CASE BY CASE: NUTRITION

# Nutritional Management of Genetic Hyperuricosuria: Case Report

***Donna Raditic**, DVM, DACVIM (Nutrition), CVA, Nutrition and Integrative Medicine Consultants, Athens, Georgia*
***Laura Gaylord**, DVM, DACVIM (Nutrition), Whole Pet Provisions, PLLC, Fuquay Varina, North Carolina*

Urate uroliths are a type of purine urolith and are the third most common type of urolith in dogs and cats.[1,2] Known risk factors for urate urolithiasis in dogs are:

- increased renal excretion and urine concentration of uric acid (hyperuricosuria)
- renal excretion, renal production, or microbial urease production of ammonium ion
- aciduria
- presence of promoters or absence of inhibitors of urate urolith formation

## FORMATION OF URATE UROLITHS

Uric acid is an end product of metabolism of purine nucleotides. Purines are derived from dietary protein and turnover of endogenous proteins that are metabolized to hypoxanthine, which is converted by the enzyme xanthine oxidase to xanthine and uric acid. In most mammals, uric acid is then converted to allantoin by the hepatic enzyme uricase, circulates as urate anions, and then is excreted into the urine in small amounts. Uric acid that forms complexes with ammonium will precipitate as ammonium urate, the most common naturally occurring purine urolith in dogs. When urine is oversaturated with these substances, urate uroliths form.[1-3]

## PREDISPOSING FACTORS

Urate uroliths can form in patients with liver disease (usually a portosystemic shunt) or an inborn error of metabolism in certain breeds, which results in

## Abstract

Urate uroliths can result from high urine levels of uric acid (hyperuricosuria) and are most common in dog breeds with a homozygous mutation that prevents hepatic conversion of uric acid (e.g., Dalmatians, English bulldogs, Black Russian terriers). Diagnosis typically involves abdominal ultrasonography, double-contrast cystography, and/or determination of 24-hour urinary uric acid excretion. Nutritional management consists of feeding low-purine diets and increasing water intake, followed by routine monitoring of weight, body and muscle condition scores, and urine and blood values.

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## Take-Home Points

- Preventing urate urolithiasis should include an appropriate diet, a feeding plan, and patient monitoring.
- Monitoring the risk for urate urolithiasis should include, at a minimum, urinalysis, but adding ultrasonography, uric acid excretion per day, and/or urine uric acid to creatinine ratios may provide more information about a diet's effect on urate urolithiasis.
- Addressing clients' concerns and beliefs while educating them about the current literature, nutrition plans, and proper monitoring may improve compliance and outcomes.
- Because pet food bags and their weights differ between and within companies, comparing the cost of diets requires determining the cost per 100 kcal.
- For a patient with ideal body weight, body condition score, and muscle condition score, a food gram scale can be used to determine the patient's exact kilocalorie intake to then determine the grams per day needed of the new diet.

hyperuricosuria. In Dalmatians, English bulldogs, and Black Russian terriers, a gene mutation in the *SLC2A9* (solute carrier family 2 member 9) transporter of uric acid has been identified as the underlying defect that results in hyperuricosuria. A homozygous mutation results in lack of hepatic conversion of uric acid to allantoin, but the definitive mechanism of urate urolith formation in Dalmatians remains unknown.[3-5] Although Dalmatians excrete relatively increased quantities of uric acid in their urine, urate uroliths will only form in a small percentage at the average age of 4.5 years old. Urate uroliths more commonly form in males than females.[3]

**TABLE 1 Laboratory Results at Baseline and at Monitoring Intervals When Fed Rayne Clinical Nutrition TheraDiet Plant-Based Dry Food**

| RESULT | BASELINE | MONTHS AFTER STARTING NEW DIET | | | |
|---|---|---|---|---|---|
| | | 1 | 3 | 6 | 12 |
| **Body weight, kg** | 21 | 21 | 21 | 23 | 21 |
| **Body condition score** | 5/9 | 5/9 | 5/9 | 6/9 | 5/9 |
| **Muscle condition score** | Normal | Normal | Normal | Normal | Normal |
| **Uric acid, mg excreted/day** | 430.7 | 259.1 | NA | 661.6 | 217 |
| **Urine UA/C ratio** | 0.5 | 0.4 | NA | 0.7 | 0.3 |
| **Urine specific gravity** | 1.044 | 1.032 | 1.045 | 1.042 | 1.035 |
| **Urine pH** | 7 | 7 | 7 | 7 | 7 |
| **Urine sediment** | 3+ urates | No crystals | No crystals | No crystals | No crystals |
| **Ultrasonography** | ▪ Some hyperechoic debris noted in the center of the apex but no shadowing to indicate the presence of any calculi<br>▪ No calculi noted within the medullary region of either kidney. No distended ureters appreciated (which would suggest calculi may be lodged in them). | ▪ NA | ▪ No stones found in the kidneys or bladder | ▪ No stones found in the kidneys or bladder | ▪ No stones found in the kidneys or bladder<br>▪ Bladder full of anechoic urine, no sediment |

*NA = not available; UA/C = uric acid to creatinine*

## PREVENTION

Preventing urate uroliths may be considered for dogs with genetic hyperuricosuria and may include nutritional management (feeding low-purine diets and increasing water intake) and medical management (urine alkalinization and xanthine oxidase inhibitors such as allopurinol).

## DIAGNOSIS

Because the radio-opacity of urate uroliths may be marginal, periodic abdominal ultrasonography or double-contrast cystography may be necessary.[3] Determination of 24-hour urinary uric acid excretion may also be useful, with the target excretion of approximately 250 to 350 mg per 24 hours. Urine uric acid to creatinine (UA/C) ratios may also be useful but are more often used to diagnose or assess the risk for urate urolith formation.[2,6]

## THE CASE

### History and Presentation

The patient was a 3-year-old spayed female Dalmatian, owned by a veterinary nurse who requested a nutrition consultation from the authors due to persistent urate crystalluria. The patient weighed 21 kg (46.3 lb) and had a body condition score (BCS) of 5/9 and a normal muscle condition score (MCS).[7,8] From genotype testing, she was homozygous for hyperuricosuria (vgl.ucdavis.edu/test/hyperuricosuria) and therefore at risk for bladder and kidney uroliths. Other diagnostic testing included urinalysis, urine culture and sensitivity, complete blood count, serum biochemistry with electrolytes, and abdominal ultrasonography. Ultrasonography revealed hyperechoic debris in the center of the bladder apex but no shadowing indicating any overt calculi. Both kidney and ureters were evaluated; no calculi were noted in the renal medulla, and the ureters were normal with no distension (which would have suggested presence of ureteroliths). All other abdominal ultrasonography findings were normal. Urinalysis indicated a specific gravity of 1.044, a pH of 7, and sediment that was normal except for 3+ urate crystals. Urine culture was negative. The remaining test results were within normal limits (TABLE 1).

### Dietary History

The patient was consuming Rayne Clinical Nutrition TheraDiet Healthy Reduction-MCS dry food, 3 cups per day divided into 2 feedings (BOX 1). Treats had been discontinued due to concern for the urate crystalluria.

**BOX 1 Determining the Patient's Current Dietary Kilocalorie and Gram Intake**

- Current diet = 92 g/cup with 3 cups = 276 g/day
- Current diet contains 3314 kcal/kg or 3.314 kcal/g
- Current kcal intake/day = 276 g/day × 3.314 kcal/g = 915 kcal/day

Although studies report a lower risk for clinical urate urolithiasis in female than male Dalmatians, the client was interested in preventing urate urolith formation because her previous Dalmatian had experienced repeated episodes of clinical urate urolithiasis and concurrent nephroliths. She also told the nutritionists that she would prefer a plant-based diet and that she would need to consider the cost of the diet. Another client concern was weight management because she was not always able to provide her Dalmatian consistent exercise as a result of her variable work schedule.

### Nutritional Considerations

#### Nutrients of Concern

The nutrients of concern for this patient were:

- water
- purine content
- protein and essential amino acids

#### Water

Urine dilution by promoting water intake is recommended for patients experiencing or at risk of urate urolithiasis. The concentration of lithogenic compounds in the urine depends on urine volume; therefore, increasing water intake can increase urine volume and decrease uric acid and ammonium concentrations. It is often recommended to feed a canned diet with approximately 75% moisture (compared with dry foods with 8% to 12% moisture) or to add water to a dry diet to increase urine volume and decrease urine specific gravity to less than 1.02.[2,3,4,9]

### Purine Content

Because urinary urate results from catabolism of dietary purines, diets with low-purine ingredients (i.e., plant-derived, egg whites) are preferred over diets with high-purine ingredients (i.e., organ meats, fish). Low-protein, low-purine diets in combination with allopurinol have been successfully used for urate dissolution.

### Protein and Essential Amino Acids

Often low-protein diets are fed to impair urine concentration by decreasing the renal medullary urea concentration (lower urine specific gravity) and to reduce the 24-hour excretion of uric acid.[2,3] However, restricted dietary intake can result in decreased lean body mass if essential amino acid intake is inadequate. Careful assessment of MCS and serum biochemistry should be part of monitoring dogs fed lower-protein diets. The AAFCO (Association of American Feed Control Officials) recommendation for adult dog maintenance is 4.5 g/100 kcal. Inadequate levels of essential amino acids, especially lysine and sulfur amino acids, may result in low levels of carnitine (lysine and methionine) and taurine (methionine and cysteine), which are essential for normal heart function.[10] Thus, with long-term feeding of low-protein diets, more comprehensive monitoring may also include echocardiography.

High-protein diets, especially those with a higher percentage of protein from animal sources, will be a potential source of urine ammonium, purines, and purine precursors. Urine acidity is a risk factor for ammonium urate urolithiasis because the solubility of purines is pH dependent and they are less soluble in acid urine.[2,4,6,9]

## Nutrition Plan

In the authors' clinical experience, client compliance with a nutrition plan is optimized if the client's concerns and preferences are addressed. Furthermore, compliance is also improved if the client is actively involved in the thinking process and decision-making regarding the final nutrition plan.

First, the nutritionists created a table of urate-preventative diets, noting which were plant based (**TABLE 2**). Increased consumer interest in unconventional pet diets such as plant-based diets may be due to the rise in pet humanization (in which pets are considered family members and the owners are vegan), concerns for sustainability, and perceived health benefits.[11,12] Plant-based pet foods should contain fewer purines because the purine content of animal sources (e.g., meat, fish) generally varies from approximately 120 to over 400 mg of purine per 100 g, whereas the purine content of plant sources (e.g., most non-soy legumes, grains, seeds, fruits, other vegetables) varies from 7 to 70 mg of purine per 100 g.[13]

The nutritionists noted the diet form (i.e., canned or dry), crude protein, and energy density (i.e., kilocalories per kilogram) and added the cost per 100 kcal for the client's consideration (**TABLE 2**). The nutritionists also added the patient's current diet to the table for comparison because the client believed that, despite the urate crystalluria, the patient was doing well on that diet and its cost worked with her budget.

It is the authors' clinical experience that clients often perceive veterinary therapeutic diets to be expensive. Therefore, it is helpful to educate clients that the pet food industry does not use standard bag or can weights, which makes it difficult for consumers to compare the costs of different pet foods. The nutritionists provided the client with an example of calculating the cost per 100 kcal that was used in **TABLE 2** but can also be used in clinical practice (**BOX 2**).

Despite the difference in cost, the owner elected to feed the Rayne Clinical Nutrition TheraDiet Plant-Based diet. She contacted the company for assurance that the

### BOX 2 Determining the Cost of Pet Diets

- **Start with the cost of the current diet:** Rayne Clinical Nutrition TheraDiet Healthy Reduction-MCS = $94.91 for 21-lb bag
- **Determine the kilograms of diet (1 lb = 0.454 kg):** 21 lb × 0.454 kg/lb = 9.53 kg of diet
- **Determine kcal/kg for the diet (BOX 1):** 3314 kcal/kg
- **Determine the total kcal in 1 bag of food:** 9.53 kg × 3314 kcal/kg = 31582 kcal in 1 bag
- **Determine the cost per 100 kcal:** ($94.91 × 100)/31852 =$0.30/100 kcal

**TABLE 2 Comparison of Current Diet and Commercial Diets Considered for Prevention of Urate Urolithiasis**

| DIET | PLANT BASED | CRUDE PROTEIN, G/100 KCAL | KCAL/KG | WEIGHT OF BAG OR CAN | COST/100 KCAL, $ (MAY VARY) |
|---|---|---|---|---|---|
| Rayne Clinical Nutrition TheraDiet Healthy Reduction-MCS dry[a] | No | 10.96 | 3314 | 21 lb | 0.30 |
| Rayne Clinical Nutrition TheraDiet Plant-Based dry[a] | Yes | 6.8 | 3339 | 24.2 lb | 0.38 |
| Royal Canin Urinary UC dry[b] | No | 5.06 | 3729 | 18 lb | 0.30 |
| Royal Canin Vegetarian dry[b] | Yes | 5.35 | 3395 | 17.6 lb | 0.31 |
| Royal Canin Vegetarian loaf in sauce[b] | Yes | 7.93 | 886 | 13.6 oz | 1.35 |
| Hill's Prescription Diet u/d Dry Dog Food (chicken flavor)[c] | No | 3.2 | 3986 | 27.5 lb | 0.24 |
| Hill's Prescription Diet u/d Dog Food loaf (chicken flavor)[c] | No | 3 | 1377 | 13 oz | 0.83 |
| Purina Pro Plan Veterinary Diets HA Hydrolyzed Vegetarian dry[d] | Yes | 5.36 | 3695 | 25 lb | 0.27 |

[a]*cdn.shopify.com/s/files/1/0471/2067/9067/files/Rayne_CANINE_Plant-Based_DRY_8.5x11_DS054-0621_DIGITAL.pdf?v=1625503184*
[b]*Royal Canin Veterinary Health Nutrition Product Book 2022 (my.royalcanin.com/UserFiles/Docs/Vet.Product.Guide.pdf)*
[c]*Hill's.* Key to Clinical Nutrition - 2022. *Hill's Pet Nutrition; 2022:43.*
[d]*Purina Product Guide 2023 (https://drive.google.com/file/d/1oyLWM4oCv88vsrVdcSogyJOd-03s8gPZ/view)*

diet was indeed plant based because she noted that it contained the fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and typically, fatty acids are found in fish oils. The company assured her that the diet was indeed plant based and that the EPA and DHA came from a plant source of omega-3 fatty acids (marine microalgae).

The nutritionists provided the client with a nutrition plan that included the amount to feed, using a food gram scale. The gram scale weight would enable the client to properly transition the patient to the new diet and to make more exact adjustments in food intake for proper weight management (**BOX 3**).

## Patient Monitoring

Unlike other veterinary therapeutic diets, the indications for the Rayne Clinical Nutrition TheraDiet Plant-Based diet did not include management of urate urolithiasis; therefore, the nutritionists and client discussed a protocol of monitoring the patient at 1, 3, 6, and 12 months after diet transition. Monitoring included physical examination, body weight, BCS, MCS, complete blood count, serum biochemistry with electrolytes, abdominal ultrasonography, and urinalysis at each interval.

Typically, urine pH should be monitored at appropriate intervals and urine sediment evaluated for crystalluria in a fresh-caught urine sample at body temperature. As urine cools or is refrigerated, spurious crystalluria may be detected. A urine pH range of 7 to 7.6 or greater is preferred for preventing urate urolithiasis. If therapy is effectively promoting the formation of urine that is undersaturated with ammonia and uric acid, ammonium urate crystals should not form in fresh urine.[2,3,9,14]

In a study of client-owned dogs with a history of clinical urate urolithiasis fed a veterinary therapeutic diet, Westropp et al evaluated uric acid excretion per day and urine UA/C ratios.[4] The nutritionists discussed that study with the client as an example of more precise monitoring of diet effects. The client agreed to add the modified 24-hour urine collection used in the Westropp et al study for improved monitoring to evaluate uric acid excretion per day and urine UA/C concentrations. Use of the urine UA/C ratio in single urine samples has been recommended not only for diagnosing urate urolithiasis but also for monitoring medical therapy.[2-4,14]

Whereas most non-Dalmatian dogs excrete approximately 10 to 60 mg of uric acid in their urine

per day, Dalmatians excrete more than 400 to 600 mg of uric acid per day.[2] Dalmatians that excrete more than 550 to 600 mg in 24 hours are at increased risk for urolith formation because at this excretion rate, precipitation is likely. The range of urine UA/C ratios for dogs that excrete low uric acid levels has been reported to be 0.23 to 0.47, and the range for dogs that excrete high uric acid levels is 1.2 to 4.[2,5]

## Follow-Up

### 1 Month

Before the patient's diet was transitioned to the Rayne plant-based diet, baseline testing showed that she was excreting 431 mg of uric acid per day with a urine UA/C ratio of 0.5 (**TABLE 1**). After 1 month of the new diet, uric acid excretion decreased to 259 mg a day with a urine UA/C ratio of 0.4. Urine specific gravity at the 1-month testing was 1.032. The nutritionists discussed with the client adding water to the dry food to try to achieve the preferred specific gravity of less than 1.02. The client declined this recommendation because previous attempts had resulted in the dog having "accidents" in her crate. All other laboratory values were within normal limits.

### 6 Months

At the 6-month evaluation, daily uric acid excretion had increased to 662 mg with a urine UA/C ratio of 0.7, but all other laboratory values were within normal limits. The patient's weight had increased from 21 kg (46.3 lb) to 22 kg (48.5 lb). When discussing the results with the client, the nutritionists learned that the client had been fostering a dog that was being fed an over-the-counter diet and that a family member had taken over feeding the dogs in the evening. The family member admitted she had not been diligent in assuring the patient was not getting into the foster dog's food. The nutritionists reviewed feeding instructions with the client and family member regarding the patient's need for strict intake of the Rayne plant-based diet only.

### 12 Months

After 1 year of the Rayne plant-based diet, repeat testing indicated that the patient was excreting 217 mg of uric acid per day and that her urine UA/C ratio was 0.3. She also lost weight and resumed an ideal BCS of 5/9, a normal MCS, and a body weight of 21 kg (46.3 lb). Abdominal ultrasonography showed no evidence of urolithiasis (bladder and kidney), and all other laboratory values were within normal limits.

On the basis of this monitoring, the nutritionists believed that the Rayne plant-based diet was suitable for managing this patient with genetic hyperuricosuria, urate crystalluria, and risk for urate urolithiasis. The nutritionists recommended routine monitoring of weight, BCS, and MCS, and biannual testing of urine and blood samples. TVP

**BOX 3 Determining Gram Intake of the New Diet and Diet Transition**

**Gram Intake of New Diet**
New diet contains 3339 kcal/kg or 3.339 kcal/g

915 kcal ÷ 3.339 kcal/g = 274 g/day of new diet

**Diet Transition**
**Days 1–3:** Feed 75% old diet (206 g) + 25% new diet (68 g) divided into 2 meals.

**Days 4–6:** Feed 50% old diet (137 g) + 50% new diet (137 g) divided into 2 meals.

**Days 7–9:** Feed 25% old diet (68 g) + 75% new diet (206 g) divided into 2 meals.

**Days 10 on:**
- Feed 274 g of new diet per day divided into 2 meals
- Always provide fresh water
- Give no treats OR use a portion of the 274 g of diet as treats (i.e., 10% or 27 g as treats with 247 g/day divided into 2 meals/day)

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## Donna Raditic

Dr. Raditic is a Board Certified Veterinary Nutritionist. She was a professor for both the Nutrition and the Integrative Medicine Services at the University of Tennessee College of Veterinary Medicine and is currently owner/founder of Nutrition and Integrative Medicine Consultants, which offers independent consulting and education. With a professional career that includes the roles of general practitioner/practice owner, academician, and independent veterinary nutritionist/consultant, she offers personal and unique perspectives on the role of nutrition, supplements, and integrative care for our veterinary patients.

## Laura Gaylord

Dr. Gaylord is a Board Certified Veterinary Nutritionist and Diplomate of the American College of Veterinary Internal Medicine (subspecialty Nutrition). She is an independent consultant and the owner/founder of Whole Pet Provisions, PLLC, a nutrition consulting company established in 2016, which offers veterinary nutrition consulting to pet owners, veterinarians, the pet food industry, and pet supplement companies. She offers homemade diet recipe formulation and commercial diet consultations through her business for pet parents and their veterinary team.


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**Table 1: Adverse Reactions in the Field Effectiveness Study**

| Adverse Reaction | ELURA (n=119) | Vehicle Control (n=69) |
|---|---|---|
| Vomiting | 35 (29.4%) | 18 (22.4%) |
| Hypersalivation | 25 (21.2%) | 0 (0.0%) |
| Hyporexia | 22 (18.5%) | 7 (10.0%) |
| Serum ALT Change* | 17 (14.4%) | 8 (15.0%) |
| Lethargy | 16 (13.6%) | 6 (10.0%) |
| Anorexia | 11 (9.3%) | 1 (1.7%) |
| Dehydration | 11 (9.3%) | 2 (3.4%) |
| Stage of CKD Increased* | 10 (8.5%) | 9 (12.5%) |
| Diarrhea | 9 (7.6%) | 2 (3.4%) |
| Urinary Tract Infection | 8 (6.8%) | 2 (3.4%) |
| Hyperglycemia | 8 (6.8%) | 2 (3.4%) |
| Upper Respiratory Infection | 7 (5.9%) | 1 (1.7%) |
| Hypercalcemia | 7 (5.9%) | 0 (0.0%) |

| Adverse Reaction | ELURA (n=119) | Vehicle Control (n=69) |
|---|---|---|
| Facial Skin Lesion | 6 (5.1%) | 0 (0.0%) |
| Hyperkalemia | 5 (4.2%) | 0 (0.0%) |
| Ataxia | 4 (3.4%) | 0 (0.0%) |
| Diabetes Mellitus | 1 (0.8%) | 0 (0.0%) |
| Congestive Heart Failure | 1 (0.8%) | 0 (0.0%) |

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