is present in the urethral plug, risk factors associated with that crystal formation, as discussed previously, are involved, at least in part. Compared with uroliths, urethral plugs contain large quantities of matrix. Components of matrix that may be important in urethral plug formation include Tamm-Horsfall mucoprotein, serum proteins, cellular debris, and virus-like particles [13,58].

Management of urethral matrix-crystalline plugs involves relieving the obstructive uropathy [59]. Modifying urine composition by feeding a therapeutic diet may be beneficial if mineral is present in the urethral plug. Increasing urine volume may help to decrease the concentration of minerals and matrix components in urine. Successful prevention of recurrent urethral obstruction using diets designed to reduce urine pH and urine magnesium and phosphorous concentrations has been reported [60]. Perineal urethrostomy may be considered in cats with recurrent urethral plug formation; however, it is associated with complications, including recurrent bacterial urinary tract infections and lower urinary tract disease [60].

Not all feline urinary tract disorders are associated with dietary factors; however, most benefit from nutritional management. It is important to understand the pathophysiology of feline lower urinary tract disease and the physiologic effects of foods and feeding so as to formulate the best nutritional and treatment plan.

References

- [1] Lawler DF, Sjolin DW, Collins JE. Incidence rates of feline lower urinary tract disease in the United States. *Feline Pract* 1985;15:13–6.
- [2] Willeberg P. Epidemiology of naturally occurring feline urologic syndrome. *Vet Clin North Am Small Anim Pract* 1984;14:455–69.
- [3] Foster SJ. The “uroolithiasis” syndrome in male cats; a statistical analysis of the problems, with clinical observations. *J Small Anim Pract* 1967;8:207–14.
- [4] Osborne CA, Kruger JM, Johnston GR, et al. Feline lower urinary tract disorders. In: *Textbook of Veterinary Internal Medicine*. Ettinger SJ, editor. Philadelphia: WB Saunders; 1989. p. 2057–82.
- [5] Lund EM, Armstrong PJ, Kirk CA, et al. Health status and population characteristics of dogs and cats examined at private veterinary practices in the United States. *J Am Vet Med Assoc* 1999;214:1336–41.
- [6] Kruger JM, Osborne CA, Goyal SM, et al. Clinical evaluation of cats with lower urinary tract disease. *J Am Vet Med Assoc* 1991;199:211–6.
- [7] Buffington CA, Chew DJ, Kendall MS, et al. Clinical evaluation of cats with nonobstructive urinary tract diseases. *J Am Vet Med Assoc* 1997;210:46–50.
- [8] Bartges JW. Lower urinary tract disease in older cats: what’s common, what’s not? In: *Health and nutrition of geriatric cats and dogs*. North American Veterinary Conference, Orlando FL, 1996.
- [9] Markwell PJ, Buffington CA, Chew DJ, et al. Clinical evaluation of commercially available urinary acidification diets in the management of idiopathic cystitis in cats. *J Am Vet Med Assoc* 1999;214:361–5.
- [10] Gunn-Moore DA, Shenoy CM. Oral glucosamine and the management of feline idiopathic cystitis. *J Feline Med Surg* 2004;6:219–25.
- [11] Brown C, Purich D. Physical-chemical processes in kidney stone formation. In: *Coe F, Favus M, editors. Disorders of bone and mineral metabolism*. New York: Raven Press; 1992. p. 613–24.
- [12] Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. *N Engl J Med* 1992;327:1141–52.
- [13] Osborne CA, Lulich JP, Kruger JM, et al. Feline urethral plugs. Etiology and pathophysiology. *Vet Clin North Am Small Anim Pract* 1996;26:233–53.
- [14] Bartges JW, Osborne CA, Lulich JP, et al. Methods for evaluating treatment of uroliths. *Vet Clin North Am Small Anim Pract* 1999;29:45–57.
- [15] Balaji KC, Menon M. Mechanism of stone formation. *Urol Clin North Am* 1997;24:1–11.

- [16] Bartges JW. Calcium oxalate urolithiasis. In: August JR, editor. Consultations in feline internal medicine. 4th edition. Philadelphia: WB Saunders; 2001. p. 352–64.
- [17] Midkiff AM, Chew DJ, Randolph JF, et al. Idiopathic hypercalcemia in cats. *J Vet Intern Med* 2000;14:619–26.
- [18] Bartges JW, Kirk C, Lane IF. Update: management of calcium oxalate uroliths in dogs and cats. *Vet Clin North Am Small Anim Pract* 2004;34:969–87.
- [19] Lulich JP, Osborne CA, Nagode LA, et al. Evaluation of urine and serum metabolites in miniature schnauzers with calcium oxalate urolithiasis. *Am J Vet Res* 1991;52:1583–90.
- [20] Ching SV, Fettman MJ, Hamar DW, et al. The effect of chronic dietary acidification using ammonium chloride on acid-base and mineral metabolism in the adult cat. *J Nutr* 1989;119:902–15.
- [21] McKerrell RE, Blakemore WF, Heath MF, et al. Primary hyperoxaluria (L-glyceric aciduria) in the cat: a newly recognised inherited disease. *Vet Rec* 1989;125:31–4.
- [22] Lulich JP, Osborne CA, Sanderson SL, et al. Voiding urohydropropulsion: lessons from 5 years of experience. *Vet Clin North Am Small Anim Pract* 1999;29:283–92.
- [23] Lulich JP, Osborne CA, Lekcharoensuk C, et al. Effects of diet on urine composition of cats with calcium oxalate urolithiasis. *J Am Anim Hosp Assoc* 2004;40:185–91.
- [24] Kirk CA, Ling GV, Osborne CA, et al. Clinical guidelines for managing calcium oxalate uroliths in cats: medical therapy, hydration, and dietary therapy. In: *Managing urolithiasis in cats: recent updates and practice guidelines*. Topeka (KS): Hill's Pet Nutrition; 2003. p. 10–9.
- [25] Kirk CA, Ling GV, Franti CE, et al. Evaluation of factors associated with development of calcium oxalate urolithiasis in cats. *J Am Vet Med Assoc* 1995;207:1429–34.
- [26] Thumchai R, Lulich J, Osborne CA, et al. Epizootiologic evaluation of urolithiasis in cats: 3,498 cases (1982–1992). *J Am Vet Med Assoc* 1996;208:547–51.
- [27] 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;217:520–5.
- [28] Terris MK, Issa MM, Tacker JR. Dietary supplementation with cranberry concentrate tablets may increase the risk of nephrolithiasis. *Urology* 2001;57:26–9.
- [29] Lekcharoensuk C, Osborne CA, Lulich JP, et al. Association between dietary factors and calcium oxalate and magnesium ammonium phosphate urolithiasis in cats. *J Am Vet Med Assoc* 2001;219:1228–37.
- [30] Robertson WG. Urinary calculi. In: Nordin BEC, Need AG, Morris HA, editors. *Metabolic bone and stone disease*. Edinburgh (UK): Churchill Livingstone; 1993. p. 249–311.
- [31] Lulich JP, Osborne CA, Bartges JW, et al. Canine lower urinary tract disorders. In: Ettinger SJ, Feldman EC, editors. *Textbook of veterinary internal medicine*. 5th edition. Philadelphia: WB Saunders; 1999. p. 1747–83.
- [32] Smith BHE, Moodie SJ, Wensley S, et al. Differences in urinary pH and relative supersaturation values between senior and young adult cats. In: *Proceedings of the 15th American College of Veterinary Internal Medicine Forum*. Lake Buena Vista, FL, 1997. p. 674.
- [33] Bai SC, Sampson DA, Morris JG, et al. Vitamin B6 requirement of growing kittens. *J Nutr* 1989;119:1020–7.
- [34] McClain HM, Barsanti JA, Bartges JW. Hypercalcemia and calcium oxalate urolithiasis in cats: a report of five cases. *J Am Anim Hosp Assoc* 1999;35:297–301.
- [35] Osborne CA, Lulich JP, Kruger JM, et al. Medical dissolution of feline struvite urocystoliths. *J Am Vet Med Assoc* 1990;196:1053–63.
- [36] Buffington T. Struvite urolithiasis in cats. *J Am Vet Med Assoc* 1989;194:7–8.
- [37] Finco DR, Barsanti JA, Crowell WA. Characterization of magnesium-induced urinary disease in the cat and comparison with feline urologic syndrome. *Am J Vet Res* 1985;46:391–400.
- [38] Osborne CA, Polzin DJ, Abdullahi SU, et al. Struvite urolithiasis in animals and man: formation, detection, and dissolution. *Adv Vet Sci Comp Med* 1985;29:1–101.

- [39] Osborne CA, Kruger JM, Lulich JP, et al. Feline lower urinary tract diseases. In: Ettinger SJ, Feldman EC, editors. *Textbook of veterinary internal medicine*. 5th edition. Philadelphia: WB Saunders, 1999. p. 1710–46.
- [40] Buffington CA, Rogers QR, Morris JG. Effect of diet on struvite activity product in feline urine. *Am J Vet Res* 1990;51:2025–30.
- [41] Buffington CA, Blaisdell JL, Sako T. Effects of Tamm-Horsfall glycoprotein and albumin on struvite crystal growth in urine of cats. *Am J Vet Res* 1994;55:965–71.
- [42] Tarttelin MF. Feline struvite urolithiasis: factors affecting urine pH may be more important than magnesium levels in food. *Vet Rec* 1987;121:227–30.
- [43] Bartges JW, Tarver SL, Schneider C. Comparison of struvite activity product ratios and relative supersaturations in urine collected from healthy cats consuming four struvite management diets. Presented at the Ralston Purina Nutrition Symposium, St. Louis, MO. 1998.
- [44] Smith BH, Stevenson AE, Markwell PJ. Urinary relative supersaturations of calcium oxalate and struvite in cats are influenced by diet. *J Nutr* 1998;128(Suppl):2763S–4S.
- [45] Finke MD, Litzenberger BA. Effect of food intake on urine pH in cats. *J Small Anim Pract* 1992;33:261–5.
- [46] Tarttelin MF. Feline struvite urolithiasis: fasting reduced the effectiveness of a urinary acidifier (ammonium chloride) and increased the intake of a low magnesium diet. *Vet Rec* 1987;121:245–8.
- [47] Bartges JW, Osborne CA, Lulich JP, et al. Canine urate urolithiasis. Etiopathogenesis, diagnosis, and management. *Vet Clin North Am Small Anim Pract* 1999;29:161–91.
- [48] Osborne CA, Bartges JW, Lulich JP, et al. Canine urolithiasis. In: Hand MS, Thatcher CD, Remillard RL, et al, editors. *Small animal clinical nutrition*. 4th edition. Marceline (MO): Wadsworth Publishing Company; 2000. p. 605–88.
- [49] Marretta SM, Pask AJ, Greene RW, et al. Urinary calculi associated with portosystemic shunts in six dogs. *J Am Vet Med Assoc* 1981;178:133–7.
- [50] Hardy RM, Klausner JS. Urate calculi associated with portal vascular anomalies. In: Kirk RW, editor. *Current veterinary therapy VIII*. Philadelphia: WB Saunders; 1983. p. 1073–8.
- [51] Brain PH. Portosystemic shunts—urate calculi as a guide to diagnosis. *Aust Vet Pract* 1988;18:3–4.
- [52] Johnson CA, Armstrong PJ, Hauptman JG. Congenital portosystemic shunts in dogs: 46 cases (1979–1986). *J Am Vet Med Assoc* 1987;19:1478–83.
- [53] Osborne CA, Bartges JW, Lulich JP. Feline xanthine urolithiasis: a newly recognized cause of urinary tract disease. [abstract]. *Urol Res* 2004;32:171.
- [54] DiBartola SP, Chew DJ, Horton ML. Cystinuria in a cat. *J Am Vet Med Assoc* 1991;198:102–4.
- [55] Osborne CA, Sanderson SL, Lulich JP, et al. Canine cystine urolithiasis. Cause, detection, treatment, and prevention. *Vet Clin North Am Small Anim Pract* 1999;29:193–211.
- [56] Milliner DS. Cystinuria. *Endocrinol Metab Clin North Am* 1990;19:889–907.
- [57] Osborne CA, Lulich JP, Albansan H, et al. Mineral composition of feline uroliths and urethral plugs: current status. In: *Managing urolithiasis in cats: recent updates and practice guidelines*. Topeka (KS): Hill's Pet Nutrition Inc.; 2003. p. 26–8.
- [58] Kruger JM, Osborne CA. The role of viruses in feline lower urinary tract disease. *J Vet Intern Med* 1990;4:71–8.
- [59] Osborne CA, Kruger JM, Lulich JP, et al. Medical management of feline urethral obstruction. *Vet Clin North Am Small Anim Pract* 1996;26:483–98.
- [60] Osborne CA, Caywood DD, Johnston GR, et al. Perineal urethrostomy versus dietary management in prevention of recurrent lower urinary tract disease. *J Small Anim Pract* 1991;32:296–305.