

## Session 6:

### Management of Proteinuria in Dogs: New awareness, new options

#### Introduction

Protein in the urine, particularly when it is of renal origin, can be an indicator of renal damage, and has been found to be associated with progression of renal disease. There are several ways that protein can enter the urine, through a damaged glomerulus, through lack of reuptake by tubular epithelial cells, and through exudation into the tubular lumen. In addition, protein can enter the urine during the collection and storage phase from hemorrhage or exudation in the ureters, bladder, urethra, prostate, or genital tract.

**Proteinuria can be classified as pre-renal, renal, or post-renal.**

Pre-renal: hemoglobin, myoglobin, immunoglobulin light chains (BJ proteins)

Cause: Strenuous exercise (rare in our patients), heat stress, seizures, fever, hemolysis, neoplasia, etc. It is indicative of underlying condition and may require additional evaluation

Renal: Indicates pathologic lesions of the kidneys. Can be further classified as glomerular, tubular, or interstitial.

Glomerular: lesions to the glomerular endothelium, basement membrane, or epithelium with damage to permselective function

Tubular: lesions that affect the ability of the proximal tubule to reabsorb small proteins that are able to pass through a normal glomerular barrier

Interstitial: secondary to inflammatory lesions of the interstitium that allow protein to exude into the renal tubules

Post-renal: Collection method artifact (blood, discharge from the genital tract), hemorrhage or exudative process from the lower urinary tract (ureters, bladder, urethra, prostate, etc.). Important: studies show that urine must have gross change in color before hematuria can lead to detectable proteinuria and that pyuria must also be significant before it affects the protein on a dipstrip. The Microalbuminuria test will likely pick up changes earlier than dipstrips in these conditions.

Note: For the purpose of this discussion, we will focus on renal causes of proteinuria, but it is important for the clinician to understand and rule out the non-renal sources in order to avoid misdiagnoses.

#### **Structure and Function of the Glomerulus:**

There are three filtration layers within the glomerulus:

1. Fenestrated endothelium
2. Glomerular basement membrane
3. Visceral epithelial cells

Filtration is primarily by size (< 60,000 daltons) and charge (positively charged particles move more easily across than negatively charged particles). These layers provide normal permselectivity which prevents large protein molecules from passing through the glomerulus into the urine. When protein is lost into the urine, the proximal tubule cells usually remove it. However, these mechanisms can be easily overwhelmed and this leads to large amounts of protein accumulation in the tubular epithelial cells and in the tubular lumen. This leads in turn to progressive tubular damage and renal disease.

Damage to the glomerulus and the subsequent breakdown in protein barrier can occur through amyloidosis or immune-complex deposition and damage to the glomerulus (due to chronic systemic inflammation or neoplasia). Proteinuria can also occur in patients with hypertension, which increases the intraglomerular pressure and damages the epithelium and basement membrane, allowing protein to pass through.

In patients with chronic renal disease, proteinuria can exist from multiple sources including glomerular damage, hypertension, proximal tubular injury, and exudative lesions secondary to interstitial nephritis and pyelonephritis.

Proteinuria is an indicator of progressive renal disease. For this reason, it is included as a sub-categorization (along with hypertension) in the International Renal Interest Group (IRIS) staging system.

#### **IRIS Stages of Chronic Renal Disease:**

	<u>Dogs</u>	<u>Cats</u>
Stage 1:	Creat < 1.4	Creat <1.6
Stage 2:	Creat 1.4 – 2.0	Creat 1.6 – 2.8
Stage 3:	Creat 2.1 – 5.0	Creat 2.8 – 5.0
Stage 4:	Creat > 5.0	Creat > 5.0

Qualified by blood pressure, proteinuria

#### **Testing options:**

Free catch urine vs. Cystocentesis: Two different studies have found that there is little difference in the UPC between free-catch and cystocentesis samples.<sup>1</sup> One minor exception is intact male dogs which may have more preputial discharge that can raise the protein level. The most ideal way is to have the owner collect a urine sample from three consecutive days and then pool equal volumes of them together for submission for protein evaluation.

#### Protein in the urine must be interpreted in light of two things:

1. Specific Gravity. Even trace protein in a dilute urine sample (< 1.020) may be significant.
2. Urine Sediment Evaluation. The presence of casts, red blood cells, white blood cells, bacteria, or epithelial cells may give the clinician a clue to the source of the proteinuria. Proteinuria in the face of an inactive sediment increases suspicion for underlying renal and particularly glomerular disease.

**\*\*Some animals may have day-to-day variations in mild proteinuria due to exercise, heat stress, or physical stress, so it is important to confirm the persistence of proteinuria 2 times with 2-3 weeks between tests.**

Dipstrip (mostly albumin): Normal urine with a high specific gravity (> 1.050) can often show trace or 1+ protein on dipstrips. Highly alkaline urine can lead to false positives, highly acidic urine can lead to false negatives. Can be negative in patients with significant proteinuria if the urine is very dilute. Patients with a positive protein level on dipstrip should have a urine sediment evaluated. If inactive, a UPC is indicated.

Microalbuminuria testing: This test is designed to detect levels of 1-30 mg/dl of albumin. This is below the detection of the dip strip and often even UPC changes. The presence of microalbuminuria may be an indicator of early renal disease but has also been associated with other conditions such as neoplasia, systemic inflammatory disease, and heartworm disease which can lead to glomerular injury through immune complex deposition. This may be a good screening test for patients with possible hereditary protein-losing nephropathies (Soft-Coated Wheaten Terriers), risk of renal disease (patients with diabetes mellitus, thyroid disease, or hypertension), and geriatric cats and dogs. If abnormal, follow-up with a UPC to further quantify magnitude of proteinuria.

Urine Protein : Creatinine ratio (UPC): Normal < 0.4 (dog) and < 0.2 (cat), allows for correlation of protein content with the concentration of the urine. Pink or red urine can lead to false elevation, as can pyuria (> 3 WBC/hpf). The degree of proteinuria very loosely correlated with the type of renal disease and cannot be used to differentiate glomerular disease from amyloidosis. UPC is generally performed if a patient has an abnormal amount of protein in the urine on dipstrip or has an elevated microalbuminuria test.

Note: Some medications (steroids, phenobarbital), and medical conditions (hyperadrenocorticism) can increase the protein in the urine. If these are present, removing the medication, or treating the underlying disease may resolve the proteinuria.

## Treatment

It is important to remember that any trafficking of protein across the glomerulus leads to further damage and inflammation in the nephron and will cause further progression of renal lesions. For this reason it is important to identify and treat any underlying disease process that may be contributing to the proteinuria. In the event that it is not possible to identify or address an underlying problem, additional measures may be taken to reduce the amount of protein crossing the glomerulus. Angiotensin Converting Enzyme inhibitors (ACEis) and Angiotensin Receptor Blockers (ARBs) such as Telmisartan will cause mild vasodilation of the efferent arteriole in the nephron, thus acting as a “pop off valve” and reducing pressure in the glomerulus. This is especially important in patients with hypertension or underlying chronic renal disease. There are likely other mechanisms of proteinuria reduction related to the inhibition of the RAAS system as well. The goal is either to bring the UPC to < 1.0 or > 50% of baseline. It is generally advised to start at low doses of ACEis and ARBs, and gradually increase the

dose, and it is not unusual to eventually need to use combinations of drugs (ACEi, ARB, and Ca Channel Blocker) to achieve these goals. Angiotensin receptor blockers may not reveal their full effect until 2-3 months after starting, so dose escalation should allow for this at each dose. The key is gradual escalation and monitoring of blood pressure, serum creatinine level, and potassium during the process. This may take several months. All patients taking ACEis and ARBs are at risk of hyperkalemia. Caution must be used with both ACEis and ARBs if the patient is in IRIS stage 3 or 4, since the reduction in proteinuria may not be worth the more clinically significant loss in GFR at this point.

Low protein diets may be of benefit in patients with CKD that is proteinuric. There is a reduction of intraglomerular capillary pressure and reduction of uremic toxin generation. The addition of omega-3 fatty acids to the diet may modulate inflammatory mediators and reduce inflammation.

### **So I performed a UPC and it is elevated, now what?**

1. Rule out non-renal causes of proteinuria (UTI, bloody urine, prostatitis). This may involve performing a urine culture to rule out bacterial infection. If the patient is being given glucocorticoids this may also increase protein loss in the urine.
2. Measure blood pressure. As many as 88% of hypertensive dogs can have significant proteinuria (UPC > 1.0) and the same is assumed for cats. If hypertensive look for underlying causes (renal disease, endocrine disease). Be sure to measure with an accurately sized cuff (width is 30-40% of circumference of measured body part).
3. Evaluate renal function. Determine if renal disease is present by evaluating BUN, creatinine, and urine specific gravity along with hydration status and urine sediment findings. Evaluation may also include imaging of the kidneys and urinary tract.
4. Look for evidence of underlying inflammatory processes including but not limited to pancreatitis, heartworm infection, tick-borne disease, chronic inflammatory disease, and neoplasia. This is not to say that every possible inflammatory disease must be tested for, but that looking at the whole animal and whether or not there are signs, such as chronic cough, that could indicate the need for testing.
5. Consider a renal biopsy to evaluate for immune-mediated glomerular disease or amyloidosis. Renal biopsy is the only definitive way to differentiate these two conditions, but given the association of amyloid with certain breeds, it is not always necessary to test for it. However, evidence of an immune-mediated process may warrant treatment with Mycophenolate mofetil or other immunosuppressive.

### **Treatment?**

1. Consider placing the patient on an ACE inhibitor or Angiotensin Receptor Blocker (Telmisartan) to reduce proteinuria, particularly if unable to identify or treat underlying disease.<sup>2</sup>
2. Place patient on a high quality, low-protein diet and consider supplementing with omega-3 fatty acids to reduce inflammation.<sup>3</sup>

3. If proteinuria does not improve on the above treatments, add in telmisartan or ACE inhibitor (if not already using) at a low dose. Gradually escalate dose as directed until achieving UPC < 1.0 or 50% reduction from baseline.<sup>4</sup> Monitor potassium and systolic blood pressure.

## **Biopsy?**

Proteinuria is one of the most common indications for renal biopsy. Biopsy will differentiate between immune-mediated disease like membranous GN (which may respond to immunosuppression) and non-immune disease like focal segmental glomerulosclerosis or FSGS (for which steroids are contraindicated). Up to 50% of dogs with non-amyloid protein losing nephropathy have immune-mediated GN and may respond to immunosuppressive treatment.<sup>5</sup> Renal biopsies are best evaluated by a specialized nephrologist.

## **International Veterinary Renal Pathology Service**

Rachel E. Cianciolo, VMD DACVP PhD  
Co-Director, International Veterinary Renal Pathology Service  
Asst. Professor, Dept. of Veterinary Biosciences  
The Ohio State University  
301 Goss Laboratory, 1925 Coffey Rd, Columbus, OH 43210  
Tel: 614-292-9717; Fax: 614-292-6473  
Email: [rachel.cianciolo@cvm.osu.edu](mailto:rachel.cianciolo@cvm.osu.edu)

## **What if I can't get a biopsy?**

There are certain conditions in which adding an immunosuppressive medication to a patient without pathologic evidence of immune-mediated disease should be considered. Per the IRIS Consensus Statements, immunosuppressive therapy may need to be considered if the serum creatinine is > 3.0 mg/dl or rapidly rising, or hypoalbuminemia is severe.<sup>6</sup>

## **What about Lyme Nephropathy?**

Patients with Lyme disease induced GN are a special case. They tend to progress very quickly, and develop over-hydration and edema easily on IV fluids. Although no studies about specific treatment have been performed, treatment with doxycycline and immunosuppression with mycophenolate mofetil is advised for this rapidly progressive glomerulonephropathy. The use of oral water (via a feeding tube) is a useful way to manage hydration with fewer problems of overhydration. Biopsy should be considered, unless there is thrombocytopenia or other hypocoagulopathy or significant hypertension.

## **References**

1. Marynissen SJ, Willems AL, Paepe D, Smets PM, Picavet P, Duchateau L, Daminet S. J Vet Intern Med. 2017 Jan;31(1):93-101.

2. Bugbee AC, Coleman AE, Wang A, Woolcock AD, Brown SA. [Telmisartan treatment of refractory proteinuria in a dog.](#) J Vet Intern Med. 2014 Nov-Dec;28(6):1871-4.
3. Zatelli A, Roura X, D'Ippolito P, Berlanda M, Zini E. The effect of renal diet in association with enalapril or benazepril on proteinuria in dogs with proteinuric chronic kidney disease. Open Vet J. 2016;6(2):121-7.
4. Brown S, Elliott J, Francey T, Polzin D, Vaden S. [Consensus recommendations for standard therapy of glomerular disease in dogs.](#) J Vet Intern Med. 2013 Nov-Dec;27 Suppl 1:S27-43.
5. Schneider SM, Cianciolo RE, Nabity MB, Clubb FJ Jr, Brown CA, Lees GE. [Prevalence of immune-complex glomerulonephritides in dogs biopsied for suspected glomerular disease: 501 cases \(2007-2012\).](#) J Vet Intern Med. 2013 Nov-Dec;27 Suppl 1:S67-75.
6. Pressler B, Vaden S, Gerber B, Langston C, Polzin D. [Consensus guidelines for immunosuppressive treatment of dogs with glomerular disease absent a pathologic diagnosis.](#) J Vet Intern Med. 2013 Nov-Dec;27 Suppl 1:S55-9.