Proteinuria is a frequent finding via urinalysis in animals with urinary tract disease. Detection of small amounts of protein in urine may indicate early glomerular disease or the presence of other pathologic processes. Glomerular disease is a common cause of renal insufficiency and failure. Protein-losing nephropathies (PLNs) may be a clinical manifestation of systemic diseases. Earlier detection may lead to identification and treatment of an underlying disease process, thereby delaying, but rarely halting, development of proteinuria when the glomerulus has been damaged.

**PHYSIOLOGY**

The functional unit of a nephron includes the glomerulus, a tuft of capillaries contained within Bowman’s capsule, and the tubules. The tubules are divided into the proximal convoluted tubule segment, the loop of Henle, the distal convoluted tubule segment, and the collecting duct. The glomerulus functions to maintain normal osmotic pressure by inhibiting the loss of serum proteins, especially albumin, into the urine while allowing water, electrolytes, and waste products to enter the tubules for either reabsorption from the tubules or excretion into urine. This selective permeability is accomplished by a barrier comprised of fenestrated endothelium, glomerular basement membrane, and epithelial podocytes. The fenestrations within the endothelium have a diameter of approximately 34 nm and normally function to restrict the loss of protein with a diameter equal to or greater than the fenestration size. Albumin has an effective diameter of 36 nm and a molecular weight of 69 kD. In addition to a mechanical barrier, the basement membrane is thought to be negatively charged, which would further increase its ability to repel negatively charged proteins such as albumin. Smaller proteins and solutes with negative or positive charges are freely filtered through the glomerulus, but many are generally reabsorbed in the tubules or catabolized and therefore may not be detected in urine. Changes in glomerular hemodynamic properties can also damage the glomerular barrier, resulting in increased protein losses in the urine filtrate. Once protein enters the tubules, they have a limited ability for reabsorption.

**PATHOPHYSIOLOGY**

Proteinuria is caused by one of three basic processes:

- Preglomerular (i.e., fever, hypothermia, strenuous exercise, venous congestion)

**ABSTRACT:**

As the quality of veterinary medicine continues to evolve, the longevity of companion animals is increasing. With the development of more diagnostic testing modalities such as microalbuminuria, proper interpretation and early intervention have become vital in delaying the progression of renal insufficiency and failure. In addition, detecting proteinuria may indicate the presence of a systemic disease, cuing veterinarians to conduct more diagnostic tests, which may help identify an underlying disease process.
Protein-Losing Nephropathy

- **Glomerular**
- **Postglomerular** (i.e., hemorrhage or inflammation of the urogenital tract, lack of tubular reabsorption)

The causes of preglomerular proteinuria usually result in mild, transient proteinuria, and most of these causes can usually be ruled out with a thorough history and physical examination. Other proteins, such as hemoglobin and myoglobin, are freely filtered through the glomerulus and may be present in urine. These proteins cause urine to remain red after centrifugation. Postglomerular causes are most commonly the result of cystitis, metritis, prostatitis, or neoplasia and usually involve concurrent inflammatory sediment or hematuria. The other possibility for postglomerular proteinuria is a lack of tubular reabsorption. A small amount of protein may be present in the ultrafiltrate, but normal tubules degrade and reabsorb this protein. The loss of electrolytes and glucose with normal glucosemia may indicate a renal tubular disorder that may accompany proteinuria (Fanconi-like syndrome).

For proteinuria to be glomerular, there has to be damage to the glomeruli, most commonly from glomerulonephritis or amyloidosis. The mesangial cells are important components of the glomerulus. These cells are located between two neighboring capillaries and have a contractile role, influencing the glomerular filtration rate (GFR). The mesangial cells also play an important role in perpetuating the immune response to glomerulonephritis. Some vasoactive substances and cytokines (e.g., endothelins, angiotensin II, vasopressin, norepinephrine, platelet-activating factor, thromboxane A₂, histamine) can cause contraction of the mesangial cells, thereby decreasing GFR. Others, such as atrial natriuretic peptide, dopamine, and cAMP, cause relaxation of the mesangial cells. The mesangial cells can also activate T lymphocytes, which can further perpetuate the disease process by recruiting other immune cells. Prostaglandins (PGs) and thromboxanes play a role in the local pathogenesis of glomerulonephritis and are foci for potential treatments. Some PGs (i.e., PGE and prostacyclin) are beneficial in that they inhibit platelet function; cause relaxation of the mesangial cells, resulting in vasodilation; and have an antiinflammatory effect in the kidneys. Conversely, thromboxanes tend to induce platelet activation, are chemotactic for neutrophils, and cause mesangial cell contraction and vasoconstriction as well as interfere with mesangial phagocytosis of immune complexes, possibly leading to a decreased GFR.

The causes of glomerulonephritis can be separated into two categories:

- **Primary (idiopathic) glomerulonephritis**—No concurrent disease is identified.
- **Secondary glomerulonephritis**—Damage to the glomerulus is the result of an identified systemic disease. The causes of secondary glomerulonephritis in dogs and cats include many infectious diseases, inflammatory conditions, neoplasia, heredity, certain drugs, and endocrinopathies (Table 1).

In immune-mediated diseases (secondary to infectious agents, organ/tissue damage), the antigen–antibody complexes within the glomeruli lead to activation of complement with infiltration of neutrophils, T lymphocytes, and macrophages. Further destruction occurs secondary to platelet aggregation, activation of the coagulation cascade, and fibrin formation. The glomerulus responds to this insult by releasing additional cytokines and growth factors, leading to mesangial cell proliferation, mesangial matrix production, inflammatory cell adhesion, increased vascular permeability, intra-glomerular coagulation, and fibrin deposition.

Damage to the glomerulus occurs when immune complexes or amyloid, respectively, is deposited in the capillary walls of the glomerulus. The antigen–antibody complexes may be circulating in the blood and subsequently deposited in the glomerulus, or the antigen becomes embedded within the glomerular capillary wall and the antibody binds to the antigen in situ. Once this glomerular damage occurs, the selective permeability is lost and protein enters the ultrafiltrate in the renal tubules. The proteins themselves increase lysosomal processing to the protein, which is toxic to the tubular epithelial cells. As a result, the lysosomes swell and...
rupture, resulting in tubulointerstitial injury, fibrosis, and eventual loss of the nephron.14 Protein casts also contribute to loss of nephrons by obstructing the tubule.16 Hyaline or protein casts detected via urinalysis may suggest excessive protein loss with glomerular disease.6,9 Hyperfiltration with increased hydraulic pressure of the remaining nephrons may damage the less affected glomeruli and worsen the proteinuria. If any portion of the nephron is irreversibly damaged, the entire nephron will be lost. Once greater than 66% to 75% of nephron function is lost, renal azotemia develops. Some dogs with PLN retain the ability to concentrate urine with concurrent glomerular azotemia. The degree of proteinuria may decrease over time as nephrons are lost. However, this should not be assumed to indicate that the glomerular disease and the PLN are improving.

In one study,6 amyloidosis was shown to be one of the most common causes of glomerular diseases in dogs, accounting for 23% of dogs with glomerular disease. Amyloidosis results from the deposition of an acute-phase reactant fragment, amyloid A. The most common type of amyloidosis in dogs is secondary or reactive. In reactive amyloidosis, serum amyloid A is synthesized by the liver in response to tissue injury. Chronic inflammation can result in a prolonged increase in serum amyloid A concentration, leading to development of reactive amyloidosis, although other factors (e.g., inherited, environmental) might be involved.6 In this same study,6 it was determined that an underlying disease process was causing amyloidosis in only 32% of cases. Beagles, collies, and Walker hounds may be at increased risk of amyloidosis.17 Familial amyloidosis is a rare cause of amyloidosis and may occur in beagles, English foxhounds, shar-peis, and

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6 All differentials are not listed.
IBD = inflammatory bowel disease; IMHA = immune-mediated hemolytic anemia; IMTP = immune-mediated thrombocytopenia; RMSF = Rocky Mountain spotted fever; SLE = systemic lupus erythematosus
Abyssinian cats. With renal amyloidosis in shar-pees and Abyssinians, the amyloid is deposited primarily in the renal medulla; thus proteinuria may not be as marked.\textsuperscript{14} Primary or immunoglobulin-associated amyloidosis involves deposition of immunoglobulin light-chain fragments into the tissue and is rare in dogs and cats. Amyloidosis, in general, is uncommon in cats.\textsuperscript{14}

**HISTORY AND PHYSICAL EXAMINATION**

Clinical signs of PLN depend on the severity of the glomerular disease.\textsuperscript{6,17,18} For example, an animal may have weight loss and a dull, unkempt haircoat or appear clinically normal and have a positive microalbuminuria test result. Some animals may show predominantly clinical signs of an associated underlying disease. In the later stages of the disease process, these animals may have more obvious abnormalities, such as anorexia, vomiting, diarrhea, polyuria, polydipsia, and anemia, as typically seen with decompensated renal failure. Some dogs with PLN retain the ability to concentrate urine with concurrent renal azotemia, assuming pre- or postrenal azotemia is not present. This is known as glomerulotubular imbalance, in which the GFR decreases, resulting in renal azotemia, but the tubules are still able to concentrate urine.\textsuperscript{5,14,19} Therefore, the presence of a concentrated urine sample does not rule out the possibility of significant glomerular disease. Animals with severe PLN can also present with clinical signs consistent with nephrotic syndrome, which is characterized by marked proteinuria, resulting in hypoalbuminemia, hypercholesterolemia (i.e., increased hepatic production in response to low oncotic pressure), and ascites or edema. Nephrotic syndrome is seen in severe cases of proteinuria and is more typical of amyloidosis and membranous nephropathy.\textsuperscript{20} Thromboembolism, hyperlipidemia, and hypertension may be seen in patients with significant proteinuria.\textsuperscript{6} The antithrombolytic protein antithrombin III is approximately the same size as albumin. The loss of antithrombin III, along with other factors, contributes to the propensity for thromboembolism to occur.\textsuperscript{6,21} Antithrombin III activity has been shown to be abnormal if serum albumin levels are below 1.8 mg/dl.\textsuperscript{6}

Cutaneous and renal glomerular vasculopathy, also known as Alabama rot, occurs in young adult racing greyhounds, which usually present with cutaneous, well-demarcated ulcers primarily on the extremities.\textsuperscript{22} Some dogs may develop proteinuria and azotemia.\textsuperscript{22} The cause of cutaneous and renal glomerular vasculopathy is unknown, and the presence of azotemia seems to result in a poorer prognosis.\textsuperscript{22}

**DIAGNOSIS**

The diagnosis of PLN is fairly straightforward based on proteinuria without an active sediment or hematuria. Because most creatinine is excreted after entering the renal tubules, it provides a good estimate of GFR.\textsuperscript{14} Therefore, if urine creatinine levels are then compared with the amount of protein in the urine by a urine protein:creatinine ratio, the amount of proteinuria can be quantified. The results of the urine protein:creatinine ratio correlate fairly closely with a 24-hour measurement of protein excretion in urine.\textsuperscript{6,23} A urine protein:creatinine ratio of less than 0.4 to 0.5 is normal in dogs and cats.\textsuperscript{14} A value greater than 1 should prompt a thorough diagnostic evaluation.\textsuperscript{15} The urine sample should be obtained by cystocentesis to minimize contamination from the urogenital tract.

Microalbuminuria indicates that the level or amount of albumin lost, rather than the molecular size (i.e., <69 kD) of the molecule lost, is below the minimal level detected by commonly used urine assays. Certain ELISAs for canine and feline microalbuminuria detect albumin levels (not other proteins) of 1 to 30 mg/dl in urine. Microalbuminuria has been shown to occur before increases in the urine protein:creatinine ratio.\textsuperscript{1–3} There are presently two commercially available tests for microalbuminuria (i.e., ERD-Screen Urine Test, Heska Corp.; VetTest Urine P:C Ratio, IDEXX). In one study,\textsuperscript{24} a commercial, semiquantitative human test strip (Clinitek Microalbumin, Bayer Corp.) for microalbuminuria proved to be unreliable for detecting microalbuminuria in dogs. In cats, the ERD-Screen Urine Test appears to have a sensitivity of 95% and a specificity of greater than 99%.\textsuperscript{25} More studies are needed to deter-
mine the significance of microalbuminuria in cats as a correlation with proteinuria and progression of renal disease.\textsuperscript{16,25}

Although conventional urine strips not specifically made for detecting canine and feline albumin can be used, these are semiquantitative and have a substantial number of false-positive and false-negative results compared with species-specific ELISAs.\textsuperscript{9,28} Urine strips detect and measure albumin values of 30 mg/dl or more, whereas the sulfosalicylic acid turbidity test can be used to confirm the presence of proteinuria (values $\geq$5 mg/dl).\textsuperscript{9} The sulfosalicylic acid turbidity test is able to detect other proteins, such as Tamm–Horsfall and Bence Jones proteins.\textsuperscript{5,9} The urine concentration and pH must also be evaluated when interpreting these tests.\textsuperscript{5} A 3+ result from a sulfosalicylic acid turbidity test is more significant in an isosthenuric urine sample than in a highly concentrated sample. Inaccurate test results may occur in urine that is highly alkaline, dilute, or turbid.\textsuperscript{9}

A minimum database for animals with proteinuria should include a hemogram, serum biochemistry profile, and urinalysis with culture and sensitivity testing. Because PLN is often a sequela of systemic disease, an aggressive attempt should be made to identify an underlying cause (Table 1). Diagnostic imaging should include radiography of the thorax and abdomen as well as abdominal ultrasonography. Serologic testing for infectious diseases and inflammatory processes specific to the geographic location should be conducted. Consideration of immune-mediated diseases and appropriate screening (i.e., antinuclear antibody testing, direct Coombs’ test, immunoelectrophoresis) may be warranted. Systemic blood pressure monitoring is essential. Careful physical examination is essential to identify potential problems such as periodontal disease or skin or rectal masses that may be causing chronic antigenic stimulation (e.g., dermatitis, parasitism, inflammatory bowel disease).

A definitive diagnosis requires histologic examination with immunofluorescent microscopy and electron microscopy of the glomeruli from a biopsy of the renal cortex.\textsuperscript{14,21} The renal medulla should be avoided because it is associated with an increased incidence of complications, such as hemorrhage. The biopsies may suggest the underlying cause of glomerular disease and better enable the veterinarian to institute a more directed treatment plan. Some of the histologic types of glomerulopathies are amyloidosis, membranoproliferative glomerulonephritis, membranous nephropathy, proliferative glomerulonephritis, hereditary nephritis, minimal change disease, and glomerulosclerosis. Care must be taken in selecting patients for renal biopsy, and clinicians should weigh the risk versus benefit for each patient; a coagulation screen is strongly recommended before biopsy. The main question that must be addressed to warrant the risk is whether the histopathologic findings would substantially alter the treatment plan for the patient. Renal biopsies are not warranted for animals that are already in renal failure. Methods of obtaining tissue and interpreting histopathology are not discussed here (see “Glomerulonephritis in Dogs and Cats: Diagnosis and Treatment” in the September 2001 issue of Compendium).

**TREATMENT**

Treatment of glomerulopathies should always be directed toward treating the underlying systemic disease process when identified, symptomatically treating azotemia when present, and decreasing the amount of protein lost. Serial urine protein:creatinine ratios are essential for monitoring trends with response to treatment or disease progression.\textsuperscript{21} Treatment of azotemia may include maintaining normal hydration status, ameliorating gastrointestinal signs secondary to uremic syndrome, dietary changes, and therapy for acid–base

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*Although conventional urine strips not specifically made for detecting canine and feline albumin can be used, they are semiquantitative and have a substantial number of false-positive and false-negative results compared with species-specific ELISAs.*
disturbances, electrolyte abnormalities, systemic blood pressure, and endocrinopathies resulting from renal disease. Additional treatments of PLN (see box on this page) may include angiotensin-converting enzyme (ACE) inhibitors, low-dose aspirin, a low-protein diet, and omega-3 polyunsaturated fatty acids (PUFAs). Specific therapies for amyloidosis have proven to be ineffective. If amyloidosis is diagnosed before renal failure, especially in shar-peis, colchicine may be helpful (see box on page 693). Colchicine reduces serum amyloid A protein release from hepatocytes and may reduce a mediator called *amyloid-enhancing factor*.27 Anecdotal success has been reported with dimethyl sulfoxide, which is thought to help by acting as an antiinflammatory in both the liver and kidneys27 (see box on page 693).

ACE inhibitors, such as enalapril maleate, have been shown to significantly decrease the amount of proteinuria by causing vasodilation of the renal arterioles, primarily the efferent arteriole.28 This reduces the hydraulic pressure across the glomerulus; thus less protein is “forced” out of the glomerulus into the ultrafiltrate in the tubule.28 Enalapril might have additional beneficial effects5,14,21,28:

- Reducing loss of glomerular heparan sulfate (helping maintain negative charge)
- Decreasing the size of the glomerular capillary endothelial pores
- Improving lipoprotein metabolism

### Additional Therapies for Protein-Losing Nephropathy in Small Animalsa

- Elimination or treatment of concurrent disease
  - ACE inhibitors
    - Enalapril (0.5 mg/kg q12–24h)
    - Benazepril (0.5 mg/kg q12–24h)
    - Lisinopril (0.7 mg/kg/day)
  - Aspirin
    - Dogs (0.5 mg/kg q12–24h)
    - Cats (0.5 mg/kg q48h)
  - Low-protein diets
    - Dogs (2–3 g/kg/day)
    - Cats (4 g/kg/day)
- Omega-3 PUFAs
- Supportive care
  - Antihypertensive medications (i.e., ACE inhibitors and/or amlodipine) and a sodium-restricted diet
  - Diuretics as needed for ascites/edema (i.e., furosemide and/or spironolactone)
  - Paracentesis for severe accumulations of body cavity effusions
- Immunosuppressive treatment
  - Controversial; use with caution

*aAll medications are not included.*
• Slowing glomerular mesangial growth and proliferation
• Inhibiting bradykinin degradation

The usual starting dose of enalapril is 0.5 mg/kg/day. If the urine protein:creatinine ratio does not decrease within 2 to 4 weeks, the dose frequency should be increased to every 12 hours. When receiving ACE inhibitors, patients should be monitored for potential deterioration in renal status, such as increasing azotemia; thus baseline blood urea nitrogen and creatinine concentrations should be obtained before therapy and repeated within 7 days. Patients unable to tolerate ACE inhibitors often have a decreased appetite. Enalapril is cleared predominately by the kidneys, and a 33% reduced enalapril dose is suggested for dogs and cats with mild renal impairment (i.e., azotemia). Conversely, dogs with renal insufficiency can adequately clear benazepril, possibly making it a better choice of ACE inhibitor in animals, especially cats, with renal insufficiency. However, neither may prove effective in cats with proteinuria secondary to systemic hypertension.

Aspirin therapy is directed at decreasing platelet aggregation and may decrease the probability of thromboembolism. At normal doses, aspirin blocks the cyclooxygenase pathway, including both thromboxane and PG production. At a much lower dosage of 0.5 mg/kg q12–24h (q48h for cats), aspirin irreversibly blocks thromboxane production by platelets without decreasing the beneficial effects of PGI2 (i.e., prostacyclin) production. By blocking thromboxane production, adverse effects of thromboxanes, such as platelet aggregation within the glomerulus and mesangial cell contraction slowing GFR, are decreased.

In the future, alternative treatment modalities may include thromboxane synthase inhibitors, which have shown promise in decreasing the amount of proteinuria in dogs with experimentally induced glomerulonephritis. Through renoprotective effects and by reducing hypertriglyceridemia and lowering systemic blood pressure in humans, omega-3 PUFAs have also proven to be beneficial in chronic renal disease. Commercial renal diets for dogs usually contain a higher ratio of omega-3 PUFA and also have the benefit of phosphorus, sodium, and protein restriction. Decreasing the amount of dietary protein may decrease the amount of proteinuria and is an important component of treatment.

Using immunosuppressive drugs to treat glomerulonephritis is controversial. Immunosuppressive drugs are indicated if the inciting cause of glomerular disease is the result of chronic inflammation or an immune-mediated disease. Prednisolone may actually induce glomerular disease and increase proteinuria. Corticosteroids are used, they should be administered with caution, including judicious serial monitoring of the urine protein:creatinine ratio to detect increasing values. Certain types of glomerulonephritis, identified only through histopathology (e.g., primary membranous nephropathy of minimal change disease), have shown improvement with steroids. Cyclosporine has been shown to be of no benefit, but future studies are needed regarding use of immunosuppressive drugs in treating various glomerular diseases.

PROGNOSIS

The prognosis for patients with PLN is variable and depends on the severity and extent of both renal disease and any underlying systemic disease as well as response to treatment. If azotemia is present at the time of diagnosis, the average time until death for dogs is less than 3 months. Poor prognostic indicators in humans include concurrent azotemia, severe proteinuria, systemic hypertension, and marked tubulointerstitial lesions; this is probably true in animals, as well.

REFERENCES


## ARTICLE #3 CE TEST

This article qualifies for 2 contact hours of continuing education credit from the Auburn University College of Veterinary Medicine. Subscribers may purchase individual CE tests or sign up for our annual CE program. Those who wish to apply this credit to fulfill state relicensure requirements should consult their respective state authorities regarding the applicability of this program. To participate, fill out the test form inserted at the end of this issue or take CE tests online and get real-time scores at CompendiumVet.com.

### 1. A normal glomerulus has fenestrations in the basement membrane approximately the same diameter as

- a. albumin
- b. urea
- c. globulins
- d. electrolytes
- e. creatinine

### 2. Which is not considered a cause of postglomerular proteinuria?

- a. myoglobinuria
- b. metritis
- c. urinary tract infection
- d. myoglobinuria
- e. cystitis

### 3. Which does not typically result in contraction of the mesangial cells?

- a. dopamine
- b. angiotensin II
- c. platelet-activating factor
- d. platelet-activating factor
- e. thromboxanes
- f. endothelins

### 4. Which is most consistent with a diagnosis of glomerulotubular imbalance in dogs with PLN?

- a. renal azotemia with the inability to concentrate urine
- b. renal azotemia with the ability to concentrate urine
c. prerenal azotemia with the ability to concentrate urine
d. postrenal azotemia with the ability to concentrate urine
e. none of the above

5. Which is not typically a component of nephrotic syndrome?
   a. proteinuria
   b. hypogammaglobulinemia
   c. hypoalbuminemia
d. hypercholesterolemia
e. ascites

6. Which diagnostic test has the greatest sensitivity when detecting levels of albumin less than 30 mg/dl in urine?
   a. a species-specific ELISA
   b. a sulfosalicylic acid turbidity test
c. commercial human urine test strips
d. a urine protein:creatinine ratio
e. none of the above

7. Which can cause inaccurate results when evaluating for glomerular proteinuria?
   a. a very diluted urine sample
   b. active urinary sediment
c. hemorrhage
d. high urine alkalinity
e. all of the above

8. A minimum database for animals with proteinuria should not include a
   a. hemogram.
b. serum biochemistry.
c. urinalysis with culture and sensitivity testing.
d. urine protein:creatinine ratio.
e. biopsy of the renal medulla.

9. Which is not a possible treatment option for PLN?
   a. enalapril
d. omega-3 fatty acids
   b. a high-protein diet
e. none of the above
c. low-dose aspirin

10. Which can result in glomerulonephritis in dogs?
    a. rickettsial diseases
    b. trimethoprim–sulfa antibiotics
c. polyarthritis
d. heartworm disease
e. all of the above