Canine Cystine Urolithiasis: Causes, Detection, Dissolution and Prevention

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“"If in doubt whether or not to give a drug, DON’T.”
D.R. Lawrence

INTRODUCTION

Cystine (also called dicysteine) is a nonessential sulfur-containing amino acid composed of two molecules of the amino acid cysteine. What is the etymology of the name cystine? A report published in 1810 described unusual bladder stones in people as “cystic oxide” (Wollenstan). The etymology of the name cystic oxide was based on the location of the stones in the urinary bladder (“kystis,” the Greek term for bladder, is spelled “cystic” in English) and “oxide” for what was thought to be these unique stone’s chemical nature. A few decades later, the fact that these stones were not an “oxide” was recognized; however, they were still considered to be composed of material that originated from the urinary bladder (or urocyst). The authors renamed the stones “cystine” (Berzelius, 1833). Subsequently, it was discovered that the stones were composed of a nonessential sulfur-containing amino acid, some of which is eliminated from the body by the urinary system (Segal and Thier, 1989). However, this amino acid is still called cystine (Rogers et al, 2007).

PREVALENCE

The prevalence of cystine uroliths in dogs varies geographically. The prevalence is 1 to 3% of the uroliths removed from dogs in the United States (Bovee and McGuire, 1984; Ling and Ruby, 1986; Osborne et al, 1986, 1999) and as high as 39% in some European centers (Hicking et al, 1981). Cystine accounted for 2.2% (7,357 of 339,886) of all canine uroliths submitted to the Minnesota Urolith Center from 2012 to 2016 (Table 38-8) and 3.0% (2,162 of 72,033) of canine uroliths submitted in 2016. Cystine accounted for 2.0% (36 of 1,898) of upper tract canine uroliths analyzed at the Minnesota Urolith Center also during this recent period (Table 38-9). The mean age of dogs at the time of cystine urolith retrieval was approximately 4.8 years (range two months to 25 years). Only 3.5% of uroliths retrieved from dogs less than 12 months of age were cystine. Our epidemiologic data indicate that Newfoundlands appear to be an exception to this generality inasmuch as cystine uroliths were commonly detected before one year of age.
Males (97.5%) were affected more often than females (1%); in the remaining submissions breed was reported as unknown. With few exceptions, other investigators have reported the predominance of cystine uroliths in male dogs. From 2012 to 2016, 179 different breeds were affected including English bulldogs (18%), mixed breeds (12%), Chihuahuas (9%), dachshunds (7%), French Bulldogs (6.5%), pit bulls (3%), Staffordshire bull terriers (3.5%), and mastiffs (3.5%). At the University of Minnesota Veterinary Medical Center, English bulldogs have surpassed dachshunds in frequency of admissions for evaluation of cystine urolithiasis.

Quantitative analysis of canine cystine uroliths submitted to our center has revealed that most are pure; however, a few contain small quantities of ammonium urate, calcium oxalate and/or silica. Like cystine uroliths, ammonium urate and calcium oxalate uroliths tend to form in acidic urine. It is also of interest that in vitro studies have demonstrated that cystine is a promoter of calcium oxalate crystal growth and aggregation (Martins et al, 2002). Secondary urinary tract infections (UTIs) with urease-producing microbes may result in uroliths with a nucleus of cystine surrounded by layers of struvite. However, this scenario is uncommon in our experience because male dogs are less likely to develop urinary tract infections.

Pure cystine uroliths are usually multiple, ovoid and smooth. They are light yellow and vary from 0.5 mm to several cm in diameter. Some have a rough exterior, but this feature is unusual.

**LOCATION**

Cystine uroliths were more commonly removed from the lower urinary tract of dogs (96%) than the upper urinary tract (2%). The number of uroliths in each patient varied from one to more than 100. It is noteworthy that, compared to other affected breeds, a relatively high incidence of cystine nephroliths have been observed in Newfoundlands (Casal et al, 1995). Some of them may fill the renal pelvis, although this finding is uncommon. This may be related to the high excretion of cystine in Newfoundlands.

**ETIOPATHOGENESIS AND RISK FACTORS**

**Overview**

Cystine is absorbed through the wall of the small intestine. It is normally present in low concentrations in plasma, and is freely filtered by glomeruli. Most filtered cystine is actively reabsorbed in the proximal tubules. The solubility of cystine in urine is pH dependent. It is relatively insoluble in acidic urine, but becomes more soluble in alkaline urine (Rogers et al, 2007). In dogs, the solubility of cystine at a urinary pH of 7.8 has been reported to be approximately double that at a urinary pH of 5.0 (Treacher, 1966).

**Genetics**

Cystinuria is an inborn error of metabolism characterized by impaired absorption of dibasic amino acids including cystine, ornithine, lysine and arginine by both the intestine and the proximal tubules of the kidneys. The amino acids other than cystine are soluble at the normal physiologic range of urinary pH, and therefore are not lithogenic. The intestinal defect in amino acid absorption is apparently harmless inasmuch as these amino acids are classified as nonessential, and their dipeptide forms are still absorbed. Two genes encode the dibasic amino acid transporter: SLC3A1 encodes the extracellular heavy chain referred to as rBAT, and SLC7A9 encodes the light chain referred to as b0,+AT. Urolithiasis associated with mutations in the SLC3A1 gene are inherited as autosomal recessive (Type 1 A cystinuria recognized in Newfoundlands, Landseers, Labrador retrievers, and English bulldogs) and autosomal dominant (Type II A cystinuria recognized in Australian cattle dogs) patterns. Urolithiasis associated with mutations in SLC7A9 are inherited as autosomal dominant pattern (Type II B Cystinuria recognized in miniature Pinchers). Dogs with a single copy of this mutated gene can present with disease; however, the presence of two mutated genes may lead to considerably worse cystinuria. Formation of cystine uroliths in some breeds has been classified as androgen dependent (Type III cystinuria) in which castration may dramatically reduce or correct cystinuria. Androgen dependent Cystinuria has been recognized in Mastiffs, and English and French bulldogs. The precise genetic mode of inheritance of canine cystinuria in most affected breeds is unknown.

**Table 42-1. Key nutritional factors for foods for canine cystine urolith dissolution and prevention.**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Dietary recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Water intake should be encouraged to achieve a urine specific gravity &lt;1.020</td>
</tr>
<tr>
<td></td>
<td>Moist food will increase water consumption and formation of less concentrated urine</td>
</tr>
<tr>
<td>Protein</td>
<td>Avoid excess dietary protein</td>
</tr>
<tr>
<td></td>
<td>Restrict high quality dietary protein to 10 to 18% dry matter</td>
</tr>
<tr>
<td>Sodium</td>
<td>Restrict sodium to less than 0.3% dry matter</td>
</tr>
<tr>
<td>Urinary pH</td>
<td>Feed a food that maintains an alkaline urine (urinary pH = 7.1 to 7.7)</td>
</tr>
</tbody>
</table>

Small Animal Clinical Nutrition
Aminoaciduria

Cystinuria is characterized by abnormal transport of cystine and other dibasic amino acids by the renal tubules and intestines. Unlike normal dogs, some cystinuric dogs reabsorb a much smaller proportion of the amino acid from the glomerular filtrate (Bovee, 1984). Some may even have net cystine secretion. When measured, plasma concentrations of cystine in affected dogs were normal, indicating faulty tubular reabsorption and/or tubular secretion rather than hyperexcretion through glomeruli (Bovee, 1984, 1984a; Bovee and McGuire, 1984). Levels of plasma methionine, a precursor of cystine, have been found to be elevated in some cystinuric dogs.

In dogs with cystinuria, the pattern of dibasic aminoaciduria reported by various investigators has been variable (Bovee, 1984; Clark and Cuddeford, 1971; Cornelius et al, 1967; Crane and Turner, 1956). Apparently there are several different populations of cystinuric dogs (Bovee, 1984; Casal et al, 1995). One group had cystinuria without significant loss of other amino acids, Another group had cystinuria and a lesser degree of lysinuria. Our studies indicate that cystine urolith-forming English bulldogs have cystinuria and lysinuria. Another group had cystinuria, glutaminuria, threoninuria and citrullinuria (Hoppe et al, 1993). A fourth group had cystinuria, ornithinuria, lysinuria and arginuria, a pattern commonly encountered in people with this disorder (Bovee, 1984; Sanderson et al, 1995). This pattern of aminoaciduria may be remembered with the acronym COLA (cystine, ornithine, lysine, arginine).

Unless protein intake is severely restricted, abnormalities associated with loss of amino acids have not resulted in recognizable disorders, with the exception of formation of cystine uroliths. One general exception to this is cystinuric dogs with concomitant carnitiniuria. Carnitric dogs consuming foods with reduced quantities of carnitine are predisposed to dilated cardiomyopathy (Sanderson et al, 1995). We have observed a cystinuric dachshund with carnitinuria.

The magnitude of cystinuria varies widely between cystinuric dogs, between serial measurements of the same dog and may decline in older dogs. In one study, four of 14 dogs with a history of cystine urolith formation had urine cystine concentrations that fell within the normal range of those found in control dogs (Bovee, 1984). One explanation may be that male dogs with androgen dependent cystinuria were neutered. Diurnal variations in urinary cystine excretion may also account for some of the change. Variability may also be related to differences in diets consumed by cystinuric dogs, and differences related to urine collections during fasting and postprandial states. In a study of human cystinuric patients, analysis of six-hour urine samples revealed transient episodes of cystine saturation that were not observed in corresponding 24-hour urine samples.

The major causes of morbidity and mortality recognized in association with this disorder are sequelae of urolith formation. Unfortunately, the exact mechanisms of cystine urolith formation are unknown. Because not all cystinuric dogs form uroliths, and because not all dogs with cystine crystalluria form uroliths, cystinuria is a predisposing rather than the sole cause of cystine urolith formation.

Cystine is sparingly soluble at the usual urinary pH range of 5.5 to 7.5. However, a substantial increase in cystine solubility occurs at urinary pHs above 7.5.

### BIOLOGIC BEHAVIOR

Cystine uroliths are not recognized in most affected dogs until after they reach maturity. The average age at detection in many breeds is approximately two to five years old. This is surprising inasmuch as one might expect an earlier onset of clinical manifestations of an inherited disorder. It is notable that cystinuria and cystine uroliths have been detected in male and female Newfoundlands less than one year of age (Casal et al, 1995).
Table 42-3. Summary of recommendations for combined dietary and medical/surgical treatment and prevention of canine cystine uroliths.

1. Perform appropriate diagnostic studies including complete urinalysis, quantitative urine culture and diagnostic radiography and/or ultrasonography. Determine precise location, size and number of uroliths. The size and number of uroliths are not a reliable index of probable therapeutic efficacy.

2. If uroliths are available, determine their mineral composition. If they are unavailable, determine their composition by evaluation of appropriate clinical data.

3. Consider surgical correction if uroliths obstruct urine outflow and/or if correctable abnormalities predisposing the patient to recurrent urinary tract infection are identified by radiography or other means. Small urocystoliths may be removed by voiding urohydropropulsion (Figure 38-5 and Table 38-7). Ureteroliths may be removed by lithotripsy.

4. Initiate therapy with an appropriate litholytic food (Table 42-2). For optimal results, no other food or mineral supplements should be fed to the patient. Compliance with dietary recommendation is suggested by a reduction in urea nitrogen concentration (usually <10 mg/dl).

5. Initiate therapy with N-(2-mercaptopyropionyl)-glycine (2-MPG)* at a daily dosage of approximately 30 mg/kg body weight, divided into two equal subdoses.

6. If necessary, administer potassium citrate orally to eliminate aciduria. Strive for a urinary pH of approximately 7.5 (range = 7.1 to 7.7).

7. If necessary, eradicate or control urinary tract infections with appropriate antimicrobial agents.

8. Devise a protocol for followup therapy.
   a. Try to avoid diagnostic followup studies that require urinary catheterization. If they are required, give appropriate peri-catheterization antimicrobial agents to prevent iatrogenic urinary tract infection.
   b. Perform serial urinalyses. Urinary pH, 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.
   c. Perform serial radiography monthly to evaluate urolith location(s), number, size, density and shape. Intravenous urography may be used to identify radiolucent uroliths in the kidneys, ureters and urinary bladder. Antegrade contrast cystourethrography may be required for radiolucent uroliths located in the bladder and urethra.

9. Continue litholytic food, 2-MPG and alkalinizing therapy for approximately one month after disappearance of uroliths as detected by radiography.

10. Prevention. Feeding a low-protein food that promotes alkaline urine (Table 42-2) has been effective in minimizing cystine urolith recurrence. If necessary, low doses of 2-MPG may also be given.

*Thiola, Mission Pharmacal, San Antonio, TX, USA.

Compared to other breeds, the magnitude of the tubular transport defect for cystine in Newfoundlands is more severe. This provides a plausible explanation for the earlier onset of detectable cystine urolith formation in this breed and for the involvement of the kidneys in addition to the urinary bladder in female as well as male dogs (Casal et al, 1995). Because cystinuria is an inherited defect, uroliths commonly recur in two to 12 months unless prophylactic therapy has been initiated. In some older dogs, the rate of recurrence declines as a consequence of a reduction in magnitude of cystinuria. Spontaneous partial dissolution of cystine uroliths occurred in a 10-year-old neutered male dachshund. This dachshund was eating a moist maintenance food because it would not eat foods designed to minimize some risk factors for cystine urolithiasis. The patient was not known G-N-(2-mercaptopyropionyl)-glycine (2-MPG)* to manage its cystine uroliths because on a previous occasion it developed protein-losing glomerulonephropathy while being treated with this drug.

**DIAGNOSIS**

**Urinalysis**

Detection of flat colorless hexagonal cystine crystals provides strong support for a diagnosis of cystinuria. The six sides of cystine crystals may or may not be equal, and the crystals tend to aggregate and appear layered. Caution: cystine crystals are not constantly present in dogs with cystinuria or cystine uroliths. However, acidification of urine with glacial acetic acid, refrigeration and centrifugation may foster cystine crystal formation. Cystine crystals are insoluble in acetic acid, alcohol, acetone, ether and boiling water. They are soluble in ammonia and hydrochloric acid (pH <2).

We have observed crystals from a cystinuric, leucinuric female Scottish terrier that appeared similar to leucine crystals. Leucine crystals are highly refractile yellow to brown spheres with concentric circles or radial striations.

**Assessment of Aminoaciduria**

If a sufficient quantity of cystine is present in urine (75 to 125 mg/g of creatinine; 10 mmol/mol creatinine), the colorimetric cyanide-nitroprusside test result will be positive. Sodium cyanide reduces cystine to cysteine, and the free sulphydryl groups subsequently react with nitroprusside to form a characteristic purple color. Ampicillin and sulfur-containing drugs have been reported to cause false positive reactions to this test. Screening patients for cystinuria with the nitroprusside test may be aided by submitting fresh urine samples, or urine allowed to dry on 3-mm filter paper, to the Metabolic Screening Laboratory, Section of Medical Genetics, Veterinary Hospital, University of Pennsylvania, Philadelphia 19104-6010 (fax number 215-573-2162). Contact this center for specific instructions about DNA testing, urine and blood sample preservation and sample submission. Their website address is www.vet.upenn.edu/penngen/research/ (Henthorn and Giger, 2007).
Evaluation of urine amino acid excretion rates may provide additional definitive information about cystinuria and associated aminoacidurias. The most commonly used techniques are high-pressure liquid chromatography, and automated amino acid analyzers.

In breeds with Type 1 cystinuria, in which the mode of inheritance is simple autosomal recessive, cystinuria may occur in the offspring of phenotypically normal parents. Unfortunately from a diagnostic standpoint, obligate carriers of the disease have no clinical signs, normal cystine urine concentrations and normal renal absorption of amino acids. Genetic carriers can be identified with genetic testing.

**Radiography and Ultrasonography**

The size of cystine uroliths varies from that just detectable by the unaided eye to more than three centimeters. The number present in each patient may vary from one to more than 100. Most canine cystine uroliths are smooth and spherical. However, their appearance includes uroliths that are also mildly bosselated to rough.

The radiodensity of cystine uroliths compared to soft tissue is similar to struvite, less than calcium oxalate and calcium phosphate and greater than ammonium and sodium urate. Thus, when of sufficient size, cystine uroliths can be detected by survey radiography.

In our experience, double-contrast cystography is more sensitive in detecting small cystine urocystoliths than survey radiography and most techniques of ultrasonography. Cystine uroliths appear radiolucent when surrounded by, but not completely submerged in, radiopaque contrast medium.

Survey radiography may be insensitive for detecting cystine urethroliths. Positive-contrast urethrography may be required to detect and localize cystine uroliths that have passed into the urethral lumen.

Although uroliths can be detected by ultrasonography, this method does not provide information about the degree of their radiodensity or shape. Evaluation of the density and shape of uroliths often provides useful information in predicting their mineral type.

**Urolith Analysis**

Quantitative analysis of uroliths provides a definitive diagnosis of cystinuria. Uroliths may be collected with a tropical fishnet during the voiding phase of micturition, by catheter-assisted retrieval (Figure 38-6) (Lulich and Osborne, 1992) or by voiding urohydropropulsion (Figure 38-5 and Table 38-7) (Lulich et al, 1993). Samples may be submitted to the Minnesota Urolith Center for quantitative analysis (urolithcenter.org).

**KEY NUTRITIONAL FACTORS**

The key nutritional factors for foods intended for dissolution and prevention of cystine uroliths in dogs are discussed below and summarized in Table 42-1.

**Table 42-4. Expected changes associated with combined dietary and medical therapy of cystine uroliths.**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Pre-therapy</th>
<th>During therapy</th>
<th>Prevention therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyuria</td>
<td>±</td>
<td>1+ to 3+</td>
<td>1+ to 3+</td>
</tr>
<tr>
<td>Pollakiuria</td>
<td>0 to 4+</td>
<td>↓ then ↓</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0 to 4+</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>Variable</td>
<td>1.004-1.020</td>
<td>1.004-1.020</td>
</tr>
<tr>
<td>Urinary pH</td>
<td>&lt;7.0</td>
<td>&gt;7.0</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>Pyuria</td>
<td>0 to 4+</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Cystine crystals</td>
<td>0 to 4+</td>
<td>Variable</td>
<td>0</td>
</tr>
<tr>
<td>Bacteriuria</td>
<td>0 to 4+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bacterial culture of urine</td>
<td>0 to 4+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dl)</td>
<td>Variable</td>
<td>&lt;15</td>
<td>≤15</td>
</tr>
<tr>
<td>Urolith size and number</td>
<td>Small to large</td>
<td>↓</td>
<td>0</td>
</tr>
</tbody>
</table>

**Water**

Increasing urine volume to reduce urine cystine concentration is likely to be of benefit. Feeding moist rather than dry foods is recommended. Strive to obtain a urine specific gravity value less than 1.020.

**Protein**

High-protein foods should be avoided in dogs at risk for cystine urolithiasis. These include high-protein dry diets, especially those rich in methionine (a precursor of cysteine). Besides most meats, other food ingredients high in methionine include eggs, wheat and peanuts.

Reduction of dietary protein has the potential of minimizing formation of cystine uroliths. Pilot studies performed on cystinuric dogs at the University of Minnesota revealed a 20 to 25% reduction in 24-hour urine cystine excretion when subjects consumed a low-protein, moist veterinary therapeutic food vs. when they received a moist, canine adult maintenance food. Reducing the concentration of urea in the renal medulla associated with reduced consumption of protein, and the associated reduction in urine concentration is an important indirect effect (Osborne et al, 1985). Protein levels in foods for dogs with cystine urolithiasis should be between 10 to 18% dry matter (DM). The minimum recommended allowance for protein in foods for healthy adult dogs is 10% DM (NRC, 2006).

**Sodium**

Data derived from studies in cystinuric people suggest that dietary sodium may enhance cystinuria (Jaeger et al, 1986). In one study of cystinuric people, dietary restriction of sodium reduced the urinary excretion of cystine. Further studies are required to evaluate the effect of dietary sodium on urinary excretion of cystine in dogs. Until data indicate otherwise, dietary sodium should be limited to less than 0.3% DM in cystine litholytic and prevention foods. Typically, commercial dog foods contain...
Table 42-5. Managing cystine uroliths refractory to complete dissolution.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Identification</th>
<th>Therapeutic goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Client and patient factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate dietary compliance</td>
<td>Question owner</td>
<td>Emphasize value of feeding dissolution food</td>
</tr>
<tr>
<td></td>
<td>Persistent cystine crystalluria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urea nitrogen &gt;10-17 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urine specific gravity &gt;1.010-1.020</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary pH &lt;7.0-7.5 during treatment with Prescription Diet u/d Canine* (use lower values for the moist food)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inadequate 2-MPG** administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Question owner</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Count remaining pills</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinician factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inaccurate prediction of mineral type</td>
<td>Analysis of retrieved urolith</td>
<td>Adjust therapy based on correct identification of mineral type</td>
</tr>
<tr>
<td>Inadequate 2-MPG dose for degree of diuresis</td>
<td>No change in urolith size after two months of appropriate therapy</td>
<td>Increase 2-MPG dose to 20 mg/kg body weight q12h</td>
</tr>
<tr>
<td><strong>Disease factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound urolith</td>
<td>Radiographic density of nucleus and outer layer(s) of urolith are different Analysis of retrieved urolith</td>
<td>Adjust therapy based on identification of new mineral type</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uroliths not causing clinical signs should be monitored for potentially adverse consequences (obstruction, urinary tract infection, etc.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinically active uroliths may require surgical removal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Remove small uroliths by voiding urohydropropulsion (Figure 38-5 and Table 38-7); consider removing urethroliths by lithotripsy</td>
</tr>
</tbody>
</table>

*Hill’s Pet Nutrition, Inc., Topeka, KS, USA.  
**2-MPG = N-(2-mercaptopropionyl)-glycine. Thiola. Mission Pharmacal, San Antonio, TX, USA.

FEEDING PLAN

Current recommendations for dissolution of cystine uroliths encompass reducing urine concentration of cystine and increasing the solubility of cystine in urine. This may be accomplished by various combinations of: 1) dietary modification, 2) administration of thiol-containing drugs and 3) alkalinization of urine, if necessary. Small cystine urocystoliths may be removed by voiding urohydropropulsion (Figure 38-5 and Table 38-7) (Lulich et al, 1993) or retrieval with a urinary catheter (Figure 38-6) (Lulich and Osborne, 1992). Urethroliths may be removed by lithotripsy.

Assess and Select the Food

Table 42-2 lists selected veterinary therapeutic foods that can be considered for dissolution and prevention of cystine uroliths and compares their key nutritional factor content to the recommended levels. Select the food that is most similar 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. Dogs consuming dry foods may be at greater risk.

two to three times this amount. The minimum recommended allowance for sodium in foods for healthy adult dogs is 0.08% DM (NRC, 2006).

**Urinary pH**

The solubility of cystine in urine is pH dependent. Foods that promote formation of acidic urine are risk factors for cystine urolithiasis in susceptible dogs. Cystine is relatively insoluble in acidic urine but becomes more soluble in alkaline urine (Rogers et al, 2007). In dogs, the solubility of cystine at a urinary pH of 7.8 has been reported to be approximately double that at a urinary pH of 5.0 (Treacher, 1966). Changes in urinary pH that remain in the acidic range have minimal effect on cystine solubility. A protein-restricted alkalinizing food without other therapy was observed to have a beneficial effect in promoting reduction in cystine urocystolith size in a three-year-old male dachshund (Osborne et al, 1989). Urinary pH values greater than 7.7 should be avoided until it is determined whether or not they provide a significant risk factor for formation of calcium phosphate uroliths. Thus, a food that produces a urinary pH range of 7.1 to 7.7 is recommended for dogs with cystine urolithiasis.
for urolithiasis than dogs consuming moist foods. Dry foods are often associated with higher urine concentrations of urolith constituents and more concentrated urine. Therefore, when possible, moist foods should be selected. If treats are fed, their sodium content should be checked. Treats should contain no more than 0.3% DM sodium (the same as the food recommendation) and they should be limited to less than 10% of the daily total food regimen (volume or weight basis).

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

Assess and Determine the Feeding Method
Transitioning a patient from its current food to a new food selected for the management of cystine uroliths 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 new food on Day 1. On Day 2, feed half of each food. On Day 3, feed 75% of the new food and 25% of the old. By Day 4 or 5, feed only the new food.

Moist foods increase water intake and produce less concentrated urine; therefore, encourage clients to feed specific amounts (meal fed) of moist food two to three times per day rather than free-choice feeding. Moist foods can spoil if left 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, increased water intake can be facilitated by: 1) Ensuring 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. 2) Bowls should be clean and kept filled with fresh water. 3) Small amounts of flavoring substances (e.g., salt-free bouillon) can be added to water sources to encourage consumption. 4) Ice cubes can be offered as treats or snacks. 5) If a dry food is selected, ask the client to add liberal quantities of water; however, as with moist foods left at room temperature for prolonged intervals, potential food safety issues might arise (Chapter 11).

If the patient has a normal body condition score (BCS 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 probably be a good starting place.

ADJUNCTIVE MEDICAL MANAGEMENT

Thiol-Containing Drugs
2-MPG
Drugs that increase the solubility of cystine in urine contain a thiol group that can dissociate and then bind with the sulfide moiety of cysteine. The resulting complexes are more soluble in urine than cystine (dicysteine).

2-MPG is commonly called tiopronin.a Tiopronin is a second-generation cysteine chelating agent that decreases the concentration of cystine by a thiol-disulfide exchange reaction. Studies in people and dogs indicate that the drug is highly effective in reducing urinary cystine concentration and has less toxicity than D-penicillamineC (Hoppe et al, 1988, 1993; Osborne et al, 1989).

Oral administration of 2-MPG at a daily dosage of approximately 30 to 40 mg/kg of body weight (divided in two equal doses) was effective in inducing dissolution of multiple cystine urocystoliths in nine of 17 dogs evaluated (Hoppe et al, 1993; Osborne et al, 1989). Dissolution required two to four months of therapy. One dog developed nonpruritic vesicular skin lesions following three months of therapy. One month following reduction of the daily dosage of 2-MPG from 30 to 25 mg/kg of body weight, the skin lesions healed.

Thrombocytopenia, anemia and elevated hepatic enzyme activities have also occurred in a few cystinuric dogs treated with 2-MPG (Osborne et al, 1989). During therapy with 2-MPG, we encountered protein-losing glomerular disease in a cystinuric dachshund.

Unfortunately, dogs that become hypersensitive to D-penicillamine may also simultaneously become hypersensitive to 2-MPG. The beneficial action of both drugs is dose dependent as are the associated side effects. To avoid this predicament when thiol-containing drugs are needed, we discourage use of D-penicillamine and encourage use of the less toxic 2-MPG. Appropriate evaluations should be performed, especially if 2-MPG is used in dogs with a history of D-penicillamine hypersensitivity.

In our experience, a combination of a litholytic food and 2-MPG therapy is more effective in promoting dissolution of uroliths than either alone. We induced dissolution of 18 episodes of cystine urocystoliths affecting 14 dogs using this combination of diet and drug therapy (Osborne et al, 1989). The mean time required to dissolve the cystine uroliths was 78 days (range 11 to 211 days).

D-Penicillamine
D-penicillamine,c also called dimethylcysteine, is commonly referred to as a first-generation cysteine chelating drug. It is a nonmetabolizable degradation product of penicillin that may combine with cysteine to form cysteine-D-penicillamine disulfide (Bovec, 1984a). This disulfide exchange reaction is facilitated by an alkaline pH. The resulting compound has been reported to be 50 times more soluble than free cystine (Lotz et al, 1966). The cysteine-D-penicillamine complex does not react with nitroprusside as does cystine, providing a marker to aid in titrating dosage of the drug (Pahira, 1987).

Although D-penicillamine is effective in reducing urine cystine concentrations, drug-related adverse events limit its use. With the availability of 2-MPG, we have discontinued use of D-penicillamine.

The most commonly used dosage of D-penicillamine for dogs has been 30 mg/kg body weight/day given in two divided...
doses. Higher dosages frequently cause vomiting and may cause other undesirable reactions. If nausea and vomiting occur with the aforementioned dosage, the drug may be mixed with food or given at mealtimes. In some instances, it may be necessary to prevent gastrointestinal disturbances by initiating therapy with a low dose and gradually increasing it until a therapeutic dosage is reached.

D-penicillamine has been associated with a variety of adverse reactions in people, including immune complex glomerulonephropathy, fever, lymphadenopathy and skin hypersensitivity (Pahira, 1987). We observed fever and lymphadenopathy in a dachshund given D-penicillamine at a dosage of 30 mg/kg body weight/day (Osborne et al, 1995). The signs subsided following withdrawal of the drug and administration of a short course of glucocorticoids. To minimize such adverse drug events, we prefer to use 2-MPG rather than D-penicillamine.

**Captopril**

Captopril is a thiol-containing angiotensin-converting enzyme inhibitor that is primarily used as an antihypertensive agent. Captopril has been reported to form a thiol-cystine disulfide that is markedly more soluble than cystine; the mechanism of action is similar to that of 2-MPG and D-penicillamine.

Results of uncontrolled clinical trials of treatment of cystinuric people with captopril have been interpreted to suggest a beneficial effect. However, the clinical value of thiol-containing angiotensin-converting enzyme inhibitors in the management of cystinuria remains unproved by properly controlled clinical trials. Note: the angiotensin-converting enzyme inhibitor enalapril is not a thiol-containing drug.

**Bucillamine**

Bucillamine is a third-generation cysteine chelating agent that may have greater affinity for cysteine than 2-MPG. Bucillamine has been used to treat human patients with rheumatoid arthritis and apparently has been well tolerated. We have not critically evaluated the efficacy and safety of this drug.

**Urine Alkalinizing Agents**

The solubility of cystine is pH dependent. In dogs, the solubility of cystine at a urinary pH of 7.8 has been reported to be approximately double that at a urinary pH of 5.0 (Treacher, 1966). Changes in urinary pH that remain in the acidic range have minimal effect on cystine solubility. Therefore, if lack of cystine urolith dissolution occurs in dogs whose urinary pH does not become sufficiently alkaline following compliant initiation of dietary therapy, a sufficient quantity of potassium citrate should be given orally in divided doses to sustain a urine pH of approximately 7.5. Caution: recall that alkalization of urine is a risk factor for calcium phosphate uroliths.

Data derived from studies in cystinuric people suggest that dietary sodium may enhance cystinuria (Jaeger et al, 1986). Therefore, potassium citrate may be preferable to sodium bicarbonate to alkalize urine.

It is of interest that UTIs caused by urease-producing bacteria in an adult male human patient with cystine nephroliths resulted in extreme urine alkalinity and subsequent urolith dissolution (Gutierrez Millet et al, 1985).

**REASSESSMENT**

Therapy should be initiated in a stepwise fashion (Table 42-3). The goal of therapy is to promote cystine urolith dissolution. To be consistently effective, we have found that this requires careful and planned monitoring (Tables 42-4 and 42-5).

Dietary management should result in formation of less concentrated urine without cystine crystalluria. Strive to achieve urine specific gravity values less than 1.020 (range of 1.015 to 1.020). If the urinary pH remains acidic despite dietary therapy in patients known to be compliant with dietary recommendations, orally administered potassium citrate may be considered.

We recommend that a urinalysis and survey abdominal radiographs be performed approximately every four weeks when dissolving cystine uroliths. Reduction in serum urea nitrogen concentration and urine specific gravity values provides supportive evidence that the client and patient are complying with recommendations to feed a moist food with reduced quantities of protein.

**PREVENTION**

Because cystinuria is an inherited metabolic defect, and because cystine uroliths recur in a high percentage of young to middle-aged dogs within two to 12 months after surgical removal, prophylactic therapy should be considered. In dogs with androgen dependent cystinuria, castration may normalize cystine excretion. For dogs with other forms of cystinuria dietary therapy and if necessary, urine alkalization may be initiated with the objective of minimizing cystine crystalluria and promoting a negative cyanide-nitroprusside test result. If necessary, 2-MPG may be added to the regimen in sufficient quantities to maintain a urine concentration of cystine less than approximately 200 mg/liter. If the dosage cannot be titrated by measurement of urine cystine concentration, 2-MPG may be given at a dosage of 15 mg/kg body weight q12h. Continuous therapy of urolith-free cystinuric dogs with 2-MPG has been effective in preventing formation of cystine uroliths in studies performed in Sweden and at the University of Minnesota (Hoppe et al, 1988, 1993a; Osborne et al, 1999a).

**ENDNOTES**

1. Thiola. Mission Pharmacal, San Antonio, TX, USA.

**REFERENCES**

The references for Chapter 42 can be found at www.markmorris.org.
CASE 42-1

Dysuria in a Dachshund

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Patient Assessment

A four-year-old, neutered male dachshund was examined for vomiting, depression, dysuria and anuria of two days’ duration. Dysuria and pollakiuria were present for two weeks. Physical examination revealed a depressed, mildly dehydrated dog with a large urinary bladder. The dog weighed 6.5 kg and had a normal body condition score (3/5).

Survey radiographs confirmed obstructive uropathy due to multiple urethroliths with marginal radiodensity (Figure 1). Blood and urine were collected for routine diagnostic tests. The urethroliths were flushed back into the bladder lumen by urohydropropulsion after the bladder was decompressed via cystocentesis (Figure 2). Lactated Ringer’s solution was given subcutaneously to correct the dehydration and oral amoxicillin-clavulanic acid (Clavamoxa) was given to prevent urinary tract infection.

Results of the complete blood count were normal. The major serum biochemistry abnormalities were azotemia (urea nitrogen = 52 mg/dl, normal 4 to 26 mg/dl; creatinine = 3.1 mg/dl, normal 0.4 to 1.5 mg/dl) and hyperphosphatemia (phosphorus = 8.4 mg/dl, normal 2.9 to 6.4 mg/dl). Urinalysis results included the following: specific gravity = 1.025, pH = 6.5, hematuria, pyuria, proteinuria and numerous cystine crystals.

The diagnosis was obstructive uropathy due to urethroliths and postrenal azotemia.

Assess the Food and Feeding Method

The dog was fed a commercial dry adult maintenance food free choice and received a vitamin-mineral supplement each day.

Questions

1. What is the most likely mineral composition of this dog’s uroliths?
2. Outline a treatment and feeding plan for this patient.

Answers and Discussion

1. The key diagnostic findings in this dog include: 1) multiple, smooth uroliths with marginal radiodensity, 2) urinary pH = 6.5, 3) cystine crystalluria, 4) sterile urine, 5) normal serum biochemistry profile results, other than azotemia and hyperphosphatemia and 6) dachshund breed. All these findings are consistent with cystine uroliths.

2. Fluid therapy should be continued if azotemia persists. Urohydropropulsion can be repeated if urethral obstruction occurs again. Combined dietary and medical dissolution of canine cystine uroliths is accomplished by a combination of N-(2-mercaptopropionyl)-glycine (2-MPGb) and dietary management with a food that reduces urinary excretion of cystine, promotes formation of alkaline urine and reduces urinary concentration. A veterinary therapeutic food that closely matches the key nutritional factor recommendations for cystine dissolution/prevention was selected (Prescription Diet u/d Caninec). 2-MPG reduces the urine concentration of cystine by combining with cysteine to form cysteine-2-MPG, which is more soluble than cystine. In studies conducted at the University of Minnesota, mean dissolution time with this combination of therapy was 10 weeks (range two to 30 weeks). Drug-induced adverse events associated with 2-MPG are uncommon in dogs, but when they occur they include Coombs positive spherocytic anemia, thrombocytopenia and
increased hepatic enzyme activity. Antibiotics should also be continued for at least 10 more days. The vitamin-mineral supplement is unnecessary and should be discontinued.

**Progress Notes**
The azotemia and hyperphosphatemia resolved by the second day of hospitalization, confirming their prerenal origin. The combination of amoxicillin and clavulanic acid was continued. The dog was released from the hospital with instructions for the owner to give 2-MPG at a dosage of 15 mg/kg body weight, per os, twice daily. The food was changed to moist Prescription Diet u/d Canine and the vitamin-mineral supplement was discontinued. Radiographs taken 40 days after initial hospitalization showed no evidence of uroliths (Figure 3). Urinalysis results included un-concentrated alkaline urine with amorphous crystals. The serum urea nitrogen concentration was 4 mg/dl, which confirmed that the low-protein food was being fed at home. 2-MPG was discontinued and Prescription Diet u/d Canine was continued. Examination 75 and 232 days after initial hospitalization revealed that the urine continued to be unconcentrated and alkaline with no evidence of crystalluria. The urea nitrogen concentration remained low (5 to 6 mg/dl), which indicated that the owner was compliant with the feeding plan.

**Endnotes**
a. Pfizer Animal Health, Exton, PA, USA.
b. Thiola. Mission Pharmacal, San Antonio, TX, USA.
c. Hill’s Pet Nutrition, Inc., Topeka, KS, USA.

**Bibliography**