

Minnesota Urolith Center * UNIVERSITY OF MINNESOTA

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Common Questions on Dogs Forming Cystine Stones

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How will I know if my dog has cystinuria?

1. 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).
2. As urine cystine concentration increases, a positive urine nitroprusside test, cystine crystals and cystine stones are indicators of disease.
3. 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.
4. 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).

Will castration prevent recurrence of cystine stones?

1. Surgical or medical castration can resolve/cure cystinuria in the subset of male dogs with androgen dependent cystinuria.
2. 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.
3. To determine if castration reduces cystinuria, measure urine cystine (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.

Is a negative nitroprusside test following castration an indication that your dog will not reform stones?

1. Possibly, but not for certain.
2. The nitroprusside test is a qualitative screening test for disease (quantitative tests are better).
3. 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.
4. 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.

What diets prevent cystine stones?

1. A 25% reduction in 24-hour urine cystine was associated with consumption of Hill's Prescription diet u/d.
2. Avoid diets that promote formation of acidic and concentrated urine, which are risk factors for stone formation.
3. 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.
4. 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

Chillaron, J. et al. Pathophysiology and treatment of cystinuria. Nat. Rev. Nephrol. 2010;6:424-434

Brons et. al. SLC3A1 and SLC7A9 mutations in....canine cystinuria. JVIM 2013;27:1400.

Brady et al. Cyanide-Nitroprusside Colorimetric Assay: a rapid colorimetric screen..... JALM. 2017;2:55

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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

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.

Sahota, A: Novel Cystine Ester Mimics for the Treatment of Cystinuria-induced Urolithiasis in a Knockout Mouse

Model: UROLOGY 84: 1249.e9e1249.e15, 2014

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

Osborne C, et al: Canine Cystine Urolithiasis: Causes, Detection, Dissolution, and Prevention: Small Animal Clinical Nutrition 5, Mark Morris Institute <http://bookstore.markmorrisinstitute.org/> (download at no cost)

Resources for cystinuria testing (urine nitroprusside/genetic testing/metabolic screening):

PennGen Laboratories - <http://research.vet.upenn.edu/penggen>

Resources for Urine Amino Acid Testing:

UC Davis Amino Acid Laboratory - www.vetmed.ucdavis.edu/labs/amino-acid-laboratory