Urate Urolithiasis

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Abstract: Urate uroliths belong to the purine family of uroliths and are the third most common urolith type in dogs and cats. In dalmatians, an autosomal recessive trait is responsible for hyperuricosuria and a predisposition to urate urolithiasis. In other dog breeds and in cats, urate uroliths are predominantly associated with liver disease, specifically portosystemic vascular anomalies. Idiopathic urate uroliths may occur in animals without liver disease. Ammonium urate uroliths are most common. Urate uroliths are amenable to medical dissolution. This article reviews the pathogenesis and management of urate urolithiasis.

Pathogenesis

Ingested protein and endogenous protein turnover are sources of purines, which are metabolized to hypoxanthine. Through the action of xanthine oxidase, hypoxanthine is converted to xanthine and uric acid (Figure 1). In most mammals, uric acid is converted to allantoin by the action of hepatic uricase, and only scant amounts of uric acid are excreted in urine. Allantoin is very soluble compared with uric acid. Uric acid excreted in the urine may complex with various cations (e.g., ammonium, sodium) to form urate salts. Ammonium is exceptional in its ability to precipitate uric acid in the form of ammonium urate (Figure 2). As urine becomes supersaturated with urate salts, urate uroliths may form.

Whether uric acid complexes with other substances to form a less soluble salt depends on several factors. Hyperuricosuria is one factor implicated in the development of urate urolithiasis. Other factors include increased renal excretion or microbial urease production of amm-
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nium ions, aciduria, and the presence of promoters (e.g., cellular debris, crystals) or lack of inhibitors (e.g., urinary glycoproteins) of urolith formation.1

Dalmatians

It is hypothesized that despite adequate concentrations of hepatic uricase, dalmatians have a defect in transmembrane transport of uric acid in hepatocytes and renal tubular cells.10 Early studies have shown that the hepatic membrane transport defect plays a significant role in hyperuricosuria in this breed.10 As a result, these dogs have a higher serum concentration of uric acid, and filtered uric acid is poorly reabsorbed in the renal tubules.10

Although dalmatians exhibit relative hyperuricosuria, not all form uroliths.1 Urate urolith–forming dalmatians have been shown to excrete higher levels of uric acid in their urine; however, the pathogenesis in uric acid-forming dogs is multifactorial.1,6,9–11 Approximately 92% to 97% of the urate uroliths from dalmatians that are submitted for analysis are from male dogs11,12 (FIGURE 2). The estimated prevalence of urate urolithiasis in male dalmatians ranges from 27% to 34%.13 Differences in anatomy, genetic factors, and urine composition are thought to account for the disparity in incidence between male and female dalmatians. In general, the urethra of female dogs is shorter and wider than that of males, which may allow small stones to be voided before detectable clinical signs develop. In one large, retrospective analysis of breed-related data for stone formation,14 male dalmatians were shown, in general, to have a significantly increased risk of urolith formation compared with females. Differences in the relative levels of inhibitors or promoters of calculogenesis may also exist between the sexes.15

An autosomal recessive mode of inheritance controlled by a single autosomal gene pair (CFA03) was recently demonstrated for hyperuricosuria in dalmatians.16 However, it is not yet clear that this genetic marker will help breeders in identifying urolith-forming dogs.16

Other Breeds

In non-dalmatian breeds, most uric acid is metabolized in the liver to allantoin. The small amount of uric acid that is filtered at the glomeruli is largely reabsorbed by the proximal tubules, and trace amounts are excreted in the urine. Relatively little is known about naturally occurring urate urolithiasis in non-dalmatian breeds of dogs.17 Among these, English bulldogs have the highest incidence.3,18 Mildly elevated serum uric acid levels have been documented in English bulldogs with urate urolithiasis and normal hepatic function.1

Hepatic Dysfunction

Hepatic insufficiency and portovascular anomalies can predispose dogs and cats to urate urolithiasis by reducing hepatic conversion of uric acid to allantoin and of ammonia to urea. Urate urolithiasis is a common finding in patients with portovascular anomalies, but it is infrequently associated with hepatic insufficiency due to other causes.3

QuickNotes

Dalmatians and English bulldogs have a genetic predisposition to urate urolithiasis.
Urate Urolithiasis

**Diagnosis**

**Clinical Signs**

Clinical signs are usually referable to the level of the urinary tract affected and are indistinguishable from those of other lower urinary tract disease. Signs consistent with hepatic encephalopathy or liver failure may be noted if urate stones are a consequence of hepatic dysfunction. The average age at which urate urolithiasis is detected in dalmatians is 4.5 years (range: <1 to 16 years).

**Laboratory Evaluation**

The results of a complete blood count and serum biochemical profile are usually normal. Azotemia, metabolic acidosis, and hyperkalemia are common in cases of obstructive uropathy. Changes compatible with concurrent liver dysfunction may be present. Alkaline phosphatase and alanine aminotransferase activities may be normal or increased and albumin and glucose levels may be decreased. Increased fasting and postprandial bile acid levels and/or increased plasma ammonia concentrations are concurrent findings in animals with portovenous anomalies. Urinalysis may reveal urate crystalluria. This finding should be considered abnormal in cats and non-dalmatian dogs; however, urate crystalluria is not synonymous with urate urolithiasis. The chemical composition of a removed urolith can be confirmed by submission to a reference laboratory for quantitative analysis. Quantitative analysis can provide definitive information about mineral composition and guide therapy. Reference laboratories should be contacted for specific sample handling and submission instructions. In addition to urinalysis, urine should be submitted for culture to rule out concurrent infection as a complicating factor in management.

**Imaging**

Approximately 97% of urate uroliths are found in the bladder or urethra, with only 3% found in the kidneys or ureters. The stones are radiolucent, usually small (range: <1 mm to 1.5 cm), and round or ovoid. These characteristics lead to a 20% false-negative detection rate with survey radiography. Larger stones and those mixed with other components (particularly secondary infection–induced struvite) may be more visible. Double-contrast cystography is the best method for determining the size, shape, and number of stones. This technique has a detection rate of 78% for stones >1.0 mm and allows urethral calculi to be visualized. Ultrasonography may be used to visualize urate uroliths in the bladder or kidney. Ureteroliths often require excretory urography for detection.

**Treatment**

**Diet**

Urate uroliths are often amenable to dissolution through a combination of dietary modification, urine alkalization, and control of secondary infections. Protein (particularly purine) restriction is the foundation of medical management. Currently, two veterinary diets are marketed for this purpose in dogs. These diets are formulated to maintain alkaline urine. Protein restriction indirectly alters renal medullary tonicity by lowering blood urea nitrogen (BUN) content, which limits concentrating ability. Feeding a canned diet or adding water to dry formulations further increases urine volume. Diets severely restricted in protein content are contraindicated in growing or lactating animals. Recipes for homemade diets and modifications of commercially available formulas have been published, but their effectiveness has not been established.

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**QuickNotes**

Male dalmatians are overrepresented for clinical disease.
**Clinical signs:** hematuria, dysuria, pollakiuria, or breed predisposition

**Diagnostic imaging:** survey radiography ± contrast study

- **Urolith present**
  - Obstructing
  - Assess number and size: double-contrast cystography or ultrasonography
    - Is urate likely?
      - Yes: **Medical dissolution:**
        - Diet (purine-restricted)
        - Alkalize urine
        - Allopurinol (15 mg/kg PO bid)
        - Antibiotics as indicated
        - 4 weeks:
          - Urinalysis
          - Double-contrast cystography or ultrasonography
        - Urolith present: refer to prevention summary
        - No uroliths: refer to prevention summary
        - Uroliths: catheter-assisted retrieval
        - No uroliths: refer to prevention summary
      - No: Regional removal: cystotomy, lithotripsy, or voiding urohydropropulsion
        - Submit for analysis
        - Urate: refer to prevention summary
        - Not urate: continue therapy
    - No: **Xanthine:**
      - Stop allopurinol
      - Continue diet
      - Alkalize urine
      - 4 weeks: double-contrast cystography or ultrasonography
      - No uroliths: refer to prevention summary
      - Uroliths: catheter-assisted retrieval

- **No urolith**
  - Nonobstructing
  - Assess number and size: double-contrast cystography or ultrasonography
    - Is urate likely?
      - Yes: **Medical dissolution:**
        - Diet (purine-restricted)
        - Alkalize urine
        - Allopurinol (15 mg/kg PO bid)
        - Antibiotics as indicated
        - 4 weeks:
          - Urinalysis
          - Double-contrast cystography or ultrasonography
        - Urolith present: refer to prevention summary
        - No uroliths: refer to prevention summary
        - Uroliths: catheter-assisted retrieval
      - No: **Xanthine:**
        - Stop allopurinol
        - Continue diet
        - Alkalize urine
        - 4 weeks: double-contrast cystography or ultrasonography
        - No uroliths: refer to prevention summary
        - Uroliths: catheter-assisted retrieval

**Decrease in size or number:**
- **Urate:** increase allopurinol by 10% to 15%
- **Urate:** decrease allopurinol by 25%

**No change in size or number:**
- **Catheter-assisted retrieval**

**Treatment algorithm for canine urate urolithiasis.**
Urate Urolithiasis

Urine Alkalnization

Urine pH is an important modifier of urate solubility. The optimum target range for urine pH is 7.0 to 7.5.1,8–10,19 Urine pH values >7.5 may predispose dogs to the formation of calcium phosphate uroliths.1,19 Additional agents are used when optimal urine pH is not achieved with diet alone (FIGURE 3). Potassium citrate (initial dose: 40 to 90 mg/kg PO q12h) is the preferred agent. Deposition of calcium phosphate over existing uroliths may complicate dissolution.

Xanthine oxidase inhibitors are used to decrease uric acid production. Allopurinol, a synthetic isomer of hypoxanthine, is a potent inhibitor of xanthine oxidase22 that inhibits the conversion of hypoxanthine to xanthine and of xanthine to uric acid. Its biotransformation takes place primarily in the liver.22 Allopurinol is poorly bound to plasma proteins and is excreted primarily by the kidneys; therefore, it should be used cautiously in animals with hepatic or renal dysfunction. Its half-life in dogs is approximately 2.5 hours. The bioavailability of allopurinol is not affected by food.

The initial dose of allopurinol is 15 mg/kg PO bid for 4 weeks, at which time, the size, shape, and number of calculi should be reevaluated. The level of uric acid excretion in the urine may be used to guide dose adjustments after the first month. Measurement of urinary uric acid excretion over 24 hours (target level: <300 mg urate/24 hr) gives the most accurate value; however, it is difficult to obtain a complete 24-hour urine collection.23 Single urinary uric acid:creatinine ratios can be used to document a decrease in uric acid excretion.24

On average, urate cystoliths dissolve over 3.5 months (range: 1 to 18 months) when a combination of diet, pH modification, and xanthine oxidase inhibition is used.1 In male dogs, dissolving cystoliths may move into the urethra and cause clinical signs of obstruction. Retrograde urohydropropulsion can be used to relieve obstructions.21

Allopurinol should not be used in patients with portosystemic shunts.5 Decreased hepatic metabolism may result in a prolonged half-life and adverse effects, including augmented xanthine oxidase inhibition that causes xanthine urolithiasis. Allopurinol is also an inhibitor of the hepatic microsomal P450 system and should be used judiciously with other drugs that depend on biotransformation in the liver.25 Adverse effects noted in people include skin rash, gastrointestinal disturbances, thrombocytopenia, vasculitis, and hepatitis with other immune-mediated reactions. Many of these reactions were noted in people with existing renal dysfunction.26 There is only one report of potential immune-mediated hemolytic anemia and trigeminal neuropathy in a dog.26

Allopurinol should be used only in conjunction with a protein-restricted diet. Excessive purine precursors in the diet may predispose patients to xanthinuria and the formation of xanthine uroliths.27 If xanthine urolithiasis occurs, allopurinol should be discontinued for 1 to 2 months while dietary therapy and urine alkalization is continued to allow the uroliths to dissolve. Xanthine exhibits solubility characteristics similar to those of urate in alkaline urine. Following resolution of xanthine urolithiasis, allopurinol can be reintroduced with a 25% reduction in dose.

In patients with cystic uroliths that are smaller in diameter than the distended urethra, voiding urohydro propulsion or catheter-assisted retrieval may be used to retrieve remaining uroliths and monitor therapy1 (FIGURE 3).

Infection Control

Any existing urinary tract infection should be eliminated. Infections are generally considered to be secondary to urolith-induced trauma or to catheterization or other invasive procedures.28

Nonmedical Management

If medical dissolution is not pursued, surgical and nonsurgical options are available. Surgery is the most definitive method of treatment.1 Surgical attenuation is recommended for definitive treatment of identified cystic calculi.5 In patients with portosystemic shunts, correction of the shunt may result in spontaneous dissolution of urate uroliths if hepatic perfusion is reestablished. If shunt correction is contraindicated, dietary management is recommended.5 Voiding urohydropropulsion has been described as a means of obtaining stones for analysis and for removing cystic uroliths, when appropriate.19 Retrograde urohydropropulsion can be used to temporarily relieve any urethral obstruction while a patient is stabilized for surgery.19,4

QuickNotes

Urate uroliths are amenable to medical dissolution.
Lithotripsy is a recent addition to the list of management options for urinary calculi in dogs and cats. Shock wave lithotripsy and laser lithotripsy techniques have been described.29–31 Although extracorporeal shock wave lithotripsy (ESWL) is useful in managing nephroliths and ureteroliths, its use for urate uroliths is poorly described, perhaps partly because these urate uroliths occur infrequently in the upper urinary tract.29 Successful resolution was achieved in two of five dogs with purine uroliths of the upper urinary tract using ESWL.30 ESWL is not currently recommended for treatment of cystic urate uroliths in dogs and cats.

Laser lithotripsy has been evaluated for the treatment of ureteral, cystic, and urethral urate uroliths. Laser lithotripsy has become more widely available and may be more practical than ESWL for veterinary patients. When a holmium:YAG laser is used to fragment urate uroliths, stone composition does not have a significant effect on fragmentation time.29 Laser fragmentation of urate uroliths can result in uric acid conversion to cyanide.31 The risk of clinical toxicity is considered to be very low, and laser lithotripsy has been used for urate uroliths without complications.30 As more experience is gained with laser lithotripsy and this procedure becomes more widely available at referral institutions, it may replace other therapies for cystic urate urolithiasis.

**Evaluating Response to Medical Therapy**

Periodic evaluation is necessary to assess owner compliance and the rate of urolith dissolution. After the initial enumeration and measurement of uroliths, patients should be reevaluated monthly until uroliths are no longer present. Double-contrast cystography or ultrasonography is usually necessary. Urine pH, specific gravity, and sediment analysis should be evaluated along with BUN to determine the success of medical therapy. If uroliths fail to decrease in size, or if they increase in size during the initial 8 weeks of therapy, the diagnosis should be reevaluated or an alternative management option pursued.1

**Prevention**

The foundation of preventive therapy is increased water consumption and dietary modification (TABLE 1). The aforementioned prescription diets are appropriate for long-term feeding. Feeding of an exclusively canned diet is recommended. Use of ultralow-protein diets has been associated with dilated cardiomyopathy in English bulldogs and a few dalmatians.32,33 Taurine and/or carnitine deficiency may underlie the development of dilated cardiomyopathy in predisposed dogs.32 Oral taurine supplementation has not been definitively shown to affect outcome.33 It has been suggested that English bulldogs be fed a low-protein renal diet instead of an ultralow-

### TABLE 1 Summary of Urate Prevention Strategies

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comments</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Foundation of all prevention strategies; may be useful as sole therapy</td>
<td>Restricted purine content</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alkalized urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased water consumption</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Use as needed for refractory cases</td>
<td>Alkalized urine</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Recheck urinalysis and BUN every 4–8 weeks</td>
<td>Urine pH 7.0–7.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine specific gravity &lt;1.020</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No urate crystals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BUN &lt;10 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If no recurrence for 2–4 months, recheck every 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If urate uroliths recur, refer to Figure 3</td>
</tr>
</tbody>
</table>

### BOX 1 Purine Content of Common Foods

- **High content: foods to avoid**
  - Organ meats
  - Fish (salmon, tuna, mackerel, sardines)

- **Moderate content: moderate use**
  - Other fish
  - Legumes
  - Spinach
  - Peas
  - Mushrooms

- **Negligible**
  - Breads
  - Fats
  - Cheese
  - Eggs
  - Fruits
  - Carbohydrates
  - Milk
  - Nuts

*Not an all-inclusive list.*
Urate uroliths are radiolucent on survey radiographs.

Urate uroliths are the third most common urolith type in cats, accounting for approximately 6% to 9% of feline uroliths submitted for analysis. Unlike struvite and calcium oxalate uroliths, the incidence of urate uroliths seems to have remained stable over the past 2 decades. In cats, urate uroliths are found almost exclusively in the bladder, and males and females are equally affected. With the exception of portovascular anomalies, the pathogenesis of urate uroliths in cats is unknown. Screening for occult hepatopathy is recommended in all cats with urate-containing uroliths. Suggested risk factors in cats include the formation of highly acidic, highly concentrated urine associated with diets high in purine precursors.

Surgery remains the treatment of choice in cats, as medical dissolution protocols have not been developed for this species. Additional studies of the efficacy and safety of allopurinol in cats are needed. Successful dissolution has been noted only anecdotally. Any concurrent infections should be treated based on culture and sensitivity testing. Prevention is similar to that in dogs and is centered on feeding a low-protein diet, limited in purine precursors, that promotes formation of moderately dilute urine of neutral pH. There is no feline equivalent of the canine prescription diets; however, prescription feline diets for the management of renal disease have been used with success. Many of these diets are formulated with potassium citrate. Prevention of recurrence was noted to be >90% with one such diet. The addition of supplemental potassium citrate can be used to achieve an appropriate urine pH.

**Conclusion**

Urate and xanthine uroliths are generally uncommon, except in dalmatians. Ultrasonography and double-contrast cystography are the best imaging techniques for diagnosing these radiopaque calculi. The presence of urate uroliths or crystalluria in a breed that is not predisposed should prompt evaluation for a portosystemic shunt. Urate uroliths are generally small and may be removed by dissolution, nonsurgical, or surgical techniques. Purine- and protein-restricted diets that alkalinize the urine are recommended for dissolution, as well as for prevention in male dalmatians. Allopurinol is used in some cases to aid dissolution and prevention.

**References**


<table>
<thead>
<tr>
<th>1.</th>
<th>A genetic predisposition for urate urolith formation is suspected in _______.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Yorkshire terriers.</td>
</tr>
<tr>
<td>b.</td>
<td>shih tzu.</td>
</tr>
<tr>
<td>c.</td>
<td>English bulldogs.</td>
</tr>
<tr>
<td>d.</td>
<td>miniature schnauzers.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2.</th>
<th>The major excretory end product of purine metabolism in dogs and cats is _______.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>xanthine.</td>
</tr>
<tr>
<td>b.</td>
<td>allantoin.</td>
</tr>
<tr>
<td>c.</td>
<td>uric acid.</td>
</tr>
<tr>
<td>d.</td>
<td>ammonia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3.</th>
<th>The suspected mechanism of hyperuricosuria in dalmatians is _______.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>congenital uricase deficiency.</td>
</tr>
<tr>
<td>b.</td>
<td>portosystemic vascular anomaly.</td>
</tr>
<tr>
<td>c.</td>
<td>transmembrane transport defect of hepatocytes and renal tubular cells.</td>
</tr>
<tr>
<td>d.</td>
<td>recurrent urinary tract infection.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4.</th>
<th>The target urine pH for prevention of urate crystalization is _______.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>&lt;6.5.</td>
</tr>
<tr>
<td>b.</td>
<td>6.6-7.0.</td>
</tr>
<tr>
<td>c.</td>
<td>7.0-7.5.</td>
</tr>
<tr>
<td>d.</td>
<td>&gt;7.5.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5.</th>
<th>A predisposition for formation of urate uroliths is suspected in _______ cats.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Siamese.</td>
</tr>
<tr>
<td>b.</td>
<td>Persian.</td>
</tr>
<tr>
<td>c.</td>
<td>Himalayan.</td>
</tr>
<tr>
<td>d.</td>
<td>Abyssinian.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6.</th>
<th>What percentage of urate uroliths are found in the upper urinary tract?</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>3%.</td>
</tr>
<tr>
<td>b.</td>
<td>5%.</td>
</tr>
<tr>
<td>c.</td>
<td>8%.</td>
</tr>
<tr>
<td>d.</td>
<td>20%.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7.</th>
<th>Which parameter is not useful when evaluating response to medical therapy for urate urolithiasis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>serum BUN</td>
</tr>
<tr>
<td>b.</td>
<td>urine sediment</td>
</tr>
<tr>
<td>c.</td>
<td>survey radiographs</td>
</tr>
<tr>
<td>d.</td>
<td>urine pH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8.</th>
<th>The detection rate of urate urocystoliths using double-contrast cystography is _______ for stones &gt;1.0 mm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>65%.</td>
</tr>
<tr>
<td>b.</td>
<td>78%.</td>
</tr>
<tr>
<td>c.</td>
<td>85%.</td>
</tr>
<tr>
<td>d.</td>
<td>100%.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.</th>
<th>_______ is a recognized side effect of allopurinol therapy in dogs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Pyodermia</td>
</tr>
<tr>
<td>b.</td>
<td>Liver failure</td>
</tr>
<tr>
<td>c.</td>
<td>Xanthine urolithiasis</td>
</tr>
<tr>
<td>d.</td>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10.</th>
<th>Use of ultralow-protein diets formulated for prevention of urate urolithiasis is implicated in the development of _______ in predisposed English bulldogs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>dilated cardiomyopathy</td>
</tr>
<tr>
<td>b.</td>
<td>liver failure</td>
</tr>
<tr>
<td>c.</td>
<td>renal disease</td>
</tr>
<tr>
<td>d.</td>
<td>xanthine urolithiasis</td>
</tr>
</tbody>
</table>