Purina Institute
Advancing Science for Pet Health

UROLITHIASIS IN CATS:
Nutritional Management

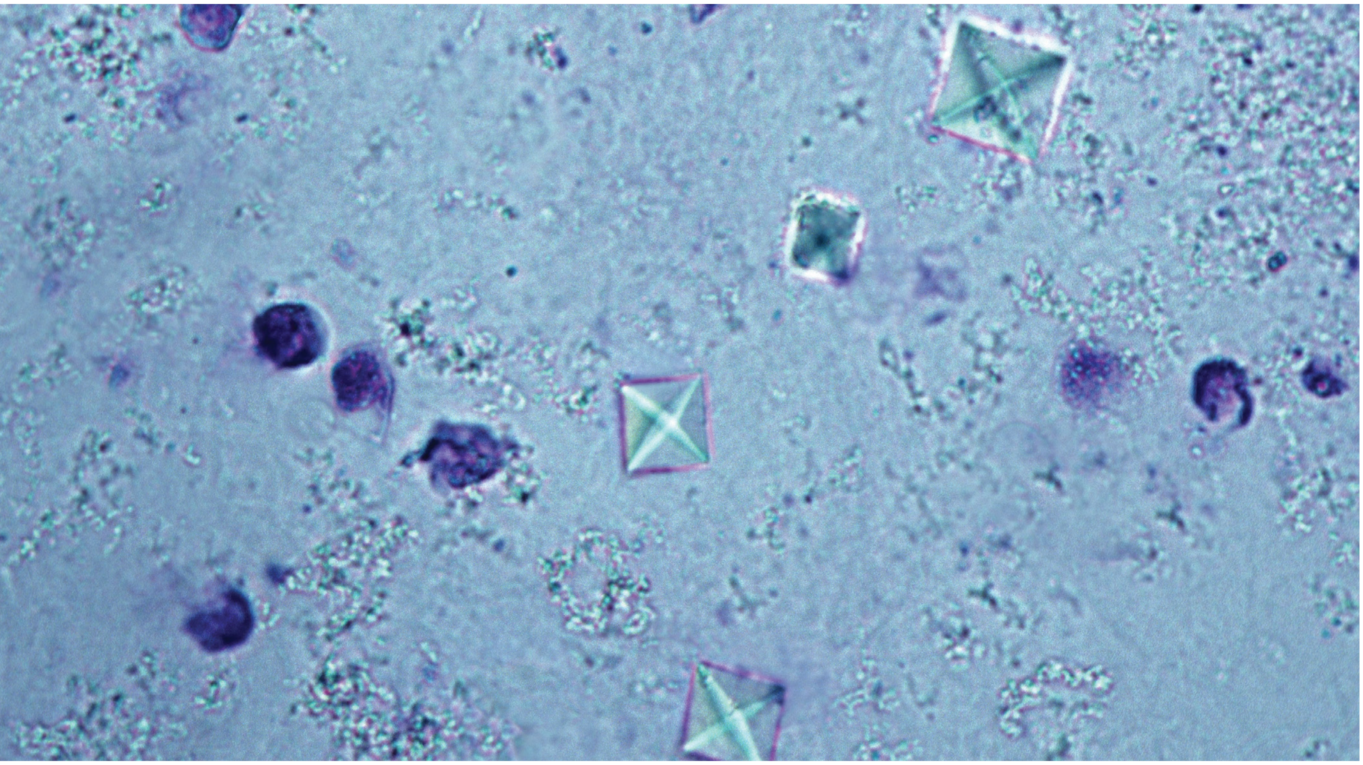
Advancing Science for Pet Health

UROLITHIASIS IS ONE OF THE MOST COMMON FELINE LOWER URINARY TRACT DISEASES

Urolithiasis comprises 7–22% of lower urinary tract cases in cats and, although less common, may also occur in the upper urinary tract.[1-6] Uroliths may recur.

Development or recurrence of urolithiasis may significantly decrease a cat's quality of life and/or, especially with inappropriate urination, may damage the bond between the cat and owner. Either of these impacts may ultimately lead to relinquishment of the cat to a shelter or to elective euthanasia.[4,7-10]

Thus, effective and timely management is critical. Nutritional intervention plays a major role in the management of struvite and calcium oxalate uroliths, the two most common mineral types in cats.



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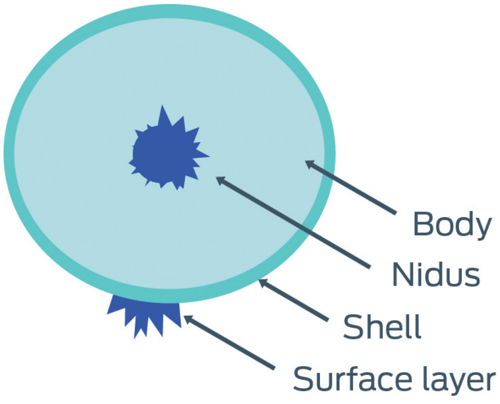
WHAT ARE UROLITHS?

Uroliths have been defined as "solidified aggregates of mineral and nonmineral crystalloids that form in the urinary tract when urine becomes oversaturated with crystallogenic precursors."[11]

The stages of crystal and urolith formation encompass:[12,13]

- **Nucleation:** Precipitation begins, forming the first crystal nuclei.
- **Aggregation:** Crystal nuclei bind to each other.
- **Growth:** Additional mineral ions precipitate onto existing crystal nuclei.

A urolith may have up to four layers: a nidus—where crystals first precipitated—enclosed by a body (or stone) layer, which makes up the majority of the urolith, with an outermost full shell layer and/or an incomplete surface layer.[11,14] A urolith may be comprised of a single mineral or multiple minerals. Multiple minerals in a single urolith may be interspersed or in discrete layers.



Common urolith minerals and location

Magnesium ammonium phosphate (MAP or struvite) and calcium oxalate (CaOx) are the two most frequently found minerals in feline uroliths.[2,15-18]

While struvite uroliths in dogs are typically associated with urease-producing bacterial urinary tract infections, feline struvite uroliths are usually sterile.[19,20] When struvite uroliths develop secondarily to urease-producing bacterial infection in cats, it is typically in kittens or cats over 10 years old.[19,21]

Struvite and CaOx uroliths are most commonly found in the bladder.[22-24] Uroliths may be present in multiple locations within the urinary tract in an individual cat.[16,24-26] Of uroliths located in the upper urinary tract, i.e., kidney(s) and/or ureter(s), most are CaOx.[23-25,27-30]

Clinical signs and significance

Uroliths in the lower urinary tract cause clinical signs such as:[2]

- Hematuria – blood in the urine.
- Stranguria – slow, painful urination; affected cats may strain to urinate.
- Periuria – inappropriate urination (i.e., urinating outside of the litter box).
- Pollakiuria – increased frequency of urination.
- Dysuria – difficult and painful urination, often associated with vocalization.
- Pain on bladder palpation.

Cats with upper urinary tract uroliths may be hematuric and appear painful on abdominal palpation.

Uroliths in the urethra may cause obstruction and must be managed with appropriate emergency care.[8,31,32] Cats with urethral obstruction may die due to, e.g., rupture of the bladder, uremia, electrolyte imbalances, and/or metabolic acidosis, especially when treatment of urethral obstruction is delayed.[4,32,33]

Obstruction may also occur in the ureter(s) and, as with urethral obstruction, should be managed with appropriate emergency care.[34]

Urolithiasis can be challenging to manage and is prone to recur. It may adversely impact a cat's quality of life and/

or, especially with inappropriate urination, may damage the bond between the cat and owner. The end result may be relinquishment of the cat to a shelter or elective euthanasia.[4,7-10]

Urinary crystals

Urinary crystals may be but are not always present when uroliths occur, and the type of urinary crystals may not correspond to the type of urolith.[35,36] Crystals may also be seen in the urine of healthy cats.[35,37,38] Crystals may form as artifacts in urine that is not analyzed immediately after collection, i.e., refrigerated or otherwise stored.[36,39,40]

RECURRENCE OF UROLITHS

A study published in 2009 presented the rate and time of recurrence for cats that had initial uroliths submitted for analysis to one stone analysis laboratory during a 1-year period.[41]

Researchers determined of over 1,800 cats with initial struvite uroliths:

- A first episode of recurrence occurred in 49 (2.7%) of the cats at a mean of 2.4 ± 1.3 years later. Struvite uroliths were found in the majority (41) of the recurrent cases, CaOx in 5, and ammonium urate in 3.
- A second recurrent episode occurred in 3 (0.2%) of the cats at a mean of 3.3 ± 1.7 years after the initial episode. Two cats had recurrent struvite uroliths with the remaining cat having CaOx.

Of nearly 2,400 cats with initial CaOx uroliths, researchers found:

- A first episode of recurrence occurred in 169 (7.1%) of the cats at a mean of 2.1 ± 1.2 years later. Most of these cases (163) were recurrent CaOx uroliths with the remainder struvite.
- A second recurrent episode of urolithiasis occurred in 15 (0.6%) of the cats at a mean of 3.2 ± 1.0 years after the initial episode. All but 1 cat had recurrent CaOx uroliths with the remaining cat having struvite.
- A third recurrence occurred in 2 (0.1%) of the cats at a mean of 4.0 ± 1.1 years after the initial episode. The 2 cats had recurrent CaOx uroliths.

Whether recurrence rate was affected by nutritional management was not known since dietary history was not recorded.

A more recent study with, however, a considerably smaller dataset of 21 cats with urolithiasis (type not specified) that were evaluated at a veterinary teaching hospital in Germany found the following recurrence rates for uroliths:[4]

- Overall: 11 (52%) of the 21 cats. Of the recurrent cases, 4 cats had one recurrent episode, 3 cats had two, 2 had three, and 2 cats had four or more.

Veterinarians removing a recurrent urolith may not submit the urolith for analysis, assuming it is the same type as the initial urolith, which could skew reported recurrence rates. Note also the possibility of pseudorecurrence, in which uroliths have not truly recurred, but rather were not completely removed initially by either surgical or minimally invasive techniques.[42] Of 29 cats that underwent cystotomies at 2 veterinary teaching hospitals, uroliths were left behind in 4 cats (14%). Radiographs are recommended post-procedure to minimize the likelihood of overlooking uroliths.

FACTORS AFFECTING UROLITH FORMATION

Urine saturation and other urinary factors

Whether crystals precipitate, aggregate, and grow into uroliths or dissolve is affected by the degree of urine saturation with the mineral ions that form crystals:[12,13,43]

- In an undersaturated (or stable) solution, in this case urine, crystals dissolve when chemically possible (dependent on composition) and do not precipitate, aggregate, or grow.

- In metastable supersaturated urine, new crystals are unlikely to form spontaneously. However, crystals and stones already present in a metastable solution may aggregate and grow and do not dissolve. Mineral ions may also precipitate onto other existing matter, such as cells or foreign material, e.g., sutures.
- In unstable (or labile) supersaturated urine, new crystals form spontaneously. Crystals aggregate, grow, and do not dissolve.

The concentration at which an undersaturated solution becomes metastable is the thermodynamic solubility product.[43,44] This measure is determined in pure water with pure crystals and is a fixed value at a specific temperature. The thermodynamic solubility product is used to calculate relative supersaturation (RSS), an indicator of the risk of urolith formation (see definition of RSS and further discussion under "Evaluation of urolith risk"). The concentration at which a metastable supersaturated solution becomes unstable is the thermodynamic formation product.

Whether a urolith forms is strongly influenced by these urinary factors:

- **Urine pH.** Due to high solubility in acidic urine and lower solubility in alkaline urine, struvite uroliths tend to dissolve in acid urine and form in alkaline urine.[35,36,45-48]

  Changes in struvite solubility can be rapid. In a crossover study with feeding periods of 10–14 days, struvite RSS of urine was significantly higher, suggestive of an increased risk for urolith formation, for cats fed diets producing a more alkaline urine pH versus diets producing a more acidic urine pH.[49]

  However, urine pH is not the only driver of RSS. Another study examined urine from healthy cats fed 9 different diets which all induced acidic urine.[50] Although there were instances where both urine pH and struvite RSS significantly differed between foods, there were also instances where urine pH was statistically similar between 2 foods, but mean RSS values significantly differed. This demonstrates that urine pH is but one factor affecting struvite urolith risk as measured by RSS.

  A shift in the relative prevalence of struvite and CaOx in cats, with CaOx becoming more prevalent, was observed in the late 1980s and early 1990s and was linked to manufacturer reformulation of cat foods to make them more urine-acidifying (see discussion under "Relative prevalence of struvite and CaOx uroliths").[47,51-53] An association between acidifying diets and elevated risk of CaOx urolithiasis has been demonstrated in humans,[54] and some research in cats has suggested a similar association.[47,55,56]

  With newer diet formulations based on a better understanding of how foods can be formulated to induce a more acidic pH, and the use of RSS to evaluate urine from cats fed different foods, it is now understood that CaOx is less pH dependent than previously thought. Newer research has shown that, as with struvite uroliths, urine pH is not the sole determinant of CaOx urolith risk: In a crossover study, CaOx RSS did not differ significantly when cats were fed diets producing a urine pH of 6.4, 6.2, 6.0, or 5.9 for 10–14 days.[49]

  Note that urinary pH can vary based on proximity to a meal (see further discussion under "Feeding management").[57,58]

The research shows that moderately acidifying diets, provided the diets' calcium oxalate RSS is in the metastable supersaturation range, can help prevent calcium oxalate urolith growth and recurrence while dissolving and helping prevent recurrence of struvite uroliths.

- **Urine specific gravity.** A higher specific gravity (i.e., urine that is more concentrated) may increase the risk of urolith formation.[59] (See further discussion under "Nutritional management of struvite and calcium oxalate urolithiasis.") A more concentrated urine may also increase the concentration of urolith inhibitors and/or promoters.

- **Urolith inhibitors.** Urine contains hundreds of compounds, and their impact on stone formation is not fully understood. Urolith inhibitors may block nucleation, aggregation, and/or growth.[43,60,61]

- **Urolith promoters.** As above, urolith promotors fall into an area that has not been fully investigated. A promotor is a condition or compound that increases the likelihood of crystal formation and/or aggregation.[36,43,60]

- **Noncrystalline matrix.**[43,60] Other compounds such as sloughed cells or suture material in the urine may act as a scaffolding for crystal deposition.

- **Urine retention.**[60] This allows more time for crystal precipitation, aggregation, and growth to occur to form uroliths.

Demographic risk factors

Demographic factors that have been shown to affect the likelihood of developing struvite or CaOx uroliths include:

- **Sex.** Male cats are predisposed to CaOx uroliths, with the exception of CaOx uroliths in the upper urinary tract to which female cats are predisposed.[15,16,23,26,28] Female cats are otherwise more likely to have struvite uroliths.

- **Neuter status.** Neutered cats were reported to be 6.7x and 9.5x more likely to develop struvite and CaOx uroliths, respectively, than intact cats.[16]

- **Age.** Younger cats (under 7 years of age) are more likely to have struvite uroliths and older cats (7 years and older) more likely to have CaOx uroliths.[18,23,28] Mean age did not significantly differ between cats with CaOx uroliths in the lower versus upper urinary tract.[28]

- **Breed.** Various breed predispositions have been reported.[15,16,28]

  Burmese, Himalayan, and Persian cats had a higher risk of CaOx uroliths in two studies.[15,28] Siamese cats were also reported to have a higher risk of CaOx and Domestic Long Haired cats a higher risk of struvite.[15] Compared to Domestic Short Haired (DSH) cats, Domestic Medium Haired cats had a higher risk of struvite.[28]

  Data from 1981–1997 showed that Chartreux, DSH, Foreign and Oriental Shorthair, Himalayan, and Ragdoll were most likely to have struvite.[16] British, Exotic, and Foreign Shorthair; Havana Brown; Himalayan; Persian; Ragdoll; and Scottish Fold were most likely to have CaOx uroliths.

  Compared to mixed breed cats, British Shorthair, Burmese, Persian, Ragdoll, and Tonkinese were at increased risk for upper urinary tract uroliths.[26] Compared to cats with chronic kidney disease (CKD) alone, cats with both CKD and upper urinary tract uroliths were more likely to be purebred.[25]

- **Genetics.** A primary inherited hyperoxaluria resulting from elevated endogenous production of oxalate secondary to faulty metabolism of glyoxylate has been reported rarely in kittens, raising the risk of CaOx urolithiasis.[62-65]

- **Weight.** A study summarizing data from a urolith analysis laboratory found an association between overweight/obesity and increased risk of struvite uroliths.[22] However, researchers noted that they were making this conclusion based on a “Yes” or “No” answer to whether the pet was overweight on the patient history questionnaire submitted with each urolith. Body condition scoring was not included. In the publication, researchers referred to any pet noted as overweight as being obese. Further research is needed to clarify the correlation or establish causation.

Dietary factors associated with struvite urolithiasis

Feline struvite urolithiasis is generally considered a dietary disease as there does not appear to be a genetic component. Foods that put cats at risk of developing struvite uroliths are higher in phosphorus and magnesium and induce a more alkaline urine pH.[47,59] Increasing dietary intake of magnesium and phosphorus has been shown to increase their urinary excretion.[66,67] However, phosphate is in a form less likely to crystallize in acidic urine.[59,66,67]

Foods that have controlled amounts of magnesium and phosphorus and induce a moderately acidic urine pH have been found to readily dissolve existing struvite uroliths and are thus assumed to prevent or reduce occurrence of struvite.[68-72]

Research has suggested a higher risk for struvite urolithiasis with a lower protein diet.[73,74]

Dietary and other factors associated with CaOx urolithiasis

The risk for CaOx urolithiasis is dependent upon urinary excretion of calcium and oxalate, urine content of inhibitors and promoters of crystal formation (nucleation, aggregation, and/or growth), and the presence of nutrients that increase urine volume/decrease urine specific gravity (see "Nutritional management of struvite and calcium oxalate urolithiasis" section).

Urinary excretion of calcium

The amount of calcium in the urine is the result of the complex metabolism of calcium in the body, in which multiple factors play a role:

- **Dietary calcium.** Feeding increased levels of calcium raised fecal calcium concentrations but did not raise urinary calcium concentrations.[75-77] Moderate calcium intake has been advised.[31,47]
- **Vitamin D metabolism.** Vitamin D plays a key role in the maintenance of calcium and phosphorus homeostasis in the body.[78,79] Excess dietary vitamin D may increase absorption of calcium from the gut and its resorption from bone, which may increase urinary calcium excretion, raising the risk of CaOx uroliths.[21]
- **Intestinal calcium binders.** Increased dietary fiber or phosphorus may bind more calcium in the gut, decreasing intestinal absorption of calcium, thus reducing urinary calcium.[66,80] However, this may leave less calcium available to bind oxalate in the gut, which may then increase oxalate absorption.
- **Urinary calcium binders.** Urinary citrate forms a soluble complex with calcium.[43,60,81] This results in less calcium available to bind to oxalate in the urine, lessening the risk of CaOx urolithiasis.

  Urine pH affects urinary citrate concentration. Acidic urine increases renal tubular reabsorption of citrate, leaving less citrate available in the urine to bind calcium.[54,60,82]
- **Dietary acid-base balance.** The acid-base status of the diet influences acid-base balance in the body.[83] In general, meat and fish proteins are acidifying. Phosphorus, chloride, and sulfur are acidifying minerals.[83,84] Fruits and vegetables tend to be alkalinizing. Alkalinizing minerals include potassium, magnesium, calcium, and sodium.

Hypercalcemia

Some cats exhibit periodic hypercalcemia/hypercalciuria, or idiopathic hypercalcemia, which increases the risk for CaOx urolithiasis.[29,31,78,85]

- Of 20 cats with idiopathic hypercalcemia, 7 (35%) had urolithiasis.[85] Upon surgical removal in 2 cats, uroliths were confirmed to be CaOx on quantitative analysis.
- In another study, 11 (almost 16%) of 71 hypercalcemic cats had urolithiasis.[86] Uroliths in 8 cats were confirmed to be CaOx on quantitative analysis.

  Nine (82%) of the 11 cats with urolithiasis also had renal disease. Calcium homeostasis may be altered in cats with CKD, with hypercalcemia detected at the time of CKD diagnosis and also reported to develop after diagnosis.[87-90]
- A review paper reported that 35% of cats with CaOx urolithiasis were hypercalcemic.[21]
- A retrospective study reported that 22 (14%) of 152 cats with ureteroliths were hypercalcemic.[29]
- Cats with upper urinary tract urolithiasis and CKD had

significantly higher serum ionized calcium levels and urinary calcium-to-creatinine ratios.[25]

- In one study, over 20% of CaOx urolith formers expressed hypercalcemia at least once over a 2-year period (cats were evaluated every 4 months).[91]
- Since hypercalcemia can be persistent or intermittent, reported percentages may be underestimates.

Urinary excretion of oxalate

Oxalate is produced endogenously and is available in the diet.[92-94]

Endogenous oxalate production occurs predominantly in the liver, largely via metabolism of glyoxylate in cats.[93,95] Glyoxylate originates from metabolism of sugars, hydroxyproline, and other amino acids.[93,95,96] In health, glyoxylate primarily participates in other metabolic pathways in the cell, which serves to restrict oxalate production.[97,98]

Dietary oxalate, found in greatest concentrations in plants, cannot be metabolized by many mammals, including cats.[99] However, oxalate may be metabolized in the colon by *Oxalobacter formigenes* and other bacteria, including *Lactobacilli* and *Bifidobacterium*.[99-101]

Circulating oxalate, whether of endogenous or exogenous origin, is eliminated in the urine.[92,93,97] Although not definitively known, endogenous production of oxalate may play a larger role in cats than dietary oxalate in affecting the degree of urinary oxalate excretion.[92,93]

Factors that may influence production or intestinal absorption of oxalate in the body and, ultimately, urinary excretion of oxalate include:

- **Dietary mineral, fiber, and carbohydrate content.** In a retrospective analysis of feeding trials in healthy cats, a higher urinary oxalate concentration (on a mmol/L basis) was correlated with lower calcium and sodium in the diet and higher nitrogen-free extract, total dietary fiber, phosphorus, and oxalate.[80]

  If dietary calcium levels decrease, less calcium is available in the gut to form insoluble complexes with oxalate.[80,102] More oxalate is absorbed from the intestine, and more oxalate is eventually excreted in the urine.

- **Hydroxyproline, a glyoxylate precursor.** Hydroxyproline is found in animal proteins, especially collagen, in the diet or may be generated from collagen turnover in the body.[93,96-98] Research has shown that increased dietary hydroxyproline increased urinary oxalate excretion in cats.[95,103]

  Excess supplementation with vitamin C, a precursor of hydroxyproline, may increase the risk of CaOx uroliths.[21,31] Cats (as well as dogs) are able to produce vitamin C endogenously, and thus there is no mandatory dietary requirement for vitamin C in cats or dogs.

- **The microbiome.** When fecal samples from healthy cats were incubated with oxalate in a culture medium ideal for growth of lactic acid bacteria, which are capable of metabolizing oxalate, levels of oxalate decreased.[101] Oxalate that is metabolized by bacteria in the colon is not available to be absorbed from the gut and thus is not ultimately excreted in the urine.

  Researchers suggested that bacteria that are able to metabolize oxalate may be present in lower abundances in cats with nephroliths, which results in more oxalate being excreted in the urine.[99] The same researchers postulated that specific bacteria in the urine may play a role in CaOx urolith formation.

  However, a clear cause and effect relationship between bacteria in the fecal and/or urinary microbiome and the occurrence of nephroliths has not been shown. Whether administration of prebiotics, probiotics and/or postbiotics affects oxalate degradation in the gut and urinary oxalate levels in cats is not yet known.

Dietary intake of calcium and oxalate is a key contributor to how much calcium and oxalate is excreted in the urine. However, their intestinal absorption is complicated by the relative proportion of calcium to oxalate and the presence of other nutrients that enhance absorption or compounds or minerals that may complex with either calcium or oxalate and prevent absorption. In addition, the abundance of oxalate-degrading bacteria in the gut impacts how much oxalate is absorbed. Endogenous production of oxalate is affected by how much glyoxylate is present in the liver, which itself is impacted by the level of glyoxylate precursors in the diet. How best to minimize urinary excretion of calcium and oxalate in order to lower the risk of CaOx urolithiasis remains an active area of research.

CaOx urolith inhibitors and promoters

Compounds that have been investigated as CaOx urolith inhibitors or promoters include:

- Tamm-Horsfall glycoprotein and nephrocalcin, which are produced in the kidneys.[43] Tamm-Horsfall glycoprotein interferes with crystal aggregation, while nephrocalcin interferes with crystal growth.
- Although not directly a "compound in the urine," a bladder foreign body, such as suture material, which may promote CaOx urolithiasis by acting as a urolith nidus.[36,104] This etiology is not common: Of feline bladder uroliths submitted for analysis to the Canadian Veterinary Urolith Centre between November of 1999 to October 2006, only 0.17% (13 cases) overall and 4% of recurrent cases appeared to be associated with suture material.[104] Sutures were associated with other types of uroliths as well. Of the 13 cases, 8 were CaOx, 2 were struvite, and 3 were compound uroliths.
- Potassium citrate. In addition to citrate acting as a urinary binder of calcium, citrate inhibits CaOx crystal nucleation.[14] Citrate also alkalinizes the urine, which decreases its own renal tubular reabsorption, leaving more citrate available in the urine to bind calcium.

EVALUATION OF UROLITH RISK

The risk of urolith formation can be assessed in the urine using various means, including the following.

- **Relative supersaturation (RSS)** of struvite or CaOx is a commonly used indicator and is calculated with one of several computer software programs.

  EQUIL programs (various versions using different computer programming languages over the years) utilize urine pH, urine concentrations of a urolith's constituent ions and other compounds (any or all of the following: ammonium, magnesium, phosphate, calcium, oxalate, chloride, citrate, potassium, sodium, sulfate, urate, carbon dioxide, and pyrophosphate), and their thermodynamic stability constants to calculate ion activity products for a given type of urolith.[44,105,106] RSS is calculated by dividing the ion activity products of the urine by the urolith's thermodynamic solubility products, which are constant values.[44,105]

  EQUIL-HL21 is the newest version of EQUIL, is Windows-based, and is an open program available for use by any research group.[105]

  SUPERSAT uses urine pH and urine concentrations of ammonium, magnesium, phosphate, calcium, oxalate, citrate, potassium, sodium, sulfate, uric acid, and chloride in its calculations.[107,108] It is a proprietary program.

- **Activity product ratio (APR)** is determined by dividing the activity product before by the activity product after the urine is incubated with the relevant seed crystals for the urolith.[12,109] This method does not appear to be widely adopted in veterinary medicine and is no longer commonly measured in research settings.

- **Calcium oxalate titration (COT)** (previously known as the calcium oxalate risk index, CORI) is determined by gradually adding a solution of sodium oxalate to a urine sample until CaOx crystal precipitation occurs.[110-113] This method has also not been widely adopted in veterinary medicine.

NUTRITIONAL MANAGEMENT OF STRUVITE AND CALCIUM OXALATE UROLITHIASIS

For struvite urolithiasis in cats, nutritional intervention is recommended for both dissolution and reduction of the risk of recurrence.[34] Calcium oxalate uroliths require removal using surgical or non-invasive procedures; however, their recurrence may be lowered with nutritional management.

The overall objective of nutritional management is to lower the concentration of minerals in the urine, to alter the chemical form of the ions in the urine by changing urine pH, and/or to influence the overall stability of the urine thus decreasing risk.

Increased total water intake

One approach is to increase water intake, which is recommended for all types of uroliths, not only those composed of struvite or CaOx, to promote a more dilute urine.[2,34,59] A more dilute urine may reduce RSS by reducing solute concentration, presumably lessening the risk of urolith formation.[2,59,60,93] A higher urine volume may increase frequency of urination, helping eliminate calculogenic minerals and microscopic concretions before they can form larger uroliths.

To promote water intake, the following strategies may be beneficial:[2,60]

- **Feeding wet diets or adding water or broth to dry food.** Although to compensate for the lower moisture content, cats will drink more free water when eating dry food compared to wet food, they may have a lower total daily water intake (a lower water to calorie ratio) when eating dry food.[114-117] Studies suggest that dietary moisture levels greater than 70–75% (wet food or dry food with added water) increase total daily water intake and urine volume and decrease urine specific gravity, i.e., make urine more dilute.[115,117,118]

  The ACVIM Consensus Recommendations on the Treatment and Prevention of Uroliths in Dogs and Cats note, "For all mineral types (except infection-induced struvite), feeding diets high in moisture is one of the cornerstones of urolith prevention strategies."[34] For CaOx uroliths in particular, the Consensus Recommendations advise targeting a urine specific gravity of under 1.030 for cats.

- **Feeding a diet with moderately increased levels of sodium (Na)/salt (NaCl) or potassium (K)/ potassium chloride (KCl).**

  The ACVIM Consensus Recommendations suggest that in pets that will not eat high-moisture diets, diets with increased levels of Na can be fed to promote water intake.[34]

  Two studies have shown that feeding cats dry diets with moderately increased levels of Na/NaCl compared to lower Na/NaCl diets for up to 21 days increased voluntary water intake and daily urine volume.[119,120] Urine was more dilute. One of the two studies showed that CaOx RSS values were significantly lower,[120] and the other study found that both struvite and CaOx RSS values were lower when the moderately increased Na/NaCl diets were fed.[119]

  In humans, urinary calcium excretion increases as the level of Na in the diet increases,[121] which may raise CaOx RSS. However, most feline studies demonstrated that moderately increased Na/NaCl diets when fed for up to 6 months did not affect urinary calcium excretion or concentration.[120,122-124]

The vast majority of published research in cats, both short- and long-term (from 2 weeks up to prospective research lasting as long as 5 years), has demonstrated that moderately increased levels of salt in diets fed to healthy and aging cats do not adversely affect heart or kidney function or affect blood pressure.[123,125-129]

In a 5-year study of 20 cats enrolled at a median age of 11.5 years old, the frequency of CKD and hypertension was similar between control and increased salt diet groups.[128] Since the sample size decreased as the study progressed, researchers compared rates of change in variables. They found no significant differences between the diet groups in rates of change in plasma creatinine, systolic arterial blood pressure, glomerular filtration rate, or multiple cardiovascular measures.

Voluntary water intake and urine volume significantly increased in healthy cats when fed a diet with moderately increased levels of KCl, a salt substitute.[130] Urine was significantly more dilute, and CaOx RSS significantly decreased.

- **Providing a nutrient-enriched flavored water supplement.** Several Purina studies support its benefit.[131,132]

In healthy cats fed a dry diet, overall mean free liquid intake was significantly higher for the group offered a nutrient-enriched flavored water supplement (nutrient water) in addition to tap water compared to the group of cats offered tap water only.[131] Nutrient water intake was a mean of 96.6% ± 3% of total daily intake, showing that the increase in free liquid consumption in the nutrient water group was due to a high nutrient water intake. The increased water intake resulted in production of a significantly higher urine volume and more dilute urine in the nutrient water group.

Researchers in a second study had similar findings.[132] Mean daily free liquid intake and urine volume significantly increased, and urine became significantly more dilute in healthy cats offered nutrient water in addition to tap water, while none of the variables changed significantly in a group of cats offered tap water only.

- **Offering different water sources (still water, circulating water, free-falling water).** While research showed that no one source was uniformly superior at encouraging water intake, individual cats did show increases in water intake with either still, circulating, or free-falling water, thus suggesting personal preferences may exist.[133-135]
- **Providing water in multiple locations around the home.** Water should be located where easily accessible and where cats will not feel threatened while drinking.
- **Offering water in different types of bowls, e.g., stainless steel, ceramic, glass, and/or wide bowls** (so that a cat's whiskers do not touch the sides of the bowl) to determine the cat's individual preference.

Therapeutic urinary diets

Therapeutic urinary diets are typically formulated to promote a urinary environment that is unsuitable for development of struvite and CaOx uroliths, targeting a specific urine pH while producing a urine in the undersaturated range for struvite and the metastable range for CaOx uroliths. These diets help dissolve struvite uroliths and reduce the risk of struvite and CaOx recurrence.

Feeding of therapeutic urinary diets has been shown to reduce struvite crystalluria and to dissolve struvite uroliths in cats in multiple studies:

- Feeding of a wet or dry formulation of a therapeutic urinary diet for 13 weeks to cats with struvite crystalluria significantly decreased the level of crystals in the urine.[136] Improvement began after week 3.
- In a Purina-supported study, of 12 shelter cats that had radiopaque cystoliths visible on radiographs and clinical lower urinary tract signs, 5 cats showed complete dissolution of the urolith at the 2-week recheck and thus were assessed as having had struvite

urolithiasis.[69] In the 7 remaining cats, uroliths were analyzed after surgical removal and were either CaOx or had a mixed composition.

- Thirty-nine pet cats with suspected struvite urolithiasis were fed either a wet or dry veterinary therapeutic diet.[71] The diets were restricted in magnesium, were urine acidifying, and had earlier been shown to produce urinary struvite RSS values consistent with undersaturated urine. Of the 37 cats completing the study, 31 cats showed total dissolution of all uroliths, thus confirming the diagnosis.

  Uroliths dissolved in a mean of 30 days, and clinical signs resolved in a mean of 19 days. Wet and dry diet groups did not significantly differ in either time to dissolution or time to resolution of clinical signs. The number of uroliths also had no significant effect on time.

  Uroliths removed from the cats that were not responsive to the diet within 12 weeks were confirmed to contain CaOx and/or urate or to be calcified tissue.

- Seventeen of 21 pet cats with suspected struvite urolithiasis fed a wet or dry therapeutic urinary diet showed complete urolith dissolution in a mean time of 18 days.[72] There was no statistical difference in time to dissolution for cats fed the wet diet versus the dry diet.

  Uroliths were removed from the 4 cats that did not respond within 12 weeks. None of the uroliths contained struvite.

- Pet cats with suspected struvite urolithiasis were fed either a therapeutic urinary diet intended for intermittent feeding (i.e., not complete and balanced) and formulated to dissolve struvite uroliths (group 1, 16 cats), or a complete and balanced therapeutic urinary diet appropriate for long-term (maintenance) feeding, which was formulated for struvite dissolution and reduction of recurrence (group 2, 21 cats).[70] All cats in group 1 and 16 cats from group 2 showed complete dissolution.

  Quantitative analysis showed that 4 of the 5 cats that did not respond to the dietary trial had ammonium urate uroliths and 1 cat had CaOx.

- Of 30 cases of suspected struvite urolithiasis in which cats were fed a therapeutic urinary diet intended for intermittent feeding, 28 showed complete dissolution in a mean of 38.5 ± 27.4 days.[68] Clinical signs resolved within 2 weeks with the exception of one cat having resolution within 4 weeks.

  One of the 2 cats that did not respond to the diet had an ammonium urate urolith and the other a mixed urolith.

- Two of 9 pet cats with suspected struvite urolithiasis fed a therapeutic urinary diet showed complete urolith dissolution by the 2-week recheck.[137] The uroliths dissolved completely in another 5 cats by the 4-week recheck. Complete dissolution occurred in another cat by day 70. In the last cat, the uroliths were found to be CaOx.

Cats with struvite uroliths fed a therapeutic urinary diet to induce urolith dissolution should be radiographed at 2- to 4-week intervals to monitor the progress of dissolution.[138] Once radiographs show no evidence of uroliths, the diet should be continued for at least another 30 days. A decrease in size at the 2-week recheck has been suggested to be useful at confirming the diagnosis of a struvite urolith.[70]

Use of a complete and balanced therapeutic urinary diet is recommended long term to reduce recurrence,[34] unless the cat needs to resume a different therapeutic diet for management of a comorbidity or in the rare case of infection-associated struvite urolithiasis.[70]

Feeding of therapeutic urinary diets to reduce recurrence or risk of recurrence of struvite or CaOx urolithiasis has been evaluated:

- In the Purina-supported study previously mentioned, the therapeutic urinary diet was continued after resolution of urolithiasis in 6 cats (3 of the cats with presumed struvite urolithiasis and 3 cats that had the uroliths surgically removed).[69] In the 1–6 month follow-up period, none had radiographic evidence of urolith recurrence.

- In cats with a history of struvite urolithiasis followed for a 2-year period, just 5% of cats fed a complete and balanced therapeutic urinary diet (wet, dry, or a combination) had recurrence compared to 22% of cats fed a control diet that was comparable to a commercial maintenance diet.[139] Cats fed the therapeutic diet had a significantly lower struvite RSS and urine pH than cats fed the control diet.
- In cats with a history of CaOx urolithiasis that were followed for a 2-year period, 29% of cats fed a therapeutic urinary diet (wet, dry, or a combination) compared to 37.5% of cats fed the control diet had recurrence.[91] Hypercalcemia occurred periodically in 23.5% of the cats fed the therapeutic diet versus 50% of the cats fed the control diet. Cats fed the therapeutic diet, cats that did not have recurrent CaOx uroliths, and those that were not hypercalcemic were found to have a significantly lower CaOx RSS as well as significantly less calcium in the urine.
- Beginning 2 weeks after removal of CaOx uroliths, cats were fed either a wet therapeutic urinary diet or their regular diet for 8 weeks, then crossed over to the other diet for another 8 weeks.[140] The mean value for CaOx RSS was significantly lower when cats were consuming the therapeutic urinary diet. Urinary calcium concentration and excretion were also significantly lower with the therapeutic urinary diet.

Feeding management

Since urine pH rises linearly with the amount of food consumed, feeding multiple small meals per day may reduce the alkaline tide that occurs postprandially and thus help reduce the risk of struvite urolithiasis.[57,58] However, for CaOx urolithiasis, research has not found a significant difference in risk for cats that were meal fed versus fed ad libitum.[55] The composition of the diet may also affect the degree of the postprandial alkaline tide.[57]

RELATIVE PREVALENCE OF STRUVITE AND CALCIUM OXALATE UROLITHS

The Feline Veterinary Medical Association (previously known as the American Association of Feline Practitioners) has reported that worldwide, struvite and CaOx uroliths comprise 90 to 95% of all feline uroliths.[2] Struvite and CaOx uroliths comprised 87% of all feline uroliths submitted to a North American urolith analysis laboratory in 2022.[17]

Prevalences of feline struvite and CaOx uroliths as reflected by urolith submissions to North American stone analysis laboratories have changed over time:

- In the 1980s, struvite uroliths were much more prevalent than CaOx.[16,23]
- Prevalence of CaOx then increased, while that of struvite decreased until around 1993 when prevalences were roughly equal.[16,23]

  It has been suggested that the change in prevalence was due to cat food manufacturers adjusting formulations to make diets more urine-acidifying to reduce the risk of struvite urolithiasis, but which may have inadvertently increased the risk of CaOx.[47,51-53]
- From 1994 to 2004, CaOx uroliths were generally more prevalent.[23,141]
- In the mid-2000s which urolith had a greater prevalence varied by laboratory.[15,28,141]
- From 2008 to 2014, CaOx was generally the more prevalent.[15,28]
- From 2015 to 2018, struvite was again more prevalent.[28]

Note that the prevalences reported here were based on analysis performed at different stone analysis laboratories, which did not all classify uroliths in the same way. Two out of the three urolith laboratories in North America classified a urolith as one mineral type if the urolith contained ≥ 70% of that mineral and did not have a nidus or shell.[15,24,141] Other uroliths were considered as mixed or compound.

The remaining North American urolith laboratory classified uroliths by all of the minerals contained within them.[23,28] Thus, one urolith containing both CaOx and struvite would have been "counted" twice—as a CaOx-containing urolith and a struvite-containing urolith.

Research also differed on whether only the first submission from a pet or, if they occurred, multiple submissions from the same pet were included in the data.

In addition, since the figures are based on urolith submissions, the reported prevalences may not reflect true prevalences in the population at large. Numbers and relative percentages of struvite and CaOx urolith submissions themselves may be skewed for reasons including the following:

- Case populations may be diverse. It has been suggested that there may be regional differences in prevalence secondary to differences in climate, breed distribution, lifestyle, diet, etc.
- Since struvite uroliths are susceptible to medical dissolution, with continuing formulation improvements to therapeutic diets over the years, relatively fewer struvite uroliths may be surgically removed and submitted for analysis. The ACVIM Consensus statement advocates for dietary dissolution over surgical removal.[34]
- There may also be increased awareness of stone analysis laboratories and subsequently more CaOx and other uroliths that are not susceptible to dissolution being submitted.
- Prior stone history may increase or decrease the likelihood the veterinarian would submit a urolith for analysis.
- Owners may elect not to pursue laboratory analysis of the uroliths.

RELATIONSHIP BETWEEN UROLITHIASIS AND CHRONIC KIDNEY DISEASE

Retrospective research has revealed an association between urolithiasis and CKD in cats:

- Of 140 cats with CKD seen at a veterinary teaching hospital, 73% had upper urinary tract urolithiasis.[25] Age, sex, or neuter status had no effect on the prevalence.
- Nearly 30% of cats with CKD in a therapeutic dietary trial had nephroliths at study entry.[142]
- Other research found that 40% of cats with uroliths were diagnosed with CKD compared to 18% of cats without urolithiasis.[143] Of hospitalized cats with urolithiasis, 56% had CKD compared to 30% of control hospitalized cats.[144]
- In a retrospective study of cats with ureteroliths that had presented to veterinary teaching hospitals, 83% were azotemic and 54% hyperphosphatemic.[29]

  Comparing cats with unilateral ureterolithiasis to cats with bilateral disease, 76% versus 96%, respectively, were azotemic. Forty-three percent versus 84%, respectively, were hyperphosphatemic. Cats with bilateral ureterolithiasis had significantly greater blood urea nitrogen, serum creatinine, and serum phosphate than cats with unilateral ureteroliths.

  Notably, 92% of the cats had a ureteral obstruction. As noted earlier and as for urethral obstructions, obstructive ureteroliths should be managed with emergency care.[34]

If a unilateral ureteral obstruction occurs, the contralateral kidney may be able to compensate resulting in no clinical signs.[52] If the other ureter obstructs in the future, imaging may then show what is known as "big kidney, little kidney" syndrome. This occurs when the kidney with the earlier (chronic) obstruction has atrophied, while the kidney with the acute obstruction had either already developed hypertrophy or has become acutely hydronephrotic.

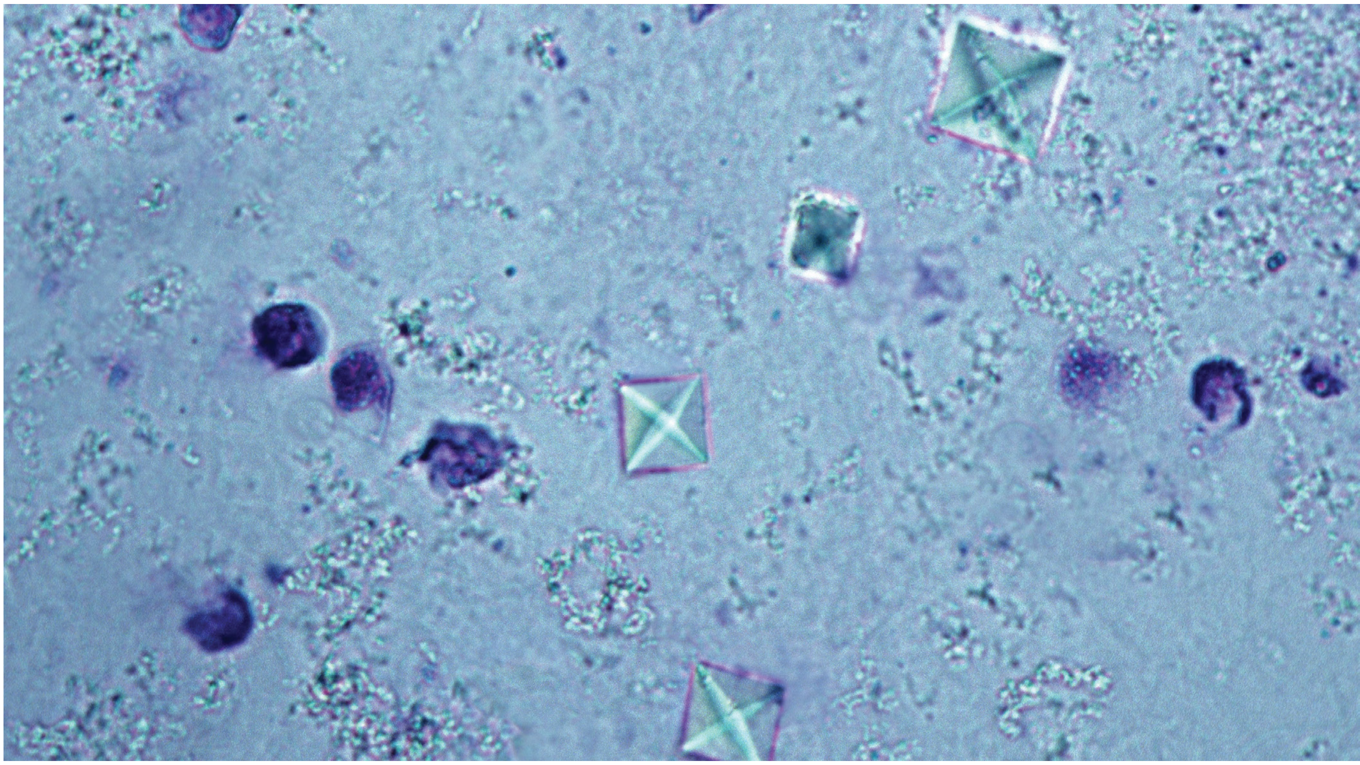
- Nearly 17% of cats with upper urinary tract uroliths seen at a veterinary referral hospital also had CKD.[26] Cats over 12 years old that had uroliths in the upper urinary tract were less likely to have obstruction than younger cats with upper urinary tract uroliths.
- Researchers noted that an association between urolithiasis and CKD did not definitively equate to a cause-and-effect relationship.[25,144,145] However, they recommended that cats with urolithiasis be screened for CKD and vice versa.

Results of research evaluating whether nephroliths affect progression of CKD have been inconsistent:

- Neither mortality rate nor CKD progression was affected by the presence of nephroliths in 7 cats with stage 2 or 3 CKD compared to 7 cats with stage 2 or 3 CKD that did not have nephroliths.[142] Researchers suggested the results supported medical management of nephroliths versus removal.
- In contrast to those results, another study found that cats with nephroliths lived significantly shorter than healthy controls: a mean lifespan of 12.5 years versus 15.2 years, respectively.[27] Researchers concluded that non-obstructive nephroliths may impact CKD progression and/or mortality. Note that healthy cats not CKD cats without nephroliths comprised the comparison group, which was different from the study above.
- At end of life, cats with CKD had the most dilute urine, cats with no history of renal disease or urolithiasis the most concentrated, and cats with CaOx nephroliths an intermediate urine specific gravity.[146] Serum functional biomarkers were significantly greater than healthy cats only in cats with CKD. Study results suggested that the nephroliths were impacting kidney function although not to the same degree as cats with CKD.

The ACVIM Small Animal Consensus Recommendations on the Treatment and Prevention of Uroliths in Dogs and Cats do not advise removal of nephroliths unless there is obstruction, pain, or recurrent infection, or the nephrolith is significantly compressing renal tissue.[34] Urinalysis, urine culture, and imaging should be performed on a repeated basis to detect if and when an "inactive" nephrolith begins to cause complications.[147] The ACVIM Small Animal Consensus Recommendations advise subcutaneous ureteral bypass or ureteral stenting procedures when obstructive ureteroliths occur.[34]

Feline urolithiasis may cause significant morbidity, damage the human-animal bond, and lead to relinquishment of the cat to a shelter or to elective euthanasia. Thus, effective management is critical. Nutritional intervention, i.e., increasing hydration and the feeding of therapeutic urinary diets, is a key component of managing feline struvite and CaOx urolithiasis and recurrence.



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