Diagnosis and Management of Chronic Kidney Disease in Dogs and Cats

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Chronic Kidney Disease
Chronic kidney disease (CKD) is defined as primary renal disease that has persisted for months to years. Chronic kidney disease has been referred to as chronic renal failure, chronic renal insufficiency, etc. These terms are not very useful in categorizing a patient to facilitate treatment and prognosis recommendations. In human nephrology, there is an elaborate staging scheme that facilitates the application of appropriate clinical practice guidelines for diagnosis, prognosis, and treatment. Recently, The International Renal Interest Society (IRIS) has recently introduced a staging system for the classification and stratification of chronic kidney disease in dogs and cats. (See IRIS staging charts following notes) The purpose of the staging system is to facilitate the application of clinical practice guidelines for evaluation and management of each stage of chronic kidney disease. Patients are assigned a specific stage of renal disease based on kidney function as determined by serum creatinine concentration. The patient is then further classified according to their systolic blood pressure and the presence or absence of proteinuria. Both hypertension and proteinuria have been identified as important contributors to progressive renal injury in many species, including the cat. Although the specific cut-off values used to categorize patients with CKD into these stages are inherently arbitrary, staging is useful for establishing prognosis and managing patients with CKD.

Diagnosing Chronic Kidney Disease
Chronic kidney disease is a common clinical diagnosis in middle-aged to geriatric cats and dogs that may significantly affect the quality of life of both the patients and their owners. Early detection of chronic kidney disease may be asymptomatic, or they may develop subtle, nonlocalized clinical signs often mistaken for age-related changes by owners. Given the high prevalence of CKD in older pets, routine laboratory screening of geriatric patients for evidence of CKD is recommended as a standard of practice. Detecting CKD in the early stages is important so that appropriate therapeutic measures may be instituted to minimize the progression of disease and delay the onset of uremia.

The diagnosis of CKD is based on identifying historical, physical, or laboratory findings which suggest that kidney disease has been present for an extended time. The medical history and physical examination are often the most revealing and reliable clues to chronicity. A history of signs as polyuria, polydipsia, weight loss, selective appetite, deteriorating haircoat occurring over several months is strong evidence for CKD. Physical exam findings of poor nutritional status, poor haircoat, small kidneys, or renal osteodystrophy (most likely evident clinically as “rubber jaw”) strongly suggest chronicity. Laboratory findings are often not helpful in establishing the diagnosis of chronic renal failure, although the presence of a hypoproliferative anemia may be suggestive of chronicity.

Diagnostic Evaluation
Upon diagnosing primary kidney disease, the next step in the diagnostic evaluation is to establish the cause of renal damage (etiology - if possible) and the clinical effects of kidney disease on the patient so that therapy can be individualized to patient needs. The initiation database should ideally include many of the following analyses as dictated by the specific needs of the patient:

Evaluation - Purpose
Blood urea nitrogen - Assess degree of azotemia
Serum Creatinine - To establish the diagnosis & measure intrinsic renal function
Urine analysis - To establish diagnosis & identify renal complications
Urine culture - To rule-out urinary tract infection
Complete blood count - To detect anemia of renal failure & inflammatory complications
Serum sodium - To detect hyponatremia or hypernatremia
Serum potassium - To detect hypokalemia or hyperkalemia
Serum total carbon dioxide - To assess metabolic acid-base status
Serum chloride - Useful in assessing serum tCO2 and Na concentrations
Serum phosphorus - To detect hyperphosphatemia
Serum calcium - To detect hypercalcemia or hypocalcemia
Serum albumin & total protein concentrations - To assess nutritional status
Body weight - To assess nutritional status
Protein:creatinine ratio (if proteinuric) - To assess magnitude of proteinuria
Blood pressure - To evaluate for hypertension
Diet therapy has been the cornerstone in the management of chronic kidney disease (CKD) for decades. In the past, the emphasis has been on reducing the protein content of the diets. Although protein content continues to play an important role in diet formulation, other diet modifications are also important in managing patients with kidney disease. Compared to adult maintenance diets, diets formulated specifically for dogs and cats with chronic kidney disease typically have reduced protein, phosphorus, and sodium content; increased potassium, B-vitamin content and caloric density; a neutral effect on acid-base balance; and an increased omega-3/omega-6 polyunsaturated fatty acid (PUFA) ratio.

Protein
Although the ideal quantity of protein to feed dogs and cats with CKD remains unresolved, a general consensus of opinion supports the fact that reducing protein intake ameliorates clinical signs of uremia in CKD and is therefore indicated for stage 4 CKD. BUN can be used as a crude measure of compliance with dietary recommendations because it declines as dietary protein intake is reduced. Although not generally regarded as an important uremic toxin, BUN is a surrogate marker for retained non-protein nitrogenous waste products and typically correlates better with clinical signs than serum creatinine concentration.

The concept of reducing dietary protein intake in CKD patients that do not have clinical signs of uremia has been questioned. Limiting protein intake has been advocated for these patients to slow progression of CKD. This suggestion derives from studies in rats indicating that dietary protein restriction limits glomerular hyperfiltration and hypertension and slows the spontaneous decline in kidney function that follows reduction in kidney mass. Studies in humans have supported the concept that protein restriction slows progression of CKD, albeit this effect may be small. In contrast, multiple studies have failed to confirm a beneficial role for protein restriction in limiting progression of kidney disease in dogs or cats. When not excessive, limiting protein intake 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 uremia. In addition, protein restriction may delay onset of clinical signs of uremia as renal disease progresses.

Phosphorus
Renal diets are limited in phosphorus content to limit phosphorus retention, hyperphosphatemia, renal secondary hyperparathyroidism, and progression of renal disease. Phosphate balance results largely from the interaction between dietary intake and renal excretion. Ingested phosphate is cleared from blood by glomerular filtration, and then total excretion is adjusted by modifying proximal tubular reabsorption. As renal function declines, renal tubular reabsorption of phosphorus declines (increasing renal excretion) in an attempt to compensate for the reduction in glomerular filtration, thereby maintaining phosphorus balance. However, if phosphorus intake continues unabated, the renal adaptive capacity soon becomes overwhelmed and phosphorus retention and hyperphosphatemia develop. Although phosphorus retention and hyperphosphatemia probably do not cause clinical signs, they may promote renal secondary hyperparathyroidism and renal mineralization that enhances progressive decline in renal function. Dietary phosphorus restriction has been shown to enhance survival and a slow decline in renal function in dogs with induced renal failure. In cats, dietary phosphorus restriction has been shown to limit renal mineralization. Because protein is a major source for phosphate, it is usually necessary to limit dietary protein to limit diet phosphate content.

Potassium
Hypokalemia is quite common in cats with chronic kidney disease and less frequently in dogs with renal tubular disorders (e.g. Fanconi’s syndrome). Clinical signs of hypokalemia may include muscle weakness and further impairment of kidney function. Renal diets are generally supplemented with potassium, however, some patients still require oral or parenteral administration of potassium salts. Potassium gluconate and potassium citrate are the preferred salts for oral administration; potassium chloride is used parenterally.
Hyperkalemia is more often encountered with acute oliguric kidney injury, or in stage 4 CKD when the renal excretory capacity has been severely compromised. However, it may also occur in association with therapeutic blockade of the renin-angiotensin system and with hyporenemic hypoaldosteronism. The primary clinical consequence of hyperkalemia is cardiotoxicity. Treatment usually involves reducing the potassium content of the diet and/or reducing the dosage of ACEI if applicable.

**Dietary buffering**

As CKD progresses metabolic acidosis develops due to impaired renal ammonia production, decreased hydrogen ion excretion, and reduced bicarbonate reabsorption. Clinical consequences associated with metabolic include increased protein catabolism, including anorexia, nausea, vomiting, lethargy, muscle wasting, and malnutrition. One study of chronic metabolic acidosis in cats demonstrated a negative calcium balance and bone deminerlization, while another indicated that chronic metabolic acidosis may promote negative potassium balance. Therapy for metabolic acidosis should be considered when the blood bicarbonate concentration remains below 17mEq/l on consecutive determinations. Given the questionable accuracy of serum total CO2 concentrations, the authors recommend blood gas analysis be performed on to confirm metabolic acidosis whenever total CO2 declines below 15mmol/L.

Treatment options for metabolic acidosis include alkalinization using diet, sodium bicarbonate, or potassium citrate. Most diet formulated specifically for animals with renal failure are designed to be neutral to slightly alkalinizing. Often, early acidosis may be controlled with diet alone. However, if the acidosis persists or worsens, oral alkalinization with sodium bicarbonate or potassium citrate should be considered.

Response to therapy should be assessed after 10-14 days with a blood bicarbonate concentration. Ideally the sample should be collected just prior to administration of the drug. The dosage of medication should be adjusted to maintain the blood bicarbonate concentration within the normal range.

**Omega-3 polyunsaturated fatty acids**

The optimum quantity of omega-3 PUFA supplementation and ratio of omega-3/omega-6 PUFA appropriate for renal diets have not been conclusively established. Although prospective clinical trials evaluating the efficacy of additional omega-3 polyunsaturated fatty acid supplementation in dogs and cats with naturally occurring disease have not yet been performed, dietary supplementation with omega-3 PUFA’s have been shown to be beneficial in dogs with induced CKD. Compared with dogs fed diets high in saturated fats or omega-6 PUFA, dogs consuming a diet supplemented with omega-3 PUFA had lower mortality, better renal function, fewer renal lesions, less proteinuria, and lower cholesterol levels. In dogs fed the omega-3 PUFA diet, renal function actually increased and remained above baseline over 20 months of study. Lesions of glomerulosclerosis, tubulointerstitial fibrosis, and interstitial inflammatory cell infiltrates were also reduced in dogs fed the diet supplemented with omega-3 PUFA’s. These benefits are thought to accrue, at least in part, by modification in prostanoid, thromboxane, and leukotriene production with anti-inflammatory, anti-thrombotic and antioxidant effects. Published data supporting the use of omega 3 polyunsaturated fatty acids in cats is limited to a single retrospective study of cats with spontaneous CKD in which cats surviving the longest were receiving the diet with the highest omega-3 PUFA concentration.

**Hydration**

Fluid balance in patients with polyuric renal failure is maintained by compensatory polydipsia. If water consumption is insufficient to compensate for polyuria, dehydration is the result. This may occur as a consequence of lack of intake or lack of access to fresh, clean, water. Cats and some dogs with CKD fail to consume sufficient water to prevent chronic or recurrent dehydration. Dehydration promotes renal hypoperfusion and prerenal azotemia that may exacerbate the clinical and laboratory abnormalities of CKD. Clinical signs characteristic of dehydration include decreased appetite, lethargy, and constipation. In some patients, prerenal azotemia may precipitate uremic crisis. Further, if dehydration and decreased renal blood flow are allowed to persist, additional ischemic renal damage may occur.

Patients that develop recurrent episodes of signs consistent with dehydration are candidates for intermediate-to long-term fluid support. If simple management techniques (water fountains, flavoured water, multiple water bowl, etc.) do not provide adequate hydration, an enteral feeding tube or subcutaneous fluid therapy should be considered. Should be employed fluid therapy to be administered at home by the owner.

Normal saline or lactated Ringer's solution are the fluids most commonly used for home subcutaneous fluid therapy. They are well tolerated by most cats and dogs and appear to be reasonable choices for most patients. However, chronic administration of lactated Ringer's solution or normal saline as the principal maintenance fluid source may cause hypernatremia because they fail to provide sufficient electrolyte-free water. Ideally, fluids selected for chronic parenteral administration should provide free water and electrolytes for maintenance. In addition to providing nutritional support and a route for administering medications, enteral feeding tubes are ideally suited to maintaining hydration as free water deficits may be replaced without as much
Diet Therapy-Evidence from Clinical Trials
The effectiveness of diet therapy in minimizing uremic episodes and mortality in dogs with naturally occurring stage 3 and stage 4 CKD has been established in a double-masked, randomized, controlled clinical trial. The study compared a renal diet (Hill’s Canine k/d) to a prototypical canine maintenance diet. The renal diet was characterized by reduced quantities of protein, phosphorus, and sodium compared with the maintenance diet, and it was supplemented with omega-3 PUFA. In this study the risk of developing a uremic crisis was reduced by approximately 75% in dogs fed the renal diet compared with dogs fed an adult maintenance diet, and the median interval before development of uremic crisis in dogs fed the renal diet was twice as long as that observed in dogs fed the maintenance diet. Further, the risk of death irrespective of the cause was reduced by at least two thirds when dogs were fed the renal diet, and renal death risk was reduced by 70%.

Dogs fed the renal diet survived at least 13 months longer than dogs fed the maintenance diet. In addition, owners of dogs fed the renal diet reported significantly higher quality of life scores for their dogs than owners of dogs consuming the maintenance diet. The delay in development of uremic crises and reduced mortality observed in dogs fed renal diet was associated, at least in part, with reduction in the rate progression of renal failure.

Likewise, we designed a randomized, double-masked, controlled clinical trial to evaluate the long-term safety and effectiveness of a renal food (Hill’s feline k/d) in cats with naturally occurring stage 2 or 3 CKD. Our hypothesis: a renal food (modified in protein, phosphorus, sodium, and lipid composition) is superior to an adult maintenance food in minimizing uremic episodes and renal-related deaths in cats with stage 2 or 3 CKD.

Our study included 45 client-owned cats with stable stage 2 or 3 CKD. After an initial screening process to confirm the diagnosis of chronic kidney disease, cats were randomly assigned to receive either a maintenance food or a diet formulated specifically for cats with renal disease. Cats were thoroughly evaluated every 3 months for up to 24 months. Clinical, biochemical and quality of life parameters were compared between the two dietary groups at baseline and during the 12 and 24 month intervals. During the 24-month study period, cats fed the maintenance food had a significantly greater number of uremic episodes compared to cats fed the renal food. A significant reduction in renal-related mortality, but not all causes of mortality, occurred in cats fed the renal food. The renal food evaluated in this study was superior to an adult maintenance food in minimizing uremic episodes and the renal-related mortality rate in cats with mild to moderate spontaneous CKD. The results of this study were similar to those obtained in a non-randomized, open clinical trial comparing a feline renal diet to no diet change. In this study, cats fed the renal diet (median survival time 633 days) survived substantially longer than cats that continued to consume their regular diet (MST, 264 days). In addition, plasma urea nitrogen, phosphorus, and PTH concentrations were reduced in cats that consumed the renal diet.

Proportions* of Uremic Crisis or Death in Cats with Spontaneous Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Event</th>
<th>Renal food (%)</th>
<th>Maintenance food (%)</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremic crisis</td>
<td>0/22 (0)</td>
<td>6/23 (26.1)</td>
<td>0.02</td>
<td>0 – 0.63</td>
</tr>
<tr>
<td>Renal-related death</td>
<td>0/22 (0)</td>
<td>5/23 (21.7)</td>
<td>0.03</td>
<td>0 – 0.72</td>
</tr>
<tr>
<td>All causes of death</td>
<td>3/22 (13.6)</td>
<td>10/23 (43.5)</td>
<td>0.07</td>
<td>0.27 – 1.02</td>
</tr>
<tr>
<td>Nonrenal death</td>
<td>3/22 (13.6)</td>
<td>5/23 (21.7)</td>
<td>0.51</td>
<td>0.36 – 1.59</td>
</tr>
</tbody>
</table>

*Number of Affected Cats/Number of Cats per Group

These studies did not selectively determine the benefits of modifying individual dietary components, but rather report the results of a composite diet effect. Although studies on individual dietary components have been reported in dogs and cats with induced renal failure, the potential interactions between components have not been examined, nor have the results of these studies been confirmed in patients with naturally occurring disease.

How can diet therapy be successfully implemented?
Many owners (and veterinarians!) are reluctant to use a renal diet as they feel that reduced palatability will adversely affect the patients food intake and nutritional status. There are some “do’s and don’ts” that are helpful to remember when recommending a diet change. While some patients easily transition from one diet to another, others (especially cats) are very selective and may require more coaxing to induce diet change. In general, it is probably best to recommend that diet changes be made very slowly rather than abruptly. Most patients can be transitioned onto a new diet in two by gradually mixing the new diet into the old diet. In my experience, cats are more likely to accept a new diet if transitioned over 3 weeks. Clinical signs of uremia 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.

It is important to consider metabolic causes for anorexia before assuming that poor appetite is diet-related. A variety of metabolic causes may be associated with poor appetite in dogs with renal insufficiency including: 1) anemia, 2) uremic gastritis, 3) dehydration, 4) metabolic acidosis, 5) hypokalemia, 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 (esophagostomy or gastrostomy) should be recommended for longer-term nutritional support.

**Monitoring**

Patients with renal insufficiency often require frequent monitoring. Frequent evaluations allow for the early detection and management of many complications associated with CKD. Frequent monitoring also encourages owner compliance, thereby improving the quality of care between office visits as well. The frequency of monitoring varies with the stage of kidney disease and the severity of their clinical signs, however, even patients with stages 1 and 2 CKD should be evaluated 2-4 times each year.
International Renal Interest Society (IRIS) Staging System for Canine Chronic Kidney Disease.

**Staging System for Chronic Kidney Disease (CKD)**

**STEP 1.** Staging is initially based on fasting plasma creatinine assessed on at least two occasions in the stable patient. Plasma creatinine concentrations apply to average size dogs - those of extreme size may vary.

**Plasma creatinine μmol/l mg/dl**

- **< 125**
- **125-179**
- **180-439**
- **≥ 440**

**Urine protein/creatinine ratio (U/P)**

- **NON-PROTEINURIC**
- **BORDERLINE PROTEINURIC**
- **PROTEINURIC**

**Risk of end organ damage from hypertension (Normal blood pressure >190)**

- **MINIMAL RISK**
- **LOW RISK**
- **MODERATE RISK**
- **HIGH RISK**


*The relative percentages of renal functions are conceptual estimates only. **This terminology has been used previously without precise definition and should be replaced by the numerical staging system.*

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International Renal Interest Society (IRIS) Staging System for Canine Chronic Kidney Disease.

STEP 2. Cases are then sub-staged based on proteinuria and blood pressure.

Note that U/P and a blood pressure vary independently of each other and the stage of CKD, so that any level of proteinuria or hypertension can occur at any stage of CKD i.e. at any level of azotemia.
International Renal Interest Society (IRIS) Staging System for Feline Chronic Kidney Disease.

STEP 1. Staging is initially based on fasting plasma creatinine assessed on at least two occasions in the stable patient.

Renal function remaining

100%  
STAGE 1

33%  
STAGE 2

25%  
STAGE 3

<10%  
STAGE 4

Plasma creatinine

< 140
< 1.6

140-249
1.6-2.8

250-439
2.9-5.0

> 440
≥ 5.0

Old Terminology

Normal renal function

Early renal disease:
No biochemical evidence.

Renal insufficiency:
No azotaemia. Decreased GFR; poor concentrating ability.

Early renal failure:
Mild azotaemia. Mal- adaptations can lead to hyperparathyroidism and hyperkalaemia.

Uraemic renal failure:
Moderate to severe azotaemia. Systemic signs present: e.g. bone pain, uraemic gastritis, anaemia, metabolic acidosis.

End-stage renal failure:
Increasing risk of systemic clinical signs and uraemic crisis.

STEP 2. Cases are then sub-staged based on proteinuria and blood pressure.

Note that proteinuria and blood pressure vary independently of each other and the stage of CKD, so that any level of proteinuria or hypertension can occur at any stage of CKD i.e. at any level of azotaemia.

Urine protein/creatinine ratio (U/P)

Risk of end organ damage from hypertension (Systolic blood pressure mm Hg)

Minimal Risk

Low Risk

Moderate Risk

High Risk

Adapted from the Manual of Canine & Feline Nephrology & Diet (Fig. 5.5) 2nd Ed. edited by J. Elliott & G. Greaves (2000) with permission of the British Small Animal Veterinary Association.

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Based on IRIS XIR staging of CKD.