Chapter 40

Canine Calcium Oxalate Urolithiasis: Changing Paradigms in Detection, Management and Prevention

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"A well-defined problem is half solved."
Carl A. Osborne

OVERVIEW

Uroliths composed of calcium oxalate monohydrate and calcium oxalate dihydrate form as a result of the interaction of several different environmental and demographic risk factors, and several different metabolic disturbances. That is, not all calcium oxalate uroliths are "created in the same way." Some of these factors are primary and some are compensatory. Identification of primary and secondary abnormalities associated with calcium oxalate urolithiasis is essential if therapy is to be consistently safe and effective.

Of the biogenic uroliths that affect dogs, cats and people, those composed of calcium oxalate have been the most problematic. However, substantial progress has been made in the last 10 years. We predict that within the next 10 years, we will understand how to identify and safely modify the underlying mechanisms involved with calcium oxalate urolithiasis. That is, within the next decade we will have reached our goal of making the surgical removal of uroliths a treatment of historical interest.

PREVALENCE AND MINERAL COMPOSITION

Calcium oxalate accounted for 38% of all canine uroliths submitted to the Minnesota Urolith Center from 1981 to 2007 (Table 38-8) and 41% (16,761 of 40,612) of all canine uroliths submitted in 2007 (**Figure 40-1**) (Osborne and Lulich, 2007). Calcium oxalate also accounted for 43% of all upper urinary tract uroliths analyzed at our Center from 1981 to 2006 (Table 38-9). From 2000 to 2006 calcium oxalate composed only 1% of uroliths retrieved from dogs less than 12 months old. The mean age of dogs at the time of calcium oxalate urolith retrieval was approximately 8.5 years (range = one to 25 years; median = 8.7 years). Males (74%) were affected more often than females (22%); the age of approximately 4% of affected dogs was not specified. A total of 214 different breeds were affected including miniature schnauzers (18%), mixed breeds (14%), Yorkshire terriers (9%), Bichon Frises (8%), Shih Tzus (7%), Lhasa apsos (5%), Pomeranians (4%), dachshunds (3%), Maltese (3%),

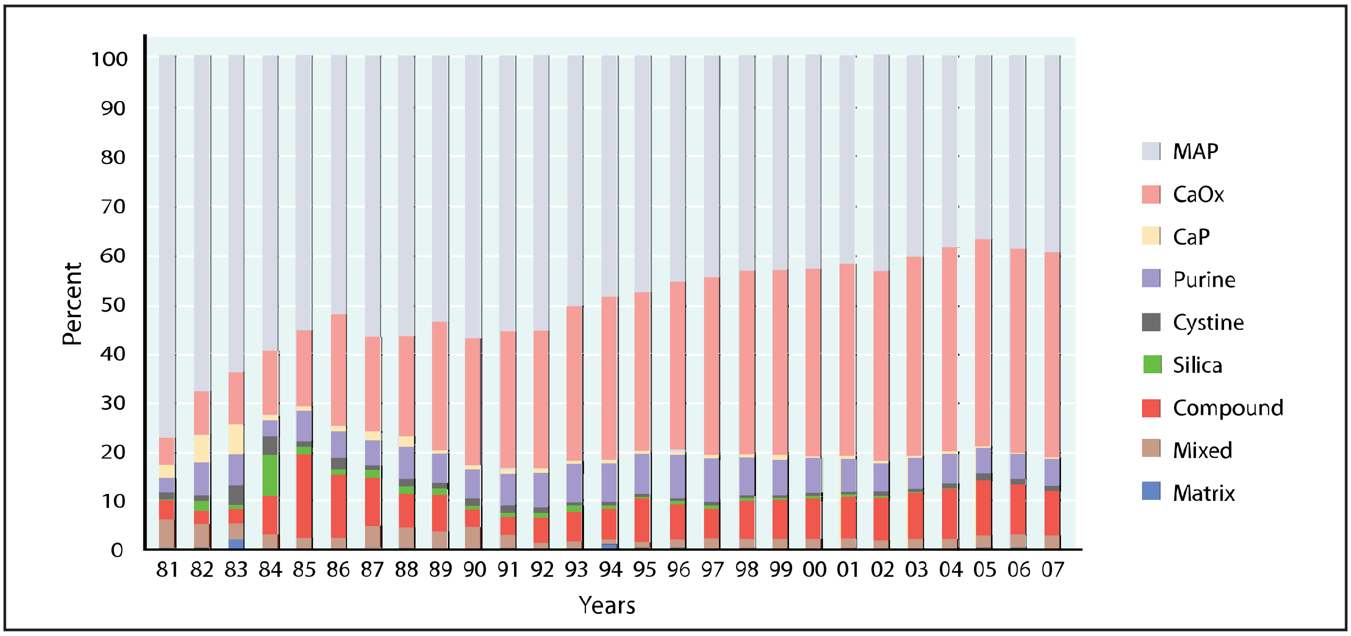

Figure 40-1. Bar graph illustrating increased occurrence of canine calcium oxalate uroliths submitted to the Minnesota Urolith Center from 1981 to 2007. Note the overall decline in struvite urolith submissions and the increase in calcium oxalate submissions. Key: MAP = magnesium ammonium phosphate (struvite), CaOx = calcium oxalate, CaP = calcium phosphate.

miniature poodles (3%), Chihuahuas (2%) and Jack Russell terriers (2%). Calcium oxalate uroliths were more commonly removed from the lower urinary tract (97%) than the upper urinary tract (3%).

Although different combinations of calcium oxalate salts have been identified in canine uroliths, the predominant form encountered has been calcium oxalate monohydrate (whewellite; Table 38-8). Pure calcium oxalate monohydrate has been observed in dogs more frequently than pure calcium oxalate dihydrate (weddelite). A similar observation has been made in cats and people with calcium oxalate uroliths. When calcium oxalate salts occur in combination in human, feline and canine uroliths, the dihydrate salt is usually found surrounding a nucleus of the monohydrate salt (Koide et al, 1982). The significance of this observation has not yet been confirmed, although it has been suggested that calcium oxalate dihydrate may form initially and then be converted to calcium oxalate monohydrate (Leusmann et al, 1984; Otnes, 1983; Schubert and Brien, 1981; Tomazic and Nancollas, 1982). In people, detection of calcium oxalate dihydrate on the outside of a urolith may indicate recent formation, whereas detection of external layers of calcium oxalate monohydrate indicates lack of recent urolith formation (Berenyl et al, 1972). If valid in dogs, this hypothesis would be of clinical significance because it would help to determine if the disorders underlying calcium oxalate urolithiasis were persistent. This in turn would provide evidence of the need for continuous therapy to minimize urolith recurrence. In one study, human patients with calcium oxalate dihydrate uroliths had more recurrences of uroliths than did patients with calcium oxalate monohydrate uroliths (Leusmann et al, 1984).

Calcium oxalate monohydrate and dihydrate uroliths are typically dense and brittle; they have relatively small quantities (~3%) of matrix. Pure calcium oxalate monohydrate and calcium oxalate dihydrate have different colors and shapes (**Table 40-1**). In people, uroliths composed of calcium oxalate monohydrate frequently assume the shape of mulberries or jackstones (Otnes, 1983). To date, only a few canine calcium oxalate jackstones have been observed at the Minnesota Urolith Center.

ETIOPATHOGENESIS AND RISK FACTORS

In order for calcium oxalate uroliths to form, urine must be supersaturated with calcium and oxalic acid. Therefore, increasing the urine concentration of calcium and/or oxalic acid promotes calcium oxalate crystal formation. Hypercalciuria has been documented to occur in dogs with calcium oxalate uroliths (Lulich et al, 1991).

At one time it was thought that increases in urine oxalic acid concentration promoted calcium oxalate urolith formation in people to a greater degree than comparable increases in urine calcium concentration (Smith, 1991). Results of more recent studies, however, indicate that oxalic acid and calcium contribute equally to urine supersaturation with calcium oxalate (Pak et al, 2004). Although hyperoxaluria apparently has not been documented to occur in dogs with calcium oxalate uroliths, the relationship between the concentrations of calcium and oxalic acid within the digestive and urinary tracts is fundamental to understanding calcium oxalate urolithiasis.

Dietary Risk Factors

Dietary ingredients that promote hypercalciuria or hyperoxaluria represent nutritional risk factors for calcium oxalate urolith formation (**Tables 40-2** and **40-3**). Therefore, reduction of dietary calcium and oxalate appears to be a logical therapeutic goal. However, it is not necessarily harmless. Reducing consumption of only one of these substances (calcium) may increase the availability of the other (oxalic acid) for intestinal absorption and subsequent urinary excretion. To minimize this undesirable shift in the modulation of oxalic acid absorption from the intestine, reduction in dietary calcium should be accompanied by an appropriate reduction in dietary oxalic acid.

Dogs with calcium oxalate urolithiasis frequently consume human food. Calcium oxalate is the most common urolith type recognized in people living in developed countries. As people feed their dogs the same dietary proportions and ingredients they feed themselves, it is logical to postulate that dogs would be exposed to similar nutritional risk factors for urolith formation (**Table 40-2**). Results of epidemiologic studies performed at the Minnesota Urolith Center support this hypothesis.

In addition to human food consumption, an association between calcium oxalate urolithiasis and consumption of commercially available treats has also been recognized. The high sodium content of some commercial dog treats may help explain this association because sodium consumption promotes hypercalciuria (Lulich et al, 1992).

Certain dietary excesses and deficiencies have also been recognized as potential risk factors. Excessive administration of vitamin D, sodium or magnesium promotes hypercalciuria. Because ascorbic acid is a precursor of oxalate, excessive quantities of vitamin C should be avoided. Although dogs with calcium oxalate uroliths have not been evaluated for pyridoxine deficiency, kittens fed pyridoxine-deficient foods exhibited hyperoxaluria (Bai et al, 1989).

Other Risk Factors

Calcium oxalate uroliths have been recognized in many breeds of dogs (see Prevalence and Mineral Composition above). Infrequently encountered breeds include boxers, bloodhounds, coonhounds, Dalmatians, English bulldogs, Newfoundlands, German shorthaired pointers, Skye terriers, wirehaired terriers, golden retrievers, Labrador retrievers and St. Bernards. Approximately 74% of calcium oxalate uroliths have affected male dogs. Most were detected in adults (mean and median age was eight to nine years).

Geographic location has been identified as a risk factor for calcium oxalate urolith formation in people living in the United States (Mandel and Mandel, 1989). In a study of approximately one million people, investigators observed a north-south and west-east gradient such that people living in the southeastern U.S. (Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North and South Carolina, Tennessee and Virginia) had the highest rate of urolith formation (Soucie et al, 1996). Studies evaluating geographic location as a risk factor for calcium oxalate urolith formation in dogs have apparently not yet been reported.

Certain clinical conditions also represent potential risk factors for calcium oxalate urolith formation. Hyperparathyroidism, hyperadrenocorticism, hypervitaminosis D, paraneoplastic hypercalcemia and furosemide administration promote hypercalciuria. In people, intestinal resection, hereditary hyperoxaluria and excessive ascorbic acid administration promote hyperoxaluria (Park and Pearle, 2007).

Table 40-1. Common characteristics of canine calcium oxalate uroliths.

Chemical names	Formulas	Crystal names
Calcium oxalate monohydrate	$CaC_2O_4 \cdot H_2O$	Whewellite
Calcium oxalate dihydrate	$CaC_2O_4 \cdot 2H_2O$	Weddellite

Variations in mineral composition
- Calcium oxalate monohydrate only
- Calcium oxalate dihydrate only
- Combinations of calcium oxalate monohydrate and dihydrate
- Calcium oxalate (monohydrate and/or dihydrate) mixed with variable quantities of calcium phosphate. Variable quantities of struvite or ammonium acid urate may also be present.
- Calcium oxalate (monohydrate and/or dihydrate) nucleus surrounded by other minerals especially infection-induced struvite

Physical characteristics

Color: Calcium oxalate monohydrate uroliths are usually tan or brown. Calcium oxalate dihydrate uroliths are usually white or cream colored. Surfaces may be red to black if uroliths are coated with blood.

Shape: Variable. Calcium oxalate monohydrate uroliths are usually round or elliptical and have a smooth, polished surface. Occasionally, they may develop a jackstone or mulberry shape. Calcium oxalate dihydrate uroliths and mixed calcium oxalate monohydrate/calcium oxalate dihydrate uroliths are usually round to ovoid and have an irregular surface caused by protrusion of sharp-edged crystals. Occasionally, they may develop a jackstone shape.

Nuclei: Radial striations and concentric laminations may occur.

Density: Very dense and brittle. Survey radiographs reveal that calcium-containing uroliths are radiodense compared with soft tissue.

Number: Single or multiple

Location: May be located in renal pelves, ureters, urinary bladder (most common) and/or urethra.

Size: Sub-visual to several centimeters

Prevalence
- Approximately 41% of all canine uroliths. More than 43% of canine upper tract uroliths.
- May be recurrent (more than 50% recur by three years after removal)

Characteristics of affected canine patients
- More common in males (73%) than females (22%)
- Mean age at diagnosis is about eight years (range <1 to >25 years)
- Most commonly observed in miniature schnauzers, Lhasa apsos, Yorkshire terriers, Shih Tzus and Bichon Frises

Hypercalciuria

Hypercalciuria can be localized into at least three subtypes according to the primary site of the underlying cause (i.e., intestine, kidney or skeleton): 1) absorptive hypercalciuria is characterized by intestinal hyperabsorption of calcium, 2) renal hypercalciuria is characterized by impaired renal tubular reabsorption of calcium and 3) resorptive hypercalciuria is characterized by bone demineralization.

Available evidence indicates that calcium homeostasis is principally achieved through the actions of parathyroid hormone (PTH) and 1,25-dicholecalciferol (1,25-vitamin D) on the intestines, kidneys and skeleton. For example, states of low

Table 40-2. Some potential risk factors for canine calcium oxalate uroliths.

Diet	Urine	Metabolic status	Drugs
Acidifying potential	Hypercalciuria	Chronic metabolic acidosis	Urine acidifiers
High protein content	Hyperoxaluria	Males	Furosemide
High sodium content	Hypocitraturia?	Breed	Glucocorticoids
Excessive calcium content	Hypomagnesuria?	Miniature schnauzers	Sodium chloride
Excessive restriction of calcium	Hyperuricuria?	Miniature poodles	Vitamin D
Low moisture content	Increased crystal promoters	Lhasa apsos	Ascorbic acid
Excessive phosphorus restriction	Decreased crystal inhibitors	Yorkshire terriers	
Excessive magnesium content	Urine concentration	Shih Tzus	
Excessive magnesium restriction	Urine retention	Bichon Frises	
Excessive vitamin D content		Older age	
Excessive vitamin C content		Hypercalcemia	
Deficient pyridoxine?		Glucocorticoid excess	
High oxalate content		Hypophosphatemia	
		Hyperoxalemia?	
		Osteolysis?	

Table 40-3. Selected human foods to limit or avoid feeding to dogs with calcium oxalate uroliths.*

Moderate/high-calcium foods	Moderate/high-oxalate foods	
Food items	**Food items**	
Meats	**Meats**	
Bologna (M)	Sardines (M)	Oranges (M)
Herring (M)	**Vegetables**	Peaches (M)
Oysters (M)	Asparagus (M)	Pears (M)
Salmon (H)	Broccoli (M)	Peel of lemon, lime or orange (H)
Sardines (H)	Carrots (M)	Pineapple (M)
Vegetables	Celery (H)	Tangerine (H)
Baked beans (M)	Corn (M)	**Breads, grains, nuts**
Broccoli (H)	Cucumber (H)	Cornbread (M)
Collards (H)	Eggplant (H)	Fruitcake (H)
Lima beans (M)	Green beans (H)	Grits (H)
Spinach (M)	Green peppers (H)	Peanuts (H)
Tofu (soybean curd) (M)	Lettuce (M)	Pecans (H)
Milk and dairy products	Spinach (H)	Soybeans (H)
Cheese (H)	Summer squash (H)	Wheat germ (H)
Ice cream (H)	Sweet potatoes (H)	**Miscellaneous**
Milk (H)	Tofu (H)	Beer (H)
Yogurt (H)	Tomatoes (M)	Chocolate (H)
Breads, grains, nuts	**Fruits**	Cocoa (H)
Brazil nuts (M)	Apples (H)	Coffee (M)
Miscellaneous	Apricots (H)	Tea (H)
Cocoa (M)	Cherries (M)	Tomato soup (H)
Hot chocolate (M)	Most berries (H)	Vegetable soup (H)

Key: M = moderate; feed in limited amounts. H = high; avoid feeding.
*Adapted from Wainer L, Resnick VA, Resnick MI. Nutritional aspects of stone disease. In: Pak CYC, ed. Renal Stone Disease, Pathogenesis, Prevention, and Treatment. Boston, MA: Martinus Nihoff Publishing, 1987; 85-120. Burroughs M. Renal diseases and disorders. In: Nelson JK, Moxness KE, Jensen MD, et al, eds. Mayo Clinic Diet Manual, 7th ed. St. Louis, MO: Mosby, 1994; 208-209.

serum ionized calcium concentration result in compensatory PTH- and 1,25-vitamin D-mediated mobilization of calcium from the skeleton, absorption of calcium from the intestine and conservation of calcium by the kidneys. High serum ionized calcium concentrations suppress release of PTH and production of 1,25-vitamin D. The result is decreased skeletal mobilization and intestinal absorption of calcium and enhanced renal calcium excretion. Thus, it is apparent that hypercalciuria can result from increased renal clearance of calcium due to: 1) excessive intestinal absorption of calcium, 2) impaired renal conservation of calcium and/or 3) excessive skeletal mobilization of calcium. Although hypercalciuria can be localized according to the site of the apparent primary defect in calcium transport, compensatory changes typically occur that involve other sites. For example, renal-leak hypercalciuria is associated with secondary hyperparathyroidism, which in turn is associated with varying degrees of bone resorption of calcium and phosphorus and varying degrees of intestinal calcium absorption. Absorptive hypercalciuria results in a positive calcium balance, which in turn suppresses production and release of PTH, decreasing renal tubular reabsorption of calcium.

Hypercalcemic hypercalciuria results from increased glo-

Table 40-4. Summary of distinguishing clinical manifestations for different types of hypercalciuria.

Features	Absorptive hypercalciuria	Renal-leak hypercalciuria	Resorptive hypercalciuria
Serum calcium	Normal	Normal	Increased
Serum parathyroid hormone	Decreased/normal	Increased	Increased
Serum phosphorus	Normal/increased	Normal	Decreased/increased*
Urine calcium			
Fasting	Normal	Increased	Increased
Dx food**	Increased	Increased	Increased
Urine oxalic acid	Normal	Normal	Normal
Urine uric acid	Normal	Normal	Normal
Bone density	Normal	Decreased	Decreased
Calcium balance (total body)	Positive	Negative	Negative

*Phosphorus is retained in serum as glomerular filtration rate declines.
**Dx food = diagnostic food used in the evaluation of normal dogs and those with calcium oxalate uroliths.

merular filtration of mobilized calcium, which overwhelms normal renal tubular reabsorptive mechanisms. This phenomenon is called resorptive hypercalciuria because excessive bone resorption is associated with increased serum calcium concentrations. In dogs, normocalcemic hypercalciuria is thought to result from either intestinal hyperabsorption of calcium (so-called absorptive hypercalciuria), or decreased renal tubular reabsorption of calcium (so-called renal-leak hypercalciuria) (**Table 40-4**). Absorptive hypercalciuria is characterized by increased urine calcium excretion and urine calcium concentration, normal serum calcium concentration and normal or low serum PTH concentration. Because absorptive hypercalciuria depends on dietary calcium, urine calcium excretion and urine calcium concentration are normal or significantly reduced during the fasting state. However, urine calcium excretion and urine calcium concentration typically increase during non-fasting conditions. Mean 24-hour urine calcium excretion in 33 normal beagles was 0.32 ± 0.2 mg/kg body weight/day during fasting and 0.51 ± 0.3 mg/kg body weight/day when dogs consumed a standard food[a] (Lulich et al, 1991a). By comparison, mean urine calcium excretion in five miniature schnauzers with calcium oxalate urolithiasis and absorptive hypercalciuria was 1.0 ± 0.5 mg/kg body weight/day during fasting and 2.84 ± 0.9 mg/kg body weight/day during non-fasting urine collections (Lulich et al, 1991).

A primary defect observed in people with absorptive hypercalciuria is apparent intestinal hyperabsorption of calcium, which results in increased excretion of excess calcium in urine. In addition to enhanced glomerular filtration of absorbed dietary calcium, decreased PTH secretion results in decreased renal tubular reabsorption of filtered calcium. The same phenomenon appears to occur in dogs with absorptive hypercalciuria.

Primary intestinal abnormalities of calcium absorption, disorders of 1,25-vitamin D production and hypophosphatemia-induced hypervitaminosis D have been recognized as causes of hypercalciuria in people (Park and Pearle, 2007). Absorptive hypercalciuria in people has recently been further subclassified as to whether increased calcium excretion is food unresponsive (Type 1) or food responsive (Type II). The underlying mechanism(s) of absorptive hypercalciuria has not been identified in dogs. However, hypophosphatemia or elevated levels of 1,25-vitamin D were not observed in five dogs with absorptive hypercalciuria.

In human studies, renal-leak hypercalciuria and resorptive hypercalciuria have been documented, but have been recognized less frequently than excessive intestinal absorption of calcium. The defect with renal-leak hypercalciuria is impaired tubular reabsorption of calcium. Patients with renal-leak hypercalciuria have high serum PTH concentrations. Increasing PTH secretion counters the effect of additional calcium lost in urine and maintains normal blood calcium levels. Hypercalcemia associated with calcium oxalate urolithiasis is the hallmark of patients with resorptive hypercalciuria. Hypercalcemia is not a characteristic of patients with excessive intestinal absorption of calcium or renal-leak hypercalciuria. An in-depth review of the pathophysiology of hypercalciuria has recently been published (Park and Pearle, 2007).

Hyperoxaluria

As described above in the discussion about dietary risk factors influencing calcium oxalate urolithiasis, the effect of oxalic acid on calcium oxalate urolithiasis depends on the interactions of calcium and oxalic acid that occur in the lumen of the intestine and in urine. Intestinal hyperabsorption or accelerated endogenous synthesis of oxalic acid can result in hyperoxaluria. In healthy people, the majority of urine oxalic acid is derived from the endogenous metabolism of ascorbic acid, glycine, glyoxylate and tryptophan. The daily quantity of endogenously produced oxalic acid is apparently minimal. In people, hyperoxaluria has been associated with inherited abnormalities of excessive oxalic acid synthesis (primary hyperoxaluria), increased consumption of foods containing high quantities of oxalic acid or oxalic acid precursors (**Table 40-3**), pyridoxine deficiency and disorders associated with fat absorption (Williams and Smith, 1983). We could not find any reports of inherited hyperoxaluria or hyperoxaluria associated with intestinal resection and fat malabsorption in dogs. However, increases in urine oxalic acid excretion have been recognized in kittens fed pyridoxine-deficient foods (Bai et al, 1989).

In people, approximately 10 to 20% of urine oxalic acid is absorbed from dietary ingredients. Urine oxalic acid excretion is inversely related to dietary intake of calcium. In the intestinal tract, oxalic acid complexes with calcium and is excreted in feces as an insoluble salt. A decrease in the combination of oxalic acid with calcium to form calcium oxalate results in an increased quantity of soluble oxalic acid available for intestinal absorption. Therefore, it is logical to assume that urolith-forming patients with intestinal hyperabsorption of calcium, or those consuming foods with inappropriately low calcium compared with oxalic acid, would be at risk for increased intestinal absorption of dietary oxalic acid, hyperoxaluria and subsequent calcium oxalate urolith formation.

Hypocitraturia

Hypocitraturia is a common physiologic disturbance in people with calcium oxalate urolithiasis. It has been reported to affect 20 to 60% of calcium stone formers (Hamm and Hering-Smith, 2002). Urine citric acid is a negative anion that combines with cationic calcium, thus reducing the quantity of calcium available to complex with oxalic acid. Calcium citrate is more soluble than calcium oxalate. Citrate is also a buffer, and as such, minimizes the formation of calcium phosphate. Citrate also directly inhibits crystallization and aggregation of calcium oxalate and calcium phosphate (Park and Pearle, 2007).

The role of low urine citric acid concentration in the etiology of canine calcium oxalate urolithiasis is not completely resolved. Hypocitraturia has been observed in dogs with calcium oxalate uroliths; however, mechanisms responsible for decreased urine citric acid excretion in dogs are as yet unknown. It is known that acid-base homeostasis influences the quantity of citric acid excreted in urine (Simpson, 1983). In normal dogs, acidosis is associated with decreased urine citric acid formation and excretion, whereas alkalosis promotes urine citric acid formation and excretion.

Several abnormalities associated with acidosis may lead to hypocitraturia. Examples include distal renal tubular acidosis, chronic diarrhea associated with systemic acidosis and excessive consumption of animal protein, which produces excess acid and promotes bone demineralization. A recent study of a high-protein, low-carbohydrate diet typified by the so-called Atkins diet revealed a significant reduction in urinary pH and citrate during the induction and maintenance phases of the diet (Reddy et al, 2002). Hypocitraturia may also occur in association with thiazide-induced hypokalemia, which produces intracellular acidosis. Idiopathic hypocitraturia may also occur independent of acidosis.

The Role of Oxalate-Degrading Bacteria

Recent studies have revealed a correlation between enteric colonization of oxalate-degrading bacteria (ODB), mainly *Oxalobacter formigenes*, and the absence of hyperoxaluria and/or calcium oxalate formation in rats and people (Sidhu et al, 1999; Troxel et al, 2003). Consider the following evidence: 1) Using a rat model, one group of investigators demonstrated a rapid reversal of hyperoxaluria after probiotic administration of *O. formigenes* (Sidhu et al, 2001). 2) Oral administration of *O. formigenes* to people with Type 1 hyperoxaluria reduced the oxalate concentration in plasma and urine (Hoppe et al, 2006). 3) In rats, *O. formigenes* colonization induced colonic secretion/excretion of endogenous oxalate and was associated with reduced oxalate levels in plasma (Hatch et al, 2006). These studies indicate that colonization of ODB in the gastrointestinal (GI) tract can prevent enteric absorption of oxalic acid and increase fecal excretion of endogenously produced oxalate. ODB possess two enzymes, formyl CoA transferase and oxalate CoA decarboxylase, that metabolize oxalic acid to formate and CO_2 (Lung et al, 1994; Sidhu et al, 1997). In addition, *O. formigenes* carries a specialized membrane transporter, oxalate/formate antiporter, to transport the substrate and product across the membrane (Ruan et al, 1992). *O. formigenes*, *Lactobacillus* spp., *Bifidobacterium lactis, Enterococcus faecalis* and *Eubacterium lentum* are major ODB found in mammalian GI tracts (Allison et al, 1986; Federici et al, 2004; Hokama et al, 2000; Ito et al, 1996; Weese et al, 2004). *O. formigenes,* an anaerobe, is solely dependent on oxalate as an energy source. It is considered to efficiently degrade oxalate in the GI tract of rats, sheep, pigs and people (Allison et al, 1985, 1986; Daniel et al, 1987).

There have been few studies reported in which ODB have been evaluated in dogs in context of calcium oxalate uroliths. Oxalate-degrading *Lactobacillus* spp. are present in healthy dogs and cats (Weese et al, 2004). However, the effect of intestinal colonization with ODB on urine oxalate excretion has apparently not been investigated. Oxalate-degrading bacterial activity in canine feces has been demonstrated (Daniel et al, 1987). However, the role of ODB in the pathogenesis of canine and feline calcium oxalate urolithiasis apparently has not been reported.

Considering the current evidence derived from human and rodent models, we hypothesize that decreased concentrations of intestinal ODB are a likely risk factor for calcium oxalate urolith formation in dogs and cats (Lulich et al, 2008). We also hypothesize that the prevalence of ODB in the intestine of dogs with calcium oxalate uroliths is lower than in clinically healthy dogs without uroliths. If our hypothesis is correct, administration of novel probiotics that deliver viable ODB to the intestine and subsequent colonization of the intestinal mucosa with *O. formigenes* should minimize calcium oxalate urolith recurrence.

Macromolecular Crystal Growth Inhibitors

In addition to urine concentration of lithogenic minerals and other ions, large molecular weight glycoproteins in urine profoundly enhance solubility of calcium oxalate. One such protein called nephrocalcin minimizes calcium oxalate crystal growth in human urine (Nakagawa et al, 1983). In studies of nephrocalcin obtained from urolith-forming patients, this crystallization inhibitor lacked appropriate quantities of carboxyglutamic acid residues and was unable to prevent crystal growth. Preliminary studies of urine obtained from dogs with calcium oxalate uroliths have revealed that nephrocalcin also lacks appropriate numbers of carboxyglutamic acid residues compared with nephrocalcin isolated from normal canine urine (Carvalho et al, 2006).

Tamm-Horsfall glycoprotein and glycosaminoglycans inhibit calcium oxalate crystal aggregation. One hypothesis is that the mechanism of action of these proteins is to block growth sites on crystals, thereby inhibiting formation of calcium oxalate uroliths (Deganello, 1993).

BIOLOGIC BEHAVIOR

Calcium oxalate uroliths may be voided in the urine or become lodged in any portion of the urinary tract. Uroliths that remain in the urinary tract may continue to grow slowly or may become inactive (no further growth). Not all persistent uroliths are associated with clinical signs. Unlike infection-induced struvite uroliths, most calcium oxalate uroliths are not associated with urinary tract infection (UTI). Uroliths composed of the dihydrate salt of calcium oxalate appear to be less likely to cause complete urinary obstruction because of their irregular surface contour. Their jagged surface may prevent them from forming a continuous seal within the lumen of the urethra. However, if uroliths remain in the urinary tract, dysuria, UTI, partial or total urinary obstruction and polyp formation are potential sequelae. Spontaneous dissolution of calcium oxalate uroliths in dogs has apparently not been reported.

In a retrospective clinical survey of 438 dogs surgically treated for urolithiasis, 111 patients had 155 known recurrences (Brown et al, 1977). Recurrence was observed in 25% of dogs with calcium oxalate uroliths. We performed two retrospective studies and found that the rate of recurrence of calcium oxalate uroliths increased with the length of time that dogs were evaluated: 3% recurred after three months, 9% after six months, 36% after one year, 42% after two years and 48% after three years (Lulich et al, 1992a). The second study evaluated urolith recurrence in Bichon Frise dogs. After one year, 37% had their first recurrence; after two years, 64% had their first recurrence and 8% had their second recurrence; after three years, 90% had their first recurrence, 15% had their second recurrence and 4% had their third recurrence. Urolith recurrence was detected in 100% of dogs evaluated at or after four years (Lulich et al, 2004). Owner and patient compliance with therapy and persistence of factors responsible for urolith initiation at the time of urolith eradication influence the frequency of urolith recurrence.

KEY NUTRITIONAL FACTORS

Because dissolution of calcium oxalate uroliths in dogs has not been reported, the focus of dietary management is to prevent calcium oxalate urolith recurrence. The goals of dietary prevention include: 1) reducing calcium concentration in urine, 2) reducing oxalic acid concentration in urine, 3) promoting high concentration and activity of inhibitors of calcium oxalate crystal growth and aggregation in urine and 4) reducing concentration of urine.

Certain dietary excesses and deficiencies have been recognized as potential risk factors for calcium oxalate urolithiasis and are the basis of key nutritional factors. **Table 40-5** summarizes the key nutritional factors for calcium oxalate prevention.

Table 40-5. Key nutritional factors for foods for prevention of calcium oxalate uroliths.

Factors	Recommended levels
Water	Water intake should be encouraged to achieve a urine specific gravity <1.020 Moist food will increase water consumption and formation of less concentrated urine
Protein	Avoid excess dietary protein Restrict dietary protein to 10 to 18% dry matter (DM)
Calcium	Avoid excess dietary calcium, especially dietary supplements given independent of diet Restrict dietary calcium to 0.4 to 0.7% DM
Oxalate	Avoid foods high in oxalic acid (**Table 40-3**)
Phosphorus	Avoid phosphorus deficiency and maintain a normal Ca:P ratio (1.1:1 to 2:1) Dietary phosphorus should be in the range of 0.3 to 0.6% DM
Sodium	Recommend moderate dietary sodium restriction Dietary sodium should be <0.3% DM
Magnesium	Avoid excess or deficient dietary magnesium Dietary magnesium should be in the range of 0.04 to 0.15% DM
Ascorbic acid (vitamin C)	Avoid pet foods, supplements or human foods that contain ascorbic acid
Urinary pH	Avoid acidifying foods Foods should produce a urinary pH 7.1-7.5

Water

Dogs consuming dry commercial foods may be at greater risk for urolithiasis than dogs consuming moist foods because dry foods are often associated with higher urine concentrations of calcium and oxalic acid and more concentrated urine. Therefore, consider moist foods, rather than dry foods, to aid in the prevention of recurrence of calcium oxalate uroliths. Water intake should be encouraged to achieve a urine specific gravity less than 1.020. In addition to decreasing urine specific gravity, increased water intake is likely to be associated with increased voiding frequency. Frequent voiding reduces crystal retention time thereby minimizing crystal growth.

Protein

Ingestion of foods that contain high quantities of animal protein may contribute to calcium oxalate urolithiasis by increasing urine calcium excretion and decreasing urine citrate excretion (Breslau et al, 1988; Lekcharoensuk et al, 2002, 2002a). Some of these consequences result from obligatory acid excretion associated with protein metabolism. Hypercalciuria occurs in normal dogs fed high-protein foods (40% dry matter [DM]). Therefore, excessive dietary protein consumption should be avoided in dogs with active calcium oxalate urolithiasis. The recommended range for dietary protein is 10 to 18% DM. The

Table 40-6. Selected human foods with minimal calcium or oxalate content.

Food items	Low-calcium foods	Low-oxalate foods
Meats and eggs	Eggs	Beef
	Poultry	Eggs
		Fish and shellfish*
		Lamb
		Pork
		Poultry
Vegetables		Cabbage
		Cauliflower
		Mushrooms
		Peas, green
		Radishes
		Potatoes, white
Milk and dairy products		Cheese*
		Milk*
		Yogurt*
Fruits		Apple
		Avocado
		Banana
		Bing cherries
		Grapefruit
		Grapes, green
		Mangos
		Melons
		Cantaloupe
		Casaba
		Honeydew
		Watermelon
		Plums, green or yellow
Breads, grains, nuts	Almonds	Bread, white
	Macaroni	Macaroni
	Pretzels	Noodles
	Rice	Rice
	Spaghetti	Spaghetti
	Walnuts	
Miscellaneous	Popcorn	Jellies
		Preserves
		Soups with allowed ingredients

*Low in oxalate, but not low in calcium content.

minimum recommended allowance for protein in foods for healthy adult dogs is 10% DM (NRC, 2006).

Calcium and Oxalic Acid

Reduction of dietary calcium appears to be a logical therapeutic goal because intestinal hyperabsorption of calcium has been identified as one mechanism promoting hypercalciuria in dogs with calcium oxalate uroliths. However, reducing consumption of calcium may increase the availability of oxalic acid for intestinal absorption and subsequent urinary excretion. As in the urinary bladder, calcium and oxalic acid in the intestinal lumen form a relatively insoluble complex, thereby preventing the absorption of one another. This provides a plausible explanation as to why an epidemiologic study evaluating risk factors for calcium oxalate urolith formation in people unexpectedly discovered that foods with higher calcium levels were associated with reduced risk for urolith formation (Curhan et al, 1993, 1997; Curhan, 2007). Therefore, in hypercalciuric patients, reduction in dietary calcium should be accompanied by an appropriate reduction in dietary oxalic acid (**Tables 40-3** and **40-6**) (Lulich et al, 2001). The increase in the urine concentration of oxalic acid can be prevented by concomitantly reducing calcium and oxalic acid in the food. Caution: severe calcium restriction should be avoided to prevent negative calcium balance. The minimum requirement for calcium in foods for healthy dogs is 0.2% DM and the minimum recommended allowance is 0.4% DM (NRC, 2006). For prevention of recurrence of calcium oxalate uroliths, reduce dietary calcium to 0.4 to 0.7% DM.

People with calcium oxalate uroliths are often cautioned to avoid milk and milk products because the carbohydrate component (lactose) of these products may augment intestinal absorption of calcium from any dietary source (Leman et al, 1969). Likewise, they are often discouraged from consuming foods containing relatively high quantities of oxalic acid (**Table 40-3**). Although there is agreement that excessive consumption of calcium and oxalic acid should be avoided, the consensus of urologists is that it is inadvisable to restrict dietary calcium unless persistent absorptive hypercalciuria has been documented. Even then, only moderate restriction is advocated to minimize development of negative calcium balance.

Phosphorus

Studies of laboratory animals, dogs and people suggest that dietary phosphorus should not be overly restricted in patients with calcium oxalate urolithiasis because reduction in dietary phosphorus is often associated with augmentation of intestinal calcium absorption and hypercalciuria (Brautbar et al, 1979). If calcium oxalate urolithiasis is associated with hypophosphatemia and normal serum calcium concentration, oral phosphorus supplementation should be considered. However, caution must be used because excessive dietary phosphorus may predispose hypercalciuric patients to formation of calcium phosphate uroliths.

Based on a recommended range for calcium (0.4 to 0.7% DM) in foods for calcium oxalate urolith prevention in canine patients, dietary phosphorus levels should be in the range of 0.3 to 0.6% DM with a calcium-phosphorus ratio range of 1.1:1 to 2:1. The minimum recommended allowance for phosphorus in foods for healthy adult dogs is 0.3% DM (NRC, 2006).

Sodium

Sodium chloride can be added to food to increase thirst and urine volume. However, excess sodium increases urine calcium excretion and therefore is a risk factor for calcium oxalate and calcium phosphate urolithiasis, particularly if the urinary pH is high. For the same reason, if oral urinary alkalinizing agents are used, potassium citrate may be a better choice than sodium bicarbonate. Supplemental sodium sources may also contribute to hypertension in salt-sensitive dogs.

In people, high dietary sodium consumption also reduces urine citrate concentration via sodium-induced bicarbonate loss. Daily urine calcium excretion of normal dogs consuming foods with 0.8% DM sodium was comparable to calcium excretion observed in dogs with calcium oxalate uroliths (Lulich, 1991). Based on this evidence, we recommend moderate dietary restriction of sodium (<0.3% DM sodium) for active calcium oxalate urolith formers (Lulich et al, 2001). Typically, commercial dog foods contain two to three times this amount. The minimum recommended allowance for sodium in foods for healthy adult dogs is 0.08% DM (NRC, 2006).

Magnesium

Although supplemental dietary magnesium contributes to formation of magnesium ammonium phosphate uroliths in some species (cats and ruminants), urine magnesium apparently impairs formation of calcium oxalate crystals (Finco et al, 1985; Kallfez et al, 1986; Meyer and Smith, 1969). Therefore, supplemental magnesium has been used in human patients in an attempt to minimize recurrence of calcium oxalate uroliths (Melnick et al, 1971). However, increased urine excretion of calcium by normal dogs given supplemental magnesium has been observed. Urine calcium excretion was 0.5 ± 0.2 mg/kg body weight/day in six normal dogs consuming a food containing 0.03% DM magnesium vs. 2.65 ± 1.7 mg/kg body weight/day when the same dogs consumed a food containing 0.38% DM magnesium (Lulich, 1991a). Pending further studies, dietary magnesium restriction or supplementation is not recommended for treatment of canine calcium oxalate uroliths. A range of 0.04 to 0.15% DM is recommended. The minimum recommended allowance for magnesium content of foods for healthy adult dogs is 0.06% DM (NRC, 2006).

Ascorbic Acid (Vitamin C)

Supplemental ascorbic acid (a precursor of oxalate) should be avoided.

Urinary pH

Urinary pH in healthy subjects reflects the acid load (acidifying effects) of a food. Although formation of acidic urine is desirable for management of struvite uroliths, foods that promote acidic urine promote hypercalciuria and hypocitraturia. Therefore, consumption of foods that result in formation of acidic urine enhances the risk of calcium oxalate urolithiasis in susceptible dogs. Thus, for prevention of calcium oxalate uroliths, the urinary pH should not be less than 7.0.

A recent study of a high-protein, low-carbohydrate food typified by the so-called Atkins diet revealed a significant reduction in urinary pH and citrate during the induction and maintenance phases of the diet (Reddy et al, 2002).

Urine Alkalinizing Agents

Dosage of urine alkalinizing agents should be individualized for each patient, depending on the status of the patient and pretreatment urinary pH values. Although sodium bicarbonate is a readily available urine alkalinizer, at recommended doses, (25 to 50 mg/kg body weight q12h), it provides a significant increase in sodium intake. Also, sodium may combine with uric acid to form sodium urate. In people, urate salts may serve as a nidus for calcium oxalate urolith formation. For these reasons, we prefer potassium citrate. Potassium citrate in wax matrix tablets (Urocit-K[b]), as a liquid (Polycitra-K[c]) or as chewable tablets (K-CIT-V[d]) may be given. An initial dose of 40 to 75 mg/kg body weight q12h is recommended. The final dose should be individualized based on patient response. Potassium citrate should be administered with meals to reduce gastric irritation. Divided doses should be administered to maintain a consistently nonacidic environment in the urinary tract. Additional supplementation is usually unnecessary when feeding foods (e.g., Prescription Diet u/d Canine canned) containing adequate quantities of potassium citrate.

The goal of treatment with urine alkalinizing agents is to maintain a urinary pH between 7.1 to 7.5. Higher values (>7.5) should be avoided until it is determined whether or not high urinary pH is a significant risk factor for formation of calcium phosphate uroliths. Owners may monitor urinary pH with pH paper or handheld "pocket" pH meters.

OTHER NUTRITIONAL FACTORS

Pyridoxine (Vitamin B_6)

A deficiency of pyridoxine should be avoided because vitamin B_6 promotes endogenous production of oxalic acid (Smith, 1992). Pyridoxine increases the transamination of glyoxylate, an important precursor of oxalic acid, to glycine. Experimentally induced pyridoxine deficiency resulted in renal precipitation of calcium oxalate and hyperoxaluria in kittens (Bai et al, 1989). Commercial foods routinely fortified with vitamin supplements would not be deficient in pyridoxine or other vitamins. However, a homemade food might be deficient in pyridoxine if a multivitamin supplement is not added. Because the ability of supplemental pyridoxine (above nutritional requirements) to reduce urine oxalic acid excretion in dogs is unknown, there is insufficient evidence to recommend or abandon this practice. The minimum recommended allowance for pyridoxine in foods for healthy dogs is 1.5 mg/kg DM (NRC, 2006).

Vitamin D

Excessive levels of vitamin D (which promote intestinal absorption of calcium) in foods for patients at risk for calcium oxalate urolithiasis should be avoided. Commercial foods are typically replete with vitamin D and should not be further supplemented. Excessive supplementation of homemade foods with vitamin D could also pose a risk. For prevention of calcium oxalate urolithiasis, restrict vitamin D in foods to between 500 to 1,500 IU/kg DM. The recommended minimum allowance for foods for healthy adult dogs is 552 IU/kg DM (NRC, 2006).

FEEDING PLAN

Although struvite, urate and cystine uroliths dissolve when urine is no longer supersaturated with lithogenic substances, dissolution of calcium oxalate uroliths in dogs has not been

Table 40-7. Recommendations for the management of calcium oxalate urolithiasis in dogs.

1. Obtain data (postsurgical radiography, complete urinalysis, serum concentrations of calcium, urea nitrogen and creatinine) to evaluate effectiveness of renal function, calcium homeostasis, surgery, voiding urohydropropulsion or lithotripsy.
2. If the dog is hypercalcemic, correct underlying cause.
3. If the dog is normocalcemic, consider foods with reduced calcium, oxalate, sodium and protein that do not promote formation of acidic urine. Ideally foods should contain additional water and citrate and have adequate phosphorus and magnesium. Avoid excess and/or supplemental vitamins C and D. Prescription Diet u/d Canine or w/d Canine* is often recommended.
4. Reevaluate patient in two to four weeks to verify dietary compliance (urine specific gravity and pH and serum urea nitrogen concentration) and amelioration of crystalluria (urine sediment examination).
5. Consider additional potassium citrate if calcium oxalate crystals and aciduria persist.
6. Reevaluate patient in two to four weeks to verify dietary compliance (urine specific gravity and pH and serum urea nitrogen concentration) and amelioration of crystalluria (urine sediment examination). Consider vitamin B_6 supplementation (2 to 4 mg/kg body weight q24 to 48 hours) if calcium oxalate crystalluria persists.
7. Again, reevaluate patient in two to four weeks to verify dietary compliance and amelioration of crystalluria. Consider administration of hydrochlorothiazide (2 mg/kg body weight q24 to 48 hours) if calcium oxalate crystalluria persists. Adverse effects of hydrochlorothiazide administration include dehydration, hypokalemia and hypercalcemia.
8. After three to six months, reevaluate patient to verify dietary compliance and amelioration of crystalluria. Check for urolith recurrence by abdominal radiography. If no uroliths are present, continue current therapy and reevaluate in three to six months. If uroliths have recurred, consider voiding urohydropropulsion (Figure 38-5 and Table 38-7), or lithotripsy. If unsuccessful and clinical signs referable to urocystoliths are persistent, consider surgery. Continue therapy to minimize urolith growth if clinical signs are not present.

*Hill's Pet Nutrition, Inc., Topeka, KS, USA.

reported. Therefore, only physical methods are currently available for removing clinically active calcium oxalate uroliths. Surgery is the time-honored method to remove calcium oxalate uroliths from the urinary tract; however, complete surgical removal of all visible uroliths may be difficult because of their small size and irregular contour. Small urocystoliths may be aspirated through a transurethral catheter (Figure 38-6) (Lulich and Osborne, 1992) or removed by voiding urohydropropulsion (Figure 38-5 and Table 38-7) (Lulich et al, 1993). Extracorporeal lithotripsy also provides a nonsurgical means of treating some dogs with calcium oxalate nephroliths and/or ureteroliths (Adams and Senior, 1999). We have had success fragmenting calcium oxalate urocystoliths and urethroliths with intracorporeal laser lithotripsy.

In some patients, calcium oxalate uroliths are clinically silent, obviating the need for intervention. For patients in which intervention is not warranted, the status of uroliths should be periodically assessed by urinalyses, renal function tests and radiography or ultrasonography. (See Reassessment below.)

Dietary and medical dissolution of calcium oxalate uroliths in dogs has not been reported. However, there is a role for dietary management in prevention of calcium oxalate urolith recurrence. In general, dietary and medical therapy should be implemented in stepwise fashion, with the initial goal of reducing the urine concentration of lithogenic substances (**Table 40-7**). Medications that have the potential to induce unwanted, sustained, detrimental alterations in the composition of metabolites should be reserved for patients with active or frequently recurring calcium oxalate uroliths. Caution should be used to ensure that side effects of treatment are not more detrimental than the effects of uroliths. The cause of hypercalcemia (e.g., primary hyperparathyroidism) should be corrected in patients with hypercalcemia and resorptive hypercalciuria. An attempt should be made to identify risk factors for urolith formation in patients with normal serum calcium concentrations (**Table 40-2**). Amelioration or control of the consequences of risk factors (e.g., urine oversaturation with lithogenic minerals) should minimize urolith growth and recurrence.

The feeding plan includes assessing and selecting the best food and assessing and determining the feeding method.

Assess and Select the Food

Table 40-8 compares the recommended levels of key nutritional factors to the key nutritional factor content of selected commercial veterinary therapeutic foods for calcium oxalate urolith prevention. Select the food that most closely matches the recommended levels of key nutritional factors for preventing the recurrence of calcium oxalate uroliths. Because these foods are intended for long-term feeding, they should also be approved by the Association of American Feed Control Officials (AAFCO), or some other credible regulatory agency. Dogs consuming dry commercial foods may be at greater risk for urolithiasis than those consuming moist foods because dry foods are often associated with higher urine concentrations of calcium and oxalic acid and more concentrated urine. When possible, moist foods should be selected.

Dogs with calcium oxalate urolithiasis frequently consume human food. Calcium oxalate is the most common urolith type recognized in people living in developed countries. As people feed their dogs the same dietary proportions and ingredients they feed themselves, it is logical to assume that dogs would be exposed to the same nutritional risk factors for urolith formation (**Tables 40-2** and **40-3**). Therefore, feeding human foods with high levels of calcium and oxalic acid should be avoided.

In addition to consumption of human food, an association between calcium oxalate urolithiasis and consumption of commercially available treats has been noted. The high sodium content of some commercial dog treats may help explain this association because sodium consumption promotes hypercalciuria (Lulich et al, 1992). Like foods, treats should not contain more than 0.3% DM sodium and they should be limited to less than 10% of the total food regimen (volume or weight basis).

Feeding foods designed to dissolve struvite uroliths provides

Table 40-8. Levels of key nutritional factors in selected veterinary therapeutic foods used to minimize recurrence of calcium oxalate urolithiasis in dogs compared to recommended levels.*

Dry foods	Protein (%)	Calcium (%)**	Phosphorus (%)**	Sodium (%)	Magnesium (%)	Urinary pH***
Recommended levels	**10-18**	**0.4-0.7**	**0.3-0.6**	**<0.3**	**0.04-0.15**	**7.1-7.5**
Hill's Prescription Diet u/d Canine	11.2	0.34	0.15	0.23	0.046	7.70
Medi-Cal Urinary SO 13	16.7	1.0	0.6	1.3	0.2	5.5-6.0
Purina Veterinary Diets NF KidNey Function	15.9	0.76	0.29	0.22	0.07	6.7-7.5
Royal Canin Veterinary Diet Urinary SO 14	17.0	0.80	0.63	1.38	0.066	5.5-6.0
Moist foods	**Protein (%)**	**Calcium (%)****	**Phosphorus (%)****	**Sodium (%)**	**Magnesium (%)**	**Urinary pH*****
Recommended levels	**10-18**	**0.4-0.7**	**0.3-0.6**	**<0.3**	**0.04-0.15**	**7.1-7.5**
Hill's Prescription Diet u/d Canine	13.3	0.35	0.17	0.28	0.049	7.4
Medi-Cal Urinary SO	18.7	1.0	0.8	1.1	0.10	5.5-6.0
Purina Veterinary Diets NF KidNey Function	16.5	0.50	0.30	0.24	0.08	6.7-7.5
Royal Canin Veterinary Diet Urinary SO	18.5	0.97	0.86	1.45	0.059	5.5-6.0

*Manufacturers' published values. Nutrients expressed as % dry matter, unless otherwise stated; moist foods are best; avoid foods with added vitamin C (ascorbic acid); avoid foods with high oxalate ingredients (**Table 40-3**).
**Calcium-phosphorus ratio should be in the range of 1.1:1 to 2:1.
***Protocols for measuring urinary pH may vary.

some benefits, but also presents several risks to patients with calcium oxalate uroliths (**Table 40-2**). The lower protein content and potential to enhance formation of less concentrated urine promote reduction of calcium and oxalic acid concentrations in urine. Although formation of acidic urine is desirable for management of struvite uroliths, foods that promote acidic urine promote hypercalciuria and hypocitraturia. Therefore, consumption of struvite litholytic foods that result in formation of acidic urine enhances the risk of calcium oxalate urolithiasis in susceptible dogs. Likewise, aggressive reduction of dietary phosphorus may also promote hypercalciuria. If struvite uroliths occur in breeds of dogs commonly affected with calcium oxalate uroliths, patients should be evaluated for calcium oxalate crystalluria after initiating dietary therapy designed to prevent struvite urolith formation. If calcium oxalate crystalluria persists, alternate methods of preventing struvite uroliths should be considered.

Another criterion for selecting a food that may become increasingly important in the future is evidence-based clinical nutrition. Practitioners should know how to determine risks and benefits of nutritional regimens and counsel pet owners accordingly. Currently, veterinary medical education and continuing education are not always based on rigorous assessment of evidence for or against particular management options. Still, studies have been published to establish the nutritional benefits of certain pet foods. Chapter 2 describes evidence-based clinical nutrition in detail and applies its concepts to various veterinary therapeutic foods.

Assess and Determine the Feeding Method

Transitioning the patient from its current food to a calcium oxalate urolith preventive food should be done gradually over several days. Begin the transition by feeding 75% of the current food and 25% of the new food on Day 1. On Day 2 feed half of each food. On Day 3 feed 75% as the new food. By Day 4 or 5, feed only the new food.

Because moist foods are recommended to increase water intake and production of less concentrated urine, specific amounts (meal fed) should be fed two to three times per day rather than free-choice feeding. Moist foods can spoil if left uneaten at room temperature for several hours (Chapter 11). Opened containers of moist foods should be refrigerated and the feeding bowl should be kept clean.

Table 40-9. Expected changes associated with dietary and medical therapy to minimize recurrence of calcium oxalate uroliths.

Factors	Pre-therapy	Prevention therapy
Polyuria	±	Variable
Pollakiuria	0 to 4+	0
Hematuria	0 to 4+	0
Urine specific gravity	Variable	1.004-1.015
Urinary pH	<7.0	>7.0
Pyuria	0 to 4+	0
Calcium oxalate crystals	0 to 4+	0
Bacteriuria	0 to 4+	0
Bacterial culture of urine	0 to 4+	0
Urea nitrogen (mg/dl)	>15	<15
Urolith size and number	Small to large	0

Besides offering moist foods, several additional approaches may facilitate increased water intake. First, ensure multiple bowls are available in prominent locations in the dog's environment; this may mean providing several bowls outside in a large enclosure or a bowl on each level of the house. Second, bowls should be clean and always be filled with fresh water. Third, small amounts of flavoring substances (e.g., salt-free bouillon) can be added to water sources. Fourth, ice cubes can be offered. Fifth, if a dry food is selected, add liberal quantities of water; however, as with moist foods, be aware that potential food safety issues might arise if moistened dry foods are left uneaten for prolonged intervals at room temperature (Chapter 11).

If the patient has a normal body condition score (2.5/5 to 3.5/5), the amount of the previous food being fed was probably appropriate. On an energy basis, a similar amount of the new food would be a good starting place.

Table 40-10. Managing highly recurrent calcium oxalate uroliths.

Causes	Identification	Therapeutic goal
Client and patient causes		
Inadequate dietary compliance	Question owner Persistent calcium oxalate crystalluria Urea nitrogen >10-15 mg/dl Urine specific gravity >1.010-1.020 Urinary pH <7.0-7.5 during treatment with Prescription Diet u/d Canine* (use lower values for the canned food)	Emphasize need to feed dissolution food exclusively
Administration of vitamin-mineral supplements	Question owner	Discontinue vitamin-mineral supplements containing calcium and vitamins C and D
Clinician factors		
Incomplete surgical removal of uroliths	Postsurgical radiography revealing uroliths Persistence of clinical signs after cystotomy or recurrence of clinical signs soon after cystotomy (within one to three months)	Uroliths not causing clinical signs should be monitored for potentially adverse consequences (obstruction, urinary tract infection, etc.) Clinically active uroliths may require surgical removal Remove small uroliths by voiding urohydropropulsion or lithotripsy
Inappropriate food choice	Persistent calcium oxalate crystalluria	Choose foods with reduced levels of calcium, oxalic acid, protein and sodium that do not promote formation of acidic urine Consider adding potassium citrate if aciduria persists
Inadequate monitoring	Postsurgical radiography to verify complete urolith removal was not performed Urinalysis or urine sediment examinations were not performed within three to six months of initiation of therapy	Perform postsurgical radiography to evaluate success of surgery Perform complete urinalysis within one to three months of initiation of therapy Once stable, urinalysis should be performed every four to six months Perform survey lateral abdominal radiography every four to six months to assess recurrence
Corticosteroid administration	Corticosteroids were prescribed to manage other disease conditions	If possible, discontinue corticosteroid administration
Disease factors		
Hypercalcemia	Elevated serum calcium concentration	Identify and, if possible, eliminate underlying cause for hypercalcemia (hyperparathyroidism, neoplasia, hypervitaminosis D, etc.)
Recurrence of uroliths despite appropriate management	Lateral radiograph of abdomen	Uroliths not causing clinical signs should be monitored for potentially adverse consequences (obstruction, urinary tract infection, etc.) Clinically active uroliths may require surgical removal Remove small uroliths by voiding urohydropropulsion or lithotripsy

*Hill's Pet Nutrition, Inc., Topeka, KS, USA.

ADJUNCTIVE MEDICAL MANAGEMENT

Citric Acid

Citric acid forms soluble salts with calcium thereby minimizing calcium oxalate crystal formation (Nicar et al, 1987). Citric acid is also beneficial because it is metabolized to bicarbonate and promotes formation of alkaline urine (Baruch et al, 1975). In dogs, chronic metabolic acidosis inhibits renal tubular reabsorption of calcium, whereas metabolic alkalosis enhances tubular reabsorption of calcium (Sutton et al, 1979). Potassium citrate is preferred to sodium bicarbonate as an alkalinizing agent because oral administration of sodium enhances urine calcium excretion. If persistent aciduria or hypocitraturia is recognized (mean urine citrate excretion of 33 normal beagles was 2.57 ± 2.31 mg/kg body weight/day), therapy with wax matrix tablets of potassium citrate (Urocit-K) should be considered. Alternatively, a liquid product (Polycitra-K) may be given to small dogs. Chewable treats containing potassium citrate (K-CIT-V) are also available. An initial dose of 40 to 75 mg/kg body weight q12h is recommended. The final dose should be based on patient response. Potassium citrate should be administered with meals to reduce gastric irritation. When feeding foods with adequate quantities of potassium citrate, additional supplementation is often not needed.

Thiazide Diuretics

Thiazide diuretics have been recommended to reduce recurrence of calcium-containing uroliths in people because of their

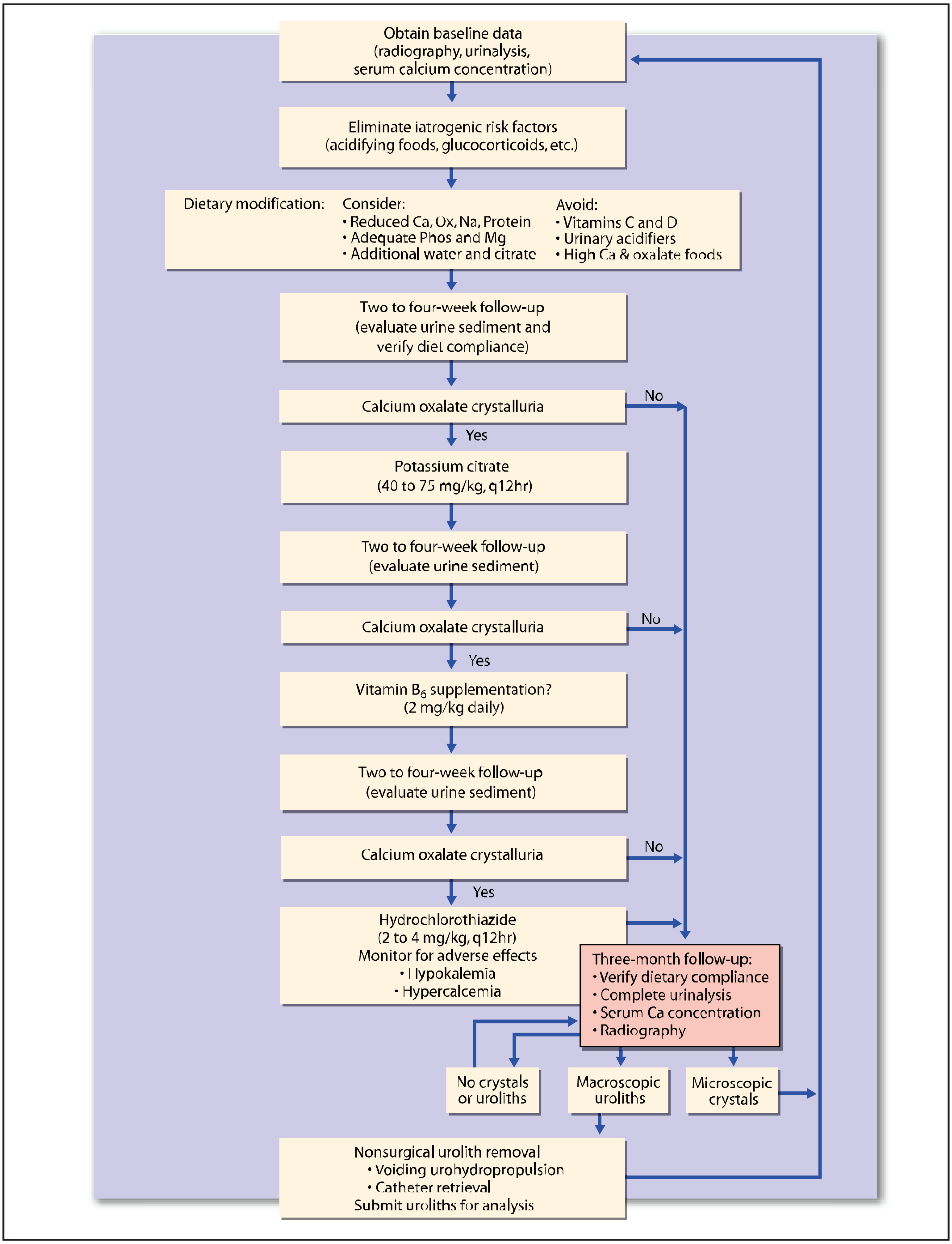

Figure 40-2. Algorithm for dietary and medical management of calcium oxalate uroliths in dogs.

ability to reduce urine calcium excretion (Churchill and Taylor, 1985). However, they should only be considered for patients with severe hypercalciuria. A beneficial reduction in urine calcium excretion in dogs with calcium oxalate urolithiasis has been observed following administration of hydrochlorothiazide (2 to 4 mg/kg body weight q12h) for two weeks. However, a reduction in urine calcium excretion was not detected following hydrochlorothiazide administration (20 to 65 mg/kg body weight q12h) to clinically healthy beagles (Lulich, 1991b). Results of a short-term study of the effects of hydrochlorothiazide on calcium excretion in the urine of adult dogs with naturally occurring calcium oxalate urolithiasis revealed that hydrochlorothiazide significantly reduced urine calcium concentration (Lulich et al, 2001). The greatest reduction in urine calcium concentration and excretion was achieved when dogs received hydrochlorothiazide and a urolith prevention diet. Thiazide diuretic administration is not recommended as first-line therapy at this time. The decision to use thiazides should be accompanied by owner informed consent and appropriate clinical and laboratory monitoring for early detection of adverse effects (dehydration, hypokalemia, hypercalcemia).

Allopurinol

Some people who form calcium oxalate uroliths associated with marked hyperuricosuria have benefited from allopurinol-induced reductions in the magnitude of hyperuricosuria. We are unaware of any counterpart of this phenomenon in dogs. In context of this discussion, it is relevant that the end product of purine metabolism in people is uric acid. However in dogs, the end product of purine metabolism is the highly soluble allantoin. Therefore, we do not recommend that allopurinol be considered for dogs that form calcium oxalate uroliths.

REASSESSMENT

The goal of therapy is to minimize calcium oxalate urolith recurrence (**Figure 40-2**). However, this expectation may be unrealistic because the primary causes responsible for urolith formation are multifactorial and incompletely understood. With the information and techniques currently available, however, veterinarians can minimize urolith recurrence and prevent the need for additional surgical removal of uroliths by appropriate monitoring and intervention.

Therapy should be initiated in a stepwise fashion (**Table 40-7**). If therapy is effective and clients remain compliant, dietary and pharmacologic management should result in formation of less concentrated urine without calcium oxalate crystalluria (**Table 40-9**). Strive to achieve urine specific gravity values less than 1.020. After this is achieved, a urinalysis and survey lateral abdominal radiographs should be performed every two to four months. Dietary and pharmacologic changes should be considered if crystalluria or concentrated urine persist (**Table 40-10**). These recommendations should facilitate detection of recurrent urocystoliths by radiography when they are small enough to remove by voiding urohydropropulsion (Figure 38-5 and Table 38-7). Likewise, urethroliths may be fragmented by intracorporeal laser lithotripsy. Nephroliths may be fragmented by extracorporeal shockwave lithotripsy. After the frequency of urolith recurrence has been established, the frequency of evaluation can be modified such that predicted recurrences can be diagnosed and managed accordingly.

ENDNOTES

a. Prescription Diet k/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
b. Urocit-K. Mission Pharmacal, San Antonio, TX, USA.
c. Polycitra-K. Willen Drug Co., Baltimore, MD, USA.
d. K-CIT-V. V.E.T. Pharmaceuticals, Inc., Fenton, MO, USA.

REFERENCES

The references for **Chapter 40** can be found at www.markmorris.org.

CASE 40-1

Urine Dribbling in a Yorkshire Terrier

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Patient Assessment

A nine-year-old, neutered male Yorkshire terrier was examined for urine dribbling and depression of two days' duration. Physical examination revealed that the dog was 8 to 10% dehydrated; capillary refill time was slightly delayed. The dog voided small spurts of reddish-brown urine onto the examination table when its abdomen was palpated. The physical examination was otherwise normal. Body weight was 5 kg; the dog had a normal body condition score (3/5). Survey radiographs revealed a large urinary bladder and a radiodense urolith in the urethra at the proximal end of the os penis and several uroliths in the urinary bladder (**Figure 1**).

The diagnosis was urolithiasis of the lower urinary tract associated with urethral obstruction. The depression was probably a consequence of postrenal azotemia.

Assess the Food and Feeding Method

The dog was fed a commercial moist adult maintenance food twice daily and various table foods.

Questions

1. What additional assessments should be performed?
2. What should be the patient's initial treatment plan?

Answers and Discussion

1. A blood sample should be submitted for biochemical analysis to evaluate the degree of azotemia and detect concurrent electrolyte abnormalities. A urinalysis and aerobic bacterial culture of the urine will help predict the mineral composition of the uroliths.
2. Replacement of the patient's fluid deficits with an appropriate fluid given intravenously is important. The urinary bladder can be evacuated by decompressive cystocentesis to enhance renal elimination of waste products. Reducing pressure in the urinary bladder also would facilitate retrograde urohydropropulsion of the urethrolith.

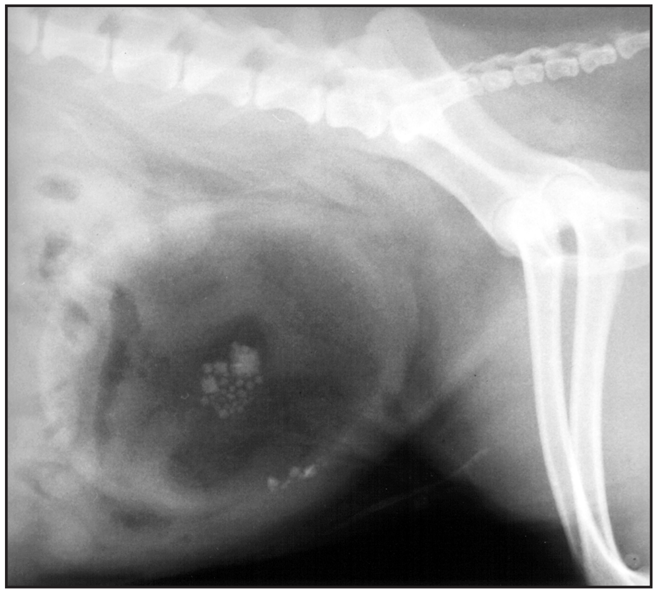

Figure 1. Survey lateral radiograph of a nine-year-old male Yorkshire terrier revealing multiple radiodense uroliths in the urinary bladder and a radiodense urolith at the proximal end of the os penis.

Further Assessment

Results of laboratory tests revealed azotemia, hyperphosphatemia and hypobicarbonatemia (**Table 1**). Serum alkaline phosphatase activity was also increased. Crystals were not observed by urine sediment examination and the urine culture was negative (**Table 2**). The urethrolith was successfully flushed into the urinary bladder by retrograde urohydropropulsion. Prophylactic antimicrobials were administered (amoxicillin-clavulanic acid, 14 mg/kg, q12h) to prevent iatrogenic bacterial urinary tract infection associated with transurethral catheterization.

Table 1. Serum biochemistry values of a nine-year-old male Yorkshire terrier with radiodense urocystoliths.*

Factors	Reference values	Day 1	Day 2	Day 3
SUN (mg/dl)	7-28	186	141	16
Creatinine (mg/dl)	0.5-1.5	6.5	1.2	0.9
Calcium (mg/dl)	9.3-11.4	8.7	8.2	8.7
Phosphorus (mg/dl)	1.9-7.0	19.2	3.5	3.2
Sodium (mEq/l)	143-150	144	149	149
Potassium (mEq/l)	3.2-5.6	4.7	3.6	3.3
ALT activity (U/l)	5-62	78	ND	ND
Alk phos activity (U/l)	10-149	223	ND	ND
Total CO_2 (mEq/l)	17-26	14.5	ND	ND

Key: SUN = serum urea nitrogen, ALT = alanine aminotransferase, Alk phos = alkaline phosphatase, ND = not done.
*Dietary therapy was initiated on Day 14.

Additional Question

What is the most likely mineral composition of these radiodense uroliths?

Answer and Discussion

The advantages and disadvantages of medical urolith dissolution and surgical urolith removal can be more accurately assessed by predicting the mineral composition of uroliths. Magnesium ammonium phosphate (struvite), calcium oxalate, calcium phosphate, silica and cystine uroliths can all be radiodense (**Table 3**). It was surmised that this patient's uroliths were probably not composed of magnesium ammonium phosphate because of the breed and gender of the dog along with findings of aciduria and a negative bacterial culture. These findings suggested that the uroliths were not composed of struvite and therefore were not amenable to medical dissolution.

Treatment and Further Assessment

The uroliths were surgically removed following resolution of azotemia on the third day of hospitalization (**Table 1**). Postsurgical radiographs verified that all uroliths were removed. Quantitative analysis revealed that the uroliths were composed of 100% calcium oxalate monohydrate.

Further Questions

1. Outline an appropriate feeding plan (food and feeding method) for this dog.

Table 2. Urinalyses of a nine-year-old male Yorkshire terrier with radiodense urocystoliths.*

Factors**	Day 1	Day 14***	Day 28	Day 60
Specific gravity	1.015	1.025	1.008	1.015
pH	6.0	6.5	7.5	7.5
Protein†	1+	1+	Trace	Trace
RBC††	100-150	8-12	0	1-3
WBC††	12-16	2-4	1-2	0
Crystals†††	None	None	None	None
Aerobic bacterial culture	Neg	Neg	Neg	Neg

Key: RBC = red blood cells, WBC = white blood cells, Neg = negative.
*Samples collected by cystocentesis.
**Glucose, bilirubin and acetone were not detected in any specimen.
***Dietary therapy was initiated on Day 14.
†Values represent semiquantitative evaluations based on a scale of 0 to 4; urine volume was not considered.
††Per high power field (x450).
†††Per low power field (x100).

Table 3. The advantages and disadvantages of medical urolith dissolution and surgical urolith removal can be accurately assessed after the mineral composition of the urolith is known or predicted. This table lists factors used to predict mineral composition of radiodense uroliths when no uroliths are available for quantitative analysis vs. clinical findings in the patient described in this case.*

Factors	MAP	CaOx	CaP	Silica	Cystine
Typical urinary pH	No	Yes	Possible	Yes	Yes
Typical crystalluria	Possible	Possible	Possible	Possible	Possible
Typical urine culture	No	Yes	Yes	Yes	Yes
Typical radiographic density	Yes	Yes	Yes	Yes	Yes
Typical radiographic contour	Yes	Yes	Yes	No	No
Typical serum biochemistry values	Yes	Yes	Possible	Yes	Yes
Typical breed	No	Yes	Yes	No	No
Typical gender	No	Yes	Yes	Yes	Yes
Typical age	No	Yes	Yes	Yes	No

Key: MAP = magnesium ammonium phosphate, CaOx = calcium oxalate, CaP = calcium phosphate.
*Characteristics of urate uroliths were not considered because they are typically radiolucent.

2. Is reassessment important for this patient?

Answers and Discussion

1. Dietary therapy to prevent urolith recurrence was initiated at the time of suture removal. Dietary recommendations included reducing calcium, oxalic acid, protein and sodium, providing additional water and citrate and maintaining adequate phosphorus and magnesium. A moist veterinary therapeutic food (Prescription Diet u/d Canine[a]) was chosen because its nutrient content matches this nutrient profile. This food avoids excess dietary protein, oxalic acid and calcium, and promotes formation of less concentrated, alkaline urine. These dietary characteristics are helpful in preventing recurrence of calcium oxalate uroliths. The food was offered in two separate meals each day (one-fourth can twice daily, total 375 kcal [1.57 MJ]). The owners were also instructed to avoid feeding the dog any human foods, commercial dog treats and vitamin-mineral supplements (especially those containing vitamins C and D and calcium).
2. Regular reassessment is important because calcium oxalate uroliths commonly recur. Results of a retrospective study on the recurrence rate of calcium oxalate uroliths in dogs indicated that the rate of recurrence increased with the length of time that dogs were evaluated: 3% recurred after three months, 9% after six months, 35% after one year, 42% after two years and 48% after three years. This dog should be examined (i.e., urinalysis, survey abdominal radiography) at regular intervals to evaluate efficacy of medical therapy and to detect uroliths while they are small enough to remove with nonsurgical techniques. This patient should also be evaluated for hyperadrenocorticism because of the increased serum alkaline phosphatase activity. Glucocorticoid administration and hyperadrenocorticism are associated with hypercalciuria and increase the risk for calcium oxalate urolith formation.

Progress Notes

Table 2 summarizes the urinalysis results following six weeks of dietary management. Prescription Diet u/d Canine was successful in promoting less concentrated, alkaline urine in this dog. Reassessment every three to six months was recommended to the owner.

Endnote

a. Hill's Pet Nutrition Inc., Topeka, KS, USA.

Bibliography

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