



## **Canine Glomerular Disease: A New Paradigm for the 21<sup>st</sup> Century**

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**THE NEW VISION:** Pathologic glomerular proteinuric diseases have become recognized increasingly as a major cause of acute and chronic renal injury in dogs and cats. They are easily detected on the basis of routine laboratory parameters and screening as well as quantitative urine tests. Proteinuria can be recognized with tremendous sensitivity with microalbumin screening and quantitated effectively with urine protein/creatinine measurements. Similarly, the clinical consequences of proteinuric renal diseases are readily recognizable admixtures of weight loss, hypoalbuminemia, hyperlipidemia, progressive renal dysfunction, hypertension, and fluid disorders. Proteinuria is recognized as an important marker of renal (glomerular and tubular) injury and contributes to the progression of chronic kidney disease. What has remained a diagnostic mystery is the spectrum of the pathologic disorders which predispose this “common denominator” clinical sign and how to approach this spectrum of conditions therapeutically.

The current diagnostic evaluation, classification, and management of proteinuric renal diseases remain enigmatic and uncharacterized compared to other renal pathology. The lack of precise assessment and classification promotes the generalized categorization of potentially diverse clinical conditions. Accurate identification of clinical and pathologically discrete conditions has potential to define specific and appropriate treatments which could be expected to yield consequential improvements in clinical outcomes for this large cohort of affected animals. In human beings, specific glomerular diseases are characterized (and thus are identified) by their light microscopic, immunopathologic, and electron microscopic features which are correlated with patient-specific clinical and clinicopathologic findings. In veterinary medicine, glomerular diseases are broadly brushed with general descriptors that preclude or prevent this important specificity.

At this point in the 21<sup>st</sup> Century veterinary nephrology and nephropathology have advanced to subspecialty niches within their respective disciplines of internal medicine and anatomic pathology. Internist and diagnostic pathologist have little difficulty recognizing overt injury to the glomerulus, but the internist is limited by a lack of therapeutic strategies with defined clinical and pathophysiologic correlations; and the diagnostic pathologist is constrained by an overly subjective

and imprecise morphologic classification system based on hematoxylin and eosin staining and light microscopy. While veterinary pathologists have attempted to characterize glomerular diseases in this manner, their efforts largely have failed to yield a consensus nomenclature, morphologic characterization, and an adequate or accurate basis for management. Over the past decade veterinary nephrologists have begun to appreciate the existence of a broad spectrum of distinct glomerular entities which heretofore have been loosely grouped into a limited collection of pathologic categories. The current pathologic diagnosis of a patient's glomerular disease provides little insight into the disorder's pathogenesis and prognosis, as well as guidelines for appropriate treatment. Veterinary nephropathology now is poised (and mandated) to abandon its simplistic, subjective, and outdated classification scheme for glomerular diseases that has been generally adopted from human pathology. Technological advances in digital pathology, distance conferencing, and global data sharing portend revolutionary opportunities for the clinical and pathologic assessment of proteinuric renal disease in the 21<sup>st</sup> century.

Clinical features of a patient's glomerular disease are equally as important as the morphologic characterization for meaningful and comprehensive classification. The diagnostic approach to proteinuric diseases must be structured to correlate the light microscopic, immunologic, and ultrastructural morphologic evaluation with the detailed clinical evaluation and clinicopathologic data to identify particular patterns of disease that might be expected to have foreseeable outcomes or predictable responses to treatment.

**CLINICAL EVALUATION OF PROTEINURIA:** The testing for protein in the urine should be performed routinely as part of the diagnostic evaluation of dogs with any clinical condition that warrants routine hematological and serum biochemical testing as well as in apparently healthy dogs in which such laboratory testing is performed for screening purposes. Urine protein assessment should also be performed routinely in animals that have known or suspected renal diseases (inherited, congenital, or acquired). Animals with chronic diseases with a predisposition to induce proteinuric renal injury should be tested for proteinuria at approximately 4 to 6 month intervals to document the onset or progression of renal injury. Detection of proteinuria and quantitation of its magnitude will depend on the testing methods utilized and the inherent sensitivity of the specific method. Generally urine is tested qualitatively to provide a "yes" or "no" answer, and then more specific testing is performed to further confirm or validate the qualitative assessment and to estimate the magnitude and/or the selectivity of the proteinuria. Finally, serial assessments are performed to determine if the proteinuria is transient or persistent

**Screening Testing:** *Dipstick colorimetric tests* are considered the minimum routine evaluation method for urine protein detection. These test strips provide a crude semiquantitative measurement (negative, trace, positive @ 1+ to 4+) of the protein content of the urine. All screening methods are influenced by the degree of urine concentration, such that a positive test on a poorly concentrated urine specimen predicts a more significant magnitude of proteinuria than a comparable reaction in a highly concentrated urine specimen. Although dipstick measurements are convenient, quick, and cost effective; they are subject to false positive reactions in urine specimens that are highly

concentrated or highly alkaline. Consequently, positive reactions on urine dipsticks should be confirmed by the sulfosalicylic acid (SSA) turbidometric test. A negative dipstick reaction predicts no overt protein excretion but does not exclude the presence of microalbuminuria.

***Sulfosalicylic acid test (SSA):*** The SSA test is a simple turbidometric screening test for urinary proteinuria. The SSA test can be used alone as a screening test as it is less subject to false positive reactions than the dipstick methods, or as a confirmation screening test for positive dipstick reactions. A positive reaction or a confirmatory reaction for a dipstick result should prompt additional quantitation. A negative SSA test, alone or as confirmation of a positive dipstick reaction, predicts no overt protein excretion but does not exclude the presence of microalbuminuria.

***Microalbuminuria test-Heska (E.R.D.-Screen™ Urine Test) species-specific point-of-care test:*** Microalbuminuria is the mildest degree of detectible proteinuria and is predictive of early or mild glomerular (or renal) injury that alters glomerular permselectivity or tubular protein reabsorption. It is seen both in animals that have early but progressive renal diseases and those with mild stable and subclinical chronic kidney disease. Sequential monitoring for the presence and increasing magnitude of microalbuminuria likely is a sensitive means to document active and progressive renal disease that may be functionally compensated and subclinical.

***Quantitative Testing: Urine protein:creatinine ratio (Up/c) [or urine albumin:creatinine ratio (Ua/c)]*** is a clinically applicable test that further quantitates the magnitude of proteinuria. The test is performed on non timed urine samples collected from animals with confirmed positive screening test. There is little indication to perform a Up/c on urine that is consistently negative on routine screening testing. The non proteinuric range is considered to be a Up/c <0.2. Dogs with a Up/c value between 0.2 and 0.5 are borderline proteinuric, while dogs with a Up/c greater than 0.5 are likely to be proteinuric. Up/c values >2.0 generally reflect glomerular injury, although postrenal urinary proteinuria may result in Up/c values approaching 5.0. There is accumulating evidence that dogs with chronic kidney disease that have a Up/c ratio >1.0 are at increased risk of uremic morbidity and mortality; and the risk of adverse consequences increases as the magnitude of proteinuria increases.

***Absolute quantitation*** of urinary protein excretion is the “gold standard” to document the magnitude of proteinuria and must be performed on precisely timed complete urine collections. Animals usually need urinary catheterization and accurate collection of 12 or 24 hour urine output. This testing is informative but is clinically time consuming, moderately invasive, and generally not clinically applicable. The urine collection also can be used to measure GFR by endogenous creatinine clearance as an estimate of residual renal function.

***Urine protein electrophoresis*** is an additional procedure performed on timed or non-timed urine specimens to evaluate the spectrum (size distribution) of the proteinuria. It is frequently paired with electrophoresis of serum proteins for comparison to the urine proteins. Paired serum and urine

electrophoresis is also used to document dysproteinemias (e.g., multiple myeloma) that produce highly selective proteinuria.

**DIAGNOSTIC APPROACH TO A POSITIVE PROTEIN TESTING:** The diagnostic approach to the detection of a positive urine protein reaction is dependent on the clinical condition(s) associated with the animal and the magnitude of the proteinuria. It is always important to determine if the proteinuria is transient or persistent. In some cases it is appropriate merely to monitor the presence and magnitude of the proteinuria over time, whereas in other animals the level of proteinuria may dictate immediate additional diagnostic testing or therapeutic intervention. The following are recommended guidelines:

Low grade incidental finding–screening laboratory test:

- Repeat test (days to a few weeks)
- Repeat test with urine culture
- Repeat testing with a more sensitive/quantitative test (e.g., Up/c ratio)

Significant range screening proteinuria:

- Confirm with quantitative test (Up/c; quantitative collection)
- Look for underlying LOWER URINARY DISEASE
- Urine culture
- Look for underlying SYSTEMIC DISEASE (infectious, inflammatory, neoplastic, pancreatitis). Establish a minimum clinical database:
  - a) Standardized medical history
  - b) Standardized physical examination
  - c) CBC
  - d) Complete chemistry profile (including at least: blood urea nitrogen; serum creatinine, calcium, phosphorus, total protein, albumin, sodium, chloride, potassium, bicarbonate (or total CO<sub>2</sub>), alkaline phosphatase)
  - e) Urinalysis
  - f) Urine culture
  - g) Urine protein:creatinine ratio
  - h) Blood pressure
  - i) Antithrombin III
  - j) Serologies appropriate for the geographical area (Ehrlichia, RMSF, Borrelia, heartworm, borellia, )
  - k) ANA (if indicated)
  - l) Chest & abdominal radiographs
  - m) Abdominal ultrasound

Persistent renal proteinuria or microalbuminuria in nonazotemic animals:

- Prospective monitoring if microalbuminuria at 1 to 3 month intervals.
- Prospective monitoring if Up/c is >0.5 but <1.0. Monitoring should be at 1 to 3 month intervals if the patient is clinically stable and nonazotemic.

- Investigate for underlying causes of disease as described above and treat any identified underlying conditions if the microalbuminuria or magnitude of proteinuria increases or if the Up/c is >1.0.
- Intervene with specific or symptomatic therapy (renal diet, ACE inhibitor) if the Up/c is >2.0.

Persistent renal proteinuria in azotemic animals with acute or chronic kidney disease:

- Investigate for underlying causes of disease as described above if Up/c is less than 0.5.
- Investigate and treat any identified condition or treat symptomatically (renal diet, ACE inhibitor) if Up/c is greater than 0.5 (dogs).

Percutaneous renal biopsy is being recommended for the specific evaluation of persistent pathologic renal proteinuria in animals with suspected proteinuric glomerular disease. Unlike other subspecialties of anatomic pathology in which light microscopy is sufficient to establish a specific diagnosis, glomerular pathology requires multiple imaging modalities including, light, immunofluorescence, and electron microscopy by pathologists with specialty expertise in glomerular pathology. Currently, there are no well-established standards for the classification of glomerular pathology, and pathologic diagnoses are derived subjectively from opinion based solely on qualitative assessment of light microscopy by a single anatomic pathologist. In an effort to improve the status quo, there is an active effort to create a paradigm transition in which future diagnoses of protein-losing glomerular diseases will be founded on quantitative lesion assessment of multiple microscopic modalities, consensus opinion of a consortium of nephrologists and nephropathologists, and assignment to an internationally defined classification scheme based therapeutic outcomes.

To provide greater objectivity, independence, flexibility, and quantitative evaluation to the pathologic description, a scoring system has been established to characterize the extent and magnitude of identifiable lesions of the renal glomeruli, tubular epithelium, interstitium, and vasculature. A regional Diagnostic Renal Pathology Center has been developed by Dr. George Lees at Texas A&M University as part of the WSAVA International Veterinary Renal Pathology Initiative which seeks to create a global network of identical, quality-controlled procedures to process and share high-resolution digital micrographic images of kidney specimens for light, immunofluorescent, and transmission electron microscopic evaluation. At the core of each Center is an Aperio digital slide scanning system for the production of virtual whole-slide images that can be reviewed simultaneously throughout the world. The digital slide is interfaced with a robust digital imaging and data management platform to facilitate sharing and analysis of the digital imagery to provide a greater understanding of the pathobiology of proteinuric diseases of animals and the most effective, evidence-based therapeutic approach. This fusion of comprehensive morphologic assessment and quantitative annotation and scoring will serve as a basis for an objective and unbiased classification system for proteinuric dogs. The resulting classification system will enable more precision in the diagnosis and the ability for statistical comparison of future therapeutic strategies subjected to clinical trial.

A potential classification scheme based on the comparable human classification is illustrated below. However, importantly, the finalized canine classification will not be forced to confirm to the conventional human scheme if canine glomerular characteristics are different. A more precise and expanded classification system will permit a quantum shift in the vision for the clinical and pathologic assessment of proteinuria in dogs. The strategic and implementable components of this pathologic initiative holds great promise to improve the recognition and management of glomerular disease and to promote opportunity to identify distinct glomerular diseases for which specific prognoses and therapeutic guidelines can be validated.

### Potential Renal Pathology Classification for Canine Glomerular Disease

<b>Morphologic Classification</b>	<b>Light microscopic findings</b>	<b>Ultrastructural findings</b>	<b>Immuno-pathology</b>	<b>Current status in dogs</b>
Amyloidosis	Nodular hyalinosis of capillary wall; positive Congo Red or STBlue staining	Mesangial and subendothelial fibrils	Immune deposits absent	Most often dxed in advanced stage of disease; early stages poorly recognized
Membranoproliferative glomerulonephritis (MPGN) type I/III	Increased glomerular cellularity and capillary wall thickness, magenta deposits with Trichrome, spikes with PAS	Subendothelial, and mesangial deposits, may also be subepithelial	Primarily IgG, C3 and other immunoglobulins may be present	Requires EM for accurate dx, specific Ig classes or type of MPGN inconsistently described in dogs
MPGN type II	As MPGN type I	Intramembranous linear dense deposits	Deposits composed of C3	Not yet described in dogs
Membranous GN (MGN), stage I – IV	Diffuse capillary wall thickening, normal cellularity, magenta deposits with Trichrome, PASH spikes	Subepithelial deposits	Primarily IgG	Early cases not detected with LM alone
Exudative/postinfectious GN	Increased cellularity, neutrophil and monocyte infiltrates	Subepithelial humps (poststreptococcal), mesangial and/or subendothelial deposits	Primarily IgG	Occasionally reported
Mesangioproliferative GN/IgA nephropathy	Typically increased mesangial cellularity, other lesions possible	Mesangial deposits	IgA	Difficult to dx with LM, requires FA
Focal segmental glomerulosclerosis (FSGS)	Segmental hypercellularity and solidification of capillary tuft affecting some glomeruli	Deposits not present	Not typically present	May be primary (associated with nephrotic syndrome in people, suspected in dogs) or secondary to decreased renal mass
Minimal change disease	Normal histology	Foot process effacement	Not present	Rarely described in dogs
Crescentic GN (rapidly progressive GN)	Crescents in > 80% of glomeruli	May or may not have deposits	Ig present or absent (ANCA associated?), fibrin	Rarely described in dogs
Glomerular vasculopathy (DIC, HUS)	Fibrin thrombosis, endothelial swelling, vasculitis	Fibrin, endothelial swelling/necrosis	Fibrin	Described in greyhounds, occasionally suspected in other dogs
Hereditary nephritis	Nonspecific and varied changes	Thin or focally/diffusely split GBM	Not expected	Described in several breeds, suspected in others

**MANAGEMENT OF GLOMERULAR DISEASE:** Therapeutic strategies for the management of glomerular disease in animals are largely empirical. Initial therapy is directed to eliminating the underlying etiology in an attempt to halt progression of the disease. However, it is uncommon that the specific underlying causes are identified to facilitate their elimination. In some cases, the disease regresses spontaneously suggesting resolution of the underlying condition(s) promoting the glomerular injury. As a result, glomerular diseases are usually managed supportively and symptomatically according to the identified clinical signs.

**Proteinuria**--Efforts to decrease the magnitude of urinary protein loss to its greatest nadir are necessary to prevent negative nitrogen balance, weight loss, nephrotic syndrome, thromboembolism, and progression of renal damage associated with protein-losing glomerular disease. There is reasonable evidence to indicate proteinuria is an identifiable risk factor for progressive renal injury. More than a mere indicator, proteinuria likely participates in the pathogenesis of renal injury and progressive nephrosclerosis. Dietary protein reduction and inhibition of the renin-angiotensin-aldosterone system (RAAS) with angiotensin converting enzyme inhibitors (ACEi) have become standard of care to modify proteinuria. In both experimental models of glomerulonephritis and in dogs with naturally occurring glomerular disease, moderate dietary protein restriction has been shown to lessen the magnitude of the proteinuria and accompanying azotemia without further reductions in serum albumin or body weight. Dietary protein modification should be provided by a therapeutic renal diet appropriate for the degree of azotemia of the patient. Feeding a therapeutic renal diet can independently lower the degree of proteinuria by 20% to 50%. Serum albumin, urine protein:creatinine ratio, and body weight should be monitored frequently to insure the degree of protein reduction is not too severe.

Angiotensin converting enzyme inhibitors also have become a standard of care for the management of proteinuria. ACEi effectively reduce glomerular capillary hydraulic pressure and interfere with mediators of glomerular proliferation and inflammation. Enalapril and benazepril are the ACEi with the greatest therapeutic application in dogs and should be prescribed routinely in patients with significant proteinuria. Enalapril can be provided at 0.5 mg/kg every 24 hours for dogs with Stage I CKD or 0.25 mg/kg every 24 hours for dogs with Stage II or higher CKD. The dose is increased to the maximum tolerable dose that produces the greatest nadir in the proteinuria. If there is no reduction in the proteinuria, if the Up/c does not reduce to normal, or if the ACEi therapy is not tolerated, alternative attempts to suppress the RAAS should be considered. With use of ACEi in dogs with Stage II or greater chronic kidney disease, serum creatinine should be monitored closely within 3-5 days of initiating or changing therapy, since these drugs have potential (transiently) to impair GFR and exacerbate the filtration failure and azotemia.

Angiotensin receptor blockers (ARB) directly interfere with the angiotensin II type 1-receptor to prevent ATII binding and can provide more complete suppression of the RAAS. This class of drug has been used successfully in dogs but current experience remains limited. Losartan, irbesartan, and telmisartan are candidate agents in this pharmaceutical class. Losartan has been used most commonly in dogs as a single agent or in combination with an ACEi. Telmisartan is more lipophilic and has a longer half-life, has a higher affinity for the angiotensin-1 receptor, and a greater percentage of binding compared with losartan and may have potential benefits over losartan to correct proteinuria in dogs (untested). There appears to be additive or synergistic benefit to combination therapy of an ARB with an ACEi than with single use of an ARB or ACEi. A potential adverse effect of blocking the angiotensin II type 1 receptor with an ARB is a compensatory increase in renin activity which could compete with the ARB effects and promote incomplete block of the RAAS. The suggested starting dose for losartan is 0.5 mg/kg each 24 hours with progressive titration of the dose to 1.0 to 2.0 mg/kg every 12 hours to achieve the greatest nadir in the proteinuria. Although ARBs appear to have less adverse influence on GFR than ACEi, they should be used with the same precautions in animals with chronic kidney disease, and therapy should be monitored similarly.

The renin inhibitor, Aliskiren, may provide renoprotection and antiproteinuric efficacy in dogs but remains untested. By blocking the catalytic site of renin, it interferes with the generation of angiotensin I but may not completely block the formation of angiotensin II which can form by the actions of alternative kinases. Similarly, the venerable aldosterone receptor antagonists, spironolactone, may have antiproteinuric actions and be indicated in animals undergoing long-term treatment with ARBs and ACEi which can promote hyperaldosteronism. It now seems tenable to creatively mix and match drugs directed at multiple target sites to suppress the RAAS pharmacologically to achieve maximal efficacy against this mediator of proteinuria and proliferative responses to intrinsic glomerular cells.

*Hypercoagulability/Thromboembolism*--Animals with antithrombin III levels <70% of normal, fibrinogen concentrations >400 mg/dl, or serum albumin concentrations <2.0 gm/dl are at risk for thromboembolism and should be treated routinely with low-dose aspirin (1.0-3.0 mg/kg every 12 hours). Aspirin, a nonspecific cyclo-oxygenase inhibitor, inhibits platelet aggregation, and has been effective to prevent the incidence of embolic complications in patients with glomerular disease. In addition, low-dose aspirin therapy has potential effects to decrease glomerular inflammation without interference with the beneficial effects of prostacyclin generation.

*Systemic Hypertension*--Hypertension is a consistent finding in dogs with either acute or chronic glomerular injury and should be controlled to prevent further glomerular and renal parenchymal damage. The management of hypertension involves the judicious restriction of dietary sodium and the staged administration of antihypertensive drugs including diuretics, adrenergic antagonists, ACE inhibitors, calcium channel blockers, and vasodilators.

*Nephrotic Syndrome*--Patients with severe hypoalbuminemia and nephrotic syndrome have a total body sodium excess in addition to excessive urinary protein loss and hypoalbuminemia.

Positive sodium balance should be controlled by reducing dietary sodium to approximately 0.5% to 0.3% of the dry matter basis of the diet and eliminating salty treats, processed foods, and iatrogenic sodium loads. Severe edema or ascites is managed with furosemide (1-2 mg/kg one to three times daily) as required to control the fluid accumulation. In animals with severe hypoproteinemia, aggressive diuretic administration combined with salt restriction may reduce intravascular volume and promote sodium depletion, hypovolemia, hypotension and progressive filtration failure. Paracentesis to remove ascitic fluid should be reserved for animals in which the abdominal distension compromises respiratory function or causes severe abdominal discomfort.

*Renal Failure*--Management of the uremic complications of glomerular disease is the same as for other causes of renal failure.

*Immunosuppressive Therapy* – The vast majority of glomerular diseases have an immune basis, and dysregulation of the immune and inflammatory systems initiates or promotes the glomerular injury. The extent, nature, and localization of the immune damage within the glomerulus dictates the morphologic, structural, and clinical features of the disease. The pathophysiologic characterization of immune injury is founded on light, immunofluorescent, and electron microscopy and serologic criteria. From these diagnostic criteria, the clinical signs of glomerular injury can be understood more readily and demonstrated to reflect the interaction of the immune, inflammatory, and coagulation systems with the specific anatomical compartments of the glomerulus, ie epithelial, endothelial, or mesangial.

On the basis of this premise, a therapeutic approach designed to interrupt the immunologic and inflammatory basis of the disease with immunosuppressive, anti-inflammatory and cytotoxic drug therapy would seem logical. Despite the widespread use of these drugs, there is little substantive basis for treatment guidelines and recommendations remain anecdotal. In general the use of anti-inflammatory or immunosuppressive doses of corticosteroids has been of little benefit in altering the progression of disease or clinical well-being in dogs. Corticosteroids put the patient at increased risk for proteinuria, muscle wasting, thromboembolism, and complications of the therapeutic agents. Unless the predisposing disease is known to be responsive to corticosteroids, their use in the treatment of protein-losing glomerular disease in dogs may not be warranted.

Immunosuppressive and cytotoxic drugs have been used in all forms of glomerular disease with varying anecdotal responses. It is clear from studies in human patients that different pathologic forms of protein-losing glomerular disease respond differently to different treatments. Yet in veterinary medicine we have lacked the tools and diagnostic distinctions required to define specific glomerular diseases in order to recognize effectiveness of therapeutic interventions in the performance of clinical trials. Azathioprine, chlorambucil, cyclophosphamide, and cyclosporine are recommended most commonly either alone, in combination, or combined with corticosteroids. Their use remains unproven in any form of protein-losing glomerular disease but may be helpful in selective patients in which the immunologic foundations of the disease are documented on renal biopsy. However, the use of immunosuppressive drugs cannot be endorsed explicitly until more definitive information based on controlled clinical trials is available. It is prudent to reserve use of

these drugs during the initial weeks of evaluation to determine if the disease will regress spontaneously or remain stable without therapy. If the proteinuria, azotemia and clinical appearance of the animal is stable, cautious refrain from drug therapy may be advisable. Rapidly progressive, biopsy-proven proliferative or membranoproliferative glomerulonephritis with evidence of immune product deposition rarely regress spontaneously and may warrants a trial of a single or combination of immunosuppressive drugs for 3-4 weeks. Combinations of azathioprine and chlorambucil or azathioprine and cyclophosphamide have been the most effective. The use of corticosteroids is not recommended for dogs.

The treatment of amyloidosis is palliative and symptomatic for the consequences of renal failure and proteinuria. Corticosteroids and cytotoxic therapy have been unsuccessful in animals. For systemic reactive forms of the disease, the underlying inflammatory process should be resolved to prevent further deposition of amyloid protein. Dimethyl sulfoxide (DMSO) has been recommended anecdotally and may delay progression of the disease.

**OUTCOME/PROGNOSIS:** The prognosis for animals with protein-losing glomerular disease depends on the nature of predisposing and concurrent diseases, and the severity of the proteinuria and renal failure. Spontaneous remission is possible in some types of glomerular disease (especially membranous nephropathy), but in general these diseases progress to endstage renal failure in the majority of patients. A large number of dogs are euthanatized after initial evaluation because of the severity of the renal failure, grave prognosis for recovery or presence of concurrent life-threatening complications/diseases (thromboembolism, cancer, cardiovascular failure).

In summary, protein-losing glomerular disease is a complex, poorly understood syndrome. Specific therapies have not been established, but patient survival may be improved by early detection of proteinuria and prevention of complications such as thrombosis. Until specific therapies are developed, the prognosis for these disorders remains guarded.