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AUTHORS: Shelly L. Vaden and Jonathan Elliott

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Management of Proteinuria in Dogs and Cats with Chronic Kidney Disease

AUTHOR NAMES AND DEGREES

Shelly L. Vaden, DVM, PhD, DACVIM

Jonathan Elliott MA Vet MB PhD Cert SAC Dip ECVPT MRCVS

AUTHOR AFFILIATIONS

Professor of Internal Medicine

Department of Clinical Sciences

College of Veterinary Medicine

North Carolina State University

Raleigh, NC

Professor of Veterinary Clinical Pharmacology

Department of Comparative Biomedical Sciences

Royal Veterinary College, University of London

London UK

AUTHOR CONTACT INFORMATION

1052 William Moore Drive

Raleigh, NC 27607

slvaden@ncsu.edu

Royal Veterinary College

Royal College Street

London NW1 0TU

UK

jelliot@rvc.ac.uk

CORRESPONDING AUTHOR

Shelly Vaden

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KEY WORDS

Urine protein: creatinine ratio, proteinuria, hypertension, angiotensin, aldosterone, glomerular, chronic kidney disease

KEY POINTS

In dogs and cats proteinuria is a negative prognostic for chronic kidney disease and is associated with degree of functional impairment as well as the risk of a uremic crisis, progressive worsening of azotemia or death.

Normal dogs and most normal cats should have a urine protein:creatinine ratio that is <0.4 and <0.2 , respectively; persistent proteinuria above this magnitude warrants attention.

Administration of angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers is considered a standard of care in dogs and cats with renal proteinuria where the UPC is $>0.5-1$ and $>0.2-0.4$ respectively.

Blood pressure control and nutritional modification are also important considerations and part of the standard of care for dogs and cats with renal proteinuria.

Renal biopsy and administration of immunosuppressive agents should be considered in dogs with glomerular proteinuria that have not responded to standard therapy.

SYNOPSIS

Proteinuria is a negative prognostic indicator for dogs and cats with for chronic kidney disease and is associated with degree of functional impairment as well as the risk of a uremic crisis or death. The normal kidney is so highly efficient at preventing passage of proteins into the filtrate and reabsorbing the proteins that do get through that a normal

dog or cat should excrete very little protein and have a urine protein:creatinine ratio that is <0.4 or <0.2 , respectively; persistent proteinuria above this magnitude warrants attention. Administration of angiotensin converting enzyme inhibitors (e.g., benazepril, enalapril) and/or angiotensin receptor blockers (e.g., telmisartan), blood pressure control and nutritional modification are considered a standard of care in dogs and cats with renal proteinuria. Renal biopsy and administration of immunosuppressive agents should be considered in dogs with glomerular proteinuria that have not responded to standard therapy; glomerular proteinuria is uncommon in cats. Targeted patient monitoring is essential when instituting management of renal proteinuria.

Proteinuria as a Prognostic Indicator in Chronic Kidney Disease

Proteinuria is a negative prognostic indicator for both dogs and cats with chronic kidney disease. In dogs with chronic kidney disease, an initial urine protein: creatinine ratio (UPC) of >1.0 was associated with a threefold greater risk of developing a uremic crisis and death (Jacob et al, 2005). The relative risk of adverse outcomes increased 1.5 times for every increase in the UPC by 1. In another canine study, proteinuria correlated with the degree of functional impairment, as measured by glomerular filtration rate; dogs with UPC of <1.0 lived 2.7 times longer on average than dogs with a UPC >1.0 (Wehner et al, 2008).

When nonazotemic cats were prospectively and longitudinally evaluated, proteinuria was found to be significantly associated with the development of azotemia by 12 months (Jepson et al, 2009). Both proteinuria and serum creatinine were related to shortened survival in cats with chronic kidney disease (Syme et al, 2006; King et al, 2007).

This was true even when cats had UPC as low as 0.2-0.4.

Chronic proteinuria has been shown to be associated with interstitial fibrosis as well as tubular degeneration and atrophy, although the exact mechanisms of injury are a subject of debate (Toblli et al, 2012; Pollock et al, 2007). There is some evidence that reabsorbed proteins and lipids are directly toxic to the tubular epithelial cells, triggering inflammation and apoptosis. In addition, excessive lysosomal processing of proteins leads to lysosomal rupture and the intracellular release of cytotoxic enzymes. Proteinuria may increase the workload of the tubular epithelial cell beyond its capabilities. Proteinaceous casts cause tubular obstruction, which further injures the cells. Glomerular injury results decreased perfusion of the tubulointerstitium, resulting in cellular hypoxia. Increased glomerular permselectivity increases the filtration of other substances, such as transferrin, that cause additional tubular injury.

Because proteinuria is associated with negative outcomes it is imperative that the practice veterinarian has a thorough understanding of appropriate assessment and management of proteinuria in dogs and cats with chronic kidney disease.

Normal Renal Handling of Protein

The glomerulus is a complex structure that functions as a filter, across which an ultrafiltrate of the plasma is formed. This filtration system, made up by the fenestrated endothelium, glomerular basement membrane and visceral epithelial cells (podocytes) is freely permeable to water and small dissolved solutes, but retains cells and most macromolecules, such as proteins. The podocyte is the most differentiated cell in the glomerulus and essential to the filtration unit (Tobilli et al, 2012). In addition to these

factors, glycocalyx has been found to play an important role in maintaining glomerular permselectivity by restricting the passage of proteins (Singh et al, 2007). The major determinant of passage into the filtrate is molecular size. Low-molecular weight proteins, such as insulin and immunoglobulin fragments, pass freely through the filter, but as molecules increase in size they are retained with increasing efficiency. Only small amounts of substances larger than 60,000 to 70,000 daltons pass in to the filtrate. The podocyte foot processes, epithelial slits, basement membrane and endothelium are all rich in negatively charged glycoproteins that create an ionic charge barrier and impede the passage of negatively charged molecules more than would be expected based on their size alone. Albumin, a negatively charged protein with a molecular weight of 69,000 daltons, is normally largely excluded from the filtrate. Despite this complex filtration system, the glomerulus normally leaks albumin. Rapid endocytosis and hydrolysis of these proteins by proximal tubular cells occurs. Filtered albumin and other proteins are ultimately released to the blood as amino acids. A normal animal should excrete virtually no protein in the urine, but certainly an amount that is below the limit of detection of routine urine protein assays (Maack, 2011).

Laboratory Tests for Urine Protein

The urine dipstick, the sulfosalicylic turbidimetric test (SSA, bumin test) or the UPC can be used to measure total urine protein. The urine dipstick is the most readily available test of urine protein but is also the least reliable. Both false positives and false negatives occur. The sensitivity and specificity of the urine protein dipstick are as low as 54% and 69%, respectively, in the dog and 60% and 31%, respectively, in the cat. While the urine

dipstick primarily detects albumin, it also measures globulins. The SSA is more reliable than the urine dipstick for the detection of proteinuria (both albumin and globulin); however, use of this test requires either having the appropriate reagents and standards on hand or sending the urine sample to a reference lab. The amount of protein that is present in the urine of normal dogs and cats is below the lower limit of detection for both of these tests. When both urine dipstick and SSA test results are available, the results of the SSA test should be given greater consideration than those of the urine dipstick. Positive results with either of these tests must be interpreted in light of the urine specific gravity.

Dogs and cats with repeat positive dipstick or SSA results in urine sample that is free of pyuria or a color change from hematuria should have urine protein losses quantified by the UPC. The UPC is determined using a quantitative test for total urine protein, the results of which are expressed as a ratio to urine creatinine thereby eliminating the need to consider the urine specific gravity when interpreting the results. The ratio correlates well with 24-hour urine protein losses and can be measured either in-house or as a send out test. Normal dogs, female cats and neutered male cats should have a UPC that is <0.2 (Table 1). Normal intact male cats can have UPC up to 0.6, most likely due to the excretion of large amounts of cauxin.

Persistent microalbuminuria is the mildest, and often earliest, detectable form of proteinuria. Urine albumin can be measured quantitatively through a commercial reference laboratory using a species-specific assay. The urine is diluted to a standard concentration (1.010) prior to assay, eliminating the need to consider urine specific gravity when interpreting the test results. Alternatively, some labs report urine albumin as a ratio to creatinine (i.e., mg albumin/g creatinine). Microalbuminuria is defined as concentrations of

albumin in the urine that are greater than normal but below the limit of detection using the urine dipstick. By this definition, the upper end of urine albumin concentrations that are still considered to be microalbuminuria is 30 mg/dl (or 300 mg albumin/g creatinine). Urine albumin concentrations above this are called overt albuminuria. Proteinuria of this magnitude can often be detected using the UPC.

Clinical Assessment of Proteinuria

Accurate assessment of proteinuria involves 3 key elements: persistence, localization, and magnitude (Lees et al, 2005). Persistent proteinuria is defined as proteinuria that has been detected on 3 or more occasions, 2 or more weeks apart. Persistent proteinuria should be localized as being pre-renal, post-renal, or renal (Table 2). Identifying the cause of proteinuria in an affected dog or cat is important so that appropriate therapeutic measures can be implemented. Renal proteinuria that is glomerular or tubulointerstitial in origin is the most relevant form of proteinuria when managing dogs with chronic kidney disease. However, it is important to ensure that proteinuria is not due to pre-renal or post-renal causes because the management of these disorders varies substantially from the management of chronic kidney disease. Functional proteinuria is not very common in dogs and cats, or at least poorly documented.

Once pre-renal and post-renal causes of persistent proteinuria are eliminated, magnitude is used to help determine if renal proteinuria is glomerular or tubulointerstitial in origin. Magnitude is assessed using a quantitative test for urine protein (generally UPC but could also be urine albumin). Once pre-renal and post-renal causes of proteinuria have been excluded, it is recommended that a UPC be evaluated in all dog and cats with

persistent proteinuria as determined by dipstick or SSA.

The International Renal Interest Society (IRIS) has recommended substaging dogs and cats with chronic kidney disease on the basis of their UPC (Table 1). Dogs that have renal proteinuria and a UPC ≥ 2.0 usually have glomerular disease, whereas dogs with UPC < 2.0 might have either glomerular disease or tubulointerstitial disease. Glomerular diseases occur much less commonly in cats but should be suspected when the UPC is ≥ 2 . Concurrent hypoalbuminuria is added evidence that glomerular disease is present.

Urine sodium-dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) can be used to help determine if renal proteinuria is glomerular or tubulointerstitial in origin (Nabity 2010). Finding predominantly low molecular weight proteins is consistent with tubulointerstitial disease whereas glomerular damage is more likely associated with a pattern of intermediate and high molecular weight proteins. When there is concurrent glomerular and tubulointerstitial disease, a mixture of sizes is expected. In addition to SDS-PAGE, there are certain novel biomarkers that may prove in the future to identify tubulointerstitial damage is present (e.g., retinol binding protein, kidney injury molecule-1).

Inhibition of RAAS to Manage Proteinuria

Hemodynamic forces influence the transglomerular movement of proteins and it follows that altering renal hemodynamics would be effective in reducing proteinuria (Brown et al, 2013). The renin-angiotensin-aldosterone system (RAAS) has been the major target system for this approach to reducing proteinuria (Figure 1). Agents that target RAAS include the angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers

(ARB), and aldosterone receptor antagonists (Table 3). Although renin inhibitors are being used in people, they have not been used to any great extent in dogs and cats. All RAAS inhibitors have antihypertensive effects although most of them only minimally reduce blood pressure (i.e., 10-15%). These drugs likely reduce proteinuria by several mechanisms in addition to the expected decrease in glomerular capillary hypertension. Likewise, the reduction in proteinuria is greater than would be expected on the basis of their antihypertensive effects alone. RAAS inhibition is considered a standard of care in dogs and cats with renal proteinuria where the UPC is >0.5-1 and >0.2-0.4 respectively. The inhibitors of RAAS reduce proteinuria in populations of animals but the effect in individual animals might vary. It may take trial and error with different drugs or combinations of drugs before the target antiproteinuric effect is achieved (see Monitoring Drug Therapy below); some animals may never achieve target reductions.

Angiotensin Converting Enzyme Inhibitors

ACEi administration has been associated positive outcomes in dogs, cats and people with chronic kidney disease (Grauer et al, 2015; Tenhundfeld et al, 2009; King et al, 2006; Mizutani et al, 2006). Enalapril significantly reduced proteinuria and delayed the onset or the progression of azotemia in dogs with glomerulonephritis (Grauer et al, 2015). In dogs with partial nephrectomies, enalapril treated dogs had a reduction in glomerular and tubulointerstitial lesions following 6 months of treatment (Brown et al, 2003). Likewise, dogs with chronic kidney disease that were given benazepril had higher glomerular filtration rates and lower UPCs when compared to a placebo-treated group (Tenhundfeld et al, 2009).

In cats, benazepril administration was associated with reduced glomerular capillary

pressure in cats with induced chronic kidney disease (Brown et al, 2001). In cats with naturally occurring chronic kidney disease, benazepril was associated with a reduction in proteinuria, even in the subgroup of cats with initial UPC of <0.2 ; cats with initial UPC >1 demonstrated better appetites when given benazepril vs placebo. Although these drugs reduce proteinuria in cats, studies have not yet demonstrated a positive event on survival or progression of chronic kidney disease.

Proposed mechanisms for these effects include decreased efferent glomerular arteriolar resistance leading to decreased or normalized glomerular transcapillary hydraulic pressure, reduced loss of glomerular heparan sulfate, decreased size of the glomerular capillary endothelial pores, improved lipoprotein metabolism, slowed glomerular mesangial growth and proliferation, and inhibition of bradykinin degradation.

Initially an ACEi is given once daily, but more than half of the dogs will need twice daily administration eventually and perhaps additional dosage escalations (Figure 2) (Grauer et al, 2000). Many veterinarians are concerned about administering an ACEi to a dog or cat that is already azotemic. In people, the renoprotective effects of ACEi are independent of the baseline renal function and ACEi slowed progressive disease even in patients with severe renal failure (Ryan and Tuttle, 2008). In reality, it seems to be uncommon for dogs and cats to have severe worsening of azotemia (i.e., $>30\%$ increase from baseline) due to ACEi administration alone provided animals are clinically stable prior to the introduction of these agents. Dogs that are dehydrated may be at highest risk for worsening of azotemia after initiating ACEi therapy; euolemia should be achieved before initiating an ACEi to these patients. Furthermore, some caution is warranted when administering an ACEi to a dog or cat in late stage 3 or stage 4 CKD (e.g., low initial starting

dose with small incremental increases).

Many veterinarians wonder if one drug is better than another in animals with reduced renal function. The pharmacokinetics of ACEi are complicated and the effects of disease on the pharmacodynamics of these drugs is not necessarily predictable. There is no scientific basis to support that one ACEi has superior pharmacodynamic action. Benazepril and its active metabolite, benazeprilat, are largely eliminated by the biliary route with a smaller fraction being excreted in the urine; impaired renal function does not affect the clearance of this drug in dogs (Lefebvre et al, 1999). On the other hand, enalapril and its active metabolite, enalaprilat, are primarily eliminated by the kidney. Animals in IRIS late stage 3 or stage 4 CKD may require a lower dosage of enalapril to achieve target antiproteinuric effects.

Angiotensin Receptor Blockers

ARBs block the angiotensin II type 1 receptor. Several ARBs have been studied extensively in people with glomerular disease and lead to a reduction in proteinuria similar to that which is seen with ACEi. People treated with losartan had an average reduction in proteinuria of 35% from baseline during a 3.4 year follow up period; much of this reduction was in the first 6 months of therapy (Bakris et al, 2008). In irbesartan treated patients, every 50% reduction in proteinuria during the first 12 months of therapy reduced the risk of a negative renal outcome by more than half (Bakris et al, 2008).

The use of ARBs in dogs and cats with proteinuric chronic kidney disease is still being developed. The one that seems to be the most effective is telmisartan; however, losartan has been used more extensively (Sent et al, 2015; Bugbee et al, 2014). Even though dogs do not appear to produce one of the major active metabolites of losartan, there is good

evidence that losartan exerts pharmacodynamic effects in dogs (Christ et al, 1992).

Contrary to this, pharmacodynamic studies suggest that losartan may not be effective in cats, at least in attenuation of pressor responses (Jenkins et al, 2015).

Telmisartan is more lipophilic, and has a longer half-life than losartan; its blocking effects persist for longer than would be predicted from its plasma half-life. Furthermore, it has a higher affinity for, and dissociates more slowly from, the angiotensin-1 receptor. Therefore, it is not surprising that telmisartan was shown to be more effective in reducing proteinuria in people with diabetic nephropathy (Bakris et al, 2008) Telmisartan was as effective as amlodipine in controlling blood pressure in people with chronic kidney disease (Nakamura et al, 2007). Similarly telmisartan attenuated angiotensin I-induced blood pressure response to a greater degree than did benazepril in normal cats (Jenkins et al, 2015). If this is true in dogs and cats, telmisartan might be the initial RAAS inhibitor of choice when proteinuria and systemic hypertension are both present. A randomized controlled clinical trial comparing the effects of telmisartan and benazepril on proteinuria in cats with naturally occurring CKD demonstrated overall, telmisartan was as effective as benazepril in preventing an increase in UPC occurring over a 6-month treatment period. Indeed, telmisartan reduced UPC relative to the pre-treatment value at all time points evaluated in the 6-month trial whereas benazepril only reduced UPC at very early time points (Sent et al, 2015).

Combined Therapy with ACEi and ARB

There may be an added benefit to combined administration of an ACEi and an ARB because of the inability of either class of drug to provide complete RAAS blockade when given alone (Bakris et al, 2008). Although not evaluated in dogs and cats, studies in people

have suggested that these drugs may be additive or perhaps even synergistic in reducing proteinuria (Linaz 2008). The dosage of each individual drug might be reduced during combined therapy, thereby reducing the likelihood of adverse effects. However, the approach of combining these two agents must be used cautiously in light of a human study where elderly patients prescribed this combination had a higher risk of kidney failure and death (McAlister et al 2011). Controlled studies are needed in dogs to determine if the antiproteinuric effects of ACEi and ARBs are optimized by combination therapy or monotherapy with individualized dosage escalation.

Aldosterone Breakthrough

Complete blockade of the RAAS system is generally not achieved with RAAS inhibitors. In the absence of angiotensin converting enzyme, angiotensin II is produced by other kinases and is therefore, not completely suppressed by an ACEi alone. Blockade of the angiotensin II type 1 receptor with an ARB, may give rise to a compensatory increase in renin activity, and therefore an incomplete block of the RAAS (Laverman et al, 2002). Combination therapy increases the degree of blockade, but it is still may not be more than 75-80% complete.

Serum aldosterone increases over time in some people treated even with maximal dosages of RAAS inhibitors, a phenomenon referred to as aldosterone breakthrough. The incidence of aldosterone breakthrough in people treated with RAAS inhibitors for chronic kidney disease, systemic hypertension or heart failure is between 10 and 53% (Bomback and Klemmer 2007). Prolonged hyperaldosteronism can have adverse effects on the heart, systemic blood vessels and glomeruli. Therefore, it is not surprising that some people that experience aldosterone breakthrough during treatment for various glomerular diseases

have more negative outcomes (e.g., higher magnitude proteinuria, greater reduction in glomerular filtration rate) (Horita et al, 2006; Schjoedt et al, 2004). Preliminary studies have demonstrated that aldosterone breakthrough may occur in up to one-third of dogs with proteinuric renal diseases that are receiving RAAS inhibitors (Ames, unpublished data). More study is needed to determine if aldosterone breakthrough is associated with poorer treatment outcomes in dogs.

Aldosterone Receptor Antagonists

Aldosterone-receptor antagonists have been shown to reduce proteinuria and stabilize kidney function in an additive fashion to ACEi and/or ARB in people, particularly if they have evidence of aldosterone breakthrough before adding the aldosterone-receptor antagonist (Bianchi et al, 2006). Eplerenone may be the drug of choice in people because the relative lack of binding to androgen and progesterone receptors produces fewer endocrine side effects. However, endocrine side effects of spironolactone in dogs are less problematic and the preference is unclear in veterinary medicine. Although spironolactone has been used most commonly in veterinary medicine, there is little evidence supporting the efficacy of this drug in dogs in the management of glomerular disease. Spironolactone should only be effective if serum or urine aldosterone concentrations are increased, indicative of aldosterone breakthrough. This drug could be tried in dogs that have high serum or urine aldosterone concentrations and persistent proteinuria in spite of treatment with an ACEi and/or ARB. The drug should not be used in cats until more is known about its efficacy and safety in this species.

Monitoring Drug Therapy

The UPC, urinalysis, systemic blood pressure and serum albumin, creatinine and

potassium concentrations (in fasting samples) should be monitored at least quarterly in all animals being treated for proteinuric renal disease. However, those that are having new drugs introduced or dosage modifications being made for drugs already being administered should be monitored more frequently (Figure 2). One to 2 weeks after an ACEi or ARB is added or changed, the UPC, serum creatinine, serum potassium and systemic blood pressure should be evaluated to verify that the recent change in therapy has not resulted in a severe worsening of renal function (i.e., >30% increase in serum creatinine), a concerning increase in serum potassium concentrations, or hypotension (an unlikely occurrence with these drugs).

Day-to-day variations in the UPC occur in most dogs with glomerular proteinuria, with greater variation occurring in dogs with UPC >4 (Nabity et al, 2007); variations also occur in cats but these have not been as well characterized. Changes in urine protein content are most accurately measured by assessing trends in the UPC over time. Because there is greater day-to-day variation in dogs with UPC >4, consideration should be given to either averaging 2-3 serial UPC or measuring a UPC in urine that has been pooled from 2-3 collections (LeVine et al, 2010). In one study, demonstration of a significant difference between serial values in proteinuric dogs required a change by at least 35% at high UPC values (near 12) and 80% at low UPC values (near 0.5) (Nabity et al, 2007). Thus a reduction in UPC near these reported magnitudes without an increase in the serum creatinine concentration is required to indicate improvement or response to therapy.

Making Therapeutic Adjustments for RAAS Inhibitors

An ACEi is the initial therapy in most dogs and cats with proteinuria, with the typical starting dosage of 0.5 mg/kg q24h (Figure 2). However, the ARB telmisartan may soon

become a reasonable alternative for an initial agent. In dogs and cats, the ideal therapeutic target is a reduction in the UPC to <1 without inappropriate worsening of renal function. Because this ideal target is not achieved in most animals, a reduction in UPC of 50% or greater is often the target. The degree to which worsening of renal function is tolerated will in part depend upon the stage of CKD the dog is in. Dogs with stage 1 and 2 CKD can have an increase in serum creatinine of up to 30% without modifying therapy. The goal in dogs with stage 3 CKD would be to maintain stable renal function, allowing only for a 10% increase in serum creatinine. If renal function deteriorates beyond these allowances, therapeutic adjustments may be indicated. Dogs with stage 4 CKD are generally intolerant of worsening of renal function and any deterioration may have clinical consequences. Whereas RAAS inhibitors can be used in this subset of patients, the initial starting doses and incremental dose increases should be very low and renal function should be monitored closely; therapeutic adjustments may be needed to maintain baseline renal function.

If the target reduction in UPC is not achieved, the plasma potassium concentration is <6 and any changes in renal function fall within the tolerable limit, dosages may be increased every 4-6 weeks. If the target reduction in UPC is not achieved with a maximal dosage an ACEi, the next step should be to add an ARB. Alternatively an ARB can be used as monotherapy in dogs who appear to be intolerant of an ACEi.

Managing Hyperkalemia

Hyperkalemia appears to be a common side effect of RAAS inhibition in dogs with kidney disease but is probably uncommon in cats. Pseudohyperkalemia, often associated with thrombocytosis, can also occur in dogs and needs to be ruled-out by measuring the potassium concentration in lithium heparin plasma before taking further action. Because of

the cardiotoxic effects of potassium, dogs or cats with true hyperkalemia of > 5.5 mEq/L should be monitored closely; therapy should be modified if serum potassium concentrations are >6 to 6.5 mEq/L. When plasma potassium concentrations are >6 mEq/L, an ECG should be evaluated for cardiac conduction disturbances. True hyperkalemia can be managed by reducing the ACEi or ARB drug dosage, discontinuing spironolactone administration, or by feeding diets that are reduced in potassium (note that renal diets may be supplemented with potassium). The use of an intestinal potassium binder (e.g., kayexelate) has been limited in dogs. Rarely hyperkalemia would be severe enough to warrant hemodialysis. Potassium-reduced home-prepared diets that were formulated by a veterinary nutritionist have been shown to effectively correct hyperkalemia long-term in dogs with chronic kidney disease (Segev et al, 2010).

Management of Hypertension

The kidney is one of the target organs for hypertensive damage and sustained hypertension may lead to an increased magnitude of proteinuria, rate of decline of renal function, frequency of uremic crises and mortality (Jepson et al, 2009, Finco et al, 2004; Brown et al, 2007). The goal of antihypertensive therapy is to reduce the blood pressure so that the risk of continued target organ damage is minimized (Table 4). Inhibitors of RAAS are generally only weak antihypertensive agents, leading to a reduction in blood pressure by only about 10-15%. Dogs and cats that have sustained systolic blood pressures ≥ 160 mmHg while being administered a RAAS inhibitor have a moderate to high risk of future target organ damage and may need additional therapeutic consideration. In these animals, the first step is to increase the dose of the RAAS inhibitor. If the upper end of the dosage

range is being administered and the risk of target organ damage remains moderate to high, the next step is to add a calcium channel blocker. Amlodipine is usually used with a starting dose of 0.2-0.4 mg/kg q24 hours but can be incrementally increased to a total daily dose of 0.75 mg/kg, which can be divided to q12h. There is evidence that amlodipine will activate the RAAS system; therefore it should not be used as monotherapy for the management of hypertension in dogs (Atkins et al, 2007). However in cats monotherapy may be more appropriate because giving multiple drugs is harder, amlodipine alone may bring the UPC down to <0.2 in hypertensive cats and amlodipine-induced increases in plasma renin activity are not associated with an increase in aldosterone in cats (Jepson et al, 2014).

Systolic blood pressure should be monitored during therapy and maintained >120 mmHg in treated dogs and cats. High salt intake should be avoided although salt restriction alone will not adequately reduce blood pressure.

Diet

In animal models of chronic kidney disease, the magnitude of proteinuria can be reduced by dietary modification – specifically by modifying the polyunsaturated fatty acid ratio and protein content (Brown et al, 2013). Dietary supplementation with n-3 polyunsaturated fatty acids or feeding a diet that has a reduced n-6/n-3 ratio that is close to 5:1, as found in most commercially available renal diets is expected to alter the long term course of renal injury and reduce the magnitude of proteinuria. It is generally accepted that feeding a renal diet that is modified in protein content reduces intraglomerular pressure as well as the magnitude of proteinuria and the generation of uremic toxins. However, the magnitude of this reduction in proteinuria is small. Renal diet alone should not be expected

to adequately reduce proteinuria in most animals.

Renal Biopsy

Nearly 60% of dogs with glomerular proteinuria will have either immune-complex mediated glomerulonephritis or amyloidosis (Schneider et al, 2013), both of which may represent an aberrant or excessive immune or inflammatory response to an infectious, neoplastic or inflammatory condition. Cats rarely get glomerulonephritis but a percentage of these cats would also be expected to have developed this secondary to a systemic disease. Therefore, in dogs or cats with glomerular proteinuria it is indicated to pursue extended diagnostic testing, the extent of which might vary depending upon patient characteristics and potential exposure to regional infectious agents (Littman et al, 2013). It is possible that complete or partial resolution of proteinuria will follow successful treatment of any causative systemic diseases.

Renal biopsy should be considered in animals with persistent glomerular range proteinuria that do not have any contraindications to renal biopsy and have not responded to standard therapy (Littman et al, 2013). Some of the more common contraindications to biopsy include chronic kidney disease with serum creatinine >5 mg/dL, uncontrolled hypertension, pyelonephritis, renal cystic disease, coagulopathy, hydronephrosis, and severe anemia. When biopsy samples are processed correctly, clinical decisions regarding the diagnosis, treatment, and prognosis can be made from the information obtained through renal biopsy in dogs. Experienced personnel should be involved with procuring, preparing and interpreting the renal biopsy that has been processed for light, electron, and immunofluorescence microscopy.

From a therapeutic standpoint, the primary purpose of the renal biopsy is to determine if immunosuppressive therapy is indicated or not. Finding electron-dense deposits in subendothelial, subepithelial, intramembranous, or mesangial locations of the glomerulus by EM or demonstrating positive and unequivocal immunofluorescent staining for immunoglobulins and/or complement in an immune-complex and antiglomerular basement membrane pattern of deposition in peripheral capillary loops or the mesangial compartment with IFM provides compelling evidence to initiate a trial of immunosuppressive therapy (Segev et al, 2013). Probable evidence of an immunopathogenesis can be documented by LM with one of the following: red granular staining of capillary walls with Masson's trichrome, spikes along the GBM or holes within the GBM with Jones Methenamine silver stain. These findings would be expected in just under 50% of dogs with glomerular disease (Schneider et al, 2013). When renal biopsy results are not available it becomes more difficult to make a decision about using immunosuppressive treatment because approximately 50% of dogs with glomerular disease would be expected not to have an immunopathogenesis of their disease. Consensus recommendations are to consider immunosuppressive drugs in the treatment of dogs with glomerular disease when the source of proteinuria is clearly glomerular in origin, the drugs are not otherwise contraindicated, the dog breed and age of disease onset are not suggestive of a familial nephropathy, amyloidosis has been deemed unlikely and the serum creatinine is >3.0 mg/dl or progressively increasing, or the serum albumin is <2.0 g/dl (Pressler et al, 2013).

Immunosuppressive Agents

Empirical administration of immunosuppressive or anti-inflammatory therapy has been recommended for dogs that have no known contraindications for the specific drugs being considered and have severe, persistent, or progressive glomerular disease in which there is renal biopsy-supported evidence of immune-mediated pathogenesis (Segev et al, 2013). Dogs with more severe disease or rate of progression should be treated more aggressively than those with more stable disease. Single agent or combination therapy for rapid onset of immunosuppression should be considered in dogs with high magnitude proteinuria with hypoalbuminemia, NS, or rapidly progressive azotemia (Segev et al, 2013). Mycophenolate, or cyclophosphamide, with or without short-term administration of glucocorticoids, has been suggested as the first choice. Glucocorticoids should be limited to short-term therapy because of the potential association with corticosteroid excess and proteinuria. Dogs with stable or more slowly progressive disease that have only partial or no response to standard therapy might be given drugs that have either a rapid or a more delayed onset of drugs, such as mycophenolate, chlorambucil or cyclophosphamide. Cyclosporine has also been suggested as a first choice for stable or slowly progressive dogs. It is important to note that this is the only drug that has been studied prospectively in dogs with glomerular disease and was found to be of no benefit, although there were flaws in the design of that study (Vaden et al, 2995).

All dogs treated with immunosuppressive therapy for their glomerular disease should be monitored closely. Treatment should be discontinued or adjusted if adverse drug effects develop. In the absence of adverse effects, 8-12 weeks of therapy should be provided before changing the course of treatment. If the therapeutic response is suboptimal at the end of 8-12 weeks, an alternate drug protocol should be considered.

However, if after 3-4 months a therapeutic response has not been achieved, consideration should be given to discontinuing immunosuppressive drug administration. If after this time, a response has been noted, the drug dose or schedule should be tapered to one that maintains the response without worsening of proteinuria, azotemia or clinical signs (Segev et al, 2013).

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Table 1: International Renal Interest Society classification of proteinuria in dogs and cats with chronic kidney disease.

Substage	Cat*	Dog
Nonproteinuric (NP)	<0.2	<0.2
Borderline Proteinuric (BP)	0.2-0.4	0.2-0.5
Proteinuric (P)	>0.4	>0.5

*Applies to normal female and neutered male cats; normal intact male cats may have a UPC as high as 0.6.

Table 2. Categorization of Potential Causes of Proteinuria in Dogs and Cats

Category	Mechanism	Potential Causes
Pre-renal	Greater than normal delivery of low molecular weight plasma proteins to the normal glomerulus	<ul style="list-style-type: none"> • Hemoglobinuria from intravascular hemolysis • Myoglobinuria from rhabdomyolysis • Immunoglobulin light chains from multiple myeloma or lymphoma
Renal	Abnormal renal handling of normal plasma proteins caused by one of the following subcategories:	
<i>Functional (Physiological)</i>	Altered renal physiology in response to transient stressor	<ul style="list-style-type: none"> • Strenuous exercise • Fever • Seizure • Exposure to extreme heat or cold
<i>Glomerular</i>	Altered permselectivity of the glomerular basement membrane	<ul style="list-style-type: none"> • Any cause of glomerular injury or dysfunction (e.g., membranoproliferative glomerulonephritis, glomerulosclerosis, amyloidosis)
<i>Tubular*</i>	Impaired tubular recovery of plasma proteins that are normally found in the glomerular filtrate	<ul style="list-style-type: none"> • Any cause of renal tubular dysfunction (e.g., acute tubular necrosis, Fanconi syndrome)
<i>Interstitial*</i>	Exudation of proteins from the interstitial space into the urinary space	<ul style="list-style-type: none"> • Interstitial nephritis
Post-renal	Entry of protein into the urine in association with exudation of blood or serum into the lower urinary or genital tracts	<ul style="list-style-type: none"> • Urinary tract infection • Urolithiasis • Transitional cell carcinoma • Vaginitis

* Tubular and interstitial can be difficult to separate in a clinical setting and are often referred to as tubulointerstitial.

Table 3: Inhibitors of RAAS used in dogs and cats with chronic kidney disease

Class	Drug	Initial Dose	Escalating Dose Strategy
Angiotensin converting enzyme inhibitors	Benazapril	0.25-0.5 mg/kg PO q24 hr* Dog or cat	Increase by 0.25-0.5 mg/kg to a maximum daily dose of 2 mg/kg; can be given q12h
	Enalapril	0.25-0.5 mg/kg PO q24 hr* Dog or cat	Increase by 0.25-0.5 mg/kg to a maximum daily dose of 2 mg/kg; can be given q12h
	Lisinopril	0.25-0.5 mg/kg PO q24 hr* Dog or cat	Increase by 0.25-0.5 mg/kg to a maximum daily dose of 2 mg/kg; can be given q12h
	Ramipril	0.125 mg/kg PO q24h Dog	Increase by 0.125 mg/kg q24h to a maximum of 0.5 mg/kg q24h; usually given q24h
	Imidapril	0.25 mg/kg PO q24h Dog	Increase by 0.25 mg/kg q24h to a maximum of 2 mg/kg q24h; usually given q24h
Angiotensin receptor blockers	Telmisartan**	0.5-1.0 mg/kg PO q24h Dog Dog or cat	Increase by 0.25-0.5 mg/kg to a maximum daily dose of 5 mg/kg; usually given q24h
	Losartan***	0.25-0.5 mg/kg PO q24 hr Dog	Increase by 0.25-0.5 mg/kg to a maximum daily dose of 2 mg/kg; can be given q12h
Aldosterone receptor blocker	Spironolactone****	0.5-2 mg/kg PO q12-24h Dog	

*Smaller starting doses should be used in animals with in stage 3 or 4 CKD or if there are concurrent medical problems that have the potential to lead to dehydration or reduced appetite.

**Can be used a single agent or combined with an ACEi.

***Concurrent administration of an ACEi is generally recommended.

****Only recommended in dogs with glomerular disease that have increased serum or urine aldosterone concentrations and have failed or not tolerated an ACEi or ARB.

Table 4: Staging of blood pressure in dogs and cats according to the risk for future target organ damage.

Blood Pressure Stage	Systolic (mmHg)	Diastolic (mmHg)
APO - Risk none to minimal	<150	<95
AP1 - Low risk	150-159	95-99
AP2 - Moderate risk	160-179	110-119
AP# - High risk	≥180	≥120

Figure Legends

Figure 1. The renin-angiotensin-aldosterone system and its inhibitors.

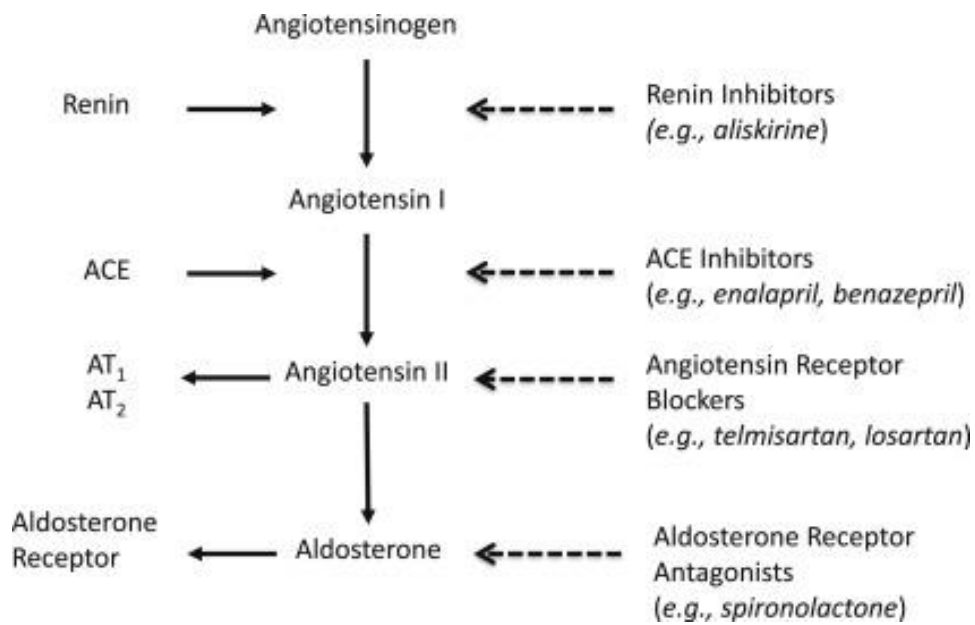


Figure 2. Making adjustments to RAAS inhibition therapy in dogs with renal proteinuria.

