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Consensus Statement
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Consensus Guidelines for Immunosuppressive Treatment of Dogs with Glomerular Disease Absent a Pathologic Diagnosis

IRIS Canine GN Study Subgroup on Immunosuppressive Therapy Absent a Pathologic Diagnosis, B. Pressler, co-chair, S. Vaden, co-chair, B. Gerber, C. Langston, and D. Polzin

Background: In certain situations, veterinarians must decide whether or not to recommend immunosuppressive therapy for dogs with suspect glomerular disease in the absence of renal biopsy-derived evidence that active immune mechanisms are contributing to glomerular injury. The purpose of this report is to provide guidelines for the use of immunosuppressive drugs under these conditions.

Animals: Animals were not used in this study.

Methods: Recommendations were developed by a formal consensus method.

Results: Four recommendations were developed and accepted at a high level of consensus (median 92.5% agreement). Renal biopsy should not be performed when contraindications are present or when results will not alter treatment or outcome. Immunosuppressive drugs should not be given when the source of proteinuria is unknown, they are otherwise contraindicated, or a familial nephropathy or amyloidosis is likely. However, they should be considered when dogs are already being given standard therapy and the serum creatinine is >3.0 mg/dL, azotemia is progressive, or hypoalbuminemia is severe. Thorough client communication regarding pros and cons of such treatment as well as close and careful patient monitoring is required.

Conclusion and Clinical Importance: These recommendations can help guide the decision about renal biopsy in patients with proteinuria as well as the use of immunosuppressive drugs in those patients where the decision was made not to perform renal biopsy.

Key words: Canine; Glomerulonephritis; Glomerulopathy; Proteinuria.

There is no substitute for a pathologic diagnosis in the formulation of therapeutic plans for dogs with glomerular diseases. However, there are times when renal biopsy cannot be performed because of medical, practical, or financial limitations. In these situations, veterinarians may have to decide whether or not to recommend immunosuppressive/anti-inflammatory therapy for dogs with glomerular diseases in the absence of firm knowledge of whether an active immune mechanism is contributing to glomerular injury. Herein, we provide guidance on when to recommend immunosuppressive/anti-inflammatory therapy for dogs with a presumptive diagnosis of glomerular disease absent pathologic findings from a renal biopsy.

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Proteinuric dogs suspected of having glomerular disease, but absent a renal pathologic diagnosis, should generally be managed initially using standard therapy and regular monitoring. However, standard therapy for canine glomerular disease rarely leads to complete resolution of the renal injury. Furthermore, adverse effects of drugs used for standard therapy may limit their use in some dogs. If the targeted reduction in proteinuria is not achieved and the addition of immunosuppressive/anti-inflammatory therapy is being considered, it is prudent to reconsider recommending a renal biopsy. Nonetheless, in some situations, it may not be possible to obtain a renal biopsy (see the section entitled "Recommendations for When Not to Perform Renal Biopsy"). Furthermore, in some situations, it is clear that immunosuppressive/anti-inflammatory therapy is inappropriate (see the section entitled "Recommendations for Exclusion Criteria for Using Immunosuppressive/Anti-inflammatory Therapy in Dogs with Glomerular Disease"). When use of immunosuppressive/anti-inflammatory therapy is not contraindicated, the risk-to-benefit assessment for the patient should consider the arguments for and against using immunosuppressive drugs in dogs with glomerular disease (see the section entitled "Arguments for and Against Immunosuppressive/Anti-inflammatory Therapy in Dogs with Glomerular Disease Absent a Renal Pathologic Diagnosis").

Recommendation 1:
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.

95% of voting consensus members agreed with Recommendation 1 and 75% of these voters expressed "strong agreement."

Relative contraindications to renal biopsy include severe azotemia (ie, creatinine >5 mg/dL, which is associated with increased risk of bleeding and other postbiopsy complications), coagulopathy, cystic disease or moderate-to-severe hydronephrosis, pyelonephritis or perirenal abscess, uncontrolled hypertension (systolic blood pressure consistently >160 mmHg), severe anemia, pregnancy, and lack of access to a renal diagnostic pathology center equipped and qualified to perform and interpret electron and immunofluorescent microscopy as well as light microscopy using an appropriate array of special stains (including H&E, PAS, trichrome, Congo red and Jones methenamine silver stains) performed on 3 micron sections.[1]

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 (ie, serum creatinine <5.0 mg/dL). 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.

Recommendation 2:
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.

95% of voting consensus members agreed with Recommendation 2 and 60% of these voters expressed "strong agreement."

Verifying Proteinuria Is of Renal Origin

Proteinuria may be prerenal, renal, or postrenal, and renal proteinuria may be caused by glomerular disease, tubular disease, or inflammatory/exudative disease of the kidneys. When the source of proteinuria has not been definitively localized, immunosuppressive drugs are not indicated because, in general, immunosuppressive drugs are only indicated for treatment of glomerular disease.

Urinary tract infection, inflammation, or macroscopic hematuria may increase UPC above reference range, and must be excluded as causes for proteinuria.[2] Overload proteinuria, which occurs when large amounts of low molecular weight plasma proteins within the glomerular ultrafiltrate exceed tubular resorptive capacity (eg, neoplastic production of paraproteins or Bence Jones proteinuria and excessive hemolysis or rhabdomyolysis), must also be excluded before empiric treatment with immunosuppressive medications.

Mild proteinuria is common in dogs with acute or chronic tubular injury. Collective anecdotal experience of this consensus panel suggests that dogs with chronic tubulointerstitial disease rarely have UPC values >2.0–3.0, although occasionally, acute kidney injury may transiently be associated with greater UPC results (ie, ≥5.0). However, it is believed that UPC ranges from dogs with glomerular disease versus acute or chronic tubulointerstitial disease overlap, and therefore results must be interpreted in conjunction with other clinicopathologic findings when predicting type of disease. Thus, dogs with UPC values <2.0 in conjunction with increased serum creatinine concentration and persistent isosthenuria or absence of proteinuria at the time of initial diagnosis of kidney disease should not receive treatment with immunosuppressive/anti-inflammatory therapy without biopsy-supported evidence of active immune-mediated glomerular injury.[3]

Contraindications to Immunosuppressive Therapy

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.

Familial Nephropathy

Familial disease should be suspected when multiple related dogs are diagnosed with similar proteinuric renal disease or when a dog is diagnosed with proteinuric renal disease that is characteristic of a familial disease reported to occur in that breed. Familial proteinuric renal disease has been reported in Bull Terriers, English Cocker Spaniels, Dalmatians, Samoyeds, Rottweilers, Bernese Mountain Dogs, Newfoundlands, Doberman Pinschers, Pembroke Welsh Corgis, Bullmastiffs, French Mastiffs, Chinese Shar Peis, Beagles, English Foxhounds, and Soft-Coated Wheaten Terriers.[4] The pathogenesis, clinical findings, and progression of disease vary among these breeds. Veterinarians are cautioned, however, that while dog breed, age of onset of proteinuria, and suspected or confirmed proteinuric kidney disease in related dogs may increase suspicion of a familial nephropathy, this diagnosis should be considered presumptive until confirmed by renal biopsy.

Familial nephropathies in most of the above-listed breeds are steroid-resistant.[4] Treatment of dogs with hereditary or spontaneous familial glomerular diseases with immunosuppressive drugs, particularly prednisone, has thus far been unrewarding and morbidity attributable to drug side effects outweighs the likelihood of a responsive disease phenotype. Exceptions to this guideline may be glomerular disease in Soft-Coated Wheaten Terriers and Bernese Mountain Dogs. Soft-Coated Wheaten Terriers with concurrent glomerular disease and enteropathy may benefit from immunosuppressive drugs.[5] Bernese Mountain Dogs are predisposed to developing membranoproliferative glomerulonephritis, which may be responsive to some immunosuppressive protocols.[6]

Amyloidosis

Although indirect evidence suggests that reactive amyloidosis in dogs is associated with a dysregulated immune response, immunosuppressive therapy in people and dogs is either of no benefit or may contribute to more rapid progression of disease.[7,8] Although glomerular amyloidosis in dogs can be associated with very high UPC values, there is too much overlap in UPC values between dogs with amyloidosis and dogs with other glomerulopathies to reliably use the UPC value to predict histopathologic diagnosis.[9] Renal amyloidosis may be more likely in dog with glomerular disease when (1) the affected dog is of a breed known to be predisposed to amyloidosis (eg, Shar Pei); (2) additional clinical signs associated with hereditary amyloidosis in Shar Peis are present, including cyclical fever or distal joint effusion[10]; or (3) amyloid deposition has been confirmed in other organs, particularly the liver.[11]

Recommendation 3:
Immunosuppressive drugs should be considered in dogs with glomerular disease that are being given standard therapy and do not have a biopsy-confirmed renal pathologic diagnosis when (1) serum creatinine is >3.0 mg/dL, or azotemia is progressive; or (2) hypoalbuminemia is severe (ie, <2.0 g/dL).

90% of voting consensus members agreed with Recommendation 3 and 60% of these voters expressed "strong agreement."

Currently, the evidence that immunosuppressive therapy ameliorates glomerular disease in dogs is weak.[12] However, clinical studies of canine glomerular disease based on renal pathologic diagnosis have not yet been performed. In human beings, immunosuppressive agents may be effective for the treatment of membranous- and membranoproliferative glomerulonephritis.[13] These forms of glomerulonephritis in humans are typically characterized by the presence of immune complexes, evidence of an immune process affecting the glomerulus. These same renal disorders are common glomerular diseases in dogs. As reported elsewhere in this supplement,[14] 241 of 501 (48.1%) renal biopsies obtained from dogs suspected of having clinical evidence of glomerular disease had evidence of immune complex glomerular disease and thus would be candidates for immunosuppressive/anti-inflammatory therapy. Thus, approximately 1 of every 2 dogs with clinical evidence of glomerular disease would likely be candidates for immunosuppressive/anti-inflammatory therapy.

Reported survival times for dogs with azotemia, nephrotic syndrome, or both as a result of glomerular disease are short, with a median of <60 days.[9] However, survival of nonazotemic dogs without nephrotic syndrome can be substantially longer, with a reported median of 605 days.[9] Because survival can be short in dogs with glomerular disease characterized by either azotemia or nephrotic syndrome and nearly 50% of dogs with clinical evidence of glomerular disease have immune complex glomerular disease possibly responsive to immunosuppressive drugs, a therapeutic trial might be warranted.

There are select situations where immunosuppressive therapy might be considered in dogs with glomerular range proteinuria without the benefit of a renal biopsy. One such situation would be if renal biopsy is not possible and the glomerular disease is rapidly progressive in spite of standard therapy. In some cases, the dog may have an acute crisis and need to be stabilized via emergency treatment before performing a biopsy. Immunosuppressive therapy might also be indicated in dogs with rapidly progressive disease immediately after renal biopsy, but before results of the biopsy are not yet available. Specifically, aggressive immunosuppression may be considered if (1) azotemia is acutely severe, progressive, or both (ie, creatinine >5 mg/dL, IRIS AKI Stages 4 or 5) at the time of diagnosis and there is no evidence of chronic disease; or (2) hypoalbuminemia is severe (serum albumin <2.0 g/dL). In these situations, the protocols for peracute and rapidly

progressive diseases should be followed (see "Guidelines for Immunosuppressive Treatment of Dogs with Glomerular Disease Based on Established Pathology" in this supplement).

Likewise, immunosuppressive therapy might be indicated if biopsy is not possible, neither age nor breed is indicative of familial renal disease, and other contraindications to immunosuppressive therapy are not present. In this situation, the protocols for more protracted disease should be followed (see "Guidelines for Immunosuppressive Treatment of Dogs with Glomerular Disease Based on Established Pathology" in this supplement).

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.

Recommendation 4:
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.

90% of voting consensus members agreed with Recommendation 4 and 74% of these voters expressed "strong agreement."

Veterinarians are fond of reminding each other to "above all do no harm." Another way of saying this is "given an existing problem, it may be better not to do something, or even to do nothing, than to risk causing more harm than good." In this case, the question is whether we do harm by recommending an unproven immunosuppressive/anti-inflammatory treatment for a dog with clinical evidence of glomerular disease that may not benefit from the treatment. However, it is important to remember that canine glomerular disease can lead to serious complications or death. Failure to provide a potentially helpful treatment in this setting may result in more harm than the potential risks of the treatment. Thus, it is important to consider both the potential risks and potential benefits of recommending immunosuppressive/anti-inflammatory treatment for dogs with clinical evidence of glomerular disease absent the findings of a renal biopsy.

As reported elsewhere in this supplement, there is approximately a 50 : 50 chance that we would appropriately recommend immunosuppressive/anti-inflammatory therapy for a dog with clinical evidence of glomerular disease absent a renal biopsy.[14] Likewise, there is a 50 : 50 chance that recommending such treatment could be inappropriate for the patient without a biopsy. However, the risk of adverse effects of immunosuppressive/anti-inflammatory treatment in dogs with clinical evidence of glomerular disease may depend on many factors including some that remain unknown. The decision to proceed with treatment requires a case-by-case consideration of the risks of treatment.

Potential Benefits of Immunosuppressive/Anti-Inflammatory Treatments in Dogs with Clinical Evidence of Glomerular Disease

The view that immunosuppressive/anti-inflammatory therapy may be effective in improving clinical outcomes in dogs with some forms of glomerular disease is based on observations in humans with glomerular disease as well as recent anecdotal evidence. Cyclosporine, the only drug that has been studied prospectively in dogs with glomerular disease, was found to be of no detectable benefit, although the dose of cyclosporine used in this study may have been too low to be effective against glomerular disease.[1] However, dogs were included in this study regardless of renal pathologic diagnosis and thus it can be argued that some portion of the study dogs probably had glomerular disease that was not likely to respond to immunosuppressive/anti-inflammatory therapy. We hypothesize that a treatment effect would have been found if only dogs with documented immune complex-mediated glomerular disease were studied. No other studies of the use of immunosuppressive agents in dogs with glomerular disease have been published. As a consequence, it is difficult to predict a positive treatment effect with any accuracy.

Potential Risks of Immunosuppressive/Anti-Inflammatory Treatments in Dogs with Clinical Evidence of Glomerular Disease

Immunosuppressive drugs are widely recognized as having many potential adverse effects.[15] The principal adverse effect of mycophenolate in dogs appears to be diarrhea that is largely dose-dependent, whereas vomiting and anorexia are less common adverse effects. Cyclophosphamide may cause bone marrow suppression as well as vomiting and diarrhea, and occasionally sterile hemorrhagic cystitis.[15] Glucocorticoids have numerous adverse effects including polyuria, polydispia, polyphagia, weight gain, weakness, exacerbation of hypertension, increased susceptibility to urinary tract infections, hepatopathy, and promote proteinuria.[15–17] In addition, approximately 15% of dogs with glomerular proteinuria will likely have amyloidosis, and corticosteroids are contraindicated in the management of amyloidosis in humans.[7] Azathioprine, a commonly used immunosuppressive drug, can produce bone marrow suppression in dogs and has also been associated with the development of pancreatitis.[15] Cyclosporine can cause vomiting, diarrhea, and anorexia and has multiple recognized drug interactions.[15] Methotrexate causes bone marrow suppression and may be hepatotoxic.[15]

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