UNIVERSITY OF CALGARY
FACULTY OF VETERINARY MEDICINE

This review accompanies the relevant episode of the Cutting Edge veterinary podcast. In each episode of this podcast, 3rd year students in the University of Calgary's veterinary medicine program fill you in on the most up-to-date literature and evidence-based practices on topics that matter to you, the practising veterinarian.

A Clinician's Guide to Proteinuria: The Unfiltered Edition

STUDENTS: Steffany Schluessel and Mackenzie Campsall
FACULTY MENTOR: Dr. Serge Chalhoub

We will be discussing the current recommendations and guidelines for small animal veterinary clinicians working up proteinuria cases in light of current research. Many of our canine patients get misdiagnosed with Chronic Kidney Disease (CKD) upon discovery of protein in the urine, leading to inappropriate treatments and poorer outcomes. In reality, it is much more common for felines to have true CKD but for dogs, protein-losing nephropathies (PLN) prevail. We aim to review the literature and discuss the pathophysiology, diagnostics, and treatments available for suspected PLN patients, as well as post-diagnosis monitoring required.

Pathophysiology

Proteinuria is often overlooked during routine screening but should always be taken seriously in light of clinical signs. Confounding pathologies such as urinary infections and hematuria can cause falsely elevated protein levels in the urine, so these should be ruled out when working up cases. Besides these causes and cats with highly concentrated urine, there is no such thing as benign proteinuria and it can suggest a more sinister process is at play. Causes of proteinuria are categorized as pre-renal, renal, or post-renal. When referring to proteinuria caused by PLN, the pathogenesis is renal and is caused by injury to the glomerulus [1]. In normally functioning glomeruli, the basement membrane (BM) cleans the blood by selectively filtering out small, non-charged molecules, leaving larger ones such as albumin in the circulatory system. When the BM undergoes damage, these larger molecules are permitted passage and cause necrosis and fibrosis of the interstitial tubules. Over time, the kidney will start to lose function as more tubules become damaged. The kidney is a special organ in that it maintains adequate status within the body until >75% of functionality is lost. Once the kidney has gotten to this point, the damage is almost always irreversible, and the patients will begin to show severe and sudden signs of azotemia such as hypertension, edema and effusion, dehydration, weakness, vomiting, and diarrhea [2]. These patients are at an increased risk of thromboembolic events which can be life-threatening [3]. Due to the loss of albumin through the glomeruli, these patients can often show a concurrent hypoalbuminemia and hypercholesterolemia when presenting with proteinuria [2]. This means that once a patient is showing clinical signs related to renal damage, it is usually too late to treat.

There are several causes of damage that can lead to a diagnosis of PLN, including glomerulonephritis (GN), infections, immune-mediated diseases, endocrinopathies, neoplasia, inflammation, and amyloidosis [4]. In this guide, we will focus on four commonly seen etiologies: immune-mediated, inflammatory, idiopathic, and neoplastic [5]. Glomerulonephritis is a cause of proteinuria that can be categorized into primary/idiopathic, secondary, and familial categories. Within the secondary GN category, pre-renal causes predominate and include infectious diseases such as heartworm, lyme or other tick-borne diseases, fungal disease, and more. Secondary GN also encompasses immune-mediated diseases such as IMHA, lupus, IMTP, and immune-mediated polyarthropathy, as well as inflammatory causes such as IBD, pancreatitis, prostatitis, and hepatitis [2]. Neoplasias such as leukemia, transitional cell carcinoma, mast cell tumors, and lymphoma also fall under the category of secondary GN. There is a long list of diseases and pathogens that can cause PLN, which makes treatment patient-specific as the underlying cause will help to shape the clinical outcome.

Diagnostics

When diagnosing PLN in the face of proteinuria, firstly, a persistent positive result must be demonstrated. Some of the literature states urine should be rechecked within 30 days [1] whereas others state persistent proteinuria can be concluded if tested again 14 days later [6]. In many cases, the initial patient presentation is unrelated to proteinuria, and is found during screening tests. The symptoms of PLN primarily arise from the subsequent azotemia only seen in end-stage disease, leading to poorer prognoses in these cases. However, if the proteinuria is caught early on during routine screening, it can be treatable [7].

In cases of proteinuria, it is important to follow up with further diagnostics after a urinalysis and determine the Urine Protein-Creatinine ratio (UPC). The UPC will give more information as to where the protein is originating from, and a UPC > 2.0 is suggestive of PLN [8]. To properly treat PLN, the underlying cause must be determined. Testing for infectious causes such as heartworm, tick-borne, and fungal diseases should be performed, as well as immune-mediated disease testing to rule out pre-renal causes and secondary GN [9]. As mentioned above, urine cultures are vital to rule out falsely elevated UPC values, though patients with urinary infections often have accompanying clinical signs. For other underlying causes such as neoplasia, medical imaging such as abdominal and thoracic ultrasound and radiographs should be performed as indicated. Similarly, post-renal causes such as urinary stones, prostatitis, and neoplasia should be ruled out with imaging and physical exam. If no other inciting diseases are found, idiopathic GN can be considered through exclusion.

Treatment

The treatment for PLN depends on the primary cause of the disease and the presence of azotemia in the bloodwork. Since PLN does not show markers of azotemia until the kidneys are in end-stage disease, attempting treatment is rarely successful at this stage. Unlike CKD, which is a disease that involves the progressive loss of renal function, PLN shows a less progressive, more rapid trajectory once critical. A generally acceptable treatment goal is to decrease UPC by >50% or value <2.0 with GN cases and reduce structural damage [6]. The two main goals of treatment include reducing the level of proteinuria and addressing the underlying cause.

If caught earlier, the proteinuria must first be approached by treating the underlying disease process, such as neoplasia, inflammation, immune-mediated diseases, or other. Concurrently, there are several reliable treatment options to decrease further damage to the kidneys. Initially, renal diets supplemented with omega 3 fatty acids should be implemented [10, 11]. As suspected, diets that are high in protein can increase intraglomerular pressure and can amplify the pre-existing proteinuria and subsequent tubular damage. With most prescription renal diets, higher quality proteins are used in restricted volumes to combat this effect while maintaining minimum protein requirements. Importantly, these diets also are limited in phosphorus and have controlled levels of potassium, as the damaged kidney has difficulty filtering these compounds from the bloodstream [11]. Omega 3 fatty acids, specifically eicosapentaenoic acid (EPA) are often found within the renal diets, but have been shown to decrease renal inflammation when used supplementally in GN dogs at a dose of 0.25-0.5 g/kg/d [11].

Pharmacological treatments aim to lower the amount of filtration required by the nephrons by reducing glomerular pressure. ACE Inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs) are the two main drugs used for this purpose, usually in conjunction with a blood thinner such as clopidogrel or aspirin to prevent thromboembolism. In small animal veterinary medicine, the main ACEi used are enalapril or benazepril. The mechanism of action involves inhibiting angiotensin-converting enzyme which functionally opposes efferent arteriole constriction, allowing for increased renal perfusion and clearance, and lowering glomerular filtration rate (GFR) [12]. Recommended dose of ACEi in dogs is 0.5-1.0 mg/kg/day, starting once daily [13]. If the UPC is not resolving adequately, dosing can be changed to twice daily. Preliminary studies suggest that the combined use of ACEi and ARBs may show more profound effects on reducing proteinuria and hypertension, however there are early indicators that potassium levels may become elevated and further studies are required [14, 15]. The primary ARB recommended for PLN treatment is telmisartan 1 mg/kg/day, although it is currently off-label use in dogs [16]. ARBs work in the same renin-angiotensin-aldosterone-system (RAAS) pathway as ACEi, but instead block angiotensin receptors to prevent vasoconstriction [17]. At the level of the kidney, this provides protection by reducing hypertension [18, 19]. Lastly, regular doses of blood thinners, either clopidogrel or aspirin, are recommended in patients with UPC >3.0 to prevent life-threatening thromboembolism, as PLN dogs have a sequelae of hypercoagulation of unconfirmed etiology [3, 7]. Using a low dose of aspirin such as 0.5 mg/kg once to twice daily has been shown to inhibit platelet function or similarly, clopidogrel (Plavix) at 1-2 mg/kg/day [20, 21].

Monitoring

Once PLN has been diagnosed and treatment initiated, clinicians must create an appropriate monitoring plan to ensure values are following a positive trend. Values that should be rechecked include UPC, renal indicators (serum albumin, SDMA, creatinine, BUN), potassium, and blood pressure [6]. Additionally, specific tests to monitor for the identified inciting disease should be considered. As mentioned previously, one main goal of treatment is to reduce UPC by >50%, or to obtain a value <2.0. One current model for treatment monitoring is to recheck by the following schedule: 1-2 weeks, 4 weeks, 8 weeks, 2 months.

In the circumstance that UPC is not declining at an appropriate rate, clinicians should reconsider the treatment plan. If UPC remains >2.0, they may attempt higher dosages of ACEi and ARBs. Additionally, renal biopsy or immunosuppression treatments may provide more insight into an underlying cause that is not heavily affected by standard treatments [7]. It has been shown that roughly half of GN renal biopsies are positive for immune complexes, so some may argue that biopsy is a futile diagnostic [7]. Instead, if the UPC is not responding to the first-line therapies, mycophenolate can be attempted at an oral dose of 10 mg/kg twice daily [22]. While it is important to monitor levels of azotemia, it is worthwhile to note that ACEi and ARBs can worsen azotemia due to decreased GFR by inhibiting efferent arteriole vasoconstriction [13]. If the UPC lands between 1.0-2.0, it can be considered acceptable and left up to the clinician on whether they would like to attempt further reduction or continue monitoring as is. Ideal UPC levels will be below 1.0, and in this case you would maintain current treatment and recheck in 2-3 months [6].

As discussed, severe or prolonged PLN can progress into CKD, but most patients showing clinical signs of azotemia are at a poor prognosis [8, 23]. It is important to discuss expectations and outcomes with clients in PLN cases as these patients may only have weeks to live if symptomatic.

Conclusion

Proteinuria is rarely benign in dogs and clinicians should be vigilant to monitor and investigate as indicated. If PLN is confirmed by persistent UPC >2.0, diagnostics should first be targeted at determining the underlying disease. In the case of neoplasia, infection, inflammation, or the like, the inciting cause should be managed with appropriate treatment while simultaneously treating the proteinuria.

Prognosis will depend on the underlying disease, response to proteinuria treatment, presence of severe azotemia, and client willingness. If no or mild clinical signs are present, these patients have a good chance at living a long and healthy life with dietary changes, daily medications and regular rechecks.

Acknowledgements

Many thanks are due to Dr. Serge Chalhoub for his mentorship and continued support while preparing this manuscript.

References

1. Littman MP. Protein-losing nephropathy in small animals. Veterinary Clinics Small Animial. 2011 01 [cited 2022 12]; 41(1): 31-62.
2. Wallace MS. Strategies for protein losing nephropathy. VIN. 2001 [cited 2022 12].
3. Lennon EM, Hanel RM, Walker JM, Vaden SL. Hypercoagulability in dogs with protein-losing nephropathy as assessed by thromboelastography. Journal of Veterinary Internal Medicine. 2013 05 [cited 2022 12]; 27(3): 462-468.
4. Langston CE. Protein losing nephropathy (Proceedings). DVM 360; 2009 03 [cited 2022 12]. Available from: https://www.dvm360.com/view/protein-losing-nephropathy-proceedings
5. Harley L, Langston CE. Proteinuria in dogs and cats. Canadian Veterinary Journal. 2012 06 [cited 2023 01]; 53(6): 631-638.
6. Lees GE, Brown SA, Elliot J, Grauer GF, Vaden SL. Assessment and management of proteinuria in dogs and cats: 2004 ACVIM forum consensus statement (small animal). Journal of Veterinary Internal Medicine. 2005 [cited 2022 12]; 19: 377-385.
7. Ignatescu RM, Giants AM, Badulescu AM, Braslasu D, Ionita L. Clinical and therapeutical approach to protein-losing nephropathy in dogs - a review. Science Works Series C Veterinary Medicine. 2019 [cited 2022 12]; 65(1): 51-59.
8. Cianciolo R, Hokamp J, Nabity M. Advances in the evaluation of canine renal disease. The Veterinary Journal. 2016 [cited 2023 01]; 215: 21-29.
9. Grauer GF. Canine glomerulonephritis: new thoughts on proteinuria and treatment. Journal of Small Animal Practice. 2005 [cited 2022 12]: 46(10): 469-478.
10. Cortadellas O, Talavera J, Fernández del Palacio MJ. Evaluation of the effects of a therapeutic renal diet to control proteinuria in proteinuric non-azotemic dogs treated with benazepril. Journal of Veterinary Internal Medicine. 2014 01 [cited 2022 12]; 28(1): 30-37.
11. Brown SA, Brown CA, Crowell WA, Barsanti JA, Allen T, Cowell C, Finco DR. Beneficial effects of chronic administration of dietary omega-3 polyunsaturated fatty acids in dogs with renal insufficiency. Journal of Laboratory and Clinical Medicine. 1998 05 [cited 2022 12]; 131(5): 447-455.
12. Kramer HJ. Inhibition of the angiotensin-converting enzyme - effect on kidney function and electrolyte balance. Z Kardiol. 1988 [cited 2023 02]; 77(3): 39-45.
13. Drug Monograph. Plumb's Drug Handbook. Benazepril: [revised 2022 03; cited 2022 12]. Available from: https://app.plumbs.com/drug-monograph/PGVZkcnorQPROD?source=search&searchQuery=benazepril
14. Fowler BL, Stefanovski D, Hess RS, McGonigle K. Effect of telmisartan, angiotensin-converting enzyme inhibition, or both, on proteinuria and blood pressure in dogs. Journal of Veterinary Internal Medicine. 2021 03 [cited 2022 12]; 35(3): 1231-1237.
15. Lecavalier J, Fifle L, Javard R. Treatment of proteinuria in dogs with telmisartan: a retrospective study. Journal of Veterinary Internal Medicine. 2021 07 [cited 2023 01]; 35(4): 1810-1818.
16. Drug Monograph. Plumb's Drug Handbook. Telmisartan: [revised 2022 04; cited 2022 12]. Available from: https://app.plumbs.com/drug-monograph/gbcEyW6bg1PROD?source=search&searchQuery=telmisartan
17. Galle J. Reduction of proteinuria with angiotensin receptor blockers. Nature Clinical Practice Cardiovascular Medicine. 2008 07 [cited 2022 12]; 5: 36-43.
18. Bugbee AC, Coleman AE, Wang A, Woolcock AD, Brown SA. Telmisartan treatment of refractory proteinuria in a dog. Journal of Veterinary Internal Medicine. 2014 11 [cited

2022 12]; 28(6): 1871-1874.

19. Miyagawa Y, Akabane R, Sakatani A, Ogawa M, Nagakawa M, Miyakawa H, Takemura N. Effects of telmisartan on proteinuria and systolic blood pressure in dogs with chronic kidney disease. Research in Veterinary Science. 2020 12 [cited 2023 01]; 133: 150-156.
20. Drug Monograph. Plumb's Drug Handbook. Aspirin: [revised 2020 03; cited 2022 12]. Available from: https://app.plumbs.com/drug-monograph/N5RHyd93hgPROD?source=search&searchQuery=aspirin
21. Drug Monograph. Plumb's Drug Handbook. Clopidogrel: [revised 2022 03; cited 2022 12]. Available from: https://app.plumbs.com/drug-monograph/KcfMszf90JPROD?source=search&searchQuery=clopidogrel
22. Drug Monograph. Plumb's Drug Handbook. Mycophenolate: [revised 2021 06; cited 2022 12]. Available from: https://app.plumbs.com/drug-monograph/dq2CNd72VPPROD?source=search&searchQuery=mycophenolate
23. Acierno MJ, Brown S, Coleman AE, Jepson RE, Papich M, Stepien RL, Syme HM. ACVIM consensus statement: guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. Journal of Veterinary Internal Medicine. 2018 11 [cited 2022 12]; 32(6): 1803-1822.