Chronic Kidney Disease in Cats  
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Chronic kidney disease (CKD) is the most common renal disease in the cat and can result from any condition that causes progressive and irreversible damage. The prevalence of CKD seems to be increasing over time and affects about one-third of all cats over 15 years of age.(1) However, most owners will not notice clinical signs of disease in the early stages.

Diagnosis and staging  
CKD is diagnosed based on finding renal azotemia, poorly concentrated urine (less than 1.035), and compatible historical and/or physical examination findings. Common clinical signs include:

- Weight loss  
- Muscle wasting  
- Poor hair coat  
- Poor appetite (may go unnoticed by owners)  
- Nausea  
- Constipation  
- Polyuria and polydipsia (may go unnoticed by owners)

Weight loss is an important predictor of disease in cats, even in the absence of other signs. In one study, cats that eventually died from CKD, cancer, or hyperthyroidism had weight loss as early as 2.5 years before death.(2) Another retrospective study compared 1,230 cats with CKD to age-matched healthy control cats.(3) The cats with CKD were found to have suffered 12% median weight loss in the six to 12 months before diagnosis compared with only 2% median weight loss in the control cats.

The American Assoc. of Feline Practitioners and the American Animal Hospital Assoc. recommend an annual preventive health care visit and minimum database (MDB) for mature cats (7-10 years).(4,5) A preventive health care visit is recommended every six months for senior/geriatric cats (11 years and older), with a MDB at least annually.

The utility of routine health screening was recently examined in 100 apparently healthy cats over 6 years of age.(6) All cats underwent blood pressure measurement, physical examination, blood and urine analysis, indirect fundoscopy and bilateral Schirmer tear tests. Physical examination and laboratory abnormalities were common in these apparently healthy cats. Abnormalities were especially common in cats over 10 years of age, including low body weight (11%), azotemia (29%), dilute urine specific gravity (15%), and mild-moderate proteinuria (27%).

Predictors of the development of azotemia in cats have been evaluated. One study prospectively followed 95 non-azotemic cats 9 years of age and older with evaluations every six months.(7) At one year, 30% were azotemic. Multivariable logistic regression analysis for predictors of progression showed that a urine protein:creatinine ratio (UPC) greater than 0.2 and/or serum creatinine greater than 1.6 mg/dL (141 µmol/L) at the start of the study correlated with a risk of developing azotemia. It’s important to remember that serum creatinine values in the upper end of the laboratory reference range likely represent some decrease in glomerular filtration rate (GFR). The authors concluded, “Monitoring UPC in conjunction with plasma creatinine concentration should therefore be advocated as part of geriatric screening programs for cats.”
Some cats with CKD will merit further investigation, based on age, examination findings, breed, etc. Concurrent conditions, such as hypertension and urinary tract infection, are common in CKD patients. At the time of diagnosis, and as part of ongoing monitoring, blood pressure assessment and urine culture should be performed. Although the most common “cause” of CKD is chronic tubulointerstitial nephritis, other causes include lymphoma, amyloidosis, pyelonephritis, glomerulonephritis, and polycystic kidney disease. (8) Additional diagnostics may include imaging (radiographs, ultrasound) and kidney biopsy.

Cats with CKD should be staged according to guidelines established by the International Renal Interest Society (IRIS; www.iris-kidney.com). The purpose of staging is to determine the most appropriate treatments, answer the owner’s questions about prognosis, and ensure consistency in terminology in medical records. Only patients with stable disease are staged. The primary measure is serum creatinine in a well hydrated patient, ideally measured twice over a one to two week period. Secondary staging is based on blood pressure assessment and UPC. Some patients with mild renal azotemia (early IRIS stage 2) will have serum creatinine values within the laboratory reference range. Proteinuria and hypertension should be assessed and managed according to the American College of Veterinary Internal Medicine consensus statements (9,10).

**Treatment**

The goals of therapy are to:

- Minimize clinical signs of uremia
- Minimize disturbances of electrolytes, vitamins, minerals
- Provide adequate nutrition
- Modify disease progression

Three main studies have evaluated the role of nutrition in cats with CKD and documented beneficial effects of therapeutic diets (11–13). Diets for management of CKD have modifications other than protein restriction:

- Restricted phosphorus
- Moderate sodium
- N-3 fatty acid supplementation (known to decrease CKD progression in dogs; no data in cats)
- Potassium supplementation
- B vitamin supplementation
- Alkalining to counteract a tendency to systemic acidosis
- Higher in fat and energy

One of the most important issues is when to start a patient on a therapeutic renal diet. It makes sense to consider instituting a renal diet in mid- to late IRIS stage 2 while the patient is still eating reasonably well, has mild clinical signs, and may accept a diet change. (14) Available therapeutic diets have differing protein levels and caloric densities so the diet choice can be customized for each patient, rather than recommending one renal diet for all patients. It is possible to control important dietary factors without using a renal diet when needed (e.g., phosphorus can be restricted with phosphate binders, potassium and vitamin B can be supplemented).

Appetite stimulants are appropriate for some patients, especially those that are still eating but may not be eating enough to satisfy daily caloric requirements. Appetite stimulation is never a primary effect of the drug; these drugs are intended for the treatment of depression, allergies, etc. The effects are often short-lived and may not restore adequate food intake. It is therefore important to teach owners how to determine the actual amount of food their cat has eaten. The most commonly recommended appetite stimulant for cats with CKD is mirtazapine. In one placebo-controlled crossover clinical trial of 11 cats with stable CKD, a dose of 1.88 mg/cat, PO, every second day, increased appetite, decreased vomiting, and enabled weight gain. (15)
Control of serum phosphorus is particularly important; it is retained as GFR decreases and is a major cause of CKD progression in all species. Hyperphosphatemia occurs in about 60% of CKD patients with increasing prevalence as the disease advances. Maintaining phosphorus concentrations to within the IRIS targets for CKD patients improves survival time and reduces clinical manifestations of hyperphosphatemia and secondary renal hyperparathyroidism.(16) Several intestinal phosphate binders are available, such as those based on aluminum or calcium and those containing chitosan, sevelamer, and lanthanum.

Available evidence suggests that identification and control of proteinuria is also key for CKD patients. Current recommendations typically suggest intervention when proteinuria is persistent and the UPC is greater than 0.4. However, one study showed that cats with borderline UPC (values between 0.2 and 0.4) had a hazard ratio of 2.9 compared with non-proteinuric cats (i.e., 2.9 times the risk of death).(14) This would suggest that intervening earlier may be of some benefit given that control of proteinuria is the only factor known to actually mitigate CKD progression. Two drugs are licensed to treat proteinuria associated with CKD in cats, benazepril (Fortekor, Novartis) and telmisartan (Semintra, Boehringer Ingelheim). Semintra is the first of an interesting and novel class of drugs in veterinary medicine, angiotension II receptor blockers.

Secondary renal hyperparathyroidism (SRHP) can develop early in the course of CKD and is present in up to 84% of cats with CKD, even when serum phosphorus and calcium are within normal limits.(17) The causes are complicated and include hyperphosphatemia due to decreased GFR, a compensatory increase in parathyroid hormone (PTH) synthesis, reduced calcitriol synthesis, and impaired intestinal calcium absorption. SRHP is diagnosed by finding elevated serum PTH and ionized calcium and is associated with several adverse effects, such as renal osteodystrophy (uncommon in cats, known to be painful in people), mental dullness, lethargy, weakness, anorexia, impaired immune function, and nephrocalcinosis.

Calcitriol therapy has been suggested to improve appetite and activity levels and to improve survival in cats with SRHP. Frequent monitoring of ionized calcium and PTH levels are required; serum phosphorus must be maintained at less than 5.9 mg/dL (1.9 mmol/L). In humans and dogs, studies have shown calcitriol reduces mortality by slowing disease progression. In cats with IRIS stages 2 to 4 CKD, calcitriol reduced PTH levels, but did not alter mortality, increase appetite or activity, or improve quality of life (18). Current evidence fails to support a recommendation either for or against calcitriol therapy in cats.

Hypokalemia is most common in IRIS stages 2 and 3. By IRIS stage 4, a marked decrease in GFR may cause potassium retention. Supplementation is with potassium gluconate (2-4 mEq/cat/day, PO) or potassium chloride (30-40 mEq/L with IV or SC fluid therapy).

Some CKD patients will develop normocytic, normochromic anemia due to inadequate production of erythropoietin and other factors such as chronic gastrointestinal blood loss and iron deficiency. Treatment is recommended when the PCV is less than 20%. Darbopoietin (Aranesp) has a long half-life and is suggested to decrease the risk of antibody formation that is known to occur in some patients with the use of erythropoietin.

**Ongoing patient assessment**

How often should CKD patients be reassessed? A good guideline is the following:

- IRIS Stage 1: every 6-12 months
- IRIS Stage 2: every 3-6 months
- IRIS Stage 3: 2-4 months
- IRIS Stage 4: as the patient needs

At each assessment, the following should be monitored:
- Weight, body condition score, muscle condition score
- Appetite, including determination of actual daily caloric intake
- Owner compliance with treatment plans
- Owner concerns
- Serum chemistry panel, complete blood count, complete urinalysis, UPC

The reassessment plan should be individualized to the patient and the owner as the disease is progressive and dynamic. Periodic reassessments help to modify the treatment plan as needed.

**Prognosis**

The rate of progression of CKD varies according to the nature of the damage and with the individual cat. Cats in IRIS stages 2 and 3 may have stable renal function for sustained periods until decompensation occurs.(1) Several studies have looked at prognostic factors.(14,19–21) Consistent predictors of disease progression include:

- Increased serum creatinine
- Increased serum BUN
- Increased leukocyte count
- Decreased PCV
- Increased serum phosphorus: consistent predictor across most studies
- Increased UPC: consistent predictor across most studies

One study followed 213 cats with CKD for at least one year.(20) Within one year, 47% of cats experienced disease progression. Increased serum phosphorus and increased UPC predicted progression in all cats. In another study of 211 cats with serum creatinine greater than 2.3 mg/dL, median survival by IRIS stage and by certain landmarks was calculated (22):

<table>
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<tr>
<th>Stage</th>
<th># cats</th>
<th>Median survival (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (Late) Crea &gt;2.3 mg/dL</td>
<td>82</td>
<td>1,151</td>
</tr>
<tr>
<td>3</td>
<td>84</td>
<td>679</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>35</td>
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</table>

<table>
<thead>
<tr>
<th>Criteria</th>
<th># cats</th>
<th>Median survival (days)</th>
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<tbody>
<tr>
<td>Diagnosis</td>
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<td>771</td>
</tr>
<tr>
<td>Weight loss onset</td>
<td>142</td>
<td>401</td>
</tr>
<tr>
<td>Start of SC fluids</td>
<td>142</td>
<td>273</td>
</tr>
<tr>
<td>Crea &gt;4.0 mg/dL</td>
<td>145</td>
<td>123</td>
</tr>
<tr>
<td>PCV &lt;25%</td>
<td>121</td>
<td>100</td>
</tr>
</tbody>
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**Summary**

For each CKD patient, establish the IRIS stage and develop an individual treatment plan, taking into account what is most appropriate for each patient and owner. Prioritize the options based on the cat’s medical needs and the owner’s preferences and abilities. Review the plan with the owner and confirm commitment. Establish a reassessment and monitoring schedule to assess the patient’s response, make any necessary changes to the treatment plan, ensure the owner understands the treatments, and uncover compliance issues.
References