KIDNEY DISEASE: ADVANCES IN EARLY DIAGNOSIS AND MONITORING

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INTRODUCTION
Chronic kidney disease (CKD) is common, with 1 in 3 cats1 and 1 in 10 dogs2 developing some form of kidney disease over their lifetime. Recent studies suggest kidney disease is even more common and until now has been underrecognized.3,4 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), nephro lithiasis 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 up to 75% of kidney function has been lost. 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 began adding SDMA to all routine chemistry panels in North America during summer 2015 and will begin offering in Europe in early 2016. SDMA is run alongside creatinine to help 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 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
Glomerular filtration rate (GFR) is the gold standard for measuring kidney function, but it is cumbersome to perform routinely 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 which were carriers of sex-linked hereditary nephropathy confirmed this strong correlation of SDMA and GFR measured by iohexol clearance ($R^2$ of 0.85, as observed by Mary Nabity, DVM, PhD, DAVCP, Texas A&M University) and even a higher correlation was found in affected male adolescent dogs ($r=-0.95$). SDMA has also been shown to strongly correlate with GFR ($R^2$ of 0.82) in cats. Naturally SDMA was shown to have a direct correlation 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 up to 75% of renal function is lost, and measuring GFR is not done frequently in the private practice setting. Clearly, there has been 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, using a 30% decrease from median GFR as the gold standard for confirmed decrease in renal function, the sensitivity (17%), specificity (100%), positive predictive value (PPV; 100%), and negative predictive value (NPV; 70%) were calculated for serum creatinine. Using a 30% decrease from median GFR as the gold standard for confirmed decrease in renal function, sensitivity (100%), specificity (91%), PPV (86%), and NPV (100%) were calculated for serum SDMA concentration. There were 2 “false” positives, whereby SDMA was increased above the reference interval but GFR was only decreased by 25% below the median; this likely represents that SDMA was able to detect CKD even earlier in these 2 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 between total lean mass and SDMA ($P>0.05$). 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 less arbitrary classification system has been developed by the International Renal Interest Society (IRIS), a multinational board of 15 independent veterinarians with particular interest in veterinary nephrology. CKD has to be first diagnosed, and then IRIS staging can be applied. IRIS staging is based initially on fasting plasma creatinine, assessed on at least two occasions in the stable patient (Table 1). The patient is then substaged based on proteinuria and blood pressure (Tables 2 and 3). One challenge with the IRIS staging system has been the ability to detect dogs and cats in IRIS Stage 1 and cats in early IRIS Stage 2 because by definition, these animals are not yet azotemic. Some other evidence of a renal abnormality needs to be detected i.e. inadequate urine concentrating ability without identifiable non-renal cause; abnormal renal palpation and/or abnormal renal imaging findings; proteinuria of renal origin; abnormal renal biopsy.
SDMA has recently been recognized by IRIS as a valuable tool to help detect dogs and cats with IRIS CKD Stage 1 disease and to help correctly stage CKD in underweight patients. The following interpretive comments for the diagnostic and therapeutic utilization of SDMA were incorporated into the 2015 IRIS CKD Staging Guidelines, which are available in their entirety at www.iris-kidney.com.

SDMA concentrations in blood (plasma or serum) may be a more sensitive biomarker of renal function than blood creatinine concentrations. A persistent increase in SDMA above 14 µg/dl suggests reduced renal function and may be a reason to consider a dog or cat with creatinine values <1.4 or <1.6 mg/dl, respectively, as IRIS CKD Stage 1.

In IRIS CKD Stage 2 patients with low body condition scores, SDMA ≥25 µg/dl may indicate the degree of renal dysfunction has been underestimated. Consider treatment recommendations listed under IRIS CKD Stage 3 for this patient.

In IRIS CKD Stage 3 patients with low body condition scores, SDMA ≥45 µg/dl may indicate the degree of renal dysfunction has been underestimated. Consider treatment recommendations listed under IRIS CKD Stage 4 for this patient.

These additions to the guidelines are preliminary, based on early data derived from the use of SDMA in veterinary patients. The IRIS board fully expects them to be updated as the veterinary profession gains further experience using SDMA alongside the long-established marker, creatinine, in the diagnosis and therapeutic monitoring of canine and feline CKD.

### 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></td>
<td></td>
<td>Dogs</td>
</tr>
<tr>
<td>1</td>
<td>Nonazotemic</td>
<td>&lt;1.4 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;125 µmol/L</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>1.4-2.0 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125-179 µmol/L</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>2.1-5.0 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>180-439 µmol/L</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>&gt;5.0 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;440 µmol/L</td>
</tr>
</tbody>
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### Table 2: IRIS Substaging by Proteinuria in Dogs and Cats with CKD

<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>Non-proteinuric (NP)</td>
<td>&lt;2.0</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>
</table>

### 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>Normotension</td>
<td>&lt;150</td>
<td>&lt;95</td>
</tr>
<tr>
<td>Borderline hypertension</td>
<td>150-159</td>
<td>95-99</td>
</tr>
<tr>
<td>Hypertension</td>
<td>160-179</td>
<td>100-119</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>≥180</td>
<td>≥120</td>
</tr>
</tbody>
</table>

### 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. If SDMA is increased and creatinine is normal in a patient it is recommended to follow the “investigate, manage, and monitor” (IMM) protocol:
Investigate
Evaluate the history, physical examination, urinalysis or other findings that could suggest kidney disease:

- Is the dog or cat polyuric and/or polydipsic?
- Do the kidneys palpate small or irregular? Or is one kidney much bigger than the other?
- Is the pet geriatric, underweight or poorly muscled?
- Has a urinalysis been performed? (If not, this is the next step.) Is the urine appropriately concentrated? Is there proteinuria? Is there an active urine sediment?
- Are there any other findings on the CBC or chemistry panel that suggest kidney disease?
- Could the dog or cat have an early acute kidney injury? If so, is there a possibility of exposure to a renal toxin?

Consider additional diagnostics to investigate and stage kidney disease:

- Urine protein:creatinine ratio.
- Urine culture and sensitivity.
- Blood pressure measurement.
- Investigation for infectious diseases (e.g., Lyme disease, leptospirosis, ehrlichiosis).
- Diagnostic imaging for uroliths, structural changes, etc.

Manage

- Use with caution any potentially nephrotoxic drugs (NSAIDs, aminoglycosides, cisplatin, etc.)
- Consider kidney-supportive diet. Includes diets that are phosphorus and sodium restricted, high in polyunsaturated fatty acids and supplemented with antioxidants. Renal therapeutic diets have these attributes and are also protein restricted. Renal diets should be considered in IRIS CKD Stage 2 patients and in IRIS CKD Stage 1 patients with proteinuria (urine protein to creatinine ratio >0.5 in dogs and >0.4 in cats).
- Consider renal-protective drugs when available and evidence supports their use (e.g., calcitriol, Semintra®).
- Provide a variety of water sources (e.g., bowls in several locations, water fountain, dripping tap).
- During anesthesia monitor and maintain blood pressure and ensure good perfusion with intravenous fluids.

Monitor

- Monitoring a dog or cat with CKD needs to be individualized. Frequency of recheck visits will depend on severity and rate of progression of the kidney disease and response to therapy. Reevaluation should be done more frequently after initial diagnosis to help determine the rate of progression of disease.
- 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 including SDMA and a complete urinalysis should be performed. UPC should be monitored as indicated as well as blood pressure measured. Relevant CBC (i.e. hemocrit) and chemistry parameters (i.e. creatinine, SDMA, BUN, electrolytes, calcium, phosphorous and albumin) should be trended over times to help determine response to treatment, rate of progression of disease and to detect a sudden worsening of CKD.

CONCLUSION

Chronic kidney disease is a common condition in dogs and cats. SDMA helps identify disease earlier and is complementary to existing kidney tests. Early identification should prompt investigation for an underlying cause, giving the potential for specific treatment. Early management may slow the progression of the disease. Closer monitoring will help identify progression and indicate when additional therapies should be initiated.

REFERENCES

4. Data on file at IDEXX Laboratories, Inc. Westbrook, Maine USA.