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Third Thursday Rounds
Lecture Notes

Urine Trouble: Understanding Diagnostic Markers of Renal Dysfunction

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Renal Disease in Veterinary Medicine

The prevalence of renal disease in veterinary medicine is not fully realized, although it is known to be significant. There are many different disease processes that impact individual species differently at different stages in their lives. For example, it is thought that 30% of cats may develop chronic kidney disease (CKD) after 9 years of age, but over the age of 15 years that percentage jumps significantly to over 50%. While CKD is not as prominent in dogs, they are much more likely to develop glomerulonephritis. Ultimately, the full extent of renal disease is significant, but not fully known.

Basic Kidney Function

The nephron is the basic unit of structure of the kidney. The nephron is responsible for converting blood into urine through the processes of filtration, reabsorption, secretion and excretion of substances. Small animals have hundreds of thousands of nephrons in each healthy kidney. Young animals even have a reserve of nephrons that are not used. As an animal ages or if there is an injury to the kidneys, there is nephron loss. Eventually, when all reserves are lost and damage or nephron loss continues, the animal will show clinical signs of kidney disease. It is believed that by the time there is an elevation in serum creatinine levels that 75% of the nephrons have been lost.

Recognition of Kidney Disease

Veterinary medicine has numerous approaches to the management and treatment of renal disease. The International Renal Interest Society (IRIS) was founded in 1998 with the goal of better understanding renal disease in small animals. They have been influential in establishing guidelines on the diagnosis and treatment of kidney disease. While great strides have been made, veterinary medicine could continue to improve on making an early diagnosis which would lead to earlier treatments and potentially to preventative medicine. Our goals when approaching kidney disease should be focused on preventing and slowing progression. This can best occur if we diagnose in very early stages of disease prior to the development of clinical signs.

Diagnostics

Urinalysis: A complete urinalysis is an important step that should not be skipped when completing routine diagnostics. Urine evaluation is highly sensitive to renal changes. In fact, it is difficult to evaluate changes in blood chemistry without the evaluation of urine. A patient's ability to dilute, concentrate or even produce urine will have a great impact on the results of blood chemistry. All parts of a urinalysis can be impacted by renal disease.

> **Urine Specific Gravity:** is the measurement of the density of urine compared to pure water. It measures the solute concentration present in urine. Therefore, urine specific gravity is able to assess the ability of the renal tubules to either dilute or concentrate the glomerular filtrate. Urine specific gravity is best evaluated using a refractometer as the results produced on urine strips is not accurate. Isosthenuria is a specific gravity that falls between 1.008-1.012 and demonstrates that the kidneys can no longer dilute or concentrate urine. In this range urine is the same specific gravity as serum. A random specific gravity of 1.010 in a dog or cat could be normal, but not in the face of dehydration. Studies have shown that urine concentrating ability is compromised when about 2/3 of the total nephron function is lost.
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> **Urine Sediment Evaluation and Culture and Sensitivity:** are key diagnostic steps in evaluating renal function. Urine dipsticks measure the chemical solutes excreted by the kidneys. Some dipstick findings can indicate or support the diagnosis of renal disease. Microscopic sediment evaluation may lead to findings such as hyaline or renal tubular casts

that indicate renal disease. A cellular urine finding in any patient with azotemia should be submitted for culture and sensitivity. Pyelonephritis and urinary tract infections are more common in patients with renal disease and can lead to worsening of clinical signs. A cellular urine can also lead to false positive results on dipstick protein measurement.
Proteinuria: can be an early measurement of renal disease in small animals. This can occur even before there are changes to the concentration of urine or development of azotemia. However, some forms of renal disease (e.g. acute kidney injury) will not lead to proteinuria. There are many false positives when evaluating protein levels on a urine dipstick. If initial dipstick evaluation is positive, further testing should be done to confirm the presence of proteins. Other factors can contribute to proteinuria such as fever, stress, myoglobin excretion or an alkaline pH. In cats, a small amount of protein on a dipstick may be a normal finding. General speaking, kidneys are not meant to filter large amounts of protein and if persistent, protein loses will lead to tubular damage and eventually CKD. There are several additional tests that can be performed to confirm proteinuria.

Urine protein creatinine ratio (UPC): measures both the creatinine and all proteins giving a quantitative measure of protein loss over 24 hours. It is required for IRIS sub-staging and is considered the most reliable measure of proteinuria.
Sulfosalicylic acid (SSA) precipitation test: has a high specificity and low sensitivity and while easy to perform, is prone to false negatives.
Microalbuminuria test: has a high sensitivity for albumin, but does not detect other proteins and is prone to false positives.

Chemistry: Azotemia and uremia are common findings in patients with more advanced stages of renal disease. Azotemia is an increased concentration of nonprotein nitrogenous compounds in the blood. These compounds are urea (commonly referred to as blood urea nitrogen- BUN) and creatine. Uremia is the clinical syndrome that occurs as a result of severe azotemia due to abnormal renal function. This is a multisystemic problem of the sequelae of inadequate renal function. Clinical signs vary and present in late stages. Patients may present with lethargy, weakness, anorexia, vomiting, and dehydration. CKD patients may present with longer developing signs such as weight loss and polydipsia/polyuria, poor body condition, and small and irregular kidneys. Occasionally you may observe uremic breath or oral ulcers.

Urea Nitrogen/BUN: produced by the liver and eliminated by the kidneys. The rate of elimination is dependent on the glomerular filtration rate (GFR). If there is a decrease in the GFR, there is an increase in the reabsorption of urea and an elevated serum concentration. Artifactual elevations can be seen with severe icterus and ammonia contamination.
Creatinine: is a by-product of muscle metabolism that trends lower in small breed dogs and young animals due to decreased muscle mass. Production and excretion of creatinine are constant with little variance for an individual animal. Creatinine is a more reliable way of evaluating GFR than BUN. Even small changes in creatinine within a short period of time indicate kidney injury.
Phosphate/Phosphorus: is primarily excreted in the urine. Hyperphosphatemia can precipitate with calcium causing mineralization of normal tissues and lead to organ damage.

Diagnostic Imaging and sampling: is another tool that can be used to identify changes to the kidneys.

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Radiography: provides limited information on the gross anatomical view. However, it is a good way to look for postrenal causes of disease such as uroliths which may be present in the kidneys, ureters or urinary bladder.
Ultrasonography: is much more sensitive to changes and can provide a significant amount of information as well as rule out causes of clinical presentation. Ultrasound allows visualization of gross anatomical measurements, parenchymal changes, and allows visualization of the renal pelvis. It also can allow visualization of other findings such as cysts, urolithiasis, hematomas, abscess, infarcts and neoplasia.
Renal Biopsies: are sometimes performed but have questionable clinical relevance. This is indicated more often with proteinuric renal diseases, renomegaly (or renal mass), familial renal disease, and acute renal failure. The sample is usually obtained using percutaneous renal biopsy that needs to be taken from the renal cortex. Therefore, this technique is performed by a trained professional using ultrasound guided techniques. Once the sample is collected, it is sent to a lab that specializes in veterinary renal pathology. Interpretation of the sample includes electron microscopy, light microscopy and immunopathologic testing.

Symmetric Dimethylarginine (SDMA): is a methylated form of the amino acid arginine, which is released intor the circulation during protein degradation and eventually excreted by the kidney. Because it is almost exclusively eliminated by renal filtration it is a sensitive biomarker for kidney function. SDMA testing is newer to veterinary medicine but is quickly finding a place in the diagnosis of renal disease. Used alongside creatinine, BUN and urinalysis it is used to evaluate kidney function. It is the most sensitive to decreases in the GFR and increases with an estimated 40% loss of kidney function as compared to creatinine which increases at about 75% loss of function. One added benefit to SDMA is that it is not impacted by extrarenal factors such as lean body mass and can be a more accurate reflection of GFR in underweight dogs and cats.

International Renal Interest Society (IRIS): once diagnosis is obtained staging principles are implemented. Staging renal disease based on guidelines established by IRIS is now common practice in veterinary medicine. These guidelines were modified in 2016 to reflect the addition of SDMA as both a diagnostic and staging tool. Staging allows the customization of therapies and allows for a more accurate prediction of prognosis for individual patients. The IRIS staging should not be used to make a diagnosis, but allows for an earlier, more patient specific approach to the management of disease.
International Renal Interest Society- http://www.iris-kidney.com

Summary:
Renal disease is a very common condition that we encounter in veterinary medicine. This is an unfortunate and progressive disease that in the past was treated in a generalized approach. However, due to advancements in diagnostic markers as well as implementation of the IRIS staging guidelines we can diagnose more quickly and initiate therapies earlier. An individualized approach based on staging will hopefully allow us to be more successful in delaying the progression of disease.

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References

Cummings School of Veterinary Medicine at Tufts University. (2016, January 15). Diagnosing Renal Disease in Rabbits – Clinical Case Challenge. Retrieved from https://news.vet.tufts.edu/2016/01/diagnosing-renal-disease-in-rabbits-clinical-case-challenge/

dvm360 Staff. (2013, April 30). Urine specific gravity measurement and interpretation in veterinary medicine. Retrieved from https://www.dvm360.com/view/urine-specific-gravity-measurement-and-interpretation-veterinary-medicine

dvm360 Staff. (2013, June 30). When urine specific gravity values go awry in veterinary practice. Retrieved from https://www.dvm360.com/view/when-urine-specific-gravity-values-go-awry-veterinary-practice

Goldstein, R. E. (2005). Feline Chronic Renal Failure - Why Do Urinalysis? Retrieved from http://www.ivis.org/proceedings/navc/2005/sae/215.pdf?la=1

Grauer, G. F. (2015, March/April). Feline Chronic Kidney Disease. Retrieved from https://todaysveterinarypractice.com/feline-chronic-kidney-disease/

IDEXX Laboratories, Inc. (2016). SDMA impacts how veterinarians diagnose and manage kidney disease in dogs and cats [PDF file]. Retrieved from https://www.idexx.com/files/sdma-data-white-paper.pdf

IDEXX Laboratories, Inc. (2019). IDEXX SDMA™ algorithm [PDF file]. Retrieved from https://www.idexx.com/files/idexx-sdma-test-algorithm.pdf

IDEXX Laboratories, Inc. (2016). Introduction to a new kidney test: IDEXX SDMA Test™ [PDF file]. https://www.idexx.com/files/intro-kidney-test-sdma.pdf

IDEXX Laboratories, Inc. (2020). A mild increase in SDMA reveals a patient's greater risk of kidney disease and is often the earliest indicator [PDF file]. https://www.idexx.com/files/sdma-persistence-data-white-paper.pdf

International Renal Interest Society. (2019). IRIS Staging of CKD. Retrieved from http://www.iris-kidney.com/guidelines/staging.html

McKinney, M. (2019, August 24). Machine learning enables prediction of early renal disease. Retrieved from https://www.dvm360.com/view/machine-learning-enables-prediction-early-renal-disease

Polzin, D. J. (2009). The Role of Renal Biopsy in Dogs with Proteinuric Kidney Disease--What Are We Learning? Retrieved from https://www.vin.com/apputil/content/defaultadv1.aspx?pId=11290&catId=33342&id=4252605

Roura, X / International Renal Interest Society (2019). CKD Risk Factors - Risk factors in dogs and cats for development of chronic kidney disease (Updated 2019). Retrieved from http://www.iris-kidney.com/education/risk_factors.html

Washington State University College of Veterinary Medicine. (2005, March 1). Chronic Kidney Disease and Failure (CKD, CRF, CRD). Retrieved from https://www.vetmed.wsu.edu/outreach/Pet-Health-Topics/categories/diseases/chronic-kidney-disease-and-failure