Review article

Diagnostic and Therapeutic approach to a Chronic Kidney Diseases in Dogs

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INTRODUCTION

Chronic Kidney Disease (CKD) is defined as the presence of structural or functional abnormalities in one or both kidneys that have been present for an extended period usually from three months or more. Nephron damage associated with CKD is usually irreversible and progressive and characterized by a wide spectrum of disease, ranging from a minor structural lesion in a single kidney to extensive loss of nephrons affecting both kidneys (Polzin, 2011).CKD is a major cause of morbidity and mortality, especially in older dogs and cats, which were recorded with an overallincidence of 1- 3 per cent in cats and 0.5 – 1.5 per cent in dogs (Brown, 2007).

Azotemia is defined as an abnormal concentration of urea, creatinine, and other nonprotein nitrogenous substances in blood, plasma, or serum. Azotemia is a laboratory finding with several fundamentally different causes. Since non-protein nitrogenous compounds (including urea and creatinine) are endogenous substances, abnormally elevated concentrations in serum may be caused by an increased rate of production (by the liver for urea; by muscles for creatinine), or by a decreased rate of loss (primarily by the kidneys).

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When the structural and functional integrity of both kidneys has been compromised to such a degree that polysystemic signs of kidney failure are clinically manifested, the relatively predictable symptom complex called uremia appears, regardless of underlying cause. In some instances, uremic crises may suddenly be precipitated by prerenal disorders or, less commonly, postrenal disorders in patients with previously compensated primary kidney failure. Uremia is characterized by multiple physiologic and metabolic alterations that result from impaired kidney function.

Classification and Staging of CKD

There are several classification systems like AKIN, KDIGO etc. have been existed and categorized the renal diseases in human medicine, whereas International Renal Interest Society (IRIS) has created to advance the scientific understanding of kidney disease in small animals particularly to help practitioners better diagnose, understand, and treat canine and feline renal disease. The IRIS has been classified into four stages of renal patients in pet animals primarily based on the serum creatinine levels and sub-staging was done considering the levels of proteinuria and systemic blood pressure (Table 1-3).

The stage of CKD is based on the level of kidney function as measured by the serum creatinine concentrations. Staging should be based on a minimum of two serum creatinine values obtained when the patient has been fasted and is well hydrated.

Table. 1: International Renal Interest Society Staging of Chronic Kidney Disease in Dogs and Cats based on the Serum Creatinine levels.

IRIS Stage of CKD	Serum Creatinine Values (mg/dl)	
	Dogs	Cats
Stage I	<1.4 (<125mmol/L)	<1.6 (<140mmol/L)
Stage II	1.4 – 2.0 (125-179 mmol/L)	1.6 – 2.8 (140-249 mmol/L)
Stage III	2.0 – 5.0 (180-439 mmol/L)	2.9 – 5.0 (250-439 mmol/L)
Stage IV	>5.0 (>440 mmol/L)	>5.0 (>440 mmol/L)

***http://www.iris-kidney.com.**

Table. 2: International Renal Interest Society sub staging of Chronic Kidney Disease in Dogsand Cats based on Proteinuria.

Classification	Urine Protein: Creatinine ratio	
	Dogs	Cats
Nonproteinuria	≤0.2	≤0.2
Borderline proteinuria	0.2-0.5	0.2-0.4
Proteinuria	>0.5	>0.5

***Based on ACVIM consensus statement on proteinuria (Lees, 2005).**

Table. 3: International Renal Interest Society sub staging of Chronic Kidney Disease in Dogsand Cats based on the blood pressure.

Hypertensive stage	Arterial Pressure	
	Systolic BP (mmHg)	Diastolic BP (mmHg)
Risk	<150	<95
Mild	150 - 159	95 - 99
Moderate	160 - 179	100 - 119
Severe	≥180	≥120

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Proteinuria is an important risk factor for the development of azotemia in cats and the progression of azotemia and decreased survival in both dogs and cats. Presence or absence of proteinuria is used to substage CKD (Table 2) in the IRIS staging system. Renal proteinuria can be glomerular and/or tubular in origin (ie, excessive filtration, decreased tubular reabsorption, or both). Renal proteinuria is persistent—with at least 2 positive tests separated by 10 to 14 days—and associated with inactive urine sediments. Urine protein/creatinine ratios (UPCs) > 2 suggest glomerular-range proteinuria, which is rare in cats compared with dogs.

IRIS blood pressure substaging is based, in part, on risk of target organ—eye, brain, heart, and kidney—damage (Table 3). In the absence of target organ damage, persistence of hypertension should be documented. Systolic blood pressure is typically measured by the Doppler methodology in dogs and cats.

Diagnosis of Chronic Kidney Disease in dogs

As the kidney performs several functions in the body, dysfunction of kidneys exerts abnormalities in multiple systems. Hence, we needs to consider several factors while assessing functional status and stage of dysfunction in renal diseases. It includes physical parameters, renal function tests, serum electrolyte concentrations, acid-base status, urinalysis, renal biomarkers and renal imaging studies.

Physical Assessment

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 with polycystic kidney disease. 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, rough hair coat, dehydration and palpable kidney abnormalities. Oral examination may reveal pale mucous membranes, ulcers and/or uremic breath. Secondary systemic hypertension may

Selected non-invasive markers of kidney disease.

Marker	Information provided[a]	Measured in serum/plasma or urine[b]
Serum creatinine	Estimate of GFR	Serum/plasma
Cystatin C	Estimate of GFR	Serum/plasma
Symmetric dimethylarginine	Estimate of GFR	Serum/plasma
Gel electrophoresis(e.g.SDS-PAGE)	Glomerular and/or tubular damage/dysfunction	Urine
Urine protein:creatinine	Glomerular and/or tubular damage/dysfunction	Urine
Albumin	Glomerular and/or tubular damage/dysfunction	Urine
C-reactive protein	Glomerular damage/dysfunction	Urine
Immunoglobulins A,G and M	Glomerular damage/dysfunction	Urine
N-acetyl-β -D-glucosaminidase	Tubular damage/dysfunction(but also increase with glomerular damage/dysfunction	Urine
Clusterin	Tubular damage/dysfunction	Urine
Cystatin C	Tubular damage/dysfunction	Urine
Gamma glutamyl-transpeptidase	Tubular damage/dysfunction	Urine
Kidney injury molecule-1	Tubular damage/dysfunction	Urine
Neutrophil gelatinase-associated lipocalin	Tubular damage/dysfunction	Urine
Retinol binding protein	Tubular damage/dysfunction	Urine
Tamm-Horsfall protein	Tubular damage/dysfunction	Urine

SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis;GFR,glomerular filteration rate.

[a] For all protein measurements in urine,interpretation assumes absence of post-renal disease(i.e.inactive sediment).

[b] For UPC and all individual urinary biomarkers,urine creatinine concentration must also be measured for normalization purposes.

Hemato-biochemical Parameters in CKD dogs and cats

Common abnormal findings on the CBC and chemistry panel include azotemia (elevation of BUN and creatinine), hypoproteinemia, hypoalbuminemia, nonregenerativeanemia, hyperphosphatemia, hypercalcemia or hypocalcemia, hypokalemia (in cats) and metabolic acidosis.

Role of biomarkers in the early diagnosis of the renal diseases

A diagnosis of CKD is typically straight forward 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.

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.

Symmetric dimethylarginine (SDMA) is a relatively newly discovered renal biomarker. SDMA is primarily eliminated by renal excretion. Therefore, it is an endogenous marker of GFR. It is not influenced by muscle mass, which is an advantage in comparison with creatinine. So far, SDMA has been used successfully to diagnose CKD in dogs and cats.

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.

List of Urinary biomarkers

Urinary marker	Causes of urinary marker elevetion
Markers of glomerular impairment	
Albumin	X-linked hereditary nephropathy (before the onset of overt proteinuria) (Lees 2002) Glomerular disease in Soft Coated Wheaten Terriers (Vaden et al.2001) Chronic kidney disease, CKD with hypertension (Basic et al.2010) Hypertension without CKD (Surman et al.2012) Systemic disease which may secondarily affect the kidneys (Whittemore et al. 2006) Diabetic nephropathy in dogs and cats (Struble et al.1998:Al-Ghazlat et al.2011) Severe inflammatory response syndrome (Schaefer et al.2011) Lymphoma and osteosarcoma in dogs (Pressler et al.2003) Hypercortisolism (Smets et al.2012)
Immunoglobulin G	X-linked hereditary nephropathy (Nabity et al.2012) Snake envenomation (Hrovat et al.2013) Pyometra (Maddens et al.2011) Leishmaniasis (Solano-Gallego et al.2003;Zaragoza et al.2003a) Leptospirosis (Zaragoza et al.2003b) Hypercortisolism (Smets et al.2012)
C-reactive protein	Pyometra (Maddens et al.2010b) Babesiosis (Defauw et al.2012) Leishmaniasis (Martinez-Subiela et al.2013)
Markers of tubular impairment	
N-acetyl-β -D-glucos-aminidase	Leishmaniasis (Palacio et al.1997) X-linked hereditary nephropathy (Nabity et al.2012) Heartworm disease with cardiac impairment (Uechi et al.1994b) Pyometra (Maddens et al.2010b) Experimental immune complex glomerulonephritis (Bishop et al.1991) Acute renal failure experimentally induced in cats (NAG-B isoenzyme) (Sato et al.2002a) CKD in cats (Jepson et al.2010a) Hypercortisolism (Smets et al.2012)
Gamma-glutamyl transpeptidase	Aminoglycoside-induced nephrotoxicity (Greco et al.1985;Grauer et al.1995;Rivers et al.1996) Renal insufficiency associated with pyometra (De Schepper et al.1989) Heartworm disease with cardiac insufficiency (Uechi et al.1994b) Leishmaniasis (Palacio et al.1997) Envenomation by the common European adder (Palviainen et al.2013) Experimental immune complex glomerulonephritis in cats (Bishop et al.1991)
Neutrophil gelatinase-associated lipocalin	Acute kidney injury (Hsu et al.2014;Segev et al.2013;Zhou et al.2014) Chronic kidney disease (Hsu et al.2014a;Steinbach et al.2014)
Retinol binding protein	Chronic kidney disease (Smets et al.2010b) Pyometra related renal impairment (Maddens et al.2010b) Babesiosis (Defauw et al.2012) Severe inflammatory response syndrome (Schaefer et al.2011) Envenomation by cytotoxic or neurotoxic snakes (Hrovat et al.2013) X-linked hereditary nephropathy before the onset of azotemia (Nabity et al.2012) Chronic renal failure and hyperthyroidism in cats (Van Hoek et al.2008) Hypercotisolism (Smets et al.2012)
Beta2-microglobulin	Early stages of X-linked hereditary nephropathy (Nabity et al.2012)
Cystatin C	Severe CKD in dogs with leishmaniasis (Garcia-Martinez et al.2015)
Cauxin	Tubular impairment (Myiazaki 2007)
Clusterin	Drug-induced acute kidney injury (Zhou et al.2014)

IRIS TREATMENT RECOMMENDATIONS

Stage 1 CKD Patients

1. Identify and correct any prerenal or postrenal disorders. Dehydration is the most common prerenal abnormality encountered, especially if urine-concentrating ability is compromised. Any clinical or suspected subclinical dehydration should be corrected with isotonic, polyionic replacement fluid solutions, such as lactated Ringer's solution either IV or SC.
2. Identify and treat any treatable primary disease processes (eg, renal lymphoma and hypercalcemia) or complicating disorders (eg, urinary tract infections and ureteroliths).
3. Pursue additional diagnostics recommended for Stage 1 CKD patients, including: Urine culture and sensitivity.
4. Identify and treat hypertension and renal proteinuria. Dietary sodium and protein reduction (eg, a renal diet) combined with ACE inhibitors, CCAs, and ARBs are used to reduce hypertension and proteinuria.
5. Discontinue all potentially nephrotoxic drugs.
6. Assess CKD stability or progression by monitoring patients at least twice a year. Dogs and cats with Stage 1 CKD are at risk for kidney disease progression; however, not all Stage 1 CKD patients progress to become azotemic. Those with borderline hypertension and proteinuria should be monitored closely.

Stage 2 CKD Patients

Dogs and cats with mid to late Stage 2 CKD often have progressive loss of renal function, although the rate of renal disease progression can be variable.

Reduce phosphorus intake with renal diets and enteric phosphate binders (if needed to meet goals).—This is a major treatment goal for dogs and cats with Stage 2 and beyond CKD.

Consider calcitriol supplementation—a potentially renoprotective treatment in dogs and cats. In dogs and cats receiving calcitriol, avoid use of calcium containing enteric phosphate binders or monitor patients closely for hypercalcemia.

Monitor patients for metabolic acidosis. Stage 2 CKD patients should be monitored for metabolic acidosis by measuring serum bicarbonate or total CO2 concentrations. If necessary, renal dietary therapy may be supplemented with oral sodium bicarbonate or potassium bicarbonate in order to maintain serum bicarbonate concentrations in the 18 to 24 mmol/L range.

Assess CKD stability or progression by monitoring patients for every 3 to 6 months.

Stage 3 CKD Patients

Continue renoprotective treatments (eg, renal diets, antihypertensive and antiproteinuric treatments) as Stage 3 CKD patients have progressive renal disease and it is important—as in State 2 CKD patients—to slow disease progression.

Initiate symptomatic treatment to improve quality of life because many dogs and cats with Stage 3 CKD, especially late Stage 3 CKD, begin showing clinical signs.

Stage 4 CKD Patients

In both dogs and cats, pursue all treatments for Stage 1, 2, and 3 CKD.

Continue renoprotective treatments (eg, renal diets, antihypertensive and antiproteinuric treatments) as these treatments are still important in early Stage 4 CKD patients but invariably the management focus shifts to making the patient as comfortable as possible given its renal failure.

Continue symptomatic treatment to improve quality of life. Owners frequently—and rightfully—equate nausea, decreased appetite, vomiting, and weight loss with poor quality of life.

Stop the catabolic spiral of calorie malnutrition— one of the primary management goals in Stage 4 CKD (Table 4). Appetite stimulants, antiemetics, and gastric acid blocking drugs become important in these patients (Table 7), but correction of metabolic deficits (eg, dehydration) and excesses (eg, hyperphosphatemia) is a higher priority.

Monitoring of serum creatinine and urea levels.Re-evaluation for every 1-2months.

TABLE 4 Diagnostic &Treatment Considerations Linked to IRIS CKD Stages

OPTIMUM IRIS STAGES	DIAGNOSTIC & TREATMENT FOCUS	CONSIDERATIONS	
		POTENTIAL PROBLEMS	DIAGNOSTICS/TREATMENT
Stage 1 Stage 2 Early Stage 3	Assess primary disease and complicating disorders Monitoring at least Q 6 months	Renal infiltrative disease Renal lymphosarcoma	Radiographs ,ultrasound±FNA, chemotherapathy
		Obstructive uropathy Ureteral obstruction	Radiographs, ultrasound± FNA, chemotherapy, SC uretral bypass
		Hypercalcemic nephropathy	Serum Ca and Ica assessment, NaCl fluid therapy, furosemide dieresis
Stage 2 Stage 3 Early Stage 4	Assess CKD stability or progression Monitoring at least Q 3 months	Nephrocalcinosis	Renal diets ,intestinal phosphorus binders
		Hypertension	CCAs, ACE inhibitors, ARBs
		Proteinuria	ACE inhibitors, CCAs, ARBs
Late Stage 3 Stage 4	Assess patient problems Monitoring at least Q 1-2 months	Anorexia,nausea,vomiting	Appetite stimulants,antiemetics, H2 receptor blocker, proton pump blockers
		Metabolic acidosis	Dietary alkalization
		Potassium depletion	Potassium supplementation
		Dehydration	Fluid therapy
		Anemia	Recombinant erythropoletin
		Calorie malnutrition	Appetite stimulants,dietary variety,feeding tube placement
		Uremia	Enteric dialysis

ACE= angiotensin-converting enzyme; ARB=angiotensin receptor blocker; Ca=calcium; CCA=calcium channel antagonist; CKD=chronic kidney disease; FNA=fine-needle aspiration; iCa=ionized calcium; NaCl=sodium chloride

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