



Advances in the Management of Chronic Kidney Disease

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Chronic kidney disease (CKD) is an important disease in small animal medicine with an approximate prevalence of 3.6% in cats and 0.37% in dogs (United Kingdom, primary care).^{1,2} Diagnosis of CKD is based on a detailed history and physical examination, including blood pressure measurement and minimal laboratory data set (hematology, biochemistry, urinalysis with urine protein: creatinine ratio [UPC]). After establishing a diagnosis of stable CKD and exclusion of any acute or chronic decompensation or other disease affecting renal function, staging of CKD is recommended using the International Renal Interest Society (IRIS) staging system.³ The IRIS staging system and treatment recommendations, available since 2009, underwent major modifications and revisions in 2015. The two most important changes are the addition of symmetric dimethylarginine (SDMA) to the staging system, as well as changes to the intervention points for proteinuria.

Modification in IRIS Staging of CKD: SDMA

Creatinine remains the main indicator of IRIS stage. However, it has long been recognized that it is an insensitive marker of glomerular filtration rate (GFR) and is influenced by extrarenal factors such as muscle mass, age, breed and body weight.^{4,5} More recently SDMA has been shown to be a more sensitive and earlier marker of renal disease in dogs and cats.⁶⁻⁹ These findings have led to the introduction of SDMA as part of the IRIS staging system in addition to serum creatinine. If SDMA values are available, the IRIS stages might be modified as illustrated in **Figure 1**.

Revision in IRIS Treatment Recommendation: Proteinuria

Proteinuria has been recognized as a major risk factor for decreased survival and progression of chronic kidney disease. Especially in cats, it could be shown, that even low-magnitude proteinuria significantly reduces survival in cats with CKD.¹⁰ This factor is now reflected in the revised IRIS treatment recommendations: proteinuric patients in IRIS Stage 1 (UPC \geq 0.5 for dogs, UPC \geq 0.4 for cats) should now be treated with an anti-proteinuric drug following confirmation of renal proteinuria and a thorough investigation into the possible cause. These recommendations are in accordance with the recently published Consensus Recommendations for Standard Therapy of Glomerular Diseases in Dogs.¹¹

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FIGURE 1**IRIS STAGING SYSTEM INCLUDING SDMA**

		Stage 1	Stage 2	Stage 3	Stage 3
Creatinine (mg/dl)	Dog	< 1.4	1.4 - 2.0	2.1 - 5.0	>5.0
	Cat	< 1.6	1.6 - 2.8	2.9 - 5.0	>5.0
		> 14	> 14		
SDMA (µg/dl)			≥ 25 ▶	Consider Stage 3	
				≥ 45 ▶	Consider Stage 4

Example: in an animal with a creatinine concentration of 2.5 mg/dl falling into IRIS Stage 2, but an SDMA higher than expected for this stage (≥ 25 µg/dl), treatment recommendations for IRIS Stage 3 should be considered. This is especially helpful in older patients or patients with progressed or comorbid diseases (e.g., heart failure, hyperthyroidism)

Besides these recent changes from the IRIS group there are many advances in the management of patients with CKD with the goal of improving the quality of life of these pets and, if possible, prolonging survival. Management of inappetence and weight loss with appropriate medical and nutritional support, early recognition and intervention in secondary renal hyperparathyroidism with phosphate restriction, appropriate management of hypertension and related target-organ damage, recognition and treatment of hypokalemia and acid base disturbances, as well as management of anemia of renal disease are some of the most important features in managing a patient with advanced CKD. For the purpose of this talk we will focus on the topics of systemic hypertension and anemia of renal disease.

Systemic Hypertension

Systemic hypertension is a common finding in the feline (20%-65%) and canine (31%-54%) patients with CKD.¹² Pathogenesis of hypertension is multifactorial and CKD may be a cause as well as a sequel of hypertension.¹³

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Possible causes for hypertension in patients with CKD include decreased sodium excretion and subsequent activation of the renin-angiotensin-aldosterone system (RAAS), relative

hyperaldosteronism, as well as stimulation of the sympathetic nervous system and endothelial dysfunction due to reduced availability of nitric oxide (NO) as reviewed by Syme¹⁴ and Jepson.¹⁵ Clinical signs of hypertension vary depending on target organ damage. Ocular manifestations such as hypertensive retinopathy, including retinal hemorrhage, retinal detachment and acute blindness are common in cats and dogs, implying the importance of the fundic exam in patients with CKD. Other target organs include the kidney itself (progression of CKD, proteinuria), the heart (hypertrophic cardiomyopathy) and the central nervous system (lethargy, behavioral abnormalities, seizures).¹⁶⁻¹⁹

Treatment options include angiotensin converting enzyme inhibitors (ACEI; e.g., enalapril), angiotensin receptor blockers (ARB, e.g. telmisartan) or calcium channel blockers (CCB; e.g., amlodipine). Blood pressure reduction with ACEI is modest, leading to a decrease of about 10 mmHg, whereas with CCB, a reduction up to 40 mmHg can be expected. Anecdotal evidence suggests that telmisartan might be more potent than enalapril or benazepril in controlling hypertension in small animals. In some patients, a combination of antihypertensive drugs may be necessary to control hypertension. It should be noted though, that combining these drugs might increase the risk for side effects. Although the combination of ACEI and ARB has been found to be safe in humans, the author recommends rechecking a serum biochemical profile (especially K, crea, BUN) after initiation of combination therapy or

dose adjustments in small animal patients.²⁰ Combination therapy with a directly vasodilating agent (CCB) and medication intervening with RAAS activation (ACEI or ARB) might be beneficial. Nevertheless, renal values should be monitored, as combination therapy has led to a significant increase in urea in healthy dogs. The rise in creatinine was not statistically significant. However, it is difficult to say how this translates to the diseased state.^{21,22}

The suggested dose of amlodipine in dogs and cats is 0.1-0.25 mg/kg q24h, and 0.1-0.5 mg/kg q24h, respectively.²³ Where compounding is unavailable, in cats a dose of 0.625 mg/cat is often recommended (1/8 of a 5 mg tablet).

A recent cross sectional study investigated the required dose of amlodipine in hypertensive cats to achieve blood pressure control (defined as systolic blood pressure (SBP) \leq 160 mmHg). This study found that cats with a higher blood pressure (median 207 mmHg, 25th-75th: 175-192) needed a higher dose of amlodipine (0.33 ± 0.09 mg/kg) compared to cats with a lower blood pressure (median 182 mmHg, 25th-75th: 194-217) needing a lower dose of amlodipine (0.17 ± 0.04 mg/kg) to achieve blood pressure control. Absolute decrease in blood pressure was independently associated with amlodipine plasma concentration. Based on these findings, the authors of this study propose a starting dose of 1.25 mg amlodipine per cat q24h for cats with SBP \geq 200 mmHg. Unfortunately, it is not reported how many cats needed a dose in excess of

1.25 mg/cat to achieve blood pressure control, and if an even higher starting dose needs to be considered for a subset of hypertensive cats.²⁴

Another study evaluating a chewable formulation of amlodipine found that a dose of 0.18 mg/kg (range 0.125-0.25) successfully controlled hyperthyroidism in 46% of cats receiving amlodipine. In the non-responding cats, the dose was increased to 0.38 mg/kg (range 0.25-0.50) and 68% of the remaining cats responded.²⁵

Although the dosages used in both of these studies are similar, the design of the second study did not allow for comparison of response stratified by severity of hypertension. An ACEI (e.g., enalapril or benazepril, 0.5 mg/kg q12-24h) are considered first line treatment for renal hypertension in dogs, as proteinuria is often present as well.²³ However, in the authors experience additional treatment with amlodipine is often necessary and amlodipine should be considered as a first line medication in animals with severe hypertension and absent proteinuria.

In comparison to cats, less data is available on amlodipine use in dogs.

In comparison to cats, less data is available on amlodipine use in dogs. One study evaluated its use in 22 dogs with hypertension due to acute kidney injury. The treatment protocol included a starting dose of 0.25 mg/kg and up-titration of the dose in 0.25mg/kg increments every 1-3h,

up to 1 mg/kg/d if the target blood pressure (SBP 140-160 mmHg) was not reached. This protocol allowed for control of hypertension in 64% of dogs within 24h and 91% of dogs within 48h with no adverse effects (hypotension) noted. The median prescribed dose was 0.38 mg/kg.²⁶

Clinical signs associated with ARD can majorly affect quality of life for animals with CKD: lethargy, weakness, and inappetence are commonly seen sequels of ARD.

Anemia of Renal Disease

Anemia of renal disease is well documented in small animal patients with CKD (or Acute Kidney Injury (AKI)) and may affect up to 35%-50% of cats with CKD.²⁷ Decreased renal functional mass leading to decreased erythropoietin (EPO), decreased erythrocyte life span, gastrointestinal blood loss secondary to uremic syndrome as well as frequent blood sampling in small patients contribute to acute renal disease (ARD).²⁸ Clinical signs associated with ARD can majorly affect quality of life for animals with CKD: lethargy, weakness, and inappetence are commonly seen sequels of ARD. Successful treatment is often required first, to realize that the exhibited signs were attributable to ARD. Despite the detrimental effects of ARD, therapy is often not considered at all or only as a last resort in far progressed cases. In the author's experience this is often related to expense of treatment as well as fear

of side effects.

Recombinant human erythropoietin (epoietin) can be used to treat ARD. Although it is effective, there is a relative high risk (20%-50%) of antibody formation, potentially resulting in pure red cell aplasia. The antibody response can persist over a long period of time and make transfusion therapy necessary. This often will lead to euthanasia of the affected animal.^{27,29}

Darbepoietin (Aranesp®) is a longer acting, recombinant human erythropoietin analogue. Data on its use in cats and dogs is sparse. In a retrospective study in 25 cats with CKD, median (range) starting doses were 0.5 µg/kg (0.45-0.71) SC once weekly for 28% of cats and 1.0 µg/kg (0.78-1.19) for 68% of cats, respectively. A single cat received a starting dose of 1.8 µg/kg. Of the 25 included cats, 14 cats showed a complete response (increased to and maintained PCV ≥ 25%), 5 cats showed an initial response but were not able to maintain their target PCV, and 6 cats did not show an adequate response to darbepoietin therapy. For most cats not responding adequately, other complicating disease processes, such as heart failure, gastro-intestinal

Adequate response was defined as a HCT ≥ 30%, which was reached by 85% of dogs treated with a median (range) response time of 29 days (6-106)

bleeding, septicemia and others, were identified. In the responder group median (range) time to reach a PCV ≥ 25% was 21 days (7-47). It is important to note that an increased reticulocyte count is not noted in all cats despite response to treatment. Median survival time for responders (238 days) was significantly longer compared to that of non-responders (83 days). Side effects noted in this study were hypertension (41%) and seizures (16%), although these findings might not entirely be related to darbepoetin administration. There was no apparent case of pure red cell aplasia, although it could not entirely be ruled out in two non-responders.³⁰

A recent retrospective study evaluated darbepoetin administration in 33 dogs with CKD. The median starting dose was 0.5 µg/kg SC once weekly.

Adequate response was defined as a HCT ≥ 30%, which was reached by 85% of dogs treated with a median (range) response time of 29 days (6-106). In 22 dogs an extended dosing interval was successful initially in maintaining target HCT, but none of the dogs maintained response with dosing interval in excess of 21 days. Although these dogs responded to an increase in dosing interval initially, 15/22 dogs required a shortening of the dosing interval at a later time. Potential side effects included, among others, hypertension (24/25), hyperkalemia (14/33), and seizures (5/33), all of which did not warrant discontinuation of the drug. Two dogs developed possible pure red cell aplasia (6%).³¹

At the author's institution darbepoetin is frequently used for animals with CKD if the PCV drops ≤ 20%, earlier if clinical signs warrant it. Additionally, patients with AKI or cats with ureteral obstruction after placement of a subcutaneous ureteral bypass (SUB) may profit from temporary darbepoetin treatment, if clinically warranted. The starting dose is usually 1 µg/kg SC once weekly. Once the target PCV is reached, we recommend increasing the interval of application (e.g., from q7d to q10d) rather than

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