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.

MINIMIZING RECURRENCE

<table>
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<tr>
<th>DIAGNOSTIC CONSIDERATIONS</th>
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<tr>
<td>Genetic testing at PennGen Laboratories</td>
<td>Castration prevents genetic transmission and reduces cystine excretion in androgen responsive mutations. Tiopronin (Thiola), 10 to 30mg/kg q24hr if castration and diet does not reduce urine cystine.</td>
<td>Canned foods with lower levels of animal proteins that do not overly acidify urine (e.g., g/d, 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 or urine cystine 3 – 6 months 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>
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<tr>
<td>Urine Nitroprusside or cystine (cystine/creatinine) prior to and after neutering. PennGen Laboratories (research.vet.upenn.edu/penngen) for urine nitroprusside or UC Davis Amino Acid Laboratory (<a href="http://www.vetmed.ucdavis.edu/labs/">www.vetmed.ucdavis.edu/labs/</a> amino-acid-laboratory) for amino acid quantification.</td>
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** 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. **
Common Questions on Dogs Forming Cystine Stones

1. How will I know if my dog has cystinuria?
   - Cystine is an amino acid that is freely filtered in urine and almost completely reabsorbed by the kidney tubules (i.e. removed from the urine).
   - As urine cystine concentration increases, a positive urine nitroprusside test, cystine crystals and cystine stones are indicators of disease.
   - Although cystinuria and cystine crystalluria do not cause clinical signs, cystine stones can irritate the lining of the urinary tract resulting in urinary accidents, urgency, straining, or bloody urine. In some cases, the stones result in life-threatening urinary obstruction. Cystine stones are not always visible on x-rays and may require special contrast studies or an ultrasound to diagnosis.
   - Genetic tests for cystinuria are available for some breeds of dogs. A genetic marker test for androgen dependent cystinuria has been developed for Mastiffs, English bulldogs and French bulldogs. There are other breeds with androgen dependent cystinuria as well as other breeds in which castration will not reduce cystinuria (Type Ia, reported in Newfoundland dogs, Labradors and Landseers, Type IIa, reported in Australian Cattle dogs and Border Collies, Type IIb, reported in Miniature Pinschers).

2. Will castration prevent recurrence of cystine stones?
   - Surgical or medical castration can resolve/cure cystinuria in the subset of male dogs with androgen dependent cystinuria.
   - The magnitude of cystinuria associated with stone formation is wide (100 to >10,000 \( \mu \text{mol/g creatinine} \)) and varies between serial measurements in the same dog. This emphasizes that other factors such as diet, urine specific gravity and urine pH influence stone formation.
   - To determine if castration reduces cystinuria, measure urine cystine at an amino acid lab, measure urine creatinine at your preferred lab (cystine/creatinine ratio) before and 3 months after castration. Reference ranges are under development; consider serial monitoring looking for a decreasing trend. Undetectable levels may indicate resolution of cystinuria. If the urine cystine remains elevated at 3 months, check again at 6 months. If the test is persistently positive, it indicates that the dog has a non-androgen dependent form of the disease. These cases are at risk for recurrence without additional therapy. Less sensitive indicators of urine cystine that can be evaluated before and after castration include urinalyses for cystine crystalluria, and recurrence of small stones.

3. Is a negative nitroprusside test following castration an indication that your dog will not reform stones?
   - Possibly, but not for certain.
   - The nitroprusside test is a qualitative screening test for disease (quantitative tests are better).
   - Some dogs with cystinuria are negative on this test even though they have the disease. If the nitroprusside test was only evaluated after castration, it is difficult to determine if castration reduced cystine excretion. In this situation, measure urine cystine concentration. In most stone-free dogs, cystine concentrations are extremely low.
   - Studies on human urine indicate that the nitroprusside test is influenced by urine specific gravity and creatinine, but not by thiola or D-penicillamine. Ampicillin and sulfur containing drugs have been reported to cause false positive results. This test may also be influenced by ascorbic acid, which dogs are able to synthesize within their body (unlike people). Therefore, the accuracy of this test in dogs should be interpreted with this in mind.

4. What diets prevent cystine stones?
   - A 25% reduction in 24-hour urine cystine was associated with consumption of Hill’s Prescription diet u/d.
   - Avoid diets that promote formation of acidic and concentrated urine, which are risk factors for stone formation.
   - Diets rich in methionine (a precursor of cysteine and a common amino acid in animal protein sources) may contribute to cystine recurrence. Consider lower protein foods with reduced quantities of animal protein.
   - Studies in cystinuric humans suggest that dietary sodium enhances cystinuria, and therefore high sodium diets (>100-150 mg/Kcal) should be avoided.

Osborne et al. Canine cystine urolithiasis: cause, detection, treatment….. VCNA. 1999;29:193
Additional Cystine Resources

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.com or 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 wedgewoodpharmacy.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/metabolic screening):
PennGen Laboratories - http://research.vet.upenn.edu/penngen

Resources for Urine Amino Acid Testing:
UC Davis Amino Acid Laboratory - www.vetmed.ucdavis.edu/labs/amino-acid-laboratory
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 heterogeneous.\(^1\)

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.\(^2\)

Medical Considerations:
- Urine nitroprusside test is an effective screening test for cystinuria.
- Genetic tests for Newfoundlands and Labrador retrievers are available at the University of Pennsylvania (research.vet.upenn.edu/penngen) to identify genetic carriers and affected dogs.
- Cystinuria in some dogs may be androgen dependent. Considering neutering to reduce cystine excretion and prevent transmission of this genetic disease.

Nutritional Considerations:
- Avoid diets that promote urine acidification. Alkaluria promotes dissolution of cystine.
- High moisture foods (i.e. canned formulations) are more effective because increased water consumption is associated with decreased urine concentrations of calculogenic minerals.
- Limit excretion of amino acids such as cystine by feeding a low protein diet.
- Limit sodium intake. In cystinuric humans, dietary restriction of sodium reduced the urinary excretion of cystine.\(^3\)
- Diets like Prescription Diet® u/d® canned diet fit these criteria.\(^4\)

Pharmacological Considerations:
- For dissolution: In addition to dietary changes, administer n-(mercaptopropionyl)-glycine (2-MPG) (Thiola™) at an approximate dosage of 15mg/kg every 12 hours. Thiola™ binds with cysteine molecules to form a complex that is more soluble in urine than cystine.
- Administration of alkalinizers may be necessary to maintain urine ph of ≥7.5.
- For prevention: If diet alone is ineffective, consider addition of Thiola™ at 10 to 30mg/kg/day to maintain a urine cystine concentration below 200mg/L.

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 urothrocystography 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 urethrocystography or ultrasonography may need (urolith recurrence is common)
- Repeat urinalysis and medical imaging if signs consistent with uroliths (hematuria, pollakiuria, inappropriate urination, etc.) recur.

Uroliths

- 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™)

- Consider voiding urohydropropulsion if uroliths are small enough to void.³
- 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.

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- USG < 1.020
- No or few cystine crystals

**Repeat urinalysis:**
- Monthly until goals are achieved, then every 3 to 6 months to validate and encourage compliance
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**Further references:**

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4. www.hillsvet.com
6. Grant D. Frequency of incomplete urolith removal...in dogs. JAVMA. 2010;210:763
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