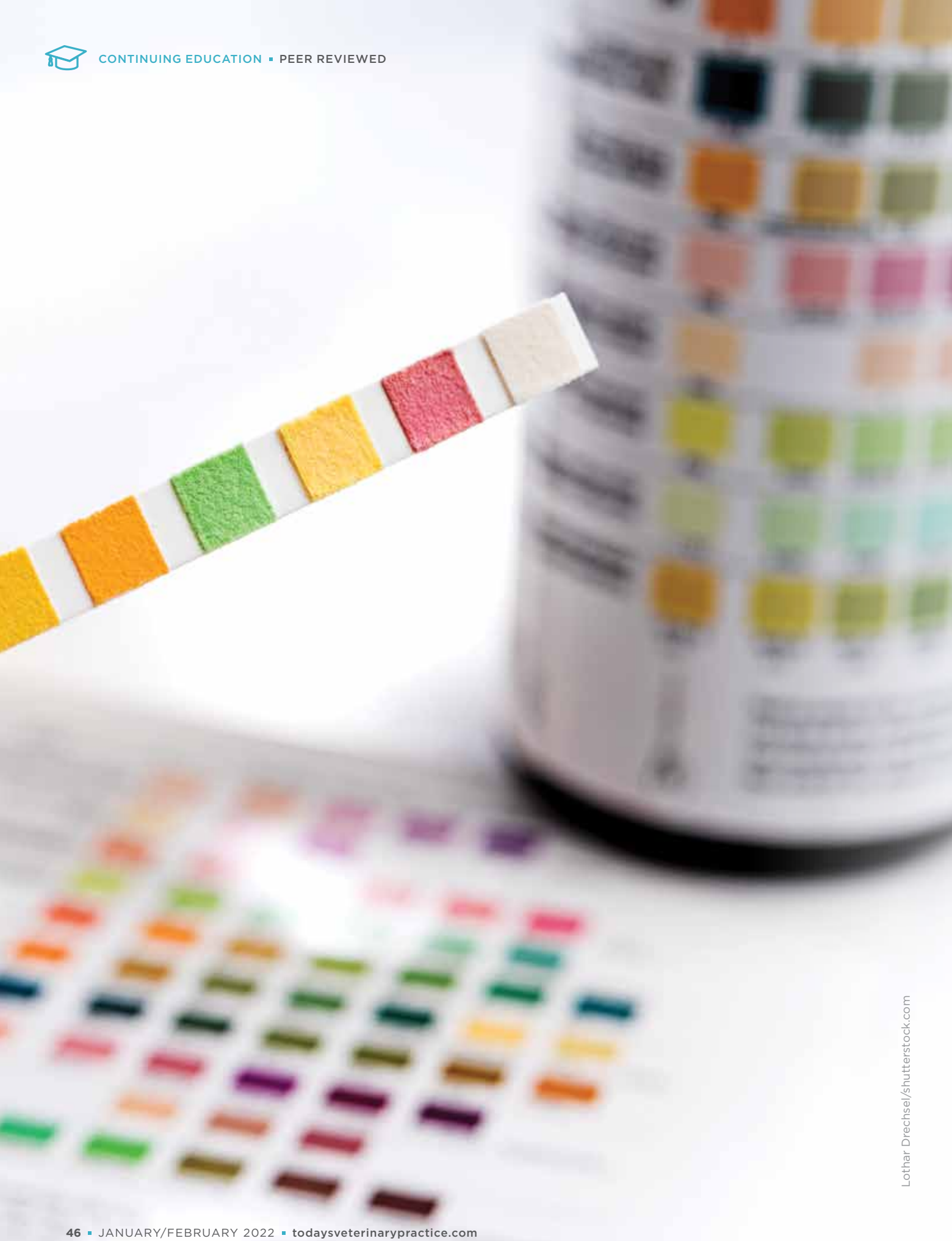

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CONTINUING EDUCATION

UROLOGY/RENAL MEDICINE

When Urine Trouble: A Clinical Approach to Proteinuria

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The clinical significance of proteinuria is evident in dogs with a severe protein-losing nephropathy (PLN). Consider Pickles, a 7-year-old male castrated cockapoo that presented for abdominal distention, difficulty breathing, and anorexia (**FIGURE 1**). Pickles was found to have bicavitary effusion and diagnosed with a severe PLN (urine protein:creatinine ratio [UPCR] 28.5, albumin 0.7 g/dL). Dogs with PLN, such as Pickles, have been shown to have a poor prognosis, with most succumbing to chronic kidney disease (CKD) or thromboembolic complications.[1]

Even when concurrent hypoalbuminemia is not present, proteinuria affects the wellbeing of dogs and cats. Proteinuria in dogs is associated with an increased risk of uremic crisis, progressive worsening of azotemia, and death.[2,3] Similarly, proteinuria in cats with CKD has been shown to be a negative predictor of survival, with one study showing that a UPCR of greater than 0.4 is associated with a 4-fold increased risk of death or euthanasia compared with a UPCR of less than 0.2.[4] Furthermore, proteinuria may be associated with the development of azotemia in cats. One longitudinal study found that nonazotemic cats with a UPCR of greater than 0.2 were 3.5 times more likely to be azotemic 12 months later.[5]

In addition to promoting progression of kidney disease, persistent proteinuria has several extrarenal consequences, including sodium retention, edema, effusion, hypercholesterolemia, hypertension, hypercoagulability, muscle wasting, and weight loss.[1,6,7] Therefore,

FIGURE 1. Severe abdominal distention and muscle wasting in a dog with a severe protein-losing nephropathy.

SEARCH FOR SIGNIFICANCE
Dipstick urinalysis can semi-quantify proteinuria as negative, trace, and 1+ to 4+ reactions, as part of the initial diagnostic testing.

incidental proteinuria on routine diagnostic workups and geriatric screens should not be ignored.

THE NORMAL FILTRATION BARRIER

Understanding the mechanisms of proteinuria requires a basic understanding of the normal glomerular filtration barrier. Blood comprises circulating proteins that are involved in hemostasis, fluid balance, and transportation. It takes a great deal of energy for the body to make proteins, and loss of these proteins would be wasteful. The glomerular filtration barrier exists to prevent their loss.

The glomerulus is a tuft of capillaries that acts as an elegant sieve, allowing waste products to be filtered into the urine while preventing the loss of proteins and blood cells. The glomerulus forms a selective barrier that is best designed to keep albumin, the most abundant circulating protein, from leaking into the urine. As albumin is a 69 kDa negatively charged protein, it makes sense that the glomerular filtration barrier best excludes proteins larger than 65 kDa carrying a negative charge.

Blood also contains proteins smaller than 65 kDa, such as retinol-binding protein, a transport protein for vitamin A. These low–molecular weight proteins are freely filtered at the glomerulus but are reabsorbed by proximal tubular cells of the nephron, thereby preventing their loss. However, when there are increased amounts of low–molecular weight proteins in the blood, the proximal tubular cells can become overwhelmed, resulting in proteinuria.

BOX 1 Classification and Causes of Proteinuria

Prerenal
- Multiple myeloma (Bence Jones proteinuria)
- Rhabdomyolysis (myoglobinuria)
- Intravascular hemolysis (hemoglobinuria)
- Drug reactions
- Acute pancreatitis

Renal
- Functional
  - Stress, strenuous exercise, fever, heatstroke, congestive heart failure
- Pathologic
  - Tubular
    - Fanconi syndrome (basenjis, chlorambucil in cats)
    - Copper storage hepatopathy (Labrador retrievers)
    - Nephrotoxins (i.e., aminoglycosides)
    - Acute kidney injury
    - Chronic kidney disease
    - Leptospirosis
  - Glomerular
    - See **BOX 2**
  - Interstitial
    - Interstitial nephritis (i.e., pyelonephritis)

Postrenal
- Urinary tract infection
- Urolithiasis
- Feline lower urinary tract disease
- Transitional cell carcinoma
- Vaginitis/prostatitis

CLASSIFYING PROTEINURIA

Proteinuria can be broadly classified as prerenal, renal, or postrenal. **BOX 1** lists conditions that are associated with each type.

Prerenal Proteinuria

Prerenal proteinuria occurs when normal proteins that are not normally present in plasma (i.e., hemoglobin or myoglobin) or abnormal proteins in the blood traverse normal glomerular capillary walls. For example, multiple myeloma results in the abnormal presence of immunoglobulin light chains in the plasma, leading to Bence Jones proteinuria. Prerenal causes of proteinuria can be excluded by evaluation of total protein to rule out dysproteinemia (the excessive synthesis of immunoglobulins).[6] The discovery of pigmenturia should prompt an investigation for hemoglobinemia and myoglobinemia.

Renal Proteinuria

Renal proteinuria can be functional or pathological. Functional renal proteinuria is secondary to altered renal physiology caused by a transient phenomenon such as strenuous exercise, seizures, or fever.[6-8] Functional proteinuria is characterized by transient, mild proteinuria that resolves once the underlying condition resolves. Consequently, treatment is not indicated. Pathologic proteinuria, however, is secondary to pathologic changes to the kidney. As a result, the proteinuria is persistent and necessitates intervention. Pathologic renal proteinuria is further classified into glomerular, tubular, and interstitial proteinuria, depending on the location of protein loss into the urine.[6-8]

Glomerular proteinuria, caused by alterations in glomerular selectivity, can result in high–molecular weight proteinuria. Patients with glomerular proteinuria often have a UPCR greater than 2. Immune-mediated glomerulonephritis, glomerulosclerosis, amyloidosis, podocytopathies, and hypertension-induced glomerulopathy can all cause this type of proteinuria, which can be associated with numerous diseases and conditions (**BOX 2**).

Tubular proteinuria is caused by impaired tubular recovery of low–molecular weight plasma proteins that normally traverse glomerular capillaries. These patients often have a UPCR less than 2. Causes include Fanconi syndrome and nephrotoxins.

Interstitial proteinuria is caused by inflammatory lesions that result in leakage of proteins into the urine from peritubular capillaries (e.g., pyelonephritis). The degree of proteinuria varies and can be marked.

Postrenal Proteinuria

Postrenal proteinuria results from entry of protein into the urine after urine enters the renal pelvis. Sources may be urinary (i.e., stones in the urinary collecting system, urinary tract infections, transitional cell carcinoma) or extraurinary (i.e., hemorrhagic or exudative processes affecting the genital tract). Postrenal causes can be excluded by collecting urine via cystocentesis, documenting a negative urine culture, and conducting imaging to rule out the presence of uroliths and neoplasia.[6]

DETECTING PROTEINURIA

Urine Dipstick

On routine urinalysis, proteinuria is initially identified using a urine dipstick, which semi-quantifies proteinuria as negative, trace, and 1+ to 4+ reactions. Traditional dipsticks generally detect urine albumin present at a concentration of greater than 30 mg/dL.

BOX 2 Causes of Glomerular Proteinuria

Vascular
- Hypertension

Infectious
- Heartworm disease
- Ehrlichiosis
- Lyme disease
- Leptospirosis
- Leishmaniasis
- Trypanosomiasis
- Hepatozoonosis
- Babesiosis
- Anaplasmosis
- Feline immunodeficiency virus
- Feline infectious peritonitis
- Coccidiodomycosis
- Chronic pyoderma
- Bacterial endocarditis
- Schistosomiasis
- Bartonellosis

Immune-mediated
- Systemic lupus erythematosus
- Immune-mediated polyarthritis

Inflammatory
- Pancreatitis
- Cholangiohepatitis
- Pyoderma

Neoplastic
- Lymphoma
- Leukemia
- Mast cell tumors
- Primary erythrocytosis
- Others

Endocrine/metabolic
- Hyperadrenocorticism
- Hyperthyroidism
- Hyperlipidemia

Drugs
- Glucocorticoids
- Trimethoprim-sulfamethoxazole drugs
- Tyrosine kinase inhibitors (masitinib, toceranib)

Breed-related
- **Renal dysplasia:** Alaskan malamute, beagle, Chow Chow, golden retriever, Lhasa apso, miniature schnauzer, Shih Tzu, standard poodle
- **Amyloidosis:** Chinese Shar-Pei, beagle, English foxhound, English bulldog, Abyssinian and Siamese cats
- **Membranous nephropathy:** Doberman pinscher
- **Membranoproliferative glomerulonephritis:** Bernese mountain dog
- **Immune-complex glomerulonephritis:** Brittany spaniel, basenji
- **Type II collagen defect:** Newfoundland
- **Type IV collagen defect:** Bull terrier, English cocker spaniel, English springer spaniel, Samoyed

This test is based on the principle that negatively charged proteins such as albumin, for which the test is most sensitive, will cause a pH indicator dye to shift color from yellow to green to blue. Consequently, alkaline urine (pH >7.5) may result in a color change even in the absence of proteinuria (false positive).[9] False-negative results may occur with Bence Jones proteinuria and dilute or acidic urine.

The first step is to determine if the degree of proteinuria is significant in light of the urine specific gravity (USG). For example, 1+ proteinuria in a dog with a USG of 1.04 is unlikely to be significant, whereas a 1+ proteinuria with a USG of 1.008 is likely to be significant and warrants further investigation with a UPCR.

Sulfosalicylic Acid Test

The sulfosalicylic acid (SSA) test is used by many laboratories to confirm proteinuria seen on a urine dipstick. In addition to albumin, the SSA test can detect Bence Jones proteins and globulins. False-positive results can occur if the urine contains radiographic contrast agents, penicillins, or cephalosporins.

Microalbuminuria Tests

Microalbuminuria tests can detect concentrations of albumin in the urine that are less than 1 mg/dL. Transient microalbuminuria can be observed in a variety of conditions. Therefore, investigation is only indicated in patients with persistent microalbuminuria, defined as microalbuminuria found repeatedly in 3 or more urine specimens obtained 2 or more weeks apart that cannot be attributed to a postrenal cause.[6]

Urine testing for microalbuminuria should be considered for animals with chronic illness that might be complicated by proteinuric nephropathies and screening of dogs and cats at risk for hereditary nephropathy, to detect onset as early as possible.

Urine Protein:Creatinine Ratio

Following detection of proteinuria on urinalysis, quantification using a UPCR may be indicated. The UPCR standardizes protein loss compared to creatinine. This adjusts the amount of protein loss for variations in USG and glomerular filtration rate. A UPCR from a spot urine sample accurately reflects the quantity of protein excreted in the urine over a 24-hour period. A result less than 0.2 is considered normal; a result of 0.2 to 0.5 in dogs and 0.2 to 0.4 in cats is consistent with borderline proteinuria.[6] Measuring a UPCR on a single urine sample, averaging UPCRs from 3 consecutive daily urine samples, and pooling 3 consecutive daily urine samples to measure a single UPCR all give similar results.[10,11] Therefore, there is no evidence that any individual method for monitoring the UPCR is superior.

To determine if this measurement is indicated, the clinician must (1) document that the proteinuria is persistent and (2) rule out prerenal and postrenal causes. Persistent proteinuria is proteinuria documented on a minimum of 3 urinalyses 2 or more weeks apart. However, if the patient is presenting for a workup of hypoalbuminemia, a UPCR is indicated even if it is the first documentation of proteinuria on a urinalysis. As inflammatory conditions such as pancreatitis can result in transient proteinuria, it is recommended that a UPCR be performed once they have resolved.

Proteinuria can result from urinary tract infections, urinary stones, and other causes of postrenal inflammation; therefore, a UPCR should not be performed in dogs with an active urine sediment or urolithiasis. A negative urine culture should be obtained prior to submitting a urine sample for a UPCR. Although hematuria can result in proteinuria, it should not significantly affect the UPCR unless gross hematuria is present. A UPCR is thought to be an accurate measure of proteinuria in cases with microscopic hematuria but grossly yellow to orange urine.

TABLE 1 International Renal Interest Society Proteinuria Substaging[a]

URINE PROTEIN:CREATININE RATIO VALUE		SUBSTAGE
DOGS	CATS	
<0.2	<0.2	Nonproteinuric
0.2 to 0.5	0.2 to 0.4	Borderline proteinuric
>0.5	>0.4	Proteinuric

[a]*International Renal Interest Society. IRIS staging of CKD. Updated 2019. Accessed November 2021. iris-kidney.com/pdf/IRIS_Staging_of_CKD_modified_2019.pdf*

PROTEINURIA AND CHRONIC KIDNEY DISEASE

As previously mentioned, proteinuria is a negative prognostic indicator in dogs and cats with CKD.[8] Consequently, every dog and cat diagnosed with CKD should be substaged with a UPCR when there is no evidence of urinary tract inflammation or hemorrhage and dysproteinemias have been ruled out by measurement of plasma proteins. The International Renal Interest Society (IRIS) substaging schematic is included in **TABLE 1**. It is recommended that patients that are persistently borderline proteinuric be reevaluated within 2 months.

WHEN TO INTERVENE: WHAT IS CONSIDERED TOO MUCH PROTEIN?

In a patient with normal kidney function, treatment is indicated when the UPCR is 2 or greater, as glomerular proteinuria is likely.[6] Diagnostic investigation for an underlying cause is recommended when the UPCR is 1 or greater or there is persistent and progressive microalbuminuria. A UPCR greater than 0.5 in a dog and 0.4 in a cat necessitates monitoring so the proper intervention can be taken should the UPCR progress.[6]

For animals with CKD, it is recommended that a UPCR greater than 0.5 in dogs or 0.4 in cats be investigated and treated. More information can be found on the IRIS website (iris-kidney.com).

DIAGNOSTIC APPROACH TO PROTEINURIA

In general, the diagnostic approach to proteinuria begins with collection of a comprehensive history, including signalment, environmental exposures, and a thorough travel history. Many dog breeds have predispositions for glomerular disease, which should be considered (**BOX 2**).

On physical examination, it is important to evaluate blood pressure along with a fundic examination. Next, a minimum database allows screening for concurrent evidence of diseases that may result in proteinuria. Azotemia is a reflection of the number of functional nephrons, whereas glomerular proteinuria results from a defect in the glomerular selectivity, independent of the number of functional nephrons. Therefore, patients with proteinuria may or may not be azotemic and azotemic animals may or may not have proteinuria.

Testing for infectious diseases associated with glomerular proteinuria (**BOX 2**) should be based on each patient's travel history and risk. For example, it is recommended that a dog living in a Lyme-endemic area be tested for antibodies against Lyme and other rickettsial diseases carried by the same tick vector (*Ixodes* species), such as *Anaplasma phagocytophilum.* Empiric treatment with doxycycline (5 mg/kg PO q12h) may be initiated while awaiting the results of vector-borne disease testing and, if well tolerated, continued for 4 weeks. In addition, tetracyclines such as doxycycline may have an anti-inflammatory effect on the glomerular basement membrane through the inhibition of matrix metallopeptidases, a family of extracellular proteinases that promote remodeling of the glomerulus.[12]

This diagnostic approach is typically sufficient for a dog or cat with incidental mild to moderate proteinuria. However, for a patient with a high level of proteinuria (UPCR >3.5), progressive proteinuria despite treatment, hypertension, hypoalbuminemia, and/or azotemia, additional diagnostics are indicated. Diagnostic imaging, including abdominal ultrasonography and thoracic radiography, should be performed. Patients with hypertension should be investigated for endocrine diseases (e.g., hyperadrenocorticism, pheochromocytoma, hyperaldosteronism), as idiopathic hypertension is relatively uncommon in dogs and cats.[13] Documentation of hypoalbuminemia warrants investigation for liver dysfunction and gastrointestinal losses with bile acids and testing for malabsorptive gastrointestinal diseases (e.g., serum cobalamin and folate, fecal flotation), respectively.

THERAPEUTIC APPROACH TO PROTEINURIA

The therapeutic approach to proteinuria can be broken down into 5 components: inhibition of the renin-angiotensin-aldosterone system, identification and treatment of systemic hypertension, nutritional considerations, anticoagulant therapy, and immunosuppression. An algorithm for the therapeutic approach to proteinuria in non-CKD patients is provided in **FIGURE 2**.

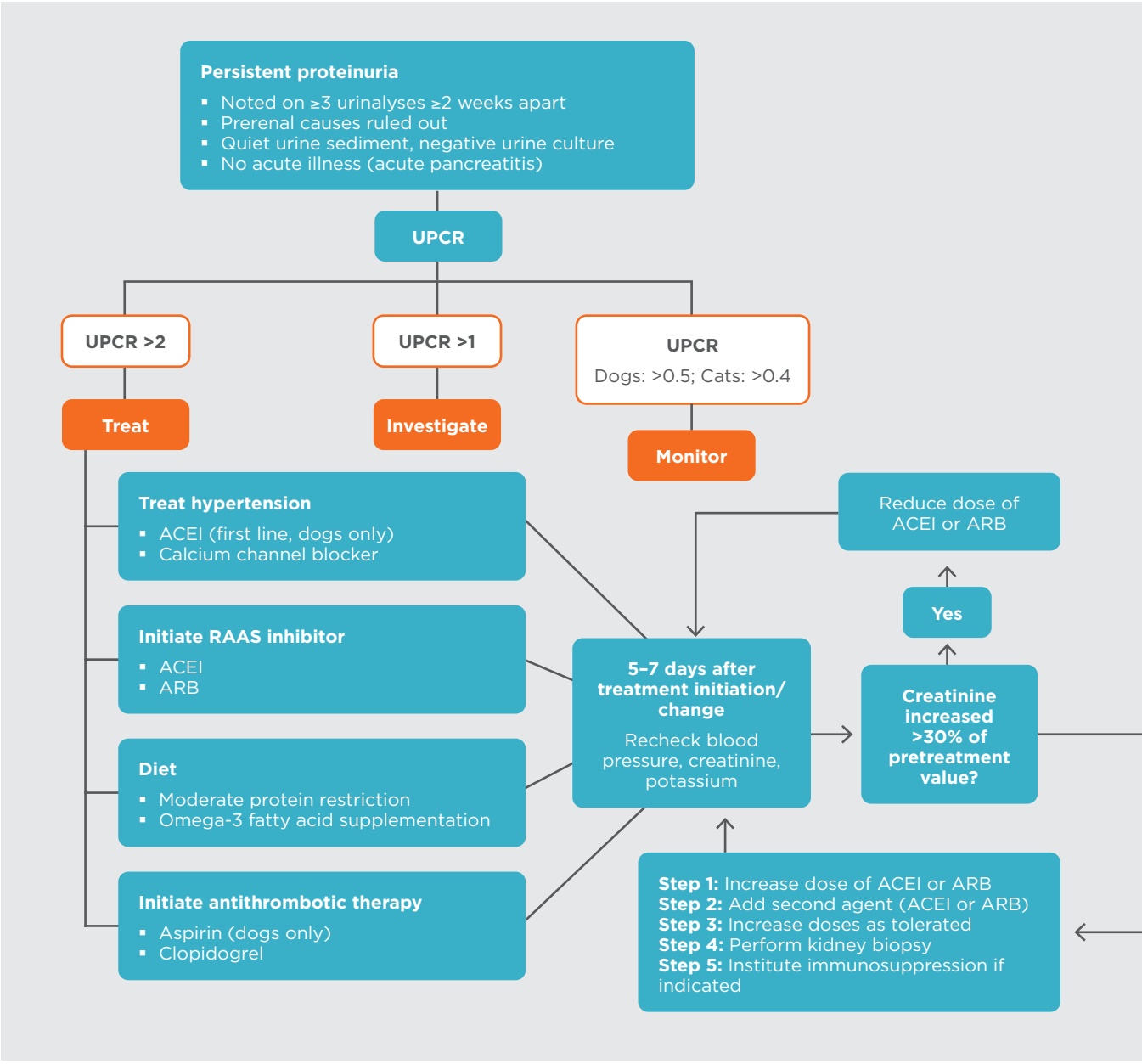
Inhibition of the Renin-Angiotensin-Aldosterone System

The mainstay of treatment for proteinuria is inhibition

of the renin-angiotensin-aldosterone system (RAAS). The goal is to lessen glomerular capillary pressure by altering the hemodynamic forces that promote transglomerular movement of proteins. In veterinary medicine, the main RAAS inhibitors used are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs; **BOX 3**).

ACEIs, such as enalapril and benazepril, are the RAAS inhibitors most commonly prescribed to treat systemic hypertension and proteinuria in dogs and cats. They function by decreasing serum concentrations of angiotensin II and aldosterone, thereby reducing glomerular transcapillary hydrostatic pressure and systemic blood pressure.[19,20] ACEIs have been shown to reduce proteinuria in dogs.[16]

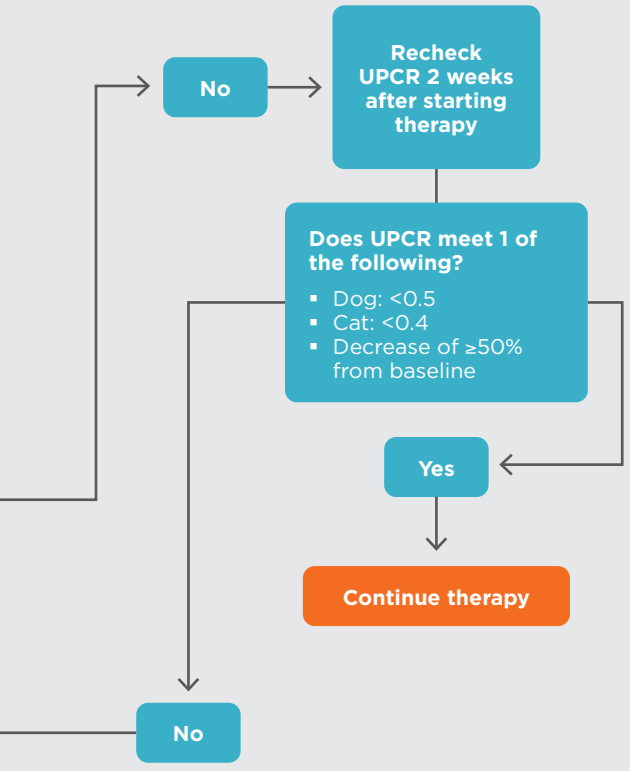
ARBs, such as telmisartan and losartan, have been used in veterinary medicine to treat systemic hypertension and, more recently, proteinuria. ARBs selectively inhibit angiotensin II subtype 1 receptors, which mediate the adverse effects of angiotensin II on the cardiovascular system and kidneys. When compared with enalapril, telmisartan has been shown to result in a greater proportion of dogs reaching a goal UPCR reduction of 50% or more of baseline after 30 days of



treatment.[21] A recent retrospective study in dogs on telmisartan alone or in conjunction with benazepril or mycophenolate confirmed that telmisartan is effective in reducing proteinuria compared with baseline and is well tolerated.[18] In cats with CKD, telmisartan has been shown to be at least as effective as benazepril in reducing proteinuria and significantly reduced UPCRs from baseline at all time points.[22]

While decreasing glomerular transcapillary hydrostatic pressure, ACEIs and ARBs also reduce glomerular filtration rate. Consequently, it is prudent to initiate therapy at a lower dosage in azotemic patients and recheck serum creatinine concentrations within 5 to 7 days. In addition, both medications reduce serum aldosterone, which may result in hyperkalemia.

FIGURE 2. Flowchart summarizing the therapeutic approach to persistent proteinuria in nonazotemic dogs and cats.
ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; RAAS=renin-angiotensin-aldosterone system; UPCR=urine protein:creatinine ratio.



Identification and Treatment of Systemic Hypertension

All patients with proteinuria warrant blood pressure evaluation, as hypertension can contribute to proteinuria and lead to target organ damage.[3,13] Given the relatively common prevalence of anxiety-induced, or "white coat," hypertension, and the knowledge that hypertension requires lifelong therapy, it is important to be absolutely certain about the diagnosis. In general, documentation of a systolic blood pressure greater than 160 mm Hg on 2 or more occasions provides a diagnosis of systemic hypertension and indicates the need for antihypertensive therapy (**BOX 3**). However, the presence of target organ damage such as retinopathy justifies initiation of treatment after a single measurement.[13]

Because of their antiproteinuric effect, RAAS inhibitors are often selected as first-line hypertensive agents in dogs. RAAS inhibitors typically reduce systolic blood pressure by only 10 to 15 mm Hg. Consequently, severely hypertensive dogs (systolic blood pressure >200 mm Hg) often require concurrent treatment with a calcium channel blocker (CCB) such as amlodipine.[13] Using CCBs alone in dogs should be avoided as they preferentially dilate the renal afferent arteriole, exposing the glomerulus to increases in glomerular capillary hydrostatic pressure, which will worsen proteinuria.[23]

In cats, ACEIs alone are unlikely to result in resolution of hypertension.[13] Consequently, the CCB amlodipine is considered the first line of treatment for hypertension in cats. A mean decrease of 28 to 55 mm Hg in systolic blood pressure is typically seen with amlodipine.[24,25] The ARB telmisartan has been shown to significantly decrease mean systolic blood pressure in cats with blood pressures up to 200 mm Hg.[26]

Nutritional Considerations

A protein-restricted diet (35 to 40 g/1000 kcal in dogs, 65 to 70 g/1000 kcal in cats) with moderate amounts of high-quality protein has been recommended for patients with proteinuria.[27] The generally accepted benefits of moderate protein restriction are to reduce the generation of uremic toxins, intraglomerular

pressure, and magnitude of proteinuria.[6,15] However, too-early introduction of a protein-restricted diet may lead to protein malnutrition and loss of lean body mass. The timing and degree of protein restriction for both dogs and cats remain a point of controversy.

In dogs with experimentally induced CKD, supplementation of omega-3 fatty acids has been shown to decrease proteinuria, lower glomerular pressure, and decrease the production of proinflammatory eicosanoids.[15,28] Patients can be supplemented with omega-3 fatty acids at roughly 300 mg of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) combined per 10 lb or dosed using previously published recommendations (140 × [weight in kg]$^{0.75}$ mg DHA and EPA combined).[29] The total daily dose should be divided with meals. It is recommended to start at 25% to 50% of the daily dose and slowly work up to lessen the occurrence of side effects such as diarrhea.

Anticoagulant Therapy

Thromboembolism is a well-recognized complication of proteinuria in dogs and people, with the prevalence of thromboembolism in dogs with proteinuric kidney disease being reported as high as 25%.[1] In addition, a recent study reported the concurrent presence of a PLN in 32 of 100 dogs with aortic thrombosis.[30]

The mechanism of thromboembolism formation in dogs with proteinuria has not been well established. Historically, it was thought that the loss of antithrombin III, which is similar in size to albumin, was the main contributor. However, it has been shown that 96% of proteinuric dogs, defined as dogs with a UPCR greater than 2, have 1 or more parameter on thromboelastography suggestive of hypercoagulability independent of antithrombin III activity.[31]

To date, there is no evidence regarding the efficacy of antithrombotic agents in venous thromboembolism prophylaxis. In cats, clopidogrel has been shown to be more effective than aspirin in reducing the likelihood of cardiogenic arterial thromboembolism.[32] Consequently, clopidogrel is the treatment of choice for cats with PLN (**BOX 4**). In dogs, treatment with aspirin or clopidogrel is currently recommended.[15] In a recent

BOX 3 Renin-Angiotensin-Aldosterone System (RAAS) Inhibition and Treatment of Hypertension

Angiotensin-converting enzyme inhibitors (both indications)

- **Enalapril**
  - **Initial dose:** 0.25–0.5 mg/kg PO q12–24h[14,15] (azotemic animals should start at 0.25 mg/kg q24h and then escalate to q12h; most dogs will need q12h dosing[15,16])
  - **Dose escalations:** 0.5 mg/kg/day
  - **Maximum dose:** 2 mg/kg/day
- **Benazepril**
  - **Initial dose:** 0.5 mg/kg PO q24h or divided to 0.25 mg/kg PO q12h[14,15,17]
  - **Dose escalation:** Increase to q12h dosing, then consider increasing dose by 0.5 mg/kg/day
  - **Maximum dose:** 2 mg/kg/day
  - **Note:** Benazepril is also eliminated via hepatic routes and therefore does not need to be dose reduced in azotemic patients.
- **Side effects:** Gastrointestinal upset (anorexia, vomiting, diarrhea), weakness, hypotension, hyperkalemia
- **Monitoring:** Creatinine (goal <30% increase),[15] potassium, and blood pressure 5–7 days after initiation of treatment and each dose change

Angiotensin receptor blockers (RAAS inhibition)

- **Telmisartan:** 0.5–1 mg/kg PO q24h up to 2 mg/kg/day[14,15,17,18]
- **Losartan:** 0.125–0.5 mg/kg PO q24h up to 1 mg/kg/day[14,15,17] (azotemic animals should start at 0.125 mg/kg q24h and not exceed 0.25 mg/kg/day)
- **Side effects:** Gastrointestinal upset (anorexia, vomiting, diarrhea), weakness, hypotension, hyperkalemia
- **Monitoring:** Creatinine (goal <30% increase),[15] potassium, and blood pressure 5–7 days after initiation of treatment and each dose change

Calcium channel blockers (hypertension)

- **Amlodipine**
  - **Dogs:** 0.1 mg/kg PO q24h titrated up to effect without exceeding 0.5 mg/kg PO q24h[14,17]
  - **Cats:** 0.625-1.25 mg/cat PO q24h titrated to effect[14,17]
- **Side effects:** Gingival hyperplasia, hypotension
- **Monitoring:** Blood pressure 5–10 days after initiation of treatment and each dose change

study of dogs with PLN receiving clopidogrel (1.8 to 3.2 mg/kg/day) or aspirin (1 to 1.2 mg/kg/day), no dogs receiving aspirin had documentation of platelet inhibition at any time point, whereas platelet function testing in most dogs receiving clopidogrel showed platelet inhibition.[34] However, it is important to note that the aspirin dose in this study may have been too low to see consistent platelet inhibition. A previous study reported that only one-third of healthy dogs receiving a low dose of aspirin (1 mg/kg/day) had consistent platelet inhibition, whereas those receiving a slightly higher dose of aspirin (2 mg/kg/day) had consistent platelet inhibition.[33] As a result, a dose of at least 2 mg/kg/day of aspirin is currently recommended.

In people with nephrotic syndrome, a severe form of PLN, low–molecular weight heparin and oral warfarin are the most often prescribed prophylactic anticoagulants.[35] These medications are not routinely used in veterinary medicine due to concerns surrounding administration, monitoring, and potential complications. In addition, heparin exerts its anticoagulant effects by potentiating antithrombin III, which is thought to be lost in the urine in dogs with glomerular disease. Factor Xa inhibitors such as rivaroxaban have not been studied in dogs with glomerular disease.

In conclusion, clopidogrel (or aspirin in dogs only) is the treatment of choice for thromboprophylaxis in dogs and cats with glomerular proteinuria.

Immunosuppression

Immunosuppression is indicated when a kidney biopsy confirms immune-complex glomerulonephritis (ICGN). However, many dogs with glomerular disease are not biopsied owing to patient stability, availability, owner preferences, and/or financial limitations. Extrapolating from a study of 501 kidney biopsies from dogs with suspected glomerular disease, it is estimated that approximately 50% of dogs with glomerular proteinuria have ICGN.[36] Considering the relatively high prevalence of ICGN, immunosuppression may be considered in patients that fail the standard therapies listed above.

In addition to failing standard medical therapy, all of the following criteria should be met before instituting immunosuppressive therapy:[37]

A. Proteinuria is confirmed to be glomerular in origin (UPCR >2).

B. Immunosuppression is not contraindicated (requires a full diagnostic workup to rule out infectious causes, including vector-borne diseases and pyelonephritis).

C. Signalment is not suggestive of a familial nephropathy or amyloidosis.

D. Serum creatinine is greater than 3 mg/kg or progressive, or serum albumin is less than 2 g/dL.

To date, there are limited data on immunosuppressive therapy in dogs with ICGN. The immunosuppressant of choice for rapidly progressive glomerular disease is mycophenolate (**BOX 5**). Alternative protocols include cyclosporine, cyclophosphamide, or chlorambucil with or without azathioprine on alternating days.[37]

Owing to the adverse effects glucocorticoids can have on the kidneys and glomerulus, they are generally avoided for long-term management of ICGM. In fulminant cases when immediate immunosuppression is required, such as glomerulonephritis associated with systemic lupus erythematosus, short-term administration of glucocorticoids may be justified.[37]

Immunosuppression is continued for a minimum of 8 to 12 weeks before concluding a failed trial.[37] Patients on immunosuppressive therapy should be closely monitored for progression of glomerular disease and side effects of immunosuppression. If life-threatening infections or clinically intolerable side effects are

BOX 4 Anticoagulant Therapy

Aspirin

- **Mechanism:** Cyclooxygenase-1 inhibitor, reduction of prostaglandin and thromboxane synthesis; irreversible inhibition of platelet function
- **Dose:**
  - Dogs: 2–5 mg/kg PO q24h[14,17,33]
  - Cats: Clopidogrel appears to be safer and more effective in cats[32]
- **Side effects:** Gastrointestinal upset (nausea, anorexia, vomiting, diarrhea), occult gastrointestinal blood loss

Clopidogrel

- **Mechanism:** Adenosine diphosphate receptor inhibitor; irreversible inhibition of platelet function
- **Dose:**
  - Dogs: 2–3 mg/kg PO q24h[14,17]
  - Cats: 18.75 mg/cat PO q24h[14,17]
- **Side effects:** Well tolerated; may cause gastrointestinal upset (vomiting, anorexia, diarrhea)

BOX 5 Immunosuppressive Therapy

Mycophenolate
- **Mechanism:** Antagonizes purine metabolism
- **Dose:** 10 mg/kg PO q12h[14,17,37] (renally excreted; azotemic animals should start at q24h)
- **Side effects:** Gastrointestinal upset (vomiting, diarrhea); can be severe
- **Therapeutic drug monitoring:** None indicated

Cyclosporine
- **Mechanism:** Calcineurin inhibitor
- **Dose:** 5 mg/kg PO q12h increased to effect[17,37]
- **Side effects:** Gastrointestinal upset (vomiting, diarrhea, anorexia), gingival hyperplasia
- **Therapeutic drug monitoring:** Peak (2 hours post-dosing) levels in patients dosed q12h*
  - **Pharmacodynamic (preferred):** T-cell interleukin-2 synthesis monitoring
  - **Pharmacokinetic:** Blood levels

**Patients dosed q24h require a trough level taken just prior to their next dose in addition to a peak level.*

encountered, immunosuppression should be discontinued. When a response is noted, it is recommended that immunosuppressive therapy be continued a minimum of 12 to 16 weeks, although, anecdotally, longer courses of immunosuppression are often necessary.[37] The decision to taper is based on resolution of proteinuria and involves close monitoring of the UPCR.

MONITORING PROTEINURIA AND ADJUSTING MEDICATIONS

After initiation of treatment, the UPCR should be reevaluated in 2 to 4 weeks. The goal is to reach a UPCR less than 0.5 in dogs and 0.4 in cats or a greater than 50% reduction in UPCR compared with baseline.[15] If neither of these parameters is met, the dose should be increased (when possible) and the UPCR rechecked 2 to 4 weeks later.

If no response is noted to an ACEI or an ARB, addition of the other medication (i.e., ACEI or ARB) may be indicated. The author's experience is that concurrent administration of an ACEI and an ARB may result in hyperkalemia and/or progressive azotemia. Therefore, it is recommended that the dose of ACEI or ARB be reduced to the low end of dosing prior to adding a second agent, then increased slowly as needed if no adverse effects are seen.

Once patients with glomerular disease have been stabilized, UPCR; urinalysis; systemic arterial blood pressure; and serum albumin, creatinine, and potassium concentrations should be monitored at least quarterly.

PROGNOSIS

The prognosis for dogs and cats with proteinuria is variable and likely depends on the underlying disease present. One study evaluating protein-losing glomerular disease in dogs reported a median survival of 28 days, with most cases succumbing to chronic renal disease (69.5%) or thromboembolic complications (22.2%).[38] However, this study included cases with amyloidosis that were more likely to be azotemic at presentation. Despite the poor prognosis, there were individual dogs that survived more than 3 years.[38]

It is likely that prognosis varies with each specific type of glomerular disease. However, most studies to date fail to provide a definitive histologic diagnosis or are biased toward death by inclusion of dogs with kidney tissue collected postmortem. As more kidney biopsies are performed, additional prognostic information will likely become available. For example, a recent study by the International Veterinary Renal Pathology Service found that dogs with focal segmental glomerulosclerosis, the most common non–immune complex glomerular disease in dogs, had a median survival time of 258 days after biopsy.[39] More studies are needed to characterize the prognosis for various types of glomerular disease in dogs and cats. It is likely that earlier detection and treatment of proteinuria will lead to better outcomes. TVP

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CONTINUING EDUCATION

When Urine Trouble: A Clinical Approach to Proteinuria

TOPIC OVERVIEW

Historically, protein in the urine (proteinuria) was only of concern when it was severe enough to result in hypoalbuminemia, effusions, or edema. With increasing evidence of proteinuria being a negative prognostic indicator for dogs and cats with chronic kidney disease, it is important for clinicians to take note of persistent proteinuria, regardless of severity. The focus of this article is on pathologic renal proteinuria as it contributes to kidney damage, as well as its investigation and treatment.

LEARNING OBJECTIVES

After reading this article, readers will be able to recognize when proteinuria is significant and develop a practical management plan for proteinuria in dogs and cats. They will gain an understanding of the different mechanisms of proteinuria and be able to name clinical examples of each. In addition, readers will learn the degrees of proteinuria at which monitoring, diagnostic intervention, and/or treatment are indicated.

This article has been submitted for **RACE approval for 1 hour of continuing education credit** and will be opened for enrollment when approval has been received. To receive credit, take the test for free by visiting **vetfolio.com** and entering the title of the article in the search bar. Free registration is required. Questions and answers online may differ from those below. Tests are valid for 2 years from the date of approval.

1. **Proteinuria does not lead to**
   a. Pulmonary thromboembolism
   b. Worsening azotemia
   c. Hypocholesterolemia
   d. Muscle wasting

2. **An 11-year-old male castrated Scottish terrier presents for straining to urinate. Urine culture results are negative, but urinalysis reveals 2+ proteinuria and a urine specific gravity (USG) of 1.018. Complete blood count and serum biochemistry results are normal. Abdominal ultrasonography reveals a large mass in the trigone of the bladder. Transitional cell carcinoma is suspected. What type of proteinuria is this, and is a urine protein:creatinine ratio (UPCR) called for?**
   a. Renal, yes
   b. Renal, no
   c. Postrenal, yes
   d. Postrenal, no

3. **What type of proteinuria is most likely to have a UPCR greater than 2 and result in hypoalbuminemia?**
   a. Prerenal
   b. Glomerular
   c. Tubular
   d. Postrenal

4. **A 6-year-old female spayed Doberman presents for a routine wellness examination. A minimum database finds 3+ proteinuria (USG 1.02) and quiet urine sediment. Complete blood count and serum biochemistry results are normal. Records show 2+ proteinuria documented on 2 routine examinations within the previous year. The owner reports that the dog is doing well. What do you recommend?**
   a. Recheck urinalysis in 2 weeks and perform a UPCR if proteinuria persists.
   b. Perform abdominal ultrasonography.
   c. Monitor; no evidence of hypoalbuminemia.
   d. Perform a UPCR, blood pressure measurement, and fundic examination.

5. **When starting an angiotensin-converting enzyme inhibitor (ACEI) in an azotemic patient, which of the following should be considered?**
   a. Start lower because ACEIs reduce glomerular filtration rate.
   b. Start higher because ACEIs are renally excreted.
   c. Start higher because the patient has more advanced disease.
   d. Start at the normal dose because ACEIs are excreted by the hepatobiliary system.

6. **What intervention should be taken in a cat with chronic kidney disease and a UPCR of 0.5?**
   a. Monitor
   b. Investigate
   c. Treat
   d. B and C

7. **Which electrolyte should be closely monitored in dogs and cats treated with ACEIs and/or angiotensin receptor blockers?**
   a. Sodium
   b. Calcium
   c. Potassium
   d. Chloride

8. **What antihypertensive therapy should be started in a dog with persistent and severe hypertension (215 mm Hg) and proteinuria?**
   a. Enalapril
   b. Telmisartan
   c. Amlodipine
   d. Enalapril and amlodipine

9. **Before checking UPCR on a boxer with persistent proteinuria, a urine sample collected via cystocentesis has 2+ blood on a urine dipstick test. Red blood cells are confirmed on urine sediment. There are no signs of infection and the dog had a negative urine culture 2 weeks ago. The urine in the syringe was yellow at that visit. What is the next step?**
   a. Submit the urine as planned; microscopic hematuria does not affect UPCR.
   b. Obtain a free catch sample in the clinic and check it for microscopic hematuria. If it is negative, submit the sample.
   c. Recommend the dog go home and the owner bring a free catch urine sample in 3 to 5 days.
   d. Recommend that since the dog is acting well, there is no need to do the UPCR.

10. **A proteinuric dog (UPCR 6) started on enalapril at the low end of the dosing range 2 weeks ago comes in for a UPCR recheck. The UPCR comes back at 4. What is the next step?**
   a. Continue the plan and recheck in 2 to 4 more weeks to monitor progress.
   b. Increase the dose of enalapril because the goal is a greater than 50% reduction in UPCR.
   c. Add telmisartan because the enalapril is insufficient and it is unlikely a dose increase will help.
   d. Continue the current dose because the goal is a greater than 25% reduction in UPCR.

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