CKD is clinically characterized by the development of variably progressive irreversible intrarenal lesions and loss of renal functions. A variety of interventions (diet and drugs) can slow the progression of the renal disease, improve the quality of life for the patient, and/or extend the quantity of life. Compensatory increases (so-called adaptations) in glomerular hemodynamics and glomerular volume may actually be maladaptive in the long term as they cause increased protein trafficking across the glomerulus. The incidence of the diagnosis of CKD in cats is made 2 to 3 times as frequently compared to dogs and is especially common in geriatric cats. The prevalence of CKD in random source cats (50%) and cats with degenerative joint disease (68.8%) was higher than expected in one study.

Tubulo-interstitial nephritis of unknown origin is the most common cause of azotemic CKD in the cat, as in the dog. Glomerulonephritis as the cause for CKD is much more common in dogs than in cats. However, cats have several renal diseases that deserve additional consideration as compared to dogs, including breed related predilection for renal amyloidosis (Abyssinian, Oriental Short Hair) and polycystic kidney disease (Persian, Himalayan). Cats have greater frequency of CKD associated with renal LSA than dogs. Perinephric pseudocyst can be associated with CKD in cats and should be considered as a differential diagnosis for apparent renal enlargement in addition to renal LSA and hydronephrosis.

**Diagnosis of CKD**

The initial diagnosis of CKD is made on some combination of findings from clinical signs, physical examination (especially large or small kidneys, irregular kidneys, hard kidneys), renal imaging, urinalysis, and serum biochemistry. A surprising number of cats with CKD have upper urinary tract uroliths at the time of initial diagnosis. Abdominal radiographs should be routinely obtained to determine the presence or absence of radiopaque stones in cats. Renal and ureteral ultrasonography should be performed in all cats in which renal or ureteral stones were found on radiography in order to tell whether or not there is an obstructive component to the CKD. T4 should be measured in all cats with suspected CKD since hyperthyroidism can mask the detection of azotemia by its effects that increase GFR and RBF; hypothyroidism may also contribute to progression of CKD through a variety of mechanisms including intraglomerular and systemic hypertension.

Conventional wisdom and experience suggest that client-owned cats with healthy kidneys elaborate urine with a specific gravity of >1.035. This concept was recently validated in a study of cats evaluated at first opinion clinics. Cats with USG < 1.035 should undergo further diagnostic investigation to determine if they have an endocrine or renal disorder with or without associated clinical signs. A surprising number of experimental and clinical cats with CKD continue to be able to elaborate urine with a USG > 1.035, so the presence of “concentrated” urine and mild to moderate azotemia does NOT exclude the presence of primary kidney disease in cats as it often does in dogs. It is important to evaluate urine from dogs that has been collected first thing in the morning before they have eaten the morning meal. Dogs consume variable amounts of water after this meal that can cause widely varying USG; this phenomenon does not happen in cats. The median USG was 1.042 in one study of first morning urine from dogs and nearly all dogs had USG > 1.030 (Chew, unpublished). When the first morning USG is < 1.030 from a dog, further investigation into possible renal and endocrine diseases may be warranted. Detection of proteinuria can be useful in diagnosis of CKD when the protein originates from the kidneys. The hallmark of renal proteinuria is detection of a significant amount of protein in the absence of an active inflammatory urinary sediment. Glomerular proteinuria is mostly characterized by albuminuria. Proteinuria and albuminuria are greater during CKD in dogs than in cats. In one study of cats, the single best test for the detection of albuminuria was a UPC ≥ 0.2. A negative dipstick reaction for protein predicted the absence of albuminuria, but a positive dipstick reaction did not always predict albuminuria in the same study.

Cats that have thin body condition, prior periodontal disease or cystitis, anesthesia or documented dehydration in the preceding year, or being a neutered male (vs. spayed female) were reported to be at increased risk for the diagnosis of CKD. The incidence of azotemic CKD was compared between dogs with and without periodontal disease in an epidemiological study. The hazard ratio for detection of azotemic CKD increased with the increasing severity of
periodontal disease. Increasing severity of periodontal disease was also associated with future development of a serum creatinine > 1.4 mg/dl and blood urea nitrogen > 36 mg/dl whether or not the veterinarian diagnosed CKD.\textsuperscript{14}

**Staging of CKD**
A staging system based on the level of serum creatinine concentration has been developed by IRIS (International Renal Interest Society) for use in dogs and cats that are hydrated and stable. A stable creatinine is defined by documentation of < 20 percent variability in serum creatinine when measured again on at least 2 occasions 2 weeks apart\textsuperscript{17} by the same lab. Substaging is then based on the degree of proteinuria as measured by UPC and also the magnitude of blood pressure. Staging using this system is designed to detect CKD much earlier than with traditional methods and also to potentially match treatments by stage. Normal and stage 1 CKD cats have serum creatinine concentrations < 1.6 mg/dl (< 140 \mu mol/L). Normal and stage 1 CKD dogs have serum creatinine concentrations < 1.4 mg/dL (< 125 \mu mol/L). Normal cats and dogs usually have a UPC < 0.2, with 0.2–0.4 for cats and 0.2–0.5 for dogs considered to be borderline increased. Overt proteinuria exists when the UPC is > 0.4 for the cat and > 0.5 for the dog. Details of this staging system can be found online at [http://www.iris-kidney.com](http://www.iris-kidney.com). This staging system does not indicate the underlying cause for the CKD, which requires other diagnostic workup to determine. It is important to remember that nearly all studies on the effect of diet or drugs have studied overtly azotemic cats and dogs (serum creatinine > 2.0 mg/dl). It has not been determined whether or not the salutary effects of treatment in azotemic cats and dogs confer the same benefits to CKD when treated at earlier stages.

**Table 1 Serum Creatinine Concentrations for Assignment of IRIS Stage of CKD in Dogs and Cats**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine Concentration (mg/dl)</th>
<th>Serum Creatinine Concentration (\mu mol/L)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 1.4 (dog) &lt; 1.6 (cat)</td>
<td>&lt; 125 (dog) &lt; 140 (cat)</td>
<td>Non-azotemic. Often discovered fortuitously during routine examination. May have evidence of decreased urinary concentrating ability or proteinuria. Usually no obvious clinical signs. May be polyuric. Cylindruria possible, abnormal renal imaging or palpation.</td>
</tr>
<tr>
<td>2</td>
<td>1.4–2.0 (dog) 1.6–2.8 (cat)</td>
<td>125–179 (dog) 140–249 (cat)</td>
<td>Mildly azotemic. Decreased urinary concentrating capacity. May have proteinuria. Clinical signs minimal. May have polyuria and polydipsia.</td>
</tr>
<tr>
<td>3</td>
<td>2.1–5.0 (dog) 2.9–5.0 (cat)</td>
<td>180–439 (dog) 250–439 (cat)</td>
<td>Moderate azotemia. Decreased urinary concentrating capacity. May have proteinuria. Many systemic clinical signs may be present.</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 5.0 (dog) &gt; 5.0 (cat)</td>
<td>&gt; 440 (dog) &gt; 440 (cat)</td>
<td>Severe azotemia. Decreased urinary concentrating capacity, proteinuria. Systemic clinical signs present and may be severe.</td>
</tr>
</tbody>
</table>

Serum creatinine is the most commonly used surrogate for GFR in the clinics, as it is not technically feasible or practical to measure GFR directly given the present technology. Serum creatinine is generally preferred over BUN for evaluation of renal function since creatinine has fewer non-renal variables. Symmetric dimethylarginine (SDMA) is a surrogate for the evaluation of GFR\textsuperscript{16} in the dog and the cat that has some advantages over measurement of serum creatinine. SDMA results from methylation of arginine that occurs in all nucleated cells. SDMA is excreted exclusively into urine and consequently increases its concentration in blood when GFR decreases. SDMA is not influenced by lean muscle mass whereas serum creatinine is related to lean muscle mass. Since creatinine arises from muscle, animals with decreased muscle mass will have lower serum creatinine concentrations than would otherwise develop. During progression of CKD, loss of lean muscle mass can parallel loss of renal function which results in little change in serum creatinine concentration. This phenomenon reduces the ability for serum creatinine to detect ongoing CKD progression early. SDMA increases before serum creatinine in some studies of CKD in the dog and the cat.\textsuperscript{17,18} SDMA is not currently an official part of the IRIS staging system for CKD. The finding of a serum creatinine concentration within the reference range and SDMA that is increased should trigger further evaluation of the patient to verify or exclude the presence of primary renal disease. It makes
sense to place patients with a normal serum creatinine and increased SDMA as part of the criteria for IRIS stage 1. IDEXX® launched SDMA as part of a routine veterinary biochemical panel in the USA July 2015 so there will be much more clinical experience with its measurement and interpretation from patients evaluated by primary care veterinarians soon. It is important to remember that the finding of normal serum creatinine and SDMA concentrations does NOT exclude the presence of primary renal disease.

**Dietary Interventions for CKD**

Dietary therapy remains the cornerstone of management of CKD. Diet modifications include phosphorus restriction (most important), providing reduced quantity but high quality protein, adequate non-protein calories from fat and CHOs, modifying sodium content (not the degree of restriction once recommended by some), supplementing potassium, B vitamins, alkali as needed and providing omega three fatty acids. In one 2-year study, cats with a serum creatinine > 2 mg/dl fed a renal diet had a median survival time that was 2.4 times longer than cats fed a maintenance diet (633 days vs. 264 days). 19 In another study, IRIS stage 2 and 3 cats were followed for 24 months. Cats fed the maintenance diet had more uremic episodes and more renal-related deaths compared with cats fed the renal diet.6 In a study of 175 CKD cats fed 1 of 7 different renal diets, the median survival time was 16 months (12 to 23 months) compared to a median survival time of 7 months for cats eating their maintenance diet. Interestingly, the longest survival period was found in cats eating a renal diet with the highest eicosapentanoic acid (diet not available in North America), otherwise the renal diets were similar in composition.20 CKD dogs that were fed a renal diet had slower progression of their renal disease based on serum creatinine and lived longer compared to dogs fed a maintenance diet.21 Patients are more likely to accept a new renal diet if offered before uremia develops and a gradual transition may be needed.

There is no evidence that dietary protein restriction itself provides renoprotection in CKD patients. The number one reason to restrict dietary protein is to provide restricted intake of phosphorus, especially animal tissues in the diet. Decreased production of nitrogenous wastes can occur in those with large increases in BUN, and consequently improve the clinical well-being of the pet even though renal function remains unchanged. If proteinuria is present, dietary protein restriction may lower the magnitude of proteinuria through obscure mechanisms. Reduced dietary protein intake may also lessen inflammatory, fibrogenic and oxidative stress pathway.22 The amount to restrict dietary protein is not definitively known, so it is currently recommended to provide at least maintenance levels. Excessive protein should be avoided but dietary protein should not be restricted below the Association of American Feed Control Officials (AAFCO) minimum recommendations for adult maintenance (5.1 grams protein per 100 kcal for dog; 6.5 grams protein per 100 kcal for cat) until late stages of disease to avoid protein-energy malnutrition and loss of lean body mass. For cats with CKD, the minimum dietary protein requirement suggested is 20 percent of calories, which equates to 24 percent protein on a dry-matter basis.22-25 Others suggest 28–35 percent (DMB) for cats.26 It is emphasized that less total dietary protein can be fed if high biologic value proteins, such as egg, are fed.24 Too much dietary protein restriction can and often does result in protein:calorie malnutrition. Protein malnutrition from any cause is strongly correlated with morbidity and mortality. If protein malnutrition becomes evident in a patient (hypoaalbuminemia, anemia, weight loss, or loss of lean muscle mass), then the amount of protein should be increased until signs are no longer evident. Patients with sarcopenia, regardless of the stage of renal disease, may require more protein than a renal diet can provide. Careful monitoring and adjustment of protein intake will be needed in these patients. Feeding a diet with protein concentration > 5.1 grams per 100 kcal was shown to help positively impact body condition in dogs with CKD.27 It has also been shown that dogs with CKD with a BCS of ≥ 4/9 have longer survival than dogs with a thinner BCS.28

Lowering animal-derived protein (source of phosphates) in the diet may be essential to lower dietary phosphorus intake needed to achieve target levels of serum phosphorus.29 Dietary phosphorus restriction is critical at least from IRIS Stage 2 onwards; there are no data to evaluate any potential benefit of Pi restriction in Stage 1. Compared to the average grocery or pet store foods, the renal friendly veterinary diets are restricted in phosphorus by 70 to 80 percent. Serum phosphorus concentration may increase in CKD pets that increase their food intake following other supportive CKD treatments. Renal diets may provide sufficient dietary phosphate restriction during early stages of CKD but often the addition of dietary phosphate binders will be needed to reach targeted control of serum phosphorus, as is detailed in the next session. Early phosphorus restriction in azotemic CKD has been shown to blunt or reverse renal secondary hyperparathyroidism in dogs and cats.30
Increasing Appetite and Decreasing Nausea/Vomiting in CKD

Pets with CKD often suffer from poor appetite that can contribute to poor body condition. This is often associated with decreased prognosis as the owners often euthanize when quality of life is perceived as unacceptable. Mirtazapine (Remeron®) may stimulate appetite and decrease uremic-associated nausea. Recent work in cats indicates mirtazapine can be administered at a low dose (1.88 mg) every 48 hours to cats with CKD, but was only studied for its effects for 3 weeks.\textsuperscript{31,32} Mirtazapine and cyproheptadine should not be administered concurrently. Cyproheptadine is used as an antidote for serotonin effects of mirtazapine overdose. NK-1 receptors are located in the chemoreceptor trigger zone (emetic center) as well as in peripheral locations and are associated with vomiting and nausea. Maropitant (Cerenia®) is an NK-1 receptor antagonist that can ameliorate vomiting/nausea in azotemic CKD patients. The original label indication for administration to dogs for acute vomiting has been extended beyond five days to treat or prevent vomiting giving tablets at 2 mg/kg/day. The label for cats is only for injectable Cerenia®. For cats, off label dosing has been given at 1 mg/kg PO once daily with apparent safety and good effect. Oral maropitant at 4 mg total daily dose per cat reduced vomiting in cats with IRIS stage 2 and 3 CKD of one report.\textsuperscript{33} Refrigeration is recommended to help alleviate the sting associated with injectable Cerenia®.\textsuperscript{34} Studies in cats have also shown omeprazole (Losec®) to be more effective than H2 blockers such as famotidine and ranitidine in decreasing gastric acidity.\textsuperscript{35} Omeprazole dose is 0.5–1 mg/kg once a day. If H2 blockers are used, dosages recommended are famotidine (Pepcid®) 0.5 mg/kg IM, SQ, PO q 12 hours or ranitidine (Zantac®) 1–2 mg/kg q 12 hours (cat). Studies have shown most cats with uremia do have elevated gastrin levels (and likely corresponding hyperacidity) but no GI ulcers.\textsuperscript{35,36} Sucralfate is not usually indicated due to lack of GI ulcers in most CKD patients. The GI bleed with uremia could be from dysregulation of the vasculature and platelet dysfunction associated with uremia.\textsuperscript{35,36} If used, a dose of 0.25–0.5 g/cat q 12 hours is recommended. In some countries sucralfate is used as an intestinal phosphate binder due to its aluminum content. Ondansetron is not highly recommended as its bioavailability is not high (maybe 30% at best in cats) and the half-life is very short (it would be best to give this drug 4 times/day).\textsuperscript{37}


