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Medicine on a Budget
Mini Series

Session One: Renal disease- It requires concentration not money

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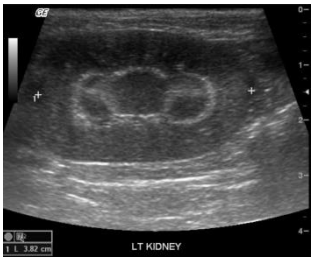

Renal Disease: It requires Concentration Not Money

The urinalysis (UA), inexpensive and easily performed, is a minimum database component that often provides crucial information to assist with diagnosis and/or patient management. Urine is the combined result of glomerular filtration plus renal tubular resorption and secretion and its analysis can provide insight to both urinary and systemic conditions. Since UA results cannot be predicted, it is reasonable to suggest that it should be included in routine screening and in any disease investigation. The most obvious need for UA is dogs and cats with polyuria and polydipsia (PU/PD); urinary tract signs (dysuria, haematuria, stranguria, pollakiuria); a history of urinary tract disease, infection, acute kidney injury (AKI), chronic kidney disease (CKD), current or previous urolithiasis; or systemic illness. Fanconi syndrome, urinary tract cancer and specific non-urinary conditions such as diabetes mellitus, diabetes insipidus, haemolytic disease and hepatic dysfunction may be better understood after reviewing UA results. When used for screening asymptomatic dogs or cats, dilute urine, proteinuria or crystalluria can indicate the need for a change in management or further investigation. UA results may be helpful in monitoring and in early detection of side-effects to medications that may impair renal function or damage renal tissue. Interpreting UA results in the context of serum biochemistry (SB) and complete blood count (CBC) results enhances value of each.

Urine Specific Gravity (USG) and Osmolality

USG is the first and most important test performed after initial visual inspection and is the only result that can provide information on renal function. Technically, USG is the ratio of urine weight to that of distilled water as estimated by its refractive index. The refractive index may be influenced by temperature and the number, type and size of solute molecules. Temperature effect is moderated in refractometers by mechanisms in the apparatus. Veterinary refractometers should have a separate scale for cat and dog urine, because their refractive indexes are distinct.

Osmolality is the measurement of solute concentration independent of molecule type. USG and osmolality are closely related but osmolality, a more reliable indicator of renal concentrating ability, is recommended for estimating urine concentration in provocative tests. One molecule of glucose and one molecule of albumin exert the same osmotic effects, but the higher weight of a protein results in greater effect on USG than does glucose. In the ratio of urine to plasma osmolality, >1 is consistent with renal concentrating and <1 renal diluting capability. If USG is above the refractometer's range, the sample may be diluted 50 : 50 with distilled water. This result can then be doubled, i.e., diluted 1.035 equals an undiluted result of 1.070. Dipstick USGs are not recommended.

No "reference range" exists for USG since healthy kidneys can produce extremely dilute or extremely concentrated urine ranging from 1.001 to >1.075. USG is influenced by hydration, electrolyte status, diet, and individual variation. Administration of fluids, glucocorticoids or diuretics lowers USG. Knowing hydration status, recent therapies, presence of protein or glucose in the urine, blood urea nitrogen and serum creatinine concentrations enhances the quality of any USG interpretation.

Glucose

Glucose passes through the glomerulus and is actively reabsorbed in proximal tubules. When capacity for reabsorption is exceeded (blood glucose concentrations (12-14 mmol/l) glucose appears in urine. While glucosuria is usually due to hyperglycaemia (diabetes mellitus, stress hyperglycaemia, medication), normoglycemic glucosuria can occur (e.g., primary renal glucosuria, Fanconi syndrome.

Ketones

Ketones (acetone, acetoacetate and beta-hydroxybutyrate) accumulate when there is a shift from carbohydrate to fat metabolism, as occurs with untreated insulin-dependent diabetes mellitus; they appear in urine when the renal threshold is exceeded. Dipstick test pads utilize nitroprusside, detecting acetone and acetoacetate but not beta-hydroxybutyrate. As diabetes is treated beta-hydroxybutyrate synthesis is reduced, but its conversion to acetoacetate can result in the continuing presence or increasing concentration of measured urine ketones, which can create a false impression of continuing or worsening illness. False positives are not common but could occur with darkly pigmented urine, use of captopril or cysteine. Delay in analysis or in appropriate refrigerated storage may cause false negatives as acetone is volatile. UTI bacteria could degrade acetoacetate. Ketonuria is extremely rare in starvation, anorexia, vomiting, or low carbohydrate intake. It is also rare in lactating females and after extreme exercise.

Bilirubin

Bilirubin is a normal product of RBC turnover as haeme is broken down within macrophages of the spleen and liver. Only conjugated ("direct") bilirubin is water soluble and therefore able to enter glomerular filtrate. Unconjugated ("indirect") bilirubin is protein bound and is not filtered. Conjugated bilirubin is light- and (room) temperature-sensitive. Concentrations decrease when less soluble free bilirubin is liberated or bilirubin is converted to biliverdin. Dipstick tests for bilirubin should be performed on uncentrifuged urine, because bilirubin can adsorb to calcium precipitates. Test sensitivity is reduced if ascorbic acid is present. Chlorpromazine can cause false positives.

Bilirubinuria with hyperbilirubinemia is expected with RBC destruction (haemolysis), intrahepatic disease, cholestasis and biliary obstruction. In dogs, since the renal threshold for bilirubin is low it may be detected in urine before hyperbilirubinemia is obvious. Canine kidneys synthesize bilirubin; thus, not all is derived from the blood. Low but detectable bilirubin concentrations may be found in concentrated samples from healthy male dogs. Bilirubinuria in cats is significant.

Blood (Haematuria, Haemoglobinuria, Myoglobinuria)

Dipstick methodology is based on the pseudoperoxide activity of haeme reacting with organic peroxide. Detection of haematuria, haemoglobinuria or myoglobinuria occurs at levels not visually apparent; test pad sensitivity is 5-20 RBCs/mcL compared with 2,500 RBCs/mcL for visual recognition. Test strips detect intact RBCs (haematuria), haemoglobinuria and myoglobinuria. When RBCs exist without free haemoglobin, colour changes on the pad are blotchy. Intact RBCs must be suspended for detection and unmixed urine can be falsely negative.

False positives may occur in urine contaminated with cleaning agents (hypochlorite, bleach, peroxide). Dipstick assessment of blood must be made in the context of USG, sediment, the appearance of serum, and muscle enzyme concentrations. Haematuria is common, while haemoglobinuria is less common and myoglobinuria rare.

Haematuria may be present due to bleeding within the urinary tract due to trauma (cystocentesis), uroliths, inflammation, infection, neoplasia, or a coagulopathy. Confirmation by sediment examination is recommended. Extraurinary (genital) sources of bleeding are possible. Haemoglobin may be present in urine either as a result of haemoglobinemia (intravascular haemolysis) or RBCs that have lysed in dilute or alkaline urine. Haemoglobin appears in urine when haptoglobin binding capacity in plasma is exceeded and renal tubular resorption mechanisms are overwhelmed. Myoglobinuria can occur if there is muscle trauma, ischemia or necrosis.

Centrifugation of urine and comparison of uncentrifuged and supernatant can assist in confirming presence of intact RBCs to explain a positive result. Haemoglobinuria due to intravascular haemolysis is expected to result in pink-tinged plasma, whereas plasma would be clear with myoglobinuria. Peripheral blood smear evidence of parasites, spherocytes, ghost cells or Heinz bodies would support intravascular haemolysis as the origin of haemoglobinuria. When urine is discoloured due to myoglobin, it may be described as red/brown rather than pink/red. Elevations in serum creatine kinase and/or aspartate aminotransferase activity would be expected with myoglobinuria. Haemoglobinuria without icterus suggests acute haemolytic disease but when combined with hyperbilirubinemia is suggestive of chronic haemolysis. Discordant results in comparing dipstick results and sediment examination occur for several reasons.

Bacteria

Both cocci and bacilli are observed in urine sediment; cocci in chains are relatively easy to identify. While normal urine is sterile, samples may contain bacteria from the distal urethra or genital tract in voided or catheter samples. Small numbers of bacteria from the urethra or genital areas, in fresh catheterized or voided samples, are common. Delay in analysis or lack of preservative may result in a significant proliferation. Therefore, when large numbers of bacteria are seen without WBCs, contamination should be suspected. False positive results may occur if debris, lipid droplets or small amorphous crystals are misidentified as bacteria or if stain is contaminated. Identification of bacteria in urine sediment may or may not be significant and failure to identify bacteria does not rule out their presence. Large bacterial numbers in cystocentesis, fresh or preserved catheterized samples are suggestive of UTI, particularly when accompanied by pyuria. Urine culture is indicated to confirm UTI. Bacteria seen on sediment but without growth on culture occurs with contaminated unpreserved stored urine, bacteria rendered non-viable by preservation method or recent antibiotic therapy.

Cylindruria (Casts)

Material concentrated in a tubule can be excreted in that shape, i.e., appearing as little tubes, called “casts” (cylinders). Casts are usually composed of cells and mucoprotein (Tamm-Horsfall) derived from the loop of Henle, distal tubules and collecting ducts. Casts from any of these areas are cylindrical, have parallel sides with rounded, square, irregular or tapered ends. Their width depends on the diameter of the tube in which they were formed; wider casts are usually formed in collecting ducts or dilated tubules.

Any material trapped in mucoprotein, such as cells, and excreted within a cast and identified is the basis of cast classification. Time within a tubule may allow degeneration of trapped material, changing its structure and classification. Low numbers of hyaline or granular casts may be observed in healthy urine but not cellular casts.

Crystalluria

Struvite, amorphous phosphate and oxalate crystals are commonly seen in urine of healthy animals. Urate, cysteine, or large quantities of calcium oxalate crystals are usually abnormal. Some crystals are indicative of significant disease or a metabolic disorder and others may provide preliminary information concerning the structure of uroliths, if present. Crystals form in supersaturated urine. Factors that influence the detection of crystals in urine include USG, temperature, time to analysis, pH and diet. Refrigeration promotes crystal formation and is not indicative of *in vivo* crystalluria. Urine samples for sediment examination should be rewarmed before analysis. The pH of urine is important because some crystals require a certain pH to form. Indeed, *in vitro* alteration of pH can make detection of certain crystals easier and may assist in identification of unusual crystals as will the medication history since some result from precipitation of drugs or their metabolites. Most common companion animal urinary crystals are easily recognized by shape, size, color and sample pH.

Glomerular Disease

Glomerular diseases are a leading cause of renal disease in dogs. In randomly selected dogs, the prevalence of glomerular lesions is as high as 43% to 90%, and the prevalence appears to increase with age. Glomerular diseases also occur in cats, although they are less common. Immune complex glomerulonephritis (ICGN), amyloidosis and glomerulosclerosis are considered to be the most common glomerular diseases of dogs, comprising nearly 84% of the lesions described in a recent report of 501 dogs with glomerular disease. Progress has been made in trying to develop a deeper understanding of the differing clinical presentations of the varied glomerular diseases that occur in dogs; fewer studies have been done in cats. Consensus recommendations have been published regarding the approach to the diagnosis, standard therapy and immunosuppressive treatment for dogs with suspect glomerular disease.

Signalment

Glomerular disease can develop at any age, but appears to be most common in middle-aged to older dogs. The prevalence of microalbuminuria, a marker of increased glomerular permeability, increases as dogs age, with more marked increases seen beyond 6 years of age. The average age of 375 dogs with a variety of glomerular diseases reported in five studies was 8.3 years. Dogs with nephrotic syndrome (NS) may present at a younger age (mean 6.2 years). Male and female dogs were equally represented. However, the average age and gender predilection seen with specific glomerular diseases varies somewhat from the overall averages. Glomerular diseases often occur secondary to another disease process. Infectious and noninfectious inflammatory diseases may be more likely in young and middle-aged animals, whereas neoplasms are more common as dogs become older. Familial glomerular diseases often are manifested at an early age. Several breeds of dogs are known to have familial glomerular diseases; many of these are discussed in detail in. Labrador Retrievers and Golden Retrievers may have a higher incidence of glomerular disease; however, the possibility that this increased representation reflects the popularity of these breeds requires further evaluation.

History

The clinical signs associated with glomerular disease vary considerably, depending on the severity of proteinuria and the presence or absence of renal failure. Many animals with glomerular disease are asymptomatic, and proteinuria is detected during routine health screening. Alternatively, animals may manifest specific signs related to an underlying inflammatory, infectious, or neoplastic condition. Signs of glomerular disease may be nonspecific (e.g., weight loss, lethargy) or consistent with chronic renal failure or uraemia (polyuria, polydipsia, anorexia, vomiting, and malodorous breath). Acute renal failure is not common in animals with glomerular disease. When urinary protein losses are severe, signs of fluid retention (e.g., abdominal enlargement consistent with ascites, peripheral edema) or thromboembolism (e.g., dyspnoea, loss of limb function) may be present. Hypertensive damage to the central nervous system, eyes, or heart may induce a variety of clinical signs.

Physical Examination Findings

The physical examination is often unremarkable in dogs with glomerular disease. Nonspecific evidence of systemic disease may be present, e.g., poor body condition or poor haircoat. Dogs with advanced renal failure may have oral ulcerations, pale mucous membranes, or dehydration. Subcutaneous oedema or ascites or both are sometimes noted. Occasionally dogs have physical evidence of thromboembolic disease, such as dyspnoea or a decreased or absent peripheral pulse. Evidence of a predisposing inflammatory, infectious, or neoplastic process may be detected during the physical examination. The kidneys of affected animals are variable in size. Animals with chronic renal failure often have small, firm, irregularly shaped kidneys, whereas those with milder disease often have normal-sized or, occasionally, enlarged kidneys.

Clinicopathologic and Imaging Findings

Proteinuria is the hallmark of glomerular disease. A urine protein–to-creatinine ratio (UPC) >0.5 is abnormal in a urine sample free of inflammation or macroscopic haematuria. With respect to the UPC, no magic number or range of numbers is diagnostic for any one renal disease and the overlap in expected ranges is too broad to be clinically reliable. In general dogs with amyloidosis or membranous nephropathy have the highest UPCs, and those with tubulointerstitial disease have lower values. Glomerular lesions have been identified in dogs without proteinuria. In three studies of urine albumin in canine models of glomerular disease, microalbuminuria was detected before increases in the UPC, and the magnitude of microalbuminuria increased over time in dogs that eventually developed an increased UPC. Therefore it seems reasonable to conclude that a dog with persistent microalbuminuria of increasing magnitude should be assessed as having an injurious process to the glomerular filtration barrier and may eventually develop overt proteinuria.

Isosthenuria is a variable finding in dogs and cats with glomerular disease. In one study of dogs with glomerulonephritis, 37% had urine specific gravities in excess of 1.035, and isosthenuria was detected in only 29%. However, dilute urine (i.e., a urine specific gravity less than 1.016) was more common in dogs with amyloidosis, occurring in 63% of dogs, whereas only 5.1% were able to concentrate above 1.035. The presence of renal azotaemia and an intact concentrating ability, called *glomerulotubular imbalance*, is indicative of glomerular disease. Cylindruria is common in dogs with glomerular disease; casts are most often hyaline but can be granular, waxy, or fatty.

It is believed that proteins are packaged into casts to protect the renal tubular epithelium from their damaging effects. Renal haematuria develops with glomerular injury in humans and is more common in specific diseases (e.g., IgA nephropathy, mesangial proliferative glomerulonephritis), but it appears to be less common in dogs with glomerulopathies. Erythrocytes that have passed through the abnormal glomerular capillary bed are often misshapen; the morphology of urine erythrocytes can be used to differentiate haematuria of glomerular origin from that resulting from other causes.

Hypoproteinemia caused by hypoalbuminemia develops in many dogs and cats with glomerular disease and is more likely in animals with heavy proteinuria. Hypoalbuminemia occurred in 60% and 70% of dogs with glomerulonephritis or amyloidosis, respectively. Azotaemia, hyperphosphatemia, and metabolic acidosis, consistent with renal failure, may be present in dogs with severe disease. Of dogs with glomerulonephritis or amyloidosis, 53% and 26%, respectively, were not azotaemic. Nonregenerative anaemia that develops secondary to renal failure or a systemic disease is observed in many affected animals. Other hematologic abnormalities also may reflect concurrent and possibly underlying systemic diseases. Thrombocytosis and hyperfibrinogenemia are common findings in dogs with glomerular disease.

The nephrotic syndrome of hypoalbuminemia, proteinuria, hypercholesterolemia, and oedema, although pathognomonic for glomerular disease, was present in only 15% of dogs with glomerulonephritis in one study. Incomplete nephrotic syndrome (i.e., without oedema or ascites) was more common, occurring in 49% of dogs. Nephrotic syndrome is expected to occur more commonly in dogs with amyloidosis, membranous nephropathy, hereditary nephritis, and minimal change disease because of the heavy proteinuria associated with these diseases. The *nephritic syndrome* is a term that has primarily been used in people to describe a set of signs that develop secondary to renal inflammation, generally acute, that extends into the glomeruli. In people this syndrome is characterized by haematuria and RBC casts with one or more of the following: subnephrotic proteinuria, edema, hypertension, azotemia, oliguria. Although the nephritic syndrome has not been fully characterized in dogs, perhaps because of the probable low prevalence of acute glomerulonephritides in dogs, it is possible that dogs with acute lyme nephritis may have a “nephritic-like” syndrome.

On abdominal radiographs the kidneys may appear normal or small and irregular. Some animals may actually have enlarged kidneys. Similar changes in shape and size can be seen with ultrasonographic scans, on which increased echogenicity of the cortex and loss of corticomedullary distinction may also be noted. The renal pelvis may be mildly dilated if polyuria is present or fluids are being administered.

Dogs and cats with proteinuria should be thoroughly evaluated for underlying infectious, inflammatory, or neoplastic diseases. This evaluation should include a thorough physical examination, and diseases of the oral cavity or skin should not be overlooked as potential underlying diseases. Aspiration cytology should be performed on all cutaneous and subcutaneous masses. Serologic testing for regional infectious diseases, as well as antinuclear antibody testing, should be performed. During radiographic or ultrasonographic evaluation of the abdomen, attention should be given to other organs to detect any other disease process. Thoracic radiographs should also be evaluated, and in middle-aged to older dogs, particular emphasis should be given to the evaluation for any evidence of neoplastic disease.

Histologic Diagnoses

Renal biopsy provides a definitive diagnosis of glomerular disease, but may not be needed if treatment of a potential underlying disease leads to resolution of the proteinuria or end-stage renal disease is already present. When evaluated appropriately, renal biopsy specimens can provide important clinical information about the type and severity of lesions in dogs and cats with glomerular disease. In fact obtaining an accurate histologic diagnosis may be one of the more important factors in successful management of the dog or cat with glomerular disease. Clinical decisions regarding the diagnosis, treatment, and prognosis can be made from the information obtained through renal biopsy.

Standard Therapy of Glomerular Disease

In addition to specific management that might be implemented with the various glomerular diseases, some therapeutic interventions are standard considerations for all dogs with glomerular disease. This therapy can be divided into three major categories: (1) treatment of potential underlying diseases processes, (2) reduction of proteinuria, and (3) management of uraemia and other complications of generalized kidney disease.

ICGN or amyloidosis develop after a strong, potentially malorganized, immune or inflammatory reaction, respectively, that has developed in response to a stimulus—often infectious, inflammatory or neoplastic. Accordingly, an underlying disease might have initiated the glomerular disease in up to 63% of affected dogs; a thorough evaluation for underlying diseases is warranted. Sometimes, the inciting agent is not obvious at first presentation because the offending disease is no longer present or is occult. Continued observation and scrutiny are necessary, because the causative disease process may become obvious in the ensuing months after presentation. The initial step in the management of a persistently proteinuric dog or cat is to treat and eliminate, if possible, any potential predisposing diseases. Animals that are seropositive for infectious diseases should be given specific anti-infective treatment immediately, even when there is not direct evidence that the infection is causing the proteinuria, and consideration should be given for immunosuppressive treatment using the same guidelines presented in the following discussion. The dog should be subsequently evaluated for resolution of the proteinuria, which may occur slowly over a period of months. If proteinuria does not resolve or worsens, a renal biopsy to determine the histologic diagnosis may be warranted.

Antiproteinuric agents should be considered when the UPC is persistently above 0.5 in a dog; ACE inhibitors (e.g., enalapril, benazepril) are the drugs of choice for most affected dogs. Enalapril significantly reduced proteinuria and delayed either the onset or the progression of azotaemia in dogs with GN. Treatment of dogs with glomerular diseases with ACE inhibitors is now considered a standard of care. ACE inhibitors may reduce proteinuria and preserve renal function by several possible mechanisms. The decreased efferent glomerular arteriolar resistance brought about by ACE inhibitors leads to decreased glomerular transcapillary hydraulic pressure and decreased proteinuria. Other proposed mechanisms include reduced loss of glomerular heparan sulfate, decreased size of the glomerular capillary endothelial pores, improved lipoprotein metabolism, slowed glomerular mesangial growth and proliferation, and inhibition of bradykinin degradation. Typically enalapril or benazepril (0.5 mg/kg given orally) is administered once a day, although approximately half of the dogs may eventually need twice daily administration.

The initial dosage can be gradually increased to achieve the therapeutic target of UPC <0.5 (ideal target) or >50% reduction from baseline (alternate target). Serum creatinine concentration should be monitored; it is uncommon for dogs to have dose-limiting worsening of azotaemia (i.e., >30% increase in serum creatinine or progression to IRIS CKD stage 4 CKD) because of ACE inhibitor administration alone. Hyperkalaemia is a common side effect in dogs with glomerular disease that are treated with an ACE inhibitor and can be controlled by feeding a potassium-reduced home-prepared diet that has been formulated by a veterinary nutritionist. If severe hyperkalaemia develops or proteinuria is not adequately controlled with an ACE inhibitor, an angiotensin receptor blocker (ARB; telmisartan, losartan) can be substituted or added. Combination therapy with an ACE inhibitor and an ARB may lead to a greater reduction in proteinuria than monotherapy with either an ACE inhibitor or an ARB but should be used with caution and careful patient monitoring until results of controlled studies become available.

Renal biopsy should not be performed in dogs (1) with IRIS CKD Stage 4; (2) when other medical contraindications are present and cannot be mitigated (including coagulopathy, renal cystic disease, moderate-to-severe hydronephrosis, pyelonephritis, perirenal abscess, uncontrolled hypertension, severe anemia, and pregnancy); or when results of renal biopsy are deemed unlikely to alter treatment, outcome, or prognosis.

If results of renal biopsy are deemed unlikely to alter treatment, outcome, or prognosis, then renal biopsy should not be recommended. If the kidneys are small, the damage present is likely irreversible, and it would be unlikely that the renal biopsy will contribute to patient care more so than less invasively obtained biochemical parameters, renal biopsy should not be recommended. When chronic azotemia is present, renal changes may be irreversible and histopathology less likely to alter treatment. However, if the duration of azotemia cannot be established, renal histopathology may establish chronicity and predict potential reversibility. An exception to these guidelines may include suspected chronic glomerular disease in which the disease process may still be active and modifiable, despite azotemia being mild to moderate. Lastly, if a rational presumptive diagnosis of acute kidney injury can be made noninvasively (eg, exposure to ethylene glycol without observed ingestion, recent hypotensive episode), then renal biopsy is unlikely to substantially change the therapeutic approach. Other factors that may preclude performing a renal biopsy include financial constraints of the owner, ethical concerns of the owner, or lack of available experienced personal to perform renal biopsy.

Immunosuppressive/anti-inflammatory therapy should not be administered to dogs with proteinuria before renal biopsy when (1) proteinuria is not definitively glomerular in origin; (2) immunosuppressive therapy is otherwise contraindicated; (3) the dog breed and age of disease onset suggest that a nonimmune-mediated familial nephropathy is likely; or (4) amyloidosis is the most likely histopathologic diagnosis.

Immunosuppressive therapy should not be administered to dogs with concurrent illnesses for which immunosuppression is contraindicated. Common diseases where these drugs should be avoided include diabetes mellitus, hyperadrenocorticism, and fungal or bacterial infectious diseases. In addition, specific immunosuppressive drugs may be contraindicated with particular conditions (eg, glucocorticoids in dogs with pancreatitis or uncontrolled hypertension, azathioprine in dogs with bone marrow suppression, hepatic dysfunction, or pancreatitis). Dogs from geographic regions, where infectious diseases associated with

glomerular damage and proteinuria are more prevalent, should be appropriately evaluated for possible occult infection before initiating immunosuppressive therapy.

In the absence of a renal biopsy to help predict the likelihood of response, immunosuppressive therapy should be considered a therapeutic trial. If there is no response to treatment after 8–12 weeks, it is recommended that immunosuppressive/anti-inflammatory therapy be discontinued and the previous decision to not perform a renal biopsy be revisited.

Immunosuppressive drugs should be administered to dogs in the absence of a renal pathologic diagnosis only after thorough client communication regarding the arguments for and against the use of these drugs in this setting. These agents should be administered cautiously, with close and careful patient monitoring.