Introduction
Chronic kidney disease (CKD) is a common disease in dogs and cats. The prevalence of CKD in cats increases with increasing age with up to 30% of cats over the age of 15 years being affected. The prevalence for CKD in dogs varies widely depending on age and population studied with prevalence reported as low as 0.37% in U.K. practices, 5.8% in four U.S. veterinary teaching hospitals and 10% in geriatric dogs. Although CKD is a progressive disease, early diagnosis and management may modify the rate of progression and improve patient quality and quantity of life.

Etiology
The cause of CKD is difficult to determine when diagnosed in later stages of disease. Damage can occur to any part of the nephron, including the glomerulus, tubule, interstitial tissue or vasculature, which can result in irreversible damage and loss of function of the nephron. The more common causes of CKD in dogs and cats include incomplete recovery from an acute renal injury (toxic, infectious, other), pyelonephritis, glomerulonephritis (more common in dogs), nephrolithiasis and ureterolithiasis (more common in cats), tubulointerstitial disease, feline infectious peritonitis in cats, Lyme disease in dogs, amyloidosis, neoplasia, hypercalcemia, various hereditary nephropathies, polycystic kidney disease (PKD) in cats and Fanconi syndrome. Diagnostics that facilitate early recognition of kidney disease should allow for earlier investigation and identification of an underlying cause; this could lead to more specific therapy and an opportunity to reverse or slow progression of kidney disease in some cases.

Clinical presentation
In dogs polyuria (PU) and polydipsia (PD) may be the first indication of CKD. Cats maintain their urine concentrating ability further into the disease process than dogs; therefore, PU/PD is often not recognized in early stages of CKD in cats. As urine concentrating ability is lost later as the disease progresses, cat owners are more likely to recognize PD than PU. In addition, dogs and cats in IRIS stages 3 and 4 often present with nonspecific signs, including poor body condition, weight loss, decreased appetite, lethargy and dehydration. Intermittent vomiting secondary to uremic gastric ulceration may occur.

Physical examination findings in CKD patients will vary depending on the stage of disease. Early in the disease (IRIS stages 1 and 2), physical examination may be within normal limits. Palpable renal abnormalities may be detected especially in cats (e.g., small, firm and irregular kidney[s], one big kidney and one little kidney, enlarged kidneys [PKD]). As CKD progresses to IRIS stages 3 and 4, clinical signs will become more apparent and reflect the chronic nature of the disease. General physical examination findings include poor body condition, unkempt hair coat, dehydration and palpable kidney abnormalities. Oral examination may reveal pale mucous membranes, ulcers and/or uremic breath. Secondary systemic hypertension may cause retinal hemorrhages, arterial tortuosity or detached retinas presenting as acute blindness.

Laboratory results
A diagnosis of CKD is typically straightforward once the disease is in its later stages and there is clinical suspicion based on history and physical examination findings, azotemia evident on biochemical profile and loss of urine concentrating ability (<1.030 in dogs and <1.035 in cats). However, recognition of CKD can be challenging early in the course of disease since clinical signs may be absent, mild or attributed to another concurrent condition. Additionally, azotemia does not typically develop until approximately 75% loss of nephron function, and in cats especially, PU/PD may not be evident or noticed by owner.

Serum creatinine and blood urea nitrogen (BUN) are routinely used biochemical tests to help diagnose kidney disease. BUN can be influenced by several extrarenal factors, including dehydration, protein content of the diet, gastrointestinal bleeding and liver insufficiency. Creatinine is a breakdown product of muscle and is a better indicator of glomerular filtration rate (GFR) than BUN, but it can be influenced by a reduction in muscle mass, which is not uncommon especially in older animals with CKD. When nonrenal variables have been eliminated, an increase in creatinine above the reference interval indicates that at least 75% of nephrons are not functioning. Performing creatinine measurements routinely during wellness visits can establish a normal baseline for an individual animal. An upward trend in creatinine while it is still within the reference interval can be helpful to identify CKD earlier prior to creatinine increasing above the reference interval.

Other common abnormal findings on the CBC and chemistry panel include a nonregenerative anemia, hyperphosphatemia, hypercalcemia or hypocalcemia, hypokalemia (in cats) and metabolic acidosis. Common findings on a urinalysis include inappropriate urine specific gravity, casts, evidence of a urinary tract infection and proteinuria. A urine protein:creatinine ratio (UPC) is recommended to determine the degree of proteinuria. This will guide whether investigation for a disease process leading to proteinuria should be undertaken, when intervention is required or if only monitoring is recommended, depending also on the stage of kidney disease. Animals with glomerular disease not only have significant proteinuria but may have hypoalbuminemia and increased cholesterol.

Introducing a new kidney biomarker: SDMA
Symmetric dimethylarginine (SDMA) is a revolutionary new kidney function test. IDEXX Reference Laboratories will begin adding SDMA to routine chemistry panels during summer 2015, creating a new standard for chemistry panels. SDMA will be run alongside creatinine to help you diagnose kidney disease earlier and with more confidence. SDMA is a methylated form of the amino acid arginine, which is released into the circulation during protein
degradation and is excreted almost exclusively by the kidneys. The three key attributes of SDMA are the following: it is a biomarker for kidney function, it increases earlier than creatinine in dogs and cats with CKD, and it is specific for kidney function.

**SDMA is a biomarker for kidney function**

Performing a GFR clearance test is the gold standard for estimating GFR and assessing kidney function, but it is cumbersome to perform and rarely done in practice. A meta-analysis of 18 studies involving human patients showed that SDMA concentrations correlated highly with GFR by inulin clearance ($r = -0.85$). The first evidence for using SDMA to assess renal disease in dogs was published in 2007 which showed a strong correlation of SDMA with GFR by inulin clearance ($r = -0.851$). A more recent study performed with 24 female dogs that were carriers of X-linked hereditary nephropathy confirmed this strong correlation of SDMA and GFR measured by iohexol clearance ($R^2$ of 0.85 in dogs, as observed by Mary Nabity, DVM, PhD, DAVCP Texas A&M University), and an even higher correlation was found in a study with affected male adolescent dogs ($r = -0.95$). SDMA has also been shown to strongly correlate with GFR ($R^2$ of 0.82) in cats. Not surprisingly, SDMA was shown to strongly correlate with creatinine in all of these studies as well. Therefore, SDMA should be considered complementary to creatinine, and SDMA and creatinine should be evaluated together when evaluating kidney function in dogs and cats.

**SDMA increases earlier than creatinine**

It is generally accepted that creatinine does not increase until 75% of renal function is lost, and measuring GFR is done infrequently in the private practice setting. Clearly, there is a need for a more sensitive test of renal function.

A recently published study in 21 cats with CKD found that SDMA increased on average 17 months earlier than creatinine and on average when there was a 40% reduction in GFR. In this study, serum SDMA had a sensitivity of 100%, specificity of 91%, positive predictive value (PPV) of 86% and negative predictive value (NPV) of 100% when using a 30% decrease from median GFR as the gold standard for confirmed decrease in renal function. Whereas, in this same study, serum creatinine had a sensitivity of only 17%, specificity of 100%, PPV of 100% and NPV of only 70%. For SDMA, the specificity and PPV were impacted by what were considered as 2 “false” positives. In both of these cases, SDMA was increased above the reference interval, but GFR was only decreased by 25% below the median; this might actually represent that SDMA was able to detect CKD even earlier in these cats. A similar study in 24 dogs with CKD found that SDMA increased on average 9.5 months earlier than creatinine.

**SDMA is specific for kidney function**

SDMA, like creatinine in most cases, is specific to kidney function. SDMA is not increased in animals with various diseases including liver disease, Cushing’s disease and heart disease unless there is concurrent kidney disease. Unlike creatinine, SDMA is not impacted by lean muscle mass. Loss of total lean body mass associated with aging and chronic disease can lower creatinine concentrations resulting in a poor estimation of renal function. A study in older cats, confirmed that as cats aged, they lost muscle mass and creatinine decreased even as the GFR decreased. SDMA increased as kidney function declined with no correlation to lean body mass ($P > 0.05$). A similar study performed in dogs revealed that lean body mass and creatinine were positively correlated ($r = 0.55; P < 0.001$) whereas there was no correlation between SDMA and total lean body mass ($P > 0.05$).

**Staging CKD**

Historically, CKD has been classified as mild, moderate or severe, based on laboratory findings and clinical signs. A more objective classification system has been developed by the International Renal Interest Society (IRIS). CKD has to be first diagnosed, and then IRIS staging can be applied. IRIS recommends fasting plasma creatinine, assessed on at least two occasions in the stable patient before staging (table 1). The patient is then substaged based on proteinuria and blood pressure (tables 2 and 3).

One challenge in identifying animals with IRIS stage 1 and early IRIS stage 2 disease is that by definition, these animals are not yet azotemic. Some other evidence of a renal abnormality needs to be detected, such as inappropriate urine concentration ability without identifiable nonrenal cause, abnormal renal palpation and/or abnormal renal imaging findings, proteinuria of renal origin, abnormal renal cytology or biopsy. SDMA should help identify some animals with IRIS stage 1 or early IRIS stage 2 kidney disease, the dog’s urine and entering urine-contaminated areas.

**Table 1. IRIS staging system for CKD in dogs and cats**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Renal Azotemia</th>
<th>Serum creatinine concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nonazotemic</td>
<td>$&lt;1.4$ mg/dL, $&lt;125 \mu$mol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$&lt;1.6$ mg/dL, $&lt;140 \mu$mol/L</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>$1.4–2.0$ mg/dL, $125–179 \mu$mol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$1.6–2.8$ mg/dL, $140–249 \mu$mol/L</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>$2.1–5.0$ mg/dL, $180–439 \mu$mol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2.9–5.0$ mg/dL, $250–439 \mu$mol/L</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>$&gt;5.0$ mg/dL, $&gt;440 \mu$mol/L</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Substage</th>
<th>Urine Protein:Creatinine Ratio (UPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dogs</td>
</tr>
<tr>
<td></td>
<td>Cats</td>
</tr>
<tr>
<td>Nonproteinuric (NP)</td>
<td>$&lt;0.2$</td>
</tr>
<tr>
<td>Borderline proteinuric (BP)</td>
<td>$0.2–0.5$</td>
</tr>
<tr>
<td>Proteinuric (P)</td>
<td>$&gt;0.5$</td>
</tr>
</tbody>
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**Table 3. IRIS substaging by blood pressure in dogs and cats with CKD**

<table>
<thead>
<tr>
<th>Substage</th>
<th>Systolic BP in mm Hg</th>
<th>Diastolic BP in mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk (N)</td>
<td>$&lt;150$</td>
<td>$&lt;95$</td>
</tr>
<tr>
<td>Low risk (L)</td>
<td>$150–159$</td>
<td>$95–99$</td>
</tr>
<tr>
<td>Moderate risk (M)</td>
<td>$160–179$</td>
<td>$100–119$</td>
</tr>
<tr>
<td>High risk (H)</td>
<td>$\geq 180$</td>
<td>$\geq 120$</td>
</tr>
</tbody>
</table>

*Risk is defined as the likelihood that high blood pressure will further damage the kidney and other end organs.
Implications of early diagnosis of CKD

Historically, treatment for CKD has been initiated fairly late in the disease process because of the difficulty in diagnosing this disease early. Because SDMA will help clinicians diagnose CKD earlier when dogs and cats are likely to still be in IRIS stage 1 or early IRIS stage 2, early intervention strategies are needed. Early identification of CKD should prompt investigation for an underlying cause, giving the potential for specific treatment. It will allow substaging of the CKD so that proteinuria and hypertension can be detected and managed earlier in the disease process. Early management of CKD may slow progression of the disease. Closer monitoring will help identify progression and when additional therapies should be initiated.

Monitoring CKD

Monitoring a dog or cat with CKD needs to be individualized. The frequency of recheck visits will depend on the clinical status of the patient, whether an underlying disease was identified and what treatments have been initiated. The rate of progression of the kidney disease will depend on the severity of the disease, presence of concurrent diseases, treatments given and response to therapy. An initial recheck 2 weeks after kidney disease is first suspected or identified would be reasonable to determine if the disease is stable and to allow IRIS staging. After this initial recheck, in a stable animal with early CKD and no hypertension or proteinuria, a recheck in 2–3 months would be reasonable. However, an animal being treated for an underlying condition, such as pyelonephritis or Lyme disease, in later stages of CKD with moderate to severe azotemia or who is being treated for hypertension and/or proteinuria will need to be rechecked sooner (e.g., days to weeks). Adjustments to the therapeutic plan should be made as needed depending on the patient response and as the disease worsens. During each visit, a thorough history should be taken, noting in particular the patient’s appetite, drinking and urinating habits, activity level and overall attitudes. Body weight should be monitored closely. A CBC, chemistry panel with SDMA and electrolytes, urinalysis, UPC and blood pressure measurement should be performed at follow-up visits. This will allow trending over time to help determine response to treatment, assess rate of progression of disease, decide when additional therapies are indicated and to detect a sudden worsening of CKD.

References


The information contained herein is intended to provide general guidance only. As with any diagnosis or treatment, you should use clinical discretion with each patient based on a complete evaluation of the patient, including history, physical presentation and complete laboratory data. With respect to any drug therapy or monitoring program, you should refer to product inserts for a complete description of dosages, indications, interactions and cautions. Diagnosis and treatment decisions are the ultimate responsibility of the primary care veterinarian.