Consensus Statement
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Consensus Recommendations for Immunosuppressive Treatment of Dogs with Glomerular Disease Based on Established Pathology

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The purpose of this report was to provide consensus recommendations for the use of immunosuppressive therapy in dogs with active glomerular diseases. Recommendations were developed based on comprehensive review of relevant literature on immunosuppressive therapy of glomerular disease in dogs and humans, contemporary expert opinion, and anecdotal experience in dogs with glomerular disease treated with immunosuppression. Recommendations were subsequently validated by a formal consensus methodology. The Study Group recommends empirical application of immunosuppressive therapy for dogs with severe, persistent, or progressive glomerular disease in which there is evidence of an active immune-mediated pathogenesis on kidney biopsy and no identified contraindication to immunosuppressive therapy. The most compelling evidence supporting active immune-mediated mechanisms includes electron-dense deposits identified with transmission electron microscopic examination and unequivocal immunofluorescent staining in the glomeruli. For diseases associated with profound proteinuria, attendant hypoalbuminemia, nephrotic syndrome, or rapidly progressive azotemia, single drug or combination therapy consisting of rapidly acting immunosuppressive drugs is recommended. The Study Group recommends mycophenolate alone or in combination with prednisolone. To minimize the adverse effects, glucocorticoids should not be used as a sole treatment, and when used concurrently with mycophenolate, glucocorticoids should be tapered as quickly as possible. For stable or slowly progressive glomerular diseases, the Study Group recommends mycophenolate or chlorambucil alone or in combination with azathioprine on alternating days. Therapeutic effectiveness should be assessed serially by changes in proteinuria, renal function, and serum albumin concentration. In the absence of overt adverse effects, at least 8 weeks of the rapidly acting nonsteroidal drug therapy and 8–12 weeks of slowly acting drug therapy should be provided before altering or abandoning an immunosuppressive trial.

Key words: Canine; Formal consensus; Immunosuppression; Kidney biopsy; Proteinuria.

There are many causes and pathogenic mechanisms associated with glomerular diseases in dogs.[1–3] The etiopathogenesis may be linked to genetic mutations, infectious agents, inflammatory, neoplastic, and immune-mediated diseases.[4] In the majority of instances, the underlying cause remains unknown, and the disease is classified as idiopathic. There has been a dramatic improvement in treatment outcomes in human patients over the last 3–4 decades after establishment of the World Health Organization classification scheme for human glomerular disease, based on light, immunofluorescent, and electron microscopic imaging, and subsequent controlled clinical trials of pathologic entities based on this classification scheme.[5] To date, data are available on the efficacy and improved outcomes attending use of immunosuppressive therapy across all types of primary and secondary glomerular diseases in human patients.[6] Classification of human glomerular diseases based on the patient's clinical and pathological characteristics has proven useful in enhancing the therapeutic response in affected individuals.

Abbreviations:

CBC	complete blood count
CKD	chronic kidney disease
GBM	glomerular basement membrane
IRIS	International Renal Interest Society
PCR	polymerase chain reaction
UPC	urine protein to creatinine ratio
WSAVA RSP	World Small Animal Veterinary Association Renal Standardization Project

As a consequence of the World Small Animal Veterinary Association Renal Standardization Project (WSAVA-RSP), more comprehensive light histopathologic imaging,[a] as well as electron microscopic and immunofluorescent microscopic imagery, has become readily available for use in dogs with glomerular disease. Examination of kidney biopsies using these advanced imaging techniques allows greater insight into the morphologic features of glomerular pathology and foundation for an improved and more discriminating classification system for glomerular diseases of dogs. Establishment of more specific pathological diagnoses holds the potential to improve conventional therapeutic and prognostic recommendations for dogs with glomerular disease. When kidney biopsy establishes evidence of an immune-mediated contribution to the glomerular disease, use

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of immunosuppressive/anti-inflammatory therapy may be rational and indicated. However, despite the logic of immunosuppressive strategies for these diseases, compelling evidence supporting this therapeutic practice in dogs is lacking. Currently, any use of immunosuppressive drug therapy, which may portend detrimental effects, should be founded on substantive criteria to objectively balance potential benefits against predictable adverse effects.[7]

Materials and Methods

The recommendations presented in this report were developed with consideration of a comprehensive review of pertinent literature on immunosuppressive therapy of glomerular disease, expert opinion, and review of a selected group of dogs with glomerular disease treated with immunosuppressive therapies. Recommendations were subsequently validated by a formal consensus methodology (see, "Development of Clinical Guidelines for Management of Glomerular Disease in Dogs" in this supplement). The Pubmed Medline database was searched for relevant studies published from 1975 to 2013 (literature search date) using the following MeSH terms and text words: immunosuppression, kidney, glomerular disease, chronic kidney disease, cyclosporine, mycophenolate mofetil, azathioprine, chlorambucil, cyclophosphamide, glucocorticoids, and dog. The search included combinations of terms and text words at the discretion of the authors to detect potentially relevant citations. The literature search was not limited to certain study designs or languages.

Use of Immunosuppressive Drugs in Dogs with Glomerular Disease

Recommendation 1:
The empirical application of immunosuppressive/anti-inflammatory therapy is recommended for dogs with severe, persistent, or progressive glomerular disease in which there is renal biopsy–supported evidence of an active immune pathogenesis and no identified contraindication to immunosuppressive therapy.

100% of voting consensus members agreed with Recommendation 1 and 60% of these voters expressed "strong agreement."

The rationale underlying the recommendation to initiate immunosuppressive therapy is based on the prediction that suppression of humoral or cell mediated immunity and the associated glomerular inflammatory response will favorably influence the progression, severity, and clinical outcome of the disease. Currently, there is limited experience or evidence available to predict which specific therapy will influence positively or negatively the clinical outcome, specific patterns of glomerular injury, or immunologic activity. Until such evidence becomes available, recommendations remain anecdotal and consensus-based and should be applied cautiously on a case-by-case and trial basis. The treatment should be discontinued or modified if it fails to achieve treatment goals or if the treatment promotes intolerable adverse effects (see below). Before applying immunosuppressive protocols, a systemic search using PCR and serology-based diagnostics is indicated to identify any underlying or concurrent infectious disease (see Recommendations for Therapy for Dogs with Serology Positive Glomerular Disease).

Evidence Supporting an Immune-Mediated Pathogenesis in Canine Glomerular Disease

The most definitive criteria implicating an immunopathogenesis in glomerular disease is identification of components of the immune system associated with active and ongoing pathologic injury in the glomerulus. By extension, a documented immunopathogenesis should be established before the use of immunomodulatory therapy. Regrettably, there are no readily available serologic or peripheral markers or noninvasive diagnostic modalities in dogs to characterize and establish these criteria. The evidence must come from the glomerulus itself and is evident only with specialized light, immunofluorescent, and electronmicroscopic imaging of appropriately processed kidney biopsies. An immunopathogenesis is most compelling when there is consistent and multifaceted coherence of findings across these imaging modalities, which correspond with the clinical features in the animal. When there is a lack of correspondent information or an incomplete set of diagnostic imaging, decisions supporting an immunopathogenesis, and the justification to use immunosuppressive therapy, must be prioritized from a hierarchy of information from the available imaging modalities and observations.

Recommendation 2:
Evidence of an active immune-mediated pathogenesis is supported by the following findings:
The most compelling evidence supporting active immune-mediated mechanisms promoting the glomerular injury identified in the kidney biopsy include:

- By Electron Microscopy: Clear and definitive identification of electron-dense deposits in subendothelial, subepithelial, intramembranous, or mesangial locations in the glomerulus (Fig 1).
- By Immunofluorescent Microscopy: Positive and unequivocal immunofluorescent staining for IgG, IgM, IgA, light chains, and/or complement in an immune-complex (intermittent) or antiglomerular basement membrane (GBM) (linear) pattern of deposition in peripheral capillary loops and/or the mesangial compartment (Fig 2).

Probable evidence supporting active mediated immune mechanisms promoting the glomerular injury identified by light microscopy in the kidney biopsy include:

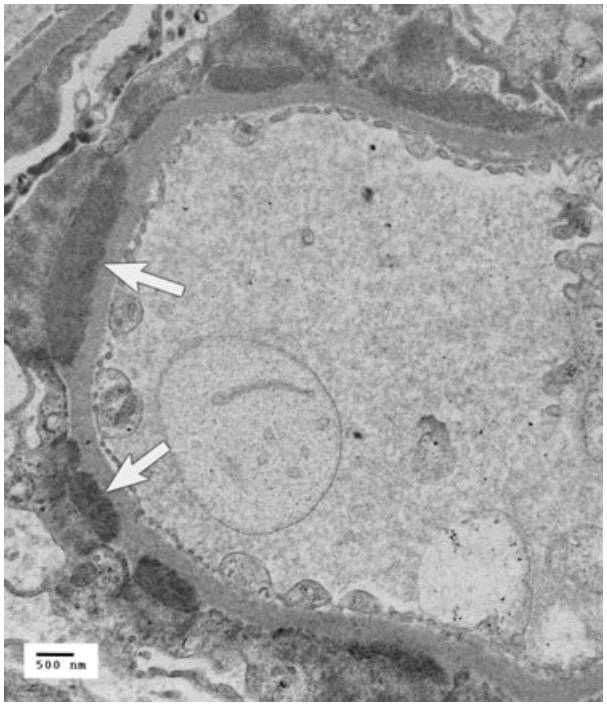

Fig 1. Transmission electron micrograph (15,000×) of a canine glomerular capillary loop demonstrating deposition of multifocal 0.25–2.0 micron nodular, subepithelial electron-dense deposits (arrows) consistent with immune complexes (Courtesy of Drs George E. Lees and Fred J. Clubb, Texas Veterinary Renal Pathology Service).

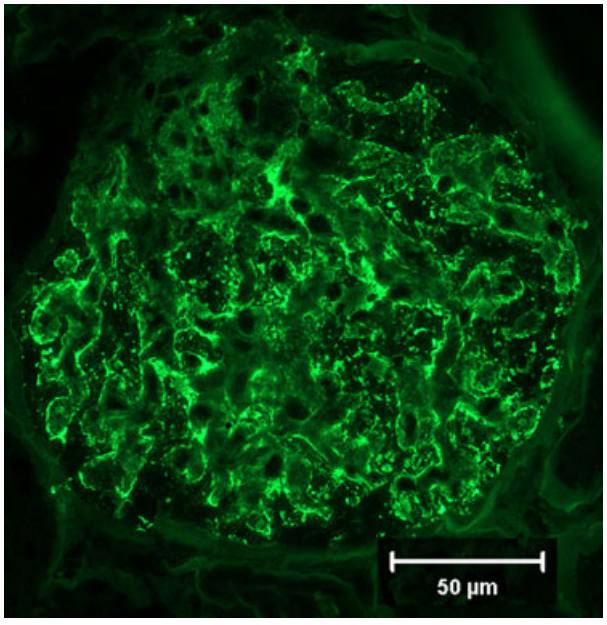

Fig 2. Immunofluorescent image of a canine glomerulus (40×) immunostained for IgG demonstrating extensive global coarse granular capillary wall staining and segmental fine granular mesangial staining documenting immune deposits and predicting an immune-driven pathogenesis to the glomerular injury (Courtesy of Dr George E. Lees, Texas Veterinary Renal Pathology Service).

- Convincing identification of "red granular" staining on the capillary walls on Masson's trichrome-stained sections (probable immune deposits) (Fig 3).
- Convincing identification of "spikes" along the glomerular basement membrane on Jones Methenamine silver-stained sections (Fig 4).
- Identifiable "holes" within the glomerular basement membrane on Jones Methenamine silver-stained sections (Fig 4).

91% of voting consensus members agreed with Recommendation 2, and 60% of these voters expressed "strong agreement."

As a caveat to these recommendations, it is possible to identify intramembranous electron-dense material with electron microscopy that represents residual immunological material deposited in the GBM during a previous immunological insult that is no longer associated with active or ongoing immunological events or susceptible to immunosuppressive therapy. Note also that if the EM findings provide evidence for chronicity, complete or rapid response to treatment may not be expected. Similarly, it is possible to identify "spikes" or "holes" on silver-stained sections using light microscopy that represent residual pathological reactions and remodeling of the GBM to a previous immunological insult that has resolved and is no longer active or susceptible to immunosuppressive therapy. Pathologic immune-product deposition also must be distinguished from nonspecific immunoglobulin entrapment in the

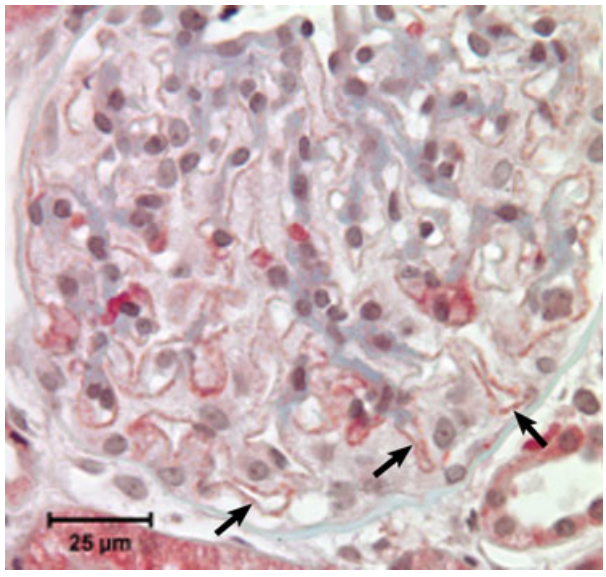

Fig 3. Light histologic image of a Masson's Trichrome-stained canine glomerulus (100×) demonstrating extensive red granular deposits along the subepithelial aspect of the capillary walls (black arrow) consistent with immune deposits on the glomerular basement membrane (Courtesy of Dr George E. Lees, Texas Veterinary Renal Pathology Service).

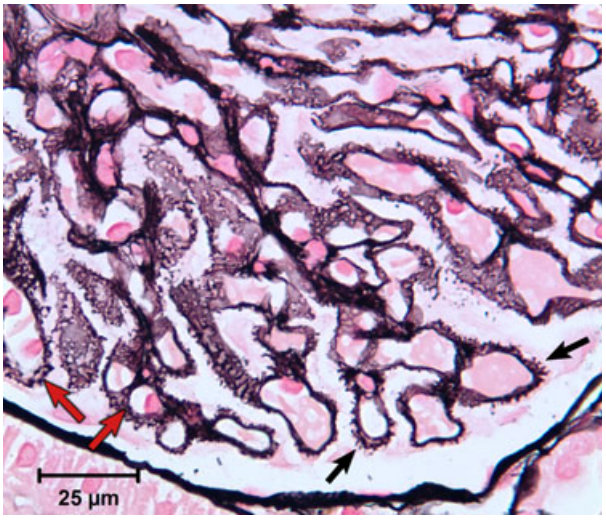

Fig 4. Light histologic image of a Jones Methenamine silver-stained canine glomerulus (100×) demonstrating numerous prominent spikes of glomerular basement membrane (GBM) material (black arrow) and holes (white arrow) within the GBM on the subepithelial surface. These features represent remodeling of the GBM around deposited immune deposits on or in the GBM (Courtesy of Dr George E. Lees, Texas Veterinary Renal Pathology Service).

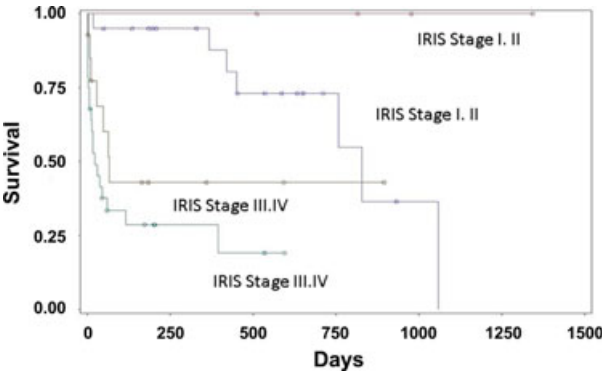

Fig 5. Plot of survival in dogs with unclassified proteinuric glomerular diseases with IRIS Stage I, II CKD, or IRIS Stage III, IV CKD, respectively, who were treated or untreated with immunosuppressive therapy. Although there were no statistical differences between the treated and untreated groups at each IRIS Stage, the trends suggest a survival benefit in dogs managed with immunosuppressive (and potentially anti-inflammatory) therapy (Courtesy, Drs Beth Orchutt and David Polzin, University of Minnesota, 2011).

filtration path of some lesions without an immunopathogenesis, ie, amyloidosis.

The judgment as to the involvement and active status of an immune process in the genesis of the glomerular disease is the purview of the reviewing nephropathologist(s) as the interpretative coherence of these lesions is beyond the scope and experience of the attending clinician. Care must be exercised not to overinterpret out-of-context descriptors provided in pathologic reports necessarily as evidence or proof of immunologic injury. This is especially true when descriptions are derived singularly from limited staining and review of light microscopic preparations.

Drug Options for Immunosuppressive Therapy of Glomerular Disease in Dogs

Recommendation 3:
The immunosuppressive strategy selected to manage dogs with documented glomerular disease of an apparent immune-mediated pathogenesis should be selected on the basis of the severity of the disease and its rate of progression. For diseases associated with high magnitude proteinuria, attendant hypoalbuminemia, nephrotic syndrome, or rapidly progressive azotemia, single drug, or combination therapy consisting of rapidly acting immunosuppressive drugs is recommended.

100% of voting consensus members agreed with Recommendation 3, and 60% of these voters expressed "strong agreement."

In the absence of controlled clinical trials of specific immunosuppressive drugs performed in dogs with glomerular disease of defined immune-mediated pathogenesis, no single drug recommendation can be made at this time. The use and selection of any immunosuppression protocol must be founded on an understanding of the actions, adverse effects, and costs of the selected agent(s). The following list of potential agents that may be effective in dogs with acute or rapidly progressive glomerular disease is based on their mode of action, their use in human patients with glomerular disease, uncontrolled or anecdotal experience of their use in dogs with spontaneous glomerular disease, or their use in dogs with other immune-mediated diseases.

Glucocorticoids

Glucocorticoids have an established basis in veterinary therapeutics for a variety of immune-mediated diseases in dogs, but they have been largely avoided in the management of glomerular disease unless associated with concurrent conditions known to be glucocorticoid responsiveness (eg, dogs with canine glomerular disease and immune-mediate polyarthritis). The avoidance of glucocorticoid therapy likely stems from the characteristic adverse effects (relative to benefits) of these agents in dogs compared to humans and other species. Expected adverse effects include polydipsia/polyuria, polyphagia, pendulous abdomen, panting, increased proteinuria, negative nitrogen metabolism, hypercatabolism and muscle loss, increased hypercoagulable and thromboembolic potential, sodium and fluid retention, systemic hypertension, behavioral changes, and adrenal suppression. Furthermore, the use of glucocorticoids should be considered carefully in the

presence of systemic or urinary tract infections to prevent worsening of these conditions (eg, pyelonephritis). These clinical perceptions are weakly supported by an observational study demonstrating worse outcomes in dogs with glomerulonephritis when managed with prednisone.[8]

In contrast with management schemes in dogs, management of glomerular disease in humans often relies heavily on the use of daily or pulse glucocorticoid therapy as a first-line treatment or in conjunction with other immunosuppressive agents for the management of virtually all types of primary glomerular disease.[5,9] This difference in therapeutic practice may be predicated on the tendency of glucocorticoids to promote proteinuria in dogs, perceived species differences in the risk-to-benefit ratio in human versus dogs, respectively, possible differences in the immunopathogenesis of canine glomerular diseases, or the lack of documented evidence-based efficacy assessment for glucocorticoids in canine glomerular diseases. Clinicians should be aware of this difference, when seeking information, therapeutic guidance, or both from the human literature. A proportion of human patients within most glomerular disease categories may be categorized as "steroid-resistant" and switched to other protocols until a treatment effect is observed. The apparent species differences in the clinical and pathophysiological responses to corticosteroids should prompt careful selection of patients if they are to be used.

Recommendation 4:
Short-term administration of glucocorticoids may be appropriate in fulminate cases where immediate immunosuppression is required if their use is adjusted to minimize their adverse effects. Potential benefits of alternative treatment regimens, ie, pulse therapy versus continuous therapy, should be considered.[10] However, on the basis of current practice perceptions and anecdotal experience, the use of glucocorticoid therapy should be tapered to the minimally effective dose as quickly as possible because of predictable adverse effects. Glucocorticoids may also be appropriate in the acute management of multisystemic immune-mediated diseases where their use has proven beneficial (eg, concurrent polyarthritis, immune-mediated hemolytic anemia).

100% of voting consensus members agreed with Recommendation 4, and 40% of these voters expressed "strong agreement."

Mycophenolate

Mycophenolate is an immunosuppressive agent that inhibits inosine monophosphate dehydrogenase, the rate-limiting enzyme in the de novo synthesis of guanosine nucleotides. Its immunosuppressive activity results from selective inhibition of both T-cell and B-cell proliferation that is dependent on the synthesis of purines. Mycophenolate appears to promote less toxicity (including myelotoxicity and hepatotoxicity) than alkylating agents, which affect all tissues with a high proliferative or mitotic activity.[11–13] Mycophenolate has been used in veterinary therapeutics as a treatment for myasthenia gravis, aplastic anemia, and immune-mediated hemolytic anemia.[14–16] Gastrointestinal adverse effects including anorexia, vomiting, and diarrhea are reported to be the main adverse effect of this drug; however, they usually are reversible upon dose reduction or withdrawal of the drug.[17] Evidence for the effectiveness of mycophenolate in the management of glomerular diseases in human medicine is mounting[18]; however, the veterinary literature is limited to a single case report supporting its use in a dog with glomerulonephritis of uncharacterized pathology.[19]

Recommendation 5:
Although randomized, controlled clinical trial evidence is lacking, based on preliminary, uncontrolled clinical experience with mycophenolate and its low rate of severe complications, mycophenolate is recommended as the first choice for treatment of dogs with peracute or rapidly progressive glomerular disease of an apparent immune-mediated pathogenesis.

82% of voting consensus members agreed with Recommendation 5; however, only 35% of these voters expressed "strong agreement."

Cyclosporine

The main activity of cyclosporine is exerted by its binding to the cytosolic protein, cyclophilin. The cyclosporine-cyclophilin complex inhibits calcineurin, which is essential for the transcription of interleukin 2 and interleukin 2 activation of T lymphocytes.[11] The effectiveness of cyclosporine in dogs with spontaneous glomerular disease has been evaluated in a randomized, controlled clinical trial, but was found to provide little apparent benefit.[20] A limitation of this study was the lack of precise pathologic characterization of the tested glomerular diseases for evidence of active immune-mediated injury potentially responsive to cyclosporine. It also is unknown if adequate blood levels of cyclosporine were achieved in the dogs in this study, as they were not measured. Further studies on the effectiveness of cyclosporine in dogs with glomerular disease have not been reported, and the use of cyclosporine cannot be recommended explicitly for the management of glomerular diseases in dogs until further evidence supporting its effectiveness emerges.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that interferes with DNA replication, RNA transcription and

replication, and consequent disruption of nucleic acid function. In veterinary medicine, it has been used in the management of a variety of neoplastic and immune-mediated disorders[11]; however, there are no studies in the veterinary literature to support or negate its use in dogs with glomerular diseases. Although shown to be effective in some glomerular diseases in humans, it is more likely to be associated with side effects than many other of the drugs discussed here. Potential adverse effects include gastrointestinal signs, myelosuppression, and hemorrhagic cystitis.[21] Cyclophosphamide may be administered as pulse therapy in cases of rapidly progressive disease. In humans, it is considered to be fairly effective for a variety of immune-mediated diseases including glomerular disease, and it has a rapid onset of action.[22]

Chlorambucil

Chlorambucil is an alkylating agent generally associated with minimal adverse effects, such as mild myelotoxicity.[11] In veterinary medicine, it has been used mainly in the management of neoplastic diseases. The efficacy of chlorambucil as monotherapy has not been demonstrated in veterinary literature for the management of glomerular disease.

Azathioprine

Azathioprine is a purine analog that interferes with normal cell DNA and RNA synthesis promoting cytotoxicity to lymphocytes and interference with cell-mediated immunity and antibody production.[23,24] It is used routinely in the management of a variety of immune-mediated disorders in veterinary medicine (eg, immune-mediated hemolytic anemia, inflammatory bowel disease) including immune-mediated glomerular disease.[25] However, in dogs with glomerular disease requiring acute onset of drug action, azathioprine may not be an ideal selection because it reportedly has a delayed onset of action and may take up to 2–5 weeks or more of administration to be fully effective in dogs (reportedly 3–4 months in humans).[23] Although it may not be an appropriate choice when used alone for patients requiring a rapid initial response, it may have a role when combined with more rapidly effective agents.[11,23] The predictable adverse effects of azathioprine include myelosuppression, gastrointestinal upset, hepatic disease or failure, and acute pancreatitis.[26,27] Although these adverse effects are generally manageable, patients receiving azathioprine must be monitored closely for evidence of these adverse effects of treatment. Azathioprine may be an inappropriate drug selection for dogs with a history or predispositions to acute pancreatitis.[23,28]

Although there are no randomized clinical trials to support or negate the use of azothioprine for the management of glomerular diseases in dogs, there is uncontrolled anecdotal clinical experience supporting its efficacy, usually in combination with chlorambucil.

Selecting an Immunosuppressive Protocol for Dogs with Glomerular Disease

Clinical presentations of canine glomerular diseases can be classified broadly as (1) peracute, rapidly progressive, or both; or (2) stable, slowly progressive, or both. Dogs with peracute, rapidly progressive glomerular diseases, or both are characterized by profound proteinuria, hypoalbuminemia (eg, albumin <2.0 g/dL), or overt clinical signs of nephrotic syndrome (eg, edema) or progressive azotemia. Dogs with stable or slowly progressive glomerular disease or both are characterized by protracted or minimally progressive proteinuria and azotemia with normoalbuminemia or minimal hypoaluminemia (ie, serum albumin concentration >2.0 g/dL) and no evident edema or clinical signs of uremia. These presentations dictate the optimum characteristics of the immunosuppressive drug and protocol most appropriate for a specific patient; however, when selecting a drug protocol targeted to the presentation of the disease, the probability of therapeutic success should be balanced against the potential for toxic and adverse effects of the immunosuppressive agents or protocols. Regardless of the immunosuppressive protocol selected for management of a patient, it is assumed that it will be used in combination with recommendations for "standard therapy" (see "Consensus Recommendations for Standard Therapy of Glomerular Disease in Dogs" in this supplement).

Recommended Protocols for Peracute or Rapidly Progressive Glomerular Disease or Both

Recommendation 6:
Dogs with peracute or rapidly progressive glomerular disease should receive induction therapy with a potent immunosuppressive protocol characterized by a rapid onset of immunosuppression. The following immunosuppressive agents are suggested for these presentations (see Table 1 for dosages and adverse effects):

- Mycophenolate alone or in combination with prednisolone
- Cyclophosphamide (continuous or pulse therapy) alone or in combination with prednisolone

87% of voting consensus members agreed with Recommendation 6, and 45% of these voters expressed "strong agreement."

The suggested use of mycophenolate is based on its rapidly growing application in the management of glomerular diseases in humans. In humans with glomerular disease, mycophenolate (alone or combined with glucocorticoids) has been found to be variably superior or equally effective to traditional immunosuppressive protocols incorporating cyclophosphamide, azathio-

prine, or cyclosporine (alone or combined with glucocorticoids) and generally provides a more favorable safety profile.[18,29] Although the efficacy and safety of mycophenolate in dogs with glomerular disease is not well established, preliminary uncontrolled anecdotal and observational studies in dogs suggest that it has potential for effectiveness in management of canine glomerular disease and appears to have a low incidence of serious adverse effects.

Although cyclophosphamide is also a reasonable option for dogs with peracute or rapidly progressive glomerular disease, its use entails a notably greater risk of adverse effects and requires more aggressive (and expensive) monitoring. Nonetheless, cyclophosphamide may be a reasonable alternative therapy when mycophenolate appears to be ineffective.

Recommendation 7:
There is no clear evidence to support or reject a recommendation for glucocorticoids in induction therapy in dogs with glomerular disease. To minimize the adverse effects associated with glucocorticoid therapy in dogs, the use of glucocorticoids as a sole treatment is not recommended, and when used concurrently with mycophenolate or cyclophosphamide, glucocorticoids should be tapered as quickly as possible to the minimally effective dose with the goal to discontinue the corticosteroid component within as soon as possible.

100% of voting consensus members agreed with Recommendation 7, and 40% of these voters expressed "strong agreement."

Recommended Protocols for Stable or Slowly Progressive Glomerular Disease or Both

Dogs with stable or slowly progressive glomerular disease or both may be managed with protocols including drugs with either rapid onset or more protracted onset. This classification does not necessarily imply that drugs with less rapid onset (alone or in combination) are less valuable or less effective in dogs with more severe or progressive glomerular diseases. In fact, there is limited anecdotal evidence for the efficacy of these slower onset protocols in acute glomerular diseases, and they should be considered as an alternative to the rapidly acting protocols once an initial response is achieved or when initial protocols need alteration because of the emergence of adverse effects.

Recommendation 8:
Dogs with active but stable or slowly progressive glomerular diseases with an immune-mediated foundation or slowly progressive diseases that are only partially responsive to standard therapy may receive induction therapy with either drugs having a rapid onset or drugs with more delayed onset including:

- Mycophenolate
- Chlorambucil alone or in combination with azathioprine on alternating days
- Cyclophosphamide and glucocorticoids
- Cyclosporine

91% of voting consensus members agreed with Recommendation 8, and 40% of these voters expressed "strong agreement."

Monitoring Immunosuppressive Therapy

Systematic clinical and laboratory monitoring is essential to optimize the therapeutic management of dogs with glomerular disease. Regular follow-up evaluations should include (1) clinical signs (adverse drug effects), (2) dietary intake, (3), body weight, (4) body condition score or body composition assessment, (5) assessment of peripheral or pulmonary edema, ascites, pleural effusion, (6) blood pressure, and (7) quality-of-life assessment. Follow-up laboratory assessment should include[b] (1) CBC, (2) serum chemistry profile including serum albumin, creatinine, urea nitrogen, phosphorus, electrolytes, hepatic enzymes, and cholesterol, (3) urine protein/creatinine ratio (UPC), and (4) assessment of identified underlying disease(s) (see "Consensus Recommendations for the Diagnostic Investigation of Dogs with Suspected Glomerular Disease" in this supplement).

Initial assessments should be performed no later than 1–2 weeks after initiation of the treatment and every 2 weeks thereafter for the first 4–6 weeks of treatment. Thereafter, assessments are recommended at least every 4 weeks for the next 3 months and then at quarterly intervals until resolution of the disease.

Criteria for Assessing Effectiveness of Treatment and Re-evaluation of the Treatment Plan

Clear expectations for therapeutic goals should be established before considering immnosuppressive therapy for use in canine glomerular disease. This is especially important in light of the predictable risks of the immunosuppressive approaches available. Although patient and renal survival times are the ultimate measures of outcome, changes in certain clinical and biochemical characteristics of canine glomerular disease may provide guidance as to the patient's response to treatment. The WSAVA Renal Standardization Project initiated in 2008 is a first attempt to assess the natural history for canine glomerular diseases, but outcome assessment of specific therapeutic strategies will require carefully designed prospective clinical trials to better understand the clinical benefits versus therapeutic risks of current and future recommendations.

Until more evidence-based and conclusive data are available to validate therapeutic recommendations, the therapeutic approach should be directed by surrogate clinical markers that are likely to correlate with patient

and renal survival. Therapeutic effectiveness can be assessed by the impact of treatment on (1) proteinuria (as measured by UPC), (2) renal function (as measured by serum creatinine concentration), and (3) serum albumin concentration. Responses to treatment may be characterized as (1) complete response, (2) partial response, or (3) therapeutic failure. Although performed uncommonly, the response to treatment may also be assessed by changes in renal biopsies obtained before and after the course of standard or immunosuppressive therapy or both.

Change in the Magnitude of the Proteinuria

Reduction in the magnitude of proteinuria is a marker of response to treatment and should be assessed to document improvement beyond standard therapy alone. It also should be recognized that day-to-day variance in the UPC ratio may be substantial in dogs with glomerular disease and should be considered when determining whether a measured change represents a clinically significant response (beneficial or adverse) to the therapeutic intervention. The absolute change in UPC necessary to predict a therapeutic improvement or worsening differs depending on the baseline magnitude of the proteinuria. At low UPC values (near 0.5), a minimum change of 80% is required to demonstrate a significant difference, whereas at high UPC values (near 12), a minimum change of 35% is necessary.[30] In humans with glomerular disease, reduction in proteinuria has been shown to be useful in predicting renal survival and the rate of progression of renal dysfunction. The magnitude of reduction in proteinuria in humans is related to the likelihood for favorable outcomes in renal survival and patient quality-of-life. Based on these observations, it seems likely that the therapeutic goal should be to achieve the greatest nadir in the proteinuria possible (as assessed by the UPC) while minimizing adverse effects of treatment. To achieve this goal, UPC should be assessed serially and treatment adjusted, extended, or both (within the constraints of therapeutic risks) to promote the maximal sustained reduction in proteinuria. Although UPC may normalize in some patients, this magnitude of response is unlikely an achievable goal in all dogs, especially if the disease affecting the glomerulus has promoted permanent structural alterations to the glomerular filtration barrier or treatment incompletely controls the pathogenesis.

When glucocorticoids are included as part of the immunotherapy, it may promote a transient or persistent increase in proteinuria. Although this effect appears to be contrary to the therapeutic goals defined above, these effects may be transient and reversible. It remains unclear whether this effect is a contraindication for corticosteroid therapy in dogs with glomerular disease. If a treatment fails to achieve the expected response goals, an alternative drug strategy should be considered.

Recommendation 9:
Response to treatment as measured by changes in UPC is defined as follows[c]:

- A complete response is defined as a reduction in the UPC to less than 0.5.
- A partial response is defined as a reduction in the UPC by greater than 50% of the highest pretreatment UPC after standard therapy or with standard therapy if both were initiated simultaneously.
- Therapeutic failure is defined as a reduction in UPC of less than 50% of the highest pretreatment UPC after standard therapy or with standard therapy if both were initiated simultaneously.

91% of voting consensus members agreed with Recommendation 9, and 45% of these voters expressed "strong agreement."

One has to consider that the magnitude of proteinuria may decrease in animals in late stages of progressive kidney disease because of a reduction in the number of remaining nephrons through which protein loss can occur.

Improvement or Stabilization of Renal Function

In patients with acute presentation, renal function and markers of azotemia (serum creatinine and urea nitrogen) may return to reference ranges spontaneously or in response to standard therapy, immunosuppressive therapy (complete response), or both. By contrast, in dogs with long-standing, persistent proteinuria and chronic kidney disease or in dogs with acute presentations, the glomerular damage may not repair and may remain abnormal, progress, or resolve incompletely (partial response). For partial responders, some degree of sustained azotemia may be expected, and the maintenance of stable renal function can be regarded as a therapeutic goal.

Response to treatment also should be assessed by changes in kidney function and measured by changes in serum creatinine concentration in normally hydrated animals. Serum creatinine should be compared to the baseline serum creatinine concentration defined as the mean value of documented serum creatinine concentrations during the 30 days preceding initiation of immunosuppressive therapy.

Recommendation 10:
The response to treatment as measured by changes in serum creatinine concentration is defined as follows[d]:

- A complete response is defined as reduction in serum creatinine concentration to less than

1.4 mg/dL (124 μmol/L) (or the patient's last known serum creatinine concentration before onset of the glomerular disease).
- A partial response is a sustained reduction in serum creatinine concentration by 25% or greater than baseline serum creatinine concentration most proximate to starting treatment.
- Therapeutic failure is defined as a reduction in serum creatinine concentration less than 25% baseline serum creatinine concentration most proximate to starting treatment.

91% of voting consensus members agreed with Recommendation 10, and 45% of these voters expressed "strong agreement."

Improvement in Serum Albumin Concentrations (improvement in serum globulins, total plasma protein, antithrombin, and fibrinogen may also represent improvement in glomerular permselectivity)

Although small increases in serum albumin concentration may reflect a response to treatment, the therapeutic goal is to achieve a serum albumin concentration greater than 2.0 gm/dL (20 g/L). Presumably, an increase in serum albumin concentration reflects a decrease in urinary loss; however, it may also occur consequent to decreased protein filtration resulting from progressive excretory failure independent of improvement in glomerular permselectivity. Consequently, improvement in serum protein concentrations should be compared to simultaneous measurement of serum creatinine and UPC values.

Recommendation 11:
Response to treatment as measured by changes in serum albumin concentration from baseline (defined as the mean of serum albumin concentration values during the 30 days preceding immunosuppressive therapy) is defined as follows:

- A complete response is a sustained increase in serum albumin concentration to greater than 2.5 g/dL (25 g/L)
- A partial response is either (1) a sustained increase in serum albumin concentration to 2.0–2.5 g/dL (20–25 g/L) or (2) a sustained increase of 50% or more in serum albumin concentration from the baseline serum albumin concentration.
- A therapeutic failure is defined as failure to increase serum albumin concentration to greater than 2.0 g/dL (20 g/L) or by less than 50% increase from baseline serum albumin concentration.

77% of voting consensus members agreed with Recommendation 11, however, only 30% of these voters expressed "strong agreement."

Improvement in Glomerular Histology

Resolution or improvement in the pathologic alterations of glomerular architecture may be the "gold standard" for evaluating therapeutic efficacy and outcome. However, obtaining sequential kidney biopsies to assess responses to treatment is not a conventional practice pattern in veterinary medicine. Nevertheless, serial kidney biopsy should be considered as a monitoring option in patients with suboptimal or incomplete responses to treatment. Similarly, serial kidney biopsy may provide a more objective and sensitive outcome marker in clinical trials testing therapeutic efficacy and recommendations.

Secondary Therapeutic Goals

Secondary therapeutic goals must be assessed in concert with standard therapy as the goals of standard therapy may not be achievable (eg, resolution of nephrotic signs, improvement in body composition, or correction of blood pressure) until there is maximal therapeutic resolution of the proteinuria and renal dysfunction, which standard therapy may not address.

Recommendation 12:
Secondary therapeutic goals include:

- *Improvement in blood pressure*. In conjunction with standard therapy, systolic blood pressure should be maintained at <150 mmHg.[31] (See, "Consensus Recommendations for Standard Therapy of Glomerular Disease in Dogs" in this supplement.)
- *Resolution of nephrotic signs-peripheral and/or pulmonary edema, ascites, pleural effusion*.
- *Stabilization (or improvement) of body weight and body condition or body composition as measures of nitrogen metabolism*. Establish body weight to historical reference or body composition score to "ideal".

100% of voting consensus members agreed with Recommendation 12, and 45% of these voters expressed "strong agreement."

Termination of Immunosuppression Therapy

Immunosuppressive treatment should be discontinued when clinically intolerable (eg, GI signs) or life-threatening (eg, pancreatitis, systemic bacterial or fungal infection, hepatotoxicity) adverse effects (compared to the underlying disease) can be attributed to the treatment per se. If neutropenia (<3000 cells/$10^3/\mu L$) is present, immunosuppression should be discontinued or modified transiently until the leucopenia is improved. Treatment should be discontinued or adjusted if any other adverse effects are reported by the owner that can be attributed to the immunosuppressive therapy.

Table 1. Recommendation 14—Recommended dosages and adverse effects of representative immunosuppressive drugs for the management of glomerular disease with a known immune basis.

Generic Name	Main Mechanism of Action	Recommended Dose	Main Adverse Effects
Azathioprine	Antagonizes purine metabolism	2 mg/kg PO q24h for 1–2 weeks, then 1–2 mg/kg q48h	GI upset, myelosuppression, acute pancreatitis, GI disorders, hepatotoxicity, infection, malignancy
Chlorambucil	Alkylating agent	0.2 mg/kg PO q24–48h	GI upset, myelosuppression
Cyclophosphamide	Alkylating agent	Pulse therapy 200–250 mg/m^2 every 3 weeks Continuous therapy—50 mg/m^2 PO 4 days/week	Myelosuppression, GI upset, hemorrhagic cystitis, infection
Cyclosporine	Calcineurin inhibitor	5–20 mg/kg PO q12h (consider tapering dose upward from low to higher doses to avoid gastrointestinal complications)	GI upset, gingival hyperplasia,
Mycophenolate	Antagonizes guanosine metabolism	10 mg/kg PO q12h	GI upset
Prednisolone (or other glucocorticoids at an appropriate dosage and route of administration)	Inhibition of PLA2, reduction in cytokines release, inhibition of neutrophils migration, down regulation of the Fc receptor	1 mg/kg PO q12h initially. Taper down as soon as possible	PU/PD, polyphagia, muscle wasting, panting, haircoat changes, weight gain, induction of liver enzymes, GI ulceration, lipidemias, infection, adrenal suppression, thromboembolism

86.4% of voting consensus members agreed with Recommendation 14, and 35% of these voters expressed "strong agreement."

Recommendation 13:
In the absence of overt adverse effects, at least 8 weeks of the rapidly acting non steroidal drug therapy (eg, mycophenolate) and 8–12 weeks of slowly acting drug therapy (eg, azathioprine) should be provided before altering or abandoning an immunosuppressive trial. If no response is evident or therapeutic goals are not achieved within these time intervals, consideration should be given to an alternative drug or dosing protocol. If no therapeutic response is noted after 3–4 months, consideration should be given to discontinue immunosuppressive therapy. Immunosuppressive therapy should be continued in dogs demonstrating a complete or partial response to initial treatment for a minimum of 12–16 weeks. Thereafter, consideration should be given to tapering the treatment to a dose/schedule that maintains the response without worsening of the proteinuria, azotemia, or clinical signs.

82% of voting consensus members agreed with Recommendation 13; however, only 25% of these voters expressed "strong agreement."

Footnotes

[a] Enhanced histopathologic studies include use of "thin-section" (3 micron) tissue sections stained by an array of stains (including H&E, PAS, Jones methenamine silver, Masson's Trichrome and Congo Red.

[b] Frequency of evaluation of these tests will depend on the treatment protocol as well as the clinical response of the patient.

[c] Pooled UPC determinations may be a more reliable means of assessing true changes in the magnitude of proteinuria.

[d] Although creatinine and albumin are identified in the recommendations as "serum creatinine or albumin," it is intended to be interchangeable with "plasma creatinine or albumin."

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