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Consensus Recommendations for Standard Therapy of Glomerular Disease in Dogs

IRIS Canine GN Study Group Standard Therapy Subgroup, S. Brown, chair, J. Elliott, T. Francey, D. Polzin, and S. Vaden

Standard therapy forms the basic foundation for care of dogs with glomerular disease, as it is herein recommended for use in all affected animals regardless of causation of the disease. Consensus recommendations target the evaluation and management of proteinuria, inhibition of the renin-angiotensin-aldosterone system, modification in dietary intake with special consideration for those nutrients with renal effects, diagnosis and treatment of systemic hypertension, and evaluation and management of body fluid volume status in dogs with glomerular disease.

Key words: Amyloidosis; Chronic renal failure; Glomerulonephritis; Protein losing nephropathy.

The goal of the present report was to provide consensus recommendations for the management of canine glomerular disease, regardless of the inciting cause. As such, these recommendations should be viewed as forming the basis of standard, or routine, care of dogs with glomerular disease.

Canine glomerular disease is here considered to be primary if the process that initiates renal injury originates in the glomerulus. In most renal diseases, regardless of the site of the initiating renal injury, there are pathologic changes that occur in glomeruli after injury in other compartments (eg, tubulointerstitial disease or generalized loss of nephrons), and these changes are termed secondary glomerular disease. The recommendations outlined below apply to canine glomerular diseases in general, both primary and secondary.

In the management of dogs with glomerular disease, some recommendations are standard therapeutic considerations for all dogs with glomerular disease, regardless of the cause or severity. Although the present recommendations are considered a standard part of treatment in all canine glomerular diseases, their institution in a patient requires considerable prudence on the part of the veterinarian and individualized therapeutic plans, with adjustments based on severity of the glomerular disease and other patient

Abbreviations:

ACEi	angiotensin-converting enzyme inhibitor
ARB	angiotensin-receptor blocker
ATE	arterial thromboembolism
BP	systemic arterial blood pressure
CKD	chronic kidney disease
GFR	glomerular filtration rate
IRIS	International Renal Interest Society
NS	nephrotic syndrome
PUFA	dietary polyunsaturated fatty acids
RAAS	renin-angiotensin-aldosterone system
TOD	target organ damage
UPC	urine protein-to-creatinine ratio
VTE	venous thromboembolism

factors. The severity of a glomerular disease is usually reflected in the magnitude of proteinuria,¹ assessed as the urine protein-to-creatinine ratio (UPC), especially early in the disease process.

Recommendation 1:

For the purposes of standard therapy recommendations, the magnitude of proteinuria, as assessed by serial measurement of the UPC, should be used to make decisions about therapeutic intervention in dogs with glomerular disease.

100% of voting consensus members agreed with Recommendation 1 and 70% of these voters expressed “strong agreement.”

There is evidence in spontaneous renal disease that dogs, including those with primary glomerular disease, exhibit more adverse outcomes if the UPC exceeds 2.0² and in an experimental model of secondary glomerular disease³ that intervention, which reduces the UPC below 0.5, improves renal structural outcomes. These data provided support for the following recommendation.

Recommendation 2:

Intervention with standard therapies should be considered whenever renal proteinuria is causing

Department of Physiology & Pharmacology, University of Georgia College of Veterinary Medicine (Brown), Athens, GA; Department of Comparative Biomedical Sciences, Royal Veterinary College, University of London (Elliott), London, UK; Division of Small Animal Internal Medicine, Department of Clinical Veterinary Medicine, Vetsuisse Faculty, University of Bern (Francey), Bern, Switzerland; Department of Veterinary Clinical Sciences, University of Minnesota College of Veterinary Medicine (Polzin), St. Paul, MN; and Department of Clinical Sciences, North Carolina State University College of Veterinary Medicine (Vaden), Raleigh, NC. All members of the IRIS Canine GN Study Group Standard Therapy Subgroup contributed equally in the preparation of this manuscript.

Corresponding author: Scott Brown, College of Veterinary Medicine, University of Georgia, Athens, GA 30602; e-mail: sbrown01@uga.edu

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the UPC to persistently exceed 0.5 in a dog with glomerular disease, whether the glomerular injury is primary or secondary. In general, a reduction in the UPC to <0.5 (or a reduction in the UPC of 50% or more) should be considered as evidence of therapeutic success.

89% of voting consensus members agreed with Recommendation 2 and 50% of these voters expressed "strong agreement."

Inhibition of the Renin-Angiotensin-Aldosterone System (RAAS)

Because hemodynamic forces influence the trans-glomerular movement of proteins, it follows that altering renal hemodynamics would be effective in reducing proteinuria. The RAAS has been the major target system for this approach to reducing proteinuria (Fig 1). Agents that target RAAS include an angiotensin-converting enzyme inhibitor (ACEi; eg, enalapril, benazepril), angiotensin-receptor blocker (ARB; eg, losartan, telmisartan), and aldosterone-receptor blocker (eg, spironolactone). Although renin inhibitors (eg, aliskirine) are being used in people, they have not been used to any great extent in dogs. The mechanisms of agents interfering with the RAAS have not been fully elucidated, but it appears that they reduce proteinuria greater than would be expected on the basis of their antihypertensive effects alone.

Angiotensin-Converting Enzyme Inhibitors (ACEis)

An ACEi may, in part, reduce proteinuria and preserve renal function by decreasing efferent glomerular arteriolar resistance leading to decreased (normalized) glomerular transcapillary hydraulic pressure.^{3,4} In addition, proposed mechanisms for RAAS inhibitors to reduce proteinuria include 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 degrada-

tion.⁵ Enalapril significantly reduced proteinuria and delayed the onset or the progression of azotemia in dogs with glomerulonephritis.⁶ In large part because of their established effects,^{3,6} interference with the RAAS, particularly with ACEi, is considered part of standard care of dogs with glomerular disease.

Typically, an ACEi is given once daily initially, but more than half of the dogs will eventually need twice-daily administration and perhaps additional dosage escalations (Table 1).⁶ Further dosage escalations may be required as described below. Although the serum creatinine concentration should be monitored, it seems to be uncommon for dogs to have severe worsening of azotemia (ie, >30% increase from baseline) attributable to ACEi administration alone. Dogs that are dehydrated may be at highest risk for worsening of azotemia after initiating ACEi therapy. 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.⁷ However, although ACEi administration is appropriate, caution is warranted when administering an ACEi to a dog in International Renal Interest Society (IRIS) Chronic Kidney Disease (CKD) stage 4.

Benazepril and its active metabolite, benazeprilat, are largely eliminated by the biliary route with a smaller fraction being excreted in the urine. The clearance is not affected in dogs with impaired renal function.⁸ On the other hand, enalapril and its active metabolite, enalaprilat, are primarily eliminated by the kidney. Thus, dogs in late IRIS CKD stage 3 or stage 4 may achieve a similar antiproteinuric effect with a lower dosage of enalapril. However, the pharmacokinetics of ACEi is complicated and the effects of disease on the pharmacodynamics of these drugs are not necessarily predictable. Although interdrug differences are known, there are currently no published studies in dogs with glomerular disease to support the recommendation that one ACEi is superior in its pharmacodynamic action to another.

Angiotensin-Receptor Blockers (ARBs)

The ARBs in clinical use block the angiotensin II type 1 receptor. Several ARBs have been studied extensively in people with glomerular disease (eg, losartan, irbesartan, telmisartan) and lead to a reduction in proteinuria similar to that which is seen with ACEi. There are limited data on the use of ARBs in dogs with glomerular disease and it is anticipated that the addition of information to the literature could alter our selection or method of use of these agents. The ARB that seems to be used most commonly in dogs is losartan. 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.⁹ Furthermore, there is anecdotal evidence that losartan has an antiproteinuric effect in dogs, particularly in combination with ACEi.

In human patients, losartan resulted in an average reduction in proteinuria of 35% from baseline during a

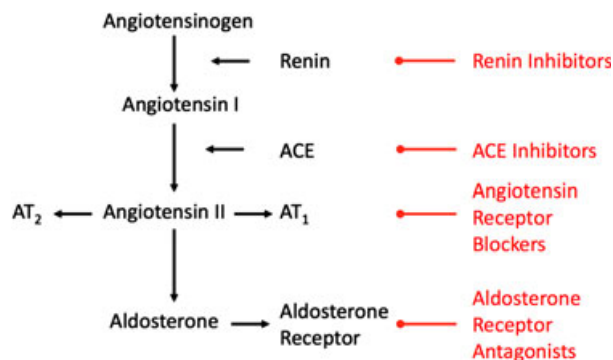


Fig 1. The renin-angiotensin-aldosterone system and approaches to its inhibition.

Table 1. Dosages of common inhibitors of the renin-angiotensin-aldosterone system used in the management of proteinuria in dogs with glomerular disease.

Drug	Indication	Initial Dose	Escalating Dose
Benazapril	Angiotensin converting enzyme inhibitor ^a	0.5 mg/kg PO q24h	Increase by 0.5 mg/kg/d to a maximum of 2 mg/kg PO per day. Can give q12h
Enalapril	Angiotensin converting enzyme inhibitor ^a	0.5 mg/kg PO q24h	Increase by 0.5 mg/kg/d to a maximum of 2 mg/kg PO per day. Can give q12h
Ramipril	Angiotensin converting enzyme inhibitor ^a	0.125 mg/kg PO q24h	Increase by 0.125 mg/kg/d to a maximum of 0.5 mg/kg PO per day. Usually give q24h
Imidapril	Angiotensin converting enzyme inhibitor ^a	0.25 mg/kg PO q24h	Increase by 0.25 mg/kg/d to a maximum of 5 mg/kg PO per day. Usually give q24h
Telmisartan	Angiotensin receptor blocker	1.0 mg/kg PO q24h	Increase by 0.5 mg/kg once daily up to 2 mg/kg/d
Losartan	Angiotensin receptor blocker ^b	0.125 mg/kg/d in azotemic dogs 0.5 mg/kg/d in nonazotemic dogs	0.25 mg/kg/d in azotemic dogs 1 mg/kg/d in nonazotemic dogs
Spironolactone	Aldosterone-receptor blocker ^c	1–2 mg/kg PO q12h	

^aACEi and ARBs are antiproteinuric drugs that generally have weak antihypertensive effects.

^bConcurrent administration of an ACEi is generally recommended.

^cReserved for the management of proteinuria in dogs that have increased serum aldosterone concentrations and either have failed or are intolerant of ACEi and ARBs.

3.4-year follow-up period; much of this reduction was in the first 6 months of treatment.^{10,11} In irbesartan-treated patients, every 50% reduction in proteinuria during the first 12 months of treatment reduced the risk of a negative renal outcome by more than half.^{10,11} Telmisartan, an ARB that is more lipophilic and has a longer half-life than losartan, was shown to be more effective in reducing proteinuria than was losartan in patients with diabetic nephropathy.¹¹ Telmisartan also has a higher affinity for the angiotensin-1 receptor and dissociates more slowly when compared with losartan and thus, its blocking effects appear to be insurmountable and persist in vivo for longer than would be predicted from its plasma kinetics. In normal dogs, telmisartan (1 mg/kg PO q24h) more effectively blocks the pressor response to intravenous administration of angiotensin I than enalapril (0.5 mg/kg PO q12h), warranting further study of this ARB in proteinuric dogs with glomerular disease (Hanford C, Coleman A, Schmiedt C, Brown S: Unpublished observations, 2013).

Combined Therapy with ACEi and ARB

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.¹² Furthermore, an ACEi may incompletely block the formation of angiotensin II, particularly within the kidney. Hence, there may be an added benefit to combined therapy with an ACEi and an ARB because of the inability of monotherapy with either class of drug to provide complete RAAS block-

ade.^{10,11} Blockade may be more complete when ACEi is combined with an ARB, although it is still only 75–80% complete. Although there have not been any studies in dogs, studies in people have suggested that these drugs may be additive or perhaps even synergistic in reducing proteinuria.¹³ Because the dosage of each individual drug can be reduced during combined therapy, adverse effects may be less likely.

However, the approach of combining these 2 agents must be used cautiously in light of a recent study published in people where elderly patients prescribed this combination had a higher risk of kidney failure and death.¹⁴ There is limited information available related on the use of ARBs in dogs with glomerular disease. Experience (Vaden S: Unpublished observations, 2013) with its use in 11 dogs with proteinuria and glomerular disease suggests that it can be used safely in combination with ACEi (enalapril) and calcium channel blockade (amlodipine) and is associated with a reduction in proteinuria in most animals (7 of 11 dogs; typically reducing the UPC by ~25%), although its use is associated with a modest increase in serum creatinine (6 of 11 dogs) or potassium (4 of 11 dogs) in some animals. 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-Receptor Blockers

Serum aldosterone increases over time (ie, aldosterone escape) in people treated even with maximal

dosages of ACEi and ARB. Prolonged hyperaldosteronism may have adverse effects on the heart, systemic blood vessels, and kidneys. Aldosterone receptor blockers have been shown to reduce proteinuria and stabilize kidney function in an additive fashion to ACEi and ARB in people.¹⁵ People who have high aldosterone concentrations are more likely to have a reduction in proteinuria in association with administration of an aldosterone receptor blocker. Eplerenone may be the drug of choice in people because of its relative lack of affinity for androgen and progesterone receptors, producing fewer endocrine side effects. However, endocrine side effects of spironolactone appear to be less problematic in dogs, making a rationale for use of eplerenone unclear in veterinary medicine. Although spironolactone has been used most commonly in veterinary medicine, there are little published data or anecdotal information supporting efficacy of this drug in dogs in the management of glomerular disease. Spironolactone would be expected to offer benefit only if serum aldosterone concentrations are increased. This drug could be tried in animals that have high serum aldosterone concentrations and persistent proteinuria in spite of treatment with an ACEi, ARB, or both with the understanding that its efficacy in reducing proteinuria has not been established.

Monitoring RAAS Inhibition

Recommendation 3:

The UPC, urinalysis, systemic arterial blood pressure (BP), and serum albumin, creatinine, and potassium concentrations (in fasting samples) should be monitored at least quarterly in all dogs being treated for glomerular disease.

95% of voting consensus members agreed with Recommendation 3, and 50% of these voters expressed "strong agreement."

In dogs with glomerular disease, introduction of a new drug or dosage modifications are important indications for frequent monitoring (Fig 2). One to 2 weeks after an ACEi or ARB is added or changed, the UPC, serum creatinine, serum potassium, and BP should be evaluated to verify that the recent change in treatment has had the desired therapeutic effect (ie, reduction in UPC), not resulted in a severe worsening of renal function (ie, >30% increase in serum creatinine), a concerning increase in serum potassium concentration, or hypotension (an unlikely occurrence with these drugs). Dogs with marked azotemia, late IRIS CKD stage 3 or stage 4, should be monitored more carefully.

Day-to-day variations in the UPC occur in most dogs with glomerular proteinuria, with greater variation occurring in dogs with UPC >4.¹⁶ Changes in urinary protein content are most accurately assessed by determining 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 to 3 collections.¹⁷ In 1 study, demonstration of a significant difference among serial values for UPC in proteinuric dogs required a change of at least 35% at high UPC values (near 12) and 80% at low UPC values (near 0.5).¹⁶ The reliability of the UPC is adversely impacted by changes in the glomerular filtration rate (GFR), which may occur as a result of disease progression or the hemodynamic effects of RAAS inhibitors. 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 treatment.

Managing Hyperkalemia

Hyperkalemia appears to be a common side effect of RAAS inhibition in dogs with renal disease. Dogs with serum potassium concentrations of >6 mmol/L should be monitored closely. Pseudohyperkalemia, because of the high potassium content of some blood cells, may occur in dogs with glomerular disease. Before modifying treatment, pseudohyperkalemia should be eliminated as a cause by measuring the potassium concentration in lithium heparin plasma. Because of the cardiotoxic effects of potassium, treatment should be modified in dogs with serum potassium concentrations >6.5 mmol/L. In dogs with plasma potassium concentrations of >6 mmol/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, feeding diets that are reduced in potassium, or administering an intestinal potassium binder (eg, kayexelate). Potassium-reduced home-prepared diets that were formulated by a veterinary nutritionist have been shown to effectively correct hyperkalemia in dogs with CKD.¹⁸

Making Therapeutic Adjustments of RAAS Inhibitors

Recommendation 4:

An ACEi should be initial treatment for most dogs with proteinuria. The initial choice of drug and starting dose may vary, but can be gradually increased to achieve a therapeutic target. The ideal therapeutic target is a reduction in the UPC to <0.5 without inappropriate worsening of renal function. However, as this ideal target is not achieved in most dogs, a reduction in UPC of 50% or greater is the recommended alternate target.

95% of voting consensus members agreed with Recommendation 4, and 60% of these voters expressed "strong agreement."

As previously mentioned, it is appropriate to adjust the target UPC to reflect the expected day-to-day

variations in this parameter (Fig 2). The degree to which worsening of renal function is tolerated will in part depend on the IRIS stage of the canine CKD. Dogs with stage 1 and 2 CKD can have an increase in serum creatinine of up to 30% without modifying treatment. The goal in dogs with stage 3 CKD would be to maintain stable renal function; if renal function deteriorates, 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, renal function should be monitored closely and therapeutic adjustments made as needed to maintain baseline renal function.

If the target reduction in UPC is not achieved, the plasma potassium concentration is <6 mmol/L, and any changes in renal function fall within the tolerable limit, then dosages may be increased every 4–6 weeks, starting with a change to 0.5 mg/kg q12h. If the target reduction in UPC is not achieved when a dosage of 2 mg/kg/day of an ACEi is reached, a reasonable next step would be to add an ARB. Higher ACEi dosages may be used but only with caution. Alternatively, an ARB can be used as monotherapy if dogs appear to be intolerant of an ACEi.

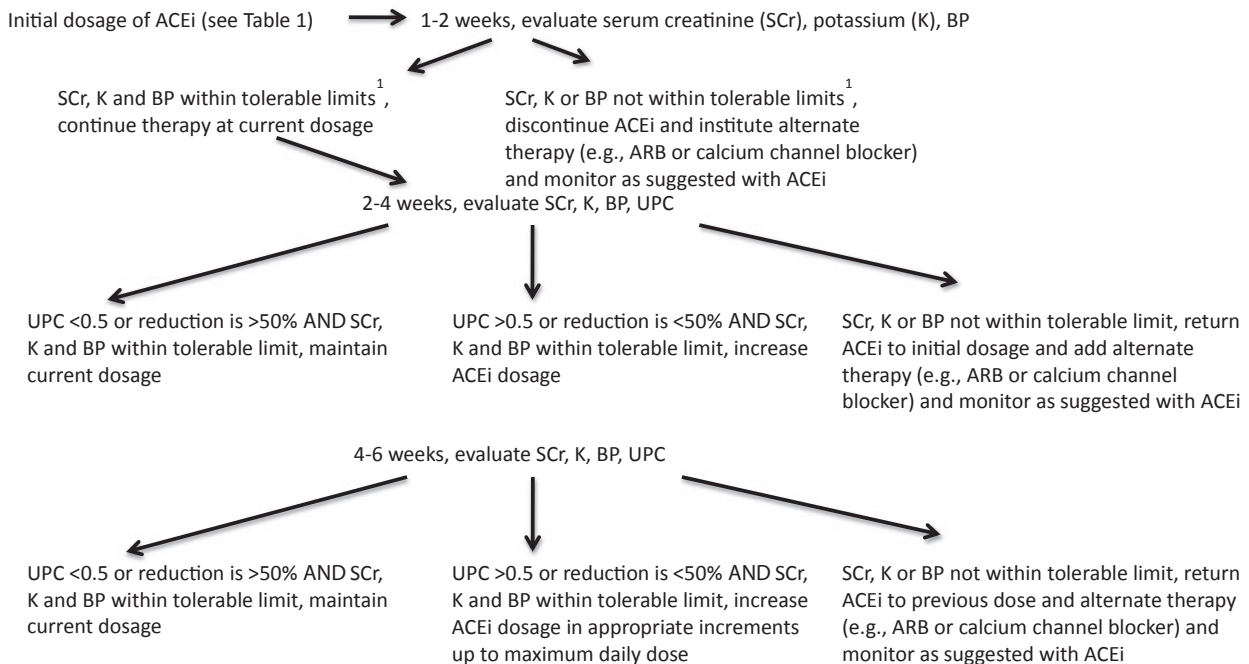
Dietary Therapy in Dogs with Glomerular Disease

Nutrition plays a central role in the management of kidney diseases in veterinary medicine. In dogs, the kidney is susceptible to progressive injury, which has been linked to the magnitude of proteinuria² and the extent of proteinuria may be modified by adjustments in dietary intake in models of CKD^{19–21} including those characterized by marked proteinuria,^{22,23} and the same is true in spontaneous CKD.⁶ Furthermore, alterations in dietary intake can affect the progression of CKD in induced models of CKD,^{20,21,25,26} genetic models of CKD²³ and in spontaneous CKD.²⁴ Substantially less is known about the effects of dietary modification in proteinuric dogs with unstable kidney function, although diet did effect the magnitude of proteinuria and renal hemodynamic response to an acute reduction in renal function in 1 laboratory study of induced CKD in dogs.²¹

Dietary Polyunsaturated Fatty Acids (PUFA)

In laboratory studies of canine kidney disease characterized by secondary glomerular injury, dietary supplementation with n-3 PUFA altered the long-term

Making Adjustments to RAAS Inhibition Therapy in Dogs with Glomerular Disease



1. Tolerable limits: SCr change generally considered tolerable in CKD stage 1 or 2 if $<30\%$ above baseline; in CKD stage 3 $<10\%$ but in stage 4 no increase in SCr may be tolerable. K tolerable when <6.0 mmol/L. Systolic BP should be AP2 (160–179 mmHg) or lower; BP decline acceptable as long as systolic BP >120 mmHg.

Fig 2. Protocol for making adjustments in renin-angiotensin-aldosterone (RAAS) inhibitor therapy.

course of renal injury,²⁰ the hemodynamic response to acute reduction in renal function,²¹ and the magnitude of proteinuria. Dogs with spontaneous CKD exhibit alterations in vasoactive urinary eicosanoid excretion; these changes were interpreted to support a role for glomerular hyperfiltration in progressive canine renal injury.²⁷ Interestingly, short-term studies in dogs with naturally occurring kidney disease indicate that supplementation with n-6 PUFA led to increased GFR.²⁷

In laboratory studies, dietary supplementation with fish oil (specifically docosahexaenoic acid and eicosapentaenoic acid) lowered glomerular pressure, decreased renal eicosanoid series-2 excretion, and provided renoprotection.²¹ Dietary supplementation with lesser amounts of these same PUFA (providing approximately 0.6% n-3 PUFA on a dry weight basis) reduced the dietary n-6 : n-3 PUFA ratio from 50 : 1 to 5 : 1, lowered glomerular capillary pressure, altered urinary excretion of eicosanoids and, in chronic studies, delayed the progression of CKD.²⁸ This latter dietary maneuver is believed to be of long-term benefit to delay progression of renal injury, although the benefits of n-3 PUFA supplementation alone remains to be established in dogs with spontaneous CKD. Although a diet with high n-3 PUFA content prolonged survival,²⁴ there were other potentially beneficial dietary modifications in this study.

In dogs with CKD, dietary supplementation with n-6 PUFA may increase GFR in the short term and dietary supplementation with n-3 PUFA may offer renoprotection in the long term. As these PUFA act competitively, it is not possible to achieve both affects simultaneously in the same animal. Until further information is available, the presently recommended approach is to utilize n-3 PUFA supplementation (specifically docosahexaenoic acid and eicosapentaenoic acid) for dogs with glomerular disease. Although the source and type of PUFA vary, commercially available "kidney diet" preparations that are supplemented with docosahexaenoic acid and eicosapentaenoic acid, providing n-6/n-3 ratios close to 5 : 1, are preferred for dogs with glomerular disease.

The effects of n-3 PUFA supplementation as monotherapy in spontaneous canine glomerular disease have not been well studied. In people with proteinuric renal diseases, specifically IgA nephropathy and lupus nephritis,²⁹ there is evidence of benefit in slowing progression, reducing proteinuria, or both with n-3 PUFA supplementation²⁹ or of a synergistic effect³⁰ of co-administration of n-3 PUFA with drugs that interfere with the RAAS. However, this is controversial, with some studies showing no benefit in people.²⁹

The efficacy of adding n-3 PUFA to diets already containing these fatty acids or the addition of n-3 PUFA to diets with a high n-6/n-3 ratio has not been evaluated in dogs with spontaneous glomerular diseases, but would seem an appropriate consideration. One concern is that supplementation with large amounts of n-3 PUFA alters the function of a variety of nonrenal tissues, including immunologic and hemostatic functions. However, hemostatic and

immunologic dysfunction were not reported in dogs with induced kidney disease fed a diet containing 4% n-3 PUFA, and an n-6/n-3 ratio of less than 0.5, for 20 months.²⁰ Higher levels of n-3 PUFA were shown to be safe and more efficacious than routine n-3 PUFA-supplemented diets in the treatment of canine osteoarthritis.³¹ On the basis of studies to date, where dietary supplementation with n-3 PUFA is chosen, a dosage of 0.25–0.50 g/kg body wt of docosahexaenoic acid and eicosapentaenoic acid should be considered. As PUFA within cell membranes are subject to oxidative damage, the addition of PUFA to the diet increases an animal's antioxidant (eg, vitamin E) requirements. Furthermore, tubular hypermetabolism in CKD³² and the regenerative phase of ongoing kidney damage are believed to expose the kidney to oxidative injury. In this setting, high PUFA diets may enhance oxidative injury and dietary antioxidants have been shown to increase survival in laboratory models of canine CKD.²⁸ Appropriately, commercially available "renal diets", which are PUFA supplemented, contain a variety of supplemental antioxidants. Augmenting dietary PUFA content further would be expected to increase antioxidant requirements. Supplementation with vitamin E was utilized in one long-term laboratory study (1.1 IU of supplemental vitamin E/g of added fish oil).²⁰

Recommendation 5:

Dogs with glomerular disease should be fed a diet with a reduced n-6/n-3 PUFA ratio, approximating 5 : 1. Where dietary supplementation with n-3 PUFA by the owner is used to alter this ratio, a dosage of 0.25–0.50 g of n-3 PUFA/kg body wt, containing eicosapentaenoic acid and docosahexaenoic acid, appropriate for a typical canine diet.

95% of voting consensus members agreed with Recommendation 5, and 40% of these voters expressed "strong agreement."

The PUFA within a diet or stored oil may also be oxidized. Although pet food manufacturers generally add specific antioxidants to diets to address this concern (eg, BHA, BHT, and ethoxyquin), care should be taken to utilize these diets according to recommended expiration dates. Free oils or capsules intended for addition to diets should be stored at 20°C or lower and used in a timely manner.

Dietary Protein

The generally accepted benefits of modification in dietary protein content in canine glomerular disease are to reduce intraglomerular pressure, the magnitude of proteinuria, and the rate of generation of uremic toxins. There is evidence that reduction in protein intake reduces proteinuria²² and that dietary modification, which includes protein restriction,²³

slows progression in genetic models of proteinuric CKD. Furthermore, it has been established that dietary modification, including the use of lower protein intake, is beneficial in spontaneous canine CKD.²⁴

Recommendation 6:

Modified protein diets should be fed to dogs with glomerular disease.

95% of voting consensus members agreed with Recommendation 6, and 80% of these voters expressed "strong agreement."

Dietary Sodium

Although normal dogs are apparently not as salt-sensitive as people or some inbred strains of rats, it is likely that dogs with kidney disease,³³ particularly those with nephrotic syndrome (NS), are salt-sensitive. Furthermore, salt restriction enhances the antihypertensive efficacy and renal hemodynamic effects of some antihypertensive agents in dogs³⁴ and cats,³⁵ particularly those that interfere with the renin angiotensin system.

Recommendation 7:

Based on evidence from laboratory studies, the study group recommends feeding diets formulated to contain reduced sodium chloride content to dogs with glomerular disease.

95% of voting consensus members agreed with Recommendation 7, and 25% of these voters expressed "strong agreement."

Antithrombotic Therapy in Dogs with Glomerular Disease

Thromboembolism is a recognized complication of proteinuria in dogs and humans.^{36–38} The prevalence of thromboembolism in dogs with proteinuric kidney disease (glomerular diseases) has been reported to be as high as 25%.³⁸ In humans with NS, thromboembolism is primarily attributed as venous thromboembolism (VTE) rather than arterial thromboembolism (ATE) with a prevalence of VTE reported to be as high as 42% and ATE as high as 5.5%.³⁹ Although both VTE and ATE have been described in dogs, clinical observations suggest that VTE may also be the more common cause for thromboembolism in dogs.^{36,38} The ratio of proteinuria to serum albumin has been reported to be predictive of VTE in humans with NS.³⁷ Although the relationship between the magnitude of proteinuria and development of thromboembolism has not been well established in dogs, it is generally accepted that the risk of thromboembolism increases as the concentrations of antithrombin III and serum albumin decline consequent to proteinuria.

Virchow postulated 3 main causes of thrombosis: stasis of the blood, changes in the vessel wall, and changes in the composition of blood. Factors in the first and third of Virchow's groups are linked to development of VTE.⁴⁰ The mechanisms underlying the thrombotic diathesis associated with proteinuria (NS) are poorly understood, but loss of antithrombotic substances into the urine is often invoked. However, this explanation probably grossly oversimplifies the circumstances. Decreased levels of factors IX and XI, and of antithrombin III have been recognized in humans with NS. Similarly, reduced levels of antithrombin III have also been recognized in dogs with severe proteinuria. Although there may be loss of small molecular weight factors into the urine, there is also an increase in plasma procoagulant cofactors, factors V and VIII, and fibrinogen levels.³⁹ In addition, platelet reactivity is increased (in vitro), but appears to be flow-dependent.⁴¹ Inactivity of human patients with NS has been linked to increased risk of VTE,³⁹ and venous stasis associated with volume depletion may also promote thrombus formation. Thus, the procoagulant state associated with VTE in the NS appears to be multifactorial in origin.

The pathophysiology of ATE is thought to differ from that of VTE, with changes in vessel walls and platelet activation being of greater importance. However, several studies have provided evidence that altered vessel wall activity may also promote VTE.⁴⁰ The recent observation that microalbuminuria is independently associated with increased risk for VTE in humans tends to support a possible role for vessel wall involvement in the development of VTE and ATE in glomerular diseases when viewed in the context of microalbuminuria being a marker for generalized endothelial dysfunction.⁴⁰ However, evidence of an association between endothelial dysfunction and microalbuminuria is lacking in the dog, largely because of the lack of robust methods for assessing endothelial cell function in vivo in dogs. Nonetheless, these observations may provide a pathophysiologic justification for the use of aspirin in preventing VTE in dogs with glomerular disease.

Recommendations for prophylaxis of VTE in humans as well as dogs include administration of heparin and vitamin K antagonists.^{42,43} Limited evidence suggests that antiplatelet agents may provide some protection against VTE in hospitalized human patients.⁴³ However, the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Prevention of Venous Thromboembolism does not recommend the use of aspirin alone as prophylaxis against VTE, primarily because more effective methods of thromboprophylaxis are readily available.⁴³ In support of this position, they cite a number of trials that report no significant benefit from aspirin VTE prophylaxis, or found that aspirin was inferior to other thromboprophylaxis modalities.

Options for thromboprophylaxis available for clinical use in dogs are limited with heparin and aspirin predominating.⁴⁴ Very limited studies are available to

support the value of antithrombotic therapy in dogs, and no studies specifically address the issue of antithrombotic therapy in dogs with glomerular disease. Thus, there is little conclusive evidence on which to base recommendations for prophylaxis of VTE in dogs, regardless of cause.⁴² Such evidence is difficult to derive and would require large well-coordinated multicenter randomized controlled clinical trials enrolling sufficient patients at risk and to treat them for long enough to determine whether there was a benefit in reducing the incidence rate of this sporadic complication of glomerular disease.

Although coumarin derivatives (warfarin) and heparin are the anticoagulants most commonly used to manage VTE in humans, they are not recommended for long-term use in dogs with glomerular disease because of issues with administration, monitoring, and potential complications. Hemorrhagic complications are common in humans managed with coumarin derivatives and careful and frequent monitoring of drug dosage is essential with these drugs.⁴⁴ One recent study suggested that the antithrombotic effect of heparin may be most effective in dogs with immune-mediated hemolytic anemia when heparin dosage is adjusted according to factor Xa assay results, whereas standard (unadjusted) doses of heparin may in fact promote thrombosis.⁴⁵ In addition, as heparin acts through enhancement of the inhibitory actions of antithrombin, reduced levels of antithrombin found in many dogs with NS suggest that heparin is likely to be less effective in dogs most likely to develop thromboembolism.⁴⁴

There are no evidence-based clinical studies on which to base recommendations for determining when intervention is justified or for which drugs to use for prophylaxis of VTE or ATE in dogs with glomerular disease. The current recommendation for thromboprophylaxis in dogs with glomerular disease remains low-dose aspirin (0.5–5 mg/kg daily).^{36,42} However, the optimum aspirin protocol for limiting TE in dogs is unknown and appropriate assessments of the impact of low dosages of aspirin on canine platelets are limited. In one study, platelet aggregation was significantly reduced in healthy dogs in response to 0.5 mg/kg, PO, q12h.⁴⁶ However, a recent abstract reported no effect of aspirin at this dosage on platelet function measured by aggregometry and a shear-based function test (PFA100®).⁴⁷ Instead, the authors reported 1 mg/kg to be the minimum dosage to alter platelet function in 73 healthy dogs when assessed with these methods. A more recent study found that administration of 1 mg/kg/d of aspirin failed to consistently suppress platelet function, suggesting that dosages of 1 mg/kg or less per day may not consistently impact platelet-mediated thrombosis/thromboembolism.⁴⁸ Studies documenting effectiveness of doses between 1 and 5 mg/kg of aspirin in dogs have not been published.

Preliminary evidence suggests that clopidogrel (Plavix) may be effective in reducing platelet activity, at least in normal dogs, at an oral dose of approximately 1.1 mg/kg every 24 h.⁴⁹ However, evidence that it is superior to aspirin in prophylaxis of VTE in dogs

is lacking. In a clinical trial of dogs with spontaneous primary immune-mediated hemolytic anemia, a condition commonly complicated by development of fatal venous thromboembolism, clopidogrel alone or in combination with 0.5 mg/kg/d of aspirin, was safe but had similar short-term survival compared with aspirin alone at the same dosage in a small group of animals treated with standard immunosuppressive therapy.⁵⁰ Evidence of safety and effectiveness in preventing VTE or ATE in dogs with spontaneous glomerular disease is not available. Although clopidogrel may be safe and possibly effective in dogs, it is substantially more expensive than low-dose aspirin.

Recommendation 8:

The study group recommends daily administration of low-dose aspirin (1–5 mg/kg daily) for thromboprophylaxis in dogs with proteinuric glomerular disease. Clopidogrel may be similarly effective to aspirin and may be used instead of aspirin; however, there is no compelling evidence that it is superior to low-dose aspirin in dogs with glomerular disease.

95% of voting consensus members agreed with Recommendation 8, and 40% of these voters expressed “strong agreement.”

Although evidence supporting efficacy of aspirin as prophylaxis for VTE in dogs is poor (expert opinion and uncontrolled clinical observations), it is broadly applied to proteinuric dogs and appears to be safe provided that the dogs are well hydrated and normotensive. Previous recommendations for aspirin dosage in dogs with NS have included dosages as low as 0.5 mg/kg; however, more recent studies in normal and dogs with immune-mediated hemolytic anemia (Stiller A, Armstrong PJ, Polzin DJ, Smith SA: unpublished observations, 2013) have suggested that aspirin at 0.5 mg/kg is unlikely to modify platelet function. In addition, the recommendation to administer aspirin to dogs with glomerular disease is based on studies supporting an apparent beneficial effect of a thromboxane synthetase inhibitor in ameliorating proteinuria in dogs with glomerular disease.^{51–53} Direct evidence that aspirin therapy influences renal function or pathology in dogs with spontaneous glomerular disease is lacking.

Systemic Hypertension and Target Organ Damage (TOD) to the Kidneys

Systemic hypertension is problematic because chronically sustained elevations of BP produce injury to tissues⁵⁴; the rationale for treatment of hypertension in dogs with glomerular disease is to minimize or prevent this injury in the kidney, eyes, brain, or cardiovascular system. Damage that results from the presence of sustained high BP is referred to as TOD. In the kidney, TOD is generally manifest as an enhanced rate of decline of renal function, mortality, increased fre-

quency of uremic crises, or increased magnitude of proteinuria.^{3,4,54–58} Although hypertension appears to be more prevalent in advanced CKD, it may be present in any IRIS stage. Ocular, central nervous system, and cardiovascular TOD is observed in many dogs with hypertension and effective treatment is generally believed to reduce the likelihood of further TOD in these tissues.⁵⁴

Measurement of BP

Diagnosis and management of hypertension in dogs with acute or chronic glomerular disease should be based on measurement of the patient's BP.⁵⁴ The choice of measurement device depends on operator experience and preference. Results of all BP measurements, rationale for excluding values, the final (mean) result, and interpretation of the result by the veterinarian should be noted. The animal's position and attitude, cuff size and site, and cuff site circumference (cm), and values obtained should be carefully considered and noted in the animal record.

Treatment of Hypertension

Recommendation 9:

The initial assessment of a dog with glomerular disease suspected of having systemic hypertension should include recognizing conditions that may be contributing to an increase in BP, identifying and characterizing TOD, and determining if there are any seemingly unrelated concurrent conditions that may complicate antihypertensive therapy.

100% of voting consensus members agreed with Recommendation 9, and 60% of these voters expressed "strong agreement."

Because hypertension is often a silent, slowly progressive condition requiring vigilance and life-long therapy, it is important to be absolutely certain about the diagnosis: a high BP measurement in a dog with glomerular disease could represent either secondary or artifactual (anxiety-induced or "white-coat") hypertension or a combination of both.⁵⁴ White-coat hypertension is not an indication for treatment in dogs. A decision to use antihypertensive drugs should be based on the integration of all clinically available information and multiple measurements of BP.

Decision to Institute Treatment for Hypertension

In people, any reduction in BP that does not produce overt hypotension lowers the risk of TOD. This finding is consistent with results of a laboratory study in dogs,⁵⁸ but remains to be confirmed in dogs with spontaneous glomerular disease. The ACVIM Hypertension Consensus Panel⁵⁴ and International Renal Interest Society (IRIS)⁵⁹ recommend that BP be

Table 2. Staging of blood pressure (BP; mmHg) in dogs and cats based on risk for future target organ damage.^a

Systolic	Diastolic	Risk of Future Target Organ Damage	BP Stage
<150	<95	None or minimal	AP0
150–159	95–99	Low	AP1
160–179	100–119	Moderate	AP2
≥180	≥120	High	AP3

^aWhere reliable measurements (see text) lead to different categories based on separate consideration of the patient's systolic and diastolic BP, the patient's BP stage should be taken as the higher risk.

categorized on the basis of risk of future TOD (Table 2). While there are interbreed differences in BP in dogs, at this time, only the difference (20 mmHg higher values for each category) for Sight Hounds mandates separate categorization at this time.^{59–61}

Recommendation 10:

Dogs with glomerular disease are presumed to have TOD and the general consensus is to institute treatment in a patient wherein reliable measurement of BP indicates that systolic BP (SBP) exceeds 160 or diastolic BP (DBP) exceeds 100 mmHg (AP2 or higher—see Table 2 for definitions).

90% of voting consensus members agreed with Recommendation 10, and 45% of these voters expressed "strong agreement."

Antihypertensive Therapy

Recommendation 11:

Antihypertensive therapy must be individualized to the patient and its concurrent conditions. Regardless of the initial level of BP, the goal of treatment should be to maximally reduce the risk of future TOD (Stage AP0: SBP<150, DBP <95 mmHg, or both) and to significantly lower the magnitude of proteinuria (UPC <0.5 is the primary goal; UPC reduced by 50% or more if the primary goal is not achievable). Certainly, a minimal goal of antihypertensive therapy is to achieve a reduction in stage of risk for TOD (Table 2). Except in a hypertensive crisis wherein severe ocular or central nervous system TOD is present, this is not an emergency and BP lowering should be achieved with a gradual, persistent reduction in BP achieved over several weeks.

85% of voting consensus members agreed with Recommendation 11, and 40% of these voters expressed "strong agreement."

Although available evidence suggests that sodium restriction alone generally does not reduce BP,³³ high salt intake may produce adverse consequences in some settings^{33,62} but not others.⁶³ Although the BP of normal dogs is minimally affected by variations in NaCl intake,³³ it is likely that dogs with kidney disease, particularly those with NS, are salt-sensitive. Furthermore, salt restriction enhances the antihypertensive efficacy of some antihypertensive agents, particularly those that interfere with the RAAS. This evidence serves as the basis for recommendation 7 to feed a diet with modified sodium chloride content to dogs with proteinuric kidney disease, regardless of IRIS stage.

Clinical experience indicates that RAAS inhibitors reduce BP slightly (~10–15%) and are antiproteinuric. For a variety of reasons, these agents will already be used in dogs with glomerular disease (including those classified as AP0 or AP1). If hypertension is identified in a dog with glomerular disease that is not receiving an ACEi or an ARB, institution of an ACEi is an appropriate first step. The starting dosage should be at or above the lower end of the recommended range (Table 3). The upper limit of our recommended dosage range for the ACEi is controversial as some experts will stop at or below this dosage, while others will increase the ACEi dosage even further. Most consider the addition of a calcium channel blocker (ie, amlodipine), or an ARB, to be an appropriate next consideration. If an antihypertensive agent of choice is only partially effective, the usual approach is to increase the dosage or add an additional drug.

Recommendation 12:

In dogs with glomerular disease and either severe systemic hypertension (AP3) or a hypertensive emergency (eg, systolic BP above 200 mmHg or evidence of ocular or neurologic target organ damage), co-administration of two agents with different mechanisms of action (generally an ACEi plus amlodipine) is recommended.

100% of voting consensus members agreed with Recommendation 12, and 55% of these voters expressed “strong agreement.”

Proteinuric dogs with significant hypertension will usually require more than two antihypertensive agents. In this setting, the general consensus is to add the calcium channel blocker, amlodipine, to RAAS inhibition. Some uncommon disease conditions may be best addressed with the addition of specific classes of agents in addition to RAAS inhibitors plus amlodipine, such as alpha- and beta-blockers or surgical excision for pheochromocytoma or an aldosterone receptor blocker or surgical excision of an adrenal tumor in animals with hypertension associated with hyperaldosteronism. Diuretics are not commonly used in dogs with CKD, but may be useful, especially in patients with concurrent hypertension and NS (see below).

The benefits of BP lowering on TOD within the kidney (ie, slowing of progressive decline in GFR and reduction in UPC) are directly dependent on the degree of proteinuria in people⁵⁶ and cats,⁵⁷ leading to

Table 3. Oral agents for antihypertensive therapy in dogs with glomerular disease^a

Class	Drug (Examples of Trade Name)	Usual Oral Dosage
ACEi/ARB		
Angiotensin-converting enzyme inhibitor	Benazepril (Lotensin; Fortekor)	see Table 1
	Enalapril (Vasotec; Enacard)	see Table 1
	Ramipril	see Table 1
	Imidapril	see Table 1
Angiotensin receptor blocker	Telmisartan	see Table 1
	Losartan (Cozaar)	see Table 1
CCB		
Calcium channel blocker	Amlodipine (Norvasc)	0.1–0.75 mg/kg q24h
Other Agents		
β blocker	Atenolol (Tenormin)	0.25–1.0 mg/kg q12h
	Prazosin (Minipress)	0.5–2 mg/kg q8–12h
α ₁ blocker	Phenoxybenazime (Dibenzyline)	0.25 mg/kg q8–12h or 0.5 mg/kg q24h
	Hydralazine (Apresoline)	0.5–2 mg/kg q12h (start at low end of range)
Direct vasodilator	Acepromazine (PromAce)	0.5–2 mg/kg q8h
Diuretics		
Thiazide diuretic	Hydrochlorothiazide (HydroDiuril)	2–4 mg/kg q12–24h
Loop diuretic	Furosemide (Lasix)	1–4 mg/kg q8–24h
Aldosterone receptor blocker	Spironolactone (Aldactone, Prilactone)	see Table 1

^aAgents that interfere with the renin-angiotensin-aldosterone system (ie, ACEIs, ARBs, or aldosterone blockers) are used to manage dogs with glomerular disease that exhibit proteinuria, hypertension, or both. Although the end-points differ when managing proteinuria (UPC is the end-point) and hypertension (BP and the UPC are used to assess the efficacy of antihypertensive therapy), the dosing and follow-up are essentially the same when approaching either problem or both together in a canine patient.

our consensus that achievement of BP control is more important in proteinuric dogs.

Besides the antiproteinuric effects of agents that interfere with the RAAS, other classes of agents may be considerations for the future. The CCB blocker in common use clinically (ie, amlodipine) is an L-type calcium channel blocker, which appear to be less antiproteinuric because of preferential dilatation of the afferent arteriole in dogs,^{55,64} forming the basis for the recommendation of co-administration of RAAS inhibitors. There are alternative CCB, which are L/T (eg, efonidipine)⁶⁵ and L/N blockers (eg, clinidipine)⁶⁶ both of which are more likely to effectively dilate the efferent arteriole than amlodipine. Furthermore, the L/N blockers appear to be sympatholytic.⁶⁶ Both of these newer classes of calcium channel blockers hold promise because of their potential for renoprotection but are, as of yet, not tested in the clinical setting in dogs with glomerular disease.

An exception to the above graded approach to BP reduction is dogs with AP3 and evidence of severe or progressing neural or ocular TOD, which is generally taken to constitute an emergency. In this setting, more aggressive, combination therapy with a RAAS inhibitor plus amlodipine is an appropriate first step.

Monitoring Antihypertensive Therapy

Ocular and neural TOD may result in a hypertensive crisis, necessitating rapid lowering of BP.⁵⁴ In most other situations, hypertension is not an emergency and 2–4 weeks should be allowed between dosage adjustments. There has been concern about acute exacerbation of azotemia with ACEi, although this is an unusual complication and modest increases in serum creatinine concentration (<30%) may occur and are generally tolerable in IRIS CKD stages 1–2 and early stage 3.

Recommendation 13:

A dog with glomerular disease in IRIS CKD stages 1 or 2 should be evaluated 3–14 days following any change in antihypertensive therapy. In unstable patients and those with IRIS stage 3 or 4 CKD, this recheck should be conducted in a shorter timeframe, typically 3–5 days. Patients deemed to be hypertensive emergencies and hospitalized patients, particularly those receiving fluid therapy or pharmacological agents with cardiovascular effects, should be assessed daily. The purpose of these short-term assessments is to determine if there are any findings that are unexpected (eg, new or worsening TOD) or adverse (eg, marked worsening of azotemia or systemic hypotension).

100% of voting consensus members agreed with Recommendation 13, and 55% of these voters expressed “strong agreement.”

Treatment should be adjusted downward if an increase in serum creatinine of >30% or a BP <120/60 mmHg (combined with clinical findings of weakness or syncope) is observed.⁵⁴

Re-evaluation at 1–4 month intervals is recommended, with chosen interval depending on stability of BP and stage of disease (more frequent if BP or other conditions are unstable, late stage 3 or stage 4 CKD) and level of elevation (more frequent in AP3) is appropriate. Follow-up evaluations, which are employed to assess efficacy of treatment and make adjustments if appropriate, should include measurement of BP, serum creatinine concentration, urinalysis with UPC, funduscopic examination, and other specific assessments depending on the individual circumstances (eg, TOD, causes of secondary hypertension, and concurrent conditions) of the patient. In dogs, a key predictive parameter for antihypertensive efficacy is the effect of treatment on the magnitude of proteinuria (UPC)^{1–3,20,55,64} and a benefit is predicted if the antihypertensive regimen used is antiproteinuric (ie, reduces UPC by at least 50%, preferably to <0.5). The frequency and nature of re-evaluations will vary depending on the BP substage, stability of BP, other aspects of the health of the patient, and frequency of dosage adjustment to antihypertensive therapy. As signs of progression of TOD can be subtle, BP should be closely monitored over time in patients receiving antihypertensive therapy, even when hypertension is seemingly well controlled.

Fluid and Diuretic Therapy in Dogs with Glomerular Disease

Alterations of fluid homeostasis are common in small animals with glomerular diseases and they include excesses, deficits, and intercompartmental maldistribution.^{38,67} These alterations may require interventions as a supportive measure for anesthesia (renal biopsy, unrelated surgery), as a compensation for increased losses such as those associated with gastrointestinal complications, or to decrease severe interstitial fluid accumulation in nephrotic patients. The restoration of disturbed fluid homeostasis can, however, be challenging in dogs affected with glomerular disease. Attempts to treat these animals commonly result either in exacerbation of peripheral edema and systemic hypertension with fluid administration or in worsening azotemia and uremic crisis with diuretic therapy. This difficulty is likely a consequence of our poor understanding of the mechanisms underlying edema formation and fluid maldistribution in glomerular diseases and of our limited ability to evaluate precisely and accurately the various clinical parameters of fluid balance in individual animals.

Mechanisms of Edema Formation in Glomerular Diseases and Patient Evaluation

Edema formation in nephrotic patients has been explained classically as being attributable to decreased

plasma colloid osmotic pressure resulting from the hypoalbuminemia associated with glomerular protein loss. According to this explanation, leakage of plasma water into the interstitium results in hypovolemia, activates the RAAS, causes sodium and fluid accumulation, and thus worsens edema formation.⁶⁸ However, this “underfill theory” has been challenged based on clinical observations and results of studies in models of NS, which indicate a lack of evidence of hypovolemia in most patients and a lack of efficacy of colloid therapy or RAAS blockade for the resolution of nephrotic edema.⁶⁹ Experimentally, severe hypoalbuminemia or even analbuminemia alone, is rarely sufficient to cause severe edema since the colloid osmotic pressure of the interstitium decreases in parallel to that of the plasma, maintaining a similar transcapillary oncotic gradient.⁷⁰ Clinically, except when suffering from additional fluid losses, most patients do not appear to be in a volume-contracted state.

Evidence of inappropriate renal tubular sodium retention and excessive volume expansion as a major causative mechanism for edema formation is accumulating from rodent models of NS.^{70,71} Although this “overflow theory” cannot necessarily be extrapolated to dogs, it could explain some of the controversial clinical observations such as the worsening of edema sometimes observed with colloid use, the high prevalence of systemic hypertension, and the poor response of hypertension to RAAS blockade alone.⁷² Furthermore, the “vascular hyperpermeability theory” suggests an additional contributor to interstitial fluid accumulation in some forms of systemic vascular and glomerular inflammation. A recent review of the clinical manifestations of NS did not provide conclusive evidence for or against these 3 theories, possibly indicating a combination of potential mechanisms and their respective dominance in certain defined conditions.⁶⁷

Fluid Volume Status: Patient Assessment

Recommendation 14:

As data on the prevailing mechanisms of nephrotic edema in the canine species are lacking, careful assessment of the hydration, and of the vascular volume of individual dogs with glomerular disease should be a priority both before and during fluid therapy.

90% of voting consensus members agreed with Recommendation 14, and 45% of these voters expressed “strong agreement.”

Nephrotic patients are, per definition, overhydrated. However, this interstitial fluid accumulation can be associated with either vascular volume contraction or expansion.⁷³ The evaluation of the volume status of an individual animal with NS should therefore focus primarily on the intravascular volume and aim at differentiating hypovolemic-underfilled from hypervo-

lemic-overfilled dogs. Non-nephrotic animals with glomerular disease should be evaluated similarly. However, as our ability to predict iatrogenic edema formation with fluid therapy is limited, these dogs should be considered at risk with fluid therapy being prescribed conservatively, rather than assuming that they are volume contracted.

Recommendation 15:

The evaluation of the fluid status of a dog with glomerular disease should be based on anamnestic data (eg, serial body weight) and a complete physical examination with special emphasis on skin turgor, mucous membrane color and moisture, capillary refill time, temperature of the extremities, heart rate, pulse quality, and systemic BP.

95% of voting consensus members agreed with Recommendation 15, and 55% of these voters expressed “strong agreement.”

More objective techniques for measurement of body composition such as isotope dilution or bioimpedance spectroscopy could help the assessment of fluid distribution, but they are rarely available clinically and they remain to be validated for dogs in this setting. Indirect markers of vascular expansion (eg, natriuretic peptides) and echocardiographic parameters have been suggested for the evaluation of the volume status in nephrotic people⁷³ and they could prove useful for assessment of dogs in the future. A clinical study in children with nephrotic edema indicated that volume-contracted patients had a higher BUN, higher BUN/creatinine ratio, higher urine osmolality, and lower fractional excretion of sodium compared with volume-expanded patients. They also had significantly higher renin, aldosterone, and antidiuretic hormone levels.⁷⁴ Whether these simple markers could prove useful for evaluation of dogs with nephrotic edema remains to be evaluated.

Nephrotic Syndrome: Indications for Intervention

Treatment of nephrotic edema and effusion is addressed primarily through treatment of the underlying etiology and reduction in proteinuria. Specific treatment of edema and drainage of effusions are reserved for the symptomatic support of animals with significant respiratory distress, abdominal discomfort, or other severe complications caused by excessive fluid accumulation.

Recommendation 16:

Because there is no rationale for diuretic intervention in dogs with glomerular disease and mild peripheral edema, use of diuretics in dogs with edema should be limited to situations where organ function is critically impaired (eg, ascites or pleural effusion that impairs respiration).

90% of voting consensus members agreed with Recommendation 16, and 35% of these voters expressed “strong agreement.”

Overfilled, stable dogs with NS typically should not require fluid therapy either, even for short elective anesthesia such as required for ultrasound-guided renal biopsy, for example. Unstable nephrotic animals necessitating anesthesia, however, require a thorough global evaluation and the need for intervention has to be assessed individually, taking into consideration volume, oncotic, and osmotic parameters.⁷³ If deemed absolutely necessary, fluid administration should remain very conservative and be re-evaluated frequently. There are no data to support the combination of diuretics and fluids. Severe pleural and abdominal effusions are more efficiently removed by thoraco- and abdominocentesis, respectively.

Underfilled dogs with or without edema may require therapeutic volume expansion for acute clinical manifestations (eg, vomiting, diarrhea), peri-operatively, or for worsening azotemia. As the rate of complications is high in animals with glomerular disease treated with fluids, the exact indication and the specific goals of fluid therapy need to be assessed critically and the fluid rates chosen very conservatively. Careful monitoring

and re-evaluation of the response and safety of the treatment guide the fluid prescription (see Fig 3).

Non-nephrotic dogs with IRIS CKD stages 3–4 commonly benefit from subcutaneous fluid administration with improved appetite and activity. It is therefore likely that a similar benefit could be expected in dogs with glomerular disease reaching these advanced stages of CKD. The fluid and sodium load associated with this treatment should, however, be carefully considered, especially in hypertensive and volume-expanded, overfilled dogs or those with NS. Careful titration of the fluid dose, monitoring of the resorption of the administered fluid, and evaluation of potential adverse effects should be performed when this treatment is chosen.

Nephrotic Syndrome: Diuretic Therapy

When intervention is indicated, the loop diuretic furosemide is usually recommended as the initial choice for the treatment of overfilled, nephrotic humans.^{70,73,74} To promote natriuresis and diuresis, this diuretic needs to reach a threshold concentration at its site of action in the thick ascending limb of the loop of Henle, through active secretion into the proxi-

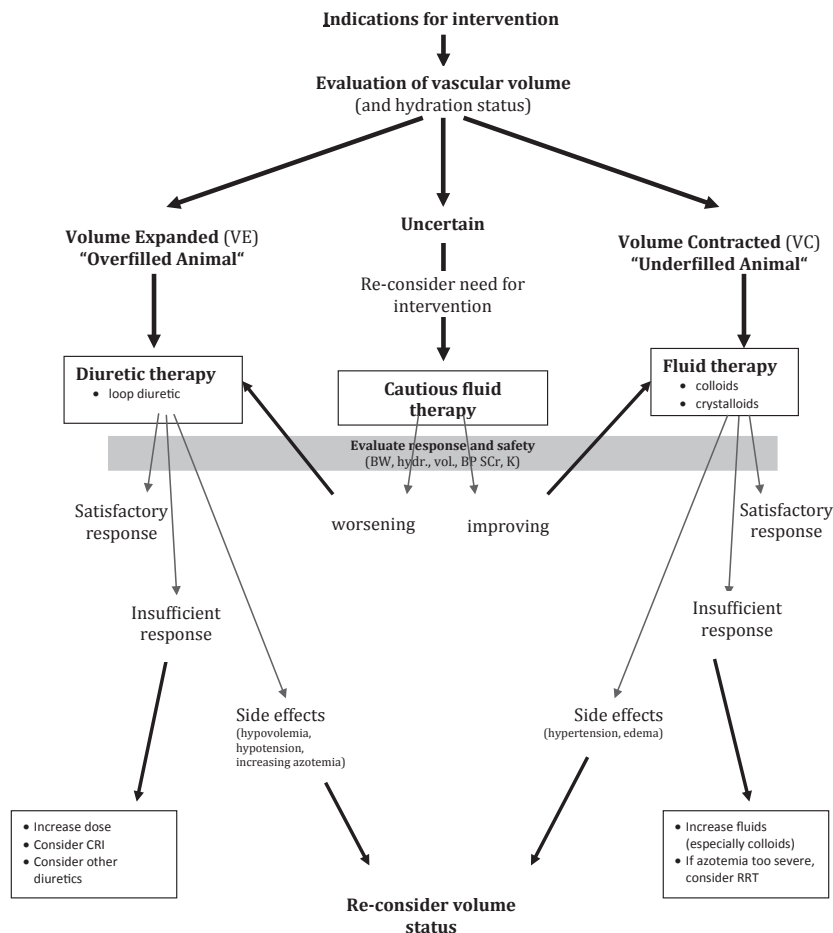


Fig 3. Algorithm for treatment of fluid imbalances in dogs with glomerular disease (BW, body weight; hydr., hydration; vol., volemia; BP, blood pressure; SCr, serum creatinine; K, potassium; CRI, constant-rate infusion; RRT, renal replacement therapy).

mal tubule. Pharmacokinetic alterations are common in patients with glomerular diseases, including decreased renal diuretic delivery and secretion, increased protein binding of the diuretic in the urine, increased renal metabolism, and increased sodium and water reabsorption in downstream segments.⁷⁰ Altered threshold of action and decreased maximal diuretic response often necessitate a careful titration with higher doses and more frequent administration in nephrotic patients.⁷⁵ Administration as a constant-rate infusion and titration to effect have been recommended for refractory cases to overcome the short half-life of loop diuretics and to avoid significant postdose sodium retention by the kidney. Increased diuretic efficacy has been shown in normal Greyhounds when furosemide was administered as a CRI as opposed to intermittent bolus injections.⁷⁶ However, no data are available for nephrotic dogs.

Furosemide is routinely co-administered with IV albumin in nephrotic humans with severely decreased serum albumin concentration aiming to overcome diuretic resistance and to avoid hypovolemia.⁷⁷ However, furosemide alone was shown to be equally safe and effective in a study involving nephrotic children⁷⁴ and there are no data to support this strategy in nephrotic dogs.

Humans commonly require a combination approach with distally acting diuretics, such as spironolactone or thiazides.⁷⁵ This sequential nephron blockade needs to be performed with caution, because a combination with thiazide diuretics can induce a marked kaliuresis and the use of potassium-sparing diuretics, such as spironolactone, can result in severe hyperkalemia, especially when combined with an ACEi or ARB for the treatment of proteinuria. Although anecdotal accounts provide some support for the efficacy of spironolactone in dogs with NS, neither single-drug nor combination protocols have been evaluated in dogs with glomerular disease.

Recommendation 17:

When indicated in a dog with glomerular disease, diuretic therapy with furosemide or spironolactone may be instituted. Furosemide may be the first choice drug in dogs with pulmonary edema or hyperkalemia and spironolactone for dogs with pleural or abdominal effusion. Furosemide may be administered at an initial dosage of 1 mg/kg q6–12h, with incremental increases of 0.5–1 mg/kg q6–12h or conversion into continuous IV infusion at a rate of 2–15 µg/kg/min after an initial loading dose of 2 mg/kg in animals with insufficient response. Spironolactone may be started at 1 mg/kg q12–24h and titrated in increments of 1 mg/kg q12–24h to a maximum of 4 mg/kg q12–24h.

76% of voting consensus members agreed with Recommendation 17, and 25% of these voters expressed “strong agreement.”

Goals of diuretic treatment should include a slow progressive decrease in the edema to a clinically acceptable condition. Overaggressive treatment should be avoided because the resulting vascular volume depletion can lead to worsening azotemia, venous stasis, and thromboembolic disease. Treatment efficacy should be assessed clinically by serial body weight measurements. Electrolytes, especially potassium, should be monitored closely in all animals with glomerular disease treated with diuretics, initially within 1 week of initiating treatment. As successful diuresis can cause exaggerated intravascular volume depletion and acute decompensation of renal function, physical examination and serum creatinine should be monitored even more closely, as early as 1–2 days after initiation of diuretic therapy in critical patients.

The use and efficacy of additional measures to mobilize edema is controversial and based purely on pathophysiological considerations.⁷⁸ Dietary sodium restriction may seem logical and useful in the light of inappropriate renal sodium retention in the pathogenesis of nephrotic edema. Mild and regular exercise may help eliminate excessive fluid accumulation and decrease risk of thromboembolism.⁷⁹ Although sometimes recommended for dogs with severe edema, recommendations to institute cage rest in dogs with NS are not supported by evidence and this approach could potentially prove detrimental by worsening vascular stasis and thrombotic risk.

Nephrotic Syndrome: Fluid Therapy

Recommendation 18:

Fluid replacement therapy should be used with great caution in dogs with glomerular disease because they are predisposed to fluid overload. Intravenous fluid therapy is indicated for hemodynamic stabilization (eg, a patient with dehydration, poor tissue perfusion) of the patient. Colloids or plasma/albumin should not be administered solely on the basis of decreased oncotic pressure, serum albumin concentration, or total protein concentration, or for mobilizing edema. The end-point of treatment should be the patient's response to treatment (ie, correction of tissue hypoperfusion, hypotension, hypovolemia, dehydration). Judicious administration of colloids should be considered when crystalloid fluid support has failed to correct the patient's hemodynamic dysfunction.

95% of voting consensus members agreed with Recommendation 18, and 30% of these voters expressed “strong agreement.”

Early evaluation of the clinical response should guide changes in fluid type and administration rate. Further monitoring should include at least twice-daily physical examination, with special attention to hydration and blood volume; twice daily monitoring

of body weight, BP, and urine output; and daily measurement of serum creatinine, BUN, and electrolytes.

Although the pathophysiologic basis of the “underfilled theory” supports the use of colloids in dogs with NS, there are limited clinical data on their utility in dogs with glomerular disease. Recent studies in people have suggested that colloids should not be routinely administered for mobilizing edema^{80,81} and may have adverse effects on the kidney.⁸⁰ It is appropriate to consider the judicious administration of colloids whenever crystalloid fluid support has failed to correct the patient’s hemodynamic dysfunction (ie, tissue hypoperfusion, systemic hypotension, hypovolemia, dehydration).

When the fluid status cannot be established with certainty, a very conservative approach should be chosen, with critical re-evaluation of the real or perceived needs of the animal. Initially, a similar fluid therapy protocol as for hypovolemic dogs seems safe and probably appropriate for most animals. It should, however, be monitored even more closely for adverse effects and complications, with physical examinations, urine production, and BP monitoring every 6 h. The trend of the clinical status will either confirm the treatment choice or, in case of worsening edema and systemic hypertension, a change in strategy using diuretics should be considered to improve salt or water excretion or both.

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