

## Evidence-based Nutritional Decisions for Chronic Kidney Disease

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Chronic kidney disease (CKD) is a common clinical diagnosis, particularly in older cats and dogs, and significantly affects the quality of life of both the patients and their owners. Early detection allows earlier intervention to help minimise the progression of the disease and may result in more successful outcomes.

The kidneys have three major functions:-

- To excrete waste products of metabolism such as urea and creatinine.
- To regulate fluid, electrolyte, and acid-base balance.
- To produce (or activate) hormones necessary for blood cell production (erythropoietin), to regulate blood pressure (renin) and to maintain calcium balance (calcitriol)

The diagnosis of CKD requires a thorough medical history and physical examination, as well as a number of laboratory tests. As the kidneys deteriorate they lose their ability to concentrate urine, resulting in the voiding of large quantities of dilute urine with resulting increased thirst. Owners may report increased thirst and increased urination or accidents in the house. As the kidneys can no longer extract by-products and nitrogenous wastes of metabolism from the bloodstream, these wastes build up in the body and cause many of the clinical signs (nausea, loss of appetite, vomiting, mouth ulcers) associated with CKD. Other clinical signs include gradual weight loss, listlessness and a rough coat. The laboratory diagnosis of CKD is typically based on demonstrating azotaemia (elevated blood urea nitrogen [BUN] and creatinine), concurrently with inadequately concentrated urine. Importantly, kidney disease is difficult to detect until it is well advanced, since increased blood markers such as urea and creatinine (+/- phosphorus) are not elevated until at least 75% of both kidneys are damaged. Urine markers such as urine specific gravity are not affected until at least 66% of both kidneys are damaged, although proteinuria and abnormal urine sediment may be detected earlier.

### Staging Chronic Kidney Disease

The International Renal Interest Society (IRIS) has introduced a staging system for the classification of chronic kidney disease in dogs and cats (<http://www.iris-kidney.com>). Patients are classified as having a specific stage of renal disease based on their kidney function as determined initially by serum creatinine concentration (**Table 1**). It is important to understand that a single instance of elevated serum creatinine is not sufficient to make a definitive diagnosis of chronic kidney disease. Ideally, two or more serum creatinine values, obtained when the patient is fasted and well hydrated, should be determined over several weeks to diagnose and stage CKD. Serum creatinine should never be interpreted without consideration of other clinical and laboratory findings from the patient, such as urine specific gravity. Although the reference ranges used to categorise patients with CKD into stages are

inherently arbitrary, staging is useful for establishing a prognosis and managing patients with CKD.

**Table 1: Stages of CKD in Dogs and Cats**

	Serum Creatinine $\mu\text{mol/L}$	
	Dogs	Cats
<b>Stage 1</b>	<125	<140
<b>Stage 2</b>	125-179	140-249
<b>Stage 3</b>	180-439	250-439
<b>Stage 4</b>	>440	>440

The patient is then further classified according to the presence or absence of proteinuria and their systolic blood pressure measurement (**Tables 2 and 3**). Quantification of proteinuria should be done by measuring the urine protein: creatinine ratio of a urine sample without evidence of infection, inflammation or haemorrhage. Persistent proteinuria should also be demonstrated by checking the urine protein: creatinine ratio 2-3 times over at least 1 or 2 months. Patients with borderline proteinuria should be re-evaluated after 2 months and reclassified if necessary. It is also important to note that, in some patients, the classification of proteinuria may change due to the natural course of the disease or in response to therapy.

**Table 2: Quantifying and Classifying Proteinuria**

Classification	Urine Protein: Creatinine Ratio	
	Dogs	Cats
<b>Non-proteinuric (NP)</b>	<0.2	<0.2
<b>Borderline Proteinuric (BP)</b>	0.2 – 0.5	0.2 – 0.4
<b>Proteinuric (P)</b>	>0.5	>0.4

Hypertension is now a well-recognised complication of CKD in both cats and dogs. It is very important that blood pressure is measured frequently in pets with CKD as many animals do not show clinical signs associated with hypertension. Left untreated, hypertension may lead to end organ damage (kidneys, brain, eyes, and heart). For example, a common presenting sign of hypertension in cats is acute blindness due to retinal detachment. Immediate and aggressive control of hypertension may allow the retinas to reattach and the pet to regain some vision.

Blood pressure measurements should ideally be done by the same individual in a quiet room, after the animal has been allowed to acclimatise to the surroundings. The current recommendation is that blood pressure be determined using an oscillometric technique in both cats and dogs. Several readings should be obtained using a consistent

cuff size and location. Studies have demonstrated that hypertension is a risk factor for shortened survival times in dogs with CKD and the same is likely true of cats.

The variability of and difficulty in obtaining blood pressure measurements in dogs and cats has contributed to the lack of consensus as to what constitutes true hypertension. If available, it is preferable to use breed specific ranges for normal values. The patients' blood pressure readings can then be compared to the upper limit of the normal range for the breed. Sighthounds, in particular, have a higher reference range than most breeds of dog.

**Table 3: Risk Associated with systolic blood pressure in cats and dogs with CKD**

<b>Blood Pressure Sub-stage</b>	<b>Systolic Blood Pressure</b>	<b>If breed specific reference range is available</b>
<b>0 minimal risk</b>	< 150	<10mmHg above reference range
<b>1 low risk</b>	150-159	10-20 mmHg above reference range
<b>2 moderate risk</b>	160 – 179	20-40mmHg above reference range
<b>3 high risk</b>	≥ 180	≥ 40mmHg above reference range
<b>No complications (NC)</b>	No evidence of end organ damage/complications	
<b>Complications (C)</b>	Evidence of end organ damage/complications	
<b>Risk not determined (RND)</b>	Blood pressure not measured	

### **Management of CKD**

The general goals of medical management of patients with primary CKD are to:

- Control clinical signs of uraemia
- Maintain adequate fluid, electrolyte, and acid-base balance
- Provide adequate nutrition
- Slow the progression of the disease

Although nutrition is listed in one goal, it plays an important role in the other goals as well.

### **Food is Therapy!!**

It is important to detect CKD in the early stages so that appropriate measures may be instituted to minimise its progression. Routine laboratory screening of senior cats for evidence of CKD is recommended as standard practice. Prevention of malnutrition by ensuring adequate nutrient intake is crucial to successful management.

Dietary therapy has been the cornerstone of the management of canine and feline CKD for decades. The earlier the patient is transitioned to a therapeutic food, the greater the likelihood that the food will be accepted. On the basis of current evidence, to optimise clinical outcomes, therapeutic renal food is indicated when serum creatinine exceeds 179µmol/l.<sup>1,2</sup>

Compared to adult maintenance rations, diets formulated specifically for dogs and cats with

chronic kidney disease typically have:

- Reduced levels of protein, phosphorus, and sodium
- Increased levels of potassium, B vitamins, soluble fibre, omega-3 polyunsaturated fatty acids and antioxidants
- Higher caloric density
- Neutral effect on acid-base balance.

## How to decide which renal food to feed

There are several foods formulated for renal disease currently available in Australia. While therapeutic renal foods have some general features in common, they are different in other ways. Two of the main factors to evaluate and consider when selecting a food include nutrient differences between foods and evidence supporting effectiveness of specific renal foods (length and quality of life).

### 1. Nutrients

**Controlled protein** - Although the ideal quantity of protein to feed dogs and cats with CKD remains unresolved, the general consensus is that reducing protein intake improves clinical signs, especially those in stages 3 and 4. Many of the uraemic toxins are actually by-products of protein metabolism. Limiting protein intake (within reason) while increasing its quality does not appear to have any adverse effects, and it may be easier to initiate treatment with renal diets before the onset of clinical signs of uraemia. Protein restriction may delay the onset of clinical signs of uraemia as renal disease progresses, reduce the acid load, and limit dietary intake of phosphorus. The goal is to increase the quality of the dietary protein, while avoiding protein excess.

**Controlled phosphorus** - Reduced renal excretion of phosphorus (due to destruction of nephrons) leads to phosphorus retention, which in turn stimulates increased parathyroid hormone (PTH) production by the parathyroid gland. Increased phosphorus inhibits renal tubular activation of the enzyme responsible for the conversion of inactive vitamin D to its active form calcitriol. Decreased calcitriol concentrations, along with decreased ionised calcium and increased phosphorus, contribute to the development of renal secondary hyperparathyroidism. Clinically, this can lead to soft tissue calcification and renal osteodystrophy (bone demineralisation).

Limiting dietary intake of phosphate and, if necessary, administering intestinal phosphate binding agents should minimise phosphate absorption from the intestinal tract and resulting hyperphosphatemia. The ultimate goal of therapy is to prevent or minimise renal secondary hyperparathyroidism and its various adverse consequences. Because the primary goal is limiting absorption of phosphate contained in the diet, administration of phosphate binding agents should be timed to coincide with feeding. These agents are best administered with or mixed into the food, or just prior to each meal.

**Neutral to alkalinising** - Animals with kidney disease are often not able to clear acids effectively from the blood and they also tend to lose an excessive amount of bicarbonate. The net result is a state of metabolic acidosis. Several clinical signs have been associated with metabolic acidosis including increased protein catabolism, anorexia, nausea, vomiting, lethargy, muscle wasting, and malnutrition. Most diets formulated specifically for animals with renal failure are designed to be neutral to slightly alkalinising. Often, early acidosis may be controlled with diet alone, however, if the acidosis persists or worsens oral alkalinisation with sodium bicarbonate or potassium citrate should be considered.

**Avoid excessive sodium chloride (salt)** - Systemic hypertension may accelerate progression of kidney disease via direct transmission of systemic pressures to glomerular capillaries. Excess sodium intake has been shown to cause a significant progression of subclinical renal disease in cats in just 3 months.<sup>3</sup> Feeding a veterinary therapeutic renal food with decreased sodium (Hill's Prescription Diet™ k/d™ Hill's Pet Nutrition, Inc., Topeka,

KS, USA), has been associated with increased survival time and reduced renal-related deaths in both dogs and cats compared to feeding maintenance foods containing more sodium.<sup>1,2</sup>

**Increased calorie content** – Animals with CKD are often inappetent, so increasing the calories per volume fed is recommended. If caloric intake is inadequate, muscle protein may be catabolised as an energy source.

**Increased n-3 fatty acids** – Omega-3 polyunsaturated fatty acids (from oily fish) have been shown to be 'renoprotective' in that they conserve renal function, reduce intraglomerular hypertension (lower systemic BP), and preserve renal structure.<sup>5</sup>

**Potassium supplemented (cats)** - Hypokalaemia is quite common in cats with stage 2-4 CKD, but less common in dogs. Hypokalaemia can result from decreased dietary intake due to anorexia, or increased losses from vomiting or polyuria. Clinical signs of hypokalaemia may include muscle weakness and further impairment of kidney function. Renal foods are generally supplemented with potassium, however, some patients still require oral or parenteral administration of potassium salts.

**Supplemental B vitamins** – levels of B vitamins in animals with CKD tend to be low due to inappetence and increased loss due to polyuria. Providing an increased dietary level is recommended.

**Soluble fibre** (oat fibre, soy fibre, psyllium) increases bacteria in the large intestine. Blood urea then diffuses into the large intestine and is used by these bacteria as a protein source, which is subsequently excreted in faeces. The net effect is increased faecal urea excretion and reduced urea in the blood.

**Antioxidants** - Increased free radicals may contribute to progression of CKD. Antioxidants may help to reduce oxidative DNA damage in cats with renal insufficiency. Dietary supplementation with antioxidants such as vitamin E, vitamin C,  $\beta$ -carotene and selenium is recommended.

## 2. Evidence Supporting Effectiveness of Renal Foods

Evidence-based veterinary medicine (EBVM) provides a framework for making decisions and understanding the risk-benefit relationship of various therapeutic plans. EBVM is defined as the integration of the best research evidence, clinical expertise, and patient / client values. Best research evidence means clinically relevant research, especially from patient-centred clinical studies. The intent is not for current best evidence to *replace* clinical skills, judgment, or experience, but to provide another dimension to the decision-making process.

Guidelines have been developed which categorise the quality of evidence into the following grades. Grades 1 and 2 evidence have the highest quality; that is, grade 1 and 2 studies are most likely to predict results seen in clinical practice.

- Grade 1: evidence obtained from at least one properly designed, randomised, controlled study in the target species
- Grade 2: evidence obtained from at least one properly designed, randomised, controlled study in the target species but performed in a laboratory or research colony setting
- Grade 3: evidence obtained from appropriately controlled studies without randomisation; evidence obtained from appropriately designed cohort or case-control studies, preferably from more than one centre or research group; or dramatic results for uncontrolled studies, models of disease.

- Grade 4: reports of expert committees, descriptive studies, case reports, and opinions of respected experts developed on the basis of their clinical experience. In vitro studies, extrapolations from other species.

### **Evidence for therapeutic renal foods**

The first prospective dietary study testing cats with naturally occurring CKD was published in 2000.<sup>4</sup> Feeding Walthams Feline Low Phosphorous/Low Protein diet controlled hyperphosphataemia and hyperparathyroidism associated with spontaneous CKD, and was associated with increased survival time (Waltham® Veterinary Diet is a trademark owned by Mars, Incorporated). There were several significant limitations to this study. Firstly, cats were not randomly assigned to a food group. All owners were offered treatment with a renal food and cats that would eat the renal food were assigned to the renal food group. Those that refused the renal food were fed their usual cat food with varying amounts of fresh meat or fish. It is possible that the more stable cats self-selected to consume the renal food, which could falsely increase survival time in this group. Second, neither the owner nor the veterinarian was blinded to the food groups, which may have introduced bias into the study. Finally, cats in the renal food group were not fed the same diet throughout the study as the renal diet changed from Whiskers Feline Low Protein diet (canned) to Waltham Feline Low Phosphorous/Low Protein diet (dry and canned) during the study. This study represents Grade 3 evidence.

Two years later a Grade 1, double-blinded, randomised controlled clinical trial in dogs with spontaneous Stage 3 and 4 CKD was published.<sup>1</sup> Thirty-eight dogs with CKD were randomly assigned to be fed either Hill's Prescription Diet™ k/d™ (Hill's Pet Nutrition, Inc., Topeka, KS, USA), or a maintenance diet. Dogs fed k/d™ had a 72% reduction in the relative risk of developing a uraemic crisis and remained free of uraemic signs almost 2.5 times longer than dogs fed the maintenance food. Dogs fed the renal food had a median survival time over 3 times longer than dogs fed the maintenance food (594 days for the renal diet group vs 188 days for the maintenance food). An important contributing factor to the longer survival times observed in dogs fed the renal food appeared to be a slowing of the rate at which renal function declined. Dogs fed the renal food also had better owner reported health-related quality-of-life scores than dogs consuming the maintenance food.

A similar Grade 1 study was conducted over 2 years to determine if a renal diet was superior to an adult maintenance diet in minimising uraemic episodes and renal related deaths in 45 cats with stage 2 and 3 CKD.<sup>2</sup> None of the cats fed Hill's Prescription Diet™ k/d™ Feline (Hill's Pet Nutrition, Inc., Topeka, KS, USA), suffered a uraemic crisis, while 26% of the control cats did. There was also a significant decrease in the number of renal-related deaths, with none of the renal diet group dying as opposed to 22% of the maintenance diet group.

These two Grade 1 clinical trials not only had a rigorous experimental design but also were conducted in clinical patients with naturally occurring kidney disease, using the renal diet as it would be used in the clinic setting. Given differences in the nutrient levels between various brands, other renal foods should also be validated in properly controlled clinical trials.

Nutritional therapy is considered the cornerstone in the management of dogs and cats suffering CKD. Although there are a number of commercially available renal foods, some owners still prefer to use home-prepared diets. A recent study evaluating 67 recipes of diets recommended for dogs or cats with CKD suggests these should be used with caution,<sup>6</sup> as many problems with nutritional adequacy were detected. None of the recipes provided adequate concentrations of all essential nutrients for adult dogs and cats, many did not accommodate currently accepted nutritional strategies for managing CKD, and none

provided guidelines for use at any particular stage or type of disease. The authors concluded that use of the recipes could result in highly variable and often inappropriate diets being fed. Many recipes would not meet nutritional and clinical needs of individual patients and should be used cautiously for long-term feeding.

### **Acceptance of a renal food**

Some owners (and veterinarians!) are reluctant to use a renal diet as they feel that reduced palatability will adversely affect the patient's food intake and nutritional status. It is important to realise that a pet with kidney disease is more likely to accept a new food earlier in the course of the disease, when they are feeling better, rather than when kidney disease has advanced to the point the pet is nauseous.

There are some "do's and don'ts" that are helpful to remember when recommending a dietary change. It is very important to educate pet owners about the role of nutrition in the management of CKD. When they understand that feeding a therapeutic renal food is the only treatment that has been shown to prolong survival time in cats with kidney disease and one of two treatments with the same effect in dogs, they will be more likely to do what it takes to get their pet eating a renal food, and not give up when things get tough.

It's critical to let them know up front that while some patients easily transition from one diet to another, others (especially cats) are very selective and may require more coaxing. It is best to recommend that dietary changes be made very slowly. Most patients can be transitioned onto a new diet in 3-4 weeks by gradually mixing the new food into the old food. This can be achieved by mixing the current diet with the renal diet in gradually increasing amounts so that, by the end of week 1, the pet should be eating a mixture of  $\frac{3}{4}$  old food and  $\frac{1}{4}$  new food, and by the end of week 4, the pet would be eating all new food. Others may take 6 to 8 weeks or even longer, particularly cats or fussy dogs. Clinical signs of uraemia should be controlled prior to the introduction of a new diet - attempting to introduce a new diet when an animal is nauseated is likely to result in food aversion.

In general, it is best to start by using the same form of diet the patient is used to eating (i.e. dry food versus canned food). Often the addition of flavour enhancers (low sodium chicken broth, tuna juice, etc), encourage food consumption. It is best to avoid additives that contain excessive protein, phosphorus, or salt. Another important consideration is how most owners feed their cats. Data from over 800 cat owners surveyed in the 2002 Hill's Habits and Practices Study revealed that 99% of cat owners feed dry food alone (33%) or together with moist food (66%). Only 1% feed moist food only. If you don't dispense both canned and dry food, owners may 'top-dress' the dry renal diet with an over-the-counter canned food which is detrimental for cats with CKD.

A cafeteria-style feeding method, where patients are allowed to self-select from several renal foods offered simultaneously, is not recommended. Firstly it is difficult to determine how much food the patient has actually eaten. Secondly, offering all the commercial renal foods available for sampling while a patient (particularly a cat) is feeling sick and stressed is a good way to create multiple food aversions to all the foods that the patient may need to be fed in the long term.

It is important to consider metabolic causes for anorexia before assuming that poor appetite is food-related. A variety of metabolic causes may be associated with poor appetite in dogs with renal insufficiency including: 1) anaemia 2) uraemic gastritis 3) dehydration 4) metabolic acidosis 5) hypokalaemia, and 6) renal secondary hyperparathyroidism. Most of these conditions can be managed with appropriate therapy.

Providing frequent small meals may be helpful in increasing calorie intake in patients that are partially anorexic. Medications should not be mixed with the food as they may alter taste, resulting in food aversion. If the patient is showing a progressive decline in body condition, an enteral feeding tube (oesophagostomy or gastrostomy) should be recommended for longer-term nutritional support.

## Appendix

### General medical management

It is beyond the scope of these notes to discuss medical management in depth, however some general advice follows.

**Hydration** - It is important that patients with any stage of CKD remain well hydrated at all times to preserve remaining renal function. Patients with any stage of kidney disease are particularly at risk for dehydration when they are not feeling well or have limited access to water (e.g. if their water bowl becomes empty during the day) or they are not eating or drinking. Their kidneys no longer have the ability to conserve water when intake is low, so they continue to lose water through their urine. If simple management techniques (water fountains, flavoured water, multiple water bowls, etc) do not provide adequate hydration, an enteral feeding tube or subcutaneous fluid therapy should be considered.

**Hypertension** - May increase the progression of the disease and may develop at any stage of CKD. Once confirmed, hypertension should be aggressively managed to minimise the risk of systemic end organ damage.

**Proteinuria** - As with hypertension, proteinuria may occur at any stage of kidney disease and should be treated. It is important that proteinuric animals be thoroughly evaluated to identify treatable concurrent disease processes.

**Calcitriol** - There is evidence to suggest that the judicious use of calcitriol in dogs with stage 3-4 CKD may prolong survival, providing serum phosphorous is controlled and ionised calcium and parathyroid hormone are very closely monitored. Calcitriol is the major renal hormone responsible for calcium metabolism. Because CKD may impair production of calcitriol, calcitriol deficiency may be one factor promoting renal secondary hyperparathyroidism. Calcitriol supplementation has been advocated as a means of normalising hyperparathyroidism. Serum total and ionised calcium concentrations must be monitored during therapy with calcitriol to prevent hypercalcaemia.

**Anaemia** - It is very common for patients to develop anaemia in stage 3-4 CKD. As functional kidney mass declines, the kidneys are no longer able to produce enough of the hormone erythropoietin. Erythropoietin (EPO) is normally produced by the kidneys when they sense that the body requires more red blood cells. Once produced by the kidneys, EPO travels to the bone marrow, where it stimulates the production of new red blood cells. As functional kidney mass decreases, the levels of EPO produced also decrease, and red blood cell production falls.

**Gastrointestinal signs** - During stage 3 CKD, some patients will begin to show gastrointestinal signs. Kidney disease can directly and indirectly cause vomiting due to the accumulation of uraemic toxins within the blood. Vomiting secondary to uraemia is mediated both centrally due to the direct effects of uraemia toxins on the chemoreceptor trigger zone in the brain, and peripherally due to gastrointestinal irritation. Treatment options include a variety of antacids and anti-emetics. If decreased appetite persists despite correction or management of these secondary causes, appetite stimulants may be used short term, however, for long term nutritional support, an enteral feeding tube should be seriously considered. Anecdotal reports suggest that tube feeding can reverse the progressive weight loss associated with chronic kidney disease and improve overall quality of life. Options include either oesophagostomy tubes or percutaneous gastrostomy tubes. Tube placement requires anesthesia, but can be readily performed in a short time, and feeding tubes can remain in place as long as necessary for supportive care.

Thanks to Sherri Ross for allowing the use of her material for the preparation of these lecture notes. (Sheri J. Ross, BSc, DVM, PhD, Dipl. ACVIM (Internal Medicine), Coordinator Nephrology/Urology/Hemodialysis Service, University of California Veterinary Medical Center)

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