Chapter 43

Canine Struvite Urolithiasis: Causes, Detection, Management and Prevention

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"Diagnoses are often a matter of opinion rather than a matter of fact. It is one thing to make a diagnosis, and another thing to substantiate it."
Carl A. Osborne

PREVALENCE AND MINERAL COMPOSITION

Currently, the second most common type of mineral encountered in uroliths from dogs is magnesium ammonium phosphate (MAP) hexahydrate, also known as struvite (Figure 40-1 and Table 38-8). Struvite accounted for 43% of all canine uroliths submitted to the Minnesota Urolith Center from 2000 to 2006 and 39% (16,124 of 40,612) of all canine uroliths submitted during 2007. Struvite accounted for 26% of canine upper urinary tract uroliths analyzed at the Minnesota Urolith Center from 2000 to 2006 (Table 38-9).

Although urolithiasis is most commonly recognized in adult dogs, approximately 1.0% of the total canine uroliths analyzed at the Minnesota Urolith Center were obtained from dogs less than 12 months old. Of 800 uroliths retrieved from dogs less than one year of age, approximately 56% were struvite, 23% were purines (ammonium, sodium and calcium urate, uric acid), 8% were compound uroliths (minerals in the center of uroliths were different from minerals in outer layers), 5% were calcium oxalate, 4% were of mixed mineral composition, 2% were calcium phosphate, 2% were cystine and less than 1% were silica.

The mean age at the time of MAP retrieval from dogs was six years (range one month to 24 years). Females (85%) were affected more often than males (12%; 3% of affected breeds were of unknown gender). A total of 239 different breeds were affected, including mixed breeds (24%), Shih Tzus (11%), miniature schnauzers (9%), Bichon Frises (8%), pugs (4%), dachshunds (4%), Labrador retrievers (3%), miniature poodles (2%), Pekingese (2%), cocker spaniels (3%) and Lhasa apsos (2%). Struvite uroliths were more commonly removed from the lower urinary tract (99%) than the upper urinary tract (1%). They form in a variety of shapes and sizes (**Table 43-1**).

ETIOPATHOGENESIS AND RISK FACTORS

Infection-Induced Struvite Uroliths

Sequential Steps in Urolith Formation

Urine must be supersaturated with MAP hexahydrate for stru-

Table 43-1. Common characteristics of canine struvite uroliths.

Chemical name	Formula	Crystal name
Magnesium ammonium phosphate hexahydrate	$MgNH_4PO_4 \cdot 6H_2O$	Struvite

Variations in mineral composition
Struvite only
Struvite mixed with lesser quantities of calcium apatite and/or ammonium acid urate
Nucleus of a different mineral surrounded by variable layers composed primarily of struvite. Small quantities of calcium apatite and/or ammonium acid urate also may be present.

Physical characteristics
Color: Struvite uroliths are usually white, cream or light brown. The surface of uroliths is commonly red because of concomitant hematuria and may be green due to bile pigments.
Shape: Variable. Solitary urocystoliths are commonly round or elliptic. Multiple urocystoliths may be any shape, but are often pyramidal. Rapidly growing uroliths with a large quantity of matrix may form a cast of the lumen (renal pelvis, ureter, bladder, urethra) in which they are formed.
Nuclei and laminations: Common in infection-induced uroliths
Density: Variable. Soft if they contain a large quantity of matrix. Dense and harder to cut if little matrix is present. A combination of hard and soft internal density may occur within the same urolith. Radiodense compared with non-skeletal tissue on survey radiographs. Degree of radiodensity is related to the quantity of matrix (inversely proportional) and other minerals, especially calcium apatite (more proportional).
Number: Single or multiple
Location: May be located in the kidney, ureter, urinary bladder and/or urethra. Most occur in the urinary bladder.
Size: Subvisual to a size limited by the capacity of the structure (kidney and urinary bladder) in which they form. Very large uroliths are often composed of struvite.

Predisposing factors
Urinary tract infections with urease-producing microbes in patients whose urine contains a large quantity of urea
Alkaline urinary pH
Unidentified factors

Characteristics of affected patients
Mean age: Six years (range = ≤1 to more than 24 years).
Especially common in Shih Tzus, pugs, Bichon Frises, miniature schnauzers and dachshunds; however, any breed may be affected. More common in females (~85%) than males (~15%).

$$NH_2\text{-}C(=O)\text{-}NH_2 + H_2O \xrightarrow{\text{urease}} 2NH_3 + CO_2$$

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \leftrightarrow CO_3^{=}$$

$$NH_3 + H_2O \leftrightarrow NH_4^+ + OH^-$$

Figure 43-1. Illustration of factors leading to formation of struvite, calcium apatite and carbonate apatite as a consequence of degradation of urea by microbial urease. See text below for details.

vite uroliths to form (Osborne et al, 1999). However, acidic urine from people and presumably dogs is normally undersaturated with respect to MAP (Elliot et al, 1958, 1959). Normally, physiologic concentrations of urine ammonium (NH_4^+) increase only when the kidneys excrete high concentrations of acid catabolites. The increase in urine concentration of ammonium in this situation represents a normal compensatory response by the renal tubular cells to secrete ammonia (NH_3) into the tubular lumen to reduce acidity by subsequent formation of ammonium.

Whereas ammonia is lipid soluble and can penetrate tubular cell walls, ammonium is lipid insoluble and cannot penetrate cell walls (so-called ion trapping). Likewise, excretion of alkaline urine under physiologic conditions is associated with reduced renal production of ammonia; thus the quantity of ammonium ions in urine is reduced. However, when urinary tract infections (UTIs) with urease-producing microbes occur in animals forming urine with a sufficient quantity of urea, the unique combination of concomitant elevation in the concentrations of ammonium and carbonate (CO_3^{2-}) in an alkaline environment may develop. These conditions favor formation of uroliths containing struvite [$MgNH_4PO_4 \cdot 6H_2O$], calcium apatite [$Ca_{10}(PO_4)_6(OH)_2$] and carbonate apatite [$Ca_{10}(PO_4CO_3OH_4)_6(OH)_2$] (**Figure 43-1**). The following mechanisms are involved (Osborne et al, 1999). First, urease (a metalloenzyme containing nickel) produced by some types of bacteria or ureaplasmas hydrolyze one molecule of urea to form two molecules of ammonia and one molecule of carbon dioxide. Second, the ammonia molecules react spontaneously with water to form ammonium and hydroxyl ions (pK of NH_3 = 9.03), which alkalinize urine by reducing hydrogen ion concentration. The solubility of struvite and calcium apatite decreases in alkaline urine (Hedelin et al, 1984). In addition to alkalinization of urine, the newly generated ammonium ions are available for formation of MAP crystals. Third, the newly generated molecules of carbon dioxide combine with water to form carbonic acid, which in turn dissociates to form bicarbonate (pK = 6.33) and hydrogen ions. In an extremely alkaline environment, bicarbonate may lose its proton to become carbonate (pK = 10.1). Carbonate anions may displace phosphate anions in calcium apatite crystals to form carbonate apatite crystals. Fourth, in the progressively alkaline environment induced by microbial hydrolysis of urea, dissociation of monobasic hydrogen phosphate (H_2PO^{4-}) results in an increased concentration of dibasic hydrogen phosphate ($H_2PO_4^{2-}$) and anionic phosphate (PO_4^{3-}). Given a constant concentration of total phosphate, a change in pH from 6.8 to 7.4 increases the PO_4^{3-} concentration by a factor of approximately 6 (Burns and Finlayson, 1982). Anionic phosphate is then available in increased quantities to combine with magnesium and ammonium to form struvite or with calcium to form calcium apatite. Fifth, ammonium ions may combine with urates to form ammonium urate (Garcia de la Pena and Cifuentes Delatte, 1981; He et al, 1984).

Both urea (molecular weight = 60 daltons) and urease (molecular weight = 483,000 daltons) are required for ammonia production, alkalinization, supersaturation and subsequent precipitation of struvite, calcium apatite and carbonate apatite crystals. The majority of urea in urine originates from dietary protein (Abdullahi et al, 1984), whereas the urease in vertebrates must be derived from microbes (some bacteria, some yeasts or ureaplasmas) (Delluva et al, 1968; Griffith and Klein, 1983; Kornberg et al, 1954; Levenson et al, 1959). The high

Table 43-2. Some potential risk factors for canine infection-induced struvite uroliths.

Diet	Urine	Patient/metabolic	Drugs
High protein content (source of urea)	Urease-positive UTI	Females	Glucocorticoid-associated bacterial UTI
Urine alkalinizing potential	High urea concentration	Breeds	
High phosphorus content	Hyperammonuria	Miniature schnauzers	
High magnesium content	High-ionic phosphorus concentration	Bichon Frises	
	High magnesium levels	Shih Tzus	
	High pH	Pugs	
	Urine retention	Dachshunds	
	Concentration of urine and thus lithogenic substances	Hyperadrenocorticism associated with bacterial UTI	

Key: UTI = urinary tract infection.

concentration of urea normally present in urine of individuals that consume dietary protein in excess of the daily requirement for protein anabolism makes urine an environment well suited to support the pathogenic effects of urease-producing microbes. Because of the importance of urease in the etiopathogenesis of struvite urolithiasis in people and many other animals, the name "urease stones" has been proposed (Griffith, 1978). Following a parallel line of reasoning in context of pathophysiologic events, the name "urea stones" would also be appropriate (Osborne et al, 1985).

Continued production of ammonia and perhaps other toxic reactants as a consequence of urease-induced ureolysis appears to induce an inflammatory response in the urothelium and adjacent structures (Griffith, 1978a; Krawiec et al, 1984, 1984a). In fact, urease production contributes to the virulence of uropathogens that produce this enzyme (Brande and Siemienski, 1960; MacLaren, 1968; Parsons et al, 1984; Rosenstein and Hamilton-Miller, 1984). The associated increase in urine concentration of proteinaceous inflammatory products acts as a form of matrix and contributes to lithogenesis.

Another mechanism that has been hypothesized to predispose patients with UTIs to urolithiasis is a bacteria-mediated reduction in the urine concentration of citrate (Conway et al, 1949; Robertson and Peacock, 1982; Scott et al, 1943). Citrate is often called a crystallization inhibitor because it can combine with cations such as calcium and magnesium to increase their solubility (Schwille et al, 1979). It has also been suggested that bacteria may produce lithogenic matrix substances (Stegmayr and Stegmayr, 1983).

Bacterial UTIs

Clinical and non-clinical studies involving dogs have repeatedly demonstrated a close relationship between formation of struvite uroliths and UTIs caused by urease-producing bacteria (Osborne et al, 1999). Bacterial UTIs have been such a common finding in dogs with struvite uroliths that they are sometimes called infection stones (Griffith, 1978; Osborne et al, 1981).

Several in vitro observations indicate that bacterial urease-induced supersaturation of urine with MAP is the primary (but not necessarily the only) cause of infection-induced struvite uroliths (Griffith, 1978; Griffith et al, 1976; Griffith and Musher, 1975). First, growth of urease-producing *Proteus* spp. in urea-free urine, or in urine containing a urease inhibitor, did not cause alkalinization, supersaturation or crystallization of struvite and apatite. Second, growth of weak urease-producing bacteria (*Klebsiella* spp. and *Pseudomonas* spp.) and non-urease-producing bacteria (*Escherichia* spp.) was not associated with alkalinization, supersaturation and subsequent precipitation of struvite and apatite crystals.

Staphylococcus and *Proteus* spp. are consistent and potent urease producers and have been commonly isolated from animals and people with infection-induced struvite uroliths (Griffith, 1978, 1978a; Osborne et al, 1981). For unexplained reasons, staphylococci have been more commonly associated with struvite uroliths in dogs than *Proteus* spp., whereas *Proteus* spp. are more commonly associated with struvite uroliths in people (Osborne et al, 1999; Griffith and Klein, 1983; Feit and Fair, 1979; Krajden et al, 1984; Lewis et al, 1984; Stamey, 1980). It appears that some strains of *Proteus mirabilis* have special affinity for the urinary tract of people (Senior, 1979). In pilot studies involving dogs at the University of Minnesota, better success occurred in inducing struvite uroliths with clinical isolates of staphylococci than with *Proteus* spp. Results of studies in rats were interpreted to indicate that different strains of staphylococci had different lithogenic potential (Vermeulen and Goetz, 1954).

Although other organisms such as *Klebsiella* and *Pseudomonas* spp. have potential to produce varying quantities of urease (Griffith, 1978), they have not been as commonly associated with initiation of struvite urolith formation in people or dogs. Likewise, *E. coli* and other non-urease-producing microbes have not been linked to naturally occurring struvite uroliths, presumably because they infrequently produce urease (Griffith, 1978; Lesher and Jones, 1978). However, it has been reported that urease activity may be transferred by bacterial plasmids (Grant et al, 1981).

The bacterial flora of urine may change after formation of struvite uroliths in dogs as a result of staphylococcal UTI. The change in bacterial flora may be associated with damage to local host defense mechanisms by uroliths, iatrogenic infection induced by urinary catheters or administration of antimicrobial agents.

A very small percentage of dogs with struvite uroliths have

Table 43-3. Key nutritional factors for dissolution and prevention of canine struvite uroliths.

Factors	Dietary recommendations
Water	Water intake should be encouraged to achieve urine specific gravity <1.020
	Moist food will increase water consumption and formation of less concentrated urine
Protein	Avoid excess dietary protein
	Dissolution: restrict dietary protein to ≤8%, dry matter (DM)
	Prevention: restrict dietary protein to <25% DM
Phosphorus	Avoid excess dietary phosphorus
	Dissolution: restrict dietary phosphorus to ≤0.1% DM
	Prevention: restrict dietary phosphorus to <0.6% DM
Magnesium	Avoid excess dietary magnesium
	Dissolution: restrict dietary magnesium to <0.02% DM
	Prevention: restrict dietary magnesium to 0.04 to 0.1% DM
Urinary pH	Feed a food that maintains an acidic urine
	Dissolution: urinary pH = 5.9 to 6.1
	Prevention: urinary pH = 6.2 to 6.4

sterile urine. In some of these cases, however, urease-forming bacteria have been isolated from the inside of uroliths even though the urine surrounding the uroliths was sterile. This observation indicates that bacterial infection of the urinary tract may undergo spontaneous remission after initiating urolith formation in some patients. Bacteria that become trapped within struvite uroliths may remain viable for long periods. Several studies have revealed that lithogenic bacteria harbored within uroliths are protected from the destructive effects of antimicrobial agents in urine by biofilms (Nikkila et al, 1989; Fowler, 1984; Nemoy and Stamey, 1971; Rocha and Santos, 1969; Takeuchi et al, 1984).

In contrast to struvite uroliths, bacterial infection of the urinary tract is not a consistent finding in dogs with non-struvite uroliths (ammonium urate, calcium oxalate, cystine, silica, etc.). When infection does occur in association with these so-called metabolic uroliths, it appears to be a sequela rather than a predisposing cause of urolith formation.

Ureaplasma UTIs

Ueaplasmas differ from all other mycoplasmas because they produce urease and, therefore, hydrolyze urea (Ford and MacDonald, 1967; Shepard and Lunceford, 1967). Urea is required for growth of these organisms. Ureaplasmas were recognized as etiologic agents in struvite urolithiasis when struvite uroliths were rapidly produced in male rat urinary bladders by intrarenal or intravesical injection of urease-producing ureaplasmas isolated from people (Friedlander and Braude, 1974; Lamm et al, 1977).

Ureaplasma urealyticum has been isolated from struvite uroliths removed from the renal pelves of people (Hedelin et al, 1984; Pettersson et al, 1983). However, ureaplasmas could not be isolated from nephroliths composed of calcium oxalate, calcium phosphate or uric acid. Large numbers of ureaplasmas were isolated from an adult female basset hound with uroliths presumed to be composed of struvite and located in the renal pelves and urinary bladder.[a] Although the urine from this dog contained urease, urease-producing bacteria could not be isolated from it.

Efforts at the University of Minnesota to isolate ureaplasmas from urine of other dogs with nonbacterial struvite uroliths have been unsuccessful. Further studies are necessary, however, because ureaplasmas are fastidious and cell associated. Factors reported to limit growth of ureaplasmas in broth cultures include pH values greater than 7.5 (Ford and MacDonald, 1967; Shepard and Lunceford, 1967), osmotic activity more than 600 mOsm/kg (Kenney and Cartwright, 1977) and a high ammonia concentration (Rosenstein and Hamilton-Miller, 1984; Ford and MacDonald, 1967).

Food

The quantity of dietary protein catabolized for energy influences formation and dissolution of infection-induced struvite uroliths. Consumption of dietary protein in quantities that exceed daily protein requirements for anabolism results in formation of urea from catabolism of amino acids. Hyperammonuria, hypercarbonaturia and alkaluria mediated by microbial urease are influenced by the quantity of urea (the substrate of urease) in urine (**Table 43-2**).

Abnormal urinary excretion of minerals as a result of enhanced glomerular filtration rate, reduced tubular reabsorption or enhanced tubular secretion is not required for initiation and growth of infection-induced uroliths.

Genetics

The high incidence of struvite urolithiasis in some breeds of dogs such as miniature schnauzers suggests a familial tendency (**Table 43-2**). Susceptible miniature schnauzers apparently inherit some abnormality of local host defenses of the urinary tract that increases their susceptibility to UTIs (Klausner et al, 1980, 1980a). Hereditary factors thought to be associated with inbreeding have been reported to increase the incidence of struvite uroliths in beagles (Kasper et al, 1978). The incidence of struvite uroliths was 10.7% in an inbred line vs. only 2.0% in an outbred line of beagles.

Sterile Struvite Uroliths

Clinical studies indicate that microbial urease is not involved in formation of struvite uroliths in some dogs (Bovee and McGuire, 1984; Osborne et al, 1985, 1999). Several observations suggest that dietary or metabolic factors may be involved in the genesis of sterile struvite uroliths. Pilot studies involving clinical cases of struvite uroliths in dogs at the University of Minnesota revealed a population of patients (nine of 20) whose urine was frequently alkaline but did not contain identifiable bacteria or detectable quantities of urease. Microscopic examination of demineralized, gram-stained sections of some struvite uroliths removed from dogs with bacteriologically sterile urine did not reveal gram-positive bacteria (Clark, 1974).[a] Whereas infection-induced struvite uroliths from people frequently contain calcium apatite or carbonate apatite, a substantial number of the canine sterile uroliths were 100% struvite.

Recurrent urocystoliths apparently composed of sterile struvite were encountered at the University of Minnesota in three related English cocker spaniels: a sire and two of its male offspring from different dams (Bartges et al, 1992). These dogs were followed for several years and had several episodes of struvite urocystolithiasis associated with alkaluria, but not with bacterial UTI, urinary urease enzyme activity or renal tubular acidosis (RTA). Since that time, other investigators have also observed sterile struvite urocystoliths in English cocker spaniel dogs (Lees et al, 1998).

Although struvite is less soluble in alkaline than acidic urine, the mechanism(s) of sterile struvite urolith formation in dogs is unclear. Under physiologic conditions associated with alkaluria, urine contains low concentrations of ammonia (and thus ammonium ions) (Tannen, 1983). Therefore, alkaline urine formed in the absence of ureolysis would not be expected to favor formation of crystals that contain ammonium ions (e.g., MAP hexahydrate). Clinical studies of naturally occurring urolithiasis in people support this generality (Griffith and Klein, 1983).

Formation of persistently alkaline urine in the absence of urease-mediated ureolysis may predispose patients to formation of uroliths containing hydroxyapatite $[Ca_{10}(PO_4)_6(OH)_2]$ but not carbonate apatite. Pathologic conditions that may result in this sequence of events include distal RTA (Coe and Flavus, 1991), incomplete distal RTA (Backman et al, 1981) and perhaps primary hyperparathyroidism (Coe and Flavus, 1991; Klausner et al, 1987). Because alkaline urine favors dissociation of monobasic phosphate ($H_2PO_4^-$) to dibasic phosphate (HPO_4^{2-}) and phosphate ion (PO_4^{3-}), formation of calcium phosphate is enhanced. Patients with distal RTA have impaired ability to acidify urine associated with hypercalciuria and excretion of reduced concentration of urine citrate (Coe and Flavus, 1991; Dedmond and Wrong, 1962; Morrissey et al, 1963; Thornhill, 1977).

BIOLOGIC BEHAVIOR

Struvite uroliths can rapidly form (within two to eight weeks) after infection with urease-producing staphylococci (Klausner et al, 1980, 1980a). Struvite urocystoliths associated with UTI caused by staphylococci or *Proteus* spp. have been detected in puppies as young as five weeks of age (Hardy et al, 1972).

Spontaneous dissolution of uroliths appears to be uncommon. Five cases (two nephroliths and three urocystoliths) of struvite urolithiasis in dogs have been observed in which uroliths underwent spontaneous dissolution (Klausner and Osborne, 1979). Others have also reported spontaneous dissolution of canine nephroliths (Kirby et al, 1980). Bilateral nephroliths were reported to exist for about four years in a miniature schnauzer before causing death from renal failure (Pollack and Wagner, 1976). Urocystoliths frequently pass into the urethra. In male dogs, they commonly lodge behind the os penis, but in female dogs they are frequently voided. Small nephroliths may pass into the ureters. The rapid rates at which struvite uroliths form and the potential they have to migrate to lower portions of the urinary tract are of clinical importance. If several days have elapsed between the date of diagnostic imaging and the date scheduled to remove uroliths, the number and location of uroliths should be reevaluated by radiography or other suitable imaging technique.

Struvite uroliths have a tendency to recur after surgical removal or dietary and medical dissolution (Brown et al, 1977; Kasper et al, 1978; Brodey, 1955). Miniature schnauzers have been observed with at least seven known recurrences following surgery. However, many episodes of multiple recurrences have been associated with lack of removal of all uroliths at the time of surgery (pseudo-recurrence), and poor control of recurrent UTI with urease-producing microbes. With the advent of effective therapeutic and preventive antimicrobial protocols to control recurrent or persistent UTI, the frequency of recurrent infection-induced struvite urolithiasis in dogs has markedly declined. Multiple recurrences of sterile struvite uroliths have been observed in dogs, presumably because the underlying mechanisms causing their formation persisted following dietary and medical dissolution or surgical removal.

The rate of recurrence following dietary and medical dissolution of canine struvite uroliths is less frequent than that associated with surgery. In addition, time elapsed between recurrent episodes is longer following dietary and medical dissolution. The apparent higher rate of recurrence associated with surgical removal of uroliths may be associated with inability to remove all uroliths, especially those located in inaccessible sites or those that are subvisual. The tendency for uroliths to recur after surgery may also be associated with persistence of an environment that favors initiation and growth of struvite at the time of removal.

KEY NUTRITIONAL FACTORS

Urine must be saturated with magnesium, ammonium and phosphate for struvite uroliths to form (Osborne et al, 1999). However, as described above, the process is complex, including multiple interactions. Altering nutrient levels and specific food ingredients can modify several of these interactions, which are reflected in the following key nutritional factors for dissolution and prevention of struvite uroliths. **Table 43-3** summarizes these key nutritional factors.

Water

Increasing urine volume is an effective means of reducing the urinary concentration of urolith constituents. One way to increase urine volume is to increase the water content of the food. Total water intake increases as the moisture content of the food increases. Therefore, consumption of moist foods, which generally contain between 75 to 80% water, effectively increases urine volume. Foods can also be supplemented with sodium chloride to stimulate thirst and induce compensatory polyuria. However, the risks and benefits of adding sodium chloride should be considered in each individual patient, especially those with comorbid diseases that may be aggravated by excessive dietary sodium.

Dietary protein restriction can also increase urine volume by contributing to obligatory polyuria due to a decrease in renal medullary urea concentration resulting from a reduction of hepatic urea production. (See below.)

As a generality, as long as the struvite uroliths are present in the urinary tract, water intake should be encouraged with the goal of promoting a urine specific gravity <1.020.

Protein

The quantity of dietary protein catabolized for energy can influence formation and dissolution of infection-induced struvite uroliths. Consumption of dietary protein in quantities that exceed daily protein requirements results in increased formation of urea due to the deamination of the excess amino acids so that they can be used for energy. The majority of urea in urine originates from dietary protein (Abdullahi et al, 1984). Urease in vertebrates must be derived from microbes (some bacteria, some yeasts or ureaplasmas) (Delluva et al, 1968; Griffith and Klein, 1983; Kornberg et al, 1954; Levenson et al, 1959).

If patients have urinary tract infections caused by urease-producing microbes, and their urine contains a sufficient quantity of urea (the substrate of urease), the result is a unique combination of concomitant high urinary concentrations of ammonium and carbonate in an alkaline environment. These conditions favor formation of struvite (and calcium apatite and carbonate apatite) (**Table 43-2**). One goal of dietary management for patients with infected struvite uroliths is to reduce urinary concentration of urea.

Studies indicate that protein restriction is not essential for dissolution of canine sterile struvite uroliths (Boistelle et al, 1984). High ammonia concentrations were not necessary for formation of struvite crystals provided the concentration of (Mg) x (NH_4) x (PO_4) was of sufficient magnitude at a given pH. Corresponding in vivo studies in dogs have not been performed, but it is probable that similar observations would occur.

Acidification of urine to approximately 6.0 has been effective in promoting sterile struvite urolith dissolution (Osborne et al, 1987). In this respect, canine struvite uroliths are similar to feline sterile struvite uroliths. Dietary protein restriction has the additional advantage of contributing to obligatory polyuria by decreasing renal medullary urea concentration and thus enhancing the rate of sterile struvite urolith dissolution.

The minimum recommended allowance for protein in foods for adult dogs is 10% for foods providing 4 kcal/g dry matter (DM); the minimum requirement is 8% DM (NRC, 2006). For dissolution of struvite uroliths, high quality dietary protein should be restricted to 8% or less DM. For prevention of struvite uroliths, food protein content should be less than 25% DM.

Foods high in protein are generally high in phosphorus unless special ingredients are used in their formulation.

Phosphorus

Abnormal urinary excretion of minerals is not required for initiation and growth of infection-induced struvite uroliths. However, phosphate concentrations in dog urine relate directly to the amount of phosphorus consumed in food (Morris and Doering, 1978).

Although not validated by experimental or clinical studies in dogs, foods high in phosphorus (and magnesium) would be expected to predispose susceptible dogs to sterile struvite urolith formation. In vitro studies in which magnesium (in the form of $MgSO_4$), ammonium (in the form of ammonium of NH_4Cl) or phosphate (as $NH_4H_2PO_4$ or NaH_2PO_4) added to sterile human urine (ranging in pH from 5.0 to 9.6) revealed that struvite crystals could be induced to form in an acidic or an alkaline environment (Boistelle et al, 1984). It is probable that similar observations would occur in dog studies.

The minimum recommended allowance for phosphorus in foods for adult dogs is 0.3% DM (NRC, 2006). The recommended level for phosphorus in foods for dissolution of struvite uroliths should not exceed 0.1% DM. Patients consuming foods with this level of phosphorus could possibly be in negative phosphorus balance for the relatively short period of time they need to be fed a dissolution food. An older study noted that puppies fed a purified food containing 0.11% DM phosphorus from age two months through adulthood (age 34 months) had equivalent performance compared to dogs fed the same food with 0.63% DM phosphorus (Gershoff et al, 1958). Struvite dissolution using a food containing 0.1% DM phosphorus has been safely accomplished in puppies (Osborne et al, 1986; Lulich et al, 1989). For prevention of recurrence of struvite uroliths, phosphorus levels should be less than 0.6% DM.

As discussed above, urinary phosphate can exist in several states. Anionic phosphate is the important form in either the precipitation or dissolution of struvite. Furthermore, as discussed above, urinary concentration of anionic phosphate is reversibly influenced by pH.

Magnesium

Abnormal urinary excretion of minerals as a result of enhanced glomerular filtration rate, reduced tubular reabsorption or enhanced tubular secretion is not required for initiation and growth of infection-induced uroliths. Apparently, however, for sterile struvite precipitates to form, excess dietary magnesium would be required (Boistelle et al, 1984). Avoiding excessive dietary magnesium can reduce the urinary concentration of magnesium (Morris and Doering, 1978).

The minimum requirement for magnesium in foods for healthy adult dogs is 0.018% DM; whereas the minimum rec-

Table 43-4. Summary of recommendations for dietary and medical dissolution of canine struvite uroliths.

1. Adult dogs with urinary tract infection (UTI)
   a. Perform appropriate diagnostic studies including complete urinalysis, quantitative urine culture and diagnostic imaging. Determine precise location, size and number of uroliths. The size and number of uroliths are not a reliable index of probable therapeutic efficacy.
   b. If uroliths are available, determine their mineral composition. If unavailable, determine their composition by evaluation of appropriate clinical data.
   c. Consider lithotripsy or surgical correction if urethroliths obstruct urine outflow. Consider surgery if correctable abnormalities predisposing the patient to recurrent UTIs are identified by diagnostic imaging or other means. Small urocystoliths may be removed by voiding urohydropropulsion (Figure 38-5 and Table 38-7) or lithotripsy.
   d. Eradicate or control UTIs with appropriate antimicrobial agents. Maintain full-dose antimicrobial therapy during and for three to four weeks after urolith dissolution.
   e. Initiate therapy with litholytic foods. Other foods or mineral supplements should not be fed to the patient. Compliance with dietary recommendations is suggested by a reduction in urea nitrogen concentration (usually <10 mg/dl).
   f. Devise a protocol to monitor efficacy of therapy.
      1) Try to avoid diagnostic followup studies that require urinary tract catheterization. If they are required, give appropriate pericatheterization antimicrobial agents to prevent iatrogenic UTIs.
      2) Perform serial urinalyses. Determination of urinary pH and specific gravity and microscopic examination of sediment for crystals are especially important. Remember, crystals formed in urine stored at room or refrigeration temperatures may represent in vitro artifacts.
      3) Perform serial imaging monthly to evaluate urolith location(s), number, size, density and shape.
      4) If necessary, perform quantitative urine cultures. They are especially important in patients infected before therapy and in patients catheterized during therapy.
      5) Feed patients a litholytic food for one month following disappearance of uroliths as detected by survey radiography.
      6) Consider alternative methods if uroliths increase in size during dietary management, or do not begin to decrease in size after four to eight weeks of appropriate dietary and medical management. Difficulty in inducing complete dissolution of uroliths by creating urine that is undersaturated with the suspected lithogenic crystalloids should prompt consideration that: a) the wrong mineral component was identified, b) the nucleus of the uroliths is of different mineral composition than other portions of the urolith (i.e., a compound urolith) and/or c) the client or the patient is not complying with dietary and medical recommendations.
   g. Consider administration of acetohydroxamic acid (25 mg/kg body weight/day divided into two equal doses) to patients with persistent uroliths and persistent urease-producing microburia despite the use of antimicrobial agents and litholytic foods.
2. Adult dogs with persistently sterile urine
   a. Follow the protocol described above, but do not administer antimicrobial agents or acetohydroxamic acid.
   b. Periodically culture urine specimens obtained by cystocentesis to detect secondary UTIs. Initiate antimicrobial therapy if a UTI develops.
   c. Monitor urinary pH with a reliable pH meter. Monitor urine specific gravity with a reliable refractometer. Evaluate urine sediment for evidence of calcium oxalate, calcium phosphate and/or struvite crystalluria.
3. Immature dogs
   a. Use caution when feeding protein-restricted foods to growing dogs.
   b. Short-term therapy with litholytic foods has been effective in dissolving struvite urocystoliths. If initiated, monitor the patient for evidence of nutritional deficiencies (especially protein-calorie malnutrition).
   c. Acetohydroxamic acid has not been evaluated in growing dogs.
   d. Small urocystoliths may be removed by voiding urohydropropulsion (Figure 38-5 and Table 38-7) or lithotripsy. Pending further studies, surgery remains the safest means of removing large uroliths from immature dogs.

ommended allowance is 0.06% DM (NRC, 2006). For dissolution of struvite uroliths, the recommendation for magnesium in food is less than 0.02% DM. The recommendation for prevention of recurrence is 0.04 to 0.1% DM.

Urinary pH

Urinary pH can affect the concentration of important struvite constituents, including anionic phosphate (PO_4^{3-}). As discussed above, as urine becomes more acidic, anionic phosphate is converted to monobasic hydrogen phosphate (H_2PO^{4-}) and dibasic hydrogen phosphate ($H_2PO_4^{2-}$), thereby reducing the concentration of anionic phosphate for incorporation into struvite precipitates. Conversely, as urine becomes more alkaline, the reaction proceeds in the opposite direction and anionic phosphate is then available in increased quantities to combine with magnesium and ammonium to form struvite. Given a constant concentration of total phosphate, a change in pH from 6.8 to 7.4 increases the PO_4^{3-} concentration by a factor of approximately 6 (Burns and Finlayson, 1982).

Urinary tract infections caused by urease-producing microbes can modify urinary pH and anionic phosphate concentration. In the progressively alkaline environment induced by microbial hydrolysis of urea, dissociation of monobasic hydrogen phosphate results in an increased concentration of dibasic hydrogen phosphate and anionic phosphate.

In sterile urine, pH also influences the concentration of ammonium ions (NH_4^+), but in the opposite direction of anionic phosphate. In acidic urine, ammonia (NH_3) combines with hydrogen ions to form ammonium, a struvite constituent. The resolution of this seeming paradox results from the fact that the effect of acidic urine on anionic phosphate concentration is greater than its effect on ammonium; the net effect of urine acidification is a reduction in the likelihood of formation of struvite precipitates. Acidification of urine to approximately 6.0 has been effective in promoting sterile struvite urolith dissolution (Osborne et al, 1987). In this respect, canine sterile struvite uroliths are similar to feline sterile struvite uroliths.

However, if patients have UTIs caused by urease-producing microbes, and their urine contains a sufficient quantity of urea (See Protein, above.), the result is a unique combination of concomitant high urinary concentrations of ammonium and carbonate in an alkaline environment, further contributing to the likelihood of formation of struvite precipitates.

Urinary pH can be modified by food ingredients and by feeding method. (See Feeding Methods, below.) The target urinary pH range for dissolution of struvite uroliths is 5.9 to 6.1. The target urinary pH range for prevention of recurrence of struvite is 6.2 to 6.4.

FEEDING PLAN

Current recommendations for dietary and medical dissolution of canine struvite uroliths include: 1) eradication or control of UTI (if present), 2) use of litholytic foods and 3) administration of urease inhibitors (acetohydroxamic acid) to patients if struvite uroliths persist because of persistent UTI caused by urease-producing microbes (**Table 43-4**). **Table 43-4** also summarizes the overall dietary/medical/surgical management of struvite urolithiasis in adult dogs with a UTI, adult dogs with sterile urine and immature dogs.

Assess and Select the Food: Struvite Dissolution

Table 43-5 lists commercially available litholytic foods and compares their key nutritional factor content with the recommended levels of key nutritional factors. Select a food that most closely matches the recommended key nutritional factors and/or has the best efficacy evidence. Avoid treats and vitamin-mineral supplements.

Encouraging water consumption is recommended. If possible, feed a moist food. Although understandably difficult to accomplish in some patients, fluid intake should be encouraged throughout the day to help promote a constantly high urine volume. Ensure water is readily available and is neither too cold nor too warm.

Certain nutrients in properly formulated canine litholytic foods are very restricted (See Key Nutritional Factors, above.); nutrient levels are near the minimum requirements for the majority of the dog population. For some patients, these foods may only be marginally adequate. As a result, serum biochemistry profiles of patients undergoing dietary dissolution of struvite uroliths may be altered. Consumption of a struvite litholytic food by dogs with induced staphylococcal UTIs and struvite uroliths was associated with a marked reduction in the serum concentration of urea nitrogen and mild reductions in the serum concentrations of magnesium, phosphorus and albumin (Abdullahi et al, 1984). A mild increase in the serum activity of hepatic alkaline phosphatase was also observed. These alterations in serum chemistry values were of no clinical consequence during six-month experimental studies or during clinical studies. However, they underscore the fact that struvite litholytic foods are designed for short-term (weeks to months) dissolution therapy rather than long-term (months to years) prophylactic therapy.

The anticipated reduction of serum urea nitrogen in such patients can be useful. Appropriate reduction in concentrations of serum urea nitrogen obtained while the patient is eating a properly formulated struvite litholytic food compared to values obtained while the patient was eating a maintenance food may be used as one index of client and patient compliance with dietary management (**Table 43-6**).

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.

Precautions with Litholytic Foods

There are several points to consider when feeding struvite litholytic foods. These include affected puppies and adult patients with certain medical conditions. Besides the benefits of feeding litholytic foods, there are also risks for certain patients. Not all patients are candidates for dietary dissolution. Included are patients with abnormal fluid retention, azotemic primary renal failure and patients at risk for pancreatitis. Benefits and risks of litholytic foods should be considered and discussed with the client if these health problems coexist in dogs with struvite uroliths, or if risk factors for their development are present. During such discussions with clients, avoid making "all or none" and "always or never" statements because risk factor associations are not synonymous with cause and effect relationships.

IMMATURE DOGS

Struvite urocystoliths can be successfully dissolved in immature dogs (**Table 43-4**). One such case involved a 12-week-old female miniature dachshund with a sterile struvite urocystolith (Osborne et al, 1986[a]). The urocystolith was dissolved within two weeks after feeding was begun with a struvite litholytic food. Another dog was a nine-week-old, male, mixed-breed puppy with a vesicourachal diverticulum, urethral stricture, *Staphylococcus intermedius* UTI and multiple struvite urocystoliths (Lulich et al, 1989). These urocystoliths dissolved within nine days of initiation of therapy with the litholytic food and a combination of amoxicillin and clavulanic acid. The food was discontinued on Day 10. Slight reductions in serum albumin concentration (from approximately 3.2 to 2.7 g/dl) were observed in both dogs during the two weeks of dietary therapy. Serum albumin concentrations returned to reference values soon after the puppies resumed eating a normal growth food.

Based on uncontrolled clinical experience, litholytic foods should not be fed to immature dogs with struvite uroliths for more than two weeks. If circumstances warrant that the food be fed for longer periods, serial monitoring of body weight,

Table 43-5. Key nutritional factors in selected commercial veterinary therapeutic foods used for dissolution of struvite uroliths in dogs compared to recommended levels.*

Dry foods	**Protein (%)**	**Phosphorus (%)**	**Magnesium (%)**	**Urinary pH****
Recommended levels	**≤8**	**≤0.1**	**<0.02**	**5.9-6.1**
Royal Canin Veterinary Diet Control Formula	23.9	0.84	0.130	6.0-6.3
Royal Canin Veterinary Diet Urinary SO 14	17.0	0.63	0.066	5.5-6.0
Moist foods	**Protein (%)**	**Phosphorus (%)**	**Magnesium (%)**	**Urinary pH****
Recommended levels	**≤8**	**≤0.1**	**<0.02**	**5.9-6.1**
Hill's Prescription Diet s/d Canine	7.9	0.10	0.024	5.935
Royal Canin Veterinary Diet Control Formula	22.8	0.66	0.078	6.0-6.3
Royal Canin Veterinary Diet Urinary SO	18.5	0.86	0.059	5.5-6.0

*Manufacturers' published values; nutrients expressed on a dry matter basis; moist foods are best.
**Protocols for measuring urinary pH may vary.

Table 43-6. Characteristic clinical findings before and after initiation of dietary and medical therapy, or dietary therapy alone, to dissolve struvite uroliths in nonazotemic dogs.*

Factors	**Pre-therapy**	**During therapy**	**After successful therapy****
Polyuria	±	1+ to 3+	Negative
Pollakiuria	1+ to 4+	Transient ↑; subsequent ↓	Negative
Gross hematuria	0 to 4+	↓ by 5 to 10 days	Negative
Abnormal urine odor	0 to 4+	↓ by 5 to 10 days	Negative
Small uroliths voided	±	Common in females	Negative
Urine specific gravity	Variable	1.004 to 1.014	Normal
Urinary pH	≥7	Decreased (usually acidic)	Variable
Urine protein	1+ to 4+	Decreased to absent	Negative
Urine RBC	1+ to 4+	Decreased to absent	Negative
Urine WBC	1+ to 4+	Decreased to absent	Negative
Struvite crystals	0 to 4+	Usually absent	Variable
Other crystals	Variable	May persist	May persist
Bacteriuria	0 to 4+	Decreased to absent	Negative
Quantitative bacterial urine culture	0 to 4+	Decreased to absent	Negative
Serum urea nitrogen	>15 mg/dl	<10 mg/dl	Dependent on food
Serum creatinine	Normal	Normal	Normal
Serum alkaline phosphatase	Normal	↑ by 2 to 5 times	Normal
Serum albumin	Normal	↓ by 0.5 to 1 g/dl	Normal
Serum phosphorus	Normal	Slight decrease	Normal
Urolith size (radiographic)	Small to large	Progressive decrease	Negative
Hemogram	Normal	Normal	Normal

*For dogs with urinary tract infection, therapy consists of a litholytic food and antimicrobial agents. For dogs without urinary tract infection, therapy consists of a litholytic food.
**All forms of therapy withdrawn.

body condition, serum albumin concentration and packed cell volume for evidence of protein-calorie malnutrition should be considered. Adjustments in dietary management should be made if marked reductions in these variables are observed. The urocystoliths may be removed by voiding urohydropropulsion (Figure 38-5 and Table 38-7) or lithotripsy, if their size has been reduced enough to permit their passage pass through a distended urethra (Lulich et al, 1993).

ABNORMAL FLUID RETENTION

Properly formulated struvite litholytic foods are restricted in protein and supplemented with sodium chloride. Both could affect fluid balance. Therefore, the food should not be routinely fed to patients with comorbid diseases associated with positive fluid balance (e.g., heart failure, nephrotic syndrome) or hypertension.

AZOTEMIC PRIMARY RENAL FAILURE

Complete obstruction of urine outflow caused by uroliths in patients with a concomitant UTI should be regarded as an emergency. In this situation, a combination of obstruction and pyelonephritis caused by a rapid spread of infection throughout the kidneys is likely to induce acute renal failure and then septicemia. Dietary dissolution of struvite uroliths located in the upper urinary tract should not be considered until adequate urine flow has been restored, and life-threatening deficits and excesses in fluid, electrolyte, acid-base and endocrine balance have been corrected.

Nonobstructing struvite nephroliths have been dissolved in patients with nonazotemic renal failure caused by ascending pyelonephritis (Osborne et al, 1985, 1986). But, protein-restricted litholytic foods should be used with caution in patients with azotemic primary renal failure. Such foods may induce protein malnutrition if fed for prolonged periods to dogs with moderate azotemic primary renal failure (Polzin et al, 1983).

To minimize adverse drug reactions/events, adjustments in doses and maintenance intervals of drugs excreted primarily by the kidneys should be considered in patients with azotemic primary renal failure.

PATIENTS AT RISK FOR PANCREATITIS

Approximately one in 250 dogs seen in private veterinary practices is affected by pancreatitis (0.4%). There appears to be no relationship between pancreatitis and gender, but there is a significant relationship between the disease and age. The mean age of dogs with pancreatitis in private veterinary practices is eight years (vs. 5.5 years for the general canine population). Breed is another strong risk factor for pancreatitis. For example, miniature schnauzers have a fivefold increase in risk for pancreatitis (i.e., about one in 50 miniature schnauzers can be expected to have pancreatitis). Other breeds at increased risk include Bichon Frises, Yorkshire terriers, Chihuahuas, Jack Russell terriers, Japanese spaniels, Labrador retrievers, Maltese and Shetland sheepdogs.

Investigators conducting an independent epidemiologic study asked veterinarians to ascertain the health of dogs fed a commercial veterinary therapeutic pet food.[b] This study disclosed an association between feeding a struvite litholytic food and acute pancreatitis. The risk of a dog developing pancreatitis when fed the struvite litholytic food was comparable to that of a miniature schnauzer developing acute pancreatitis, or about one in 40 (i.e., about one in 40 dogs fed the struvite litholytic food might develop pancreatitis).

The litholytic food that was tested is relatively high in fat, which increases the energy density of the food so that restriction of other specified nutrients is more readily accomplished. Because dietary fat is a risk factor for pancreatitis, the serum activity of pancreatic enzymes (amylase, lipase, trypsin-like immunoreactivity) should be monitored before initiating therapy with high-fat struvite litholytic foods in patients known to be at increased risk for pancreatitis. These tests should be repeated if signs of pancreatitis develop during treatment with the litholytic food. Because abnormal increases in activity of these enzymes are not pathognomonic for pancreatitis, other relevant findings should also be considered.

Female miniature schnauzers are at increased risk for infection-induced struvite uroliths and pancreatitis. Likewise, patients with hyperadrenocorticism are at increased risk for UTIs (which could include staphylococci) and pancreatitis. Although risk factors are not synonymous with cause and effect, clients should be informed of these associations and advised of how to respond to adverse events if they occur. They should be informed about adverse events that need medical attention and those that need medical attention only if they continue.

Assess and Determine the Feeding Method: Struvite Dissolution

Transitioning the patient from its current food to a litholytic food should be done gradually 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 an important part of overall dietary management of struvite urolithiasis. Free-choice feeding is often associated with more persistent aciduria compared to meal feeding. Because moist foods are recommended to increase water intake and produce less concentrated urine, clients should be advised to feed specific amounts (meal feed) two to three times per day rather than free-choice feeding. More frequent feedings are desirable if the client can feed multiple meals per day. Moist foods often spoil if left uneaten at room temperature for several hours (Chapter 11). Opened containers of moist foods should be refrigerated and the feeding bowl should be kept clean.

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

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

ADJUNCTIVE MEDICAL AND SURGICAL MANAGEMENT

Eradication or Control of UTIs

The importance of UTIs with urease-producing bacteria in the formation of many struvite uroliths in dogs emphasizes the need to eliminate or control infection. Because of the quantity of urease produced by bacterial pathogens, it may be impossible to consistently acidify urine with urine acidifiers administered at dosages that do not cause systemic acidosis (Musher et al, 1974). Therefore, sterilization of urine appears to be an important objective in creating a state of struvite undersaturation that would prevent further growth of uroliths or promote their dissolution.

Appropriate antimicrobial agents selected on the basis of susceptibility or minimum inhibitory concentrations 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 (Ling and Hirsch, 1983). Antimicrobial agents should be administered as long as uroliths can be identified by survey radiography. This recommendation is based on the fact that bacterial pathogens harbored inside uroliths may be protected from antimicrobial agents (Nickel et al, 1985). Although the urine and surface of uroliths may be sterilized following appropriate antimicrobial therapy, the original and secondary infecting microbes may remain viable below the surface of the urolith. Therefore, discontinuation of antimicrobial therapy may result in relapse of bacteriuria and infection.

Although use of antimicrobial agents alone may result in dissolution of struvite uroliths in some patients, studies in rats (Musher et al, 1974a) and dogs[a] and clinical studies in people (Feit and Fair, 1979; Lewis et al, 1983; Senior et al, 1984)[a] indicate that this phenomenon represents the exception rather than the rule. In one controlled study, six dogs with induced struvite uroliths were given therapeutic dosages of oral ampicillin (16 mg/kg body weight/day divided into three equal subdoses) and were fed a maintenance food. Only two uroliths dissolved; the remaining four uroliths increased in size.[a] In addition to the unpredictable response to this form of therapy, the time required to induce urolith dissolution with antimicrobial agents is usually measured in multiples of months rather than in multiples of weeks.

The litholytic effects of various combinations of antibiotics (ampicillin given orally at a dosage of 16 mg/kg body weight/day), acetohydroxamic acid and a struvite litholytic therapeutic food were studied in dogs with staphylococcal-induced struvite uroliths.[a] After five months of therapy, four uroliths increased in size and two dissolved in six dogs given ampicillin and an adult maintenance-type food. Four of six uroliths dissolved and two decreased in size in six dogs given ampicillin and the litholytic food over the same time frame. All uroliths in six dogs dissolved six weeks after initiation of therapy with a combination of the litholytic food, ampicillin and acetohydroxamic acid.

Similar results were obtained when a combination of the litholytic food and antimicrobial agents was given to 11 dogs with naturally occurring urease-positive UTIs and urocystoliths presumed to be composed of struvite (Osborne et al, 1984, 1985). The mean time required to induce urocystolith dissolution in these dogs was approximately three months (range two weeks to seven months).

Urease Inhibitors

Studies in dogs have revealed that administration of microbial urease inhibitors in pharmacologic doses is capable of inhibiting struvite urolith growth and promoting struvite urolith dissolution. Acetohydroxamic acid given orally to dogs at a dosage of 25 mg/kg body weight (divided into two daily subdoses) reduced urease activity, struvite crystalluria and urolith growth (Krawiec et al, 1984). By reducing the pathogenicity of staphylococci, acetohydroxamic acid may also result in less severe dysuria, bacteriuria, pyuria, hematuria and proteinuria.

Although higher dosages of acetohydroxamic acid may result in urolith dissolution, they are not recommended because they may cause a reversible hemolytic anemia and abnormalities in bilirubin metabolism (Krawiec et al, 1984; Kobashi et al, 1971). Likewise, acetohydroxamic acid should not be administered to pregnant dogs because it is teratogenic (Bailie et al, 1986).

Acetohydroxamic acid has not been used routinely in promoting dissolution of infection-induced struvite uroliths in dogs because of the efficacy of the litholytic food and antimicrobial therapy. However, acetohydroxamic acid has been used in combination with litholytic foods and antimicrobial agents in patients that have recalcitrant urease-producing UTIs associated with persistent struvite uroliths. Acetohydroxamic acid may be added to the therapeutic regimen if infection-induced struvite uroliths do not dissolve after an appropriate therapeutic trial with diet modification and antimicrobial agents.

INFECTION-INDUCED STRUVITE NEPHROLITHS

Nephroliths and ureteroliths causing outflow obstruction and marked impairment of renal function should be managed by surgical intervention or, if possible, by percutaneous nephropyelolithotomy, especially if associated with concomitant bacterial infection (Ross et al, 1999). Dietary and medical therapy designed to induce urolith dissolution over several weeks is unlikely to be effective in patients with poorly functioning kidneys because uroliths must be completely surrounded by urine that is undersaturated with struvite for prolonged periods to be dissolved. Intermittent passage of urine through a partially obstructed kidney or ureter would logically preclude dissolution of struvite nephroliths or ureteroliths.

Dissolution of nephroliths presumed to be composed of infection-induced struvite in six dogs has been reported. The mean time required for dissolution was 184 days (range 67 to 300 days). Although the dogs had varying degrees of impaired capacity to concentrate urine as a result of pyelonephritis, none had primary renal azotemia at the time therapy was initiated with the veterinary therapeutic struvite litholytic food and antimicrobial agents. This point is emphasized because dogs with moderate to severe primary renal failure require a greater quantity of protein for anabolism than normal. The litholytic food used could induce or aggravate protein malnutrition if given for prolonged periods to dogs with moderate azotemic primary renal failure, or other comorbid disorders associated with protein malnutrition (Polzin et al, 1983).

REASSESSMENT

Because litholytic foods stimulate thirst and promote diuresis, the magnitude of pollakiuria in dogs with urocystoliths may increase for a variable time following initiation of dietary therapy. However, pollakiuria and the abnormal urine odor caused by bacterial degradation of urea usually subside as infection is controlled and uroliths decrease in size (**Table 43-6**). Reduction in ammonia-induced chemical inflammation as a result of ureolysis may also be involved in remission of these clinical signs. **Table 43-7** summarizes mean times for struvite urolith dissolution.

The size of uroliths should be periodically monitored by survey radiography or ultrasonography (typically, monthly intervals are recommended). Survey radiography or ultrasonography is usually preferred to retrograde double-contrast urocystography because use of transurethral catheters during retrograde radiographic studies may result in iatrogenic UTI. Alternatively, intravenous urography may be considered.

Periodic evaluation of urine sediment for crystalluria also may be considered. Struvite crystals should not form in fresh uncontaminated urine if therapy has been effective in promoting formation of urine that is undersaturated with MAP.

UTIs may persist despite antimicrobial therapy in patients having infection-induced struvite uroliths and consuming the litholytic food. In most patients, however, the magnitude of bacteriuria is markedly reduced (i.e., from more than 100,000 to approximately 1,000 cfu (colony forming units)/ml of urine) and the associated inflammatory response progressively subsides. Difficulty in eradicating the infection while uroliths persist may be related to persistence of viable microbes within the uroliths (Nickel et al, 1985). Diet-induced diuresis should be considered when formulating dosages of antimicrobial agents that will achieve minimum inhibitory concentrations in urine. Excellent success may be achieved in inducing dissolution of struvite uroliths despite persistent bacteriuria during antimicrobial and dietary treatment. Even though the urine is not sterile, reduction in bacterial colony counts by logarithmic magnitudes (e.g., from 10^6 to 10^4 cfu/ml) has a marked effect in reducing the quantity of microbial urease in urine (Griffith and Osborne, 1987). Concomitant use of litholytic foods, antimicrobial agents and acetohydroxamic acid is the most effective method of inducing dissolution of uroliths when UTI complications persist.

Urine collected by cystocentesis should be quantitatively cultured during therapy and five to seven days after antimicrobial therapy is discontinued. Results of urine culture may not be the same as results obtained before therapy or from cultures of the interior of uroliths. Rapid recurrence of UTI caused by the same type of organism (relapse) or a different type of bacterial pathogen (reinfection) following withdrawal of antimicrobial therapy may indicate residual uroliths within the urinary tract or other abnormalities in local host defense mechanisms that predispose the patient to UTI and recurrent struvite urolithiasis (Osborne and Stevens, 1999a).

Because small uroliths may escape detection by survey radiography or ultrasonography, continue the struvite litholytic food and (if necessary) antimicrobial agents for at least one "insurance" month after radiographic or ultrasonographic documentation of urolith dissolution. Recall that survey radiography may not detect uroliths ≤0.3 mm in size. This protocol is likely to prevent recurrence of clinical signs from remaining uroliths that were missed by conventional survey radiography or ultrasonography. Alternate methods of management should be considered if uroliths increase in size during therapy or if urolith size remains unchanged after approximately eight weeks of appropriate dietary and medical therapy. Small uroliths that become lodged in the urethra of male or female dogs during therapy may be readily returned to the urinary bladder lumen by retrograde urohydropropulsion (Figure 38-5 and Table 38-7). They may also be removed by lithotripsy. Complete obstruction of a ureter or renal pelvis with a urolith, especially with concomitant UTI, is an indication for surgical intervention.

Attempts to induce dissolution of struvite uroliths may be hampered if the uroliths are heterogeneous in composition (**Table 43-8**). This has not been a significant problem in dogs with uroliths composed primarily of MAP with lesser quantities of calcium apatite because the solubility characteristics of the two minerals are similar. However, some clinicians have encountered difficulty in dissolving uroliths composed primarily of struvite with an outer shell composed primarily of calcium apatite. Difficulty will also be encountered in attempting to induce complete dissolution of a urolith with a nucleus of calcium oxalate or silica and a shell of struvite because the solubility characteristics of these minerals are dissimilar. This phenomenon should be considered if dietary and medical therapy seems to be ineffective after initially reducing the size of a urolith.

PREVENTION

Table 43-9 lists commercial veterinary therapeutic foods intended for the prevention of recurrence of struvite urolithiasis and compares them to the key nutritional factor targets. Because these foods are intended for long-term feeding, they should also be approved by the Association of American Feed Control Officials (AAFCO), or some other credible regulatory agency. However, recommendations for the use of these foods are not straightforward. Caveats regarding their use depend upon whether the struvite uroliths are infection-induced or form in sterile urine. Also, concurrent or alternative medical management must be considered.

Infection-Induced Struvite Uroliths

Eradication or control of UTIs due to urease-producing bacteria is the most important factor in preventing recurrence of most infection-induced struvite uroliths (Osborne and Stevens, 1999a). If UTI persists or is recurrent, indefinite therapy is indicated with prophylactic dosages of antimicrobial agents eliminated in high concentration in urine. These may include amoxicillin, nitrofurantoin and trimethoprim-sulfadiazine; however, the final choice is best determined by the results of the most recent antimicrobial susceptibility test. In light of the effectiveness of litholytic foods in inducing dissolution of struvite uroliths, use of these same foods (**Table 43-5**) to minimize recurrence of uroliths is logical and feasible. However, the long-term (measured in years) effects of low-protein litholytic foods in dogs that may be predisposed to urolith formation are not yet known. Litholytic foods induce polyuria, varying degrees of hypoalbuminemia and mild alterations in hepatic enzyme activities and morphology. Therefore, long-term use of litholytic foods with severely reduced protein levels should be recommended only if patients develop frequently recurrent urolithiasis despite attempts to control infection, augment fluid intake and urine acidification. In other words, the benefits of therapy should outweigh the risks.

Results of experimental and clinical studies to evaluate the effectiveness of acetohydroxamic acid indicate that this drug

Table 43-7. Mean times for struvite urolith dissolution.

Urolith location and infective status	Mean time for dissolution	Comments and precautions
Infection-induced urocystoliths	Approximately 2.5 months (range two weeks to seven months)	Use appropriate caution in dogs at increased risk for pancreatitis, dogs with renal failure and dogs with hypoalbuminemic edema
Sterile urocystoliths	Three to four weeks	If idiopathic, appropriately monitor for recurrence
Infection-induced struvite urocystoliths in immature dogs	Less than two weeks	If circumstances warrant feeding for a longer period, serial monitor body weight, body condition, serum albumin concentration and packed cell volume for evidence of protein-calorie malnutrition
Infection-induced nephroliths	Approximately 184 days (range 67 to 300 days)	Contraindicated in dogs with concomitant obstruction to urine outflow

Table 43-8. Managing magnesium ammonium phosphate uroliths refractory to complete dissolution.

Causes	Identification	Therapeutic goal
Client and patient factors		
Inadequate dietary compliance	Question owner Persistent struvite crystalluria Urea nitrogen >8-12 mg/dl Urine specific gravity >1.010-1.015 Urinary pH is alkaline during treatment with the litholytic food*	Emphasize need to feed dissolution food exclusively
Inadequate antibiotic administration	Question owner Count remaining antibiotic pills	Emphasize need to administer the full dose of antibiotics 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	Analysis of retrieved urolith	Alter therapy based on identification of mineral type
Inappropriate antibiotic choice	Positive urine culture with poor susceptibility for chosen antibiotic	Choose antibiotics based on susceptibility testing
Inappropriate antibiotic dose for degree of diuresis	Positive quantitative urine culture with same bacterial species and same susceptibility; number of bacteria may be lower (See text.)	Administer antibiotic at the higher recommended dose or consider a higher dose than recommended
Premature discontinuation of antibiotic	Discontinuing antibiotic before complete urolith dissolution Positive urine culture with same bacterial species and the same susceptibility (See text.)	Prescribe full antibiotic dose for the entire period of urolith dissolution
Disease factors		
Change in bacterial susceptibility	Positive urine culture with susceptibility results different from those of previous culture	Choose antibiotic based on susceptibility testing
New bacterial infection	Positive urine culture identifying new bacterial species	Choose antibiotic effective against both bacteria Avoid procedures requiring urinary tract catheterization
Compound urolith	Radiographic density of nucleus and outer layer(s) of urolith is different Analysis of retrieved urolith	Alter therapy based on identification of 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 removal Remove small uroliths by voiding urohydropropulsion or lithotripsy

*See **Table 43-5**.

Table 43-9. Key nutritional factors in selected commercial veterinary therapeutic food used to minimize recurrence of struvite urolithiasis in dogs compared to recommended levels.*

Dry foods	Protein (%)	Phosphorus (%)	Magnesium (%)	Urinary pH**
Recommended levels	**<25**	**<0.6**	**0.04-0.1**	**6.2-6.4**
Hill's Prescription Diet c/d Canine	22.3	0.59	0.111	6.22
Hill's Prescription Diet w/d Canine	18.9	0.56	0.088	6.40
Hill's Prescription Diet w/d with Chicken Canine	19.1	0.56	0.080	6.30
Medi-Cal Preventive Formula	23.9	0.8	na	na
Medi-Cal Urinary SO	16.7	0.6	0.2	5.5-6.0
Medi-Cal Weight Control/Mature	19.5	0.8	na	6.4
Purina Veterinary Diet DCO Dual Fiber Control	25.3	0.93	0.130	6.0-6.2
Purina Veterinary Diet OM Overweight Management	31.1	0.89	0.130	6.2-6.4
Royal Canin Veterinary Diet Control Formula	23.9	0.84	0.130	6.0-6.3
Royal Canin Veterinary Diet Urinary SO 14	17.0	0.63	0.066	5.5-6.0

Moist foods	Protein (%)	Phosphorus (%)	Magnesium (%)	Urinary pH**
Recommended levels	**<25**	**<0.6**	**0.04-0.1**	**6.2-6.4**
Hill's Prescription Diet c/d Canine	23.6	0.51	0.079	6.16
Hill's Prescription Diet w/d Canine	17.9	0.52	0.088	6.40
Medi-Cal Preventive Formula	23.8	0.7	na	na
Medi-Cal Urinary SO	18.7	0.8	0.1	5.5-6.0
Medi-Cal Weight Control/Mature	21.5	0.6	na	6.6
Purina Veterinary Diet OM Overweight Management	44.1	1.06	0.190	6.2-6.4
Royal Canin Veterinary Diet Control Formula	22.8	0.66	0.078	6.0-6.3
Royal Canin Veterinary Diet Urinary SO	18.5	0.86	0.059	5.5-6.0

Key: na = information not available from the manufacturer.
*Manufacturers' published values; nutrients expressed on a dry matter basis; moist foods are best.
**Protocols for measuring urinary pH may vary.

should be considered in an effort to minimize recurrence of infection-induced struvite urolithiasis in dogs with persistent UTI with urease-producing bacteria despite appropriate antimicrobial therapy. Administration of 25 mg of acetohydroxamic acid/kg body weight/day to dogs with urinary bladder foreign bodies (zinc disks) and induced urease-positive staphylococcal UTIs was effective in preventing formation of and minimizing the growth rate of uroliths (Krawiec et al, 1984a). Acetohydroxamic acid has also been reported to be effective in preventing struvite uroliths induced by ureaplasmas in rats.[a]

Previously, acidifying foods with mild to moderately reduced levels of protein, magnesium and phosphorus (**Table 43-9**) have been recommended as part of the therapeutic strategy to minimize recurrence of infection-induced struvite uroliths. However, clinical experience with use of such foods has prompted modification of this recommendation for two primary reasons. First, because infection-induced uroliths cannot form without an infection with urease-producing microbes, eradication of the UTI should be the first priority in context of the pathophysiology associated with this type of urolith. Infection-induced struvite will likely not recur in the absence of a urease-producing microbe. Second, prolonged use of this type of food has been associated with calcium oxalate crystalluria and/or calcium oxalate uroliths, especially in dogs predisposed to calcium oxalate uroliths. In addition, appropriate caution should be used in deciding whether or not to induce prophylactic diuresis in patients with a history of struvite uroliths induced by recurrent UTI. Although formation of less concentrated urine tends to minimize the supersaturation of urine with lithogenic crystalloids (a benefit), it tends to counteract innate antimicrobial properties of urine (a risk). Studies performed in rats and cats indicate that diuresis tends to minimize pyelonephritis, but enhance lower UTIs. This is not an "all or none; always or never" recommendation. However, pending the results of properly controlled clinical trials, this seems to be the safest and most effective ethical course of action.

Sterile Struvite Uroliths

Although apparently uncommon, sterile struvite uroliths have a greater tendency to recur than infection-induced struvite uroliths in which the UTI has been eradicated or controlled. Administration of urine acidifiers should be considered if the urinary pH of patients with sterile struvite uroliths remains persistently alkaline. The prophylactic value of concomitant restriction of dietary phosphorus, magnesium and urine acidification has not yet been conclusively determined primarily because of lack of clinical cases to perform double-blind controlled studies. Unfortunately, the infrequency with which dogs with sterile uroliths are encountered does not lend itself to such clinical studies. Nonetheless, it seems unreasonable and unethical to do nothing for patients with recurrent struvite uroliths until clinical trials are completed. Therefore, pending the availability of appropriate data, therapy should be designed to first do no harm. When considering dietary management (**Table 43-9**), emphasize minimizing recurrence of calcium oxalate and calcium phosphate uroliths, because these types of uroliths cannot be dissolved by dietary and medical management. Should struvite uroliths recur, they often can be dissolved by dietary management and antimicrobial agents (if necessary). When foods designed to produce acidic urine are used, urinary pH should be closely monitored with the aid of a reliable pH meter rather than commercially available reagent strips with a pH pad. Likewise, urine output should be estimated with the aid of a reliable refractometer designed to provide reproducible urine specific gravity values. Urine sediment should be evaluated for crystals and evidence of infection by microscopic examination of freshly voided urine.

Uncontrollable risk factors (i.e., defective inhibitors of crystal formation and/or defective inhibitors of crystal aggregation) may be present in those situations in which dogs have documented occurrences of either calcium oxalate or calcium phosphate followed by struvite urolithiasis. If struvite urolithiasis is associated with urease-positive UTIs, appropriate therapy should be devised to eradicate the UTI and minimize its recurrence.

ENDNOTES

a. Osborne CA. Unpublished data. 1987.
b. Hill's Pet Nutrition, Inc., Topeka, KS, USA.

REFERENCES

The references for **Chapter 43** can be found at www.markmorris.org.

CASE 43-1

Dysuria in a German Shepherd Crossbred Dog

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Patient Assessment

A 12-year-old neutered female German shepherd crossbred dog was examined for dysuria and pollakiuria of two months' duration. Other than nonspecific dermatitis and a perianal adenoma, the dog had no previous history of illness.

Physical examination revealed an alert, active, overweight dog (body weight 27 kg, body condition score 4/5). Multiple uroliths were palpated in the urinary bladder. No other abnormalities were detected. Results of a complete blood count and a serum biochemistry profile were normal except for a mild elevation in alkaline phosphatase activity (**Tables 1** and **2**). Analysis of a urine specimen collected by cystocentesis (**Table 3**) revealed an alkaline pH, struvite crystalluria and findings typical of inflammation (i.e., hematuria, pyuria, proteinuria). Quantitative culture of urine revealed more than 10^5 colony-forming units of urease-producing *Staphylococcus intermedius* organisms per ml of urine. The bacteria were susceptible to most antimicrobial drugs. Survey radiographs of the abdomen revealed three uroliths within the bladder lumen (**Figures 1** and **2**); the sizes of the kidneys and liver were normal.

Assess the Food and Feeding Method

A commercial dry adult maintenance food was offered free choice. Table foods were fed frequently.

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. How should therapeutic efficacy be monitored?

Answers and Discussion

1. The most likely mineral composition of the uroliths is struvite based on: 1) urease-positive staphylococcal urinary tract infection, 2) alkaline urinary pH, 3) struvite crystalluria (no oxalate, cystine or urate crystals) and 4) detection of radiodense uroliths.
2. Although surgery may be effective, dietary and medical protocols have been developed to dissolve struvite uroliths. Surgical removal of urocystoliths has the obvious advantage of rapid correction of the disease process. Dietary and medical therapy may also be effective and includes using a proven commercial veterinary therapeutic struvite litholytic food.[a] Concurrent treatment of the urinary tract infection with appropriate antimicrobials is an essential part of the treatment protocol. The litholytic food should be fed until radiographic evidence of urolith dissolution is obtained. The food is usually fed for one additional "insurance" month following dissolution because survey radiography is not sufficiently sensitive to detect small uroliths (≤3 mm).
3. Therapeutic efficacy should be monitored by monthly evaluation of clinical signs, radiographs, urinalyses and urine cultures. Clinical signs often resolve within three to five days of initiating therapy. Consumption of the litholytic food is usually associated with polyuria, formation of less concentrated acidic urine, marked reduction in serum urea nitrogen concentration, reduction

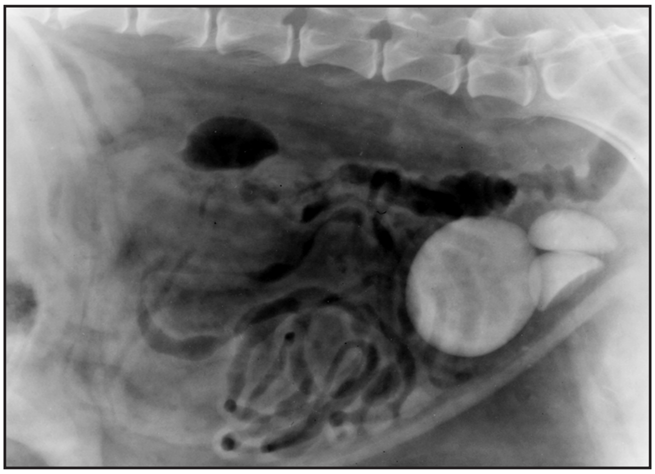

Figure 1. Survey lateral abdominal radiograph illustrating multiple radiodense uroliths in the urinary bladder of a 12-year-old spayed female German shepherd crossbred dog.

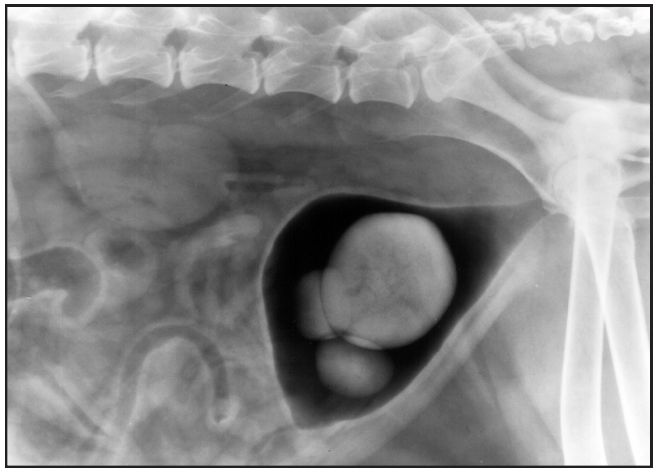

Figure 2. Pneumocystogram of the dog described in Figure 1. Note a diverticulum at the vertex of the urinary bladder.

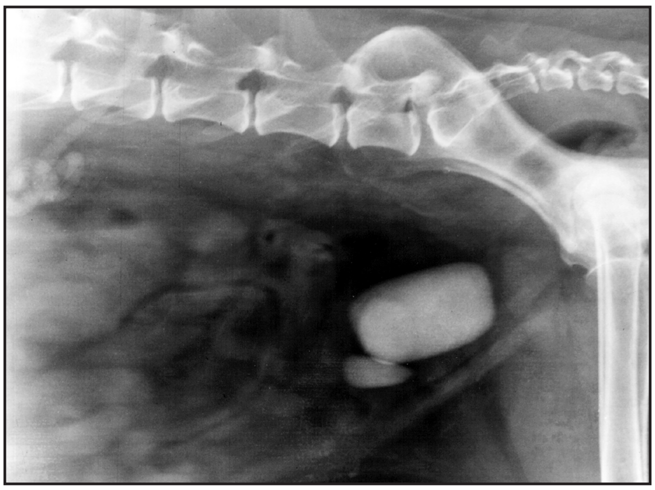

Figure 3. Survey lateral abdominal radiograph of the dog described in Figure 1. This radiograph was obtained 30 days after initiation of litholytic therapy. (Compare this Figure with Figures 4 through 6.)

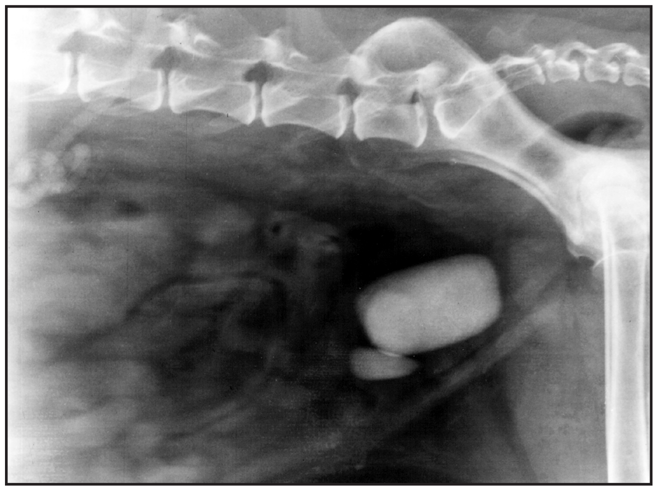

Figure 4. Survey lateral abdominal radiograph of the dog described in Figure 1. This radiograph was obtained 58 days after initiation of litholytic therapy. (Compare this Figure with Figures 5 and 6.)

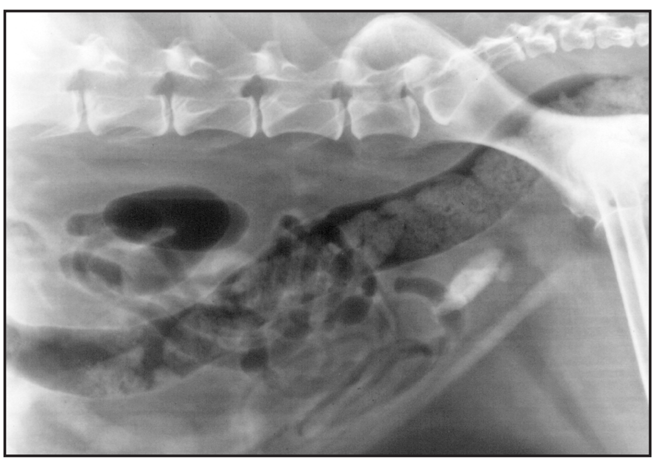

Figure 5. Survey lateral abdominal radiograph of the dog described in Figure 1. This radiograph was obtained 97 days after initiation of litholytic therapy. (Compare this Figure with Figure 6.)

Figure 6. Survey lateral abdominal radiograph of the dog described in Figure 1. This radiograph was obtained 127 days after initiation of litholytic therapy.

Table 1. Hemograms of a 12-year-old spayed female German shepherd crossbred dog with urocystoliths.

Factors*	**Reference values**	**Day 1****	**Day 35**	**Day 63**	**Day 102**	**Day 132**	**Day 159**	**Day 196**	**Day 256**
PCV (%)	38.5-56.7	41	40	41	39	38	38	38	40
Hb (g/dl)	13.5-19.9	15.6	15.3	15.1	15.8	15.2	14.7	15.0	16.4
WBC (10^3/µl)	4.1-13.3	16	8.9	7.3	6.2	8.9	9.4	7.4	4.7
Lymphocytes (10^3/µl)	0.3-5.1	1.6	2.6	3.4	2.3	4.2	3.4	2.6	4.6
Neutrophils (10^3/µl)	2.1-11.2	7.5	7.1	6.0	6.9	5.2	5.5	5.8	5.1
Eosinophils (10^3/µl)	0.0-1.2	1	0	2	2	3	5	9	2
Monocytes (10^3/µl)	0.0-1.2	8	3	4	6	3	4	6	1

Key: PCV = packed cell volume, Hb = hemoglobin, WBC = white blood cells.
*Platelets were estimated on a blood film and considered adequate in all specimens. Normoblasts and basophils were not observed.
**Therapy with a litholytic food and an antimicrobial agent was initiated on Day 5 and discontinued on Day 159.

Table 2. Serum biochemistry values of a 12-year-old spayed female German shepherd crossbred dog with urocystoliths.

Factors	**Reference values**	**Day 1***	**Day 35**	**Day 63**	**Day 102**	**Day 132**	**Day 159**	**Day 196**	**Day 256**
SUN (mg/dl)	7-28	24	4	3	3	3	3	29	40
Creatinine (mg/dl)	0.5-1.5	1.3	1.4	1.4	1.4	1.4	1.3	1.7	1.5
Calcium (mg/dl)	9.3-11.4	10.2	9.7	10.0	10.1	10.4	10.0	10.7	10.3
Phosphorus (mg/dl)	1.9-7.0	3.5	3.5	4.3	3.0	3.6	3.1	3.6	4.7
Magnesium (mg/dl)	1.5-2.7	2.3	1.9	2.0	1.8	1.7	1.8	2.1	2.1
Sodium (mEq/l)	143-150	149	147	145	147	146	144	147	148
Potassium (mEq/l)	3.2-5.6	4.6	5.0	5.5	5.6	5.1	5.3	4.8	5.2
Chloride (mEq/l)	108-125	119	119	119	118	118	118	117	115
Albumin (g/dl)	2.4-3.8	2.4	2.2	2.2	2.3	2.3	2.1	2.8	-
ALT activity (U/l)	5-62	56	46	32	26	25	28	31	35
Alk phos activity (U/l)	10-149	238	1,270	1,580	1,920	1,470	695	337	208
Total bilirubin (mg/dl)	0.1-0.6	0.1	0.1	0.2	0.2	0.1	0.2	0.1	0.1

Key: SUN = serum urea nitrogen, ALT = alanine aminotransferase, Alk phos = alkaline phosphatase.
*Therapy with a litholytic food and an antimicrobial agent was initiated on Day 5 and discontinued on Day 159.

Table 3. Urinalyses of a 12-year-old spayed female German shepherd crossbred dog with urocystoliths.*

Factors**	**Day 1*****	**Day 35**	**Day 63**	**Day 102**	**Day 132**	**Day 159**	**Day 196**	**Day 256**
Specific gravity	1.019	1.008	1.007	1.008	1.007	1.006	1.019	1.018
pH	8.5	6.5	7.0	7.5	6.5	5.0	6.0	7.0
Protein†	4+	2+	2+	1+	1+	Trace	1+	2+
RBC††	TNTC	TNTC	TNTC	9-11	0	0	0	0
WBC††	75-85	1-2	0	1-3	0	0	0	0
Crystals†††	Struvite	Struvite	Struvite	Amorphous phosphate	0	0	0	0

Key: RBC = red blood cells, TNTC = too numerous to count, WBC = white blood cells.
*Samples collected by cystocentesis.
**Glucose, bilirubin and acetone were not detected in any specimen.
***Therapy with a litholytic food and an antimicrobial agent was initiated on Day 5 and discontinued on Day 159.
†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).

in serum magnesium concentration and an increase in serum alkaline phosphatase activity. Hematuria, pyuria and bacteriuria should resolve with dietary and appropriate antimicrobial therapy.

Progress Notes

Therapy was initiated with Prescription Diet s/d Canine (1,150 kcal [4.8 MJ], one can fed twice daily) and ampicillin administered orally (7 mg/kg body weight q12h). Survey radiographs obtained monthly revealed progressive reduction in the size of the uroliths (**Figures 3** to **6**). Radiodense uroliths could not be detected by survey radiography on Day 132 (**Figure 6**).

Following initiation of antimicrobial therapy, bacteria could not be cultured from urine specimens obtained by cystocentesis. Urinalysis revealed acidification of urine and disappearance of pyuria and hematuria (**Table 2**). Consumption of the litholytic food was associated with formation of less concentrated urine, reduction in serum urea nitrogen concentration, reduction in serum magnesium concentration and an increase in serum alkaline phosphatase activity (**Tables 2** and **3**). Results of complete blood counts were normal over the treatment period. Most laboratory parameters returned to baseline values following withdrawal of antimicrobial therapy and a return to a commercial adult maintenance-type food on Day 159 (**Tables 2** and **3**).

Because the dog was overweight at the beginning of therapy, the owners fed a reduced amount of food to promote weight loss. The dog lost 1.6 kg during therapy.

Further Discussion

This case typifies dietary and medical dissolution of large urocystoliths. Reduction in the concentration of urea nitrogen, acidification of urine and formation of urine with a low specific gravity indicate that the owner and the dog were complying with therapy. Microbial sterilization of urine indicated that the proper antimicrobial agent was being given at the correct dosage and was being excreted in effective concentrations in urine. However, urine sterilization is not always achieved during medical therapy designed to induce urolith dissolution. Inability to sterilize urine during therapy may be related to: 1) release of bacteria from the urolith during dissolution, 2) induction of diuresis, which impairs the antimicrobial effects of urine, 3) induction of diuresis, which reduces the concentration of antimicrobial agent in urine and/or 4) reduced clearance of urea, which may impair the antimicrobial effects of urine. However, despite persistence of bacteriuria during therapy, uroliths composed of struvite will dissolve and the associated inflammatory response will subside. Antimicrobial therapy should be continued until the uroliths completely dissolve.

Varying degrees of elevated serum alkaline phosphatase activity frequently occur in dogs fed very low-protein foods such as the veterinary therapeutic food fed to this patient. Studies in dogs indicate that the alkaline phosphatase is of hepatic origin. The greatest increases in serum alkaline phosphatase activity occur in dogs that do not consume an adequate amount of the veterinary therapeutic food. Contrary to the situation in this case, the litholytic food should not be fed with a goal of weight reduction because this practice may contribute to negative nitrogen balance. Weight reduction should be achieved with an appropriate food after resolution of the urocystolith problem.

Endnote

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

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CASE 43-2

Dysuria in a Puppy

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Patient Assessment

A nine-week-old, male, mixed-breed puppy was examined for dysuria, anorexia, vomiting and depression of one day's duration. The history was incomplete because the owners had acquired the puppy only five days earlier. Physical examination was unremarkable except for an overdistended, painful urinary bladder. Palpation of the urinary bladder induced a micturition reflex, but the puppy was unable to void. The puppy's body weight (5 kg) and condition (body condition score 3/5) were normal.

Survey abdominal radiographs revealed multiple, radiodense uroliths in the penile urethra. Following decompression of the urinary bladder by abdominal cystocentesis, the urethroliths were returned to the urinary bladder lumen by urohydropropulsion (**Figure 1**). Analysis of an aliquot of urine collected by cystocentesis revealed an inflammatory response associated with bacteriuria (**Table 1**). Quantitative aerobic and anaerobic culture of urine revealed >10^5 colony-forming units/ml of urease-positive *Staphylococcus intermedius*. The bacteria were susceptible to most commonly used antimicrobial agents. Results of a complete blood count were normal except for a stress-induced mature neutrophilic leukocytosis. Results of a serum biochemistry profile were unremarkable (**Table 2**).

A small urolith was spontaneously voided and submitted for quantitative mineral analysis one day later.

Assess the Food and Feeding Method

The dog was fed a commercial dry specialty brand growth food (Science Diet Canine Growth[a]) twice daily.

Questions

1. What is the most likely urolith type in this patient?
2. What additional diagnostic tests might be important?
3. Outline an appropriate treatment and feeding plan for this puppy.

Answers and Discussion

1. The most likely urolith type in this patient is magnesium ammonium phosphate (struvite). This "guesstimate" is based on finding a urinary tract infection with a urease-producing staphylococcal bacteria and radiodense uroliths. Infection-induced struvite uroliths can form within days and may occur in dogs at any age including very young dogs.
2. Anatomic defects of the urinary tract can predispose animals to bacterial infection. Ultrasound and/or contrast radiography should be considered to evaluate the lower urinary tract for such defects.
3. Dietary and medical or surgical protocols can be used to treat this puppy. Dietary and medical therapy designed to induce struvite urolith dissolution includes an appropriate orally administered antimicrobial agent and a food with restricted levels of protein, magnesium and phosphorus that is metabolized to produce an acidic urinary pH. Because foods formulated to aid in dissolution of struvite uroliths contain reduced quantities of protein, calcium, magnesium and phosphorus and thus are not designed to meet the long-term nutritional requirements of immature dogs, the feeding plan should be monitored closely. Monitoring serum biochemistry parameters (albumin, phosphorus, calcium, etc.) is an acceptable means of determining nutritional status in young dogs. An alternate treatment method includes a cystotomy to remove the uroliths; however, anesthesia and surgery in an immature dog are also associated with some degree of risk.

Progress Notes

Quantitative analysis of the voided urolith revealed that it was composed of 95% magnesium ammonium phosphate hexahydrate and 5% carbonate apatite. Retrograde positive-contrast urethrocystography and double-contrast cystography revealed a diverticulum located at the bladder vertex (**Figures 2** and **3**). The urethral lumen was also narrowed just distal to the site normally occupied

Table 1. Urinalyses of an immature male, mixed-breed dog with dysuria.*

Factors	Day 1**	Day 10	Day 25	Day 39	Day 73	Day 226
Specific gravity	1.021	1.005	1.042	1.050	1.030	1.052
pH	6.5	5.5	6.0	6.0	7.0	6.5
Protein***	3+	Trace	1+	1+	Neg	1+
RBC†	TNTC	20-30	20-30	TNTC	0	0
WBC†	TNTC	0	2-3	20-25	0	0
Bacteria†	Many cocci	0	0	0	0	0
Crystals††	0	0	0	0	0	0
Culture	*S. intermedius*	Neg	Neg	Neg	Neg	Neg

Key: Neg = negative, RBC = red blood cells, TNTC = too numerous to count, WBC = white blood cells.
*Samples collected by cystocentesis.
**Dietary and medical therapy for urinary tract infection and urolith dissolution was initiated on Day 2 and discontinued on Day 10. Antibiotic therapy for urinary tract infection was initiated on Day 2 and discontinued on Day 39.
***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).

Table 2. Serum biochemistry values of an immature male, mixed-breed dog with dysuria.

Factors	Reference values	Day 1*	Day 10	Day 25	Day 39	Day 73	Day 226
SUN (mg/dl)	7-28	28	2	8	20	12	12
Creatinine (mg/dl)	0.5-1.5	1.0	0.7	0.5	0.7	0.9	1.2
Calcium (mg/dl)	9.3-11.4	9.5	11.3	11.3	11.1	11.3	11.0
Phosphorus (mg/dl)	1.9-7.0	8.9	6.7	9.3	9.5	7.6	5.1
Sodium (mEq/l)	143-150	139	148	147	151	147	148
Chloride (mEq/l)	108-125	104	114	110	113	109	111
Potassium (mEq/l)	3.2-5.6	3.9	6.8	5.2	4.8	4.6	4.4
Albumin (g/dl)	2.4-3.8	3.2	2.7	3.1	3.3	3.7	4.1
ALT activity (U/l)	5-62	32	27	58	61	55	68
Alk phos activity (U/l)	10-149	180	349	207	186	113	62
Total bilirubin (mg/dl)	0.1-0.6	0.2	0.6	0.2	0.3	0.2	0.2
Total CO_2 (mEq/l)	17-26	20.5	21.1	20.8	23.4	21.6	20.1

Key: SUN = serum urea nitrogen, ALT = alanine aminotransferase, Alk phos = alkaline phosphatase.
*Dietary and medical therapy for urinary tract infection and urolith dissolution was initiated on Day 2 and discontinued on Day 10. Antibiotic therapy for urinary tract infection was initiated on Day 2 and discontinued on Day 39.

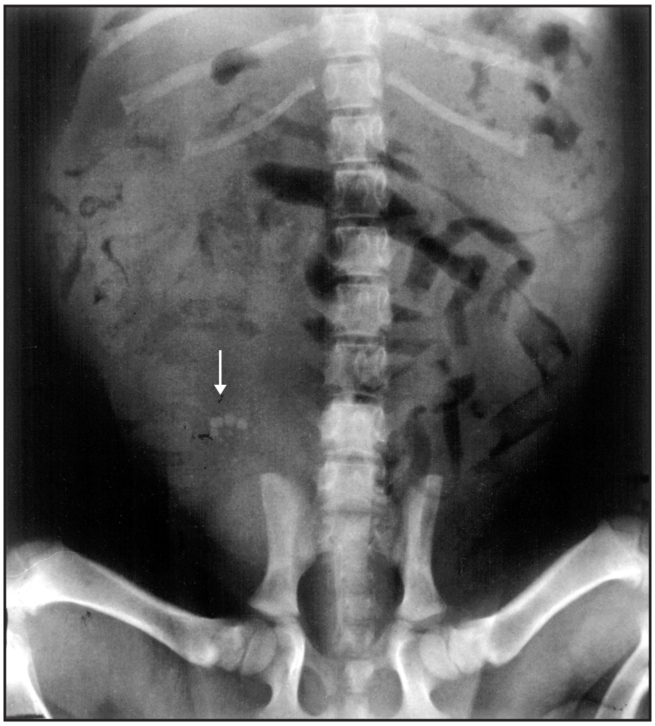

Figure 1. Ventrodorsal survey abdominal radiograph of a nine-week-old male dog with multiple radiodense urocystoliths (arrow).

Figure 2. Positive-contrast retrograde urethrocystogram of the same dog described in Figure 1. Note the vesicourachal diverticulum (top arrow) and narrowing of the proximal portion of the urethra (bottom arrow).

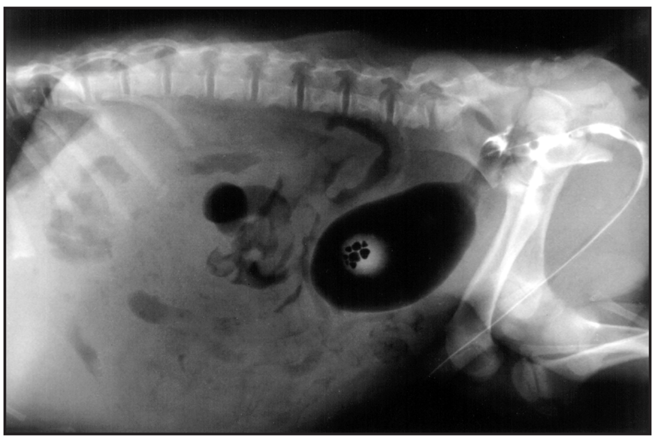

Figure 3. Double-contrast cystogram with at least eight uroliths in the bladder lumen. Radiopaque contrast medium has refluxed into the periurethral tissue in the area of the prostate gland. The urethral lumen contains air bubbles surrounded by contrast medium.

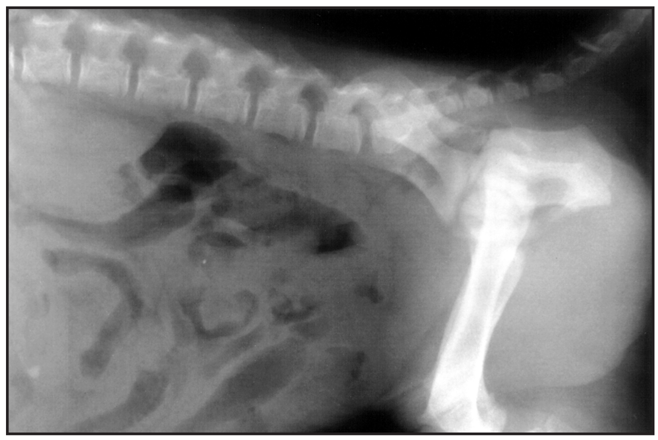

Figure 4. Survey abdominal radiograph obtained 10 days following initiation of therapy with an antibiotic and a food designed to dissolve struvite uroliths. Radiodense uroliths cannot be detected within the urinary tract.

by the prostate gland.

Dietary and medical therapy included a combination of amoxicillin and clavulanic acid (Clavamox[b]) given orally and feeding a food designed to aid in dissolution of struvite uroliths (Prescription Diet s/d Canine[a]). Compared with typical dog foods, Prescription Diet s/d Canine is greatly reduced in protein (7.9% dry matter [DM]), reduced in phosphorus (0.10% DM), calcium (0.31% DM) and magnesium (0.02% DM) and produces a more acidic urine (target urinary pH = 5.9 to 6.1). The puppy was fed one-half can three times daily (700 kcal [2.93 MJ]).

Gross hematuria and dysuria progressively declined. A urine sample collected by cystocentesis 10 days later revealed acidification of the urine and marked reduction in the inflammatory response (**Table 1**). Formation of less concentrated urine (reduction in renal medullary urea concentration) and marked reduction in serum urea nitrogen concentration (**Table 2**) was attributed to the low-protein food. Aerobic culture of urine resulted in no growth. Survey abdominal radiography, positive-contrast urethrocystography and

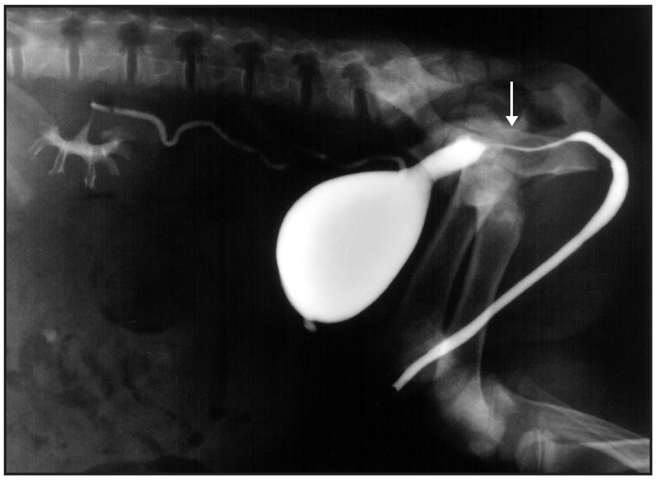

Figure 5. Positive-contrast retrograde urethrocystogram obtained 39 days following diagnosis of uroliths and a vesicourachal diverticulum. There is no evidence of a vesicourachal diverticulum, but narrowing of the lumen of the proximal urethra is still present (arrow).

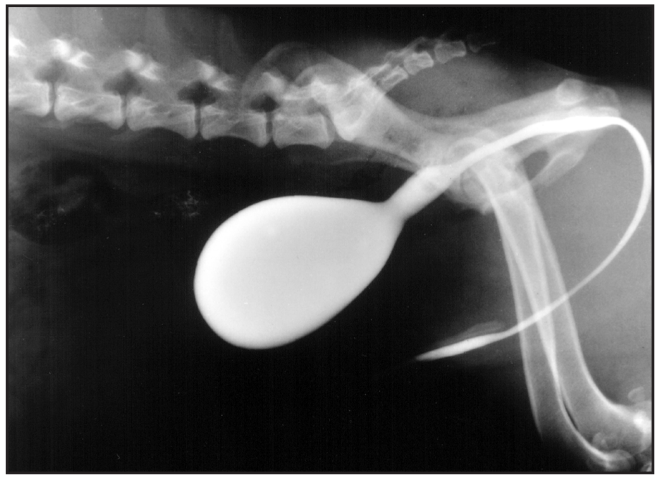

Figure 6. Positive-contrast retrograde urethrocystogram obtained 226 days following initial assessment. The lower urinary tract appears normal.

double-contrast cystography revealed no evidence of uroliths in the lower urinary tract. The vesicourachal diverticulum was still present but reduced in size (**Figure 4**). Serum albumin (2.7 g/dl), phosphorus (6.7 mg/dl) and urea nitrogen (2 mg/dl) concentrations had decreased from initial values (**Table 2**).

Because urolith dissolution was complete and because of diet-related alterations in serum phosphorus and albumin concentrations, the food was changed to a moist product designed for growing dogs (Science Diet Canine Growth), fed twice daily. The oral antimicrobial agent was continued for an additional two weeks.

Reevaluation of the dog 25 days after the initial diagnosis revealed further reduction in the size of the vesicourachal diverticulum. The dog was forming concentrated urine, but still had microscopic hematuria (**Table 1**). Serum albumin and phosphorus concentrations were normal (**Table 2**). Antimicrobial therapy was continued.

Fourteen days later (39 days after the initial diagnosis), survey and contrast radiographs revealed no evidence of the vesicourachal diverticulum or uroliths (**Figure 5**). However, the urethral lumen adjacent to the prostate gland was still reduced. Nevertheless, the dog had no clinical signs of lower urinary tract disease. Although bacteria could not be cultured by aerobic techniques, urinalysis revealed an inflammatory response (**Table 1**).

No clinical or laboratory evidence of disease was present 73 days after the initial diagnosis (**Tables 1** and **2**). Antimicrobial therapy was discontinued. Evaluation at 10 months of age revealed a normal dog with no detectable radiographic abnormalities of the lower urinary tract (**Figure 6**).

Endnotes

a. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
b. Pfizer Animal Health, Exton, PA, USA.

Bibliography

Osborne CA, Lulich JP, Bartges JW, et al. Canine and feline urolithiasis: Relationship of etiopathogenesis to treatment and prevention. In: Osborne CA, Finco DR, eds. Canine and Feline Nephrology and Urology. Baltimore, MD: Williams & Wilkins, 1995; 798-888.

CASE 43-3

Recurrent Urinary Tract Infection in a Rottweiler

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Patient Assessment

A five-year-old, 41-kg, neutered male rottweiler was examined for recurrent dysuria and pollakiuria of six months' duration, presumed to be caused by bacterial urinary tract infection. These clinical signs had been treated intermittently with a variety of orally administered antibiotics given for intervals ranging from 10 to 21 days. Treatment was associated with remission of dysuria and pollakiuria, but these signs recurred a short time following cessation of therapy.

The results of physical examination, including rectal palpation and body condition assessment (body condition score 3/5), were normal. Micturition was normal. Analysis of a urine sample collected by cystocentesis revealed that the urine was slightly concentrated (specific gravity 1.015), had a neutral pH and contained evidence of inflammation, most likely due to an infectious process (**Table 1**). Crystals were not observed. Aerobic culture of an aliquot of urine revealed significant numbers (>10^5 colony-forming units/ml) of urease-producing *Staphylococcus intermedius*, which was susceptible to many antimicrobial agents. Results of a complete blood count and serum biochemistry profile were normal (**Table 1**).

Problems identified on the basis of the animal assessment included bacterial urinary tract infection with staphylococci characterized by dysuria and pollakiuria, possible impaired urine concentrating capacity, and hematuria, pyuria, proteinuria and bacteriuria.

Assess the Food and Feeding Method

The dog was fed a commercial dry adult maintenance food free choice and offered commercial treats/snacks several times each day.

Questions

1. What is the anatomic site or sites of the bacterial urinary tract infection?
2. Are further diagnostic tests justified for this patient?

Answers and Discussion

1. Dysuria and pollakiuria suggest involvement of the lower urinary tract but formation of urine with a specific gravity of 1.015 in absence of azotemia suggests that ascending infection may have involved the medullary portions of the kidney.
2. Additional diagnostic tests should be considered because: 1) the bacterial urinary tract infection appears to be recurrent, 2) the sites of infection and inflammation have not been confirmed and 3) the predisposing causes of infection are unknown. There is no evidence of diabetes mellitus or hyperadrenocorticism, both of which are frequently associated with recurrent bacterial urinary tract infection. Another urinalysis is indicated to assess the concentrating capacity of the kidneys. Survey and contrast abdominal radiography and/or ultrasonography will help evaluate the patient for uroliths, neoplasia and anatomic abnormalities. These imaging procedures will also assist in evaluation of the prostate gland.

Further Assessment

Results of a second urinalysis included a urine specific gravity of 1.021. Hematuria, pyuria, proteinuria and bacteriuria were still present. Survey radiography and ultrasonography of the abdomen revealed a large urolith in the pelvis of the right kidney (**Figures 1** and **2**). Retrograde positive-contrast urethrocystography revealed normal size, shape and position of the lower urinary tract and prostate gland. Double-contrast cystography revealed a few uroliths approximately 1 mm in diameter in the bladder. An intravenous urogram revealed no evidence of outflow obstruction in the ureters (**Figure 2**).

Further Questions

1. On the basis of the available data, what is the most likely mineral composition of this patient's uroliths?
2. Why were crystals not identified in the urine sediment even though the patient had multiple uroliths?
3. Outline a treatment and feeding plan for this dog.

Answers and Discussion

1. The mineral composition of the nephrolith and urocystoliths most likely is infection-induced struvite because: 1) staphylococci may cause formation of struvite uroliths, 2) very large radiodense nephroliths are usually composed of infection-induced struvite, 3) the urinary pH was not acidic and 4) crystals associated with other types of uroliths were not detected.
2. The combination of risk factors necessary for struvite crystals to form was not present at the time urine samples were collected

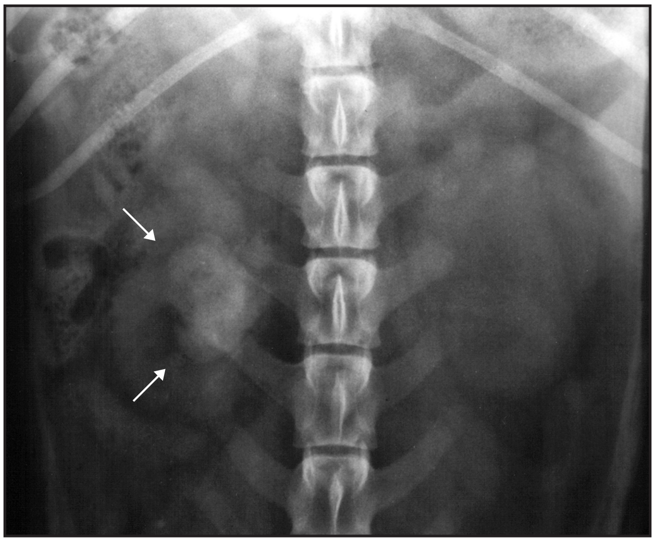

Figure 1. Survey ventrodorsal abdominal radiograph illustrating a large radiodense nephrolith (arrows) in the renal pelvis of the right kidney of a five-year-old neutered male rottweiler.

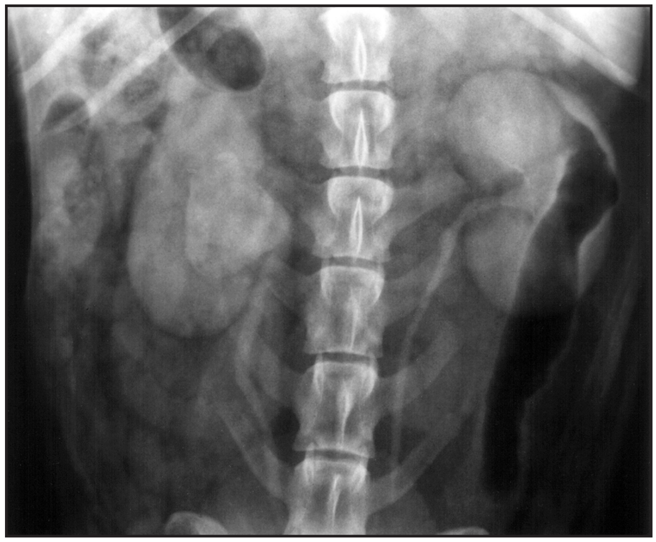

Figure 2. Intravenous urogram of the same dog described in Figure 1 showing both ureters filled with contrast material and no evidence of outflow obstruction.

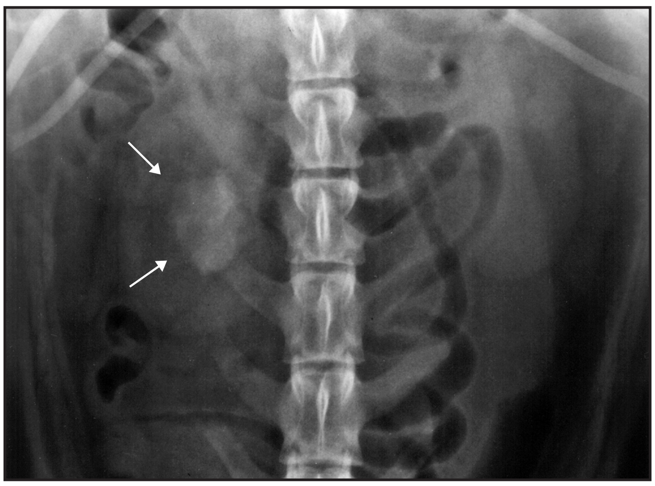

Figure 3. Survey ventrodorsal radiograph obtained five weeks after initiation of therapy with a litholytic food and antibiotics. The nephrolith (arrows) is about 75% of its original size.

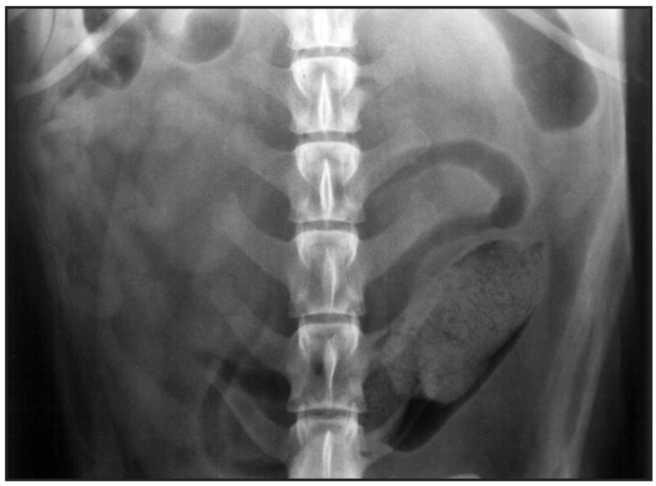

Figure 4. Survey ventrodorsal abdominal radiograph obtained 18 weeks after initiation of therapy. There is no evidence of the nephrolith in the right kidney.

for analysis. Consumption of food that usually results in acidic urine, administration of an antibiotic and formation of poorly concentrated urine may have reduced the likelihood of struvite crystalluria.

3. Dissolution of nephroliths presumed to be composed of infection-induced struvite can be accomplished using a combination of a commercial veterinary therapeutic struvite litholytic food[a] and antimicrobial therapy. In studies conducted at the University of Minnesota, the mean time required for dissolution of infection-induced nephroliths was 26 weeks (range nine to 42 weeks). Nephroliths and/or ureteroliths causing complete outflow obstruction and marked impairment of function in the associated kidney should be managed by surgical intervention. Surgical removal of uroliths has the obvious advantage of rapid correction of the mechanical components of the disease process; however, surgery cannot be relied upon to remove very small uroliths or to prevent their recurrence. Likewise, nephrectomy is always associated with destruction of nephrons, the magnitude of which is influenced by the number of renal end arteries that are transected.

Progress Notes

The owners requested dietary and medical treatment. A combination of a struvite litholytic food and a bactericidal antimicrobial agent (amoxicillin and clavulanic acid[b]), chosen on the basis of antimicrobial susceptibility results, was used. The daily energy requirement was estimated to be approximately 1,800 kcal (7.5 MJ) (1.4 x resting energy requirement) or 1.5 cans of Prescription

Table 1. Results of selected urinalysis and serum biochemistry parameters of a five-year-old neutered male rottweiler with recurrent urinary tract infection.*

Factors	Reference values	Week 0	Week 5	Week 9	Week 13	Week 18	Week 25	Week 29	Week 34
Urine specific gravity	-	1.015	1.007	1.007	1.007	1.015	1.008	1.022	1.015
Urinary pH	-	7	6	6	8	7	7	7.5	6
Hematuria	-	+	+	+	0	0	0	0	0
Pyuria	-	+	0	0	0	0	0	0	0
Bacteriuria	-	+	0	0	0	0	0	0	0
SUN (mg/dl)	7-28	26	5	9	5	6	6	13	11
Creatinine (mg/dl)	0.5-1.5	1.6	1.4	1.4	1.4	1.1	1.1	1.5	1.1
Magnesium (mg/dl)	1.5-2.7	2.3	1.9	1.8	2.0	1.8	1.6	1.8	2.0
Albumin (g/dl)	2.4-3.8	3.5	3.1	3.3	3.3	3.4	2.9	3.5	3.4
Alkaline phosphatase (U/l)	10-149	28	56	67	65	123	164	43	29

Key: + = present, 0 = absent, SUN = serum urea nitrogen.
*Therapy with a litholytic food and antibiotics was initiated during Week 1 and discontinued on Week 25.

Diet s/d Canine[a] twice daily. In order to facilitate dietary compliance, the owners were asked to restrict treats to baked slices of the moist therapeutic food. Therapeutic efficacy was monitored by physical examination and serial evaluation of survey radiographs (a ventrodorsal view is usually best for nephroliths, and a lateral view is usually best for urocystoliths), urinalyses, urine cultures, serum biochemistry profiles and complete blood counts (**Table 1**). Reduction in the serum urea nitrogen concentration and formation of less concentrated urine indicates compliance with the feeding plan.

Survey abdominal radiographs obtained at four- to five-week intervals revealed progressive reduction in the size of the nephrolith (**Figure 3**). Radiodense uroliths could not be detected on Week 18 (**Figure 4**). After initiation of antimicrobial therapy, bacteria could not be cultured from urine samples collected by cystocentesis. Urinalysis revealed progressive reduction in hematuria and pyuria (**Table 1**).

Consumption of the litholytic food was associated with polyuria, formation of less concentrated urine, reduction in the serum concentration of urea nitrogen and magnesium and an increase in serum alkaline phosphatase activity. Clinically significant changes were not observed in serial hemograms. Dietary and antimicrobial therapy was discontinued on Week 25. Most diagnostic parameters returned to baseline values by Weeks 29 and 34 (**Table 1**).

The owners indicated that the dog readily consumed the food and gained 3.5 kg during the treatment period. Decreasing the amount of food offered and consumed during the treatment period may have prevented significant weight gain.

Endnotes

a. Prescription Diet s/d Canine. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
b. Pfizer Animal Health, Exton, PA, USA.

Bibliography

Osborne CA, Lulich JP, Bartges JW, et al. Canine and feline urolithiasis: Relationship of etiopathogenesis to treatment and prevention. In: Osborne CA, Finco DR, eds. Canine and Feline Nephrology and Urology. Baltimore, MD: Williams & Wilkins, 1995, 798-888.