

THE BIG PICTURE It is important to assess a diet's complete nutritional profile, rather than relying on the general marketing, when assessing if it is appropriate for patients.

CASE REPORT: NUTRITION

Dietary Elimination Trial in a Dog with Protein-Losing Nephropathy

Deborah Linder, DVM, MS, DACVN
Cummings School of Veterinary Medicine at Tufts University

TODAY'S VETERINARY PRACTICE

CASE REPORT CHALLENGE

BROUGHT TO YOU BY
DECHRA VETERINARY PRODUCTS

Who Will Win the Grand Prize? A panel of judges will choose 5 finalists whose case reports will be published in *Today's Veterinary Practice* during 2021. *TVP's* Facebook followers will then select the grand prize winner from among the 5 finalists; the winner will receive a trip to VMX 2022, including registration, hotel, and airfare.

Managing patients with multiple medical conditions can prove challenging when those conditions have contradicting nutritional goals or when a diet that meets the needs of both conditions does not exist, as in the case described here. In these instances, a problem list can be created to compare nutritional goals, priorities, and nutrients of concern among all diet options. Sometimes a trial-and-error approach is required and the deciding factor is the patient's response to the diet.

This case report discusses a dog with protein-losing nephropathy and the need for a dietary elimination trial to diagnose potential food allergies. The dog was referred to the Cummings School of Veterinary Medicine nutrition service for nutritional management that would support his concurrent medical conditions. Diet and management options discussed in this report illustrate the approach taken for this specific patient and should not be generalized to all dogs with similar conditions.

HISTORY

The patient was a 1-year-old intact male boxer originally presented to his primary care veterinarian for polyuria, polydipsia, and incontinence, as well as persistent vomiting and diarrhea with weight loss. He had a history of pruritus that was controlled with oclacitinib (Apoquel; Zoetis, zoetisus.com). His previous diet was Purina Savor Lamb and Rice Canine (dry) and Sojos Complete Beef Freeze-Dried Raw Meat Grain-Free (dry).

His primary care veterinarian diagnosed protein-losing nephropathy (PLN) and initiated medical management, including clopidogrel and enalapril. Empirical treatment for his gastrointestinal signs included a short course of tylosin tartrate and probiotics (Visbiome; ExeGi Pharma, visbiome.com). Initially, his stool quality improved greatly; however, he continued to have intermittent episodes of borborygmus, nausea, vomiting, and anorexia. The patient's diet was changed to Hill's Prescription Diet z/d Canine, dry and canned,



and when this diet change did not fully resolve his symptoms, he was referred to our nutrition service to determine the best diet for both his PLN and his ongoing gastrointestinal signs.

REFERRAL ASSESSMENT

Physical Examination Findings

Physical examination by the nutrition service revealed a body weight of 28 kg and a body condition score (BCS) of 2/9 (based on the World Small Animal Veterinary Association [WSAVA] body condition score system of BCS 1 through 9; [wsava.org/wp-content/uploads/2020/01/Body-Condition-Score-Dog.pdf](https://www.wsava.org/wp-content/uploads/2020/01/Body-Condition-Score-Dog.pdf)).

His medical record indicated a previous weight of 31.8 kg, BCS of 5/9, and moderate muscle wasting (based on WSAVA muscle condition score [MCS] system of normal, mild, moderate, or severe muscle wasting; [wsava.org/wp-content/uploads/2020/01/Muscle-Condition-Score-Chart-for-Dogs.pdf](https://www.wsava.org/wp-content/uploads/2020/01/Muscle-Condition-Score-Chart-for-Dogs.pdf)). The remainder of his physical examination revealed no significant abnormalities.

Diagnostic Tests and Results

Diagnostics included testing for parasites (blood and

intestinal), urinalysis, and blood chemistry. Results were negative for parasites and positive for proteinuria, isosthenuria, and microalbuminuria; blood urea nitrogen (BUN) was slightly elevated (**TABLE 1**).

Abdominal ultrasonography showed hyperechoic renal cortices with poor corticomedullary demarcation, which could be consistent with either renal dysplasia or chronic nephritis/glomerulonephritis. Considering the patient's young age, renal dysplasia was of highest concern, but chronic nephritis/glomerulonephritis could not be excluded. Mildly reactive mesenteric lymph nodes were noted but were a nonspecific finding. No gross gastrointestinal tract abnormalities were detected.

Differential Diagnoses

For the patient's history of poor stool quality, the primary causes under consideration were malabsorptive or protein-losing enteropathies or dysbiosis. The gastrointestinal differentials were:

- Inflammatory bowel disease
- Food allergy
- Food intolerance (i.e., fat or fiber intolerance or sensitivity)
- Fiber-responsive diarrhea

TABLE 1 Initial Diagnostic Tests and Results

TEST	RESULT (REFERENT)	INTERPRETATION
RUN BY PRIMARY VETERINARIAN		
Accuplex 4 (Antech, antechediagnostics.com)	Negative for <i>Borellia burgorferi</i> , <i>Anaplasma</i> , <i>Ehrlichia</i> , <i>Dirofilaria immitis</i>	
Fecal flotation	Negative	
RUN BY REFERRAL NUTRITION SERVICE		
URINALYSIS		
Appearance	Yellow, cloudy	
Urine specific gravity	1.006	Isosthenuria
pH	6.5	
Protein	3+	
White blood cells	2-3 cells/high power field	
Albumin	>30 (<2.5) mg/dL	High, microalbuminuria
Urine protein-creatinine ratio	1.7 (<0.5)	High
Culture	No growth	
BLOOD CHEMISTRY*		
Blood urea nitrogen	33 (6-31) mg/dL	Slightly high
Creatinine	1.4 (0.5-1.6) mg/dL	
Total protein	5.8 (5.0-7.4) g/dL	

*All other chemistry values were within reference range.

- Stress colitis
- Pancreatitis
- Biliary vomiting syndrome

The renal differentials were:

- Congenital renal dysplasia
- Chronic nephritis/glomerulonephritis

TREATMENT PLAN

Medical management was continued by the primary care veterinarian. For nutritional management, we started by developing nutritional goals and creating a list of nutrients of concern for the patient's multiple confirmed and suspected conditions. Considerations that needed to be addressed included conducting a dietary elimination trial to determine a potential food allergy while balancing nutrient modifications recommended for protein-losing nephropathy. The nutrients of concern for his stage of renal disease

(avoiding high protein and phosphorus) did not directly contradict the nutrients of concern for his potential food allergy (hydrolyzed protein diet appropriate for dietary elimination trial); however, in this case, there was not a diet available on the market that met both those needs. We thus had to carefully consider the possible consequences of each potential diet and prioritize the nutrients of concern to select the most appropriate diet available. Dietary management was also not straightforward because the exact cause(s) of the patient's gastrointestinal signs were not known and required a dietary trial. These limitations necessitated a trial-and-error approach to diet while monitoring renal values.

Nutritional Goals

- Provide a complete and balanced diet to achieve ideal body weight (target weight 70 lb [32 kg]); this goal was of the highest priority.

TABLE 2 Nutritional Content of Select Therapeutic Diets*

PRODUCT†	KCAL/CAN OR CUP	PROTEIN (G/100 KCAL)	FAT (G/100 KCAL)	PHOSPHORUS (MG/100 KCAL)	CRUDE FIBER (G/100 KCAL)
Hill's Prescription Diet z/d Canine, canned	352	5.2	3.6	140	1.3
Hill's Prescription Diet z/d Canine, dry	354	4.9	3.7	150	1.1
Purina Pro Plan Veterinary Diets HA Hydrolyzed Chicken Flavor Canine Formula, canned	341	7.7	3.6	380	2.5
Purina Pro Plan Veterinary Diets HA Hydrolyzed Chicken Flavor Canine Formula, dry	342	5.3	3.2	220	0.4
Purina Pro Plan Veterinary Diets Hydrolyzed Canine Formula (Vegetarian), dry	314	5.4	2.7	230	0.4
Royal Canin Veterinary Diet Hydrolyzed Protein HP Dry Dog Food	331	5.2	4.8	200	0.4
Royal Canin Veterinary Diet Hydrolyzed Protein Adult Loaf Canned Dog Food	395	5.8	3.6	170	1.4
Royal Canin Veterinary Diet Hydrolyzed Protein Moderate Calorie Dry Dog Food	306	6.2	3.2	160	0.4
Royal Canin Veterinary Diet Hydrolyzed Protein Small Dog Dry Dog Food	373	6.2	4.2	210	0.3
Royal Canin Veterinary Diet Multifunction Renal Support + Hydrolyzed Protein Dry Dog Food	385	3.4	4.7	50	0.5
Royal Canin Veterinary Diet Ultamino Dry Dog Food	316	4.7	4.3	210	0.6

*AAFCO minimum for adult dogs: protein 4.5 g/100 kcal, fat 1.4 g/100 kcal, phosphorus 100 mg/100 kcal.

†Some diets listed here have undergone reformulation since this case was initially reported, so confirming the most recent formulations from each company's product guides is recommended.



- Avoid diets with high protein and phosphorus because of the proteinuria and elevated kidney values.
- Avoid diets with high fat because of the history of gastrointestinal signs and potential for fat sensitivity.
- Consider performing a dietary elimination trial as an initial strategy, using a novel or hydrolyzed protein diet.
 - If signs improve, consider limited-ingredient diets after rechallenge with protein sources.
 - If signs do not improve, consider trial and error to determine optimal nutrient profile.

Nutrients of Concern

- **Calories:** Provide enough calories for weight gain.
- **Protein:** Meet Association of American Feed Control Officials (AAFCO, aafco.org) minimum of 4.5 g/100 kcal initially, then modify according to response.¹
- **Phosphorus:** Meet AAFCO minimum of 100 mg/100 kcal but keep under 200 mg/100 kcal.
- **Fat:** Initially feed the diet with the lowest fat among the diets that otherwise meet nutritional goals. Determining the optimal fat content for minimizing clinical signs while encouraging weight gain may require a trial-and-error approach.
- **Fiber:** Initially feed a diet with low crude fiber, then consider increasing fiber for secondary trial-and-error testing.²
- **Omega-3 fatty acids:** Consider supplementing with docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) after the patient is stabilized and stool quality is controlled.³

Dietary Elimination Trial

To determine which diet would best meet nutritional goals, we analyzed all the hydrolyzed protein diet options. Because the patient's previous dietary history was unknown to the family, selecting a diet with novel protein sources would have been very challenging, so we considered only hydrolyzed protein options (**TABLE 2**).

Although the patient's current diet (Hill's Prescription Diet z/d Canine) met many of his nutritional goals, the client was concerned that the dog's gastrointestinal signs (episodes of borborygmus, nausea, vomiting, and anorexia) had not resolved. A full dietary history revealed that the dog was still receiving flavored preventives and treats (he was regularly given commercial Milk-Bone biscuits). The client was given the option of pursuing a strict dietary trial with the current diet or considering another option, which may

not have been ideal for meeting the other nutritional goals (e.g., protein, phosphorus). Given the patient's proteinuria, a decision was made to pursue a short (6 to 8 weeks) trial with the diet with the lowest hydrolyzed protein that still met the AAFCO minimum for protein: Royal Canin Veterinary Diet Ultamino dry (royalcanin.com). Although we considered Royal Canin Veterinary Diet Multifunction Renal Support + Hydrolyzed Protein dry, given the moderate muscle wasting, we decided to not initially restrict protein too severely and to modify as needed based on response to diet. The clients gradually transitioned the diet to Royal Canin Veterinary Diet Ultamino dry over 7 days, with strict instructions to not give any other food items (including treats, table food, toothpaste, flavored medications, flavored supplements, or flavored toys). To encourage weight gain, they fed him ad libitum.

If the dog needed something to chew on or distract him from getting into other pets' food, human food, or the trash, we recommended that a portion of the dry food be made into a slush with water and frozen into a rubber Kong toy as a substitute for treats, chews, and toys. For enrichment, we also recommended food-dispensing toys.

For medication administration, we recommended that the family learn how to administer pills without food, although as an emergency backup option, we suggested that medication could be given in 1/8 teaspoon of honey. We also considered putting the medications into a slush of the diet, but concerns of food aversion (which had happened previously) eliminated that option. The Visbiome was continued; the capsule was opened and the powder was sprinkled directly onto the food, which did not affect the dog's appetite.

OUTCOME

After 2 weeks of eating the Royal Canin Ultamino Canine dry diet, tylosin was discontinued and the dog's stools remained firm. After 8 weeks, body weight increased to 31 kg, BCS increased to 5/9, and MCS improved to mild muscle wasting. By the end of the dietary trial, the nausea, vomiting, and borborygmus episodes had not completely resolved but had become much more infrequent. Therefore, even without a rechallenge trial, we considered this a positive response to the trial and made a presumptive diagnosis of food allergy.

Diagnostics to determine the effects on the patient's kidney disease after an 8-week dietary trial indicated

relatively stable renal values (slightly increased BUN and creatinine), with significantly improved urine protein–creatinine (UPC, 50% reduction). Slight hematuria and granular casts were possibly indicative of a bacterial infection, but urine culture was negative. (TABLE 3).

Because food allergy cannot be 100% confirmed without a rechallenge, we discussed with the clients rechallenge with dietary proteins to confirm a food allergy and determine the source of the protein allergy. The clients, however, elected to not make any changes at that time, given the patient’s improved gastrointestinal signs and UPC and stable azotemia.

DISCUSSION

Patients with multiple conditions can be challenging to manage nutritionally, particularly if dietary modification is necessary to diagnose one of the conditions, such as in this case with a suspected food allergy. Although we were able to initiate a dietary elimination trial without exacerbating the patient’s other medical condition (renal disease), we lacked the information that might have been gleaned from a dietary rechallenge. Without a rechallenge trial, the food allergy was thus a presumptive diagnosis but not absolutely confirmed. The clients’ reluctance, however, is not surprising in that, in the author’s experience, many clients are hesitant to challenge or make changes after a dietary regimen has resolved clinical signs.

One interesting consideration of this case was the patient’s improvement on one hydrolyzed diet and not

another. This discrepancy may have resulted from 1 of 3 possible mechanisms: 1) when the first hydrolyzed diet was fed, treats and flavored medications were not discontinued and thus, a strict dietary elimination trial was not conducted with that food; 2) the patient may have responded to the second hydrolyzed diet because the protein was more hydrolyzed and the patient had an extreme sensitivity to allergens; or 3) the patient does not have a food allergy but rather has a nutrient intolerance and responded to a change in the nutrient profile (i.e., response to higher or lower fat or fiber levels that can affect gastrointestinal signs). Without further rechallenge and trial and error, we cannot know which of the 3 mechanisms applies to this patient.

At that time and without a rechallenge or diet change, we recommended frequent monitoring of all renal values (e.g., BUN, creatinine, phosphorus, potassium), particularly while he was receiving enalapril, and urine protein levels. The UPC reduction from 1.7 to 0.8 was promising and met the glomerular disease goal of a 50% reduction, per the American College of Veterinary Internal Medicine consensus statement.¹ Of biggest concern with the current dietary regimen is the phosphorus level, which is higher than ideal for a dog with renal impairment. However, should phosphorus values increase, a phosphate binder could be added if all other values are stable. In addition, if/when kidney disease advances, the next step could be giving a 50:50 mixture of 2 diets (the current Royal Canin Veterinary Diet Ultamino dry and the Royal Canin Veterinary Diet Multifunction Renal Support + Hydrolyzed Protein dry) and gradually transitioning fully to the latter diet as worsening kidney disease may warrant.

TABLE 3 Recheck Diagnostic Tests and Results (8 Weeks After Start of Diet Trial)

TEST	RESULT (REFERENT)	INTERPRETATION
URINALYSIS		
Urine specific gravity	1.011	
pH	5.0	
Protein	3+	
Glucose, ketones, urobilinogen, bilirubin	Negative	
Blood	25 cells/hpf	Possible bacteriuria, inflammation, cystocentesis
Urine protein–creatinine ratio	0.8 (<0.5)	
Casts	Granular	Possible bacteriuria
Culture	Negative	
BLOOD CHEMISTRY		
Blood urea nitrogen	38.7 (6–31) mg/dL	
Creatinine	1.5 (0.5–1.6) mg/dL	

At our most recent communication, the clients reported that the dog's gastrointestinal signs were stable and that they planned to have laboratory work rechecked every 3 to 6 months as recommended by their primary care veterinarian. We hope that they may also consider a diet rechallenge trial in the future.

TAKE-HOME POINTS

- Creating a fully inclusive list of nutritional goals requires a full nutritional assessment, including physical examination, BCS, MCS, dietary history, and diagnostic workup.
- Because patients, especially those with gastrointestinal disease, can exhibit varied individual responses to diet, trial and error is often necessary.
- Ensuring appropriate diet selection for each patient requires consideration of a diet's nutritional profile (i.e., calories, protein, fat, fiber) and not just the marketing or advertising of a diet.
- For patients with multiple medical conditions, monitoring is especially important for assessing responses and reprioritizing nutritional goals as each condition may progress. **TVP**

References

1. IRIS Canine GN Study Group Standard Therapy Subgroup; Brown S, Elliott J, Francey T, et al. Consensus recommendations for standard therapy of glomerular disease in dogs. *J Vet Intern Med.* 2013;27(Suppl 1):S27-43. doi: 10.1111/jvim.12230
2. Linder DE. Featuring fiber: understanding types of fiber & clinical uses. *Today's Vet Pract.* 2017;7(1):69-74.
3. Bauer JE. Therapeutic use of fish oils in companion animals. *JAVMA.* 2011;239(11):1441-1451.

Deborah Linder

Dr. Linder is a board-certified veterinary nutritionist at Cummings School of Veterinary Medicine at Tufts University, where she also earned her DVM degree. Dr. Linder's interests include nutritional management, client education, and human/animal interaction. Her current research focuses on safe and effective weight-loss strategies for pets as well as the effects of obesity on pet and human wellbeing. She is also co-director of the Tufts Institute for Human-Animal Interaction.



RECONCILE® (fluoxetine hydrochloride) Chewable Tablets For complete prescribing information, see full package insert. **Caution:** Federal law restricts this drug to use by or on the order of a licensed veterinarian. **Indications:** RECONCILE chewable tablets are indicated for the treatment of canine separation anxiety in conjunction with a behavior modification plan. **Contraindications:** RECONCILE chewable tablets should not be used in dogs with epilepsy or history of seizures, nor given concomitantly with drugs that lower the seizure threshold (e.g., phenothiazines). RECONCILE chewable tablets should not be given in combination with, or within 14 days of discontinuing, a monoamine oxidase inhibitor (MAOI). RECONCILE chewable tablets are contraindicated in dogs with a known hypersensitivity to fluoxetine HCl or other SSRIs. Observe a 6-week washout interval following discontinuation of therapy with RECONCILE chewable tablets prior to the administration of any drug that may adversely interact with fluoxetine or its metabolite, norfluoxetine. **Human Warnings:** Not/or use in humans. Keep out of reach of children. In case of accidental ingestion seek medical attention immediately. **Precautions:** RECONCILE chewable tablets are not recommended for the treatment of aggression and have not been clinically tested for the treatment of other behavioral disorders. Studies in breeding, pregnant or lactating dogs and in patients less than 6 months of age have not been conducted. Seizures may occur in dogs treated with RECONCILE chewable tablets, even in dogs without a history of epilepsy or seizures (see **Adverse Reactions**). Before prescribing RECONCILE chewable tablets, a comprehensive physical examination should be conducted to rule out causes of inappropriate behavior unrelated to separation anxiety. RECONCILE chewable tablets have not been evaluated with drugs that affect the cytochrome P450 enzyme system and should be used with caution when co-administered with any drug that affects this system. Studies to assess the interaction of RECONCILE chewable tablets with tricyclic antidepressants (TCAs) (e.g., amitriptyline, clomipramine) have not been conducted. The minimum washout period to transition dogs from TCAs to RECONCILE chewable tablets has not been evaluated. Data demonstrate that TCAs are cleared 4 days following discontinuation.^{1,2} **Adverse Reactions:** In two North American field studies involving 427 dogs, the following adverse reactions were observed at a rate of $\geq 1\%$ in dogs treated with RECONCILE chewable tablets (n=216): calm/lethargy/depression (32.9%), decreased appetite (26.9%), vomiting (17.1%), shaking/shivering/tremor (11.1%), diarrhea (9.7%), restlessness (7.4%), excessive vocalization (including whining) (6.0%), aggression (4.2%), otitis externa (2.8%), disorientation (2.3%), incoordination (2.3%), constipation (1.4%) and excessive salivation (1.4%). **Other adverse reactions: Seizures:** One of 112 dogs in the control group and three of 117 dogs that received RECONCILE chewable tablets experienced the serious adverse reaction of seizures during or after the end of the treatment period. One dog that was treated with RECONCILE chewable tablets experienced two seizures 10 days after the end of therapy and, despite escalating phenobarbital doses, died in status epilepticus approximately six months after the first seizure. In the second study, one of 99 dogs treated with RECONCILE chewable tablets and one of 99 dogs treated with the control tablet experienced the serious adverse reaction of seizures. Lastly, in a European multi-site study, one dog treated with a daily dose of 0.4 mg/kg for one month experienced one seizure one week after discontinuing therapy. **Weight loss:** In field studies, a weight loss $\geq 5\%$ (relative to pre-study body weight) was observed in 58 (29.6%) of dogs treated with RECONCILE chewable tablets and 24 (13.0%) of control dogs. No dogs were withdrawn from clinical studies due to weight loss alone. **Dose reduction:** Twenty dogs in the RECONCILE chewable tablet group and five control dogs required a dose reduction due to unacceptable adverse reactions, the majority intermittent and mild, generally anorexia, vomiting, shaking and depression. Lowering the dose eliminated or reduced the severity of these reactions in the RECONCILE chewable tablet group only, while resumption of the full dose resulted in a return of the initial adverse reactions in approximately half the affected dogs. One dog experienced recurrence of severe adverse reactions, which necessitated withdrawal from the study. Additionally, two dogs required a second dose reduction of RECONCILE chewable tablets. **Post Approval Experience (Rev. 2010):** The following adverse events are based on post-approval adverse drug experience reporting with Reconcile® chewable tablets. Not all adverse reactions are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data. The following adverse events are listed in decreasing order of reported frequency: decreased appetite, depression/lethargy, shaking/shivering/tremor, vomiting, restlessness and anxiety, seizures, aggression, diarrhea, mydriasis, vocalization, weight loss, panting, confusion, incoordination and hypersalivation. For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, contact Pegasus Laboratories at 1-800-874-9764. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDAVETS or <http://www.fda.gov/AnimalVeterinary/SafetyHealth>. **Effectiveness:** In one randomized multi-centered, double-blinded, vehicle-controlled study of 8 weeks' duration, 229 dogs were evaluated at 34 investigative sites in the United States and Canada. One hundred seventeen dogs were randomized to 1-2 mg/kg/day of RECONCILE chewable tablets and 112 dogs were randomized to the control group. Both groups underwent concurrent behavior modification. In seven of the eight weeks, the percentage of dogs with improved overall separation anxiety scores was significantly higher ($p < 0.05$) among dogs treated with RECONCILE chewable tablets compared to dogs that received the control tablet. At the end of the study, 73% of dogs treated with RECONCILE chewable tablets showed significant improvement ($p=0.010$) as compared to 51% of dogs treated with behavior modification alone. Dogs treated with RECONCILE chewable tablets also showed improvement in destructive behavior, excessive vocalization and restlessness over dogs that received the control tablet. In addition, dogs in both groups experienced improvement in inappropriate urination, inappropriate defecation, excessive salivation, excessive licking/grooming, shaking/shivering and depression. Overall separation anxiety severity scores improved more rapidly for dogs taking RECONCILE chewable tablets than those dogs receiving the control tablet. The same effect was also noted for the individual scores for excessive vocalization and depression. **To obtain full product information please call 800-874-9764 or visit Reconcile.com • 10-20175 NADA #141-272 • Approved by FDA • Pegasus Laboratories, Inc.**

¹Plumb DC. Amitriptyline. *Veterinary Drug Handbook 5th Edition (Pocket Edition)*. Iowa State Press. Ames, IA. Page 39, 2002.

²Hewson CJ, et al. The pharmacokinetics of clomipramine and desmethylclomipramine in dogs: parameter estimates following a single oral dose and 28 consecutive daily doses of clomipramine. *J Vet Pharmacol Therap* 21 :214-222, 1998.