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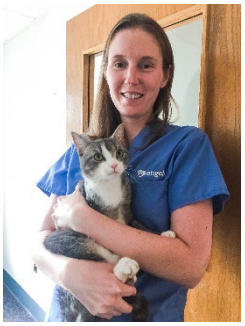
Proteinuria in Dogs



By Lisa Gorman, DVM, DACVIM

angell.org/internalmedicine

internalmedicine@angell.org

617-541-5186

Proteinuria is a commonly identified abnormality in dogs and can occur due to a number of disease and physiologic processes. Overt proteinuria (UPC > 0.5) has been found to occur in 11-13% of apparently healthy elderly dogs,[1, 2] emphasizing the importance of screening for proteinuria routinely so that any underlying disease states can be diagnosed and treated. Proteinuria associated with chronic kidney disease has been consistently shown to be a negative prognostic indicator. It is associated with a higher incidence of uremic crisis and death in CKD patients.[3] Diagnosis and control of proteinuria thus may have significant implications for the health and longevity of dogs.

Proteinuria can be caused by many factors and is not always due to renal disease. Postrenal causes of proteinuria are very common and include anything that results in lower urinary tract inflammation, such as urinary tract infection, urolithiasis, or lower urinary tract neoplasia. In contrast, prerenal proteinuria occurs when there are large numbers of low molecular weight proteins in circulation, which spill over into the urine and overwhelm the capacity of the renal tubules to reabsorb them. This may occur with hemolysis, severe muscle injury causing rhabdomyolysis, and multiple myeloma. Hyperadrenocorticism (and, similarly, exogenous glucocorticoid administration) have also been associated with proteinuria in dogs. Although not well-documented in dogs, transient physiologic proteinuria may occur with fever, heat stroke, seizures, or strenuous exercise. [4]

If postrenal and prerenal conditions are ruled out, and proteinuria is persistent, proteinuria is determined to be renal in origin. In the nephrons of normal kidneys, the glomerulus prevents the vast majority of proteins from leaking out from the blood into the glomerular filtrate, and the renal tubules reabsorb any smaller proteins that may make it through the glomerulus. This means that there should be essentially no protein in the urine of normal dogs. Tubular proteinuria occurs when the renal tubules are not functioning to reabsorb protein, which can happen with various tubular diseases, including Fanconi syndrome and

leptospirosis.[4] Because the glomerulus is still functional in cases of strict tubular proteinuria, most protein is still not able to enter the urine in the first place. Hence, the magnitude of the proteinuria is relatively mild. By contrast, glomerular proteinuria occurs when the glomerulus is damaged and allows larger proteins to enter the urine, which quickly overwhelms the ability of the tubules to reabsorb them. Significant glomerular damage can result in severe proteinuria, which is why renal proteinuria with a UPC > 2 indicates glomerular disease.

Initial diagnostic evaluation of proteinuria should include a urinalysis, urine protein: creatinine ratio (UPC), complete blood count, and chemistry panel, as well as infectious disease testing relevant to the area and the dog's known travel history.[5] Multiple infectious diseases have been associated with proteinuria in dogs, including Lyme disease, Anaplasmosis, Ehrlichiosis, Leishmaniasis, Leptospirosis, and rickettsial infections, among others.[6] Urine culture is also routinely performed in dogs with proteinuria to rule out occult urinary tract infection, although recent evidence suggests that the prevalence of occult UTI in dogs with proteinuria is low (<3%). This indicates that urine culture may not be required in proteinuric dogs lacking pyuria, bacteriuria, or lower urinary tract disease signs.[7] Blood pressure should be measured in all persistently proteinuric patients, as hypertension is both a common sequela of proteinuric kidney disease and may contribute independently to proteinuria by increasing the filtration pressure across the glomerulus. Additional diagnostics, including abdominal ultrasound and thoracic radiography, may be warranted in some patients to evaluate for neoplasia that may result in secondary immune-mediated glomerulonephritis. Ultimately, renal biopsy is recommended for a definitive diagnosis if all other causes of proteinuria are ruled out and the proteinuria is consistently in the glomerular range (UPC >2).[5] However, this is performed infrequently due to the risks associated with the procedure and the specialized processing (and associated cost) required for useful results.

UPC is the gold standard for diagnosing and quantifying proteinuria and is used to guide treatment decisions. Dogs with a UPC of <0.2 are considered non-proteinuric, those with a UPC of 0.2-0.5 are considered borderline proteinuric, and those with a UPC >0.5 are considered proteinuric.[8] When determining whether to treat renal proteinuria, it must first be confirmed that the proteinuria is persistent. Persistence is generally established by measuring UPC at two to three different time points at least two weeks apart.[8] However, if UPC is markedly elevated more than once and prerenal and postrenal causes are ruled out, earlier treatment is recommended, as this may indicate more severe glomerular disease.[5]

Although previous guidelines recommended treatment of proteinuria when the UPC was persistently >2 in stage I CKD patients and >0.5 in stages II-IV CKD patients,[9] current IRIS recommendations are to treat any persistent proteinuria with UPC >0.5 regardless of stage.[10] A renal diet is recommended for any patient with significant renal proteinuria, as feeding a renal diet has been shown to improve UPC and blood pressure in proteinuric patients receiving concurrent medical therapy.[11] Initial drug treatment is most commonly with an ACE inhibitor such as benazepril or enalapril. Benazepril is typically favored as, unlike enalapril, it is not renally excreted; however, enalapril is still a reasonable choice for non-azotemic patients. These drugs reduce proteinuria by inhibiting angiotensin-converting enzyme (ACE), which prevents the production of angiotensin II. This leads to dilation of the efferent arteriole and subsequent reduction in the filtration pressure across the glomerulus. ACE inhibitors are typically started at a dose of

0.5-1 mg/kg/day and gradually increase over time pending response. Because ACE inhibitors may reduce glomerular filtration rate (GFR) and also commonly cause hyperkalemia, monitoring of creatinine and potassium is required when using these medications. Monitoring of blood pressure, creatinine, and potassium should be performed one to two weeks after starting an ACE inhibitor and one to two weeks after each dose increase to ensure that it is well-tolerated. ACE inhibitors may take time to reduce proteinuria, so rechecking UPC is not usually done until about one month into treatment or after each dose change. Doses of 2 mg/kg/day may be required to provide an adequate response, although the development of hyperkalemia or azotemia may limit the ability to increase to this dose.[12]

There is growing evidence to support using the angiotensin receptor blocker (ARB) telmisartan as a first-line treatment for proteinuria or as an alternative option if the response to an ACE inhibitor is inadequate. One study found that combination treatment with an ACE inhibitor and telmisartan significantly reduced proteinuria and blood pressure compared with an ACE inhibitor alone, supporting telmisartan's efficacy.[13] Furthermore, a recent randomized controlled trial found that dogs started on telmisartan had a significantly greater improvement in UPC by 30 days than those started on enalapril and that dogs on telmisartan had their UPC reduce to <50% of baseline much faster than those on enalapril (30 vs. 90 days, respectively). Dogs in the telmisartan group also had a greater reduction in blood pressure when compared to dogs in the enalapril group.[14] These results indicate that telmisartan may be a preferable first choice for treating severely proteinuric dogs or in proteinuric dogs with significant hypertension, as it controls proteinuria faster and provides improved anti-hypertensive effects. Telmisartan should be started at a dose of 1 mg/kg/day, and the dose may be titrated upwards to 2 mg/kg/day based on response and tolerability.[12] Side effects are similar to ACE inhibitors, with hyperkalemia and reduced GFR being the main concerns. Therefore, monitoring of creatinine and potassium should be performed similarly to what is described for ACE inhibitors, and blood pressure monitoring should also be performed. While combination therapy with an ACE inhibitor and telmisartan can be considered for dogs with refractory proteinuria, this should be done only cautiously, as significant reductions in GFR may occur. In one study, combination therapy resulted in clinically significant increases in creatinine in 31% of dogs, and in human patients, the combination is no longer recommended due to a high rate of side effects without significant improvement in renal outcomes.[14]

Dogs with glomerular disease have been consistently at increased risk of thromboembolic complications, with thromboembolism detected in 12-21% of patients.[15] Therefore, it is recommended that these patients be treated with thromboprophylactic medication. Although this was routinely done with low-dose aspirin, clopidogrel has been shown to provide more consistent platelet inhibition,[16] and is thus now considered the preferred option. The recommended dose of clopidogrel is 1-3 mg/kg every 24 hours.

In dogs with glomerular disease with severe proteinuria, hypoalbuminemia, or significant azotemia despite standard treatment, immunosuppressive therapy could be considered to treat possible immune complex glomerulonephritis.[17] In a large study of renal biopsies from patients with suspected glomerular disease, approximately 50% had immune complex glomerulonephritis.[18] This indicates that roughly half of patients with glomerular disease may benefit from immunosuppression. Since the prognosis of proteinuric patients with severe hypoalbuminemia or azotemia is poor, in these patients, the potential benefits of

immunosuppressive therapy may outweigh the risks.[17] The treatment of choice for glomerulonephritis in dogs is mycophenolate, given at a dose of 10 mg/kg every 12 hours. A rapidly tapering course of prednisone (1-2 weeks) could be considered in some severe cases as an induction agent, although prolonged therapy with prednisone is not recommended due to the high rate of side effects and potential to worsen proteinuria.[19] In any case in which immunosuppressive therapy is considered for treatment of glomerular disease, the client should be fully informed about all potential risks and benefits of this approach.

Proteinuria is a common finding on screening lab work and may signal significant underlying disease in dogs. Therefore, it is crucial to investigate proteinuria and, if determined to be renal in origin, to start appropriate medical management. Effective treatment of renal proteinuria in dogs can improve clinical outcomes and help affected dogs live longer, healthier lives.

References

1. Proteinuria in apparently healthy elderly dogs: persistency and comparison between free catch and cystocentesis urine. Marynissen, S.J.J. et al. *J Vet Intern Med* (2017); 31: 93-101.
2. Results of screening of apparently healthy senior and geriatric dogs. Willems, A. et al. *J Vet Intern Med* (2017); 31: 81-92.
3. Management of proteinuria in dogs and cats with chronic kidney disease. Vade, S.L. et al. *Vet Clin Small Anim* (2016); 46: 1115-1130.
4. Proteinuria in dogs and cats. Harley, L. et al. *Can Vet J* (2012); 53: 631-638.
5. Consensus recommendations for the diagnostic investigation of dogs with suspected glomerular disease. Littman, M.P. et al. *J Vet Intern Med* (2013); 27: S19-S26.
6. Consensus recommendations for treatment in dogs with serology positive glomerular disease. Goldstein, R.E. et al. *J Vet Intern Med* (2013); 27: S60-S66.
7. Characteristics associated with bacterial growth in urine in 451 proteinuric dogs (2008-2018). Grimes, M. et al. *J Vet Intern Med* (2020); 34: 770-776.
8. IRIS staging of CKD (modified 2019). International Renal Interest Society. http://www.iris-kidney.com/guidelines/staging.html.
9. Chronic kidney disease in dogs and cats. Barges, J.W. *Vet Clin Small Anim* (2012); 42: 669-692.
10. Treatment recommendations for CKD in dogs (2019). International Renal Interest Society. http://www.iris-kidney.com/guidelines/recommendations.html.
11. Evaluation of the effects of a therapeutic renal diet to control proteinuria in proteinuric non-azotemic dogs treated with benazepril. Cortadellas, O. et al. *J Vet Intern Med* (2014); 28: 30-37.
12. Consensus recommendations for standard therapy of glomerular disease in dogs. Brown, S. et al. *J Vet Intern Med* (2013); 27: S27-S43.
13. Effect of telmisartan, angiotensin-converting enzyme inhibition, or both, on proteinuria and blood pressure in dogs. Fowler, B.L. et al. *J Vet Intern Med* (2021); 35: 1231-1237.
14. Efficacy of telmisartan for the treatment of persistent renal proteinuria in dogs: a double-masked, randomized clinical trial. Lourenco, B.N. et al. *J Vet Intern Med* (2020); 34: 2478-2496.
15. Consensus on the rational use of antithrombotics in veterinary critical care (CURATIVE): domain 1 – defining populations at risk. deLaforcade, A. et al. *J Vet Emerg Crit Care* (2019); 29: 37-48.
16. Platelet aggregometry testing during aspirin or clopidogrel treatment and measurement of clopidogrel metabolite concentrations in dogs with protein-losing nephropathy. Shropshire, S. et al. *J Vet Intern Med* (2020); 34: 710-718.

17. Consensus guidelines for immunosuppressive treatment of dogs with glomerular disease absent a pathologic diagnosis. Pressler, B. et al. *J Vet Intern Med* (2013); 27: S55-S59.
18. Prevalence of immune-complex glomerulonephritides in dogs biopsied for suspected glomerular disease: 501 cases (2007-2012). Schneider, S.M. et al. *J Vet Intern Med* (2013); 27: S67-S75.
19. Consensus recommendations for immunosuppressive treatment of dogs with glomerular disease based on established pathology. Segev, G. et al. *J Vet Intern Med* (2013); 27: S44-S54.