Protein-Losing Nephropathy: Latest Treatment Recommendations

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A normally functioning glomerulus provides an effective barrier against the passing of albumin and other proteins into the urine. In patients with a protein losing nephropathy, the barrier is disrupted and proteins are carried into the proximal tubule. Although PLNs start out as a condition that affects the glomerulus, eventually, the entire nephron becomes affected by inflammation and fibrosis.

There are two disease processes associated with disruption of the normal filtration barrier of the glomerulus and the development of protein losing nephropathy (PLN): glomerulonephritis (GN) and amyloidosis. These cannot be distinguished from each other on the basis of clinical signs or laboratory data. Only histology can differentiate the two conditions.

Amyloidosis is caused by an inappropriate deposition of fibrils into the glomerulus that act to disrupt normal function. These fibrils are formed by the polymerization of protein subunits (e.g. serum amyloid A), which are produced in the liver and are one of a number of acute-phase reactant proteins produced in response to inflammation. These fibrils have a specific structure called a beta-pleated sheet, and once polymerized, they cannot be degraded.

Glomerulonephritis results from antigen-antibody complexes that become trapped in the glomerular wall. GN can be divided into categories based on histologic appearance: membranoproliferative gomerulonephritis, membranous nephropathy, and proliferative gomerulonephritis. Membranoproliferative gomerulonephritis (MPGN) is the most common type of GN seen in the dog and accounts for up to 60% of all cases. Membranous nephropathy (MN) is the second most common type of GN lesions seen in the dog and is the most common in the cat. Proliferative gomerulonephritis is thought to account for as little as 2% of GN cases.

Clinical features of PLNs are dependent on the underlying cause and degree of azotemia. Lethargy, anorexia, vomiting and weight loss are among the more common clinical signs; although, polyuria, polydipsia and ataxia can be seen. PLN is generally a disease of middle aged to older dogs.

Diagnosis

Urine analysis

The hallmark of PLN is the finding of inappropriate amounts of urine protein. It is impossible to determine the significance of proteinuria without performing a urine protein creatinine ratio (UP:C). Healthy dogs should have a UP:C of less than 0.5 while cats should have less than 0.4 . White blood cells, bacteria, sperm and casts can artificially increase the UP:C; therefore, the UP:C should only be analyzed in tandem with a full urinalysis and sediment examination. Studies suggest that as the UP:C increases, so does day-to-day measurement variability. Submitting pooled samples that have been collected over three days and stored at 40^{o}f may decrease this variability.

Hematology

Anemia is a common finding in PLN patients. The cause of anemia is probably multi-factorial: decreased RBC life span, decreased erythropoietin production and the anemia of chronic disease. Changes in the white blood count are often non-specific. Serum chemistry findings are similar to other renal diseases and include elevations in BUN, creatinine and phosphate. Serum bicarbonate may decrease as renal dysfunction progresses.

Infectious diseases

PLNs can be secondary to an identifiable underlying disease; therefore, a thorough search for an inciting cause is essential. Infectious, neoplastic, endocrine, inflammatory and drug-related causes must be considered. Serologic tests should be selected on the basis of the patient's geographic location and the relevant travel history. Infectious diseases associated with PLN include: Rocky Mountain Spotted fever, Ehrlichiosis, Borreliosis, Leishmaniasis, Babesiosis, and heartworm disease.

Diagnostic imaging

Protein losing nephropathy can be secondary to neoplastic processes, and ultrasound and radiographic studies are an essential part of the diagnostic plan. Ultrasound can also provide information about the renal architecture and outflow tract.

Amyloidosis vs. glomerulonephritis

The only way to differentiate amyloidosis from glomerulonephritis is by renal biopsy. At one time, the degree of proteinuria was thought to differentiate between the diseases; however, there is no meaningful difference between the protein loss experienced in these two conditions. In addition, several forms of GN are now recognized, and their treatment can be quite different. These cases can only be differentiated on the basis of a renal biopsy sample examined by light, electron and immunofluorescence microscopy.

Management:

General treatment

The majority of dogs with PLN develop hypertension during the course of their disease. Blood pressure should be checked periodically and antihypertensive therapy administered as needed.

Thromboembolism is the cause of death for at least 13% of dogs with glomerular disease. Much of the blame has been placed on anti-thrombin, which is lost through the damaged glomerulus. Risk of thromboembolism is greatest when anti-thrombin is less than 75% of normal. This correlates with a serum albumin of approximately 2.0 g/dl.

A low dose of aspirin may inhibit platelet aggregation and clot formation. Although previous recommendation suggested a dose of 0.5mg/kg, 1.0 – 5.0 mg/kg q24h is now recommended. An added benefit of this therapy may be to reduce platelet aggregation in the glomerulus. Another option is clopidogrel 1.1 mg/kg Q24. Clopidogrel is a platelet aggregation inhibitor, which may be used with or in place of aspirin.

Although initially counter-intuitive, PLN patients should be fed a moderately protein-restricted diet. Studies in people with PLN have shown that feeding a high protein diet is associated with increased mortality. Patients fed a low protein diet lived longer and suffered lower morbidity. The reason for this paradox is unclear, but is likely due to the increased loss of protein into the tubule.

Amyloid-specific

Colchicine, has been shown to inhibit release of amyloid from hepatocytes and has been used in humans with Mediterranean fever to prevent onset of renal amyloidosis. The efficacy of this drug in treatment of renal amyloidosis in animals has not been documented. Colchicine has significant side-effects including vomiting, diarrhea and nausea. In addition, there is no known benefit to starting treatment after azotemia develops. The currently recommended canine dose is 0.02–0.04 mg/kg PO q24.

Dimethyl sulfoxide (DMSO) has been advocated for the treatment of amyloidosis. There are no controlled clinical studies to determine if DMSO is beneficial for small animals; however, an individual case report suggest a positive response. The canine dose is 80 mg/kg diluted 1:4 with sterile saline given subcutaneously three times a week. Methyl-sulfonyl-methane (MSM) is a derivative of DMSO that can be given orally. Theoretical benefits are the same as for DMSO but it is considered more convenient since it can be given at home. There is no clinical data in people or animals to support the use of MSM. The currently recommended canine dose is 88 mg/kg q8h.

GN

Angiotensin converting enzyme inhibiters have been shown to decrease UP:C, lower blood pressure and improve clinical outcome in patients with GN. Some of the effects may be due to decreased glomerular hypertension secondary to dilation of the efferent arteriole. Enalapril is cleared exclusively by the kidneys, while Benazepril is cleared by the kidney and liver; therefore, Benazepril (0.25–0.5 mg/kg PO Q12-Q24h) is preferred in kidney injury patients. The goal should be to decrease the UP:C into the normal range or at least 50% of baseline. In patients that do not respond to ACEI, angiotensin receptor blockers (ARBs) may be helpful. Irbesartan 1-3 mg/kg PO q24 may be helpful.

It is becoming increasingly clear that some dogs suffer from a sub-type of GN that is responsive to immunosuppressive agents. A biopsy is required to determine which patients would benefit from immunosuppressive therapy. Histopathologic examination must include electron microscopy and immunofluorescent microscopy. More importantly, only the International Veterinary Renal Pathology Service (979.845.2351) is equipped to perform such studies. Tissue samples sent to national and university laboratories universally result in disappointing results. Cases of immunosuppressive responsive GN are treated with steroids and mycophenolate (12–17 mg/kg PO Q24 or divided).

When PLN is progressive and histopathology is unavailable, the use of immunosuppressive drugs could be considered; however, the owner must be aware of potential risks. In cases of rapidly progressive GN, mycophenolate (10 mg/kg PO q12) has been recommended with or without cyclophosphamide (200-250 mg/m^2 Q 3 weeks). A complete response defined as a UPC of < 0.5, a partial response defined as a reduction of the UPC by 50%. If after 3-4 months there is no clinically significant response, therapy should be discontinued. In patients that do have a response to therapy, immunosuppressive therapy should continue for 12-16 weeks, after which the dose may be tapered while monitoring UPC and azotemia.