Consensus Statements on the Management of Proteinuria

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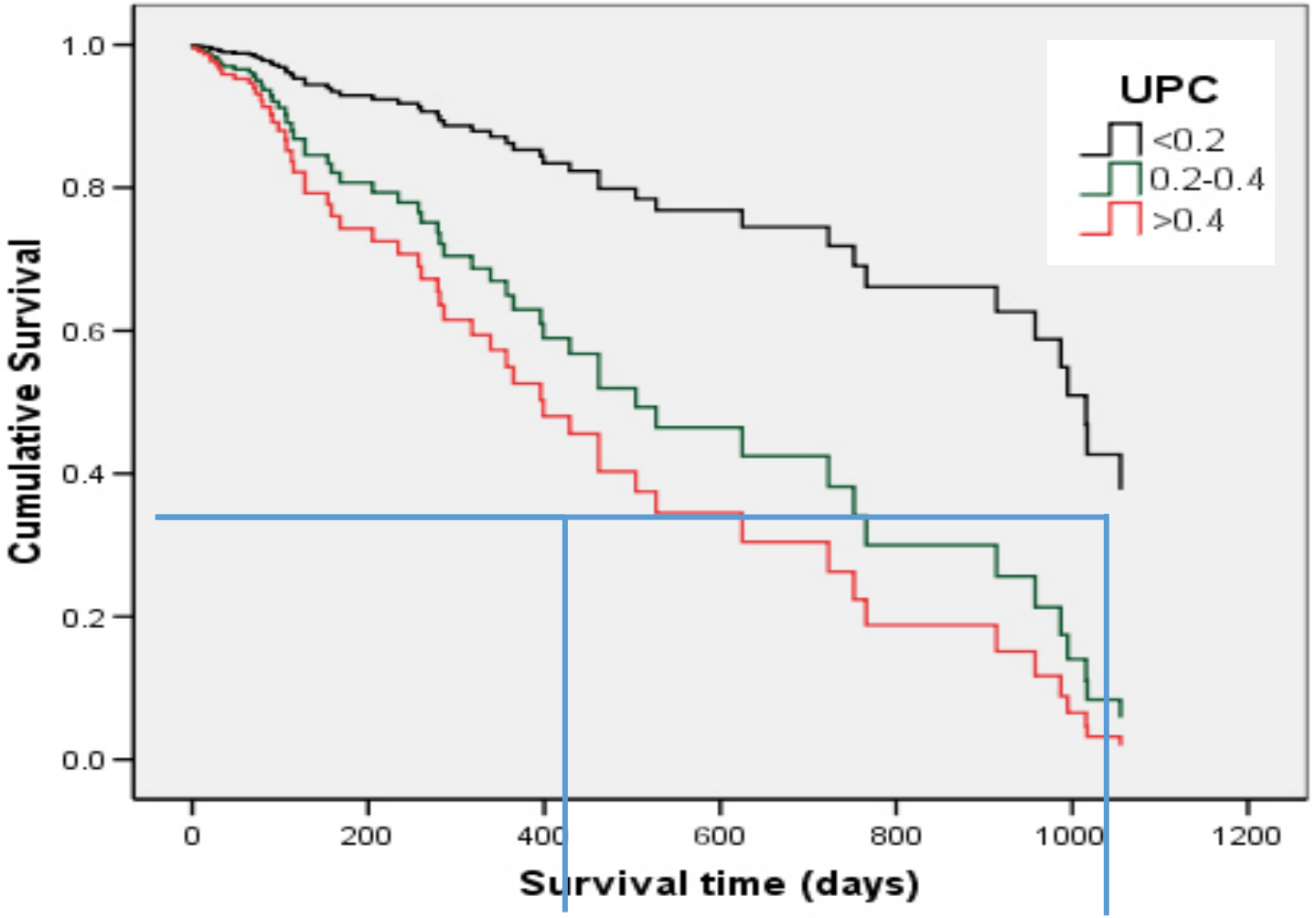
Effect of proteinuria



Syme et al. *J Vet Intern Med* 2006: 20: 528-535

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Outline

- Basics
- Recommended diagnostics for proteinuric patients
- Treatments
  - ACEis and ARBS
  - Adjunctive treatments
- Treatment goals
- Biopsy and immunosuppressive therapy

Consensus Recommendations for the Diagnostic Investigation of Dogs with Suspected Glomerular Disease

IRIS Canine GN Study Group Diagnosis Subgroup, M.P. Littman, chair, S. Daminet, G.F. Grauer, G.E. Lees, and A.M. van Dongen

- IRIS defines “primary” glomerulopathy as a nephropathy that arises with any pathological process where the primary damage is to the glomerulus
  - Whereas, “secondary” glomerulopathy is glomerular changes occurring secondary to primary tubular or whole nephron damage
- In contrast, in human medicine, the term “primary” glomerular disease is primary kidney disease and “secondary” glomerular disease indicates a disease in which kidney involvement is part of a systemic disorder

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- Proteinuria is an acknowledged hallmark of glomerular lesions in dogs
  - But it is not always attributable to renal, much less glomerular, disease
  - When detected – must be properly assessed to determine its potential clinical significance, which involves **localization, persistence, and magnitude**
- Persistent renal proteinuria leads to a suspicion of glomerular disease
  - Persistent renal proteinuria is *not always* a marker of glomerular disease
    - Renal proteinuria can be caused by tubular lesions alone
    - Proteinuria of glomerular origin → glomerular lesions are not necessarily caused by an intrinsic glomerular disease

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- Recommended Tiers:
  - Tier I: Proteinuria only
    - A: Proteinuria only
    - B: Proteinuria + **hypertension**
  - Tier II: Proteinuria associated + hypoalbuminemia
    - A: Proteinuria associated + hypoalbuminemia only
    - B: Proteinuria associated + hypoalbuminemia **+ hypertension**
  - Tier III: Proteinuria + azotemia
    - A: Proteinuria + azotemia only
    - B: Proteinuria + azotemia **+ hypertension**
    - C: Proteinuria + azotemia **+ hypoalbuminemia +/- hypertension**

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- Diagnostics recommended for all tiers:
  - Comprehensive history
    - Signalment, family, environs, exposures, etc.
    - Consider breed predispositions, eg. glomerular disease, neoplasia, Cushing's disease
    - Consider environs or travel-associated infectious diseases, eg. Lyme disease, heartworm, Ehrlichiosis, Leishmaniasis
    - Consider drug or diet exposures that can cause hypertension or glomerular disease, eg. phenylpropanolamine, steroids, raw-food diet, sulfonamides, tyrosine kinase inhibitors

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- Diagnostics recommended for all tiers:
  - Complete physical examination
    - Don’t forget your retinal and rectal examinations
    - Blood pressure measurements
      - Readings on at least 2 occasions on different days are generally required
      - Elevated blood pressure measurement found on a single occasion may be adequate to initiate treatment if found in conjunction with target organ damage

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- Diagnostics recommended for all tiers:
  - Blood and urine testing
    - CBC (including platelets)
    - Biochemical profile (including BUN, creatinine, phosphorus, calcium, sodium, potassium, albumin, globulin, glucose, ALT, ALP, bilirubin, cholesterol, and if possible, enzymatic CO2)
    - Urinalysis (including urinary sediment evaluation)
    - Urine protein/creatinine ratio (UPC, at least 2 readings)
    - Urine culture
      - If microscopic pyuria, hematuria, or bacteriuria
      - If possible occult infection: USG<1.025, azotemia, or suspected hyperadrenocorticism, diabetes mellitus
    - If living in an endemic area or travel history warrants, rule out the common diseases associated with glomerulonephritis characteristic for the area, eg, Lyme disease, heartworm, and Ehrlichiosis in endemic areas in the United States

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- A more comprehensive diagnostic investigation is warranted if:
  - High Magnitude (UPC is ≥ 3.5)
  - Progressive proteinuria
  - Hypertension
  - Hypoalbuminemia
  - Azotemia
- Including:
  - Complete abdominal ultrasound
  - Thoracic radiographs
  - More comprehensive evaluation for infectious diseases

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- Infectious Diseases:
  - Search should be guided by clinical judgment
  - Base on a patient's environs, including where it may have lived or traveled previously → test accordingly

- *Adenovirus* I antigen/antibody—PCR/ELISA
- *Anaplasma* spp. antigen—cytology, PCR
- *Anaplasma phagocytophilum/platys* antibody—in-house SNAP-4DxPlus (IDEXX), AccuPlex4 (Antech); Quant at reference labs
- *Babesia* spp. antigen—cytology, PCR (NCSU)
- *Babesia* canis/gibsoni antibody—IFA
- *Babesia* microti antibody—Protatek
- *Bartonella* spp. antigen—BAPGM culture and PCR at Galaxy Diagnostics
- *Bartonella* spp. antibody—Western blot (National Veterinary Lab), IFA (Galaxy Diagnostics)
- *Borrelia burgdorferi* natural exposure antibody—in-house SNAP-4DxPlus and Lyme C6Quant (IDEXX), AccuPlex4 (Antech), Multiplex (Cornell University), Abaxis Lyme (Abaxis)
- *Borrelia* spp. (relapsing fever group)—whole cell ELISA, IFA
- *Brucellosis* antigen—culture, PCR
- *Brucellosis* antibody—AGID, RSAT, TAT, FA, ELISA
- *Dirofilaria* antigen—in-house SNAP-4DxPlus (IDEXX), Solo Step CH (HESKA), AccuPlex4 (Antech)
- *Ehrlichia* spp. antigen—cytology, PCR
- *Ehrlichia canis/chaffeensis/ewingii* antibody—in-house SNAP-4DxPlus (IDEXX), AccuPlex4 (*E. canis*, Antech), Quant at reference labs
- *Fungal* (systemic) antigen/antibody—cytology, culture, AGID, Blastomyces urine antigen test
- *Hepatozoon* spp. antigen—PCR (Auburn)
- *Leishmaniasis* antigen/antibody—PCR; ELISA, FA, WB
- *Leptospira* spp. antigen—PCR (IDEXX)
- *Leptospira* spp. antibody—State laboratories
- *Mycoplasma* spp. antigen—PCR (IDEXX)
- *Rickettsia rickettsia* (RMSF) antigen—PCR or DFA (on tissue)
- RMSF antibody—IFA, LA
- *Trypanosomiasis*—cytology, PCR, fast dipstick test, FA, RIP

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- Hypertensive → assess for extra-renal causes of primary or secondary blood pressure elevations
  - In the absence of hypoalbuminemia and dehydration, hypertension may rarely be the primary cause of proteinuria
  - Extra-renal causes
    - Hyperadrenocorticism, pheochromocytoma, hyperaldosteronism, adverse drug effects, fluid and/or salt overload, etc.
  - Consider echocardiography to check for concentric left ventricular hypertrophy

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- If hypoalbuminemic, azotemic, or both:
  - Rule out neoplasia (imaging, possibly lymph node or bone marrow aspirate)
  - Rule out concurrent or other causes of hypoalbuminemia (e.g. liver disease, gastrointestinal losses, or malnutrition)
  - Characterize the cause, time course, and stability of identified azotemia as extrarenal (ie, prerenal or postrenal), acute kidney injury, chronic kidney disease, or acute-on-chronic kidney disease
  - Stage or grade the kidney disease with the appropriate IRIS classification scheme.

Consensus Guidelines for Immunosuppressive Treatment of Dogs with Glomerular Disease Absent a Pathologic Diagnosis

IRIS Canine GN Study Subgroup on Immunosuppressive Therapy Absent a Pathologic Diagnosis,
B. Pressler, co-chair, S. Vaden, co-chair, B. Gerber, C. Langston, and D. Polzin

- Renal biopsy is recommended, especially if the proteinuria is:
  - Substantial/severe (UPC is ≥ 3.5)
  - Unresponsive to treatment
  - Progressive despite institution of standard therapy and/or if administration of immunosuppressive drug therapy has been instituted or is being considered
  - When the kidney disease is not end-stage

*For biopsy collection → need experienced personnel at all stages of procuring, preparing, and then interpreting the renal biopsy

Renal biopsies should be evaluated by light microscopy, electron microscopy and immunofluorescence!!

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- Concurrent extra-renal diseases
  - Glomerular diseases are often secondary to disease processes primarily located in other organ systems → investigate with appropriate testing any abnormalities identified by the minimum database
  - Need to identify any disease that could cause a glomerulopathy
  - Especially important if effective treatment of the primary disease can reduce or stop glomerular injury
    - Eg: neoplasia, immune-mediated disease, Cushing's disease, infectious and noninfectious inflammatory or vascular conditions

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- Possible autoimmune disease?
  - Renal proteinuria with concurrent extrarenal clinical signs or laboratory test findings that might be explained by an immune-mediated disease
    - Examples include fevers of undetermined origin, especially those with a waxing and waning course; lameness or joint swelling that might be attributable to noninfectious (nonerosive or erosive) polyarthritis; anemia accompanied by changes (eg, spherocytes, poikilocytes) suggestive of a hemolytic process; thrombocytopenia; and certain dermatologic lesions
  - In these patients, performing tests for various autoantibodies (eg, antinuclear antibody [ANA], Coombs', Rheumatoid factor) is likely indicated as part of an investigation of suspected underlying disease

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- Biopsy
  - From collection to in-depth evaluation, should be performed by experienced personnel
    - International Veterinary Renal Pathology Service, a joint collaboration of Texas A&M and Ohio State
  - Biopsy before the disease has progressed to an advanced stage (IRIS CKD Stage IV), because secondary fibrosis and interstitial nephritis may mask the original glomerular disease
    - Therapeutic intervention at advanced stages is unlikely to be as helpful and the risk of biopsy-associated complications (eg, bleeding) increases

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

- Regardless of the inciting cause, these recommendations should be viewed as forming the basis of standard, or routine, care of dogs with glomerular disease
  - More adverse outcomes if the UPC exceeds 2.0 (demonstrated in spontaneous disease)
  - Substantial/severe proteinuria (UPC is ≥ 3.5)

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- ***Recommendation***: Intervention → when the UPC persistently exceeds 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***
  - Improves renal structural outcomes (demonstrated in experimental disease)

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- Hemodynamic forces influence the transglomerular movement of proteins → altering renal hemodynamics would be effective in reducing proteinuria
- However, effects of agents interfering with RAAS have not been fully elucidated
  - It appears that they reduce proteinuria greater than would be expected just with antihypertensive effects

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- RAAS has been the major target
  - Angiotensin-converting enzyme inhibitor (ACEi; eg, enalapril, benazepril)
  - Angiotensin-receptor blocker (ARB; eg, losartan, telmisartan)
  - 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.

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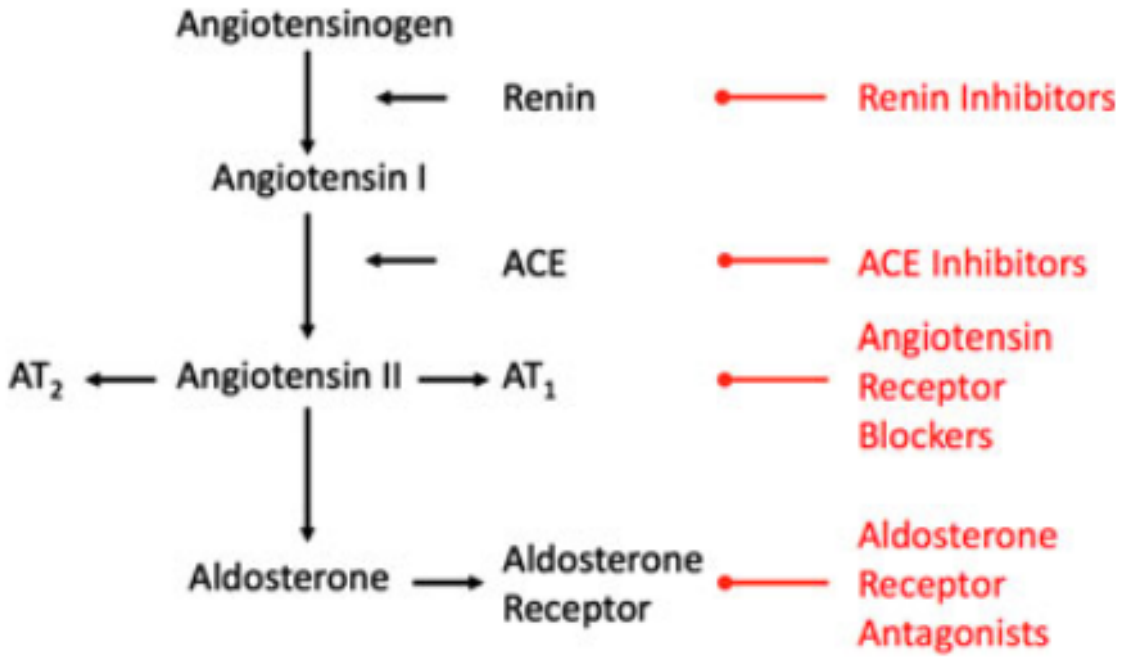

Fig 1. The renin-angiotensin-aldosterone system and approaches to its inhibition.

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- Angiotensin-Converting Enzyme Inhibitors (ACEis)
  - Reduce proteinuria and preserve renal function by decreasing efferent glomerular arteriolar resistance leading to decreased/normalized glomerular transcapillary hydraulic pressure
  - ACEis are considered part of standard care of dogs with glomerular disease
    - Well established effects:
      - Enalapril → significantly reduced proteinuria and delayed the onset or the progression of azotemia in dogs with glomerulonephritis

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- 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

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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 o 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	

[a]ACEi and ARBs are antiproteinuric drugs that generally have weak antihypertensive effects.

[b]Concurrent administration of an ACEi is generally recommended.

[c]Reserved for the management of proteinuria in dogs that have increased serum aldosterone concentrations and either have failed or are intolerant of ACEi and ARBs.

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- 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
- In starting and escalating theses drugs, monitor for severe worsening of azotemia (ie. >30% increase from baseline)
  - Uncommon for dogs to have severe worsening of azotemia
  - Dogs that are dehydrated may be at highest risk for worsening of azotemia after initiating ACEi therapy
  - Stop drug with acute on chronic renal failure

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- In people, the renoprotective effects are independent of the baseline renal function and ACEi slowed progressive disease even in patients with severe renal failure
  - Although ACEi administration is appropriate, caution is warranted in IRIS stage 4
  - I am personally more cautious/thoughtful when starting these drugs when the creatinine is in the 2.5-3.0 range.
  - Above 3.0 and I will often not start these drugs at all

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- Benazepril is largely eliminated by the biliary route
- Enalapril is primarily eliminated by the kidney
  - Dogs in late IRIS CKD stage 3 or stage 4 may achieve a similar antiproteinuric effect with a lower dosage of enalapril
  - Although interdrug differences are known, there are currently no published studies in dogs with glomerular disease to support the recommendation that one ACEi as superior in its pharmacodynamic action

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- Angiotensin-Receptor Blockers (ARBs)
  - Angiotensin-II is a central mediator of renal injury because of its ability to produce glomerular hypertension
  - Hypertension → glomerular damage, proteinuria, and activation of pro-inflammatory and profibrotic pathways.
    - Major detrimental renal effects of AT-II described above are mediated by AT1 receptors. *Telmisartan selectively blocks.
    - AT2 receptors modulate actions of AT-II that are renoprotective (vasodilation, natriuresis, inhibition of renin secretion, and anti-inflammatory, anti-ischemic and antifibrotic effects)

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- 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
  - Data is more limited on the use of ARBs in dogs with glomerular disease

J Vet Intern Med 2015;29:1479–1487

Comparison of Efficacy of Long-term Oral Treatment with Telmisartan and Benazepril in Cats with Chronic Kidney Disease

U. Sent, R. Gössl, J. Elliott, H. M. Syme, and T. Zimmering

- Non-inferiority study – telmisartan vs. benazepril
- 224 client-owned adult cats with CKD
- Cats were allocated in a 1 : 1 ratio to either telmisartan (1 mg/kg; n = 112) or benazepril (0.5–1.0 mg/kg; n = 112) PO q24 h
- Both telmisartan and benazepril were well tolerated and safe
- Telmisartan proved to be noninferior to benazepril and significantly decreased proteinuria relative to baseline at all assessment points whereas benazepril did not

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- 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
  - An ACEi may incompletely block the formation of angiotensin II, particularly within the kidney
  - There may be an added benefit to combined therapy with an ACEi and an ARB → monotherapy with either class of drug to provide complete RAAS blockade

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- No studies in dogs, but in people these drugs may be additive or perhaps even synergistic in reducing proteinuria
  - Because the dosage of each individual drug can be reduced during combined therapy, adverse effects may be less likely
- Caution in combining ACEi and ARB → study published in people where elderly patients prescribed this combination had a higher risk of kidney failure and death
- I personally combine these drugs as a last-resort

Consensus Recommendations for Standard Therapy of Glomerular Disease in Dogs

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- ***Recommendation***: 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

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- Introduction of a new drug or dosage modifications are important indications for frequent monitoring
  - 1 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 change
    - Has had the desired therapeutic effect (ie, reduction in UPC)
    - Has not resulted in a severe worsening of renal function (ie, >30% increase in serum creatinine), a concerning increase in serum potassium concentration, or hypotension
- Dogs with marked azotemia, late IRIS CKD stage 3 or stage 4, should be monitored more carefully

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- Day-to-day variations in the UPC occur in most dogs with glomerular proteinuria
  - Greater variation occurs in dogs with UPC >4
- Changes in urinary protein content are most accurately assessed by determining trends in the UPC over time
- Consideration should be given to averaging 2–3 serial UPC or measuring a UPC in urine that has been pooled from 2 to 3 collections
  - Esp. in dogs with UPC >4

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- Hyperkalemia
  - Common side effect of RAAS inhibition in dogs with renal disease
    - Serum potassium concentrations of >6 mmol/L should be monitored closely
    - Treatment should be modified with serum potassium concentrations >6.5 mmol/ L
  - 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)
  - Before modifying treatment, psuedohyperkalemia should be eliminated as a cause → potassium concentration in lithium heparin plasma

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- The degree to which worsening of renal function is tolerated will in part depend on the IRIS stage of the canine CKD
  - Stage 1 and 2 CKD – can have an increase in serum creatinine of up to 30% without modifying treatment
  - Stage 3 CKD – need to maintain stable renal function; if renal function deteriorates, therapeutic adjustments may be indicated
  - Stage 4 CKD – generally intolerant of worsening of renal function and any deterioration may have clinical consequences
    - 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

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- ***Recommendation***:
  - 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

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- Dose escalation → 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

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- Dietary protein
  - Benefits of modified dietary protein:
    - Reduce intraglomerular pressure
    - Reduce the magnitude of proteinuria
      - There is evidence that reduction in protein intake reduces proteinuria and that dietary modification, which includes protein restriction, slows progression in genetic models of proteinuric CKD
    - Reduce the rate of generation of uremic toxins
  - ***Recommendation***:
    - Modified protein diets should be fed to dogs with glomerular disease.

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- Antithrombotic Therapy
  - Thromboembolism is a recognized complication of proteinuria in dogs and humans
  - Prevalence has been reported to be as high as 25%
  - Prophylactic treatments used in humans as well as dogs include administration of heparin and vitamin K antagonists
    - Limited evidence suggests that antiplatelet agents may provide *some* protection in hospitalized human patients
    - However, aspirin alone is not considered an adequate prophylaxis in humans
    - Trials report no significant benefit from aspirin VTE prophylaxis or found that aspirin was *inferior* to other thromboprophylaxis modalities

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- Antithrombotic Therapy
  - Options are limited with heparin and aspirin predominating
    - Very limited studies are available to support the value of antithrombotic therapy in dogs
    - No studies specifically address the issue of antithrombotic therapy in dogs with glomerular disease → there is little conclusive evidence on which to base recommendations for prophylaxis of VTE in dogs, regardless of cause
    - 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

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

- Antithrombotic Therapy
  - The current recommendation for thromboprophylaxis in dogs with glomerular disease remains low-dose aspirin (0.5–5 mg/kg daily) but the optimum aspirin protocol for limiting TE in dogs is unknown
  - 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
    - However, evidence that it is superior to aspirin in prophylaxis of VTE in dogs is lacking

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

- ***Recommendation***:
  - 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

Consensus Recommendations for Standard Therapy of Glomerular Disease in Dogs

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- Hypertension
  - In people, any reduction in BP that does not produce overt hypotension lowers the risk of target organ damage (TOD)

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- Hypertension
  - ***Recommendation***: 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)

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

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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

- Hypertension
  - ***Recommendation***:
    - Antihypertensive therapy must be individualized to the patient
    - Regardless of the initial level of BP, the goal of treatment should be to maximally reduce the risk of future TOD and if able, to significantly lower the magnitude of proteinuria
    - Except in a hypertensive crisis wherein severe ocular or central nervous system TOD is present, BP lowering should be achieved with a gradual, persistent reduction in BP achieved over several weeks

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

- Hypertension
  - 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 for their BP)
    - If hypertension is identified in a dog with glomerular disease that is not receiving an ACEi or an ARB → start ACEi is an appropriate first step
    - Calcium channel blocker (ie, amlodipine) or an ARB would be the next step

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

- Hypertension
  - ***Recommendation***:
    - In dogs with glomerular disease and either severe systemic hypertension co-administration of two agents with different mechanisms of action (generally an ACEi plus amlodipine) is recommended
    - IRIS CKD stages 1 or 2 → reevaluate 3–14 days following any change in antihypertensive therapy
    - In unstable patients and those with IRIS stage 3 or 4 CKD → reevaluate in 3–5 days
    - Hypertensive emergency or hospitalized patients, particularly those receiving fluid therapy or pharmacological agents with cardiovascular effects → should be assessed daily

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

- Hypertension
  - 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
    - Follow-up evaluations should include measurement of BP, serum creatinine concentration, urinalysis with UPC, retinal examination, etc.
  - In dogs, a key predictive parameter for antihypertensive efficacy is the effect of treatment on the magnitude of proteinuria (UPC)
    - A benefit is predicted if the antihypertensive regimen used is antiproteinuric (ie, reduces UPC by at least 50%, preferably to <0.5)

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

- Hypertension

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
α_1 blocker	Prazosin (Minipress)	0.5–2 mg/kg q8–12h
	Phenoxybenazime (Dibenzyline)	0.25 mg/kg q8–12h or 0.5 mg/kg q24h
Direct vasodilator	Hydralazine (Apresoline)	0.5–2 mg/kg q12h (start at low end of range)
	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

[a]Agents 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.

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Consensus Guidelines for Immunosuppressive Treatment of Dogs with Glomerular Disease Absent a Pathologic Diagnosis

IRIS Canine GN Study Subgroup on Immunosuppressive Therapy Absent a Pathologic Diagnosis,
B. Pressler, co-chair, S. Vaden, co-chair, B. Gerber, C. Langston, and D. Polzin

- There is no substitute for a pathologic diagnosis in the formulation of therapeutic plans for dogs with glomerular diseases
- However, there are times when renal biopsy cannot be performed because of medical, practical, or financial limitation
  - In these situations, veterinarians may have to decide whether or not to recommend immunosuppressive therapy for glomerular disease without firm knowledge of whether autoimmune disease is present

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- Proteinuric dogs suspected of having glomerular disease, but absent a renal pathologic diagnosis, should generally be managed initially using standard therapy and regular monitoring
  - However, standard therapy for canine glomerular disease rarely leads to complete resolution of the renal injury
  - Also, adverse effects of drugs used for standard therapy may limit their use in some dog

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- ***Recommendation***: Renal biopsy should NOT be performed in dogs with
  - IRIS CKD Stage 4
  - When other medical contraindications are present and cannot be mitigated (including coagulopathy, renal cystic disease, moderate-to-severe hydronephrosis, pyelonephritis, perirenal abscess, uncontrolled hypertension, severe anemia, and pregnancy)
  - When results of renal biopsy are deemed unlikely to alter treatment, outcome, or prognosis
    - Small kidneys (the damage present is likely irreversible)
    - Chronic azotemia is present (renal changes may be irreversible and histopathology less likely to alter treatment)

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- Currently, the evidence for immunosuppressive therapy is weak
  - However, clinical studies based on renal pathologic diagnosis have not yet been performed
  - In humans, immunosuppressive agents may be effective for the treatment of membranous and membranoproliferative glomerulonephritis
    - Characterized by the presence of immune complexes, evidence of an immune process affecting the glomerulus
  - These same renal disorders are common glomerular diseases in dogs

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- 48.1% (241 of 501) renal biopsies obtained from dogs suspected of having clinical evidence of glomerular disease had evidence of immune complex glomerular disease and thus would be candidates for immunosuppressive/anti-inflammatory therapy
- Approximately 1 of every 2 dogs with clinical evidence of glomerular disease would likely be candidates for immunosuppressive/anti-inflammatory therapy!

Prevalence of Immune-Complex Glomerulonephritides in Dogs Biopsied for Suspected Glomerular Disease: 501 Cases (2007–2012)

S.M. Schneider, R.E. Cianciolo, M.B. Nabity, F.J. Clubb Jr, C.A. Brown, and G.E. Lees

Table 4. Categories of pathologic conditions found in dogs biopsied for suspected glomerular disease.

Category	n (%)	Male (%)	Female (%)	Age (years) Median (Range)	UPC Median (Range)
ICGN	241 (48.1%)	109 (45.2%)	132 (54.8%)	6.2 (0.3–14.0)	8.3 (0.6–42.7)
Glomerulosclerosis	103 (20.6%)	29 (28.2%)	74 (71.8%)	8.0 (2.0–13.0)	6.0 (1.6–27.0)
Amyloid	76 (15.2%)	43 (56.6%)	33 (43.4%)	7.2 (2.0–14.0)	10.3 (1.5–40.1)
Other non-IC glomerulopathy	45 (9.0%)	18 (40.0%)	27 (60.0%)	6.5 (0.4–13.0)	5.4 (1.4–20.8)
Non-IC nephropathy	24 (4.8%)	14 (58.3%)	10 (41.7%)	8.0 (0.3–13.5)	3.4 (0.5–25.9)
Primary TI disease	12 (2.4%)	5 (41.7%)	7 (58.3%)	6.0 (2.5–10.0)	3.9 (0.6–8.6)
All cases	501 (100.0%)	218 (43.5%)	283 (56.5%)	7.0 (0.3–14.0)	7.6 (0.6–42.7)

Consensus Guidelines for Immunosuppressive Treatment of Dogs with Glomerular Disease Absent a Pathologic Diagnosis

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- Specifically, immunosuppression may be considered if
  - Azotemia is acutely severe, progressive, or both (ie, creatinine >5 mg/dL, IRIS AKI Stages 4 or 5) at the time of diagnosis and there is no evidence of chronic disease
  - Hypoalbuminemia is severe (serum albumin <2.0 g/dL)
- Treatments (little evidence but expert advice)
  - Mycophenolate alone or in combination with prednisolone
  - Cyclophosphamide (continuous or pulse therapy) alone or in combination with prednisolone

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- Likewise, immunosuppressive therapy might be indicated if:
  - Biopsy is not possible, neither age nor breed is indicative of familial renal disease, and other contraindications to immunosuppressive therapy are not present
- Treatment (little evidence but expert advice)
  - Mycophenolate
  - Chlorambucil alone or in combination with azathioprine on alternating days
  - Cyclophosphamide and glucocorticoids
  - Cyclosporine

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- ***Recommendation***: Immunosuppressive/anti-inflammatory therapy should NOT be administered to dogs with proteinuria before renal biopsy when:
  - Proteinuria is not definitively glomerular in origin
  - Immunosuppressive therapy is otherwise contraindicated
  - The dog breed and age of disease onset suggest that a nonimmune-mediated familial nephropathy
  - Amyloidosis is the most likely histopathologic diagnosis

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- ***Recommendation***: Immunosuppressive drugs SHOULD be considered in dogs with glomerular disease that are being given standard therapy and do not have a biopsy-confirmed renal pathologic diagnosis when
  - Serum creatinine is >3.0 mg/dL or azotemia is progressive
  - Hypoalbuminemia is severe (ie, <2.0 g/dL)

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- Do no harm?
  - Do we do harm by recommending an unproven immunosuppressive/anti-inflammatory treatment for a dog with clinical evidence of glomerular disease that may not benefit from the treatment?
  - However, canine glomerular disease can lead to serious complications or death
    - Failure to provide a potentially helpful treatment in this setting may result in more harm than the potential risks of the treatment
    - Consider both the potential risks and potential benefits of recommending immunosuppressive/anti-inflammatory treatment for dogs with clinical evidence of glomerular disease without biopsy
  - 50/50 chance

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- In the absence of a biopsy to help predict the likelihood of response, immunosuppressive therapy should be considered a therapeutic trial
  - If there is no response to treatment after 8–12 weeks, therapy should be discontinued and the previous decision to not perform a renal biopsy be revisited

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- ***Recommendation***: Response to treatment as measured by changes in **UPC** is defined as follows:
  - A complete response is defined as a reduction in the UPC to <0.5
  - A partial response is defined as a reduction in the UPC by greater than 50% of the highest pretreatment UPC after standard therapy (or with standard therapy if both were initiated simultaneously)
  - Therapeutic failure is defined as a reduction in UPC of less than 50%

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- In humans with glomerular disease, reduction in proteinuria has been shown to be useful in predicting renal survival and the rate of progression of renal dysfunction
  - Magnitude of reduction is related to the likelihood for favorable outcomes in renal survival and patient quality-of-life
- Seems likely that the therapeutic goal should be to achieve the lowest UPC possible while minimizing adverse effects of treatment
  - UPC should be assessed serially and treatment should be adjusted, extended, or both (when possible) to promote the maximum sustained reduction in proteinuria
  - Although UPC may normalize in some patients, this magnitude of response is unlikely an achievable goal in all dogs

Consensus Guidelines for Immunosuppressive Treatment of Dogs with Glomerular Disease Absent a Pathologic Diagnosis

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- ***Recommendation***: Response to treatment as measured by changes in **serum creatinine** concentration is defined as follows:
  - Complete response → reduction in serum creatinine concentration to less than 1.4 mg/dL (or the patient's last known serum creatinine concentration before onset of the glomerular disease)
  - Partial response → sustained reduction in serum creatinine concentration by at least 25%
  - Therapeutic failure → reduction in serum creatinine concentration less than 25%

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- ***Recommendation***: Response to treatment as measured by changes in **serum albumin** concentration from baseline (defined as the mean of serum albumin concentration values during the 30 days preceding immunosuppressive therapy) is defined as follows:
  - Complete response is a sustained increase in serum albumin concentration to greater than 2.5 g/dL (25 g/L)
  - Partial response is either:
    - Sustained increase in serum albumin concentration to 2.0–2.5 g/dL
    - Sustained increase of 50% or more in serum albumin concentration from the baseline serum albumin concentration
  - Therapeutic failure is defined as failure to increase serum albumin concentration to greater than 2.0 g/dL or by less than 50% increase from baseline serum albumin concentration

Consensus Guidelines for Immunosuppressive Treatment of Dogs with Glomerular Disease Absent a Pathologic Diagnosis

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- Steroids may promote a transient or persistent increase in proteinuria
  - Although this effect appears to be contrary to the therapeutic goals defined above, these effects may be transient and reversible
  - It remains unclear whether this effect is a contraindication for corticosteroid therapy in dogs with glomerular disease
  - If a treatment fails to achieve the expected response goals, an alternative drug strategy should be considered

Summary

- Know your treatments and treatment goals for proteinuria
- Renal biopsy should be considered more frequently in the management of proteinuria
- We should be more frequently considering immunosuppression in proteinuria cases

Pathologic Evaluation of Canine Renal Biopsies: Methods for Identifying Features that Differentiate Immune-Mediated Glomerulonephritides from Other Categories of Glomerular Diseases

R.E. Cianciolo, C.A. Brown, F.C. Mohr, W.L. Spangler, L. Aresu, J.J. van der Lugt, J.H. Jansen, C. James, F.J. Clubb, and G.E. Lees

- North American and European Centers:
  - North America
    - In 2008 North American center was Texas A&M University (Texas Veterinary Renal Pathology Service)
    - Now, cooperative effort between the Ohio State University and Texas A&M University → now known as the International Veterinary RenalPathology Service (IVRPS)
  - Europe
    - Utrecht University (Netherlands) → known as the Utrecht Veterinary Nephropathology Service (UVNS)
- One goal of these centers is to evaluate a sufficient number of specimens annually to develop and maintain the technical and interpretive expertise needed to examine renal specimens light microscopy (LM), transmission electron microscopy (TEM) and immunofluorescence (IF)

Pathologic Evaluation of Canine Renal Biopsies: Methods for Identifying Features that Differentiate Immune-Mediated Glomerulonephritides from Other Categories of Glomerular Diseases

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- Goals
  - Create a strong foundation for the diagnosis of canine glomerular disease
  - Evaluate a sufficient number of specimens annually to develop and maintain the technical and interpretive expertise needed to examine renal specimens light microscopy (LM), transmission electron microscopy (TEM) and immunofluorescence (IF)
    - Revealed the deficiency of each modality when used alone
  - Focus on lesions that are definitively diagnostic for, suspicious for, or inconsistent with three main categories of glomerular disease
    - Immune complex glomerulonephritis (ICGN)
    - Amyloidosis
    - Non-immune complex glomerulonephritis (non-ICGN)

    ** These 3 broad diagnostic categories were created because they have the greatest implications for prognosis and treatment

Consensus Recommendations for the Diagnostic Investigation of Dogs with Suspected Glomerular Disease

IRIS Canine GN Study Group Diagnosis Subgroup, M.P. Littman, chair, S. Daminet, G.F. Grauer, G.E. Lees, and A.M. van Dongen

- Potentially helpful, investigational, or academic considerations:
  - Antithrombin testing
  - Thromboelastography
  - SDS-PAGE analysis on urine
  - DNA banking for future GWAS studies for predisposed breeds

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- Concurrent extra-renal diseases
  - A more vigorous and exhaustive search is appropriate for patients that have more serious complications of their nephropathies (ie, those in Tiers II and III) than those that do not (ie, those in Tier I)
    - Absence of an identifiable underlying disease is a common occurrence, despite exhaustive diagnostic searching, so it frequently is necessary to decide when to stop unproductive searching

Consensus Recommendations for the Diagnostic Investigation of Dogs with Suspected Glomerular Disease

IRIS Canine GN Study Group Diagnosis Subgroup, M.P. Littman, chair, S. Daminet, G.F. Grauer, G.E. Lees, and A.M. van Dongen

- Concurrent extra-renal diseases
  - Recognition of some concurrent diseases is important to the management strategy of the nephropathy even if they are not truly an underlying cause of the glomerular disease
    - Dermatologic or gastrointestinal disorders that are managed in part by diets or drugs that might be suboptimum or contraindicated for the nephropathy.
    - Cardiovascular problems might cause or contribute to difficulties in maintaining adequate fluid balance or distribution.

Consensus Recommendations for the Diagnostic Investigation of Dogs with Suspected Glomerular Disease

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- Possible autoimmune disease
  - But, may also test for autoantibodies when a dog has renal proteinuria but does not exhibit any signs or test abnormalities (besides the proteinuria itself) that might be explained by an immune-mediated disease
    - In this setting, a positive test result must be interpreted with great caution

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

- Primary glomerular disease → the process that initiates renal injury originates in the glomerulus.
- Secondary glomerular disease → 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)

Consensus Recommendations for Standard Therapy of Glomerular Disease in Dogs

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- Aldosterone-Receptor Blockers
  - Serum aldosterone increases over time (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
  - People who have high aldosterone concentrations are more likely to have a reduction in proteinuria in association with administration of an aldosterone receptor blocker

Consensus Recommendations for Standard Therapy of Glomerular Disease in Dogs

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- 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
  - 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

Consensus Recommendations for Standard Therapy of Glomerular Disease in Dogs

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- Dietary Polyunsaturated Fatty Acids (PUFA)
  - Dietary supplementation with n-6 PUFA may increase GFR in the short term
  - 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

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- Dietary Polyunsaturated Fatty Acids (PUFA)
  - 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
- However, 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
  - 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
  - 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).

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

- ***Recommendation***:
  - 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

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

- Antithrombotic Therapy
  - 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

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

- Antithrombotic Therapy
  - 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 nephrotic syndrome have included dosages as low as 0.5 mg/kg; however, more recent studies in normal and dogs with immune-mediated hemolytic have suggested that aspirin at 0.5 mg/kg is unlikely to modify platelet function

Consensus Guidelines for Immunosuppressive Treatment of Dogs with Glomerular Disease Absent a Pathologic Diagnosis

IRIS Canine GN Study Subgroup on Immunosuppressive Therapy Absent a Pathologic Diagnosis,
B. Pressler, co-chair, S. Vaden, co-chair, B. Gerber, C. Langston, and D. Polzin

- Familial nephropathy
  - Familial proteinuric renal disease has been reported in:
    - Bull Terriers, English Cocker Spaniels, Dalmatians, Samoyeds, Rottweilers, Bernese Mountain Dogs, Newfoundlands, Doberman Pinschers, Pembroke Welsh Corgis, Bullmastiffs, French Mastiffs, Chinese Shar Peis, Beagles, English Foxhounds, and Soft-Coated Wheaten Terriers
  - The pathogenesis, clinical findings, and progression of disease vary among these breeds but most are steroid resistant
  - Exceptions to this guideline may be:
    - Soft-Coated Wheaten Terriers with concurrent glomerular disease and enteropathy may benefit from immunosuppressive drugs
    - Bernese Mountain Dogs are predisposed to developing membranoproliferative glomerulonephritis, which may be responsive to some immunosuppressive protocols

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- Initial assessments should be performed no later than 1–2 weeks after initiation of the treatment and every 2 weeks thereafter for the first 4–6 weeks of treatment
  - Thereafter, assessments are recommended at least every 4 weeks for the next 3 months and then at quarterly intervals until resolution of the disease
- Assessments include
  - History/Exam (eg. drug side-effects, edema, blood pressure)
  - CBC/Chem/UA/UPC

Consensus Recommendations for Treatment for Dogs with Serology Positive Glomerular Disease

IRIS Glomerular Disease Study Group, R.E. Goldstein, chair, C. Brovida, M.J. Fernández-del Palacio, M.P. Littman, D.J. Polzin, A. Zatelli, and L.D. Cowgill

- Glomerular proteinuria concurrent with a positive titer for an infectious agent with recognized potential to incite glomerular disease is often interpreted to support a cause–effect relationship
- Can be risky and may erroneously influence clinical decisions (diagnostic approach, diagnosis, therapeutic strategies and risks, and outcomes of the disease)

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- Borrelia burgdorferi and Leishmania in dogs are especially problematic because of the seemingly common association of these infections with proteinuric conditions
- In some areas of the United States, common exposures to heartworm, Borrelia burgdorferi, Ehrlichia, Anaplasma, or Babesia lead to seroconversion without development of proteinuria
- In Mediterranean countries exposure to Leishmania promotes a positive IFAT result that indicates exposure to the infection but not necessarily active infection
- Thus, serology alone is not conclusive evidence that an infectious agent is the cause of a coexisting glomerular disease

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- Clinical evidence of an active infectious disease associated with proteinuria → compelling to presume the linkage between the serology and glomerular disease may be real
  - Leishmaniasis – serology has a 98% predictive sensitivity
  - Lyme – less than 30% of seropositive dogs with concurrent glomerular disease have non-renal signs consistent with active Lyme disease
    - Proteinuria is an uncommon finding in dogs with Lyme-seropositivy and may be recognized in less than 2% of seropositive dogs
    - PULL REFERENCES 1-2?

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- Clinical signs ascribed to an infectious agent like Lyme may be the result of a coinfection (Rickettsia rickettsii, Ehrlichia spp., etc) → proteinuria and similar clinical signs
- Response to anti-infective treatment also is not reliable proof of causation because other infectious agents may be sensitive to the treatment
- Therapies like doxycycline may have anti-inflammatory and antiarthritic properties sufficient to resolve clinical signs unassociated with an infectious cause

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- Renal histopathology → helpful to support an association between the seropositivity and the glomerulopathy if lesions characteristic for the disease are identified in the biopsy
  - Cannot prove a cause–effect relationship unless agent-specific antigens associated with active immune deposits in glomerular lesions are proven to be from the infectious agent
    - Currently this testing is not available clinically
    - In a study of Lyme-positive dogs with glomerular disease, 84% had Lyme-specific immune deposits in their glomeruli
    - Agent-specific immune deposits, however, may have been deposited nonspecifically in abnormal glomeruli.

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- ***Recommendation***: Serology alone cannot confirm a cause-effect relationship between an infectious agent and causation of glomerular disease.
  - Renal biopsy may provide a basis for guiding decisions to intervene (or not) with immunotherapy
  - If results of a renal biopsy are not available to guide this decision, the cautious approach is to assume that there is a role for the infectious agent in the origin of glomerular injury until proven otherwise

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- ***Recommendation***: In serologically positive dogs with glomerular disease, Standard Treatment is recommended when the urine protein:creatinine ratio (UPC) is persistent and ≥ 0.5
  - Initiate specific anti-infective treatment immediately when the coexistence of glomerular disease and seropositivity is recognized, despite the lack of evidence for causality
  - Use quantitative serology when able (eg. Lyme C6)
  - Avoid potentially nephrotoxic drugs

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- ***Recommendation***: Clinically stable dogs without azotemia, progressive increases in serum creatinine or UPC, or clinical consequences associated with their proteinuria should be managed initially only with specific anti-infective treatment against the suspected infectious agent plus Standard Treatment for glomerular disease

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- ***Recommendation***: For seropositive dogs that are azotemic or have progressive (ie. nonazotemic → azotemic) increases in serum creatinine, or have evidence of rapidly progressive glomerular disease based on clinical and/or laboratory assessments:
  - A thorough search for possible geographic specific coinfections
  - A renal biopsy
  - In the absence of a renal biopsy, immunosuppressive treatment should be considered to manage potential immune causes of the glomerular injury

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- Renal biopsy
  - May or may not be recommended in nonazotemic dogs with mildly increased UPCs and a normal albumin concentration that do not show evidence of progressive kidney disease
  - May not be as useful in dogs with stable renal function and UPCs → may no longer be active
- Standard and anti-infective therapies should not be delayed while deciding whether or not to perform a biopsy
  - The recommendation for renal biopsy should be advocated more strongly in patients with more severe clinical and laboratory abnormalities or those whose disease is progressive

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- ***Recommendation***: If the results of renal biopsy document an active immune component to the glomerular disease, appropriate immunosuppressive treatment is indicated
  - At this stage, the glomerular disease should be considered as having an immune-mediated component, and not infectious alone, and it is not likely to respond only to treatment for the underlying disease
  - Control of the immune events directed at the glomerulus are warranted and required to control this component of the disease
  - It may not be possible to delay treatment with immunosuppressive treatment for the glomerular disease while the infection is being controlled

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- Lyme nephritis
  - There is no experimental model for Lyme nephritis, and the exact pathogenesis and natural progression of this entity is unknown
  - 95% of Lyme positive dogs show no signs of illness (neither Lyme arthritis nor Lyme nephritis)

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- Lyme nephritis
  - Non-clinical seropositive dogs may have very high quantitative C6 antibody levels with circulating immune complexes and it is unknown why or how a subset of dogs with Lyme-specific circulating immune complexes develop Lyme nephritis
  - Because certain breeds are predisposed to Lyme nephritis (eg, Labradors and Golden Retrievers), it may be that an underlying genetic podocytopathy or immunodysregulatory defect causes illness with deposition of Lyme-specific antigen-antibody complexes in glomeruli

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- Lyme nephritis
  - There may be earlier stages or milder forms of the disease that are treatable with antimicrobials and standard treatment alone
    - Definitive evidence for the length of doxycycline treatment needed to eliminate Borrelia burgdorferi is lacking.
    - One month of doxycycline at 20 mg/kg/d only cleared 85% of experimentally infected dogs, based on culture and PCR of skin biopsies taken from the area where ticks were placed on the dogs
    - The criterion for effective treatment usually includes response to treatment based on improving clinical signs and laboratory findings
  - Progressive or severe disease does not respond to these general therapies, and additional aggressive immunotherapy appears warranted

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- Lyme nephritis
  - Baseline and 6-month posttreatment assessment of the quantitative C6 titer may help assess the effectiveness of treatment
  - Successful treatment may be defined as a ≥ 50% decrease from pre-treatment values
    - Anecdotally, when the initial Lyme C6 titer is relatively low, the decline may be small
    - Anecdotally, observations indicate 4Dx results often remain positive for years, despite treatment but the Lyme quantitative C6 titers usually wane, sometimes to < 30

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- Lyme nephritis
  - Doxycycline is typically initiated at 10–20 mg/kg/d
    - Optimal dose and length of treatment for Borrelia burgdorferi infection is unknown, but may be greater than 1 month of doxycycline at 20 mg/kg/d
    - Consequently, in cases of suspected Lyme nephritis doxycycline perhaps should be continued until clinical resolution or until the C6 quantitative titer is determined to have declined to less than 50% from pre-treatment values, which may take up to 6 months