**CANINE CYSTINE**

Cystine uroliths form because of inherited defects in renal tubular transporters of cystine. The transportation defect in dogs appears to be genetically heterogeneous (autosomal recessive-SLC3A1, autosomal dominant-SLC3A1 & SLC7A9, and sex linked/androgen responsive). In many dog breeds the mutation has not yet been determined.

**PREVENTION**

<table>
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<tr>
<th>DIAGNOSTIC CONSIDERATIONS</th>
<th>MEDICAL CONSIDERATIONS</th>
<th>NUTRITIONAL CONSIDERATIONS</th>
<th>MONITORING CONSIDERATIONS</th>
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<tr>
<td>Genetic testing at PennGen Laboratories (<a href="http://research.vet.upenn.edu/penngen">research.vet.upenn.edu/penngen</a>)</td>
<td>Castration prevents genetic transmission and reduces cystine excretion in androgen responsive mutations. <strong>Tiopronin (Thiola), 10 to 30mg/kg q24hr if castration and diet does not reduce urine cystine.</strong></td>
<td>Canned foods with lower levels of animal proteins that do not overly acidify urine (e.g., u/d, others).</td>
<td>Urinalysis every 3 to 6 months to adjust pH to 7 to 8.0, and urine specific gravity to 1.020 and lower. Urine Nitroprusside in 3 to 6 months (urine amino acids less commonly performed) to determine if therapy reduces cystine excretion. Medical imaging every 6 to 12 months to detect recurrent stones when small to permit their easy removal without surgery.</td>
</tr>
</tbody>
</table>

**** Review manufacturer’s therapeutic food literature to determine indications/contraindications. For pets with multiple health concerns, consult a veterinary nutritionist to select an optimal food.

In depth recommendations and references are available on our website: [urolithcenter.org](http://urolithcenter.org) under the resources tab.
**Cystine Urolith Testing/Management Options**

Neutering:
Genetic tests in some breeds are available to identify genetic carriers and affected dogs. Dogs with androgen-dependent cystinuria can be cured by medical (GnRH agonist implant for ~6 months) and surgical castration. Testing the urine for cystine (nitroprusside test) **2–4 weeks** pre and **2–4 months** post neutering can be helpful to suggest a type I/II versus androgen-dependent cystinuria. Castration is recommended to potentially provide a cure, and to prevent the spread of this inborn error of metabolism.

Nutritional Considerations:
Dietary selection is an important part of preventative therapy for cystinuric dogs. Select low sodium canned foods with lower levels of animal proteins that do not overly acidify urine. Consult a veterinary nutritionist for options.

Pilot studies performed on cystinuric dogs at the University of Minnesota revealed a 20% to 25% reduction in 24-hour urine cystine excretion during consumption of Prescription Diet® u/d® canned diet compared to a canned maintenance diet

**Thiola® (Tiopronin, 2-MPG)**
Effective September 2014, Thiola is no longer distributed by Mission Pharmacal. Thiola is available directly from the distributor Retrophin at:
Thiola Total Care Hub thiola.com/hub phone = 844-4-THIOLA (844-484-4652)

Tiopronin tablets are available through compounding pharmacies. Contact your preferred compounding pharmacy for availability. One pharmacy we have identified that offers compounded capsules and suspensions (confirmed availability: June 2016) Wedgewood Pharmacy wedgewoodpetrx.com 877-357-6613

Alternatives:
**L-cystine methyl esters**
Studies in the mouse model have shown that these compounds are effective in disrupting cystine crystal growth. Future studies hope to show that efficacy and safety profiles are superior to current thiol-binding drugs.

**Cuprimine® D-Penicillamine**
D-penicillamine, also called dimethylcysteine, is a first-generation cysteine chelating drug. Although D-penicillamine is effective in reducing urine cystine concentrations, drug-related adverse events limit its use. Therefore, we have discontinued using D-Penicillamine for cystinuric dogs and cats.

**Additional information regarding cystine urolithiasis:**
vetmed.umn.edu/centers-programs/minnesota-urolith-center/recommendations


**Resources for cystinuria testing (urine nitroprusside/genetic testing):**
PennGen Laboratories - http://research.vet.upenn.edu/penngen
CANINE CYSTINE UROLITHS

Cystinuria is an inherited defect in the transport of cystine. Cystine and several similar amino acids are normally reabsorbed by the renal tubules. Cystinuric dogs fail to reabsorb cystine from glomerular filtrate. The subsequently higher urine concentration of cystine is an important risk factor for urolith formation. As in humans, the transportation defect in dogs appears to be genetically heterogeneous1.

Epidemiologic studies of uroliths submitted to the Minnesota Urolith Center indicate that male dogs (98%) are more commonly affected than females (2%). Common breeds affected include: Newfoundlands, Dachshunds, Mastiffs, Bassett Hounds, Staffordshire Bull Terriers, and Bulldogs. The mean age at time of urolith retrieval was 4.8 ± 2.5 years.2

Consider these facts:
- Experienced surgeons failed to remove all uroliths in 15% of dogs.5,6 Therefore, be diligent during surgery, and perform medical imaging immediately following surgery to verify complete urolith removal.
- Pilot studies performed on cystinuric dogs at the University of Minnesota revealed a 20% to 25% reduction in 24-hour urine cystine excretion during consumption of Prescription Diet® u/d® canned diet compared to a canned maintenance diet.2
- Cystine uroliths are highly recurrent.
- With increasing age, dogs appear to have a decrease in cystine urolith formation.7,2
- Cystine uroliths are marginally radio-opaque. Contrast urethrocystography or ultrasonography may be needed to detect uroliths.
Managing Canine Cystine Urolith Prevention
Perform Urinalysis and Medical Imaging

Desired goals:
- pH ≥ 7.5
- USG <1.020
- No or few cystine crystals

Cystine Crystalluria

- Repeat urinalysis monthly until goals are achieved, then every 3 to 6 months to validate and encourage compliance
- Repeat medical imaging every 3 to 6 months. Contrast urothrocystography or ultrasonography may be needed (urolith recurrence is common)
- Repeat urinalysis and medical imaging if signs consistent with uroliths (hematuria, pollakiuria, inappropriate urination, etc.) recur.

Uroliths

- Consider voiding urohydropropulsion if uroliths are small enough to void.8
- Stones can be left alone in some patients without clinical signs.
- With persistent clinical signs, select appropriate method to remove uroliths.
- Submit urolith for quantitative analysis to verify composition.

- Verify persistent, in-vivo crystalluria by reevaluating an appropriately collected (in hospital) fresh urine sample analyzed within 30 minutes.
- If USG >1.020, consider canned diets or adding water to food.
- If urine pH ≤ 7, consider diets that promote formation of alkaline urine, like Prescription Diet® u/d® canned, or use of urinary alkalinizers (e.g. potassium citrate).
- Initiate or increase the dose of medications that bind cysteine in urine (e.g. Thiola™)

** Review manufacturer’s therapeutic food literature to determine indications/contraindications. For pets with multiple health concerns, consult a veterinary nutritionist to select an optimal food.

Further references:
1. Brons et. al. SLC3A1 and SLC7A9 Mutations in Autosomal Recessive or Dominant Canine Cystinuria: A New Classification System. JVIM.2013.27:1400
4. www.hillsvet.com
6. Grant D. Frequency of incomplete urolith removal...in dogs. JAVMA. 2010;210:763
8. Lulich J. Voiding urohydropropulsion a nonsurgical technique. Current Veterinary Therapy XII, SAP. 1995, p1003