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CLINICAL AND THERAPEUTICAL APPROACH TO PROTEIN-LOSING NEPHROPATHY IN DOGS - A REVIEW

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Abstract

Protein-losing nephropathy (PLN) is a general term used to describe a list of glomerular disorders characterized by protein loss. Most common breeds affected are: Soft Coated Wheaten Terrier (adult age), Bernese Mountain Dog, Chinese Shar-pei, Labrador and Golden Retrievers. The main expresion of PLN is proteinuria, which represents the presence of any excessive amount of proteine in the urine. PLNs include glomerulonephritis (GN), glomerulopathy, and amyloidosis, but only histological examination can differentiate these conditions. PLN may arise idiopathically and often co-exists with hypertension, hypoalbuminemia, moderate anemia, hypercholesterolemia, thromboembolism, edema or effusions and progressive renal disease. Diagnosis of PLN involves documenting significant proteinuria. Urine analysis should be performed as a complementary test in each routine investigation and elevated urine protein-creatinine ratio might confirm the renal origin of the proteinuria. The main therapeutic objective is the reduction of proteinuria. Resolution of PLN is possible if the underlying condition can be treated, but this is oftentimes difficult.

Key words*: protein losing nephropathy; proteinuria; glomerulonephritis; amyloidosis.*

INTRODUCTION

Protein Losing Nephropathy (PLN) is an inherited disease that affects Soft-Coated Wheaten Terriers, Bernese Mountain Dogs, Chinese Shar-pei, Labrador and Golden Retrievers and results in essential proteins being lost through the kidney.

The disease can be mild and stable for years however, it may lead to severe complications such as chronic kidney disease (CKD). Progression of the symptoms is variable and often influenced by environmental factors.

The clinical signs of PLN vary depending on the degree of proteinuria and presence and stage of CKD. In some asymptomatic animals, proteinuria is detected incidentally. Anorexia, weight loss, vomiting, and polyuria/polydipsia are common in advanced disease.

Clinical signs may also reflect complications from hypertension (retinal hemorrhage), hypercoagulability (pulmonary thrombo-embolism) or hypoalbuminemia which may lead to ascites and pleural effusion (Grant D. C. et al.,. 2001; Littman M.P., 2011; Cook A.K. et al., 1996).

MATERIALS AND METHODS

We used comprehensive and current databases to review the literature describing PLN in canine veterinary medicine using the following key-words: protein losing nephropathy, proteinuria, glomerulonephritis, amyloidosis.

We selected those articles which discuss the most important theories and supporting evidence on the pathogenesis of PLN followed by an overview of the clinical features and therapeutic management of this condition in dogs. The purpose of this article is to discuss the general management of dogs with PLN according to its etiology because any change or recovery would depend on the underlying cause of the proteinuria. Proteinuria as main expression of PLN is mentioned in the sources consulted and the challenge is to differentiate renal proteinuria from pre-renal and post-renal causes using appropriate diagnostic tools.

RESULTS AND DISCUSSIONS

Since 1997, The Soft Coated Wheaten Terriers Open Registry (SCWTOR) listed 722 dogs

documented with PLN. The real etiology was not clear enough, but it is believed that this disease is inherited.

The mode of inheritance appears complex and some affected dogs demonstrate an autosomal recessive mode of inheritance, while only some mixed breed dogs with one affected Soft Coated Wheaten Terrier parent are affected, thus suggesting a dominant mode of inheritance. The highest chances of being affected is 95%, and belongs to dogs homozygous for the mutation.

Approximately 10 to 15% of Soft Coated Wheaten Terriers are affected by the disease. PLN was also described in Bernese Mountain Dogs, Labrador Retrievers and Golden Retrievers, but the causative mutation was different. It is observed that females are more at risk than males (Littman M.P. et al., 2013; 2015).

PLN commonly results from two primary diseases: glomerulonephritis and amyloidosis. While amyloidosis is generally considered a genetic disease with certain breed predispositions, glomerulonephritis can be caused by a number of underlying diseases.

These diseases can be primarily associated with kidney injury or systemic injury (such as neoplasia, infections, immune-mediated conditions) (Cook A.K. et al., 1996).

Familial glomerulopathy is an inherited condition with abnormal glomerular collagen deposition leading to proteinuria and progressive renal disease.

In amyloidosis, abnormal amyloid protein is deposited in the glomerulus.

Proteinuria with renal amyloidosis can be massive and may lead to the development of nephrotic syndrome (Rivas, Al., 1993; Wehner, A., 2008).

The nephrotic syndrome also occurs as a result of glomerular disease and is characterised by proteinuria, hypoalbuminaemia, hyperlipidaemia and edema (Carter, 1994).

Although considered to be pathognomonic for glomerular disease, nephrotic syndrome was present in only 15% of dogs with glomerulonephritis, most commonly in dogs with heavy proteinuria (Center, S.A. et al., 1987).

PLN Pathogenesis

PLN is a broad term that describes diseases of the glomerulus that cause protein loss into the urine. Proteinuria results when the normal renal handling of protein malfunctions or is overwhelmed. Normally the small amount of protein that is present in the filtrate is passed through the glomerular capillary wall and reabsorbed by the proximal tubule. The anatomical barrier that is the glomerular capillary wall serves as the primary mechanism by which proteinuria is prevented. Thus, changes in glomerular permeability result in significant protein loss in urine (Rennke H.G., et al., 1975; Haraldsson B. et al., 2004; Tryggvason K. et al., 2006).

The glomerulus is a complex structure that functions as a filter to form an ultrafiltrate of plasma.

This filtration system, made up by the fenestrated endothelium, glomerular basement membrane and visceral epithelial cells (podocytes) is freely permeable to water and small dissolved solutes, but retains cells and most macromolecules, such as proteins.

The podocyte is the most differentiated cell in the glomerulus and essential to the filtration unit (Tobilli et al, 2012).

Despite this complex filtration system, the glomerulus normally leaks albumin. Rapid endocytosis and hydrolysis of these proteins by proximal tubular cells occurs.

Filtered albumin and other proteins are resorbed and ultimately released in the blood as amino acids. A normal animal should excrete virtually no protein in the urine, but certainly an amount that is below the limit of detection of routine urine protein assays (Maack, 2011).

In certain clinically healthy dogs, a fraction of albumin is not resorbed and may be detected in low concentrations in the urine (Stockham and Scott, 2008).

Persistent and increased protein levels in the urine are abnormal.

Renal loss of plasma proteins can determine hypoalbuminemia and alter mineral and electrolyte metabolism, coagulation, cellular immunity, hormonal status, and may determine hyperlipidemia (Littman M.P., 2011; Bernard D.B., 1988, Harley L., 2012).

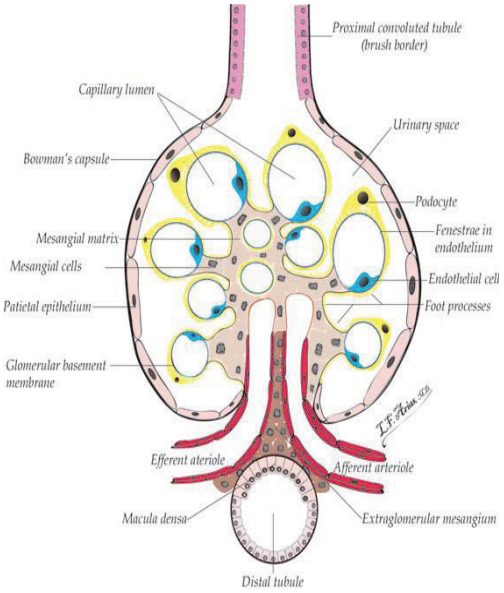

Figure 1. Schematic representation of a normal glomerulus (www.kidneypathology.com)

The origin of proteinuria

Proteinuria may be caused by physiologic conditions such as strenous exercise, fever, seizures, stress, decreased physical activity and by pathologic causes: urinary or nonurinary disorders. Transient damage to the glomerulus from fever or heatstroke may cause transient proteinuria. Some authors consider that exercise does not appear to cause proteinuria in dogs as it does in people. The interval to determine whether there is persistent proteinuria is not firmly established, but reevaluation a month later is reasonable (Grauer G. F., 2009)

Nonurinary: the production of low-molecular-weight proteinuria (dysproteinemias) or genital tract inflammation. Cystocentesis (contraindicated in pyometra) is indicated in order to reduce potential sample contamination. According to Marynissen S. J (2016), free catch urine provides a good alternative to cystocentesis for UPC in dogs.

Urinary: renal or nonrenal origin. Nonrenal proteinuria is often asociated with lower urinary tract inflammation, hemorrhage. Renal proteinuria is caused by increased glomerular filtration of plasma proteins associated with intraglomerular hypertension, structural abnormalities of the glomerular capillary wall, the presence of immune complexes or vascular inflammation of the glomerular capillaries, decreased resorption of filtred plasma proteins due to tubulointerstitial disease, inflammatory or infiltrative disorders of the kidney (neoplasia, pyelonephritis, leptospirosis). Pathologic proteinuria is a persistent finding in glomerular damage, whereas functional proteinuria is generally transient. Inflammation and neoplasia of the lower urinary tract can induce significant proteinuria, and urinary protein should always be evaluated in light of the urinary sediment and bacteriological examination and the clinical signs present. Non-glomerular renal diseases, such as pyelonephritis, severe chronic kidney disease or acute tubular necrosis may also cause proteinuria. Excessive protein delivery to the kidney ("pre-glomerular proteinuria") may lead to proteinuria, in conditions such as hemoglobinuria or multiple myeloma (Vaden S. L., 2005; Grauer G. F., 2009)

Clinicopathological evidence of PLN in dogs

PLN causes no clinical signs in the initial stages and is simply a laboratory diagnosis, but familial glomerulophaties should be taken into account. PLN's first laboratory sign, persistent proteinuria, may be occult initially, but eventually discovered along with hypoalbuminemia, hypercholesterolemia, and possibly azotemia, hyperphosphatemia, anemia, and/or isosthenuria, when dogs present with clinical signs due to progressive renal injury (decreased appetite, weight loss, dehydration, lethargy, vomiting, polyuria/polydipsia) or perhaps earlier with dramatic signs due to hypertension (such as blindness due to retinal detachment or hemorrhage), thromboembolic events, or nephrotic syndrome with cavitary effusions or edema of the extremities (Goldstein. R. E. et al., 2013; Jacob F. et al., 2005; Littman M. P. et al., 2015). Most forms of proteinuric renal disease, however, are glomerular diseases and may coexist with azotemia. Thus an animal does not have to have elevated blood urea nitrogen or creatinine to demonstrate renal damage (Harley L. et al., 2012)

Diagnosis of PLN in dogs - methods to assess proteinuria

As the measurement and sampling procedures for proteinuria have not been standardized, it is

of clinical importance to take into account the different types of urinary proteins, albumins, laboratory techniques, and urine sampling methods in order to have the best approach for an individual patient (Tobilli J. E. et al, 2012).
There are four tests to measure protein on a routine urinalysis: colorimetric reagent strip, sulfosalicylic acid precipitation test (SSA), microalbuminuria test and urinary protein-creatinine ratio (UPC) (Goanta A. M. et al., 2018).

The colorimetric reagent strip (dipstick) method is the the most common method that provides a semi-quantitative measurement of protein, which is a good screening test, but has many false positive results (Zatelli A., 2010; Nabity M. B., 2011). Even if in recent years the colorimetric reagent method has improved significantly, any positive dipstick result should be confirmed with sulfosalicylic acid testing, which is a highly specific test (Grauer G. F., 2009).

Sulfosalicylic acid precipitation test was used for confirmation of protein detected on urinalysis due to high specificity. However, the very low sensitivity (prone to false negatives) makes SSA unsuitable for use as a screening test for proteinuria. As mentioned above, because of recent improvements in the colorimetric reagent method, SSA is no longer routinely performed at most veterinary diagnostic laboratories (Vaden, S. L., 2016).

The microalbuminuria test is a very sensitive test for determining if albumin is present in the urine (1-30 mg/dl), a level that would not be detected by standard testing such as the urine dipstick or SSA test (Vaden, S. L., 2016). The microalbuminuria test is prone to false positives, and determining the clinical significance of a positive result requires follow-up testing with a urine protein:creatinine ratio (Whittemore J. C., 2006). Microalbuminuria is an important risk factor for cardiovascular disease in people and therefore is routinely measured in many patient groups. However, it does not appear to be a similar risk factor in dogs (Maniaki E., 2018).

Urine protein: creatinine ratio (UP/C) has become the gold standard test for proteinuria and should be run on any patient testing trace or greater on a urine dipstick or positive on SSA. The urine protein to creatinine ratio, performed on a single random urine sample, has a close correlation to the 24-hour urine protein quantification (Harley L. et al., 2012). In healthy dogs, the UPC is less than 0.5. Values over 1 are considered abnormal. Values between 0.5 and 1 are questionable, and should be monitored for persistence or worsening. A consensus statement recommends monitoring, investigating, or intervention depending on the level of proteinuria and the presence or absence of azotemia. In nonazotemic dogs a UPC>0.5 prompts monitoring, a UPC>1 prompts investigation, and a UPC>2 prompts intervention. In azotemic dogs, intervention is recommended at a UPC>0.5 (Monroe W.E. et al., 1989; Lees G. et al., 2005).
An urine protein: creatinine ratio >2 suggests a glomerular origin. If the sediment examination eliminates inflammatory urinary tract disease and hemorrhage as the source of proteinuria, then the degree of increase may help distinguish tubular proteinuria (typical ratio value of 0.5–2), glomerulonephritis (typical ratio value of 0.5–15), and glomerular amyloidosis (typical ratio value of 0.5–40). However, substantial overlap exists in these ranges, and a variety of glomerulopathies such as focal segmental glomerulosclerosis in dogs have yet to be well characterized. Further, the ratio tends to be low in the initial stages of a glomerulopathy, increases in severity as the disease progresses, and then decreases terminally in late stage of kidney disease, but the degree of proteinuria does not always correlate with the severity of the histopathological lesions (Jacob F. et al., 2005; Nabity M. B. et al., 2007; 2011)
According to the 2017 International Renal Interest Society (IRIS) staging guidelines for chronic kidney disease (CKD), stage 1 CKD includes persistent proteinuria of renal origin; therefore, dogs with PLN should be assessed for CKD. In cases with moderate to severe renal injury, this likely still holds true (IRIS Staging of CKD, modified 2017).

Renal biopsy is required when mildly increased UPC cannot differentiate glomerular from tubular damage. Renal biopsy is considered the gold standard for determining the type of renal damage, but it is an invasive procedure and is not feasible in every case because of financial constraints or animal health. Therefore, less invasive, inexpensive, sensitive and specific methods to evaluate the presence, character, and severity of kidney damage in dogs are needed (Salama A. D., 2011).

The World Small Animal Veterinary Association – Renal Standardization Study Group (WSAVA - RSSG) demonstrated that canine renal biopsies could be evaluated with LM (Light Microscopy), IF (Immunofluorescence) and TEM (Transmission Electron Microscopy) in a reasonable diagnostic workflow to provide timely and useful information to clinicians. In this purpose, two veterinary diagnostic renal pathology centers (in United States and Europe) were established to perform the evaluations and facilitate the collection of cases for prospective studies (Cianciolo R. E., 2013). According to Ciancolo R.E. et al. (2013), several potentially useful correlations between the magnitude of proteinuria (UPC value), degree of hypertension and histopathological findings were observed. The first is that dogs with the MPGN (membranoproliferative glomerulonephritis) pattern of injury had the most severe constellation of associated clinical abnormalities: their median UPC values were as high or higher and their median albumine values, as low or lower, than those of dogs in other clusters. Also, dogs with MPGN had higher median creatinine values and hypertension more often than dogs in any other clusters. Ciancolo states that dogs with glomerulosclerosis generally had the least severe constellation of clinical abnormalities: lower median UPC and creatinine values and higher median albumin values than those of dogs in other clusters, with hypertension only moderately often. Finally, dogs with amyloidosis were hypertensive less often than dogs in any other cluster, but they were otherwise comparable to dogs with membranous glomerulonephritis (Ciancolo R.E. et al., 2016).

Therapeutical approach

Clinicopathological manifestations of PLN as a glomerular disease marker in dogs varies in severity, therefore the therapeutic approach to glomerular disease in an otherwise healthy animal with proteinuria alone should be different from one with proteinuria and azotemia, hypoalbuminemia, hypertension and edematous extremities (Littman M. P. et al., 2013).

The therapeutical objectives in PLN should include serial measurements, identification and treatment of the underlying condition (if possible), reduction of proteinuria, management of hypertension, reduction of inflammatory mediators and thromboembolic tendency, and, if diagnosed, management of amyloidosis. There is no effective treatment for established amyloidosis. Colchicine (0.01-0.03 mg/kg PO q 24 hours) given during febrile episodes in Shar Peis may decrease amyloid deposition. There is no evidence of effectiveness once renal failure has occurred.

In order to reduce proteinuria, therapy typically involves a combination of drugs that inhibit angiotensin converting enzyme (ACE) and dietary changes (Bakris G. L., 2008).

A renal diet, containing a restricted quantity of high quality protein should be prescribed. Protein restriction decreases the amount of proteinuria and the protein trafficking in the renal tubules (Burkholder W. J. et al., 2000; Parker V. J. et al., 2012). The enhanced omega-3 to omega-6 polyunsaturated fatty acid ratio and restriction in salt and phosphorus found in canine renal diets can also be of benefit to dogs with glomerulopathies. Omega-3 fatty acid supplementation has been shown to be renoprotective in dogs with renal disease because it reduces the magnitude of proteinuria, mitigates hypertension and was shown to control serum triglyceride and cholesterol concentrations in humans with nephrotic syndrome (Brown S.A. et al., 1998; 2000). These positive effects are in part mediated through generation of prostaglandins. Sodium restriction is beneficial in the control of hypertension and fluid retention. Provision of adequate exercise may help reduce the formation of edema or ascites (Vaden S. L. et al., 2011).

With the advent of ACE inhibitors, survival in dogs with PLN without renal injury has been extended. ACE inhibitors have been proven to decrease proteinuria and delay onset of renal disease in dogs. Enalapril (0.25-0.5 mg/kg PO q 12-24 h) is a commonly used drug (Grauer G.F. et al, 2000). Benazepril also has been shown effective to reduce proteinuria in cats with CKD (King, J. N. et al., 2006; Tenhundfeld, J. et al., 2009). Because ACE inhibitors can decrease renal blood flow, reevaluation for azotemia one week after starting therapy or dose adjustment is advised (Ryan M.J. et al., 2008). These drugs can be used in normotensive patients as well as in hypertensive patients, although blood pressure should be monitored.

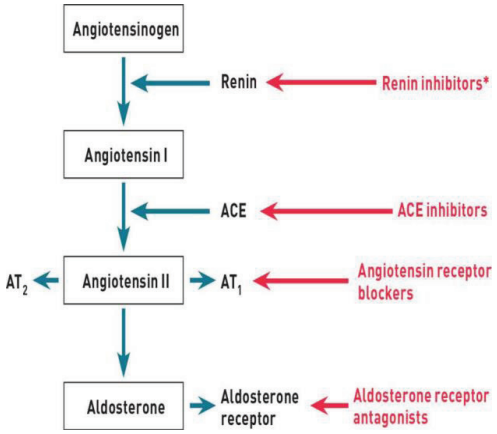

Figure 2. The renin-angiotensin-aldosterone system (RAAS) and its inhibitors. ACE inhibitors, angiotensin receptor blockers (ARB), and aldosterone receptor antagonists (ARA) have been used in the management of proteinuria in dogs. ACE, Angiotensin-converting enzyme; AT1, angiotensin II type 1 receptor; AT2, angiotensin II type 2 receptor (Vaden S., 2011)

Hypertension can lead to target-organ damage in the eyes, brain, cardiovascular system and kidneys. Untreated hypertension may cause worsening proteinuria and progressive renal injury. Many drugs are available to help control hypertension. In the setting of PLN, ACE inhibitors are the first choice, because of their combined antihypertensive and antiproteinuric effects. Inhibitors of RAAS are generally only weak antihypertensive agents, leading to a reduction in blood pressure by only about 10-15%. Ideally, systolic blood pressure should be maintained at around 160 mm Hg while under RAAS inhibitor therapy; some animals may need additional antihypertensive therapy (Linas S. L., 2008). The first step is to increase the dose of the RAAS inhibitor. If this is ineffective when the upper end of the dosage range is being administered, the next step is to add a calcium channel blocker, typically amlodipine (0.25-0.5 mg/kg q 24 h). Systolic blood pressure should be maintained >120 mmHg in treated dogs (Atkins C. E. et al., 2007). If blood pressure is not adequately controlled by ACE inhibitors or calcium channel blockers and dose escalation is contraindicated, other agents can be added. Angiotensin receptor blockers (losartan, candesartan) are commonly used in conjunction with ACE inhibitors in people, but experience in veterinary medicine is limited. Because diuretics commonly cause volume depletion and hypokalemia, they are not routinely used, although spironolactone, an aldosterone antagonist diuretic, is used by some clinicians. Short term use until peripheral edema is controlled can be considered (Christ D. D. et al., 1994; Ovaert P. et al., 2010)

In order to prevent thromboembolism, which is recognized as complication of glomerular proteinuria, antithrombotic agents (aspirin or clopidogrel) are often indicated in dogs that have UPC>3. Aspirin at a dose of 0.5 mg/kg q 12-24 hours will inhibit platelet aggregation while decreasing the risk of side effects seen at standard doses. It has a wider safety margin than anticoagulants such as coumadin, which require meticulous monitoring to avoid serious hemorrhagic events. It is used to decrease the risk of thromboembolic complications, both systemically and locally, as platelet aggregation and fibrin deposition in the glomerulus may contribute to the pathogenesis of PLN (Littman M.P., 2011; Smith S.A., 2012).

In several studies, the increase in urinary protein excretion is correlated with the tendency of the renal disease to progress more than with the underlying renal disease itself. Whenever urinary protein excretion is reduced, the decline in the glomerular filtration rate slows or stops. Interstitial inflammation and progression of disease can be effectively limited by drugs that, by ameliorating the

glomerular permselective barrier to proteins, limit both proteinuria and filtered protein-dependent signaling for mononuclear cell infiltration and extracellular matrix deposition (Perico N. et al., 2005).

Immunosuppressive drugs may be used if immune-mediated processes are suspected. There are various protocols for various conditions, a topic too large to comprehensively cover here. In addition to corticosteroids, other drugs to be considered include: cyclosporine, azathioprine, mycophenolate, cyclophosphamide, and chlorambucil, among others. The IRIS Study Group recommends empirical application of immunosuppressive therapy for dogs with severe, persistent, or progressive glomerular disease in which there is evidence of an active immune-mediated pathogenesis on kidney biopsy and no identified contraindication to immunosuppressive therapy. For diseases associated with profound proteinuria, hypoalbuminemia, nephrotic syndrome, or rapidly progressive azotemia, single drug or combination therapy consisting of rapidly acting immunosuppressive drugs is recommended (Segev G. et al., 2013). There is no evidence of efficacy for immunosuppressive in dogs, and these drugs should be used with caution. Corticosteroids are associated with proteinuria and are not recommended in dogs unless underlying disease is steroid-responsive (systemic lupus erythematosus). Cyclosporine was not beneficial in controlled study of dogs with GN. Other immunosuppressive drugs, such as azathioprine (2 mg/kg PO q 24-48 hours in dogs only) or cyclophosphamide (50 mg/m2 PO q 24 hours for 3 to 4 days, then off for 3 to 4 days) may be used but their benefit has not been proven. Mycophenolate mofetil (CellCept), a relatively new immunosuppressive agent used for human transplant recipients, is showing some promise in treating certain types of GN in people, most notably, lupus nephritis. No data is available for dogs with GN (Brown S.A. et al., 2013; Vaden S.L. et al., 2016).

CONCLUSIONS

In summary, many canine breeds have inherited glomerulopathies which are models for human disease, including glomerular basal membrane defects analogous to Alport syndrome, focal segmental glomerulosclerosis and abnormal glomerular depositions of collagen III, amyloid, or immune complexes, as well as the nephrotic syndrome. Other underlying conditions such as glomerulonephritis and amyloidosis are associated with PLN in dogs.

Urinalysis for screening and monitoring proteinuria should be routine investigations in animals and a minimal urinalysis (dipstick and sediment) should be included in all examinations. Prompt intervention for diagnosis and treatment of proteinuria is recommended. Susceptible breeds should be bianually monitored for development of proteinuria and owners should be informed of the possible occurrence of kidney disease.

A thorough diagnostic work-up is needed to identify subsets of glomerular disease and their response to specific treatment protocols. After establishing a suspicion of PLN, standard tests to uncover potentially treatable causes should include a complete blood count, serum chemistry panel, urinalysis, urine culture, titers for common tick borne diseases (Borrelia, Ehrlichia, Rickettsia) and heartworm testing in dogs, thoracic radiographs to screen for neoplasia, and abdominal imaging (radiography or ultrasonography). Other tests would be dependent on individual case characteristics. If the disease suspected is of renal origin and the animal's condition permits it, biopsy is indicated for the definitive diagnosis and prognosis.

ABBREVIATIONS

CKD - Chronic Kidney Disease
IRIS - International Renal Interest Society
SSA - Sulfosalicylic Acid
UPC - Urinary Protein: Creatinine Ratio
USG - Urine Specific Gravity
PLN - Protein Losing Nephropathy
LM - Light Microscopy
TEM - Transmission Electron Microscopy
IF - Immunofluorescence
GN - Glomerulonephritis
MPGN - Membranoproliferative glomerulonephritis
MGN - Membranous glomerulonephritis
RAAS - The renin-angiotensin-aldosterone system

ACE - Angiotensin Converting Enzyme
ARB - Angiotensin Receptor Blocker
ARA - Aldosterone Receptor Antagonists

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