Initial Evaluation of Animals with Kidney Disease with a Focus on Chronic Diseases (CKD)

For all animals with CKD, a thorough history and physical examination should be accompanied by complete clinical pathology testing, which includes a biochemical panel, hematology, and urinalysis with specific proteinuria tests and aerobic bacterial culture. Survey radiography ± abdominal ultrasonography and blood pressure measurements should be performed. This initial battery of tests allows the veterinarian to evaluate the severity of the disease, establish a prognosis, follow the response to subsequent therapy, and identify complicating factors. As part of this evaluation, renal azotemia should be distinguished from other causes of azotemia, and CKD should be distinguished from the more readily reversible acute kidney disease. Frequently, this latter differentiation may be accomplished with a careful history, physical examination, and evaluation of laboratory findings, although occasionally a renal biopsy may be required (see subsequent section on renal evaluation).

Renal Evaluation and Specific Therapy (see Table 1)

It is a high priority, especially in stage I or early stage II CKD, to attempt to identify the primary process causing the CKD. Examples of renal evaluation that may be appropriate at these early stages include renal imaging (survey ± contrast radiographic studies, ultrasonography, urinalysis with specific tests for proteinuria and urine culture, and renal biopsy). Known causes of CKD that may be diagnosed through this approach include diseases of the macrovascular compartment (e.g., systemic hypertension, coagulopathies, chronic hypoperfusion), microvascular compartment (e.g., systemic and glomerular hypertension, glomerulonephritis, developmental disorders, congenital collagen defects, amyloidosis), interstitial compartment (e.g., pyelonephritis, neoplasia, neoplastic, obstructive uropathy, allergic and immune-mediated nephritis), and tubular compartment (e.g., tubular reabsorptive defects, chronic low grade nephrotoxicity, obstructive uropathy). These conditions may be acquired or heritable. A variety of breeds are afflicted with heritable CKD, which may have pathognomonic clinical and histopathological findings, including the Abyssinian (medullary amyloidosis) and Persian (polycystic kidney disease) cats, basenji (proximal tubular reabsorptive disorder), Chinese shar pei (amyloidosis), cocker spaniel (collagen type IV defect similar to human Alport’s Syndrome), Doberman Pinscher (familial glomerulopathy), L’hasa Apso (renal dysplasia), Norwegian elkhound (proximal tubular reabsorptive disorder), samoyed (collagen type IV defect similar to human Alport’s Syndrome), shih-tzu (renal dysplasia), soft-coated wheaten terrier (renal dysplasia with proteinuria), and standard poodle (glomerular atrophy).

Specific therapy is defined as a treatment that is directed at the primary cause of the kidney disease. While it is often not possible to identify the primary cause of the CKD, in the early IRIS stages use of specific therapy is a high priority. The goal is to control the primary kidney disease, thereby reducing the magnitude of subsequent renal damage. Examples of specific therapy include antibiotic therapy in cases of CKD caused by pyelonephritis, antihypertensives for animals with hypertensive nephropathy, dietary calcium restriction for animals with hypercalcemic nephropathy, and surgery for obstructive uropathy.

Interstitial fibrosis occurs in most animals with CKD. The severity of interstitial fibrosis is positively correlated to the magnitude of decline of GFR and negatively correlated with the prognosis. When CKD is in the latter stages (III-IV), the renal histology will likely demonstrate only this marked interstitial fibrosis, which is usually termed chronic interstitial nephritis. Chronic interstitial nephritis, also known as chronic tubulointerstitial fibrosis, describes the morphologic appearance of kidneys with stage III or IV CKD of any cause, and renal evaluation (i.e., biopsy) and specific therapy become an increasingly lower priority at this time.

Progression of Chronic Kidney Disease

Since the only effective therapy for end-stage uremia (i.e., intensive fluid therapy, renal transplantation, and/or dialysis) is often prohibitively expensive, a goal of therapy should be to prevent progression of kidney disease to end-stage failure. However, dogs and cats with mild renal dysfunction often suffer progressive decrements of renal function and ultimately die of terminal renal failure. The progression to end-stage uremia can be attributed to either the primary kidney disease or inherent progression. Specific therapy directed at resolution of the primary disease process is generally not nutritional in nature and is beyond the scope of this article. On the other hand, there are two general mechanisms contributing to inherent progression that can be affected by nutritional intervention: abnormalities caused by a disruption of renal homeostatic mechanisms (complications of kidney disease) and maladaptive changes in remnant nephrons. Unfortunately, both of these inherent mechanisms represent a vicious
cycle of self-perpetuating renal injury. Nutritional intervention can modify renal adaptations and limit the extent of some complications of kidney disease, theoretically limiting progressive renal injury by interrupting these vicious cycles.

In the absence of clinical signs of uremia, the principal rationale for dietary restriction of nutrients is to limit the progression of kidney disease. In the management of progressive kidney disease, a variety of recommendations have been considered for dogs and cats with azotemic kidney disease: (1) restriction of dietary protein intake, (2) restriction of dietary phosphorus intake, (3) restriction of dietary sodium intake, (4) modification of dietary lipid intake, and (5) dietary alkalinization.

**Evaluation of Progression and Renoprotective Therapy**

A critical consideration in the treatment of dogs and cats is the progressive nature of CKD. There are several reasons that renal function will progressively deteriorate in an animal with CKD. As outlined above, of importance in stage I and early stage II is the renal damage that may be a manifestation of the primary disease process. However, in stages II–IV other processes are activated that become more important in determining the rate of loss of renal function. These lead to what has been referred to as **Hypertension of CKD** as these processes are intrinsic to CKD of any cause. Processes that are activated during stages II–IV of CKD that contribute to renal damage include systemic and glomerular hypertension, mineral imbalance, proteinuria, and renal fibrosis. Although the rate of progressive decline of renal function varies, studies to date suggest that inherent progression occurs in all animals with IRIS stages II–IV. Characterization of the rate of progression of CKD through serial determinations of plasma creatinine concentration are a high priority at this time. Measures that may slow inherent progression are referred to as **Renoprotective Therapies** (see Table 1), and these include dietary phosphorus restriction (dogs and cats), calcitriol administration (dogs), dietary fish oil supplementation (dogs), antihypertensive agents in animals with high blood pressure (dogs and cats), and administration of angiotensin converting enzyme inhibitors (dogs and cats). While renoprotective therapy is a high priority in IRIS stages II and III, it becomes increasingly less important in late stage IV, as the focus of therapy becomes management of the complications of uremia (see next section). Dietary restriction of phosphate and supplementation with fish oil (dogs) are important renoprotective therapies, and specialized “kidney” diets generally meet these requirements and should be utilized from stage II onward. Calcitriol administration (i.e., 0.5–1 ng/kg body weight orally, given separately from meals to an animal that is normocalcemic and normophosphatemic) is a renoprotective therapy in dogs (and possibly cats). If dietary restriction of phosphorus is unsuccessful in maintaining a normal level of serum phosphorus within 2–3 months, phosphate-binding gels containing calcium acetate, calcium carbonate, or aluminum hydroxide should be administered with meals (initial dosage of 30 mg/kg body weight with dosage increased as needed to achieve desired effect). Calcium containing phosphate binding agents should be avoided in animals receiving calcitriol. In dogs only, there is a clear rationale for the inclusion of dietary n-3 polyunsaturated fatty (n-3 PUFA), and this may be accomplished with the use of special “renal diets” that are already supplemented with n-3 PUFA and/or the addition of 1–3 gm of n-3 PUFA/250 Kcal of diet.

**Patient Evaluation and Symptomatic Therapy**

Patient evaluations, which include efforts to identify developing complications (e.g., systemic hypertension, potassium homeostasis disorders, metabolic acidosis, proteinuria, anemia, and bacterial urinary tract infections) should be aggressively and prospectively pursued during all routine visits regardless of IRIS stage. As CKD progresses into IRIS stage IV, clinical consequences of the reduction of GFR become apparent, and thorough patient evaluations followed by appropriate symptomatic therapy become increasingly important. Initially, uremia causes occasional vomiting and lethargy. As CKD progresses within stage IV, generally over months (dogs) to years (cats), anorexia, weight loss, dehydration, oral ulceration, vomiting, and diarrhea likely will become fully manifest. Loose teeth, deformable maxilla and mandible, or pathologic fractures may be seen with renal secondary osteodystrophy, but these are uncommon and most often observed in young dogs with end-stage congenital renal disease. Physical examination and imaging studies of animals in IRIS stages II–IV usually reveal small, irregular kidneys, although normal to large kidneys can be observed in animals with tumors, hydronephrosis, amyloidosis, or glomerulonephritis. Mucous membranes are pale in late IRIS stages III and IV, due to the presence of a nonregenerative, normocytic normochromic anemia.

In animals in the severely azotemic stage (IRIS stage IV), complications are more frequent, and patient evaluation and appropriate symptomatic therapy become an increasingly higher priority. Affected animals at this stage should
be evaluated at 1–2 month intervals. This patient evaluation should include a thorough history and physical examination, complete biochemical panel, hematology, and urinalysis aerobic bacterial culture.

Symptomatic therapy is a high priority at this time. As dietary restriction of protein may relieve some of the signs of uremia, a high-quality protein (e.g., egg protein) should be fed at a level of 2.0–2.8 g/kg body weight/day for dogs and 2.8–3.8 g/kg body weight/day for cats. Commercial diets formulated for cats and dogs with CKD generally meet this recommendation.

Administration of an H2-receptor antagonist such as famotidine (5 mg/kg, PO, 2–4 times daily) may decrease gastric acidity and vomiting. Anabolic steroids, such as oxymetholone or nandrolone, have been administered to stimulate RBC production in animals that are anemic, but this approach is not very effective. Recombinant erythropoietin (50–100 IU/kg body weight SQ three times weekly initially, dosed to effect after hematocrit reaches the target range of 30–35% with supplemental iron administration and weekly hematocrit determinations) is effective in stimulating RBC production, but anti-erythropoietin antibodies develop in a significant percentage of animals treated with the human protein, and these may result in refractory anemia; until species specific product becomes generally available, erythropoietin administration is now recommended only for animals showing apparent clinical signs of anemia (e.g., weakness, marked lethargy not attributable to other factors), which generally occurs at a hematocrit ≤ 15%. Potassium citrate or sodium bicarbonate, given PO to effect, may be indicated if the animal is acidemic (plasma bicarbonate < 15 mEq/L) or if the animal remains acidemic 2–3 weeks after diet change.

In latter stage III and stage IV, fluid therapy with polyionic solutions, given IV or SQ in the hospital or SQ by owners at home (10–50 ml/kg SQ every 1–3 days), is often beneficial in animals with intermittent signs of uremia, particularly cats. Oral vitamin D administration (i.e., calcitriol at 0.5–1.0 ng/kg orally) is another option that may help to reduce uremic signs. Placement of feeding tubes (e.g., nasogastric or PEG tubes) can have an effective role in the management of the chronically inappetant animal in late stage IV. Renal replacement therapy (renal transplantation and/or dialytic therapy) should be discussed with owners in early stage IV with implementation considered in late stage IV.

In the azotemic, nonuremic stages (IRIS stages II–III), the principles are the same for management of complications, except that the animal can be evaluated by a veterinarian less frequently, generally every 3–6 months. These patient evaluations should include hematology, biochemical panel, and urinalysis. If identified, complications should be aggressively treated as appropriate. Since dogs and cats with CKD are prone to the development of bacterial urinary tract infections, urine culture should be performed twice annually.

Patient evaluation and symptomatic therapy are a lower priority in the earlier stages (I & II). However, the systemic hypertension seen in approximately 20% of animals with CKD may be observed at any IRIS stage, and this complication is not effectively controlled by feeding a low-salt diet. There is a minimal risk of target organ damage in the kidneys, eyes, brain, and cardiovascular system when systolic blood pressure (SBP) is 150 mmHg or less. The risk for organ injury from high blood pressure is generally considered to be mild for SBP in the range of 150–159 mmHg, moderate for SBP in the 160–179 mmHg range, and severe for SBP ≥ 180 mmHg. Because of the importance of maintaining renal perfusion in animals with CKD, the usual antihypertensive medications are vasodilatory agents. The most commonly employed agents are calcium channel blockers such as amlodipine besylate (0.1–0.25 mg/kg orally once daily) or angiotensin converting enzyme inhibitors (ACEI) such as enalapril (0.5 mg/kg every 12 hours in dogs and every 24 hours in cats). While these may be co-administered at the recommended dosages, a calcium channel blocker is usually recommended as initial therapy in cats (particularly when the systolic BP exceeds 180 mmHg) and an ACEI is often used as first agent therapy in dogs.

**Nutritional Therapy**

Nutrition plays a central role in the management of CKD. The response of each animal with CKD to the disease and to nutritional intervention will vary dramatically, and individualized therapy is required; the only constant nutritional characteristic of renal insufficiency is inappetence and loss of body weight. Successful interventional nutrition must take all of these principles into account. For animals with CKD, the ideal goals of nutritional management are to maximize the quality and longevity of life by ensuring adequate intake of energy, limiting the extent of the clinical manifestations of the disease, and slowing the rate of progression of renal disease. Throughout all IRIS stages, nonspecific supportive treatment is best managed medically at home. In addition to providing a continual supply of
fresh drinking water and encouraging (and documenting) adequate dietary intake, routine use of body condition scoring should be employed to assess adequacy of intake.

Animals in the late stage I should generally be fed standard, commercially available maintenance diets, unless they are proteinuric (see section on proteinuria below). In stages II–III, nutritional modifications serve as renoprotective therapy, assuming central importance here. As noted above, the kidney is susceptible to self-perpetuating injury, an inherent property of this organ, and the extent of this injury may be modified by adjustments in dietary intake of phosphorus (reduced) and n-3PUA (supplemented).

Nutritional modifications are symptomatic therapy in late stage III and stage IV, where clinical signs of uremia may be apparent. Most of the clinically observable abnormalities produced by the disruption of renal function are influenced by dietary intake of calories, phosphorus, sodium, potassium, protein, or acid load.

**Proteinuria**

Recent findings have suggested that renal protein leak is not only a marker of severity of renal disease but also potentially a cause of renal injury. We now recognize that proteinuria is associated with increased risk of developing end-stage CKD in dogs and cats and that there may be an increased risk of mortality even in nonazotemic animals. Further, studies have shown that therapies that reduce the magnitude of proteinuria are often renoprotective.

Proper management of proteinuria mandates following a three-step paradigm. First, a finding of proteinuria should lead the clinician to monitor the patient with confirmation by a specific test for proteinuria, such as a urine protein/creatinine ratio or assessment of albuminuria. When monitoring a proteinuric patient, it is important to determine if the proteinuria is transient or persistent (at least 2 tests at 2-week intervals). If persistent proteinuria is present in a patient with CKD, it is appropriate to advance to the second step of the paradigm (investigate) and determine the site of origin of the protein (pre-renal, renal, or post-renal) and determine if renal proteinuria is a sign of a complication (e.g., systemic hypertension) or evidence of a specific renal disease (e.g., glomerular nephritis) through careful patient evaluation. Proteinuria likely confers a poorer prognosis when the urine protein-to-creatinine ratio exceeds 0.5 in dogs or 0.4 in cats. If proteinuria of this magnitude is persistent and renal in origin in an animal with CKD, the clinician should consider proceeding to the third step of the paradigm (intervene) by employing antiproteinuric therapy (e.g., ACEI, low protein diet, and/or n-3 PUFA supplementation). In this case, the antiproteinuric therapy is renoprotective and is thus of higher priority in stages II, III, and early stage IV. Serial determinations of the level of proteinuria with a specific test for albuminuria or a urine protein-to-creatinine ratio should be used to evaluate the success of this approach.

**Summary**

The proper management of a dog or cat with CKD requires a clear understanding of the diagnostic and therapeutic priorities in the stage of disease at the time the patient is being managed. Early in the disease process (IRIS stage I), a careful evaluation of the kidney to identify the primary disease process and specific therapy to eliminate this disease is critical. In the middle stages (II and III), inherent progression and renoprotective therapy are paramount. In the final stage of CKD, IRIS stage IV, more frequent and thorough evaluations of the patient with institution of appropriate symptomatic therapy becomes the primary consideration of the veterinarian.

**Table 1: IRIS* Classification of canine chronic kidney disease (CKD)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Serum Creat (mg/dL)</td>
<td>Non-azotemic CKD</td>
<td>Mild renal azotemic</td>
<td>Moderate renal azotemia</td>
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<td>CATS</td>
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<td>1.6 to 2.8</td>
<td>2.9 to 5.0</td>
<td>&gt;5.0</td>
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<tr>
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<td>1.4 to 2.0</td>
<td>2.1 to 5.0</td>
<td>&gt;5.0</td>
</tr>
</tbody>
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*IRIS: International Renal Interest Society

References/Further Reading

