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Nutritional management of canine urolithiasis

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Abigail graduated from the University of Stirling with a BSc (Hons) in 1992. After working as a research assistant at the University of Anchorage in Alaska for 6 months Abigail was appointed as a research technician at the WALTHAM Centre for Pet Nutrition in 1993 to work on feline metabolism of vitamin A and taurine. In 1995, Abigail was promoted to the position of Research Scientist working in the area of urinary tract health, and obtained her PhD on this subject in 2002. From 2002 to 2005 Abigail was responsible for the bird and fish research programs at WALTHAM. Recently Abigail moved again to take up a position in Scientific Communications at WALTHAM.

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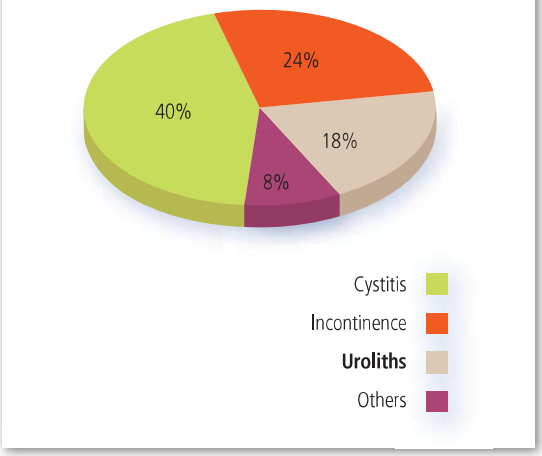
Carolien graduated from Utrecht State University and completed an internship at the University of Pennsylvania and a residency and Masters degree at Ohio State University. In between she worked in referral small animal practice. She joined the University of Liverpool in 1985 as a Lecturer in Small Animal Medicine and moved in 1990 to the Royal Veterinary College, where she later became a Senior Lecturer. She is now an independent consultant.

Carolien has published more than 100 scientific papers and book chapters, and has lectured widely in the UK and abroad. Her major research interests are in gastroenterology and liver disease. She is a Diplomate of the American College of Veterinary Internal Medicine (ACVIM), a Foundation Diplomate of the European College of Veterinary Internal Medicine - Companion Animals (ECVIM-CA), and a RCVS Diplomate in Small Animal Medicine. Carolien has been a foundation Board member of the ECVIM-CA and a member of the RCVS Small Animal Medicine and Surgery Board, and a Diploma examiner for both.

FIGURE 1 - MAIN CONDITIONS RESPONSIBLE FOR THE CLINICAL SIGNS OF LOWER URINARY TRACT DISEASE IN DOGS *(From Lulich et al, 2000)*



Urolithiasis is defined as the formation of sediment, consisting of one or more poorly soluble crystalloids, in the urinary tract. Microscopic sediment is referred to as crystals, and larger macroscopic precipitates are called uroliths.

Urolithiasis is a common problem in dogs. Uroliths can form anywhere in the urinary tract, although in dogs the vast majority occur in the bladder. Urolithiasis is responsible for about 18% of veterinary consultations in dogs with lower urinary tract disorders (Figure 1) (Lulich et al, 2000).

1 - Introduction

The four most common minerals found in canine uroliths are magnesium ammonium phosphate (struvite), calcium oxalate, ammonium urate and cystine *(Osborne et al, 1995; Osborne et al, 1999b; Houston et al, 2004)* **(Figures 2 & 3, Table 1)**. Less common urolith types are calcium phosphate, silicate, drugs and drug metabolites.

Calcium oxalate and struvite are the predominant mineral types in canine nephroliths *(Ross et al, 1999)*. The incidence of urolithiasis and the composition of uroliths may be influenced by a variety of factors including breed, sex, age, diet, anatomic abnormalities, urinary tract infection (UTI), urine pH and medications *(Ling, 1998)*. Identification of these risk factors is essential for effective management and prevention of urolithiasis. Urolithiasis often has a high recurrence rate. This has led to an increasing use of dietary management for both dissolution and prevention of uroliths, although some mineral types are more amenable to dissolution than others.

Figure 2: Calcium oxalate crystal

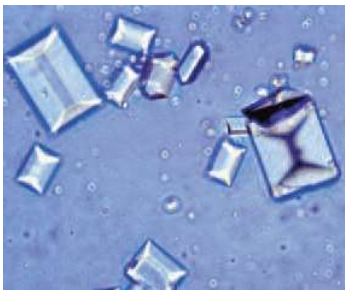


Figure 3: Struvite crystal

TABLE 1 - PREVALENCE OF THE MOST COMMON UROLITHS IN DOGS
Based on 77,000 submissions to the Minnesota Urolith Center from dogs of all ages (Adapted from Osborne et al, 1999c; Houston et al, 2004)

	1981	1982-1986	1981-1997	1997	2003*
Struvite	78%	67%	49%	45%	43.8%
Oxalate	5%	7%	32%	35%	41.5%
Urate		5%	8%	9%	
Cystine		2%	1%	<1%	
Mixed uroliths		12%	9%	8%	

Struvite uroliths used to be the most common type, but during the last twenty years the prevalence of calcium oxalate urolithiasis has been increasing and that of struvite urolithiasis decreasing; although the latter still predominates (Ling et al, 2003).

**data from the Canadian Veterinary Urolith Centre*

2 - Diagnosis

► History and clinical signs

Symptoms of urolithiasis are mainly due to irritation of the mucosa of the lower urinary tract, resulting in signs of cystitis and/or urethritis. The most common signs are hematuria, dysuria and pollakiuria. Occasionally, urolithiasis may lead to urethral obstruction, which is a medical and surgical emergency. Renal calculi may furthermore cause pyelonephritis, outflow obstruction, reduction of renal mass, azotemia and renal failure. Conversely some patients are clinically asymptomatic.

► Differential diagnosis

Other common causes of hematuria, dysuria and frequent urination, with or without urethral obstruction, are UTI, polyps and neoplasia. These can be distinguished by urine culture and imaging studies.

► Laboratory testing and imaging

Urinalysis, quantitative urine culture and imaging (plain and double contrast radiography and/or ultrasonography) are required to confirm urolithiasis and to look for predisposing factors.

Evaluation of serum biochemistries is useful for the recognition of underlying abnormalities and assessment of renal function in dogs with nephrolithiasis. Urine chemistries can furthermore reveal excessive quantities of one or more minerals contained in the urolith.

> Urinalysis

Urinalysis typically shows inflammation: proteinuria, hematuria and pyuria. Urine pH varies, depending upon stone type, presence or absence of infection, and diet. In general, struvite uroliths are associated with alkaline urine, particularly if urease-producing bacteria are present. Urate and cystine formation tends to be associated with acid to neutral pH *(Osborne et al, 1995)*. In contrast urine pH is a less important factor in calcium oxalate formation.

Crystalluria may be present without urolithiasis, and urolithiasis may occur without crystalluria. In addition, crystals are not necessarily representative of the urolith type, since they may be influenced by a urease-producing bacterial infection that could generate struvite crystals. However, ammonium urate crystals **(Figure 4)** may indicate portosystemic shunting, and cystine crystals are pathognomonic of cystinuria **(Figure 5)**. The presence of crystals depends on urine pH, temperature and concentration. Urine samples should be examined within 30 minutes of collection and should not be refrigerated.

> Urine culture

Urine bacterial culture and sensitivity should be performed in all dogs to assess for primary or secondary UTI. Bacterial culture of the inner parts of possible infection-induced stones may also be beneficial, since bacteria in the urine may not be the same as those harbored in the urolith *(Osborne et al, 1995)*. If a cystotomy is performed for stone removal, it is recommended to submit a piece of bladder mucosa for culture and sensitivity as this is more sensitive than culturing the urine *(Hamaide et al, 1998)*.

> Imaging techniques

Radiography and/or ultrasonography are indicated to verify the presence of uroliths, as well as their location, number, size, radiodensity and shape **(Figure 6)**. Uroliths have to be greater than 3 mm to be detected by survey abdominal radiography or ultrasonography. Urate uroliths are the most radiolucent and usually require double contrast cystography for visualization. Retrograde contrast studies are required to assess urethral stones, and excretory urography if renal calculi are suspected.

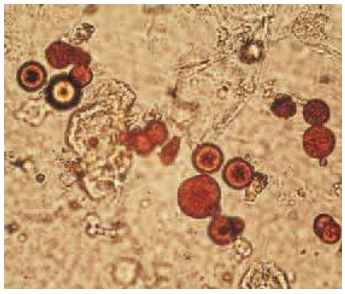


Figure 4: Ammonium urate urinary crystals

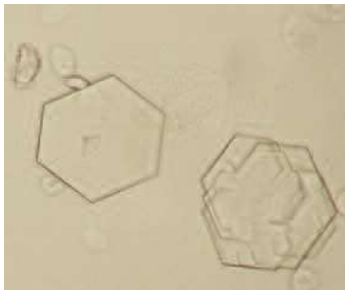


Figure 5: Cystine urinary crystals

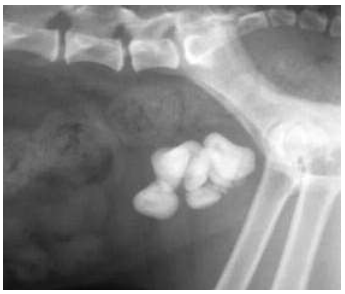


Figure 6: Radiographic appearance of cystic calculi in a dog

Cystoscopy requires specialized equipment and general anesthesia, but it can be very helpful to confirm urolithiasis and to remove small uroliths from the bladder or urethra *(Cannizzo et al, 2001)*.

► Analysis of urolith composition

Uroliths may be collected by spontaneous voiding, voiding urohydropropulsion *(Osborne et al, 1999e)*, aspiration into a urethral catheter, cystoscopy, or surgical removal. Urolith composition should be determined by

quantitative physical analyses, which are far more accurate than qualitative chemical techniques. Uroliths can contain more than one mineral type, and layer-by-layer mineral analysis may be required in compound stones. It is, therefore, important not to crush the uroliths before analysis. The initiating cause of the uroliths can be determined by the mineral composition of the nucleus, which may be different from the surrounding layers *(Osborne et al, 1999c)*.

Determination of the mineral composition of uroliths is vital for specific therapy and to prevent recurrence. Quantitative analysis performed by specialized laboratories is the most reliable method.

► Predicting urolith type

Effective dissolution of uroliths depends on knowledge of their mineral composition. Ideally a urolith should be retrieved and analyzed, and a number of factors can help in predicting urolith composition **(Tables 2, 3).**

TABLE 2 - FACTORS THAT HELP PREDICT UROLITH COMPOSITION IN DOGS
(adapted from Osborne et al, 1995)

	**Signalment**: breed, age and sex **(see Table 3)**		
	**Radiographic density of uroliths**	- Calcium oxalate, calcium phosphate - Struvite, silica - Cystine - Ammonium urate	++++ ++ to ++++ + to ++ 0 to +
	**Urine pH**	- Struvite - Calcium oxalate - Ammonium urate, silica - Cystine	Usually alkaline No predisposition Acid to neutral Acid
	**Crystalluria**	- Cystine crystals are pathognomonic for cystinuria, which predisposes to cystine urolithiasis	
	**Presence of UTI,** and type of bacteria isolated from the urine	- UTI with urease-producing bacteria (*Staphylococci, Proteus spp*) suggests struvite urolithiasis (primary or secondary)	
	**Disease associations** (serum chemistry evaluation)	- Hypercalcemia may be associated with calcium-containing uroliths - Portosystemic shunts predispose to urate urolithiasis - Hyperchloremia, hypokalemia and acidosis may be associated with distal renal tubular acidosis and calcium phosphate or struvite uroliths	
	**Urine chemistry evaluation**	- Urine relative supersaturation regarding various minerals included in the stone	
Family history of particular uroliths			
Quantitative analysis of uroliths passed during voiding, collected via catheter aspiration or by voiding urohydropropulsion			

TABLE 3 - AGE, BREED AND SEX PREDISPOSITIONS FOR UROLITHIASIS IN DOGS
(adapted from Osborne et al 1999c; Lulich et al, 2000)

Urolith type	Commonly affected ages	Commonly affected breeds		Sex
Struvite	1 - 8 years Mean 6 years	Miniature Schnauzer Bichon frisé Shih Tzu Miniature Poodle Lhasa Apso		Female (>80%)
Calcium oxalate	6 - 12 years Mean 8.5 years	Miniature Schnauzer Lhasa Apso Cairn Terrier Yorkshire Terrier Cocker Spaniel Bichon frisé Shi Tzu Miniature Poodle		Male (>70%)
Calcium phosphate	5 - 13 years	Yorkshire Terrier		Male (>70%)
Urate	Without PSS: mean 3.5 years With PSS: mean <1 year	Dalmatian, English Bulldog, Miniature Schnauzer (PSS), Yorkshire Terrier (PSS)		Male (>85%)
Cystine	2 - 7 years Mean 5 years <1 year in Newfoundland dogs	English Bulldog Dachshund Newfoundland dog		Male (>90%)
Silica	4-9 years	German Shepherd dog Old English Sheepdog		Male (>90%)

PSS = portosystemic shunts

► Specific urolith types

> Struvite

Struvite ($Mg\ NH_4\ PO_4\ 6\ H_2O$) is one of the most common minerals found in canine uroliths **(Figure 7)**. Oversaturation of urine with magnesium ammonium phosphate ions is a requirement, but several other factors – including UTI, alkaline urine, diet and genetic predisposition – may influence formation. In dogs, most struvite uroliths are associated with a bacterial UTI **(Figure 8)** with urease producing bacteria such as Staphylococcus *spp* (often S. *intermedius*) or, less commonly, Proteus spp. Urease is an enzyme that hydrolyzes urea, leading to elevations of ammonium, phosphate and carbonate, resulting in alkaline urine. Many struvite uroliths also contain a small quantity of other minerals, such as calcium phosphate and, less commonly, ammonium urate.

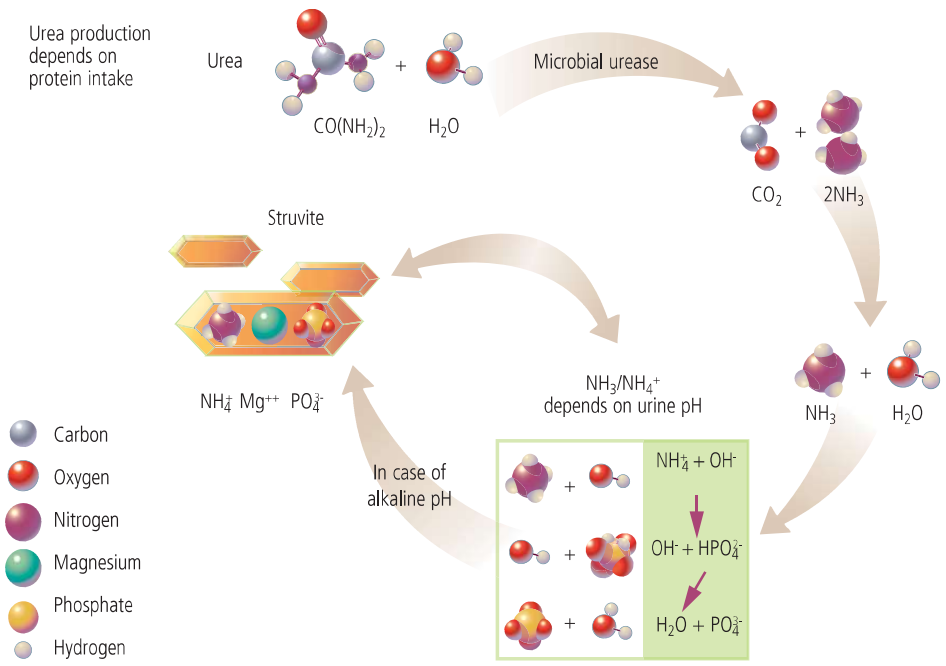
Figure 7: Struvite stones

Sterile struvite uroliths are rare in dogs; their etiopathogenesis may include dietary, metabolic or familial factors, but does not involve bacterial urease *(Osborne et al, 1995)*.

> Calcium oxalate

The main risk factor is supersaturation of urine with calcium and oxalate, with calcium relatively more important *(Stevenson, 2002, Stevenson et al 2003a)*. A major factor is intestinal hyperabsorption of calcium, which is recognized as a cause of calcium oxalate urolithiasis in both humans and dogs susceptible to calcium oxalate urolithiasis *(Lulich et al, 2000; Stevenson, 2002)*. Indirectly, this leads to hyperoxaluria, since it increases the availability of oxalate for absorption. The relationship between intestinal absorption of calcium and oxalic acid is clinically important, since reducing the concentration of calcium increases oxalate absorption, thus maintaining or increasing the risk of stone formation. Diet may have a significant role in the development of these uroliths (see risk factors) *(Lekcharoensuk et al, 2002a; 2002b)*.

FIGURE 8 - THE ROLE OF UTI IN STRUVITE UROLITHIASIS
(From P. Markwell)



Bacterial infection with urease producing organisms results in the cleavage of urea to generate ammonia and carbon dioxide. The carbon dioxide can dissociate with water to alkalinize the urine. The alkaline pH enables phosphate and ammonium ions to bind with magnesium to form a molecule of magnesium ammonium phosphate (struvite).

Diseases that increase urinary excretion of calcium and oxalic acid play a smaller role. Calcium oxalate **(Figure 9)** and phosphate uroliths have been reported in dogs with primary hyperparathyroidism, but not in dogs with paraneoplastic hypercalcemia *(Klausner et al, 1987; Lulich et al, 2000)*.

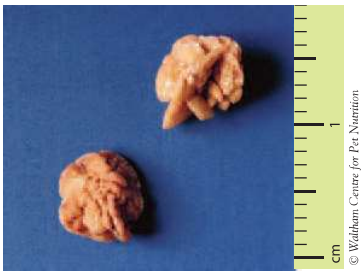


Figure 9: Calcium oxalate stones

> Urate

Uric acid is one of several biodegradation products of purine nucleotide metabolism. In non-Dalmatian dogs, almost all urate formed from degradation of purine nucleotides is metabolized by hepatic uricase to allantoin, which is very soluble and excreted by the kidneys. In Dalmatian dogs, only 30-40% of uric acid is converted to allantoin, resulting in increased serum levels and urinary excretion of urate *(Bartges et al, 1999)*. Ensuing uroliths are most commonly composed of ammonium urate **(Figure 10)**. The defective uric acid mechanism in Dalmatian dogs probably involves both alterations in the hepatic and renal pathways, but the exact mechanism is incompletely understood. Reduced urinary excretion of crystallization inhibitors may contribute to stone formation in Dalmatians *(Carvalho et al, 2003)*. Urolithiasis in the Dalmatian is probably autosomal recessive inherited *(Sorenson & Ling, 1993)*, although this does not explain the increased risk of stone formation for male dogs.

Figure 10: Urate stones

Any form of severe hepatic dysfunction may predispose dogs to urate urolithiasis, but there is a specific predisposition in dogs with congenital or acquired portosystemic shunts *(Kruger et al, 1986, Bartges et al, 1999)*. These dogs frequently develop intermittent crystalluria, urate calculi, or both. Hepatic dysfunction in these dogs may be associated with reduced hepatic conversion of uric acid to allantoin and of ammonia to urea, resulting in hyperuricemia and hyperammonemia, but the precise mechanism is uncertain.

Relatively little is known about urate urolithiasis in non-Dalmatian dogs that do not have portosystemic shunts, although a familial tendency has been suggested for English Bulldogs (*Kruger et al, 1986; Bartges et al, 1994*). Dietary risk factors for urate urolithiasis include high purine diets (e.g; diets rich in offal) and low water consumption. Urine acidity promotes urate lithogenesis, because purines are less soluble at acid pH. Consumption of diets that promote aciduria such as high protein diets are therefore also a risk factor for predisposed dogs (*Bartges et al, 1999*).

> Cystine

These uroliths **(Figure 11)** occur in dogs with cystinuria, an inborn error of metabolism characterized by a defective proximal tubular reabsorption of cystine and other amino acids. Cystinuric dogs reabsorb a much smaller proportion of cystine that is filtered by the glomerulus and some may even have net cystine secretion (*Casal et al, 1995*). Cystinuria is usually the only detectable sign of their amino acid loss unless protein intake is severely restricted. Cystine urolithiasis develops because cystine is only sparingly available at the usual urine pH of 5.5 to 7.0. Not all cystinuric dogs form uroliths, and calculi are often not recognized until maturity. They occur predominantly in male dogs, and other undetermined factors may therefore also play a role in the pathogenesis. Canine cystinuria is genetically heterogeneous and has been recognized in more than 60 breeds of dogs with variable patterns of aminoaciduria (*Case et al, 1992, 1993; Osborne et al, 1999g, Henthorn et al, 2000*).

Figure 11: Cystine stones

> Other uroliths

Calcium phosphate uroliths (Figure 12) are commonly called apatite uroliths, with hydroxyapatite and carbonate apatite the most common forms. They occur commonly as a minor component of struvite and calcium oxalate stones. Pure calcium phosphate uroliths are infrequently found, and they are usually associated with metabolic disorders (primary hyperparathyroidism, other hypercalcemic disorders, renal tubular acidosis, idiopathic hypercalciuria) and/or excessive dietary calcium and phosphorus (*Kruger et al, 1999*). Calcium phosphate crystals can trigger calcium oxalate crystallization by allowing heterogeneous crystallization to occur at a lower urinary supersaturation than homogeneous crystallization. The risks associated with calcium phosphate formation therefore should be taken in account when treating other urolith types.

Figure 12: Calcium phosphate stones

Silica urolithiasis is a recently discovered disease (*Aldrich et al, 1997*). The pathogenesis may involve consumption of an absorbable form of silica in various foods, resulting in urinary silica hyperexcretion. The recent emergence of these uroliths may have some relationship to the increased use of plant-derived ingredients such as fibers and bran in dog foods (*Osborne et al, 1995*).

Compound uroliths consist of a nucleus of one mineral type and a shell of another mineral type. They form because factors promoting precipitation formation of one type of urolith supersede earlier factors promoting precipitation of another mineral type. Some minerals types may also function as a nidus for deposition of another mineral; for instance, all uroliths predispose to UTI, which may result in secondary struvite precipitation.

3 - Epidemiology

► Causes

Urolithiasis is the result of underlying inherited, congenital or acquired disorders, resulting in increased urinary excretion of certain minerals and/or predisposition to urolith formation (*Osborne et al, 1995*). Urine composition may be altered by metabolic abnormalities. An inherited mechanism has been proven in Dalmatians (urate) and Newfoundland dogs (cystine) (*Sorenson & Ling, 1993; Henthorn et al, 2000*), and the predilection in several other breeds suggests a possible genetic basis. Congenital causes can directly (e.g. congenital cystinuria) or indirectly (e.g. urogenital malformations) predispose an individual to form uroliths. Acquired disorders include

UTI with urease forming bacteria as well as metabolic disorders that result in an increased mineral excretion (e.g. hypercalcemia). Administration of drugs may be an aggravating cause in some cases *(Osborne et al, 1999f)*.

The incidence and mineral composition of uroliths may be influenced by a complex interaction of multiple factors, including age, sex, genetic predisposition and breed, diet, water consumption, lifestyle and the presence of UTI.

► Predisposition and risk factors

> Breed, sex, age

Urolithiasis tends to affect smaller dog breeds more often than larger breeds *(Lulich et al, 2000)*. The predisposition for smaller breeds may be related to their lower urine volume, fewer numbers of micturitions, and therefore increased mineral concentrations *(Ling, 1998; Stevenson & Markwell, 2001)* **(Table 4)**.

Breed predisposition for specific mineral types may suggest a genetic basis, and is often significantly correlated with the sex **(Table 3)** *(Stevenson, 2002)*. The genetic mode of inheritance has been determined for cystinuria in Newfoundland dogs, where it has been shown that the disease is transmitted in a simple autosomal recessive pattern *(Casal et al, 1995; Henthorn et al, 2000)*.

Most forms of urolithiasis are more common in male dogs, whereas struvite urolithiasis has a high incidence in female dogs, probably related to their greater susceptibility to develop bacterial UTIs **(Table 5).**

Urolithiasis usually occurs in mature dogs, although the age range is wide. Calcium containing stones (phosphate and oxalate) tend to be found in older dogs.

> Diet and water consumption

Diet can influence urine composition and dietary factors therefore play a significant role in increasing the risk of urolithiasis, although this may differ for certain mineral types **(Table 6)**.

TABLE 4 - RISK FACTORS FOR UROLITHS IN SMALL DOGS
(Adapted from Stevenson et al, 2001)

Small breeds are more commonly affected: Bichon frisé, Dachshund, Lhasa Apso, Miniature Poodle, Miniature Schnauzer, Shih Tzu, Yorkshire Terrier

Urinary differences observed in 8 Miniature Schnauzers and 8 Labrador Retrievers.

Urinary volume * (mL/kg $BW^{0.75}$)	Miniature Schnauzer (12 ± 3) < Labrador (22 ± 15)
Number of micturitions /day	Miniature Schnauzer (1.5 ± 0.5) < Labrador (2.9 ± 1.1)
Urinary pH	Miniature Schnauzer (6.52 ± 0.18) > Labrador (6.14 ± 0.34)

* *Reduced urinary volume also observed in the Cairn Terrier (< Labrador)*

Several dietary factors have been suggested to play a role in the development of calcium oxalate urolithiasis, including low dietary moisture and sodium, and high protein content. A greater risk is associated with dry formulations *(Ling et al 1998; Lekcharoensuk et al, 2002a, 2002b)*. High moisture diets and a moderate increase in dietary sodium have been shown to reduce the risk of calcium oxalate formation in susceptible breeds of dog *(Stevenson et al, 2003b; 2003c)*. Severe purine restriction has been found to reduce urinary urate excretion in both healthy dogs and Dalmatians. There is also a strong link between silica urolithiasis and the feeding of diets high in plant ingredients such as bran or soybean hulls *(Lulich et al, 2001)*.

TABLE 5 - FACTORS THAT HELP TO PREDICT THE COMPOSITION OF CANINE UROLITHS
(Ling, 1998 ; Lulich, 2000)

	Urate	Cystine	Struvite	Oxalate
Sex	**Males: 85% of cases**	**Males: 90% of cases**	**Females: 80% of cases**	**Males: 70% of cases**
Breed predispositions	**Dalmatian** English Bulldog Miniature Schnauzer Yorkshire Terrier	**English Bulldog** Dachshund Basset Hound Yorkshire Terrier	Shi Tzu Miniature Schnauzer Miniature Poodle Bichon frisé Lhasa Apso English Cocker Spaniel	Shi Tzu Miniature Schnauzer Miniature Poodle Bichon frisé Lhasa Apso Yorkshire Terrier
Mean age	**1 - 4 years**	**1 - 8 years**	**2 - 8 years**	**5 - 12 years**
Urinary pH	**acid or neutral**	**acid or neutral**	**alkaline or neutral**	**–**
Urine infection	**–**	**–**	**2/3 cases**	**–**

> Urinary tract infections (UTIs)

UTIs predispose an individual to struvite urolithiasis, especially when associated with urease-forming bacteria. As urinary infections are more frequent in females than in males, this helps to explain why struvite uroliths occur more frequently in females and in particular spayed females.

> Environment

Differences in the pattern of urolith formation are observed between countries. Factors that predispose an individual to dehydration (e.g. hot climate, limited access to fresh water), or urinary retention in the bladder (indoor lifestyle) can increase the likelihood of urolith formation *(Franti et al, 1999)*.

> Drug administration

Diagnostic and therapeutic drugs may enhance urolithiasis by altering urine pH, tubular reab-

TABLE 6 - RISK FACTORS FOR UROLITH FORMATION LINKED TO DIET, URINE COMPOSITION AND METABOLISM IN DOGS
(adapted from Osborne et al 1999c ; Lulich et al, 2000)

Urolith type	Diet	Urine	Metabolic/other
Struvite	High magnesium* High phosphorus* Low water consumption	Alkaline pH UTI with urease-producing bacteria Low urine volume	-
Calcium oxalate	High calcium* High oxalate* (esp. when dietary calcium is low) Excess vitamin C*	Low urine volume Hypercalciuria Hyperoxaluria	Hypercalcemia Hyperadrenocorticism Chronic metabolic acidosis
Calcium phosphate	Excess dietary calcium and phosphorus*	-	Hypercalcemia (primary hyperparathyroidism) Renal tubular acidosis
Urate	High purine diets (e.g; diets rich in offal)	-	Genetically inherited defect in uric acid metabolism Hepatic dysfunction
Cystine	-	Cystinuria	Defective proximal tubular reabsorption of cystine and other basic amino acids
Silica	High dietary silica*	-	

**The level from which this dietary factor becomes important depends on the urinary environment (urinary pH, presence of inhibitors, urinary infection etc)*

sorption or secretion, and precipitation of drugs and their metabolites *(Osborne et al, 1999b,1999f)*. The prevalence of drug-induced urolithiasis is unknown, although drugs and their metabolites are more likely to precipitate in urine if uroliths are already present. The older generation sulfonamides have been most frequently implicated, although precipitation and urolithiasis may also occur with the newer generations drugs when given for prolonged times at high concentrations.

> Metabolic influences

Prolonged hypercalcemia and subsequent calciuria may increase the risk of calcium containing stones. Hyperadrenocorticism has been associated with calcium oxalate stones, since glucocorticosteroids increase mobilization of calcium from bone and reduce tubular resorption, resulting in calciuria *(Hess et al, 1998; Lulich et al, 1999)*.

Chronic metabolic acidosis may also contribute to calcium oxalate urolithiasis, which is attributed to buffering of excess hydrogen ions by bone phosphorus and carbonates, with concurrent release of calcium *(Lulich et al, 1999)* **(Figure 13)**.

Cystinuria is an inherited inborn error of metabolism that predisposes to cystine urolith formation, although not all dogs with cystinuria or cystine crystalluria form uroliths.

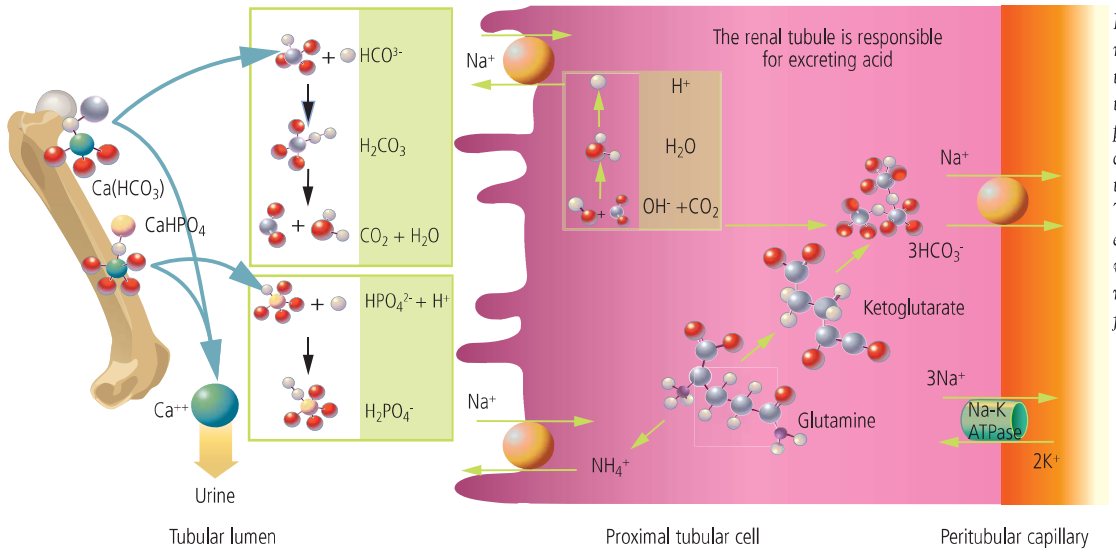
4 - Pathophysiology

► Urolith formation

> Relative supersaturation (Figure 14)

Urine supersaturation is the driving force for the formation of crystals within the urinary tract. Determination of the relative supersaturation (RSS) of urine with specific minerals has been used to identify dogs at risk for urolith formation. RSS is considered a more accurate predictor of urine crystallization potential than the formerly used activity product ratio (APR). The main limitation of the APR technique is the assumption that a steady state with respect to the solid phase will be reached by the end of the 48-hour incubation period, whereas it may take urine up to nine

FIGURE 13 - THE EFFECT OF METABOLIC ACIDOSIS ON URINARY CALCIUM EXCRETION



In the presence of metabolic acidosis the bone is stimulated to release calcium phosphates and carbonate buffers into the blood stream. The excess calcium is excreted into the urine, which increases the risk of calcium oxalate formation.

days to reach the equilibrium, particularly when coming from oversaturation *(Robertson et al, 2002; Stevenson et al, 2003c)*. In a simple solution, an RSS less than one corresponds to the undersaturated zone, and an RSS greater than one indicates the supersaturated zone. However, as urine is a complex solution, even if the urine is supersaturated, significant urine flow, inhibitors of crystallization or aggregation, and ionic forces can prevent stone formation. This is the metastable zone **(Figure 14)**. If the urine becomes even more concentrated, crystals will form spontaneously, which is called supersaturation. The RSS at which the urine will become supersatured depends upon the mineral(s) involved; it is around 2.5 for struvite and 10 to 14 for calcium oxalate in human urine *(Robertson, personal communication)*.

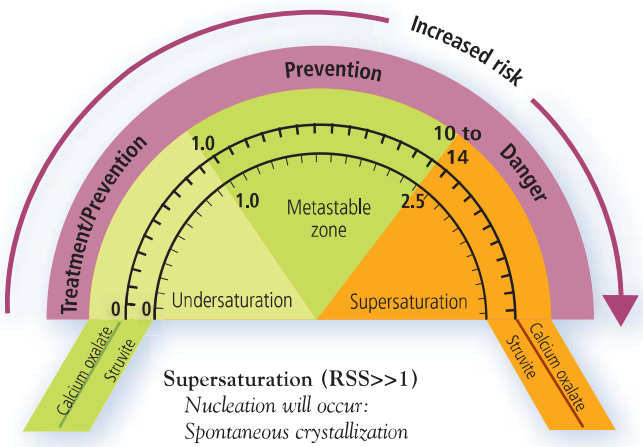
> Nucleation

The first step in the urolith development process is the formation of a crystal nidus (embryo). This phase, called nucleation, is dependent on supersaturation of urine with calculogenic substances, so that precipitation of salts and crystallization can occur *(Robertson, 1993)*. The degree of urine supersaturation may be influenced by factors such as the magnitude of renal excretion of crystalloids, favorable urine pH for crystallization **(Figure 15)**, urinary retention, and a decreased concentration of crystallization inhibitors in the urine *(Robertson et al, 2002)*.

There are many documented urinary inhibitors of calcium oxalate formation including magnesium, citrate, and macromolecular inhibitors such as nephrocalcin and glycosaminoglycans *(Robertson et al, 2002)*. The role of inhibitors within canine calcium oxalate formation has yet to be fully explored.

Urinary ion composition can affect nucleation and precipitation when there is interaction between elements in the urine. For example, magnesium binds to oxalate and citrate can bind to calcium; magnesium and citrate are therefore considered inhibitors of calcium oxalate urolithiasis.

FIGURE 14 - URINE RELATIVE SUPER SATURATION

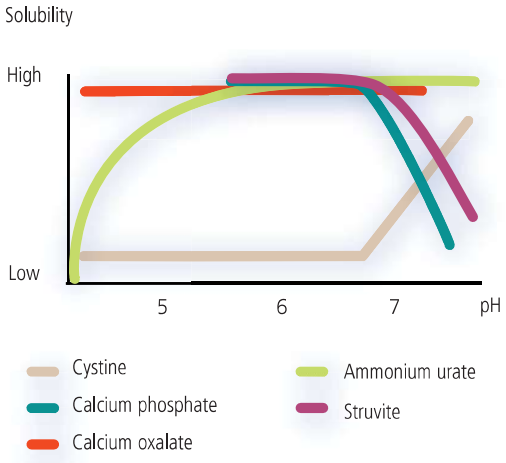


Supersaturation (RSS>>1)
Nucleation will occur:
Spontaneous crystallization
Rapid crystal growth and aggregation
Dissolution is not possible

Metastable zone (RSS>1)
Possible growth of preformed crystals
Heterogeneous nucleation may occur
Dissolution is not possible

Undersaturation (stable) (RSS<1)
No crystallization
Existing uroliths/crystals may dissolve

FIGURE 15 - SOLUBILITY AND PH
(personal communication with Dr WG Robertson)



Urinary pH can have a marked influence on the solubility of certain crystals and calculi. Struvite crystals are the most sensitive to changes in urine pH. Acidification of urine increases the solubility of struvite crystals, reducing the risk of struvite urolithiasis. Other crystals, particularly calcium oxalate, are less sensitive to urine pH.

> Growth of crystals

Once nucleation has occurred, crystal growth may occur at lesser degrees of supersaturation. Further growth of the crystal nidus then depends on the duration of its passage through the urinary tract, degree and duration of urine supersaturation for similar or other crystalloids, and crystal properties. The mechanisms leading to crystal growth are still uncertain and may include growth around a nidus or a matrix lattice, which might be facilitated by a lack of crystal aggregation inhibitors *(Osborne et al, 1995)*.

► Fate of uroliths

Uroliths may pass through various parts of the urinary tract and/or be voided, undergo spontaneous dissolution, become inactive or continue to grow. Not all persistent uroliths result in clinical signs.

5 - Nutritional management

► Stimulating diuresis

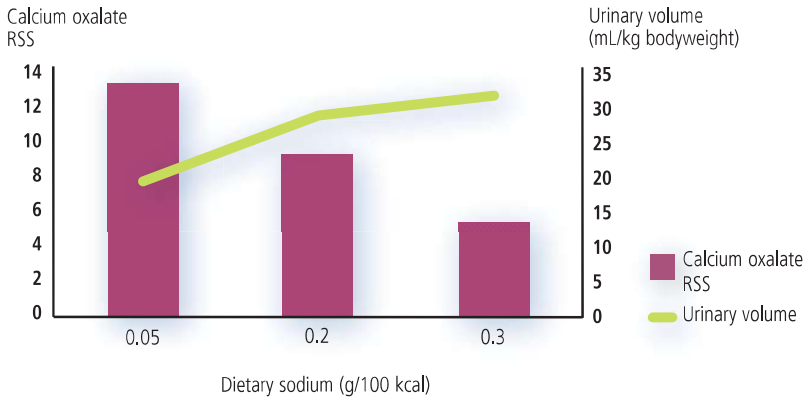
The easiest way to produce undersaturated urine is to promote diuresis. Increasing urinary flow reduces the concentration of lithogenic substances, which outweighs the disadvantage of diluting crystallization inhibitors. High urine volumes also increase the frequency of urination, which helps remove any free crystals that form in the urinary tract *(Borghi et al, 1999)*. To stimulate diuresis, drinking must be encouraged. This can be done either by feeding canned diets that contain 70 to 80% water, by adding water to the diet or by slightly increasing the sodium chloride content of dry diets. Increased dietary sodium chloride has been shown to increase water intake as well as urine production, and to decrease urine supersaturation in dogs and cats *(Stevenson et al, 2003b, Lulich et al, 2005)* **(Figure 16)**.

There has nonetheless been some controversy about the use of sodium chloride to stimulate thirst and diuresis, because it could potentially affect urinary calcium excretion and blood pressure *(Lulich et al, 1999; Osborne et al, 2000)*.

In humans, high salt intake has been associated with increased urinary calcium excretion, and similar observations were initially made in dogs *(Lulich et al, 1999; Devois et al, 2000; Biourge et al, 2001)*. This led to the assumption that salt-enriched diets could promote calcium oxalate urolithiasis and that diets for management of LUTD should thus be salt-restricted *(Osborne et al, 2000; Allen et al, 2000)*.

However, later studies failed to observe an effect of dietary salt on urinary calcium excretion in dogs *(Stevenson et al, 2003b)*. Epidemiological studies in dogs furthermore showed that increasing dietary sodium actually reduced the risk of calcium oxalate urolithiasis, because the dilutional effect of higher dietary sodium offsets the tendency towards hypercalciuria *(Lekcharoensuk et al, 2001; 2002)*.

FIGURE 16 - THE EFFECT OF DIETARY SODIUM CONTENT ON CALCIUM OXALATE RELATIVE SUPERSATURATION AND URINE VOLUME IN MINIATURE SCHNAUZERS
(Stevenson et al, 2003b)



Moderate levels of dietary sodium, which will promote diuresis, will not affect blood pressure in healthy dogs and those with moderate renal disease.

Several studies have shown that moderately increased dietary salt intakes (up to 3.2 g Na/1000 Kcal ME) do not alter blood pressure in healthy dogs, and dogs with induced renal disease (*Greco et al, 1994; Biourge et al, 2002; Kirk, 2002; Burankarl et al, 2003; Luckschander et al, 2004*).

► Changing urine pH

Changing urine pH, via dietary manipulation or medical means, can be very effective in the management of some but not all uroliths. Urine acidification markedly increases struvite solubility and is essential in the medical dissolution of these uroliths. In contrast, urine alkalinization is important in increasing the solubility of urate and cystine uroliths **(Figure 15)**. Diet efficacy is generally increased if it also reduces urinary excretion of the crystalloids that participate in urolith formation (*Lulich et al, 2000*).

Most other urolith types are less amenable to dissolution based upon pH changes. It is furthermore advisable to aim for a urine pH that prevents further precipitation and potentiates excretion of other minerals that may co-precipitate or act as inhibitors.

6 - General management of urolithiasis

Dissolution protocols are aimed at dissolving the urolith or arresting further growth by reducing the supersaturation of urine with calculogenic substances.

► Relief of urinary tract obstruction if necessary

This will generally require surgical removal once the patient has been stabilized. Urethral calculi in male dogs may be flushed retrograde into the bladder prior to surgery or medical dissolution.

► Elimination of existing uroliths

> Medical dissolution

Dietary modification may reduce intestinal absorption and urinary excretion of crystalloids and can also modulate urine pH. The balance between different nutrients (including calcium, phosphorus, sodium, acidifiers, dietary fiber and oxalate) depends on the formulation of the diet. This allows manufacturers to formulate diets that can change the urinary pH, stimulate diuresis, and reduce urinary mineral excretions, thereby assisting in the management of urinary stone diseases. Strategies vary according to stone type (see nutritional management). Calcium oxalate, calcium phosphate and silica uroliths cannot be dissolved medically at a physiologically useful rate and therefore need to be surgically removed before appropriate protocols to prevent recurrence are implemented (*Osborne et al, 1995*).

Adjunctive medical management is indicated when UTI is present, the urolith type is poorly amenable to dietary changes, or when there is further urolith growth. Certain drugs act specifically by interrupting metabolic pathways of crystalloid excretion, for example allopurinol in purine urolithiasis of Dalmatian dogs. Acidifying or alkalizing drugs can help alter urine pH.

During dissolution, uroliths become smaller and may pass into the urethra (in the male dog) or ureters, causing urinary obstruction and/or hydronephrosis. Owners should be warned about this possibility, and regular radiographic re-evaluation is required during

GENERAL TREATMENT CONSIDERATIONS

- Cystouroliths may be managed by medical dissolution, voiding urohydropropulsion, or cystotomy
- Ureteral and urethral stones are less amenable to medical dissolution because they are not consistently in contact with undersaturated urine. Ureteroliths, when associated with complete ureteral obstruction and hydronephrosis mandate surgical removal. Ureteroliths that are associated with partial ureteral obstruction can be managed conservatively as they may move into the bladder. With respect to urethroliths it is often possible to flush them retrograde into the bladder where they can be managed with medical dissolution
- Nephroliths maybe treated by surgical removal, although medical dissolution for struvite uroliths is a consideration. Benign neglect is possible in uninfected and non-obstructing nephroliths

medical dissolution of nephroliths to detect ureteral calculi before they cause hydronephrosis *(Osborne et al, 1999d, Lulich et al, 2000)*. The dissolution process can last from 1 to 6 months.

> Mechanical removal

Surgery is indicated for stone types that are not or poorly amenable to medical dissolution and too large to be voided through the urethra, or when they are causing urinary obstruction. It is also required in dogs with anatomic defects of the urinary tract (e.g. bladder diverticulum) that predispose to UTI; in these cases stone removal can be combined with correction of the defect. Surgery alone is associated with a high rate of recurrence, since it does not correct the underlying factors causing urolithiasis and because it may be difficult to remove very small stones or fragments, which can later function as a nidus for further stone formation *(Lulich et al, 2000)*. Post-operative imaging is necessary to ensure that all calculi have been removed.

THE GENERAL AIM OF DIETARY MANAGEMENT OF UROLITHIASIS IS TO REDUCE SUPERSATURATION OF URINE WITH CALCULOGENIC SUBSTANCES BY:

- increasing water intake and thus urine volume to decrease urine crystalloid concentration
- altering the urine pH to increase the solubility of crystalloids in the urine
- changing the diet to decrease the quantity of crystalloids excreted in the urine

Small uroliths in the bladder and/or urethra can sometimes be removed during voiding urohydropropulsion or cystoscopy *(Osborne et al, 1999e)*.

Lithotripsy has recently been described as a means of fragmenting uroliths. Fragmentation of renal and ureteral uroliths using electrohydraulic or extracorporeal shock-wave lithotripsy has been documented in a small number of dogs *(Block et al, 1996; Adams et al, 1999)*. Laser lithotripsy has been reported effective in fragmenting bladder uroliths *(Davidson et al, 2004)*. However, all these techniques have limited availability.

► Eliminate miscellaneous risk factors

Acidifying diets are useful in preventing struvite urolithiasis but should be avoided in dogs with urate urolithiasis.

Treatment of UTI is mandatory to reduce the risk of struvite urolith formation.

Treat underlying diseases that may potentiate urolithiasis (e.g. hyperparathyroidism, hyperadrenocorticism).

► Prevention of recurrence

Correct underlying causes.

Minimize risk factors (dietary adaptation).

Increase diuresis and reduce urinary supersaturation

Struvite uroliths are generally sensitive to medical dissolution using a calculolytic diet in association with antibiotic therapy.

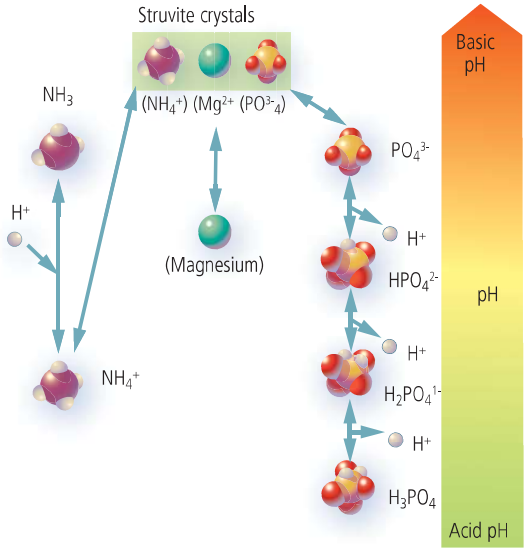
7 - Specific nutritional management

► Struvite urolithiasis

> Medical dissolution

Infection-induced struvite uroliths require a combination of appropriate antimicrobial and calculolytic dietary therapy. Sterile struvite uroliths do not need antibiotics, and can be dissolved using calculolytic dietary therapy alone or by using urinary acidifiers *(Osborne et al, 1999d; Rinkardt & Houston, 2004)* **(Figure 17)**.

FIGURE 17 - FORMATION OF STRUVITE CRYSTALS IN URINE

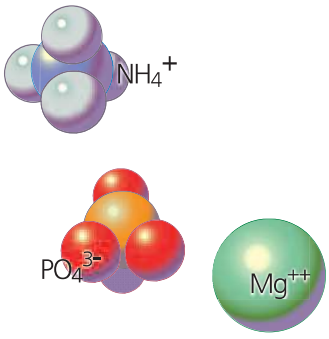


When the urine pH falls by one unit the ion balance is changed:

- *The PO_4^{3-} phosphate ions evolve towards the H_3PO_4 form and become unavailable for struvite formation (the PO_4^{3-} ion concentration is divided by 170)*
- *Ammonia (NH_3) on the other hand evolves towards the ammonium (NH_4^+) (concentration multiplied by 10)*

The final balance is that the crystal concentration of struvite is divided by 17.

STRUVITE MOLECULE



Three molecules are needed to form one struvite molecule. This reaction is reversible in an acid environment.

> Eliminate UTI

Antibiotic treatment should be based upon culture and sensitivity determination of urine obtained by cystocentesis. It should be continued until uroliths can no longer be detected radiographically, since viable bacteria may remain inside the urolith *(Seaman & Bartges, 2001)*. Urine should be sterile on repeated cultures, and antibiotics should be changed (according to sensitivity results) if UTI persists.

> Calculolytic diet to dissolve uroliths

These diets are aimed to reduce urine concentrations of urea, phosphorus and magnesium *(Lulich et al, 2000)*. Commercial calculolytic diets contain moderate amounts of protein (15-20% in a 4000 kcal/kg diet), are highly digestible, low in fiber (to reduce fecal water loss), and contain increased levels of NaCl. Dietary protein restriction reduces the amount of substrate (urea) available in urine for urease-producing bacteria. Dietary efficacy has been shown in clinical studies *(Osborne et al, 1999d; Rinkardt & Houston, 2004)*. Calculolytic diets should be given for at least one month after removal or dissolution of struvite uroliths, because uroliths too small for radiographic detection may still be present. Dogs can then be changed to a normal diet.

Dissolution therapy should be monitored with monthly abdominal radiographs or ultrasound examination and regular urinalyses (pH of morning urine should be 6.5, with no evidence of UTI). The average time for dissolution of infection-induced struvite uroliths is approximately 3 months, although clinical signs usually resolve in the first 2 weeks, probably due to control of the UTI. Sterile struvite stones tend to dissolve more rapidly, typically taking 5-6 weeks *(Osborne et al, 1999d)*.

> Drug therapy

Urinary acidifying agents such as ammonium chloride are not necessary provided a calculolytic diet and antimicrobials are given. Persistent alkaline urine pH indicates continued UTI, and pH will not go down until this is controlled *(Lulich et al, 2000)*.

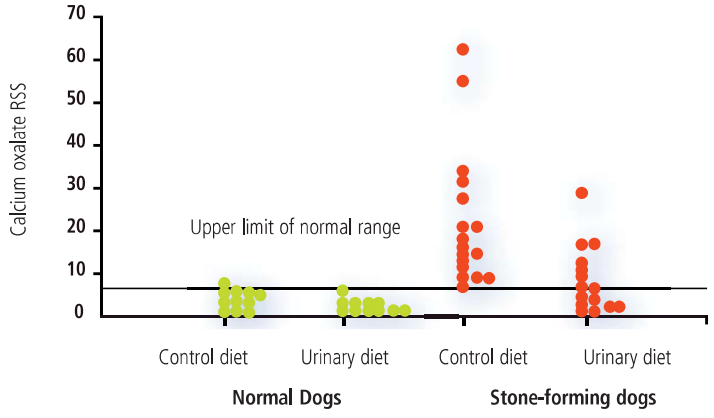
Acetohydroxamic acid (AHA) is a microbial urease inhibitor that blocks the hydrolysis of urea to ammonia, consequently lowering urine pH and ammonium concentration. It may therefore inhibit struvite growth and promote dissolution. AHA (12.5 mg/kg orally every 12 h) may be helpful in dogs with infection-induced struvite urolithiasis that is refractory to antibiotic therapy and dietary dissolution (Krawiec et al, 1984). However, this drug has many side effects, including hemolytic anemia, anorexia and vomiting. It should not be given to dogs with renal failure, since it is excreted via the kidneys, or to pregnant animals, since it is teratogenic *(Baillie et al, 1986; Osborne et al, 1995)*.

Amino acid preparations have been reported effective in the dissolution of sterile struvite nephroliths, although this concerned only 2 dogs; their efficacy is probably due to urine acidification *(Mishina et al, 2000)*. There are no reports of its use in dogs with infection-induced struvite stones.

The most important factor in preventing infection-induced struvite urolithiasis is resolution of the underlying UTI and prevention of recurrence. Preventative dietary therapy is particularly important for the rare dogs with sterile struvite calculi without concomitant infection. Only those diets specifically designed for long term feeding should be fed for prolonged periods.

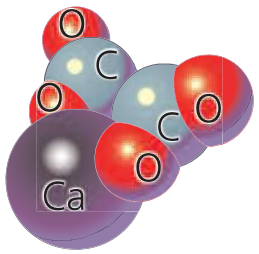
FIGURE 18 - COMPARISON OF CALCIUM OXALATE RSS IN HEALTHY DOGS AND DOGS PREDISPOSED TO CALCIUM OXALATE STONES BASED ON DIET

(Stevenson et al, 2004)



These results illustrate the influence of diet on the urinary oxalate supersaturation (RSS) in healthy dogs and dogs predisposed to calcium oxalate stones receiving either a standard food (control diet) or an acidifying food to dilute the urine (Royal Canin Veterinary Diet Canine Urinary SO canned).

CALCIUM OXALATE MOLECULE



One molecule of oxalate will associate with one molecule of calcium to form a very stable molecule of calcium oxalate.

► Calcium oxalate urolithiasis

Calcium oxalate uroliths do not respond to medical dissolution. Symptomatic calculi require mechanical removal, after which preventative medical protocols should be implemented to prevent recurrence. Dogs predisposed to calcium oxalate urolithiasis may also benefit from a preventative diet (Figure 18).

> Prevention of recurrence

These uroliths have a high recurrence rate, up to 50% by 2 years after initial removal *(Lulich et al, 1995; 1998)*. Medical protocols are therefore essential to reduce urolith recurrence following removal and dietary modification can greatly reduce the risk of recurrence in affected individuals *(Stevenson et al, 2004)*.

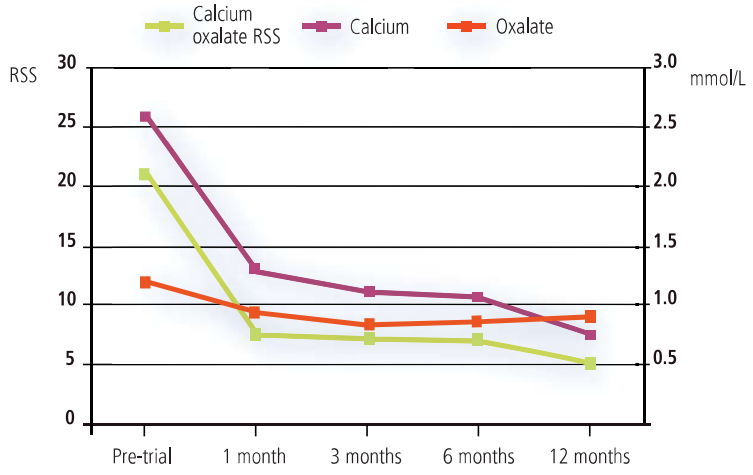
> Eliminate risk factors

If the dog is hypercalcemic or has other diseases (e.g. hyperadrenocorticism), the underlying cause should be corrected. Usually no further preventative measures will be required *(Lulich et al, 1998)*.

If the dog is normocalcemic, risk factors for urolithiasis should be identified and controlled. Dry acidifying diets that have not been formulated to increase diuresis and drugs that promote excessive urinary calcium excretion (urinary acidifiers, furosemide, glucocorticosteroids) should be avoided.

FIGURE 19 - EFFECT OF A DIET SPECIFICALLY DESIGNED TO LOWER THE URINARY CALCIUM OXALATE RSS IN DOGS WITH NATURALLY OCCURING CALCIUM OXALATE UROLITHIASIS

(Stevenson et al, 2004)



No treats or dietary supplements containing calcium, vitamin D or excessive amounts of vitamin C should be given, since these can promote increased excretion of calcium and/or oxalate *(Lulich and Osborne, 1995)*.

Calcium oxalate preventative diets should stimulate water consumption, and should not be restricted in protein, calcium or phosphorus. A recent clinical study has proven that dietary modification can reduce the risk factors associated with calcium oxalate formation thereby reducing the risk of recurrence in susceptible individuals **(Figure 19)** *(Stevenson et al, 2004)*.

> Dietary modification

• *Diuresis*

Augmenting water intake, either by feeding a canned diet or by adding water and/or sodium chloride to the food, remains the major factor in managing and preventing calcium oxalate urolithiasis *(Lulich et al, 1998; Lekcharoensuk et al, 2002b; Stevenson et al, 2003a, 2003b, Lulich et al, 2005)*.

• *Sodium*

Dry diets have been associated with a greater risk of stone formation *(Lekcharoensuk et al, 2002a)*, particularly if the diet is low in sodium chloride. This may be due to the fact that these diets do not stimulate adequate diuresis, particularly in small-breed dogs that have been shown to eliminate smaller quantities of urine less frequently than large-breed dogs *(Stevenson et al, 2001)*.

Research has shown that urinary calcium oxalate RSS, and therefore the risk of calcium oxalate formation, can be significantly decreased by increasing the dietary sodium content from 0.06 g/100 kcal to 0.30 g/100 kcal *(Stevenson et al, 2003a)*.

• *Calcium and phosphorus*

Recommendations for dietary calcium and phosphorus levels in calcium oxalate preventative diets are changing. Previously it was advised to restrict dietary calcium and phosphorus, but recent studies suggest that this may actually promote calcium oxalate stone formation *(Curhan et al, 1993; Lekcharoensuk et al, 2002a, 2002b)*. Restriction of dietary calcium without concomitant reduction in oxalate results in augmented intestinal absorption and urinary excretion of oxalate, which increases the risk of urolithiasis *(Lulich et al, 2000; Stevenson et al, 2003a)*. Dietary phosphorus restriction also increases calcium absorption *(Lulich & Osborne, 1995)*. Consequently, calcium oxalate preventative diets should not be calcium or phosphorus restricted *(Curhan et al, 1993, 1997)*.

• *Protein*

Dietary protein content is controversial. Previously it was recommended to lower protein content, since protein could increase calcium excretion and reduce excretion of citrate (citrate chelates calcium to form a soluble salt) *(Lulich et al, 1995, 2000)*. However, studies indicate that higher levels of dietary protein reduced the risk of urolithiasis *(Lekcharoensuk et al, 2002a; 2002b)*. The mechanism is unknown but may well be due to other factors, since high protein diets stimulate diuresis and also contain more phosphorus and potassium.

• *Urinary pH*

Calcium oxalate crystals are generally not sensitive to urine pH, although pH affects the minerals that co-precipitate with calcium oxalate *(Robertson, 1993)*. Marked acidification that induces metabolic acidosis can increase urinary calcium concentration to such extent that it promotes calcium oxalate stone formation *(Lekcharoensuk et al, 2002a; 2002b)*. Marked alkalinization should also be avoided since it promotes calcium phosphate urolithiasis. Diets resulting in mild acidification (pH 5.5-6.5) and increased diuresis may reduce the risk of both calcium oxalate and struvite crystal formation, useful in breeds predisposed to both stone types *(Stevenson et al, 2002)*.

> Drug therapy

Adjunct medical therapy is used if there is persistence of calcium oxalate crystalluria or recurrence of urolithiasis.

Potassium citrate has been useful in humans to prevent recurrent calcium oxalate urolithiasis, via its alkalinizing properties and by forming soluble salts with calcium.

Oral potassium citrate increases urine pH, which causes decreased tubular resorption of citrate, thus increasing urinary citrate excretion. However, oral administration of up to 150 mg/kg/day did not cause a consistent increase in urine citrate concentrations in healthy dogs, although it main-

tained a higher urine pH later in the day *(Stevenson et al, 2000)*. There was no difference between wax matrix and powder supplements.

Hydrochlorothiazide (2-4 mg/kg orally BID) reduces urine calcium excretion, possibly by promoting mild volume contraction resulting in increased proximal tubular reabsorption of several solutes, including calcium and sodium *(Lulich et al, 2000)*. Its hypocalciuric effects may be helpful in minimizing recurrence of calcium oxalate urolith formation, especially when combined with a urolith prevention diet *(Lulich et al, 2001)*. However, long-term clinical studies are needed to confirm safety and effectiveness of prolonged administration; it has the potential to cause hypokalemia, hypercalcemia and dehydration.

> Monitoring

Efficacy of therapy should initially be monitored with urinalysis (pH, specific gravity) every 2 to 4 weeks. With hydrochlorothiazide treatment serum electrolytes should also be checked. Imaging every 6 to 12 months may help to detect any new uroliths when they are small enough to be removed non-invasively (e.g. voiding urohydropropulsion) *(Lulich et al, 2000)*.

► Urate urolithiasis

> Medical dissolution in dogs without portosystemic shunts

The chief goal in dietary dissolution of urate uroliths in Dalmatian dogs is to raise urine pH and to lower urine concentrations of uric acid, ammonium and/or hydrogen ions.

> Calculolytic diet

The dietary strategy aims at decreasing the purine content of the diet. This goal is achieved through general protein restriction (18 to 10%). However, it is possible to design a low purine diet without imposing a severe protein restriction if appropriate ingredients are selected. Fish or glandular organs, which are high in purine, should be avoided. Alternative protein sources that are relatively low in purine precursors include: vegetable proteins, eggs and dairy products *(Ling & Sorenson, 1995)*. No other food supplements should be given. Low protein anti-uric acid diets may contain insufficient protein to sustain growth and lactation. Experimental diets have been designed that could meet both requirements *(Bijster et al, 2001)*. As with all urolith types, feeding a canned diet, adding supplemental water to the food, or increasing the sodium content can help to increase urinary volume. In addition, low-protein diets impair urinary concentrating capacity by decreasing the medullary concentration gradient, due to the lower urea concentration in the renal medulla.

THE MEDICAL DISSOLUTION OF URATE CALCULI INCLUDES A COMBINATION OF:

- feeding a low purine diet that has been designed to dissolve urate calculi
- alkalinization of the urine
- increasing urine volume
- controlling urinary tract infections
- administering xanthine oxidase inhibitors (allopurinol)

> Alkalinization of urine

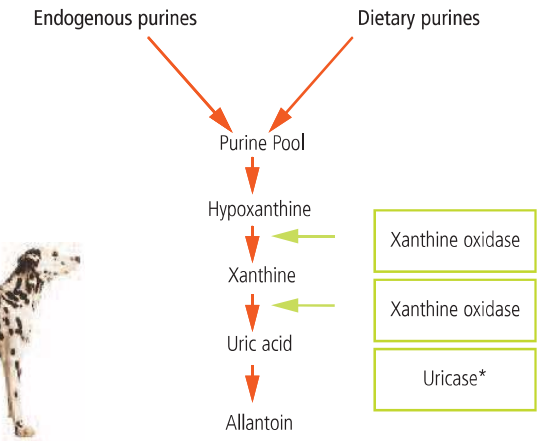
Alkaline urine contains low concentrations of ammonia and ammonium ions, and thus decreases the risk of ammonium urate urolithiasis. Low-protein diets have an alkalinizing effect, but it may be necessary to administer additional urine alkalinizing agents *(Lulich et al, 2000)*. Sodium bicarbonate (25-50 mg/kg every 12 hours) and potassium citrate (50-150 mg/kg every 12 hours) are used most commonly. The dose should be individualized to maintain a urine pH of approximately 7.0. Urine pH >7.5 should be avoided since this promotes formation of secondary calcium phosphate deposits, which will hamper stone dissolution *(Bartges et al, 1999)*.

> Xanthine oxidase inhibitors

Urinary urate excretion is lowered most effectively by using allopurinol, which is an inhibitor of xanthine oxidase, the enzyme responsible for catalyzing the conversion of xanthine and hypoxanthine to uric acid **(Figure 20)**. As a result of allopurinol therapy, xanthine and hypoxanthine concentrations in the urine increase, but urate decreases.

Allopurinol should be given in conjunction with a low-purine diet, in order to minimize the risk of xanthine stone formation *(Ling et al, 1991; Bartges et al, 1999)*. The recommended dose for dissolution of urate uroliths is 15 mg/kg every 12 hours *(Lulich et al, 2000)*. The dose must be reduced in patients with renal dysfunction, since allopurinol is excreted by the kidneys. A variety of adverse effects, including skin rashes, GI upsets and hemolytic anemia, have been described in

FIGURE 20 - NORMAL CANINE PURINE DEGRADATION



** reduced activity in Dalmatian dogs.*

humans, but these are rare in the dog. The most common adverse effect of allopurinol therapy in dogs is development of xanthine uroliths, either in pure form or as an outer shell around pre-existing urate stones. Discontinuing allopurinol and instituting a low-purine diet can sometimes dissolve xanthine uroliths *(Ling et al, 1991)*.

> Monitoring

During dissolution the size of the urolith(s) must be periodically monitored by survey and/or double contrast radiography, or ultrasonography. Excretory urography or ultrasonography are used to monitor dissolution of renal urate stones *(Bartges et al, 1999)*. Time required for dissolution is highly variable and can take between 4 and 40 weeks although average length of time in one study was 14 weeks *(Bartges et al 1999)*. Following removal or dissolution, urinalysis and ultrasonographic examination (or double contrast cystography) should be performed every 1 to 2 months for 6 months.

Even if uroliths do not reoccur the purine-restricted alkalinizing diet should be continued. Follow-up examinations can then be extended to every 2 to 4 months, and the intervals between examinations can be gradually increased.

> Medical dissolution in dogs with portosystemic shunts

Little is known about the biologic behavior of urate calculi following surgical correction of portosystemic shunts. When the urolith cannot be removed at the time of shunt ligation, postsurgical medical dissolution should be considered. However, more studies are needed to compare the relative value of calculolytic diet, alkalinization and/or allopurinol in dissolving ammonium urate uroliths in dogs with portosystemic shunts.

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In Dalmatian dogs, 82% of stones are urate stones (Bartges et al, 1994).

> Prevention

• *Dalmatian dogs*

Preventative treatment following removal or dissolution is important in Dalmatian dogs because of their high risk for urate urolith recurrence. As a first choice, low-purine diets that promote the formation of dilute alkaline urine should be fed. If urine pH is not consistently alkaline and/or crystalluria persists, alkalinizing agents may be added. Preventative treatment with allopurinol is not recommended routinely due to the risk of xanthine urolith formation, but it may be added to the protocol if difficulties persist. Long-term allopurinol therapy is not recommended.

It is not necessary to feed purine-restricted diets to Dalmatian dogs that have not had urate urolithiasis. Acidifying high-protein diets that enhance excretion of ammonium ions should however be avoided as ammonium ions are likely to get linked to urate ions to from ammonium urate crystals.

• *Non-Dalmatian dogs*

Recurrence of urate urolithiasis has been described in English bulldogs, and preventative measures as discussed for Dalmatian dogs should be implemented *(Bartges et al, 1999)*. Dogs fed protein-restricted diets (10 %) long-term may develop taurine deficiency, which might lead to dilated cardiomyopathy. Commercial protein-restricted diets are therefore now supplemented with taurine *(Sanderson et al, 2001a)*.

► Cystine uroliths

> Medical dissolution

The aim of therapy is to reduce the concentration of cystine in the urine and to increase cystine solubility. This usually requires dietary modification in combination with a thiol-containing drug.

> Calculolytic diet

Reduction of dietary protein can reduce cystine excretion, presumably because these diets contain fewer cystine precursors *(Osborne et al, 1999g)*. However, the optimal degree of protein restriction is controversial, since cystinuric dogs also excrete carnitine and therefore have the potential to develop carnitine deficiency and dilated cardiomyopathy when fed low-protein diets. It is therefore recommended to supplement cystinuric dogs eating a protein-restricted diet with carnitine as well as taurine *(Sanderson et al, 2001b)*.

> Alkalinization of urine

The solubility of cystine is pH dependent. It is markedly more soluble at urine pH of 7.5-7.8. Urine alkalinization may be achieved using a commercial moderate to low-protein alkalinizing diet. If urine pH does not become sufficiently alkaline on dietary therapy alone, additional potassium citrate may be given to sustain a urine pH of approximately 7.5 *(Osborne et al, 1999g)*. This has to done cautiously, since alkalinization can be a risk factor for calcium phosphate urolithiasis.

CYSTINE UROLITHS CAN BE DISSOLVED MEDICALLY, USING A COMBINATION OF:

- protein-restricted alkalinizing diet
- increasing urine volume
- alkalinization of urine (pH around 7.5)
- administration of thiol-containing drugs

• *Thiol-containing drugs*

These drugs react with cystine by a thiol disulfide exchange reaction, resulting in the formation of a complex that is more soluble in urine than cystine. N-(2-mercaptopropionl)-glycine (2-MPG) is most commonly used, at a dose of 20 mg/kg twice daily orally. It has proven effec tive in dissolving cystine uroliths, especially when used in conjunction with a calculolytic diet *(Lulich et al, 2000)*.

Time for dissolution ranges from 1 to 3 months. Side-effects are relatively uncommon; aggression, myopathy, anemia and/or thrombocytopenia have been reported, but signs resolved when the treatment was stopped *(Osborne et al, 1999g; Hoppe & Denneberg, 2001)*. D-penicillamine is an older thiol-containing drug that has been used with some efficacy in the past, but it is no longer used due to an unacceptable number of adverse effects, including frequent hypersensitivity reactions.

> Monitoring

Urolith dissolution should be monitored at 30-day intervals by urinalysis (pH, specific gravity, sediment) and serial radiography to evaluate stone location, number, size, density and shape. Contrast radiography may be used for radiolucent stones. The calculolytic diet, 2-MPG and alkalinizing therapy should be continued for at least one month following radiographic disappearance of uroliths.

> Prevention

Preventative therapy is important, because cystinuria is an inherited metabolic defect and because cystine uroliths recur in most stone-forming dogs within 12 months following surgical removal. Recurrence is more likely to occur if the dog excretes large amounts of cystine. A moderate to low-protein diet that promotes formation of alkaline urine can be effective in preventing cystine urolith recurrence in dogs with low to moderate cystinuria. If necessary, dietary therapy may be combined with alkalinzation therapy to increase urinary pH and prevent cystine urolithiasis *(Hoppe et al, 1993; Hoppe & Denneberg, 2001)*.

Treatment should be titrated to maintain a negative urine cyanide-nitroprusside test. The severity of cystinuria may decline with advancing age in some dogs; consequently, the dose of 2-MPG may be decreased or even stopped *(Hoppe & Denneberg, 2001)*.

► Calcium phosphate urolithiasis

> Medical dissolution

- ***Underlying metabolic disease***

Calcium phosphate uroliths may rarely dissolve spontaneously following parathyroidectomy for treatment of primary hyperparathyroidism. If stones are clinically silent, one might wait for this to occur before contemplating surgical or non-surgical removal. Medical dissolution is not effective in distal renal tubular acidosis.

- ***Idiopathic uroliths***

If a specific underlying disorder is not diagnosed, calcium phosphate uroliths are removed surgically and then managed as for calcium oxalate urolithiasis *(Lulich et al, 2000)*.

Calcium phosphate uroliths cannot be medically dissolved, and surgical removal is usually necessary. Correction of underlying metabolic abnormalities may minimize recurrence. If no underlying cause is found, management is similar to that of calcium oxalate urolithiasis.

> Prevention

Recognition and management of underlying contributing conditions is the first and most important step in the prevention of calcium phosphate urolithiasis. The patient should be assessed for evidence of primary hyperparathyroidism, hypercalcemia, excessive urine concentrations of calcium and/or phosphate, and inappropriately alkaline urine pH. There may also be a previous history of dietary therapy and administration of alkalinizing agents to prevent another urolith type.

If a specific underlying disorder is not diagnosed, calcium phosphate uroliths are generally managed similar to strategies used for calcium oxalate urolithiasis *(Lulich et al, 2000)*. One should however be careful to avoid excessive urine alkalinization, which may occur with some diets used for prevention of calcium oxalate uroliths.

► Silica urolithiasis

> Prevention

Because the initiating and precipitating causes of silica urolithiasis are not well known, only nonspecific recommendations are available.

Silica uroliths may occur in dogs with pica (i.e. eating soil) or in dogs eating diets high in cereal grains containing silicates. Empiric recommendations are to change the diet to one with high quality protein and if possible reduced quantities of non nutritive plant ingredients *(Osborne et al, 1999a)*.

As with all uroliths, increased water intake should be promoted to decrease the resulting concentration of calculogenic material in urine.

► Compound uroliths

Dissolution of compound uroliths should theoretically be aimed at implementing subsequent protocols for dissolving the various layers of the urolith, starting with the outer layer. In practice, most compound uroliths are removed surgically or by other non-surgical means. The post-removal strategy is generally aimed at preventing the reformation of the mineral that composed the core of the removed urolith, since the outer layer(s) were probably deposited secondarily due to heterogeneous nucleation *(Osborne et al, 1999c)*.

Conclusion

Following removal of compound (mixed) uroliths, medical dissolution strategies are usually based on preventing the reformation of the mineral that composed the core of the compound urolith.

Dietary modification is an important part of the management regimen for struvite urolithiasis. Diet influences the saturation of urine with struvite as it impacts urine pH, volume and solute concentration. Urine pH is the most important factor controlling struvite saturation. Reduction of urine pH through dietary manipulation is thus likely to be the most reliable means of achieving urine which is undersaturated with struvite. Restriction of dietary crystalloid intake may also be beneficial, although changes in urinary magnesium or phosphate concentration individually, have much less impact on struvite saturation than changing urine pH.

The goal of dietary management for calcium oxalate urolithiasis is to create urine that has a low saturation with calcium oxalate. Ideally, urine should be undersaturated as new crystal formation cannot occur under these circumstances; however, this may be difficult to achieve in some patients. Homogeneous crystal formation will not occur, and heterogeneous crystal formation is unlikely to occur, in the lower part of the metastable zone of supersaturation. Therefore this represents a reasonable target that should reduce the risk of recurrence in patients.

Enhancing urine volume for a given solute load will also reduce saturation, as it will decrease the concentrations of crystalloids. In addition, increasing urine volume may influence crystal transit time through the urinary tract, thus reducing the potential for crystal growth.

Frequently asked questions: urolithiasis

Q	A
A dog with signs of cystitis has cystic calculi on abdominal radiography. What is the next approach?	(1) Culture the urine to look for UTI. Primary UTI may predispose to struvite urolithiasis, and other stones may result in a secondary UTI resulting in a struvite shell around the primary stone. Treatment of the UTI will be helpful in both situations. (2) Assessment of the type of crystals in the urine may help to suspect which stones are present. (3) Spontaneous voiding, aspiration through a urethral catheter, voiding urohydropropulsion or surgical removal will identify the stone type, enabling specific therapy. Note: urate and cystine stones are usually radiolucent, and require positive contrast studies or ultrasound for demonstration. They are therefore less likely when stones are radiographically visible.
How do I treat renal calculi?	Nephroliths are generally treated by surgical removal, although medical dissolution may be possible for struvite uroliths. Lithotripsy may be available in some cases. Benign neglect is possible in uninfected and non-obstructing nephroliths.
What is the best way to manage a dog with both renal and cystic calculi?	First, find out what the composition of the stones is. Calcium oxalate, calcium phosphate and silica uroliths cannot be dissolved medically and need to be surgically removed before protocols to prevent recurrence are implemented. Adjunctive medical management is indicated when UTI is present, the urolith type is poorly amenable to dietary changes, or when there is further urolith growth.
How do I handle a dog with struvite calculi?	Struvite uroliths are generally sensitive to medical dissolution using a calculolytic diet in association with antibiotic therapy. Commercial calculolytic diets are aimed to acidify and to reduce urine concentrations of urea, phosphorus and magnesium. They should be given for at least one month after removal or dissolution of struvite uroliths, because uroliths too small for radiographic detection may still be present. Dogs can then be changed to a normal diet. Urinary acidifying agents such as ammonium chloride are not necessary provided a calculolytic diet and antimicrobials are given.
What diet should I feed to a dog after surgery for calcium oxalate uroliths?	Calcium uroliths have a high incidence of recurrence, so preventative therapy is important. First, identify and treat any underlying causes that may have contributed to calcium urolithiasis, such as hyperparathyroidism and hyperadrenocorticism. Subsequently risk factors should be minimized by dietary adaptation. It will help to feed wet diets or special sodium-enriched dry diets that promote diuresis, and to avoid drugs that promote calciuresis, e.g. furosemide and urinary acidifiers. The diet should contain normal levels of protein, calcium and phosphorus.
How to manage a Dalmatian dog with suspected ammonium urate urolithiasis?	Since this is a Dalmatian, the most likely diagnosis is ammonium urate stones. A presumptive diagnosis can be achieved by looking for urate crystals in the urine. As a first choice, low-purine diets (e.g. vegetables, eggs and dairy products) that promote the formation of dilute alkaline urine should be fed. As with all urolith types, feeding a canned diet or adding supplemental water to the food helps to increase urinary volume. Allopurinol therapy will help to further reduce urinary urate excretion.

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EXAMPLES OF HOME-PREPARED TO THE DIETETIC TREATMENT

Example 1

COMPOSITION
(1000 g diet)

Chicken, boiled ..... 300 g
Hard-boiled egg ..... 50 g
Rice, cooked ..... 560 g
Wheat bran ..... 30 g
Brewer's yeast ..... 10 g
Rapeseed oil ..... 50 g

Add a low-magnesium mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 38% dry matter and 62% water		
	% dry matter	**g/1000 kcal**
Protein	22	41
Fat	31	59
Available carbohydrate	40	75
Fiber	4	8

INDICATIVE RATIONING			
Energy value (metabolizable energy) 2040 kcal/1000 g diet prepared (5310 kcal/1000 g dry matter)			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	110	45	1110
4	180	50	1200
6	240	55	1290
10	360	60	1370
15	490	65	1460
20	600	70	1540
25	710	75	1620
30	820	80	1700
35	920	85	1780
40	1010	90	1860

Key Points

- **Acid urinary pH** to effectively combat struvite stones by limiting the availability of phosphate ions. An acid pH is also unfavorable to bacterial growth
- **Low magnesium content** to limit the presence of struvite stone precursors (or magnesium ammonium phosphate)
- **High water content**: a moist food is a natural urine diluter

* *The rationing is offered in accordance with the dog's healthy weight. For obesity, the diet must be prescribed in accordance with the ideal weight and not the real weight of the dog.*

** *Dividing the daily amount over two or three meals is recommended to limit the postprandial alkaline tide.*

DIETS ADAPTED OF UROLITHIASISA

Example 2

COMPOSITION
(1000 g diet)

Veal, shoulder . . . . . 400 g
Beef, minced meat 5% fat . . . . . 100 g
Rice, cooked . . . . . 400 g
Wheat bran . . . . . 50 g
Tomato . . . . . 25 g
Rapeseed oil . . . . . 25 g

Add a low-magnesium mineral and vitamin supplement.

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1335 kcal/1000 g diet prepared (4230 kcal/1000 g dry matter)			
Dog's weight (kg) *	Daily amount (g)**	Dog's weight (kg) *	Daily amount (g) **
2	110	45	1110
4	180	50	1200
6	240	55	1290
10	360	60	1370
15	490	65	1460
20	600	70	1540
25	710	75	1620
30	820	80	1700
35	920	85	1780
40	1010	90	1860

ANALYSIS		
The diet prepared in this way contains 32% dry matter and 68% water		
	% dry matter	g/1000 kcal
Protein	39	92
Fat	13	31
Available carbohydrate	36	86
Fiber	8	19

Contra-indications

Gestation
Lactation
Growth
Chronic renal disease
Metabolic acidosis

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

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The small breeds (Shih Tzu, Yorkshire Terrier, Miniature Schnauzer, Pekingese) are among the breeds of dog at most risk of urolithiasis.

Key Points
to remember:

The role of nutrition in the treatment and prevention of canine urolithiasis

Stimulation of water intake and diuresis

For all stone types, encouraging the dog to drink to promote the production of dilute urine is an essential part of preventing stone formation. Diluting the urine limits the concentration of the crystal precursors in the urine. There are three simple ways to encourage water intake: selecting a wet food, hydrating dry food before serving, and slightly increasing the food's sodium content. A dietary sodium content of 3.2 g /1000 kcal does not have any effect on blood pressure in a healthy dog or a dog with moderate renal pathology.

Urinary pH

Acidifying the urine is the best method to lower urinary **struvite** saturation and therefore to prevent this type of urinary stone. Struvite stones are highly soluble in acid pH, so acidification will even help to dissolve the stones.

Calcium oxalate stones are not sensitive to urinary pH. Urinary alkalinization indirectly limits the presence of precursors in the urine (by limiting the calciuria and promoting the excretion of citrate, which forms a soluble salt with calcium), but at the same time it increases the risk of struvite formation. It is preferable to combine increased diuresis with a moderate pH (6-6.5) to simultaneously prevent the appearance of both oxalate and struvite stones.

Conversely, for both **cystine and urate urolithiasis** it is necessary to achieve a more alkaline pH (around 7) to increase the solubility of these stones. However, alkalinizing the urine further increases the risk of secondary calcium phosphate urolithiasis.

Proteins

Protein restriction has been recommended to help manage both urate and cystine urolithiasis. In particular, dogs predisposed to **urate stones** (Dalmatians, English Bulldogs) need a diet that is low in purines, without necessarily reducing the overall protein ingested. These two goals are compatible when a protein source that is low in purine content is selected.

If protein restriction is implemented to assist the management of cystine stones, the diet should be supplemented with taurine and L-carnitine to help prevent the risk of dilated cardiomyopathy.

Focus on:

SODIUM

After calcium and potassium, sodium is the most abundant ion in the organism. It represents around 0.13% of the body weight of a mammal. Extracellular sodium is found in the skeleton (43% of total sodium), the interstitial fluid (29%) and the plasma (12%). The remaining body sodium is located intracellularly.

Sodium plays several essential roles in the function of the cell:

- It maintains the balance in osmotic pressure between the intra- and extra-cellular environments thus regulating the volume of extra-cellular fluids. This function of water balance regulation gives sodium an important role in the sense of hunger and micturition.

- It is involved in acid base balance

- It participates in nerve transmission

The digestive absorption of sodium is very important. The maintenance of a constant sodium level in the organism is based on regulation of both renal and intestinal excretion. Dogs do not sweat, hence they are not at risk of excessive sodium loss.

WHAT IS THE SODIUM CONTENT IN THE VARIOUS SODIUM SALTS?

- Sodium chloride (NaCl) contains 39% sodium.
1% sodium in a food therefore corresponds to approximately:
1 / 0.39 = 2.5% NaCl.

- Sodium carbonate contains 37% sodium.

- Sodium bicarbonate contains 27% sodium.

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1 • Is blood pressure affected by high dietary salt content?

In dogs, increasing the sodium content in the food has a clear role in stimulating diuresis and lowering the urinary calcium oxalate saturation. The relationship between the salt content in human food and hypertension is a subject of intense debate, hence the question of the influence of salt (NaCl) on canine blood pressure is a logical one to ask.

Vienna University in association with Royal Canin studied the development of blood pressure based on the dietary NaCl content *(Biourge et al, 2002)*.

Eight healthy female Beagles age 2 to 4 years were divided into two groups and fed for two weeks with the same dry (acidified) food. The only difference between the two diets was the NaCl content:

- the control diet contained:

0.38% Na and 1.40% Cl

- the NaCl-enriched diet contained:

0.96% Na and 2.40% Cl (DMB).

The two groups consumed the two formulations in turn, with a one-week transition period during which they were fed a standard maintenance food.

	Results	
	Control diet (0.38% Na; 1.40% Cl)	NaCl enriched diet (0.96% Na; 2.40% Cl)
Body weight	Food consumption was limited to 256 ± 31 g/day and the dogs body weight remained stable during the whole study (11.4 + 0.9 kg).	
Urinary volume (mL/kg weight/day)	22,8 ± 3,4	37 ± 3,1
Mean blood pressure (mm Hg)	152 ± 9 mm Hg	158 ± 10 mm Hg

The results of this study clearly demonstrated that moderate enrichment of NaCl in the diet increased urine volume (p<0.001) but did not alter blood pressure of healthy dogs when compared with a standard food. The blood pressure values observed are within the normal reference range (<160 mm Hg).

Four other studies have also failed to provide any evidence that moderate increases in dietary sodium (up to 3.2 g Na/1000 kcal) influences the blood pressure of dogs and cats, be they healthy or moderate renal disease patients *(Burankarl et al, 2003; Greco et al, 1994; Kirk 2002; Luckschander et al, 2002)*.

The National Research Council Committee on Animal Nutrition (NRC) has been tasked with establishing nutritional requirements for the dog and cat by the U.S. Academy of Sciences. Their latest recommendations indicate that there is no adverse health risk for the dog when the sodium content of the diet contains 3.75 g /1000 kcal in a dry food providing 4000 kcal/kg. This is equivalent to a sodium content of 1.5%.

References

Biourge V, Iben C, Wagner E et al. - Does increasing dietary NaCl affect blood pressure in adult healthy dogs? Proceedings of the 12th Congress of the European College of Veterinary Internal Medicine, Munich, 2002; 153.

Burankarl C, Mathur SS, Cartier LI et al. - Effects of dietary sodium chloride (NaCl) supplementation on renal function and blood pressure (BP) in normal cats and in cats with induced renal insufficiency. Proceeding of the WSAVA congress, Bangkok, 2003: 749.

Greco DS, Lees GE, Dzendel G et al. - Effects of dietary sodium intake on blood pressure measurements in partially nephrectomized dogs. Am J Vet Res 1994; 55: 160-165.

Kirk CA - Dietary Salt and FLUTD: Risk or Benefit? Proceedings of the 20th American College of Veterinary Internal Medicine Forum. Dallas, Texas, 2002; 553-555.

Luckschander N, Iben C, Desprez G et al. - Does increasing dietary NaCl affect blood pressure in adult healthy cats? Proceedings of the 20th American College of Veterinary Internal Medicine Forum. Dallas, Texas, 2002: 788.

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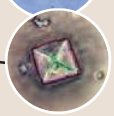
2 • Determination of the relative supersaturation of canine urine

Goals: to predict the formation of urinary crystals dependent on the urinary pH and composition induced by the consumption of a specific diet. The ultimate goal is the prevention of urinary stones in dogs.

Struvite (magnesium ammonium phosphate)



Calcium oxalate

pH analysis and acidification of urine for optimal storage

Urinalysis

- Urate, Creatinine : High Performance Liquid Chromatography (HPLC)
- Calcium, Magnesium
- Sodium, Potassium
- Ammonium, Sulfate
- Citrate, Oxalate, Phosphate

} Ionic chromatography

High Performance Liquid Chromatography (HPLC)

Ionic chromatography

Calculation of the urinary saturation values, using Supersat® program

1. Calculation of activity coefficients for monovalent, divalent, trivalent and quadrivalent ions
2. Evaluation of the concentration of different soluble complexes formed with these ions
3. Calculation of the concentrations of free ions (Ox^{2-}, Ca^{2+}, PO_4^{3-}, NH_4^+, Mg^{2+}…)
4. Calculation of the activity product for different salts involved in uroliths formation
5. Comparison with the solubility and the formation products of the considered salts ⇨ RSS estimation

Evaluation of the probability of forming of calcium oxalate and struvite uroliths in a dog fed with a specific diet