Healthy Holistic
BLUE
NATURAL
Veterinary Diet®

VOLUME NO.5

BLUE BUFFALO CLINICAL REPORT

Clinical Evidence for: KIDNEY SUPPORT

KEY POINTS

1

Multiple study findings support the formulation of BLUE Natural Veterinary Diet Kidney Support foods to provide an ideal approach for nutritionally managing pets with kidney disease:

- Controlled protein levels 16.3% (dogs); 29.3% (cats)
- Controlled levels of phosphorus and sodium
- Increased levels of omega-3 fatty acids, EPA and DHA to support a healthy immune response
- Added L-Carnitine to support muscle health and body condition
- Added antioxidants, vitamin E and carotenoids to help reduce oxidative stress
- Highly palatable
- Ingredients preferred by clients

2

BLUE Natural Veterinary Diet Kidney Support is Clinically Proven

- To produce a Calcium Oxalate Relative Supersaturation of <3
- To produce urine pH values of 6.9 (dogs) and 7.1 (cats)

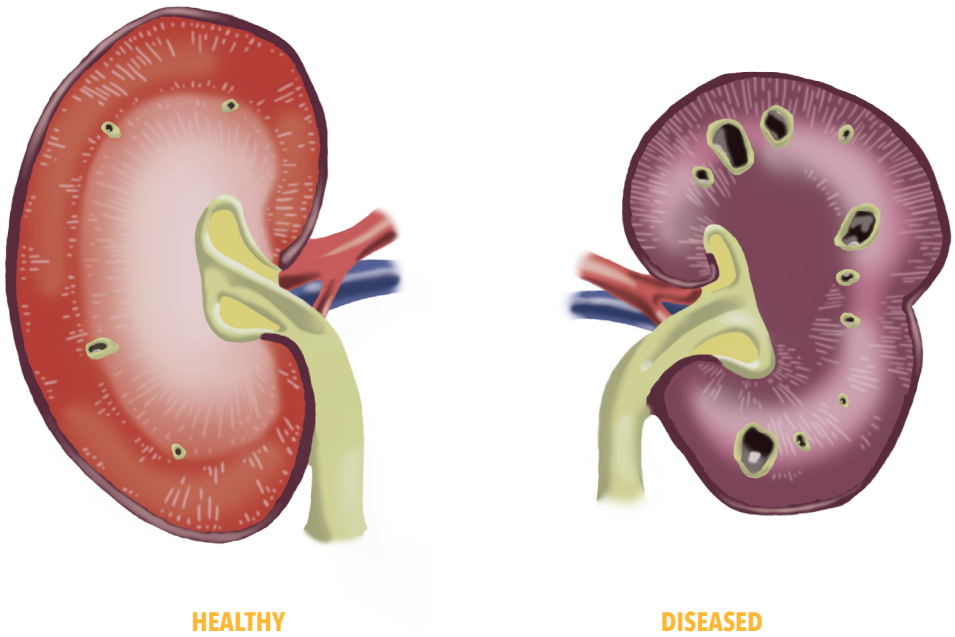


Figure 1. Progression of Chronic Kidney Desease

Chronic Kidney Disease

Chronic kidney disease (CKD) affects an estimated 0.5% to 1% of all dogs and 1% to 3% of all cats,[1, 2] An estimated 10% of geriatric dogs and 35% of geriatric cats have CKD.[3-5] A variety of compensatory and adaptive responses are likely involved in the pathogenesis and progression of naturally occurring CKD. The associated nephron damage is progressive and irreversible even though some pets with CKD have stable serum creatinine concentrations for months to years. Early diagnosis of CKD, followed by appropriate treatment, may result in improved survival. Nephrocalcinosis, systemic hypertension, intraglomerular hypertension, and proteinuria have been associated with progression of CKD.[6-9] All of these mechanisms of renal disease progression are potentially treatable. The good news is clinical evidence shows that dietary management can slow the progression of CKD[10-14] (See Figure 1).

The goals of managing patients with CKD are to improve quality and duration of life. The right nutrition plays a key role in both of these goals. In order to maximize treatment outcomes dietary changes should be implemented as soon as renal disease is identified. Current evidence indicates nutritional management with therapeutic renal foods should begin when serum creatinine exceeds 2mg/dl in dogs and cats with CKD.[15] Proteins, particularly those of animal origin, are rich in sulfur-containing amino acids; metabolism of these leads to hydrogen ion generation. Consequently, many diets fed to cats provide a net load of acid, which must be excreted by the kidney if acid-base balance is to be achieved. Unfortunately, cats with reduced renal mass are less able to excrete acid, potentially resulting in metabolic acidosis from acid retention. This is generally associated with an increased anion gap due to the accumulation

of unmeasured anions, and the acidosis may cause lethargy and inappetence. Proteinuria is toxic to renal tubules and higher nitrogenous waste levels increase the renal workload. Increased serum phosphorus leads to overproduction of parathyroid hormone, which has been shown to reduce renal function. There is general consensus that avoiding excessive dietary protein is indicated to control clinical signs of uremia in dogs and cats with CKD.[16, 17]

Hyperphosphatemia reduces survival in animals with renal disease and is associated with renal secondary hyperparathyroidism.[17, 19] Therefore, in patients with kidney disease, diets with reduced protein and phosphorus can provide significant clinical benefit.[20] Hyperphosphatemia is common and directly related to the degree of renal dysfunction and the level of dietary phosphate intake. To delay the progression of renal injury, dietary phosphorus restriction should be instituted in all cats with azotemic chronic renal failure.[18, 21] Research has shown that controlled levels of phosphorus, between 0.2 and 0.5% (dogs) and between 0.3 and 0.6% (cats), helps limit the progression of kidney disease.[15] Moreover, research has also shown that optimal nutrition for pets with kidney disease includes sodium less than 0.3% (dogs), less than 0.4% (cats) and a balanced calcium to phosphorus ratio of 1:1 to 2:1 on a dry matter basis.[15, 18, 21]

Omega-3 fatty acids are an integral part of cell membranes throughout the body and affect the function of the cell receptors in these membranes. They provide the starting point for making hormones that regulate blood clotting, contraction and relaxation of artery walls, and inflammation. Appropriate levels of omega-3 fatty acids in foods, specifically Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA), play a role in reducing oxidative stress and improving lipid profiles in patients with CKD. DHA and EPA compete with arachidonic acid in several ways to alter eicosanoid production which is considered renoprotective.[22] Docosahexaenoic acid has also been shown to reduce serum immunoglobulin deposition in kidneys and reduce proteinuria.[23] Dietary supplementation with omega-3 fatty acids and antioxidants (vitamin E, carotenoids) reduce proteinuria, prevent glomerular hypertension and decrease production of proinflammatory eicosanoids.[22]

OPTIMAL NUTRITION TO MANAGE KIDNEY DISEASE

1) NUTRITIONAL PROFILE

To optimize overall kidney health and help nutritionally manage kidney disease in dogs and cats, BLUE Natural Veterinary Diet Kidney Support foods are formulated to deliver controlled dry matter protein levels 14 to 20% for dogs and 26 to 35% for cats[15] and controlled levels of phosphorus and sodium. Increased levels of omega-3 fatty acids, EPA and DHA, provide renoprotective benefits and L-carnitine helps support healthy muscle maintenance and body condition, which is beneficial for pets with compromised renal function.[24]

TABLES 1 - 4. ANALYSIS OF KEY NUTRIENTS FOR RENAL HEALTH

TABLE 1. DOGS

	Recommended Levels* for Renal Diets [15,25]	NVD KS Kidney Support for Dogs*
Protein	14-20%	16.85%
Phosphorus	0.2-0.5%	0.38%
Sodium	<0.3%	0.22%

TABLE 2. CATS

	Recommended Levels* for Renal Diets [15,25]	NVD KM Kidney + Mobility for Cats*
Protein	28-35%	29.57%
Phosphorus	0.3-0.6%	0.52%
Sodium	<0.4%	0.27%

TABLE 3. DOGS

	NVD KS Kidney Support for Dogs*
Total Omega-3 Levels	2.34%
DHA	0.38%
EPA	0.42%

TABLE 4. CATS

	KM Kidney + Mobility for Cats*
Total Omega-3 Levels	2.4%
DHA	0.47%
EPA	0.52%

2) HIGH PALATABILITY

Due to a variety of metabolic disturbances generated by chronic kidney disease, appetite can be a significant challenge in CKD patients. Because of its impact on compliance and acceptability, high palatability is critical component of the nutritional approach to chronic kidney disease. Studies show dogs and cats prefer BLUE Natural Veterinary Diet Kidney Support food over a leading renal therapeutic pet food.[26]

CHART 1.
CANINE PALATABILITY INTAKE RATIO

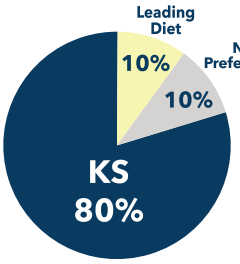
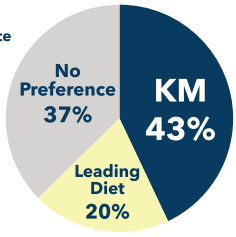


CHART 2.
FELINE PALATABILITY INTAKE RATIO



In addition to being formulated to help manage the nutritional needs of pets with CKD, BLUE Natural Veterinary Diet Kidney Support foods are clinically proven to produce a urinary pH of 6.88 (dogs) and 7.12 (cats) and to produce mean Calcium Oxalate RSS values of 1.255 (dogs) and 0.35 (cats) to reduce the risk of development and reoccurrence of calcium oxalate uroliths.

Dry Matter Basis

STUDY: URINE RELATIVE SUPERSATURATION EVALUATION

PURPOSE

To show that feeding BLUE Natural Veterinary Diet Kidney Support foods can result in clinically significant urine RSS values less than 3 for calcium oxalate, which has been shown to limit the formation of calcium oxalate uroliths (See Figure 2).

STUDY DESIGN

Four groups of adult dogs (n=10 each for Canine RSS Studies 1, 2, 3, 4) and 4 groups of adult cats (n=10 each for Feline RSS Studies 1, 2, 3, 4) were enrolled in the studies. All animals selected were clinically healthy. Animals were maintained in standard, species-appropriate housing and managed consistently during the study, including providing access to activity/exercise. The study protocols were reviewed and approved by the research facility's institutional animal care and use committee.

Animals were fed the species-appropriate dry BLUE Natural Veterinary Diet Kidney Support food for 23 days. An amount of food calculated to maintain body weight was offered once daily and available for 1 hour for dogs and for 20 hours for cats. On day 22, a 24-hour urine sample was collected from each animal, using a metabolism cage with a urine collection system for dogs and a specialized litter box for cats. From that sample, urine pH was measured via pH meter and 2 aliquots were frozen and shipped to The University of Tennessee for RSS analysis.[30] Those aliquots included a 1-ml sample that was diluted with 1.5 ml 1N HCl, and a 10- to 15-ml sample placed in a sterile container. For the RSS analysis, urine sodium, potassium, chloride, calcium, magnesium, phosphorus, citrate, oxalate, ammonia, pH, creatinine, and uric acid were measured.

RESULTS[27]

Feeding dry BLUE Natural Veterinary Diet Kidney Support foods in both dog and cat studies resulted in clinically proven urine RSS values <3 for calcium oxalate.

FIGURE 2. STATES OF URINE SATURATION[28, 29]

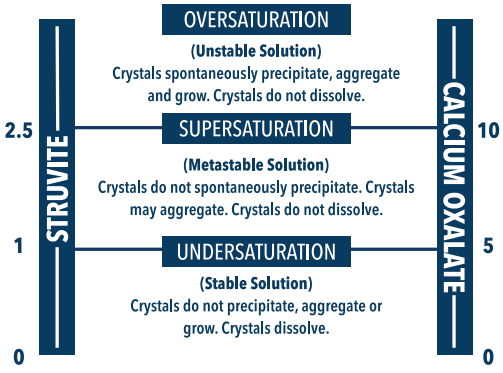


TABLE 5.
CANINE RSS STUDIES MEAN RESULTS

STUDY NO.	RSS COM (Mean)	RSS COD (Mean)
1	1.805	0.764
2	1.303	0.551
3	2.625	0.702
4	1.611	0.685
MEAN	1.836	0.675
CaOx MEAN	1.255	

TABLE 6.
FELINE RSS STUDIES MEAN RESULTS

STUDY NO.	RSS COM (Mean)	RSS COD (Mean)
1	1.38	0.58
2	0.66	0.28
3	0.55	0.24
4	0.55	0.16
MEAN	0.79	0.32
CaOx MEAN	0.55	

URINE pH STUDIES

PURPOSE

To show that feeding BLUE Natural Veterinary Kidney Support foods can consistently produce a urine pH of 6.5-7.3 (dogs) and 7.2-7.4 (cats) which includes the recommended urine pH ranges to reduce the risk of development and reoccurrence of calcium oxalate uroliths.

STUDY DESIGN

Three groups of adult dogs (n=8 each for Canine Urine pH Studies 1, 2, 3) and 3 groups of adult cats (n=8 each for Feline Urine pH Studies 1, 2, 3) were enrolled in the studies. All animals selected were clinically healthy. Animals were maintained in metabolism cages during the study. Animals were fed the species-appropriate dry BLUE Natural Veterinary Diet Kidney Support food for 5 days. An amount of food calculated to maintain body weight was offered once daily and available for 2 hours. On day 5, urine samples were collected from each animal at 0, 4, 8, and 24 hours via cystocentesis for measurement of pH.

RESULTS[27]

Feeding BLUE Natural Veterinary Diet Kidney Support food in both dog and cat studies resulted in mean urine pH values of 6.88 (dogs) and 7.12 (cats) which is within the recommended urine pH ranges to reduce the risk of development and reoccurrence of calcium oxalate uroliths.

TABLE 7.
CANINE URINE pH STUDIES MEAN RESULTS

CANINE STUDY NO.	URINE pH (MEAN)
1	7.30
2	6.75
3	6.59
OVERALL MEAN	6.88

TABLE 8.
FELINE URINE pH STUDIES MEAN RESULTS

FELINE STUDY NO.	URINE pH (MEAN)
1	7.25
2	7.28
3	6.84
OVERALL MEAN	7.12

REFERENCES

1. Lund EM, Armstrong JP, Kirk CA, et al. Health status and population characteristics of dog and cats examined at private veterinary practices in the United States. JAVMA 1999; 214:1336-1341.
2. Brown SA. Linking treatment to staging in chronic kidney disease. In August JR (ed): Consultations in Feline Internal Medicine. St. Louis: Elsevier Saunders, 2010, pp 475-482.
3. Polzin DJ, Osborne CA, Adams LG, Lulich JP. Medical management of feline chronic renal failure. In Kirk RW, Bonagura JD (eds): Kirk's Current Veterinary Therapy XI. Philadelphia: Saunders, 1992, pp 848-853.
4. Kahn C, Line S. Renal Dysfunction in Small Animals, Merck Veterinary Manual on-line edition, www.merckvetmanual.com, July 2016.
5. Lulich JP, Osborne CA, O'Brien TD, et al. Feline renal failure: Questions, answers, questions. Compend Cont Educ Pract Vet 1992; 14:127-153.
6. Chakrabarti S, Syme HM, Elliott J. Clinicopathological variables predicting progression of azotemia in cats with chronic kidney disease. J Vet Intern Med 2012; 26:275-281.
7. Jacob F, Polzin DJ, Osborne CA, et al. Association between initial systolic blood pressure and risk of developing a uremic crisis or of dying in dogs with chronic renal failure. JAVMA 2003; 222:322-329.
8. Jacob F, Polzin DJ, Osborne CA, et al. Evaluation of the association between initial proteinuria and morbidity rate or death in dogs with naturally occurring chronic renal failure. JAVMA 2005; 226:393-400.
9. Syme HM, Markwell PJ, Pfeiffer D, Elliott J. Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. J Vet Intern Med 2006; 20:528-535.
10. Elliott J, Rawlings JM, Markwell PJ, Barber PJ. Survival of cats with naturally occurring chronic renal failure: Effect of dietary management. J Small Anim Pract 2000; 41:235-242.
11. Grauer GF, Greco DS, Getzy DM, et al. Effects of enalapril versus placebo as a treatment for canine idiopathic glomerulonephritis. J Vet Intern Med 2000; 14:526-533.
12. Jacob F, Polzin DJ, Osborne CA, et al. Clinical evaluation of dietary modification for treatment of spontaneous chronic renal failure in dogs. JAVMA 2002; 220:1163-1170.
13. Mizutani H, Koyama H, Watanabe T, et al. Evaluation of the clinical efficacy of benazepril in the treatment of chronic renal insufficiency in cats. J Vet Intern Med 2006; 20:1074-1079.
14. Ross SJ, Osborne CA, Kirk CA, et al. Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats. JAVMA 2006; 229:949-957.
15. Forrester SD et al. Chronic kidney disease. In: Hand MS et al, editors. Small Animal Clinical Nutrition. 5th Ed. Topeka, KS: Mark Morris Institute; 2010. p 765-810.
16. Polzin DJ, Osborne CA, Ross S. Evidence-based management of chronic kidney disease. In: Bonagura JD, Twedt DC, eds. Kirk's Current Veterinary Therapy XIV. St. Louis, MO: Sanders Elsevier, 2009; 872-879.
17. Elliott DA. Nutritional management of chronic renal disease in dogs and cats. Vet Clin North Am Small Anim Pract 2006; 36(6):1377-1384, viii.
18. Ross LA, Finco DR, Crowell WA. Effect of dietary phosphorus restriction on the kidneys of cats with reduced renal mass. Am J Vet Res 1982;43(6):1023-1026.
19. Finco DR, Brown SA, Crowell WA, et al. Effects of dietary phosphorus and protein in dogs with chronic renal failure. Am J Vet Res 1992; 53(12):2264-2271.
20. Elliott J, Syme HM. Editorial: Proteinuria in chronic kidney disease in cats–Prognostic marker or therapeutic target? Journal of Veterinary Internal Medicine 2006; 20: 1052-1053.
21. Brown, S. A., Crowell, W. A., Barsanti, J. A., White, J. V., Finco, D. R. Beneficial effects of dietary mineral restriction in dogs with marked reduction of functional renal mass. Journal of the American Society of Nephrology 1991; 1: 1169–79.
22. Brown SA, Brown CA, Crowell WA, et al. Beneficial effects of chronic administration of dietary omega-3 polyunsaturated fatty acids in dogs with renal insufficiency. Journal of Laboratory and Clinical Medicine 1998; 131: 447-455.
23. Omega-3 Fatty Acids: An Essential Contribution, Harvard School of Public Health, http://www.hsph.harvard.edu/nutritionsource/omega-3-fats/.
24. Ringseis R et al. Mechanisms underlying the anti-wasting effect of L-carnitine supplementation under pathologic conditions: evidence from experimental and clinical studies. Eur J Nutr. 2013; 52: 1421-1442.
25. Polzin D. Chronic Kidney Disease. Ch.311 In Ettinger S et al. Textbook of Veterinary Internal Medicine. Volume 2. 7th Ed. St. Louis, MI: Saunders Elsevier; 2010. pp 1990-2021.
26. GfK scanned data, 2015.
27. Blue Buffalo Co., Ltd., data on file, 2016.
28. Stevenson A. & Rutgers C. Nutritional Management of Canine Urolithiasis. In:Encyclopedia of Canine Clinical Nutrition. Eds: Pibot P, Biourge V. Elliott D. 2006. Aniwa SAS. Pgs 284-315.
29. Bartges, Joesph W., et al. Methods of Evaluating treatment of Uroliths. Veterinary Clinics of North America: Small Animal Practice 1999;29:46.
30. University of Tennessee Pharmacology Lab, College of Veterinary Medicine, 2015.
31. Blue Buffalo Company, Ltd., Consumer Studies Data on file, 2016.

3) CLIENT INGREDIENT PREFERENCE

PET OWNER INSIGHTS [31]

In a study with 300 pet owners, owners report that they prefer the ingredients in BLUE Natural Veterinary Diet Kidney Support food 3 to 1 over the ingredients in the leading therapeutic renal diets[26] for dogs and cats. Meeting client needs and preferences is key to encouraging increased client compliance, especially with conditions like chronic kidney disease that must be carefully managed throughout a pet's life.

CLINICAL IMPACT

The results of the studies and analyses discussed in this Clinical Report provide evidence to support that BLUE Natural Veterinary Diet Kidney Support foods are formulated **to help manage pets with kidney disease** by controlling protein, phosphorus, and sodium, helping to manage oxidative stress and supporting a healthy immune response. Further, the products are clinically proven to produce a Calcium Oxalate Relative Supersaturation of <3 and to produce urinary pH values of 6.88 in dogs and 7.12 in cats to reduce the risk of development and reoccurrence of calcium oxalate uroliths. BLUE Natural Veterinary Diet Kidney Support foods deliver on BLUE's promise to provide ingredients that deliver clinical benefits while also satisfying pet owners desire for quality natural ingredients.

For more information about Blue Buffalo Quality Assurance Testing and Clinical Research please visit TrueBLUEVets.com or call 1-888-323-BLUE.

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