Glomerulonephritis in Dogs and Cats: Diagnosis and Treatment*

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ABSTRACT: Initial suspicion of glomerulonephritis (GN) arises when proteinuria is documented without evidence of urogenital tract inflammation. Diagnosis involves thoroughly evaluating the patient for concurrent diseases known to be associated with GN and ruling out prerenal and postrenal causes of proteinuria. Definitive diagnosis requires a renal biopsy. In the past, management has included elimination of the underlying cause, immunosuppression, and measures to prevent complications of GN. Immunosuppressive therapy has been successful in managing certain forms of GN in humans but does not appear helpful in dogs and cats and may even be harmful. Recently, use of angiotensin-converting enzyme (ACE) inhibitors and thromboxane synthetase inhibitors has shown beneficial effects in the management of canine GN.

Glomerulonephritis is suspected when significant proteinuria exists with an inactive urinary sediment, especially in patients with a history of lethargy, anorexia, or vomiting. Often, however, proteinuria is an incidental finding during routine urinalysis. This should prompt further investigation of the origin of the protein being lost.

DIAGNOSIS

Causes of preglomerular and postglomerular proteinuria (Box 1) should be ruled out initially with a minimum database of a complete blood cell count (CBC), chemistry profile, complete urinalysis, and urine culture. If an extraglomerular cause of proteinuria is detected, treatment should be directed toward that cause and reevaluation of proteinuria conducted during treatment and/or after resolution of the disorder. Diagnostic evaluation should continue if proteinuria persists after treatment or an extraglomerular source of proteinuria is not detected with the minimum database.

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Urinalysis

A complete analysis of urine obtained by cystocentesis should be done. The urine sediment is typically inactive in patients with GN, with the possible exception of hyaline or granular casts. If the sediment contains increased numbers of leukocytes, erythrocytes, renal tubular cells, transitional cells, or bacteria, other urinary tract diseases (e.g., infection, calculi, neoplasia) should be considered. Isoosmhenuria (urine specific gravity of 1.008 to 1.012) is present in some patients with GN. An aerobic culture of urine obtained by cystocentesis should be performed to rule out urinary tract infection (UTI) as a cause of proteinuria. If proteinuria persists after elimination of UTI, additional evaluation is indicated.

There are numerous tests for the detection of proteinuria:

- The initial test used by most practitioners is based on a color change of tetrabromophenol blue, which primarily detects albumin. The degree of color change roughly corresponds to a concentration of protein in mg/dl.
- Other commonly used tests, such as the sulfosalicylic or nitric acid test, are based on precipitation of proteins and subjective measurement of the turbidity of the subsequent suspension. These precipitation tests detect more kinds of proteins (Tamm-Horsfall proteins, albumin, Bence Jones proteins) than the dipstick.

While these tests may confirm proteinuria, they are not quantitative and thus do not verify pathologic proteinuria. 1 In addition, both tests must be interpreted in light of the urine concentration. A 2+ protein is probably of much less importance in urine with a specific gravity greater than 1.030 than in urine with a lower specific gravity.

The urine protein:creatinine ratio (UP:C) is a simple test that allows an approximation of urinary protein loss and negates urine concentration as a complicating factor. 2,3 While glomerular filtration rate and urine concentration may change, the UP:C remains constant in most instances. Urine samples should be collected by cystocentesis to decrease the likelihood of contamination from the urethra and genital tract. Prostatic reflux into the urinary bladder could still affect urine collected by cystocentesis. A UP:C greater than 1 is abnormal and highly suggestive of a protein-losing nephropathy in dogs and cats. A UP:C of 0.2 to 1 in dogs and 0.25 to 1 in cats should be considered questionable for a protein-losing nephropathy. 2,4,5

Complete Blood Cell Count and Chemistry Profile

Laboratory abnormalities are often nonspecific and are likely to reflect the underlying disease, if one exists:

- Anemia has been reported in more than 44% of dogs and 63% to 85% of cats with GN. 6–9
- Hypoalbuminemia is commonly present in dogs (61%) and cats (92% to 96%) with GN. 6,8,9
- Hypercholesterolemia is noted in both dogs (79%) and cats (73% to 90%) with GN. 6,8,9
- Azotemia is also a common finding in dogs (49% to 53%) and cats (greater than 70%) with GN. 6–9

If the UP:C is consistently greater than 1 and the minimum database has failed to identify the cause of proteinuria, additional tests should be done to identify diseases that may predispose the dog or cat to GN (Box 2).

Renal Biopsy

If a potential cause of proteinuria has not been identified after performing the diagnostics listed in Box 2 or if proteinuria persists following appropriate treatment of an identified cause, a renal biopsy should be done. Additionally, if proteinuria is severe (UP:C greater than 10), membranous GN and amyloidosis are most likely and differentiation of the two via biopsy is important. 3,10 There is much debate as to the need for a renal biopsy once a thorough diagnostic evaluation has failed to reveal a cause of GN; however, there are several situations in which renal biopsy does provide useful information. The most obvious benefit of biopsy is differentiation of GN from amyloidosis. Patients with amyloidosis have a poor to grave prognosis and usually do not respond to treatment. In contrast, some patients with GN respond favorably to correction or treatment of the underlying disease and others with idiopathic GN can be managed successfully for years. 11–13 Another
reason to perform a biopsy is to obtain a histologic classification of GN. Reports of long-term survival of cats with membranous GN emphasize the usefulness of this classification system.\(^8,9\) While it is true that this represents a small number of cases in which histologic type may provide prognostic information, our ability to assign treatment and prognosis based on identified common factors will not improve without the information that would be acquired via renal biopsies. Useful descriptions of equipment and techniques used for renal biopsy can be found elsewhere.\(^14\)

Generally accepted contraindications to renal biopsy include the following:

- Bleeding disorders
- A solitary kidney
- Uncontrollable hypertension
- Pyonephrosis
- Renal abscess
- Hydronephrosis
- A suspected unilateral renal neoplasm
- Moderate to severe uremia as it predisposes animals to bleeding
- Small end-stage kidneys

Potential complications of renal biopsy include the following:

- Hematuria
- Hydronephrosis
- Renal ischemia or infarction

Improper technique is the cause in most cases. Patients should be assessed for coagulopathies by determining a prothrombin time, partial thromboplastin time, and buccal mucosal bleeding time; however, normal results do not absolutely rule out a coagulopathy or eliminate the possibility of severe hemorrhage. Microscopic hematuria is common for several days following biopsy. Hydronephrosis as a result of clot formation in the renal pelvis is uncommon, but perioperative intravenous fluid therapy may be used in an attempt to decrease its likelihood. Unless hemorrhage is life threatening, conservative management (e.g., fluid replacement, blood transfusions) is typically indicated.\(^14\)

Renal biopsies should be limited to cortical tissue to avoid structures in the renal hilus and medulla (Figure 1). The method chosen should be based on the condition of the animal, experience of the person performing the biopsy, and risks and benefits to the patient.

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**Figure 1**—The biopsy needle should be directed into the renal cortex in such a manner as to avoid damage to structures of the renal hilus and medulla. (From Forrester SD: Diseases of the kidney and ureter, in Leib MS, Monroe WE [eds]: Practical Small Animal Internal Medicine. Philadelphia, WB Saunders Co, 1997, pp 283–331; with permission.)
**Surgical biopsy** can be performed assuming the patient is an adequate anesthetic risk. In the authors’ opinion, benefits of this method are direct visualization of physical abnormalities, acquisition of a larger section of tissue than is obtained with needle biopsy techniques, and ability to rapidly detect and treat hemorrhage. A potential disadvantage of this method is that tissue healing may be impaired due to hypoproteinemia. A previous study found no complications of intestinal biopsies in severely hypoalbuminemic dogs; however, tissue healing in hypoproteinemic animals remains a controversial topic.

**Laparoscopy** can be useful in obtaining renal biopsies and is far less invasive than laparotomy; however, equipment is not available in most practices and general anesthesia is required.

**Blind** or **ultrasound-guided, percutaneous needle biopsies** can also be obtained. General anesthesia of short duration is typically required. Blind techniques are most successful in cats because the kidneys can be immobilized. Ultrasound allows visualization of the needle and important structures (e.g., renal pelvis, renal vessels, cystic structures) that should be avoided with the needle. In addition, it allows rapid detection of hemorrhage. While percutaneous methods may be the most rapid and practical, samples obtained in this manner are generally small. A 16-gauge needle may provide a more reliably adequate sample than do smaller needles.

Laboratories should be contacted prior to renal biopsy to obtain specific requirements for tissue submission. Renal tissue specimens should be submitted for routine light microscopy, immunofluorescence studies, and if possible, electron microscopy. In most cases, samples for light microscopy should be placed in 10% formalin and will be stained with hematoxylin and eosin for morphologic examination and Congo red to evaluate for the presence of amyloid. In most cases, samples for immunofluorescence should be snap frozen or fixed in Michel’s medium, and tissue for electron microscopy should be placed in Trump’s fixative. Electron microscopy is often not done but should be considered to increase our understanding of glomerular disease in veterinary patients.

**TREATMENT**

Management of patients with GN is based on decreasing immune stimulation, modifying the immune response, and preventing or treating complicating disorders (Box 3). In patients with secondary GN, decreasing immune stimulation is achieved through treatment of concurrent disease (e.g., melarsomine for heartworm disease, chemotherapy for lymphoma). In many cases, however, the diagnosis is either idiopathic or the cause of secondary GN cannot be eliminated (e.g., some neoplasms, feline infectious peritonitis, systemic lupus erythematosus).

**Immunosuppressive Therapy**

In veterinary medicine there is only one relatively well-controlled study evaluating the efficacy of immunosuppressive therapy in patients with this condition. The use of cyclosporine in dogs with naturally occurring GN was compared with standard care (aspirin and a moderately restricted protein diet). No difference in proteinuria was seen between the two groups, and some patients receiving cyclosporine developed side effects; thus cyclosporine cannot be advocated for the treatment of canine GN.

Controlled studies evaluating the use of corticosteroids, azathioprine, or cyclophosphamide for GN in dogs or cats have not been conducted. Considering the potential for thromboembolism and hypertension that exists with GN, the use of corticosteroids may be more detrimental than helpful. In addition, results of treatment with these medications have been disappointing. Currently, immunosuppressive therapy cannot be advocated as a treatment for idiopathic GN. Immunosuppressive drugs do have a place in managing patients with GN when they are appropriate treatment for a concurrent disease (e.g., immune-mediated hemolytic anemia, neoplasia, systemic lupus erythematosus).

**Box 3. Treatment Regimen for Glomerulonephritis**

- Elimination or treatment of any concurrent disease
- Dietary protein restriction
  - Dogs: 2 to 3 g/kg/day
  - Cats: 4 g/kg/day
- Aspirin (0.5 to 5 mg/kg q12–24h)
- ACE inhibitors
  - Enalapril (0.5 mg/kg q12–24h)
  - Lisinopril (0.7 mg/kg/day)
  - Benazepril (0.5 mg/kg q12–24h)
- Supportive therapy
  - Furosemide as needed for ascites/edema
  - Paracentesis for severe accumulations of body cavity effusions

*a*Among ACE inhibitors, enalapril is the only one with documented benefit in the management of idiopathic GN in dogs. Dosages for lisinopril and benazepril are extrapolated from experimental reports.
Angiotensin-Converting Enzyme Inhibitors

Reports of the use of ACE inhibitors for reduction of proteinuria in animals and humans have emerged.\textsuperscript{17–20} The mechanism of beneficial effects provided by ACE inhibitors in proteinuric patients is uncertain. Evidence exists for reduction in efferent arteriolar pressures, thus decreasing glomerular capillary hydrostatic pressure and proteinuria.\textsuperscript{17} ACE inhibition appears to reduce the radius of endothelial cell pores and improve glomerular barrier size selectivity in human diabetic glomerulopathy.\textsuperscript{20} Other evidence exists suggesting angiotensin II has inflammatory properties and that inhibition of its effects may be useful as an antiinflammatory mechanism.\textsuperscript{21}

In a report by Brown and colleagues, lisinopril (0.7 mg/kg/day) provided significant reduction in proteinuria in uninephrectomized dogs with experimentally induced diabetes mellitus.\textsuperscript{17} Samoyed dogs with X-linked hereditary nephritis given enalapril (2 mg/kg bid) had a slower rate of increase in proteinuria and longer survival times than untreated, affected dogs.\textsuperscript{19} Recently, Grauer and coworkers performed a prospective multicenter trial evaluating enalapril versus standard care (low-dose aspirin and a moderately restricted protein diet) for the treatment of naturally occurring canine idiopathic GN.\textsuperscript{18} Dogs receiving enalapril (0.5 mg/kg PO q12–24h) had significant reductions in their UP:C over 6 months of treatment, without significant increases in serum creatinine. Placebo-treated dogs did not improve, whereas the majority of dogs in the enalapril group improved (reduction in UP:C greater than 50% with a stable serum creatinine level); however, the only animals euthanized for renal failure were in the enalapril group. An initial dose of 0.5 mg/kg PO bid appears reasonable but should be administered with caution, and patients should be monitored carefully as enalapril may exacerbate azotemia. To detect azotemia, serum creatinine and blood urea nitrogen should be evaluated before and 7 days after beginning treatment. The appropriate interval between UP:C reevaluations is unknown, but initially every 2 weeks may be reasonable. The dose should be increased only if reduction in the UP:C is not seen on three consecutive measurements.

If azotemia develops or is exacerbated during treatment, an alternative ACE inhibitor should be considered or the dosage of enalapril should be reduced. In a recent study it was shown that there is increased exposure to enalaprilat (the active metabolite of enalapril) in dogs with mild renal insufficiency, whereas this did not occur with benazeprilat (the active metabolite of benazepril).\textsuperscript{22} One potential benefit of benazepril is the increased biliary elimination of its active metabolite compared with that of enalaprilat, which is primarily eliminated by the kidneys. Lisinopril has been used with success in research models. However, enalapril should still be the initial ACE inhibitor of choice for treatment of dogs with GN because of its documented efficacy.

Thromboxane Synthetase Inhibitors

Another group of immune-response modulators that has shown great promise are thromboxane synthetase inhibitors.\textsuperscript{23–25} Thromboxane concentrations are increased in the urine of dogs with GN and are believed to have a role in the pathologic process.\textsuperscript{23–26} Thromboxane synthetase inhibitors have been shown to prevent histologic lesions, decrease proteinuria, and decrease urinary thromboxane in experimentally induced and naturally occurring GN in dogs.\textsuperscript{23–26}

Long-term treatment of one dog with naturally occurring membranous GN has been described.\textsuperscript{26} The patient presented with clinical signs of nephrotic syndrome that resolved during treatment with a thromboxane synthetase inhibitor and recurred with its discontinuation.

Unfortunately, these drugs are not currently available in the United States. They are marketed for thromboembolic disease in humans in Japan (ozagrel) and Italy (picotamide).

Aspirin

Because of the role of platelets in the pathogenesis of glomerular disease, aspirin has been recommended for patients with GN. Through its inhibition of cyclooxygenase, aspirin is also a nonspecific thromboxane synthetase inhibitor. A low dose of aspirin (0.5 to 5 mg/kg q12–24h) is recommended; however, there are no studies documenting its efficacy in dogs or cats with GN.\textsuperscript{27,28} A short-term in vivo study of the effects of aspirin on canine platelets may suggest that ultra-low dosing (0.5 mg/kg q12h) decreases platelet aggregation.\textsuperscript{29} Such low doses require reformulation in smaller patients.

Diet

Reductions in dietary protein reduce proteinuria in human nephrotic patients while increasing or maintaining serum albumin concentration.\textsuperscript{30} Additionally, protein restriction may help to alleviate clinical signs of concurrent renal failure. One recommendation is 2 to 3 g/kg/day of protein for dogs and 4 g/kg/day for cats.\textsuperscript{31} Albumin concentration and UP:C should be monitored. Increasing albumin concentrations, decreasing UP:C, and weight gain would be reasons for continuing on a protein-restricted diet.

Omega-3 fatty acid supplementation in dogs with experimentally induced renal insufficiency may be renoprotective.\textsuperscript{32,33} Omega-3 fatty acids may alter throm-
boxane formation in complement-stimulated glomerular epithelial cells in vitro. In humans with chronic glomerular disease, supplementation has also decreased proteinuria. These results appear promising as adjunctive therapy for GN, but placebo-controlled prospective clinical trials in naturally occurring GN are needed.

**PROGNOSIS**

The prognosis for GN is quite variable in dogs and cats. Survival of several years beyond diagnosis and complete remissions have been reported in as many as half of cats with idiopathic membranous GN. Those cats with evidence of renal failure died or were euthanized within a short time due to severe clinical signs. Dogs with a diagnosis of idiopathic GN that were not euthanized after initial evaluation had a median survival time of 28 days (range, 5 to 1170 days). Another study reported a median survival time of 16 months for dogs with idiopathic GN of various histologic types. In the recent study by Grauer and colleagues, all 14 of the untreated idiopathic GN patients survived the 6-month trial. Azotemia or uremia at initial evaluation may indicate a shorter survival time (3 months or less) in dogs. Prognosis may be better for secondary GN, assuming the causative disease is curable. These discordant survival times emphasize the variability in prognosis and the importance of a thorough diagnostic evaluation and differentiation of GN from amyloidosis.

**REFERENCES**

27. Forrester SD: Diseases of the kidney and ureter, in Monroe...
1. Which of the following statements regarding prognosis for dogs and cats with GN is true?
   a. GN consistently carries a grave prognosis for survival beyond 1 month.
   b. GN consistently carries a grave prognosis for survival beyond 1 year.
   c. GN is an incidental finding and carries no prognostic significance.
   d. GN has a variable prognosis.
2. An increased UP:C is likely to indicate glomerular protein loss if
   a. plasma globulins are normal, urine sediment is inactive, and urine culture is negative.
   b. plasma globulins are normal, urine sediment reveals numerous transitional cells, and urine culture is negative.
   c. plasma globulins are elevated, urine sediment is inactive, and urine culture is positive for Escherichia coli.
3. Enalapril maleate
   a. has recently been shown to reduce proteinuria associated with canine idiopathic GN.
   b. has recently been labeled for use as a treatment for canine idiopathic GN.
   c. is safe for use in patients that have concurrent GN and chronic renal failure.
   d. all of the above
4. Which of the following statements regarding the use of corticosteroids in the management of GN is true?
   a. Corticosteroids are contraindicated under any circumstance.
   b. Corticosteroids cause lymphocyte lysis and inhibit phagocytosis, thus tempering the destructive immune-mediated process and slowing the progression of idiopathic GN.
   c. Corticosteroids are used in patients with GN when they are part of an accepted therapeutic regimen for the treatment of a concurrent disease.
   d. Corticosteroids are recommended for most forms of GN.
5. The most commonly employed urine dipstick test for proteinuria predominantly detects
   a. Bence Jones proteins.
   b. hemoglobin.
   c. albumin.
   d. thromboxanes.
6. ACE inhibitors
   a. have been shown to decrease proteinuria in naturally occurring, idiopathic canine GN.
   b. may decrease proteinuria by decreasing glomerular efferent arteriolar pressures.
   c. may decrease proteinuria by decreasing endothelial pore size.
   d. all of the above
7. Renal biopsy samples should be obtained from
   a. the medulla only.
   b. the cortex only.
   c. the cortex and medulla.
   d. grossly abnormal tissue only.
8. When added as a dietary supplement, ________ may be renoprotective and decrease proteinuria in patients with chronic glomerular disease.
   a. omega-6 fatty acids
   b. omega-3 fatty acids
   c. medium-chain triglyceride oil
   d. fiber
9. UP:C ratios of ______ and ______ are considered abnormal in dogs and cats, respectively.
   a. greater than 2; greater than 2
   b. greater than 1; greater than 1
   c. greater than 0.65; greater than 0.2
   d. greater than 5; greater than 2

10. Renal biopsy samples are best evaluated for the presence of amyloid with which stain?
    a. toluidine blue
    b. periodic acid–Schiff
    c. Congo red
    d. trichrome