Chapter 39

Canine Purine Urolithiasis: Causes, Detection, Management and Prevention

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"We should provide the type of medical care that we would desire if we were the patient rather than the doctor."
Carl A. Osborne

TERMINOLOGY

Purines are catabolites derived from DNA and RNA. They include adenine, guanine, hypoxanthine, xanthine, anhydrous uric acid, uric acid monohydrate, uric acid dihydrate, salts of uric acid (e.g., ammonium urate, sodium urate, calcium sodium urate) and in most mammals, allantoin. Each of these catabolites may behave differently.

PREVALENCE AND MINERAL COMPOSITION

Purine uroliths (ammonium urate, sodium urate, calcium urate, uric acid, xanthine, etc.) accounted for 6.4% (22,412 of 350,803) of all canine uroliths submitted to the Minnesota Urolith Center from 1981 to 2007 (Table 38-8), and 4.97% (2,020 of 40,612) of all canine uroliths analyzed in 2007. Purines accounted for 13.3% of all upper tract uroliths analyzed at the Minnesota Urolith Center from 1981 to 2006 (Table 38-9). Most dogs with xanthine uroliths had a history of treatment with allopurinol. Purines composed 23% of uroliths retrieved from dogs less than 12 months old. The mean age of dogs at the time of ammonium urate urolith retrieval was approximately four years (range one month to 17 years). The mean age of dogs at the time of sodium urate and calcium urate urolith retrieval was also approximately four years (range six months to 14 years). The mean age of dogs at the time of uric acid urolith retrieval was three years (range one month to 12 years). The mean age at the time of xanthine urolith retrieval was approximately five years (range one and one-half to nine years). Males were affected more often than females with ammonium urate (90 vs. 10%), sodium and calcium urate (99 vs. 1%), uric acid (88 vs. 12%) and xanthine (81 vs. 19%) uroliths.

In our series, 66 different breeds were affected with ammonium urate uroliths including Dalmatians (61%), miniature schnauzers (7%), Yorkshire terriers (5%), Shih Tzus (4%) and English bulldogs (4%). Twelve different breeds had sodium and

Table 39-1. Common characteristics of canine purine uroliths.

Chemical names	**Formulas**
Ammonium acid urate	$C_5H_3N_4O_3NH_4•H_2O$
Sodium acid urate	$C_5H_3N_4O_3Na•H_2O$
Uric acid	$C_5H_4N_4O_3•2H_2O$
Xanthine	$C_5H_4N_4O_2$

Some variations in mineral composition
Ammonium urate only
Sodium calcium urate
Sodium urate only
Uric acid only
Xanthine only
Ammonium urate mixed with variable quantities of sodium urate, or sodium and calcium urate, magnesium ammonium phosphate and/or calcium oxalate
Sodium and calcium oxalate
Xanthine and uric acid

Physical characteristics
Color: Light or dark brown, brown-green
Shape: Variable. Usually round or ovoid in urinary bladder, may assume shape of renal pelvis (funnel shaped), may assume jackstone appearance. Usually smooth, occasionally irregular or rough.
Nuclei: Nuclei and concentric laminations are common.
Density: Usually dense and brittle. Radiographically, purine uroliths have marginal radiodensity compared with soft tissue. Some may be radiolucent.
Number: Single or multiple
Location: May be located in kidneys, ureters, urinary bladder (most common) and/or urethra.
Size: Usually small (1 mm to 1 cm in diameter), occasionally large (more than 1 cm)

Prevalence
Approximately 5 to 6% of all canine uroliths. Approximately 13% of canine nephroliths.
May be recurrent.

Characteristics of affected canine patients
In Dalmatian dogs, most common in males.
Mean age at diagnosis is four years (range <1 to >17 years).
Most commonly observed in Dalmatian dogs, English bulldogs, miniature schnauzers, Yorkshire terriers and Shih Tzus.

calcium urate uroliths; however, these uroliths were primarily encountered in Dalmatians (92%) and English bulldogs (4%). Six different breeds had uric acid uroliths; Dalmatians were affected most commonly (80%). Five different breeds had xanthine uroliths, including Dalmatians (56%) and English bulldogs (35%). Ammonium urate (97%), sodium and calcium urate (96%), uric acid (100%) and xanthine (94%) uroliths were more commonly removed from the lower urinary tract than the upper urinary tract.

Ammonium urate, sodium and calcium urate and uric acid uroliths typically appear as multiple, small, smooth, hard, round or ovoid structures with a characteristic brown-green color (**Table 39-1**). However, the physical appearance of urate uroliths may vary depending on the presence and quantity of different mineral components, the quantity of matrix they contain, the site(s) of their formation and growth and whether or not they are associated with concurrent urinary tract disorders. Rarely, they form jackstones. Examination of cross sections of urate uroliths frequently reveals concentric laminations and nuclei located in the geographic center of the urolith.

ETIOPATHOGENESIS AND RISK FACTORS

Applied Biochemistry: Uric Acid Metabolism

Uric acid is one of several biodegradation products of purine nucleotide metabolism (**Figure 39-1**) (Foreman, 1984; Gutman, 1964; Greene et al, 1969; Williams and Wilson, 1990; Wyngaarden and Holmes, 1978). Purines are made up of three groups of compounds: 1) oxypurines (hypoxanthine, xanthine, uric acid and allantoin), 2) aminopurines (adenine, guanine) and 3) methylpurines (caffeine, theophylline and theobromine). In most dogs and cats, allantoin is the major metabolic end product, and it is the most soluble of the purine metabolic products excreted in urine (Bartges et al, 1992; Cohen et al, 1965; Giesecke and Stangassinger, 1990; Roch-Ramel and Peters, 1978). Whereas uric acid provides a means for nitrogen excretion in some animals (reptiles, birds, etc.), mammals excrete nitrogen in the form of urea (ureotelics). Because people and apes lack the enzyme uricase (urate oxidase), they cannot metabolize uric acid into allantoin. It has been estimated that the serum uric acid level of people is up to 100 times greater than serum creatinine concentrations in other mammals (Rafey et al, 2003).

The serum concentration of uric acid is derived from two sources: 1) exogenously from food and 2) endogenously from de novo purine biosynthesis, involving nucleic acid turnover and production from non-purine precursors. Purine synthesis occurs in the liver and involves recycling of guanine and hypoxanthine. In people, excess nucleotides are converted to xanthine and then uric acid via xanthine oxidase (Asplin, 1996). In most dogs and cats, excess uric acid is converted to allantoin via the hepatic enzyme uricase. Allantoin is highly soluble in urine, whereas uric acid and xanthine are not. Therefore, people are at greater risk for uric acid urolithiasis than most dogs and cats (Cameron and Sakhaee, 2007). Tissue catabolism or consumption of foods high in purine content may increase purine catabolism. In people, consumption of high-purine foods can cause as much as a 50% increase in urinary excretion of uric acid compared to consumption of a purine-free diet (Fellstrom et al, 1983).

In people, it has been estimated that approximately one-third of excess uric acid is eliminated by way of the intestinal tract (Sorensen, 1965). The kidneys eliminate the remainder. Although the mechanisms involved in glomerular filtration, renal tubular absorption and renal tubular secretion of uric acid have not yet been completely defined, it appears that all three mechanisms are involved (Cameron and Sakhaee, 2007). It has been proposed that glomeruli freely filter uric acid. The proximal tubules actively reabsorb approximately 99% of filtered uric acid. Subsequently, the renal tubules secrete approximately 50% of the filtered uric acid, followed by 40% postsecretory reabsorption. The final uric acid excretion is approximately 10% (Cameron and Sakhaee, 2007).

Uric acid is a weak organic acid with an ionization constant (pKa) of 5.5. At a temperature of 37°C (98.6°F), human urine has a pKa of 5.35. Uric acid is less soluble than its base (urate) (Cameron and Sakhaee, 2007).

Uroliths composed of uric acid (anhydrous uric acid, uric acid dihydrate, sodium urate, ammonium urate) or xanthine form because urine is oversaturated with these substances (Brown and Purich, 1992; Finlayson, 1978; Porter, 1963; Smith, 1990). Ammonium urate (also known as ammonium acid urate and ammonium biurate) is the monobasic ammonium salt of uric acid. It is the most common naturally occurring purine urolith form observed in dogs (Osborne et al, 1995). Other naturally occurring purine uroliths include sodium urate (also known as sodium acid urate or monosodium urate), sodium calcium urate, potassium urate and uric acid dihydrate (Osborne et al, 1995).

Uric Acid, Sodium Urate and Ammonium Urate

Risk factors for urate lithogenesis in dogs include: 1) increased renal excretion and urine concentration of uric acid, 2) increased renal excretion or renal production of ammonium ions, 3) increased microbial production of ammonium ions, 4) aciduria, 5) formation of highly concentrated urine and 6) presence of promoters or absence of inhibitors of urate urolith formation (Kruger and Osborne, 1986). Genetic factors may be important because urate uroliths are common in certain breeds of dogs. For example, Dalmatian dogs and English bulldogs have an inherent predisposition to forming urate uroliths (See sections about Dalmatian and non-Dalmatian dogs below.) (Case et al, 1993; Sorenson and Ling, 1993). Dietary components may promote urate urolith formation in predisposed dogs because dietary purines may be digested, absorbed, incorporated into the body's purine pool and eventually excreted in urine (**Tables 39-2** and **39-3**). Thus, metabolism of dietary purines may result in oversaturation of urine with urate lithogenic substances (e.g., other related metabolites of uric acid). In studies of normal dogs, consumption of high-protein foods was associated with greater urine uric acid excretion and increased urine saturation with uric acid, sodium urate and ammonium urate, when compared with consumption of low-protein foods (Bartges et al, 1995, 1995a, 1995b). The same association was found in Dalmatian dogs (Giesecke and Tiemeyer, 1984; Lulich et al, 1995).

Xanthine

Xanthine is a product of purine metabolism and is converted to uric acid by the enzyme xanthine oxidase (Bartges et al, 1992; Parks and Granger, 1986). Hereditary xanthinuria is a rarely recognized disorder of people characterized by a deficiency of xanthine oxidase (Fildes, 1989; Holmes et al, 1974; Kario et al, 1991; Kawachi et al, 1990; Landas et al, 1989; Mateos, 1987). Consequently, abnormal quantities of xanthine are excreted in urine as a major end product of purine metabolism. Because xanthine is the least soluble of the purines naturally excreted in urine, xanthinuria may be associated with formation of uroliths (Bartges et al, 1992; Fildes, 1989; Kario et al, 1991; Ling et al, 1991; Pyrah, 1979).

Naturally occurring xanthinuria and xanthine urolithiasis have been reported to occur in a few dogs (Kidder and Chivers, 1968; Kucera et al, 1997). Xanthine urolithiasis was reported in a family of cavalier King Charles spaniels (van Zuilen et al, 1997).

Uroliths whose composition was at least 70% xanthine

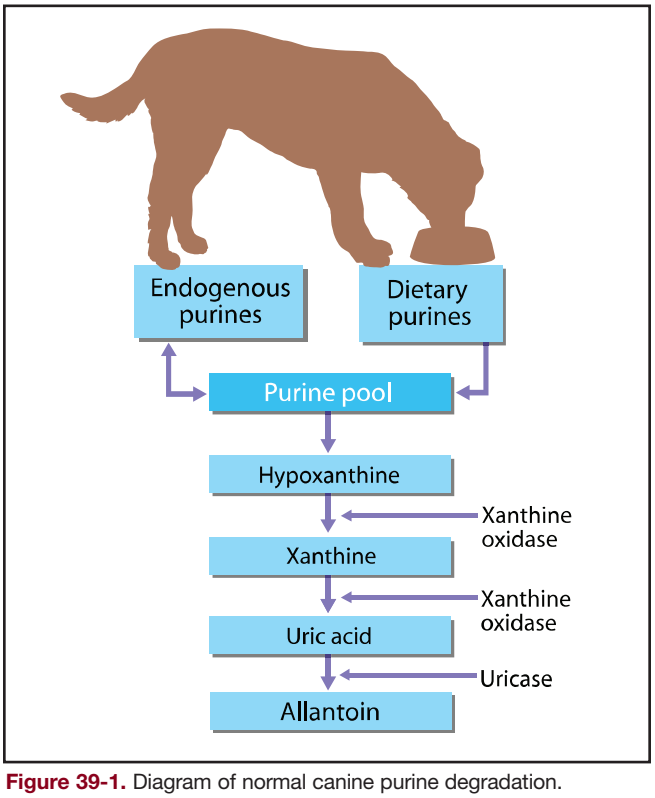

Figure 39-1. Diagram of normal canine purine degradation.

Table 39-2. Some potential risk factors for canine purine uroliths.

Food	Urine	Metabolic	Drugs
High purine content (**Table 39-3.**)	Hyperuricuria	Males	Urine acidifiers
Acidifying potential	Hyperammonuria	Breed	Salicylates
Low moisture content	Acidic pH	Dalmatians	Chemotherapeutic agents (especially 6-mercaptopurine)
Ascorbic acid?	Urine concentration	English bulldogs	
	Urine retention	Miniature schnauzers	
	Urease-producing microburia	Yorkshire terriers	
	Increased promoters?	Shih Tzus	
	Decreased inhibitors?	Hyperuricemia	
		Hyperammonuria	
		Hepatic dysfunction	
		Neoplasia with rapid cell destruction	

Table 39-3. Purine content of selected foods.

Foods to avoid (high purine concentration)	Foods to use sparingly (moderately high purine concentration)	Foods that can be fed (negligible purine concentration)
Anchovies	Asparagus	Breads (whole grain cereal products)
Brain	Cauliflower	Butter and fats
Clams	Fish*	Cheese
Goose	Legumes (beans and peas)	Eggs
Gravies	Lentils	Fruits and fruit juices
Heart	Meats	Gelatin
Kidney	Mushrooms	Milk
Liver	Spinach	Nuts
Mackerel		Refined cereals
Meat extracts including bouillon		Sugars
Mussels		Vegetable soups
Oysters		Cream soups
Salmon		Vegetables**
Sardines		Water
Scallops		
Shrimp		
Sweetbreads		
Tuna		
Yeast (baker's and brewer's)		

*Except those listed in the first column.
**Except those listed in the second column.

accounted for less than 0.1% (362 of 373,612) of all canine uroliths submitted to the Minnesota Urolith Center from 1998 to 2007. Almost all canine xanthine uroliths in our series were obtained from dogs treated with varying doses of allopurinol given orally.

At the Minnesota Urolith Center, the mean age of dogs at the time of xanthine urolith retrieval was five years (range = three to 168 months). In this regard, the cavalier King Charles spaniel breed is an exception inasmuch that naturally occurring xanthine uroliths have been recognized when these dogs were less than one year of age.

Male dogs (86%) were affected more often than females (9%) in our series (5% were of unknown gender). Of these dogs, 190 were castrated males (53%), 122 were intact males (34%), 23 were spayed females (6%), 11 were intact females (3%) and 16 were of unknown gender (4%). With the apparent exception of cavalier King Charles spaniels (six dogs in our series), the predominance of allopurinol-induced xanthine uroliths in males has also been observed by others (Bartges et al, 1993; Ling et al, 1991). In a report of 38 xanthine-containing uroliths, 36 occurred in males and two occurred in females (Ling et al, 1991).

At our center, 40 different breeds were affected including Dalmatians (50%), mixed breed (12%), English bulldogs (4%), miniature schnauzers (4%), German shepherd dogs (2%), boxers (2%) and cavalier King Charles spaniels (six dogs = 2%). Similar observations have been made by others (Ling et al, 1991). In one report, of 38 xanthine-containing uroliths, 30 were found in Dalmatians, two were found in miniature/toy poodles and one was retrieved from a Shih Tzu (Ling et al, 1991). The affected breeds for five xanthine specimens were apparently unknown. Of the 362 uroliths composed of xanthine in our series, 316 dogs were given allopurinol, 10 were given fluoroquinolones and two received sulfadiazine (34 uroliths were submitted without a drug history).

The most common cause of xanthine uroliths in dogs is formation secondary to therapy with allopurinol. Allopurinol rapidly binds to and inhibits the action of xanthine oxidase, thereby decreasing conversion of hypoxanthine to xanthine and xanthine to uric acid. The result is a reduction of serum and urine concentrations of uric acid with a reciprocal increase in serum and urine concentrations of xanthine (**Figure 39-2**). Administration of allopurinol at high doses, especially with concurrent consumption of high purine foods, will result in formation of xanthine uroliths (**Figure 39-3**).

Dalmatian Dogs

Dalmatian dogs are predisposed to urate uroliths because their ability to oxidize uric acid to allantoin is intermediate between that of people and many non-Dalmatian dogs (Bartges et al, 1994; Duncan and Curtiss, 1971; Friedman and Byers, 1948). This characteristic is due to an autosomal recessive trait (Safra et al, 2005). People normally have a serum uric acid concentration of approximately 3 to 7 mg/dl, and excrete approximately 500 to 700 mg of uric acid in their urine per day (Williams and Wilson, 1990). Of all non-Dalmatian dogs studied to date, most have a serum uric acid concentration of less than 0.5 mg/dl, and excrete approximately 10 to 60 mg of uric acid in their urine per day. Dalmatian dogs have a serum uric acid concentration that is two to four times that of non-Dalmatian dogs and excrete more than 400 to 600 mg of uric acid in their urine per day (Bovee, 1984; Ling et al, 1997).

Studies of the fate of uric acid in Dalmatian dogs have revealed unique hepatic and renal pathways of metabolism (Friedman and Byers, 1948; Duncan and Curtiss, 1971). Of these two metabolic sites, reciprocal allogenic renal and hepat-

ic transplantations between Dalmatian and non-Dalmatian dogs indicate that the hepatic mechanism is quantitatively the more significant (Cohn et al, 1965; Kuster et al, 1972). The liver of Dalmatian dogs does not completely oxidize available uric acid, even though it contains sufficient concentrations of uricase. Compared with non-Dalmatian dogs, Dalmatian dogs convert uric acid to allantoin at a reduced rate (Benedetti et al, 1997; Kocken et al, 1996; Kuster et al, 1972). It has been hypothesized that their hepatic cellular membranes are partially impermeable to uric acid (Harvey and Christensen, 1964; Tiemeyer et al, 1986).

The proximal renal tubules of Dalmatian dogs reabsorb less uric acid than those of non-Dalmatian dogs; a small amount is secreted by the distal tubules (Kessler et al, 1959). In non-Dalmatian dogs, 98 to 100% of the uric acid in the glomerular filtrate is reabsorbed by the proximal tubules and returned to the liver for further metabolism (Kessler et al, 1959; Roch-Ramel et al, 1978). The distal tubules are thought to secrete uric acid in the urine of non-Dalmatian dogs (Foreman, 1984; Mudge et al, 1968; Nolan and Foulkes, 1971; Tiemeyer et al, 1986).

The definitive mechanism(s) of urate urolith formation in Dalmatian dogs is unknown. Increased urinary excretion of uric acid is a risk factor rather than a primary cause. Urate uroliths are recognized 13 times more commonly in males than females; the average age of dogs when uroliths are diagnosed is 4.5 years (Albasan et al, 2005; Case et al, 1993). Although all Dalmatian dogs excrete relatively high quantities of uric acid in their urine, apparently only a small percentage forms urate uroliths (Case et al, 1993; Albasan et al, 2005). At one time, it was thought that urolith-forming Dalmatian dogs did not excrete greater quantities of uric acid in their urine than non-urolith-forming Dalmatian dogs. However, further studies revealed that insensitive methods for measuring urine uric acid concentration were responsible for this erroneous conclusion. When steps are taken to ensure that urine uric acid remains in solution, differences in urine uric acid concentrations between non-urolith-forming Dalmatian and urolith-forming Dalmatian dogs may be expected (Felice et al, 1990; Schaible, 1986).

Urate uroliths commonly affect Dalmatian dogs; however, not all uroliths formed by Dalmatian dogs are composed of ammonium urate. For example, of 2,020 uroliths formed by Dalmatian dogs, 93% were composed of purines (ammonium urate, sodium urate, uric acid and xanthine), 3% were of mixed composition, 1% were struvite, 1% were calcium oxalate, 2% were compound uroliths and less than 1% were cystine.

Non-Dalmatian Dogs

Comparatively little is known about urate lithogenesis in non-Dalmatian dogs that do not have portal vascular anomalies. Many breeds of dogs are affected with urate urolithiasis. Although urate uroliths are commonly encountered in Dalmatian dogs, approximately 30 to 60% of all canine urate uroliths analyzed by quantitative methods are found in other breeds (Bovee and Mcquire, 1984; Kruger and Osborne, 1986; Osborne et al, 1995). English bulldogs have a significantly higher incidence of urate urolithiasis compared with other breeds (Bartges et al, 1994). Clinical evaluation of eight male English bulldogs with confirmed ammonium urate urocystoliths revealed mild elevations in serum uric acid concentration. The size of their livers was normal, as was the serum concentration of hepatic enzymes, blood concentration of ammo-

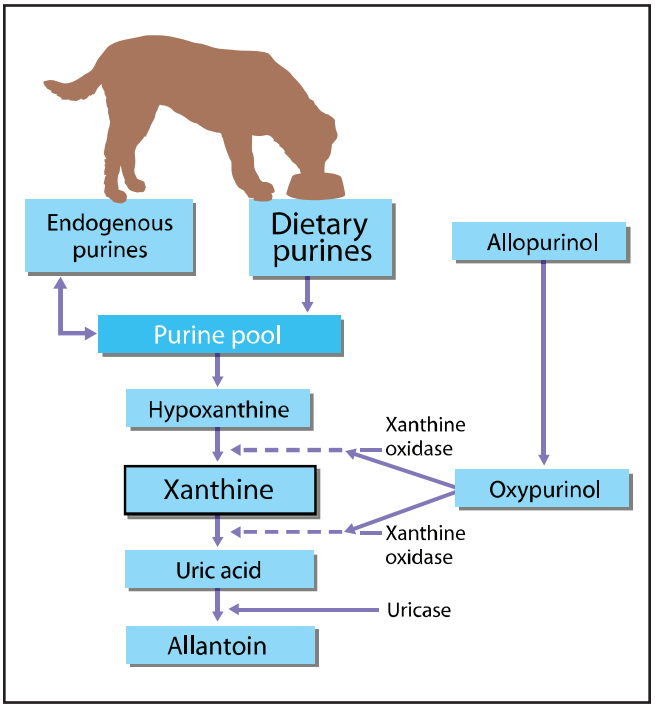

Figure 39-2. Diagram of purine degradation in dogs fed a maintenance food and given allopurinol.

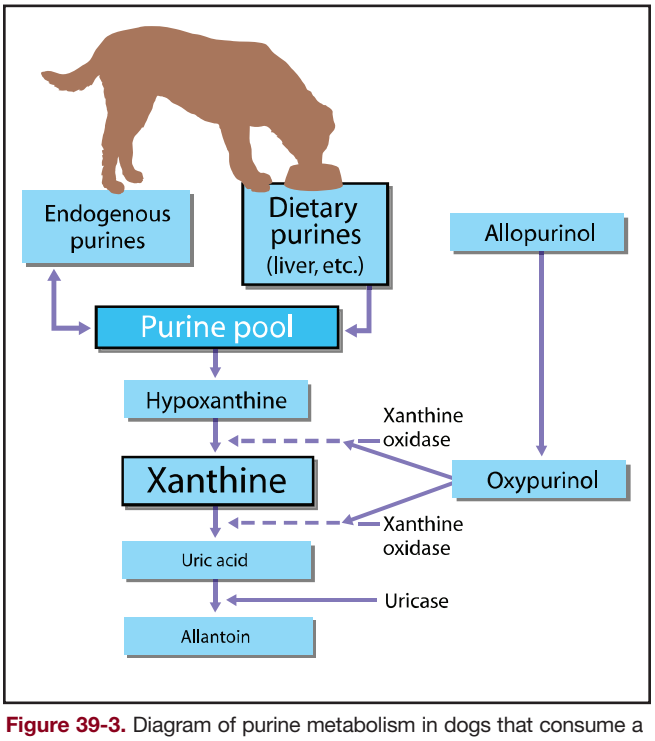

Figure 39-3. Diagram of purine metabolism in dogs that consume a purine-rich food and are given allopurinol.

nia and bromsulphalein retention. Other non-Dalmatian breeds that appear to have a significantly higher incidence of urate urolithiasis based on quantitative urolith analyses are miniature schnauzers, Shih Tzus and Yorkshire terriers (Osborne et al, 1995).

Urate uroliths from non-Dalmatian dogs have been recognized most frequently in males. Uroliths have been detected throughout the lifespan of affected dogs; however, they were most frequently detected in dogs three to six years of age.

Regardless of cause, severe hepatic dysfunction may predispose dogs to urate lithogenesis, especially ammonium urate uroliths. Observations and evidence derived from experimental models suggest that prolonged consumption of foods with markedly restricted levels of protein may be associated with formation of urate uroliths in dogs (Kruger and Osborne, 1986). Biochemical and histologic evaluation of these dogs suggests that long-term consumption of foods severely restricted in protein may induce hepatocellular dysfunction and concomitant hyperuricemia. Hepatic cirrhosis has also been associated with urate uroliths in dogs and other species (Rothuizen and van den Ingh, 1980). However, foods with severely restricted protein levels and other causes of hepatic dysfunction have been uncommon causes of ammonium urate urolithiasis. Nonetheless, their significance relative to ammonium urate lithogenesis deserves further study.

Dogs with Portal Vascular Anomalies or Hepatic Microvascular Dysplasia

Ammonium urate uroliths have frequently been observed in dogs with portal vascular anomalies. These uroliths occur in males and females and usually have been detected before dogs reach three years of age (Rothuizen and van den Ingh, 1980; Marretta et al, 1981; Hardy and Klausner, 1983; Kruger and Osborne, 1986).

Direct communication between the portal and systemic vasculature shunts blood around the liver. Severe hepatic atrophy and diminished hepatic function may occur as a result. Hepatic dysfunction in turn is associated with reduced hepatic conversion of uric acid to allantoin and reduced conversion of ammonia to urea. The predisposition of dogs with portal vascular anomalies to urate urolithiasis is probably associated with concomitant hyperuricemia, hyperammonemia, hyperuricuria and hyperammonuria (Kruger and Osborne, 1986; Hardy and Klausner, 1983). Serum uric acid concentrations in 15 dogs with portal vascular anomalies evaluated at the University of Minnesota Veterinary Teaching Hospital were increased (values ranged from 1.2 to 4.0 mg/dl) (Hardy and Klausner, 1983). Concurrent hyperuricuria, hyperammonuria, hyperuricemia and hyperammonemia were observed in an 18-month-old Bernese mountain dog with recurrent ammonium urate uroliths associated with a portal vascular anomaly (Kruger and Osborne, 1986). This dog had a urine uric acid concentration of 42 mg/kg body weight/day and a urine ammonia concentration of 3.2 mM/kg body weight/day while the dog was fed a protein-restricted food. Hyperuricuria, hyperammonuria, hyperuricemia and hyperammonemia were observed in three miniature schnauzers with ammonium urate uroliths associated with portal vascular anomalies. In these dogs, urine uric acid concentrations were approximately 50 mg/kg body weight/day and urine ammonia concentrations were approximately 1.5 mM/kg body weight/day while the dogs consumed a growth-type food. When two of these dogs consumed a purine-restricted food, urine uric acid concentrations were approximately 17 mg/kg body weight/day and urine ammonia concentrations were approximately 0.6 mM/kg body weight/day.

Not all dogs with portal systemic anomalies develop concurrent ammonium urate urolithiasis. Definition and characterization of other factors responsible for promoting or inhibiting urate lithogenesis in affected dogs require further investigation.

We have observed urate urocystolith formation in miniature schnauzers and Yorkshire terriers with hepatic microvascular dysplasia. Dogs with this disorder do not have macrovascular shunts. Rather, intrahepatic microvascular shunting apparently occurs. Clinical signs and biochemical abnormalities are similar to those seen in dogs with macroscopic vascular shunts. When affected dogs consumed a growth-type food, urinary uric acid excretion was approximately 30 mg/kg body weight/24 hours, urinary ammonia excretion was approximately 1.25 mmol/kg body weight/24 hours and urinary pH was less than 6.5 pH units. When dogs were fed a purine-restricted food, urinary uric acid excretion was approximately 16 mg/kg body weight/24 hours, urinary ammonia excretion was approximately 0.5 mmol/kg body weight/24 hours and urinary pH was greater than 7.0 pH units.

Not all dogs with portal systemic anomalies or hepatic microvascular dysplasia develop concurrent ammonium urate urolithiasis. Definition and characterization of other factors responsible for promoting or inhibiting urate lithogenesis in affected dogs require further investigation.

Dietary Risk Factors

Concentrations of lithogenic substances in urine depend on urine volume. Because commercial dry foods are associated with production of less urine compared with moist foods, consumption of dry foods is likely a risk factor for urate urolith formation.

Dalmatian dogs consuming foods containing more than 20% dry matter (DM) protein, and protein sources high in purines and purine precursors (**Table 39-3**) are at increased risk for urate lithogenesis. Because urate uroliths associated with portal vascular anomalies are often diagnosed in dogs less than one year of age, it is probable that they were consuming foods with increased protein content.

Urine acidity is a risk factor for urate lithogenesis because the solubility of most purines, especially ammonium urate, is pH-dependent. Therefore, consumption of foods that promote aciduria (e.g., high-protein foods or those with other acidifying ingredients) may be a risk factor.

BIOLOGIC BEHAVIOR

Purine uroliths have the potential to undergo spontaneous dis-

solution, remain active (grow) or become inactive (remain unchanged). Although spontaneous dissolution of non-urate-containing uroliths has occasionally been observed, spontaneous dissolution of urate uroliths has apparently not been reported.

Recurrence of urate uroliths may be influenced by several factors including: 1) persistence of underlying causes, 2) incomplete removal of all uroliths from the urinary tract at the time of lithotripsy or surgery, 3) persistence or recurrence of urinary tract infections (UTIs) with urease-producing bacteria and/or 4) failure to comply with therapeutic or prophylactic recommendations. Frequent recurrence of urate uroliths is not surprising considering the persistence of disorders associated with urate urolithiasis.

A relatively high incidence of recurrence following surgical removal is a unique characteristic of urate urolithiasis in Dalmatian and non-Dalmatian dogs. In several studies using qualitative methods of urolith analysis, recurrence was reported in 33 to 50% of dogs with urate uroliths (Brown et al, 1977; Finco et al, 1970; Weaver, 1970). In these dogs, uroliths generally recurred within one year after diagnosis and treatment. Recurrence of urate urolithiasis in non-Dalmatian dogs with portal vascular anomalies also appears to be similar (Marretta et al, 1981; Hardy and Klausner, 1983). In dogs, recurrence of urolithiasis with uroliths composed of minerals other than those present during the initial episode is uncommon. However, uroliths predominantly composed of minerals other than ammonium urate, sodium urate or uric acid may form in canine patients originally affected with urate uroliths (Porter, 1963; Brown et al, 1977).

KEY NUTRITIONAL FACTORS

The key nutritional factors for foods intended for dissolution and prevention of urate uroliths in dogs are discussed below and summarized in **Table 39-4**.

Water

Concentrations of lithogenic substances in urine depend on urine volume. Augmenting urine volume with the goal of decreasing urine uric acid and ammonium concentrations and enhancing urine flow through the excretory pathway is an important strategy. Feeding moist foods is recommended because commercial dry foods are associated with production of a smaller volume of more concentrated urine. Clients should encourage water intake to achieve a urine specific gravity less than 1.020. (See Assess and Determine the Feeding Method: Urate Urolith Dissolution below.)

Sodium chloride supplementation is sometimes recommended to increase urine volume. However, increased sodium intake poses other risks to urate urolithiasis patients. (See Sodium below.) It is noteworthy that sodium chloride given orally to normal human volunteers for 10 days did not alter urine uric acid concentration (Breslau and Pak, 1983).

Attempts at increasing urine volume through administration of diuretic drugs have been reported in people. Long-term administration (up to three years) of hydrochlorothiazide to human patients with uroliths containing calcium salts resulted in increased serum and urine uric acid concentrations (Pak et al, 1978).

Table 39-4. Key nutritional factors for foods for dissolution and prevention of canine purine uroliths.

Factors	Dietary recommendations
Water	Water intake should be encouraged to achieve a urine specific gravity <1.020
Protein and purines	Restrict dietary protein to 10 to 18% dry matter (DM) Restrict dietary purine: the first three non-water ingredients on product label ingredient panel should be low in purines (**Table 39-3**)
Sodium	Moderate sodium restriction (<0.3% DM) Avoid sodium supplements
Urinary pH	Feed a food that maintains an alkaline urine (urinary pH = 7.1 to 7.5)

Protein and Purines

Dalmatian dogs consuming foods containing more than 20% DM protein and protein sources high in purines and purine precursors (**Table 39-3**) are at increased risk for urate lithogenesis. We have observed formation of purine uroliths in some dogs consuming lesser amounts of dietary purines; therefore, other factors are apparently involved.

The range of dietary protein associated with urate urolith formation in dogs with portal vascular anomalies is unknown. In these dogs, the degree of urine saturation with purines is probably related, at least in part, to the degree of vascular shunting and to dietary protein consumption. Because urate uroliths associated with portal vascular anomalies are often diagnosed in dogs less than one year of age, it is probable that these dogs were consuming foods with increased protein content. Growth-type foods are typically higher in protein than foods formulated for adult maintenance.

High-protein foods, besides being potential sources of urine ammonium, purines and purine precursors, can also induce aciduria. Urine acidity is a risk factor for urate lithogenesis because the solubility of most purines, especially ammonium urate, is pH-dependent. On the other hand, protein restriction, to the degree that would be found in a restricted-protein, urate-litholytic food, can impair urine concentrating ability (by decreasing renal medullary urea concentration), making use of additional diuretic agents unnecessary. Furthermore, feeding low-protein, low-purine foods to patients with ammonium urate uroliths, in combination with appropriate allopurinol therapy, has resulted in urolith dissolution (Bartges et al, 1994; Osborne et al, 1986, 1995). Therefore, for urate litholytic foods, or to aid in the prevention of purine lithogenesis, recommend foods that restrict dietary protein to 10 to 18% DM. The minimum recommended allowance for protein in foods for healthy adult dogs is 10% DM (NRC, 2006). Also, if possible, clients should avoid feeding foods with a high purine content. Ideally,

at least the first three non-water ingredients in the ingredient panel on a food label should be low in purines (**Table 39-3**).

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. Also, for the same reason, if oral urine alkalinizing agents are used, potassium citrate may be a better choice than sodium bicarbonate. Besides these risks, supplemental sodium sources may contribute to hypertension in salt-sensitive dogs.

Moderate restriction of dietary sodium (<0.3% DM) in urate litholytic and prevention foods is unlikely to be harmful and may be helpful. 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).

Urinary pH

Under physiologic conditions associated with alkaluria, urine contains low concentrations of ammonia and ammonium ions (Hande et al, 1984). The specific goal of treatment with a urate litholytic food or an oral urine alkalinizing agent (e.g., potassium citrate) is to maintain a urinary pH within a range of 7.1 to 7.5. Urinary pH values greater than 7.5 should be avoided until it is determined whether or not they provide a significant risk factor for formation of calcium phosphate uroliths. Deposition of a layer of calcium phosphate crystals around existing urate uroliths may impede urolith dissolution. Potassium citrate apparently prevents acid metabolites from increasing renal tubular production of ammonia.

FEEDING PLAN

Current recommendations for dissolution of canine ammonium urate uroliths include a combination of: 1) feeding a litholytic food, 2) formation of an increased quantity of less concentrated urine, 3) alkalinization of urine, 4) administration of xanthine oxidase inhibitors (i.e., allopurinol) and 5) eradication or control of UTIs (Bartges et al, 1992, 1994; Ling, 1995; Lulich et al, 1995; Osborne et al, 1986). **Table 39-5** summarizes the recommendations for dietary and medical dissolution and prevention of canine ammonium acid urate uroliths.

Assess and Select the Food: Urate Urolith Dissolution

Urate litholytic foods have been used most successfully in patients with normal portal vasculature. However, occasional successes have been reported to occur in patients with portal vascular anomalies (Bartges et al, 1994; Osborne et al, 2000). Consumption of a properly formulated urate litholytic food by healthy and urate urolith forming dogs resulted in marked reductions in urine uric acid and ammonia excretion (Lulich et al, 1995; Bartges et al, 1995). **Table 39-6** lists selected commercial veterinary therapeutic foods used for urate urolith dissolution (and prevention) and compares their key nutritional factor content with recommended levels. Select a food that most closely matches the recommended levels of key nutritional factors. Recommend that clients avoid feeding inappropriate amounts of treats or vitamin-mineral supplements. Check the product label or contact the manufacturer to see if the product is approved by the Association of American Feed Control Officials (AAFCO) or some other credible regulatory agency for long-term feeding to adult dogs (**Box 39-1**).

Encourage clients to increase water consumption of patients with urate urolithiasis. When possible, recommend they feed a moist food. Although understandably difficult in some patients, fluid intake should be encouraged throughout the day to help promote a constantly high urine volume. Clients should ensure water is readily available and is not too cold or warm.

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.

Dogs Without Portal Vascular Anomalies

At the Minnesota Urolith Center, 25 dogs with ammonium urate uroliths were treated with dietary (urate litholytic food) and allopurinol therapy. Complete dissolution occurred in nine dogs (36%), partial dissolution in eight dogs (32%) and no dissolution in eight dogs (32%). A similar dissolution protocol in seven dogs with sodium urate uroliths resulted in complete dissolution in two dogs (29%), partial dissolution in three dogs (42%) and no dissolution in two dogs (29%) (Bartges et al, 1994). Inability to dissolve urate uroliths was usually associated with formation of xanthine. In some dogs with partial urolith dissolution, the remaining uroliths were completely retrieved using voiding urohydropropulsion (Figure 38-5 and Table 38-7) (Lulich et al, 1993) or catheter-assisted retrieval (Figure 38-6) (Lulich and Osborne, 1992). The mean time for urate urolith dissolution in 11 dogs was 3.5 months (median one month, range one to 18 months). Using the above protocol, a nephrolith presumed to be composed of urate was dissolved in nine months in a six-year-old, neutered female English bulldog.

Dogs with Portal Vascular Anomalies

Few studies have been reported about the biologic behavior of ammonium urate uroliths in dogs with portal vascular anomalies. It is logical to hypothesize that elimination of hyperuricuria and reduction of urine ammonium concentration following surgical correction of anomalous shunts would result in sponta-

Table 39-5. Summary of recommendations for dietary and medical dissolution and prevention of canine purine uroliths.

1. Perform appropriate diagnostic studies, including complete urinalysis, quantitative urine culture and diagnostic radiography. Determine precise location, size and number of uroliths. The size and number of uroliths are not a reliable index of probable therapeutic efficacy.
2. If uroliths are available, determine their mineral composition. If unavailable, determine their composition by evaluating appropriate clinical data.
3. Consider surgical correction if uroliths obstruct urine outflow. Small urocystoliths may be removed by voiding urohydropropulsion (Figure 38-5 and Table 38-7) or lithotripsy.
4. Determine baseline pretreatment serum uric acid concentrations and (if possible) 24-hour excretion of urine uric acid.
5. Initiate therapy with a purine litholytic food (**Table 39-6**). Other foods or supplements should not be fed to the patient. Reduction in serum urea nitrogen concentration (usually <10 mg/dl) suggests compliance with dietary recommendations.
6. Initiate therapy with allopurinol at a dosage of 30 mg/kg body weight/day divided into two equal subdoses (azotemic patients require a lesser dose). Xanthine uroliths may form if foods containing excessive purines are fed or if excessive allopurinol is given.
7. If necessary, administer potassium citrate orally to eliminate aciduria. Strive for a urinary pH of approximately 7.1 to 7.5.
8. If necessary, eradicate or control urinary tract infections with appropriate antimicrobial agents. Maintain antimicrobial therapy during and for an appropriate period after purine urolith dissolution.
9. Devise a protocol to monitor efficacy of therapy.
    a. Try to avoid diagnostic followup studies that require urinary tract catheterization. If they are required, give appropriate peri-catheterization antimicrobial agents to prevent iatrogenic urinary tract infection.
    b. Perform serial urinalyses. Determination of urinary pH, urine specific gravity and microscopic examination of sediment for urate crystals are especially important. Remember, crystals formed in urine stored at room or refrigeration temperatures may represent in vitro artifacts.
    c. Serially evaluate serum uric acid concentrations and (if possible) fractional excretion of urine uric acid.
    d. Evaluate the location(s), number, size, density and shape of uroliths at monthly intervals. Intravenous urography or ultrasonography may be used for radiolucent uroliths located in the kidneys, ureters or urinary bladder. Retrograde contrast urethrocystography may be required for radiolucent uroliths in the bladder and urethra.
    e. If necessary, perform quantitative urine cultures. They are especially important in patients that are infected before therapy and in patients that are catheterized during therapy.
10. Continue the litholytic food, allopurinol and alkalinizing therapy for approximately one month following the disappearance of uroliths as detected by radiography.
11. Prevention. Purine uroliths are highly recurrent. Preventive therapy should be directed at minimizing urine concentrations of ammonia and uric acid. This may be achieved by feeding a food low in protein that also promotes an alkaline urine (**Table 39-6**). The effectiveness of dietary management for the prevention of purine uroliths in dogs with portosystemic shunts is unknown. The long-term use of allopurinol is discouraged because of the potential for development of xanthine uroliths.

Table 39-6. Levels of key nutritional factors in selected veterinary therapeutic foods used for dissolution and to minimize recurrence of urate urolithiasis in dogs compared to recommended levels.*

Dry foods	**Protein (%)**	**Restricted purines (Yes/No)****	**Sodium (%)**	**Urinary pH*****
Recommended levels	**10-18**	**Yes**	**<0.3**	**7.1-7.5**
Hill's Prescription Diet u/d Canine	11.2	Yes	0.23	7.70
Medi-Cal Reduced Protein	13.7	Yes	0.2	na
Medi-Cal Renal LP	14.7	Yes	0.1	na
Medi-Cal Renal MP	18.4	Yes	0.1	na
Medi-Cal Vegetarian Formula	20.9	Yes	0.4	na
Purina Veterinary Diets NF KidNey Function	15.9	Yes	0.22	6.7-7.5
Purina Veterinary Diets HA HypoAllergenic	21.3	Yes	0.24	na
Royal Canin Veterinary Diets Vegetarian Formula	19.1	Yes	0.15	6.78
Moist foods	**Protein (%)**	**Restricted purines (Yes/No)****	**Sodium (%)**	**Urinary pH*****
Recommended levels	**10-18**	**Yes**	**<0.3**	**7.1-7.5**
Hill's Prescription Diet u/d Canine	13.3	Yes	0.28	7.4
Medi-Cal Reduced Protein	16.5	No	0.2	na
Medi-Cal Renal LP	16.8	No	0.1	na
Medi-Cal Renal MP	28.2	No	0.2	na
Medi-Cal Vegetarian Formula	26.4	Yes	0.5	na
Purina Veterinary Diets NF KidNey Function	16.5	No	0.24	6.7-7.5

Key: na = information not available from manufacturer.
*Manufacturers' published values; nutrients expressed as % dry matter; moist foods are best.
Restricted purines = products having low-purine ingredients (Table 39-3**) as the first three non-water ingredients on the ingredient panel of the product label.
***Protocols for measuring urinary pH may vary.

neous dissolution of uroliths composed primarily of ammonium urate. Appropriate clinical trials are needed to prove or disprove this hypothesis (Kruger and Osborne, 1986). Occasionally, success has been reported in dissolving urate uroliths in dogs with portal vascular anomalies. For example, dissolution of a urolith presumed to be composed of ammonium urate

Box 39-1. Nutritional Adequacy of Low-Protein Foods Recommended for Canine Patients with Urolithiasis.

A commercial veterinary therapeutic food that reduces urine concentration, produces alkaline urine and avoids excess levels of dietary protein, purines, calcium and phosphorus[a] is frequently recommended for management of several different types of canine uroliths. Some of these foods have very low protein content (10 to 11% [dry matter, DM]). This level of dietary protein is a concern for some veterinarians and their health care teams because it is less than the recommended dietary allowance for protein established by the Association of American Feed Control Officials (AAFCO) (minimum 18% DM for adult maintenance).

However, based on several criteria, these foods are nutritionally adequate for maintenance of adult, non-reproducing dogs. First, the National Research Council's minimum recommended allowance for foods for maintenance of healthy adult dogs is 10% DM. Second, many of these veterinary therapeutic foods have successfully completed AAFCO adult maintenance feeding trials (see product labels and published product information). In addition, protein digestibility in some of these low-protein foods approaches 100%, which means their essential amino acids are readily available to dogs. The final criterion is practical experience with these foods; some have been used successfully for long-term feeding of thousands of canine patients with urolithiasis.

ENDNOTE

a. Hill's Prescription Diet u/d Canine dry. Hill's Pet Nutrition, Inc., Topeka, KS, USA.

The Bibliography for **Box 39-1** can be found at www.markmorris.org.

occurred in a two-year-old female miniature schnauzer with a portal vascular anomaly. The dog was consuming a veterinary therapeutic food designed for treatment of renal failure.[a] The mechanisms involved were presumably decreased production of ammonium ions from urea and reduced formation of uric acid from dietary protein.

Likewise, a nephrolith in the right renal pelvis of a seven-year-old female malamute with a portal vascular anomaly disappeared while the dog consumed the same veterinary therapeutic food designed for treatment of renal failure.[a] A marked reduction of urine uric acid concentration was observed in a three-month-old female miniature schnauzer following surgical correction of an extrahepatic portacaval shunt. Furthermore, undersaturation of urine with ammonium urate and no recurrence of urolith formation were observed in two dogs with surgically uncorrectable portal vascular anomalies and ammonium urate uroliths. The dogs were fed a urate litholytic[b] food for prevention of recurrence of the uroliths and for management of hepatic encephalopathy.

Additional clinical studies are needed to evaluate the relative value of litholytic foods, allopurinol and/or alkalinization of urine in dissolving ammonium urate uroliths in dogs with portal vascular anomalies. The efficacy of allopurinol may be altered in such dogs because biotransformation of this drug, which has a very short half-life, to oxypurinol, which has a longer half-life, requires adequate hepatic function (Osborne et al, 1986).

Immature Dogs with Urate Uroliths

Providing safe and effective therapy for urate uroliths in immature dogs presents a challenge. Formation of urate uroliths associated with portal vascular anomalies and their management are discussed above. Growing dogs usually consume greater quantities of protein and, thus, greater quantities of purines than adult dogs. The safety and efficacy of litholytic foods in young dogs with urate uroliths are unknown. Adding non-purine-containing protein to the litholytic food may be effective (**Box 39-2**); however, no studies have yet been performed to confirm this hypothesis. The metabolism of allopurinol in young dogs has not been evaluated. Surgical removal of large uroliths remains the option with the most predictable short-term outcome.

Assess and Determine the Feeding Method: Urate Urolith Dissolution

Transitioning patients from their current food to a urate litholytic food should be done gradually (i.e., over a period of a few days). Begin the transition by feeding 75% of the current food and 25% of the litholytic food on Day 1. On Day 2, feed half of each food. On Day 3, feed 75% as the litholytic food. By Day 4 or 5, feed only the litholytic food.

As discussed above, modification of urinary pH is a significant part of overall dietary management of urate urolithiasis. Free-choice feeding is often associated with more persistent aciduria compared to meal feeding. However, if moist foods are fed, as is recommended, free-choice feeding can result in spoilage if the food is left uneaten for several hours at room temperature (Chapter 11). Opened containers of moist foods should be refrigerated and the feeding bowl should be kept clean. Ideally, moist foods should be meal fed several times per day. If that is not possible, clients should meal feed moist food as often as practical.

Besides offering moist foods, there are several additional ways to facilitate increased water intake. These include: 1) Ensuring multiple water 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. 2) Providing clean water bowls that are always filled with fresh water. 3) Offering ice cubes as treats or snacks. 4) Adding liberal quantities of water to dry foods. However, potential food safety issues might arise from leaving moistened dry foods out for prolonged intervals (Chapter 11). Using small amounts of salt-free bouillon as a flavoring substance in drinking water to encourage more water consumption is not recommended for management of urate uroliths because meat extracts such as bouillon contain increased levels of purines (**Table 39-3**).

If the patient has a normal body condition score (BCS 2.5/5 to 3.5/5), the amount of food fed previously was probably appropriate. On an energy basis, a similar amount of the new

Box 39-2. Recipes for Supplementing a Low-Protein Urate Litholytic Canine Adult Food for Use in Immature Canine Patients with Urate Urolithiasis.

Providing a safe and effective urate litholytic food for immature dogs presents a challenge. Growing dogs usually consume greater quantities of protein and, thus, purines than adult dogs. The safety and efficacy of low-protein litholytic foods in young dogs with urate uroliths are unknown. Adding non-purine-containing protein to the litholytic food may be effective; however, no studies have yet been performed to confirm this hypothesis. Also, the metabolism of allopurinol in puppies has not been evaluated. Therefore, surgical removal of large uroliths remains the option with the most predictable short-term outcome.

The dry formulation of a low-protein veterinary therapeutic food[a] often recommended for dogs with urate urolithiasis can be modified for growing dogs (**Table 1**). However, the long-term safety and efficacy of this modified food in young dogs with urate or other uroliths are unknown. Therefore, growing dogs should be appropriately monitored for protein-calorie malnutrition if fed foods based on these recipes.

Table 1. Modified recipes for growing dogs based on the dry formulation of a low-protein, low-purine veterinary therapeutic food.

Recipe A
1 cup dry Prescription Diet u/d Canine
1 tsp dicalcium phosphate
1 cup cottage cheese
Multivitamin-mineral supplement for dogs

Nutrient levels (% dry matter)	
Protein	30.5
Fat	19.5
Calcium	1.0
Phosphorus	1.0
Magnesium	0.02
Sodium	0.6
Potassium	0.5

Recipe B
1 cup dry Prescription Diet u/d Canine
3/4 tsp dicalcium
2 cooked eggs
Multivitamin-mineral supplement for dogs

Nutrient levels (% dry matter)	
Protein	17.6
Fat	27.1
Calcium	1.1
Phosphorus	1.0
Magnesium	0.02
Sodium	0.4
Potassium	0.6

ENDNOTE
a. Hill's Prescription Diet u/d Canine dry. Hill's Pet Nutrition, Inc., Topeka, KS, USA.

food would be a good starting place.

ADJUNCTIVE MEDICAL AND SURGICAL MANAGEMENT

Diuretics

Because a properly formulated low-protein urate litholytic food impairs urine-concentrating capacity by decreasing renal medullary urea concentration, additional diuretic agents are unnecessary.

Xanthine Oxidase Inhibitors

Allopurinol is a synthetic isomer of hypoxanthine (Hande et al, 1978). It rapidly binds to and inhibits the action of xanthine oxidase, and thereby decreases production of uric acid by inhibiting the conversion of hypoxanthine to xanthine, and xanthine to uric acid. The result is a reduction in serum and urine uric acid concentration within approximately two days, and a concomitant but lesser increase in the serum concentrations of hypoxanthine and xanthine (Foreman, 1984; Osborne et al, 1986). Although allopurinol has a short half-life in people with normal renal function (approximately 90 minutes), its metabolic derivative oxypurinol is also a xanthine oxidase inhibitor and has a half-life of 12 to 16 hours (Elion et al, 1966). In mongrel dogs and beagles, the half-life of allopurinol is dose dependent (approximately 2.5 hours following a 5 mg/kg body weight dose and three hours following a 10 mg/kg body weight dose). The half-life of oxypurinol is three to five hours (Bartges et al, 1993; Elion, 1966). Food does not affect availability of allopurinol; therefore, it can be administered with meals.

The dosage of allopurinol for dissolution of ammonium urate uroliths in dogs is 15 mg/kg body weight q12h (Lulich et al, 1995; Bartges et al, 1992; Osborne et al, 1986). According to the manufacturer, the drug has been given to normal dogs at this dosage for one year without causing significant abnormalities.[c] This dosage has been given to nonazotemic, urate urolith-forming dogs for up to six months without detectable consequences. However, when owners supplemented a therapeutic food with foods containing purine precursors, a layer of xanthine formed around ammonium urate uroliths (**Figures 39-2** and **39-3**). Therefore, to minimize xanthine formation, allopurinol should only be administered to patients consuming purine-restricted foods (**Figure 39-4**) (Bartges et al, 1995c; Osborne et al, 2000).

The efficacy of allopurinol may be altered in dogs with portal vascular anomalies because biotransformation of this drug, which, as mentioned above, has a very short half-life, to oxypurinol, which has a longer half-life, requires adequate hepatic function (Osborne et al, 1986). Pending further studies, we do not recommend allopurinol for treatment or prevention of urate uroliths formed by dogs as a result of portal vascular shunts or hepatic microvascular dysplasia.

Reported adverse effects of allopurinol in people include gastrointestinal disturbances, skin rashes, leukopenia, thrombocytopenia, vasculitis and hepatitis (Al-Kawas et al, 1981; Medline et al, 1978). We found only one report of a possible immune-mediated reaction (hemolytic anemia, trigeminal neuropathy) to allopurinol administration in a dog (Pedroia, 1981). Because allopurinol and its metabolites are excreted by the kidneys, the

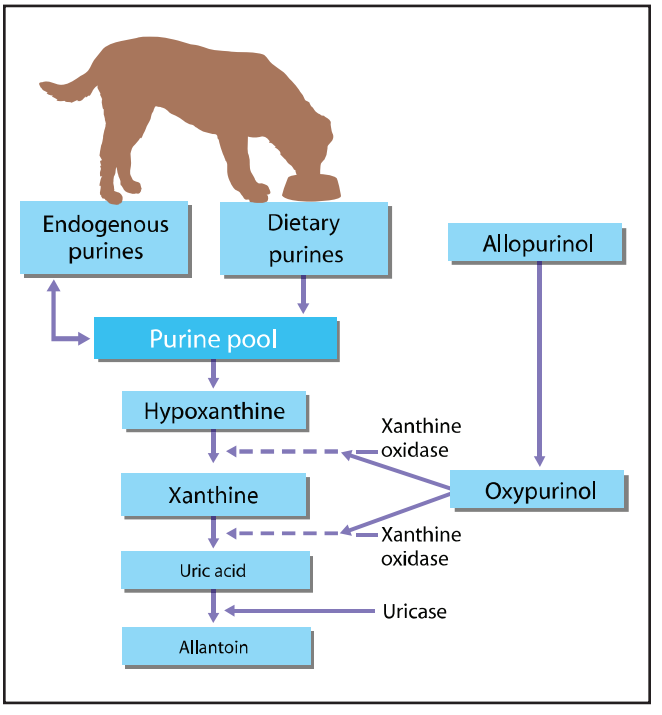

Figure 39-4. Diagram of purine metabolism in dogs that consume a purine-restricted food and are given allopurinol.

dosage is commonly reduced in people with renal dysfunction. Allopurinol has been reported to cause life-threatening erythematous desquamative skin rashes, fever, hepatitis, eosinopenia and further decline in renal function when given to people with renal insufficiency (Hande et al, 1978). Pending further studies, appropriate precautions including informed consent, should be used when considering use of allopurinol in dogs with primary renal failure.

Urine Alkalinizing Agents

Because ammonium ions and hydrogen ions appear to precipitate urates in dog urine, oral administration of alkalinizing agents (e.g., potassium citrate) may be of value in preventing acid metabolites from increasing renal tubular production of ammonia. Under physiologic conditions associated with alkaluria, urine contains low concentrations of ammonia and ammonium ions (Hande et al, 1984).

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 alkalinizing agent, effective doses, (25 to 50 mg/kg body weight q12h) result in a significant increase in sodium intake. Also, sodium may combine with uric acid to form sodium urate. Alternatively, potassium citrate in wax matrix tablets (Urocit-K[d]) or as a liquid (Polycitra-K[e]) (40 to 75 mg/kg body weight q12h) may be given. Divided doses should be administered to maintain a consistently nonacidic environment in the urinary tract. A properly formulated urate dissolution food should contain potassium citrate (check ingredient label). Consumption of potassium citrate typically results in alkaluria in dogs (Bartges et al, 1995, 1995a).

The goal of treatment with urine alkalinizing agents or the urate litholytic food 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 they provide a significant risk factor for formation of calcium phosphate uroliths. Deposition of a layer of calcium phosphate crystals around existing urate uroliths may impede urolith dissolution. Owners may monitor urinary pH with pH paper or handheld "pocket" pH meters.

Eradication or Control of UTIs

Clinical studies indicate that UTIs in dogs with ammonium urate uroliths usually occur as a consequence of altered local host defenses. These alterations may be caused by urolith-induced trauma to the urothelium, or they may occur as a consequence of catheterization or other invasive diagnostic procedures. Efforts should be made to prevent, eradicate or control infections because they may cause problems of equal or greater severity as the uroliths.

Studies of ammonium urate uroliths in people have been interpreted to suggest that UTIs caused by urease-producing microbes may be a causative factor (Garcia and Cifuentes Dellate, 1981). In this circumstance, formation of ammonium ions as a consequence of urease-mediated hydrolysis of urea may result in formation of insoluble ammonium urate crystals. If a similar phenomenon occurs in dogs, eradication or control of potent urease-producing microbes (staphylococci, *Proteus* spp. and ureaplasmas) would be especially important.

Appropriate antimicrobial agents selected on the basis of susceptibility or minimum inhibitory concentration tests should be used at therapeutic dosages. The fact that diuresis reduces the urine concentration of the antimicrobial agent should be considered when formulating antimicrobial dosages.

Surgery

There are several situations in which a combination of surgical removal of urate uroliths followed by combined dietary and medical dissolution protocols might be beneficial. One involves the inability to remove all uroliths by surgery. This occasionally occurs because ammonium urate uroliths are frequently multiple and small. The fact that they may be radiolucent creates an additional problem by interfering with their radiographic detection immediately after surgery.

In some patients, immediate surgery may be required to remove uroliths obstructing the renal pelvis, ureter(s) or urethra. Lithotripsy has proved to be highly effective in removing uroliths that obstruct the urethra. Initiation of dietary and medical dissolution protocols may prove advantageous if such patients have multiple uroliths in several locations, and if circumstances preclude their surgical removal at the time the obstructing urolith is removed.

Techniques have been devised to correct some types of intrahepatic and extrahepatic shunts in dogs. Certain patients with portal vascular anomalies and urate uroliths may benefit from a combination of surgical, dietary and medical urolith dissolution protocols. Surgical correction, by itself, of an extrahepatic por-

tacaval shunt in a three-month-old female miniature schnauzer resulted in a marked reduction of urine uric acid concentration (Osborne et al, 2000). However, the condition of the patient and factors related to anesthesia and surgery may preclude urolith removal at the time the anomalous portal vessels are corrected. In this situation, postsurgical dietary and medical therapy designed to dissolve uroliths should be considered. Also, some types of portal vascular anomalies are not amenable to surgical correction. If the uroliths cause unacceptable signs of urinary tract disease, they should be surgically removed and postsurgical preventive measures should be initiated. Voiding urohydropropulsion may be used to remove small urocystoliths (Figure 38-5 and Table 38-7) (Lulich et al, 1993).

REASSESSMENT

Ammonium urate urocystoliths have a propensity to move into the urethra of dogs. This finding may be related to their small size, round to ovoid shape and smooth surface. If small enough, they readily pass through the urethra. However, they often become lodged behind the os penis of male dogs. Owners should be informed of this likelihood and given a written summary of associated clinical signs. Urethroliths causing clinical signs may be easily returned to the bladder lumen by urohydropropulsion (Figure 38-5 and Table 38-7) (Lulich et al, 1993), or removed by lithotripsy. The physical characteristics that permit passage of these uroliths into the urethra also facilitate their removal from the urethra.

When attempting dietary and medical dissolution of urate uroliths, owners should be counseled to adhere strictly to feeding the low-purine urate litholytic food. Consumption of a high-purine food by dogs, while receiving allopurinol, will result in formation of a xanthine shell around urate uroliths or formation of xanthine uroliths (**Figure 39-3**) (Bartges et al, 1992; Ling et al, 1991; Osborne et al, 1986a). Xanthine uroliths may not dissolve. However, spontaneous dissolution of xanthine shells and underlying uroliths may occur by discontinuing allopurinol and continuing the low-purine litholytic food (Bartges et al, 1994). Alternatively, dissolution of urate uroliths may occur as a result of feeding a low-purine litholytic food and administering a lower dose of allopurinol than that associated with formation of xanthine shells.

Because allopurinol and its metabolites are excreted from the body primarily in urine, the drug should be used cautiously in patients with renal dysfunction (Bartges, 1993; Hande et al, 1984). Reduction in the dosage of allopurinol is recommended for human patients with primary renal failure. Pending further studies, a similar recommendation should be applied to dogs with primary renal failure.

The size of uroliths should be periodically monitored by survey and (if necessary) double-contrast radiography or ultrasonography (**Table 39-7**). It is more difficult to monitor changes in size and number if the uroliths are radiolucent. Double-contrast cystography is superior to ultrasonography because: 1) it is minimally invasive, 2) sedation is usually not required to perform the procedure, 3) virtually all uroliths can be visualized, including their size, shape and number and 4) uroliths may be retrieved through the catheter and submitted for quantitative analysis. If retrograde double-contrast urethrocystography is used to monitor dissolution of radiolucent urethrocystoliths, appropriate prophylactic antibiotics should be administered around the time of urinary tract catheterization to minimize iatrogenic UTIs. Excretory urography or ultrasonography may be used to monitor dissolution or recurrence of urate nephroliths.

Table 39-7. Expected changes associated with dietary and medical therapy of purine uroliths.

Factors	Pre-therapy	During therapy	Prevention therapy
Polyuria	±	1+ to 3+	1+ to 3+
Pollakiuria	0 to 4+	↑ then ↓	0
Hematuria	0 to 4+	↓	0
Urine specific gravity	Variable	1.004 to 1.015	1.004 to 1.015
Urinary pH	<7.0	>7.0	>7.0
Pyuria	0 to 4+	↓	0
Purine (urate) crystals	0 to 4+	0	Variable
Bacteriuria	0 to 4+	0	0
Bacterial culture of urine	0 to 4+	0	0
Urea nitrogen (mg/dl)	Variable	≤15	≤15
Urolith size and number	Small to large	↓	0

Urinary pH should be monitored at appropriate intervals (**Table 39-7**). Periodic evaluation of urine sediment for crystalluria should also be considered. Ammonium urate crystals should not form in fresh urine if therapy has been effective in promoting formation of urine that is undersaturated with ammonium ions and uric acid. Periodic evaluation of serum urea nitrogen concentration, serum uric acid concentration and (if possible) urine uric acid concentration is recommended. Reduction of serum urea nitrogen concentration below pretreatment values (usually <10 mg/dl in previously nonazotemic patients), reduction of urine specific gravity (usually <1.020) and an increase in urinary pH (usually >7.0) indicate owner and patient compliance with dietary therapy (**Table 39-7**). Reductions in serum and urine uric acid concentrations also indicate compliance with recommendations for dietary and allopurinol therapy.

Determination of urine urate-to-creatinine ratios in randomly collected single urine samples has been recommended to aid in diagnosis and to monitor medical and dietary therapy of dogs with urate uroliths (Schaible, 1986; Senior, 1989). However, in a controlled study, spot urine urate-to-creatinine ratios correlated poorly with 24-hour urine uric acid excretion in healthy non-urolith-forming beagles (Bartges et al, 1994a). Although urine urate-to-creatinine ratios decrease significantly in dogs with urate uroliths given allopurinol (Moentk et al, 1994), they do not correlate with 24-hour urine uric acid excretions in these dogs, nor are they useful in predicting urolith dis-

Table 39-8. Managing purine uroliths refractory to complete dissolution.

Cause	Identification	Therapeutic goal
Client and patient factors		
Inadequate dietary compliance	Question owner Persistent purine crystalluria Urea nitrogen >10-17 mg/dl Urine specific gravity >1.010-1.020 Urinary pH <7.1-7.5 during dietary management with appropriate litholytic food (**Table 39-6**) (use lower values for moist food)	Emphasize need to exclusively feed dissolution food
Inadequate allopurinol administration	Question owner Count remaining pills	Emphasize need to administer allopurinol Determine if owner is capable and willing to administer medication Demonstrate a variety of methods to administer medication
Clinician factors		
Incorrect prediction of mineral type Excessive allopurinol administration	Analysis of retrieved urolith Xanthine urolith formation	Alter therapy based on identification of mineral type Reduce allopurinol administration in conjunction with appropriate dietary therapy to minimize purine consumption Clinically active uroliths may require surgical removal Remove small uroliths by voiding urohydropropulsion (Figure 38-5 and Table 38-7)
Disease factors		
Xanthine urolith formation	Analysis of retrieved urolith Allopurinol administration without concomitant reduction in dietary protein consumption Excessive allopurinol dose	Clinically active uroliths may require surgical removal Remove small uroliths by voiding urohydropropulsion (Figure 38-5 and Table 38-7)
Inadequate hepatic function	Suspect hepatic portosystemic shunts or hepatic microvascular dysplasia in breeds other than Dalmatians and English bulldogs Elevated postprandial serum bile acid concentration Microhepatica	Clinically active uroliths may require surgical removal Remove small uroliths by voiding urohydropropulsion (Figure 38-5 and Table 38-7) Repair vascular anomaly
Compound urolith	Radiographic density of nucleus and outer layer(s) of urolith is different Analysis of retrieved urolith	Alter therapy based on identification of a new mineral type 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 (Figure 38-5 and Table 38-7)

solution. Furthermore, urine xanthine-to-creatinine ratios in these dogs did not correlate with 24-hour urine xanthine excretions, nor were they predictive for urate urolith dissolution or xanthine formation.

There is no rigid time interval after which response to dissolution therapy is unlikely. The fact that current medical and dietary protocols are not designed to induce dissolution of urolith matrix may be a factor that influences dissolution rate. The time required to induce dissolution of nine episodes of urate urolithiasis in a clinical study ranged from four to 40 weeks (mean 14.2 weeks). Reevaluation of the diagnosis and/or alternate methods of management should be considered if uroliths enlarge during therapy or do not begin to decrease in size after approximately eight weeks of appropriate medical and dietary therapy (**Table 39-8**).

If it is difficult to completely dissolve urate uroliths by creating urine that is undersaturated with uric acid and ammonium ions, consider that: 1) the wrong mineral component was identified, 2) the nucleus of the urolith was of different mineral composition than the outer portions of the urolith, 3) a xanthine shell or xanthine uroliths had formed or 4) the owner or patient was not complying with therapeutic recommendations.

PREVENTION OF URATE UROLITHIASIS

Dalmatian Dogs

Prophylactic therapy should be considered for urate-forming Dalmatian dogs because of the high risk for recurrent urate uroliths. As a first choice, urate litholytic foods that are restrict-

ed in purines and that promote formation of less concentrated alkaline urine should be considered (**Table 39-6**). In one study of naturally occurring ammonium urate urocystoliths in Dalmatian dogs, a low-protein, nonacidifying moist commercial veterinary therapeutic food[b] reduced urolith recurrence by 50% compared with an adult moist maintenance food (Lulich et al, 1998). If dry foods are fed, water should be added with the goal of maintaining a urine specific gravity less than approximately 1.025.

If urate crystalluria or hyperuricuria persists, serial urinary pH measurements are indicated to ensure appropriate alkalinization. If necessary, urine alkalinizing agents may be added to the protocol. If difficulties persist, low doses of allopurinol (approximately 10 to 20 mg/kg body weight/day) may be given cautiously. Prolonged administration of high doses (30 mg/kg body weight/day) of allopurinol may result in formation of xanthine uroliths (Bartges et al, 1992; Ling, 1995). The risk of xanthine urolithiasis is enhanced if dietary purines are not restricted during allopurinol therapy. Therefore, appropriate caution in long-term administration of this drug is indicated. Because it is possible to induce dissolution of recurrent ammonium urate uroliths, it is unnecessary to risk the use of prophylactic protocols that may themselves cause disorders.

When considering use of foods to minimize occurrence of urolithiasis, avoid an "always" or "never" approach. The final decision should be based on the overall balance of benefits to the patient and associated risks.

Non-Dalmatian Dogs

We did not find any published information concerning recurrence rates of urate uroliths in non-Dalmatian dogs; however, recurrence of urate uroliths was observed in three of five English bulldogs. Therefore, preventive measures should also be considered for non-Dalmatian dogs.

There have been few studies of the biologic behavior of ammonium urate uroliths in dogs and cats with portal vascular anomalies and/or microvascular dysplasia. It is logical to hypothesize that elimination of hyperuricuria and reduction of urine ammonium concentration following surgical correction of anomalous shunts would result in spontaneous dissolution of uroliths composed primarily of ammonium urate.

Additional clinical studies are needed to evaluate the relative value of litholytic foods, allopurinol and/or alkalinization of urine in dissolving ammonium urate uroliths in dogs and cats with portal vascular anomalies. The likelihood of adverse side effects or further deterioration in hepatic function following administration of allopurinol to dogs with portal vascular anomalies has apparently not been determined. Reversible hepatitis has been reported to be an uncommon reaction to allopurinol given to people (Al-Kawas et al, 1981; Murrell and Rapeport, 1986; Nelson and Elion, 1984). Pending further study, appropriate precautions should be taken to monitor patients for adverse reactions if allopurinol is given to dogs with portal vascular anomalies. Because tetracycline exacerbates hepatic and renal dysfunction in dogs with experimentally produced portal vascular anomalies, it should not be routinely used to treat UTIs in dogs with naturally occurring portal vascular anomalies (Faraj et al, 1982).

ENDNOTES

a. Prescription Diet k/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
b. Prescription Diet u/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
c. Zyloprim. Glaxo Wellcome, Research Triangle Park, NC, USA.
d. Urocit-K. Mission Pharmacal, San Antonio, TX, USA.
e. Polycitra-K. Willen Drug Co., Baltimore, MD, USA.

REFERENCES

The references for **Chapter 39** can be found at www.markmorris.org.

CASE 39-1

Stranguria in a Dalmatian Dog

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Patient Assessment

A three-year-old, neutered male Dalmatian dog was referred to the University of Minnesota Veterinary Teaching Hospital for inability to urinate and straining to urinate during the past 24 hours (**Figure 1**). The dog had received an antibiotic (unknown type and dosage) for the past month because of bacterial folliculitis (**Figure 2**).

Physical examination revealed a depressed dog with patchy areas of alopecia and erythema, and a distended, tense, painful urinary bladder. The dog weighed 34.2 kg and had a normal body condition score (BCS 3/5). No other abnormalities were noted.

Blood samples were submitted for a complete blood count (**Table 1**) and a serum biochemistry profile (**Table 2**). These tests revealed leukocytosis due to mature neutrophilia and an elevated serum uric acid concentration. Survey radiographs revealed three slightly radiopaque round densities in the region of the urinary bladder (**Figure 3**) and multiple urethroliths. A urine sample was collected for a complete urinalysis and aerobic bacterial culture (**Table 3**).

An 8-Fr. urinary catheter was advanced into the urinary bladder without difficulty. The catheter and many small round, smooth, green uroliths were voided. The urinary catheter was reinserted, all of the urine removed and a double-contrast cystogram was performed (**Figure 4**).

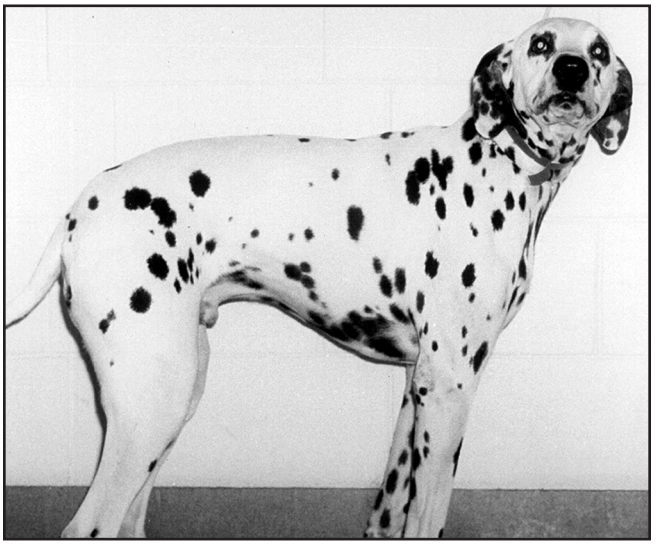

Figure 1. A three-year-old, neutered male Dalmatian dog with dysuria and inability to void urine.

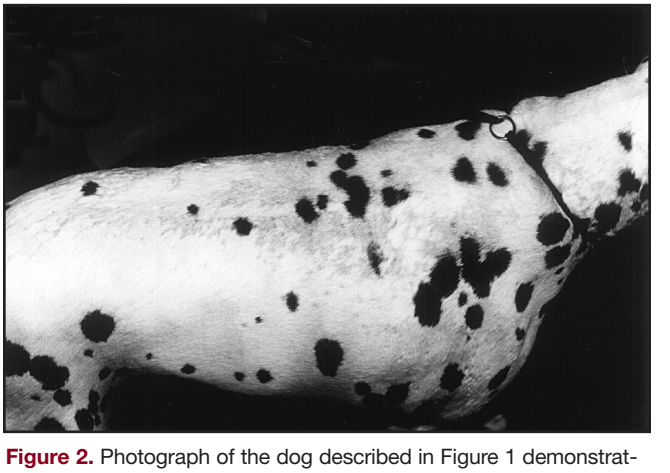

Figure 2. Photograph of the dog described in Figure 1 demonstrating patchy alopecia due to folliculitis.

Assess the Food and Feeding Method

At the time of admission, the dog was being fed a dry veterinary therapeutic food[a] that avoids excess levels of phosphorus, sodium and protein. The food was offered free choice.

Questions

1. What is the probable mineral composition of the uroliths in this dog?
2. What are the advantages and disadvantages of surgical vs. dietary and medical management of these uroliths?
3. If dietary and medical dissolution is chosen as the treatment plan, what parameters should be monitored?

Answers and Discussion

1. The most likely mineral composition of the uroliths is ammonium urate based on the physical and radiographic characteristics of the uroliths, the presence of ammonium urate crystalluria and the breed of dog. Dalmatian dogs are predisposed to formation of purine uroliths, primarily ammonium urate, because of unique purine metabolism that results in greater urinary excretion and concentration of uric acid compared with most non-Dalmatian dogs.
2. Although surgery may be effective, dietary and medical protocols have been developed to dissolve ammonium urate uroliths. Surgical removal of urocystoliths has the obvious advantage of rapid correction of the disease process. Combined dietary and medical therapy is also often effective and includes using a moist low-purine commercial veterinary therapeutic food[b] and allopurinol, a xanthine oxidase inhibitor. In a prospective controlled study of canine ammonium urate urocystoliths, complete dissolution was achieved in approximately 40% of the cases and reduction of urolith size

Table 1. Hemograms of a three-year-old, neutered male Dalmatian dog with urocystoliths.

Factors	Reference values	Day 1*	25	59	88	123	157	186	214	247	275
Hct (%)	30-58	49.6	47.6	46.1	47.6	46.0	48.6	46.5	48.7	48.0	46.2
RBC ($10^6/\mu l$)	5.2-8.1	6.95	6.77	6.48	6.74	6.53	6.80	6.65	6.92	6.82	6.53
Hemoglobin (g/dl)	10.2-16.9	17.3	16.7	15.9	16.5	16.1	16.0	19.1	16.9	16.9	19.8
MCV (fl)	63-72	71	70	71	71	70	71	70	70	70	71
MCH (pg)	22-25	25	25	25	35	25	24	29	24	25	30
MCHC (%)	34-37	35	35	35	35	35	33	41	35	35	43
Nucleated RBC (/μl)	-	0	0	0	1	0	1	1	1	0	0
WBC ($10^3/\mu l$)	5.4-15.3	23.4	11.5	11.5	11.2	13.7	12.8	12.8	13.1	10.7	13.6
Segmented neutrophils ($10^3/\mu l$)	2.75-12.85	21.18	6.56	8.34	7.49	9.86	10.6	9.02	8.06	7.92	10.0
Band neutrophils ($10^3/\mu l$)	0-150	0	0	0	0	0	0	0	0	50	70
Metamyelocytes ($10^3/\mu l$)	0	0	0	0	0	0	0	0	0	0	2,040
Lymphocytes ($10^3/\mu l$)	430-5,800	820	3,050	1,440	2,220	2,400	1,400	2,600	3,770	1,870	200
Monocytes ($10^3/\mu l$)	50-1,400	1,290	400	350	170	340	320	440	460	160	1,290
Eosinophils ($10^3/\mu l$)	0-1,400	120	1,500	1,380	1,220	1,100	380	570	720	700	0
Basophils ($10^3/\mu l$)	Rare	0	0	0	0	0	0	60	0	0	0
Platelets ($10^3/\mu l$)	160-525	378	378	381	352	395	406	644	369	358	Normal**
Total solids (g/dl)	5.8-7.5	7.3	6.6	6.5	6.8	6.7	7.0	9.3	7.1	7.3	9.1
Comments	-	-	-	-	-	-	-	Lipemic	-	-	Lipemic

Key: Hct = hematocrit, RBC = red blood cells, MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, WBC = white blood cells.
*Therapy consisting of a urate litholytic food and allopurinol was initiated on Day 2; allopurinol therapy was discontinued on Day 186.
**Platelets were estimated on a blood film and considered adequate.

Table 2. Serum biochemistry values of a three-year-old, neutered male Dalmatian dog with urocystoliths.

Factors	Reference values	Day 1*	25	59	88	123	157	186	214	247	275	924	1,268
Urea nitrogen (mg/dl)	7-26	17	9	7	7	5	6	5	4	4	3	5	4
Creatinine (mg/dl)	0.6-1.4	1.0	1.3	1.1	1.2	1.0	1.0	0.9	1.0	1.1	1.0	0.9	0.9
Alk phos activity (U/l)	3-60	53	83	66	94	142	212	258	239	335	490	854	760
ALT activity (U/l)	4-91	28	22	27	26	25	26	24	25	26	27	21	21
Total bilirubin (mg/dl)	0-0.7	0.6	0.4	0.4	0.3	0.7	0.8	1.5	0.9	0.9	1.3	0.4	0.6
Glucose (mg/dl)	79-140	136	122	123	113	127	133	113	116	125	132	129	115
Total protein (g/dl)	5.8-7.9	7.4	6.3	6.3	6.5	5.9	5.5	5.7	6.1	6.1	6.0	6.4	6.7
Albumin (g/dl)	2.6-4.0	3.8	3.3	3.2	3.3	3.1	3.3	3.4	3.1	3.3	3.3	2.6	2.7
Globulin (g/dl)	2.2-4.0	3.6	3.0	3.1	3.2	2.8	2.2	2.3	3.0	2.8	2.7	3.8	4.0
Uric acid (mg/dl)	0-0.6	1.5	0.3	0.4	0.3	0.4	0.4	0.5	0.7	2.0	1.7	0.9	0.8
CK (U/l)	36-155	394	79	70	76	57	66	90	90	57	67	50	-
Amylase activity (U/l)	220-1,400	976	779	742	997	715	805	786	851	795	963	856	912
Sodium (mEq/l)	146-156	148	150	150	140	150	151	150	150	150	151	147	148
Potassium (mEq/l)	3.8-5.1	3.6	4.5	4.0	3.6	4.4	4.4	4.0	4.3	4.0	4.3	4.5	4.5
Chloride (mEq/l)	109-122	110	114	116	112	114	111	112	113	114	111	111	110
Total CO_2 (mEq/l)	17-27	21	23	21	18	23	23	23	22	22	24	22	23
Anion gap	8-20	17	13	13	10	13	17	15	15	14	16	14	15
Osmolality (mOsm/l)	289-313	298	298	297	278	297	299	296	296	296	298	291	292
Calcium (mg/dl)	9.6-11.6	9.9	9.9	9.7	9.7	9.8	9.9	9.6	10.1	10.0	10.1	9.6	10.4
Phosphorus (mg/dl)	2.5-6.2	3.9	2.4	4.2	2.5	3.9	4.1	3.5	3.2	2.1	3.1	4.2	5.2

Key: ALT = alanine aminotransferase, Alk phos = alkaline phosphatase, CK = creatine kinase.
*Therapy consisting of a urate litholytic food and allopurinol was initiated on Day 2; allopurinol therapy was discontinued on Day 186.

and/or number occurred in another 30% of cases. With combined dietary and medical therapy, the average time for dissolution of ammonium urate uroliths is three and one-half months; however, the median time is approximately one month. Thus, most ammonium urate uroliths dissolve in approximately one month.

3. Clinical signs often resolve within three to five days of initiating therapy. Clients should be advised that urethral obstruction may occur at any time when uroliths are present in the bladder. If urethral obstruction with uroliths recurs, the urolith(s) can be retropulsed back into the bladder. Urocystoliths (bladder stones) can be dissolved but urethroliths (urethral stones) cannot. However, when necessary, urethroliths can be removed by lithotripsy. Initially, the dog should be reexamined every four weeks (urinalysis and double-contract cystography). With good compliance, the urine specific gravity should be reduced (<1.015), the

Table 3. Urinalyses of a three-year-old, neutered male Dalmatian dog with urocystoliths.

	Day									
Factors*	**1****	**25**	**59**	**88**	**123**	**157**	**186**	**214**	**247**	**275**
Method of collection	Voided	Midstream	Cysto	Cath	Cath	Cath	Cysto	Cath	Cath	Cysto
Specific gravity	1.028	1.018	1.014	1.022	1.019	1.013	1.018	1.017	1.010	1.008
pH	7.0	8.0	7.5	8.5	8.0	8.0	8.0	8.0	8.5	8.5
Protein***	1+	Trace	0	1+	1+	Trace	Trace	2+	Trace	Trace
Epithelial cells†	Rare	Few	0	Mod	0	Few	Few	Few	0	Few
WBC†	0	0	0	0	0	0	0	0	0	0
RBC†	1-2	120-150	Rare	Rare	Occ	20-24	0	0	0	0
Crystals††	Many urate	Few urate	0	0	Rare urate	Rare urate	0	Few amorphous	0	0

	(Continued from above)								
Factors*	**598**	**654**	**728**	**924**	**1,046**	**1,254**	**1,268**	**1,580**	**1,640**
Method of collection	Cath	Cath	Cysto	Cysto	Cath	Cath	Cath	Cath	Cath
Specific gravity	1.012	1.013	1.006	1.006	1.010	1.006	1.008	1.005	1.011
pH	8.5	8.5	7.0	7.5	8.0	8.0	7.5	7.0	8.5
Protein***	1+	3+	Trace	0	1+	1+	1+	Trace	1+
Epithelial cells†	Mod	Mod	0	Occ	Occ	Few	Few	Rare	Rare
WBC†	0	0	0	0	0	0	0	0	0
RBC†	Rare	0-2	25-30	0	0	0	Rare	0-1	0
Crystals††	0	0	0	0	0	0	0	0	0

Key: Cysto = cystocentesis, Cath = catheterization, Mod = moderate, WBC = white blood cells, RBC = red blood cells, Occ = occasional.
*Glucose, bilirubin, acetone and bacteria were not detected in any specimen.
**Therapy consisting of a urate litholytic food and allopurinol was initiated on Day 2; allopurinol therapy was discontinued on Day 186.
***Values represent semiquantitative evaluations based on a scale of 0 to 4; urine volume was not considered.
†Number per high power field (x450).
††Number per low power field (x100).

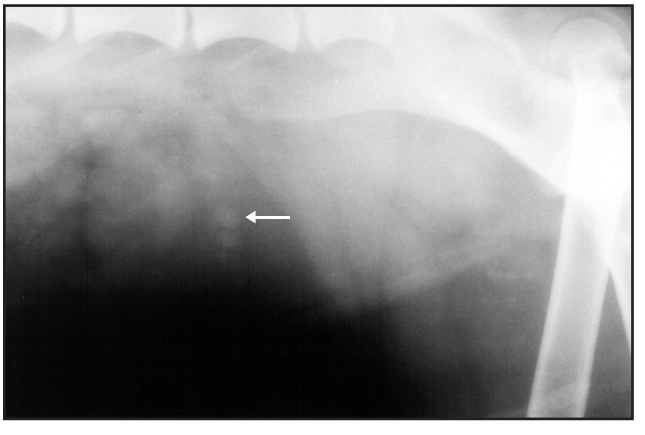

Figure 3. Survey abdominal radiograph of the dog described in Figure 1. Note the radiodense urocystoliths in the urinary bladder (arrow). Several uroliths of marginal density were also located near the os penis.

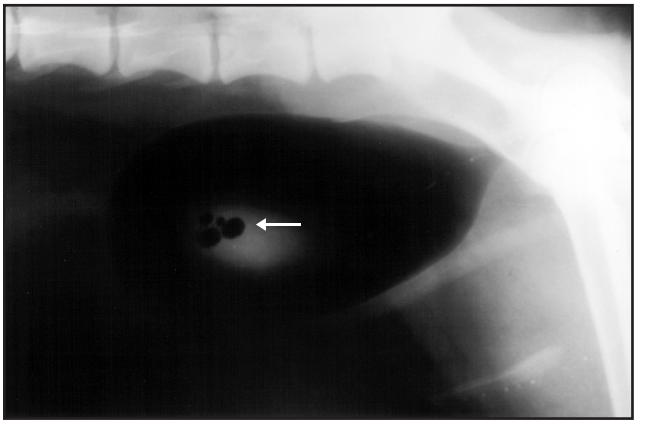

Figure 4. Double-contrast cystogram revealing urocystoliths (arrow).

urinary pH should be alkaline, no ammonium urate crystalluria should be detected and uroliths should be smaller and/or fewer as detected by double-contrast radiography. The serum urea nitrogen concentration should be low (<15 mg/dl) if additional blood work is performed.

Progress Notes

Uroliths retrieved on Day 1 were analyzed and found to be composed of 100% ammonium urate. Medical and dietary therapy was initiated with moist Prescription Diet u/d Canine and allopurinol (15 mg/kg body weight, per os, q12h). The dog's daily energy requirement was estimated to be 1,745 kcal/day (7.3 MJ) (1.5 cans twice daily). Amoxicillin-clavulanic acid (22 mg/kg, per os, q12h) was also used because of suspected superficial staphylococcal pyoderma. Twenty-five days later, the owners reported that the patient's urination was normal although an increased urine volume was noticed. Physical examination was normal and the folliculitis had resolved. The urine specific gravity and serum concentrations of urea nitrogen and uric acid were predictably decreased (**Tables 2** and **3**) and the urinary pH was alkaline. Double-contrast cystography revealed that the urocystoliths were approximately 50% smaller.

Thereafter, the dog was evaluated approximately every four weeks. Uroliths progressively decreased in size and number until they were no longer visible by double-contrast cystography (**Figure 5**, Day 186). Medical therapy was continued for an additional month at which time allopurinol was discontinued. Prophylactic therapy consisted of continuing the veterinary therapeutic food. Uroliths did not recur over the next four years (**Tables 2** and **3**). Superficial pyoderma recurred seasonally and was treated with appropriate antibiotics.

Further Discussion

Ammonium urate uroliths are highly recurrent, so prophylactic therapy should always be considered. Use of a food that avoids excessive levels of dietary purines and promotes formation of dilute, alkaline urine is effective in preventing recurrence of ammonium urate uroliths approximately 80% of the time. Allopurinol has been recommended for preventive therapy; however, recent studies indicate that prolonged administration of high doses of allopurinol may result in formation of xanthine uroliths. The risk of xanthine urolith formation is enhanced if dietary purines are not restricted during allopurinol administration.

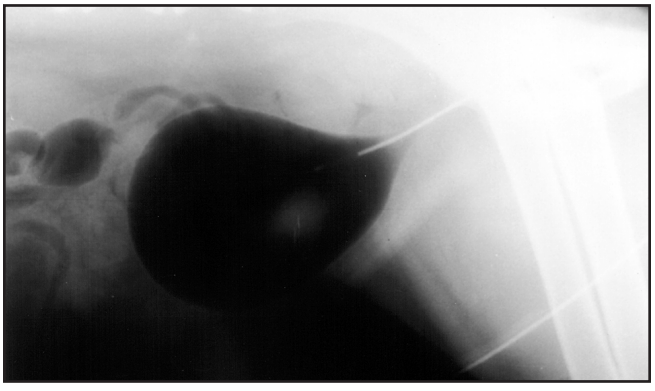

Figure 5. Double-contrast cystogram 186 days after initiating medical and dietary therapy to dissolve ammonium urate uroliths. No uroliths are detectable in the urinary bladder.

Endnotes

a. Prescription Diet k/d Canine. Hill's Pet Nutrition Inc., Topeka, KS, USA.
b. Prescription Diet u/d Canine. Hill's Pet Nutrition Inc., Topeka, KS, USA.

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CASE 39-2

Recurrent Urolithiasis in an English Bulldog

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Patient Assessment

A two-year-old, intact male English bulldog with normal body condition (body condition score 3/5) and weight (24 kg) was evaluated for recurrent urolithiasis. The dog had voided uroliths since it was a puppy. A cystotomy was performed six months earlier to remove urocystoliths, which were not submitted for quantitative mineral analysis. Urethral obstruction occurred three months ago. Urethral patency was reestablished by retrograde urohydropropulsion but the uroliths had again not been analyzed. The dog was voiding small uroliths again (**Figure 1**). Physical examination was normal; uroliths were not palpable in the bladder or urethra.

Results of a complete blood count and serum biochemistry profile were normal, except for a mildly elevated uric acid concentration. Analysis of a urine specimen obtained by cystocentesis revealed the following: specific gravity = 1.035, pH = 6.0, proteinuria, numerous urate crystals and no erythrocytes, leukocytes or bacteria (**Table 1**). Aerobic bacterial culture of an aliquot of urine was negative.

Uroliths were not detected by survey abdominal radiography (**Figure 2**). However, numerous small urocystoliths were detected by double-contrast cystography (**Figure 3**).

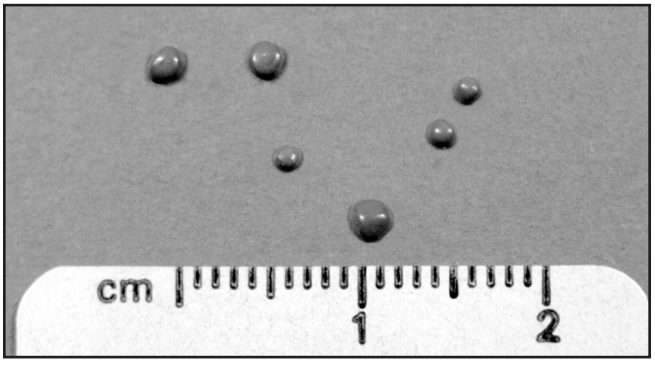

Figure 1. Photograph of ammonium urate uroliths voided by a two-year-old intact male English bulldog.

Table 1. Results of selected urinalysis and serum biochemistry parameters of a two-year-old male English bulldog with recurrent urocystoliths.

Factors	Reference values	Day 1*	Day 35	Day 78	Day 114
Urine specific gravity	-	1.035	1.005	1.006	1.027
Urinary pH	-	6	6	7.5	6
Hematuria	-	0	0	+	+
Pyuria	-	0	0	0	+
Crystals	-	Urate	0	0	Urate
Urine culture	-	Neg	Neg	Neg	Neg
SUN (mg/dl)	7-28	13	4	4	8
Creatinine (mg/dl)	0.5-1.5	1.1	0.7	0.7	0.9
Albumin (mg/dl)	2.4-3.8	3.3	3.0	3.1	3.5

Key: 0 = absent, + = present, Neg = negative, SUN = serum urea nitrogen.
*Therapy consisting of a moist urate litholytic food and allopurinol was initiated on Day 1 and discontinued on Day 78.

Assess the Food and Feeding Method

The dog was fed a commercial dry grocery brand food[a] free choice.

Questions

1. Based on the available information, what is the most likely mineral composition of the uroliths in this patient?
2. Outline a treatment and feeding plan for this dog.
3. How should response to therapy be monitored?

Answers and Discussion

1. The mineral composition of the uroliths in this dog is most likely ammonium urate based on the following: 1) multiple radiolucent uroliths, 2) urinary pH = 6.0, 3) ammonium urate crystalluria, 4) sterile urine, 5) a slight increase in serum uric acid concentration and 6) English bulldog breed. Quantitative mineral analysis of a voided urolith would be important to confirm this diagnostic assessment.
2. Dissolution of ammonium urate uroliths can be induced using a combination of a commercial veterinary therapeutic urate litholytic food[b] and allopurinol.[c] Secondary urinary tract infections should also be eradicated or controlled with appropriate antimicrobial therapy. The urate litholytic food contains low levels of dietary purines, which are the precursors of uric acid, and results in production of less concentrated, alkaline urine that enhances urate crystal solubility. Allopurinol is a xanthine oxidase inhibitor that decreases production of uric acid, and thus the quantity of uric acid in the urine.
3. Therapeutic efficacy should be monitored by physical examination and serial evaluation of radiographs, urinalyses and quantitative urine cultures, if necessary. Dietary therapy and allopurinol should be continued for one month following radiographic disappearance of uroliths. Compliance with the feeding plan is indicated by a reduction in the serum urea nitrogen concentration and formation of less concentrated, alkaline urine.

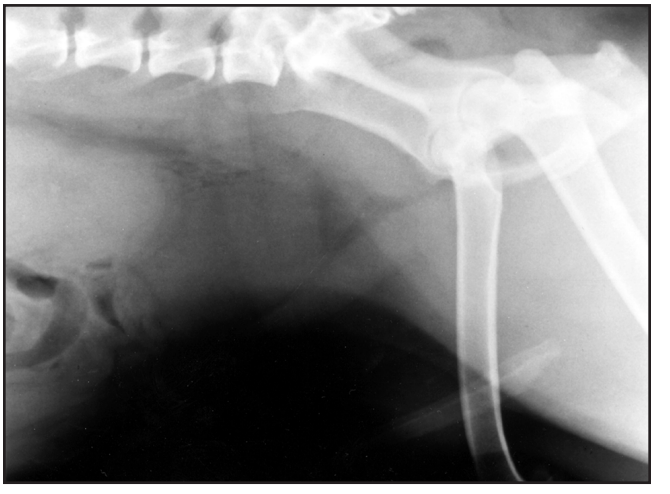

Figure 2. Survey abdominal radiograph of the same dog described in Figure 1. The dog voided small ammonium urate uroliths during micturition. Note that radiodense uroliths are not detectable in the bladder.

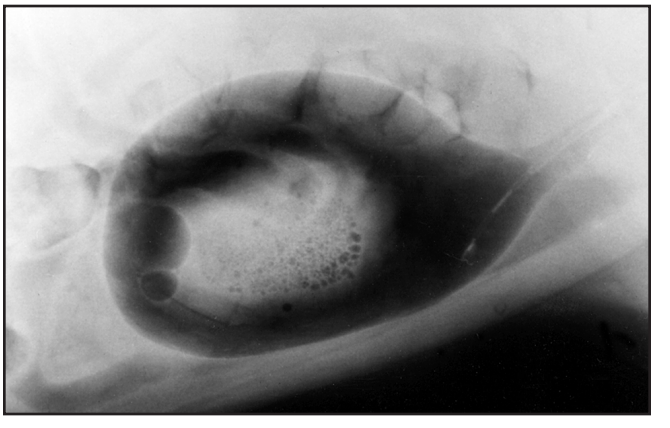

Figure 3. Double-contrast cystogram of the same dog described in Figure 1 demonstrating numerous ammonium urate urocystoliths.

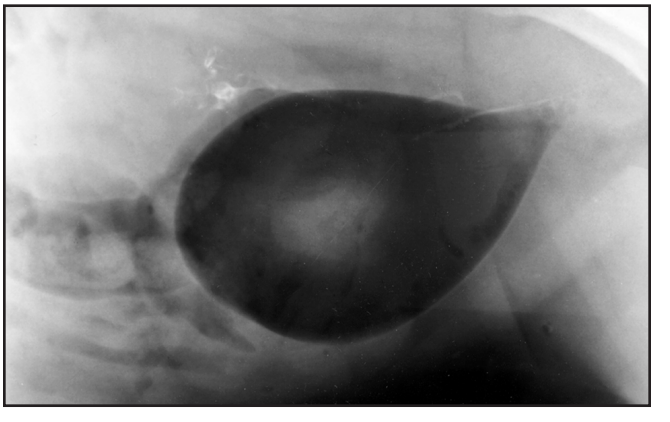

Figure 4. Double-contrast cystogram of the same dog described in Figure 1 obtained 35 days after initiating therapy. There is no evidence of urocystoliths.

Progress Notes

Quantitative analysis of a voided urolith confirmed it was composed of 100% ammonium urate. Combination therapy with the moist urate litholytic food and allopurinol (15 mg/kg body weight, per os, twice daily) was initiated. The daily energy requirement was estimated to be approximately 1,265 kcal (5.29 MJ) (1.6 x resting energy requirement) or one can of the urate litholytic food twice daily. By Day 35 following initiation of therapy, there was no radiographic evidence of uroliths (**Figure 4**). Urinalysis revealed less concentrated urine with no evidence of crystalluria. The serum urea nitrogen concentration was decreased, which implied good compliance with the feeding plan (**Table 1**). The dietary and drug therapy were continued for another month. Similar clinical findings were observed (**Table 1**, Day 78).

The owner elected to discontinue both the dietary and drug therapy. By Day 114 after the original diagnosis, urine specific gravity was increased and pyuria and urate crystalluria were evident (**Table 1**). The dog was voiding uroliths again three months later. These uroliths were found to be composed of 100% ammonium acid urate. Multiple urocystoliths were confirmed by double-contrast cystography. Combination dietary and drug therapy was used again for dissolution of the uroliths. Prevention of recurrence included continued feeding of the moist urate litholytic food and using allopurinol only as necessary to help control urate crystalluria. Monitoring over the next nine months documented one episode of bacterial urinary tract infection; however, the dog had been asymptomatic and no uroliths were detected by contrast radiography.

Endnotes

a. Purina Dog Chow. Purina Pet Care Co., St. Louis, MO, USA.
b. Prescription Diet u/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
c. Zyloprim. Glaxo Welcome Inc., Research Triangle Park, NC, USA.

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