Protein-losing Nephropathy in Small Animals

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KEYWORDS

• Proteinuria • Glomerular disease • Glomerulonephritis
• Glomerulosclerosis • Amyloidosis

The prevalence of protein-losing nephropathy (PLN) in the general population is much greater in dogs than cats but is largely unknown and probably higher than currently recognized.[1–3] Renal failure is arguably the most common organ failure in dogs and cats. The prevalence of glomerular lesions, mostly immune-mediated glomerulonephritis (IMGN), was found in 43% to 90% of random dogs.[1,3] Increased urine protein/creatinine ratio (UPC), as an indicator of glomerular disease, is a negative predictor of outcome.[4–7] Microalbuminuria (MA) is detected in about 25% of all dogs and cats, increasing with age (36% in dogs 9–11 years, 49% in dogs $\geq$12 years, 39% in cats $\geq$12 years, and 65% of cats $\geq$16 years),[8] but its clinical significance is not known. When the first insult to the nephron is at the glomerulus, proteinuria occurs, which ultimately damages the rest of the nephron. By the time end-stage renal disease (ESRD) is discovered, the initiating glomerular cause may go undetected. Because proteinuria decreases with nephron dropout and decreased glomerular filtration, hypoalbuminemia may no longer exist or it may be masked by dehydration. Therefore, glomerular disease as the initiating cause of ESRD may go unrecognized.

Renal biopsy results may not settle the question of chicken-or-egg regarding whether glomerular versus tubular damage (chronic interstitial nephritis) was the primary cause, because both are often seen in end-stage kidney samples. Even when renal biopsies are taken earlier in the disease process, pathologists' interpretations using routine histopathology techniques do not necessarily agree.[9] There is inherent subjectivity with visual analysis of membrane thickening or mesangial cell numbers present. Tissue sections traditionally cut at 5 to 6 μm for light microscopy are too thick for careful examination of renal lesions. Therefore, the incidence of subtypes of glomerulonephritis reported may not be accurate, and treatment protocols that might work for a particular subset (for instance, steroids or cyclosporine) may not seem beneficial because these cases were not properly identified.

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With the advancement of technology, there are now sensitive and specific methods to detect and monitor proteinuria and abnormalities can be identified earlier in the disease process. The source of proteinuria can be localized and the cause characterized via diagnostic tests; the trend can be followed and stability or disease progression can be monitored. Kidney biopsies can be safely taken percutaneously with ultrasound guidance, sophisticated methodology can be used with light microscopy (LM) examination of thin (3–4 μm) tissue sections, and the glomerular lesions can be characterized by transmission electron microscopy (TEM), immunofluorescence (IF), and immunohistochemistry (IHC). Specific treatments may be recommended for specific causes, as well as symptomatic and supportive therapies to reduce proteinuria, hypertension, risk of thromboembolic events, edema/effusions, and progression of renal failure.

NORMAL GLOMERULAR STRUCTURE AND FUNCTION

The normal glomerulus is a complicated, elegant sieve, filtering 20% of the cardiac output, producing liters of ultrafiltrate per day, allowing water and small molecules to cross the fenestrated vascular endothelial barrier by the force of transcapillary pressure, to penetrate the glomerular basement membrane (GBM), traverse the podocyte slit diaphragm (SD), and enter into the glomerular filtrate while holding back larger molecules based on their size and electrical charge. The endothelial cell glycocalyx is negatively charged; the underlying supportive GBM is made up of collagen type IV, laminins, nidogen, and negatively charged glycosaminoglycans.[10] Podocyte foot processes are attached to the GBM via cell membrane receptors (α3β1 integrans linked to talin, vinculin, and paxillin, and α- and β-dystroglycans linked to utrophin).[10] Recently the structure and function of a myriad of molecules in the glomerular filtration barrier of the SD (ie, the 25- to 40-nm wide pore between the foot processes) have been reviewed (**Fig. 1**).[11] Produced by podocytes, these molecules work in concert to form a dynamic three-dimensional complex at the SD; they translate outside-inside signaling, control calcium influx, and rearrange the actin cytoskeleton within the podocytes to cause their contraction and modification of their morphology as well as the intricate architecture of their interdigitating foot processes and SD aperture, thus sensing and reacting to a changing environment. Normally very few proteins with molecular weight of albumin (69,000 Da) or higher get passed into glomerular filtrate, especially if they are negatively charged as is albumin. The few proteins that do pass through into the glomerular filtrate are normally reabsorbed and degraded by tubular cells and their lysosomes, but this work can cause tubular cell damage.[12]

GENETIC ABNORMALITIES ASSOCIATED WITH PLN

Genetic mutations producing 1 or more abnormal molecules at the SD or GBM may lead to immediate malfunction of the integrity of the permselective barrier, or to a susceptibility to injury by environmental triggers, or allow increased entrapment of circulating immune complexes (CIC), which may cause later onset proteinuria. Although not yet discovered in dogs and cats, more than 100 different mutations have been identified in NPHS1, the gene for *nephrin* (the major SD transmembrane adhesion protein of the immunoglobulin superfamily)[13]; more than 40 mutations in NPHS2, the gene for *podocin* (a stomatin family member closely associated with nephrin at the SD); and various mutations in other genes including NPHS3 (phospholipase Cε1), ACTN4 (α-actinin 4), CD2AP (CD-2 associated protein), TRPC6 (transient receptor potential cation channel 6), WT 1 (WT 1 protein), LAMB2 (laminin β-2), the NEPH 1-3 complex, several mitochondrial genes, MYH9 (nonmuscle myosin11A

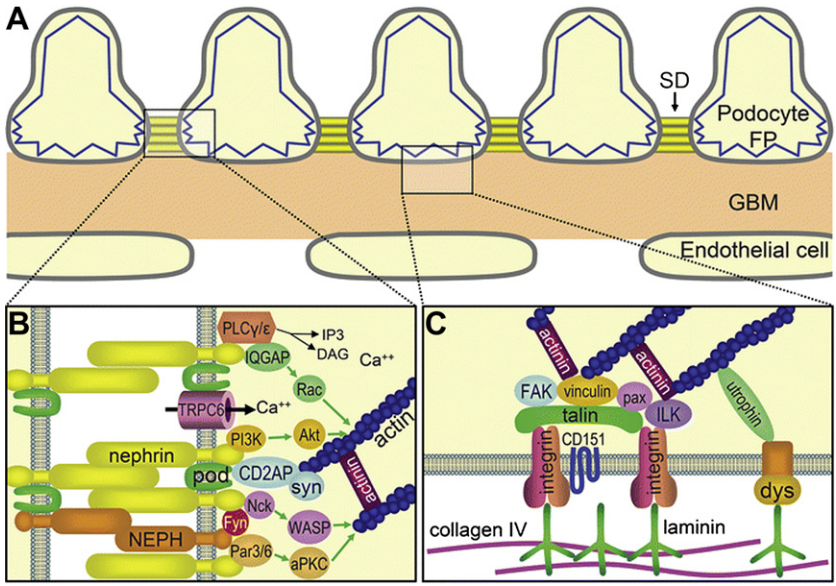

Fig. 1. The glomerular filtration barrier. (*A*) Overview of the structural components, including capillary endothelial cells, GBM, and podocyte foot processes (FP). The SD connects neighboring foot processes. Blue lines within the podocytes symbolize their actin cytoskeleton. (*B*) Molecules related to the nephrin-NEPH-podocin complex at the SD. Green arrows indicate effector pathways that have been proposed to be involved in the regulation of actin cytoskeleton reorganization. Only a subset of known molecules and interactions are shown. (*C*) Molecules at the podocytes-GBM interface and linkage to the FP actin cytoskeleton. Adhesion receptors expressed at the basal site of FP include integrin $\alpha 3\beta 1$ and dystroglycan. Only a subset of known molecules and interactions are shown. DAG, diacylglycerol; dys, dystroglycan; FAK, focal adhesion kinase; ILK, integrin-linked kinase; IP3, inositol 1,4,5-triphosphate; pax, paxillin; PI3K, phosphoinositide-3 kinase; pod, podocin; syn, synaptopodin. (*From* Zenker M, Machuca E, Antignac C. Genetics of nephrotic syndrome: new insights into molecules acting at the glomerular filtration barrier. J Mol Med 2009;87:850; with permission.)

heavy chain), and many more (too numerous to mention here).[11,14] Genetic abnormalities of the SD have been associated with many types of phenotypic expression (ie, mild to severe proteinuria); histopathology showing minimal change disease to severe focal segmental glomerulosclerosis (FSGS); onset that is congenital/infantile, childhood, or adult onset; inheritance that is autosomal recessive, dominant, possibly with low, medium, or high penetrance; and some genetic abnormalities include extrarenal abnormalities (eg, neurologic, orthopedic, or genital).[11,15] At times complex inheritance such as a triple hit (homozygosity for 1 allele and heterozygosity for another) or a 4-allelic hit (homozygosity at 2 sites) might be involved for phenotypic expression.[14,15] The expression of the phenotype may not be easily explained by just the presence of 1 or more genetic mutations but by the interplay of the entire molecular background.[14]

Genetic causes of PLN are usually steroid-resistant. Many breeds are predisposed to PLN (**Table 1**), and their genetic defects may someday be discovered to involve podocytopathies that interfere with the normal development and maintenance of the structure and function of the GBM or SD. Onset of PLN because of genetic causes

Table 1
Breeds predisposed to glomerular pathogenic proteinuria

Breed	Disease	Characterization
American foxhound[16–19]	MPGN secondary to leishmaniasis	Breed is at risk for leishmaniasis
Basenji[20,21]	Glomerulopathy with SIIPD	DDX, Fanconi syndrome
Beagle[22,23]	Primary glomerulopathy[22] Amyloidosis[23]	May present up to 8 y, at least 5 to 11 y
Bernese mountain dog[24–27]	MPGN	AR ± sex-linked modifier gene, F/M ~ 4, 2–5 y of age
Boxer[28]	Reflux nephropathy with segmental hypoplasia	Onset <5 y of age
Brittany spaniel[29]	Primary glomerulopathy	AR, associated with complement deficiency
Bull terrier[30–35]	Primary glomerulopathy	AD model of Alport syndrome, average 3.5 y, up to 10 y DDX, polycystic kidney disease (also AD)
Bullmastiff[36]	FSGS	AR, 2.5–11 y
Dalmatian[37]	Hereditary nephropathy	AD model of Alport syndrome, onset 18 mo (8 mo to 7 y)
Doberman pinscher	Primary glomerulopathy[38,39] Also IMGN caused by sulfa[40–42]	<3 y
English cocker spaniel[43–46]	Hereditary nephropathy	AR model of Alport syndrome, 10–24 mo Allele-specific PCR test to identify carrier dogs, OptiGen
English foxhound[47]	Amyloidosis	4 to 8 y
French mastiff (Bordeaux)[48]	Juvenile glomerulopathy	Cystic glomerular atrophy, glomerular hypercellularity, <2 y
German shepherd[49–52]	IMGN (MCD) secondary to *Ehrlichia canis* infection	Cell-mediated immunity abnormality Experimental Beagle model is not as severely affected
Golden retriever[53–59]	IMGN caused by Lyme nephritis (*Borrelia burgdorferi*)[53–57] JRD[58,59]	Most Lyme-positive dogs, even retrievers, do not get Lyme nephritis; average age 5.6 ± 2.6 y Experimental beagle model does not get Lyme nephritis JRD, <3 y of age, may have proteinuria, hypoalbuminemia, hypercholesterolemia
Gordon setter[60]	Juvenile nephropathy	May have proteinuria, hypoalbuminemia, <3 y
Greyhound[61–64]	GN vasculopathy (skin, renal)	6 mo to 6 y

Labrador retriever[53–57]	IMGN caused by Lyme nephritis (*Borrelia burgdorferi*)	Most Lyme-positive dogs, even retrievers, do not get Lyme nephritis; average age 5.6 ± 2.6 y Experimental beagle model does not get Lyme nephritis
Mixed Navasota dog and kindred[65,66]	Primary glomerulopathy	X-linked dominant Alport syndrome, 6 to 18 mo
Newfoundland[67]	Glomerulosclerosis	AR, 2 to 12 mo DDX, cystinuria (post-renal proteinuria, AR− DNA marker available)
Norwegian elkhound[68,69]	Periglomerular fibrosis plus tubulointerstitial disease	Mode of inheritance not known 3 mo to 4 y
Pembroke Welsh corgi[70]	Primary glomerulonephropathy	Littermates presented at 3 and 5 months of age; similar to Doberman
Rottweiler[71]	Primary glomerulopathy	<1 y of age, atrophic glomerulopathy, massive proteinuria
Samoyed and kindred[72–78]	Primary glomerulopathy	Alport syndrome, X-linked recessive (an allele-specific PCR test is available for carrier Samoyeds, VetGen) Males die at 2–15 mo; carrier females: high urinary protein at 2–3 mo of age but do not progress
Shar pei[79–83]	Amyloidosis	Mean 4.1 y; M/F 1:2.5
Shetland sheepdog[53–57]	IMGN caused by Lyme nephritis (*Borrelia burgdorferi*)	Most Lyme-positive dogs do not get Lyme nephritis; average age 5.6 ± 2.6 y Experimental beagle model does not get Lyme nephritis
Soft-coated wheaten terrier[84–91]	FSGS vs IMGN[84–89] JRD[90,91]	Unknown inheritance, F/M = 1.6:1 PLN average 6.3 ± 2.0 y; PLE/PLN combined average 5.9 ± 2.2 y 2/12 dogs with JRD had proteinuria
Abyssinian and Siamese cats[92–97]	Amyloidosis	1–5 y Proteinuria variable (medullary vs glomerular involvement)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; DDX, differentiate this from another type of renal proteinuria seen in this breed (as noted); FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IMGN, immune-mediated glomerulonephritis; JRD, juvenile renal disease (renal dysplasia); MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis; PCR, polymerase chain reaction; PLE, protein-losing enteropathy; SIIPD, small intestinal immunoproliferative disease.

Data from Lees GE. Familial renal disease in dogs. In: Ettinger SJ, Feldman EC, editors. Textbook of veterinary internal medicine. 7th edition. St. Louis (MO): Saunders (Elsevier); 2010. p. 2058–62.

is usually young to middle age,[98] but variable expression and incomplete penetrance modes of inheritance may allow for later onset. For most breeds, specific genetic mutations are yet to be identified. It is hoped that, using DNA saved from animals with well-characterized phenotypes, future genome-wide association studies (GWAS) with new SNP chip technology followed by fine mapping (gene sequencing) of areas of interest that are found, specific markers for these defects will be discovered so that by a simple polymerase chain reaction (PCR) test, carriers of at-risk genes will be identified and breeding of a dominant individual or 2 at-risk recessive carriers may be avoided. By identifying genes involved and realizing their function, the underlying physiologic defects will be better understood and appropriate therapeutic protocols can be planned.

Alport syndrome (hereditary nephritis) affects the production and maintenance of the GBM as a result of abnormal collagen IV production and assembly. Normally collagen IV is made up of heterotrimers of different types of chains, numbered α1-6. In Alport syndrome, there may be insufficient amounts or abnormalities in subtypes α3-5 chains produced. Various mutations of the encoding genes (COL4A3, COL4A4, and COL4A5) lead to nanomechanic GBM failure, and in humans may affect the inner ear and eye as well. The abnormal GBM thickening or basket weave appearance and ultrastructural splitting of the lamina densa is seen by TEM, often with intramembranous electron dense deposits. With light microscopy alone, these cases may be misinterpreted as a type of glomerulonephritis (eg, membranoproliferative) or renal cortical hypoplasia. In humans, more than 350 mutations have been found affecting COL4A5 (coding for α5) on the X-chromosome.[65] Mutations on the autosomal genes COL4A3 and COL4A4 are usually recessive. The primary glomerulopathies affecting bull terrier, Dalmatian, English cocker spaniel, Samoyed and Navasota mixbreed dogs are types of Alport syndrome and their mode of inheritance has been identified (see **Table 1**). By gene sequencing, carrier Samoyeds were found to have a premature stop codon caused by a single nucleotide substitution in exon 35 on the gene COL4A5 on the X-chromosome that codes for the α5 chain. In X-linked recessive Alport syndrome in Samoyeds, affected males have proteinuria by 4 months and ESRD at 8 to 10 months; carrier females are proteinuric early but do not progress to renal failure. In contrast, mixed breed dogs from Navasota, Texas, were found to have an X-linked dominant COL4A5 defect as a result of a 10-bp deletion on exon 9 that causes a frame shift and premature stop codon in exon 10; carriers of both sexes show early onset of proteinuria by 6 months and ESRD at 6 to 18 months.[65] There has been high clinical variability found in autosomal dominant types of Alport syndrome in humans.[99] Treatment is nonspecific (see later discussion). DNA screening tests exist for Samoyed and English cocker spaniel breeds. Early screening by MA, and early treatment may slow progression. Progression to renal failure occurs before age 2 years in affected Samoyed and English cocker spaniel dogs, but is more variable (up to 10 years) in Dalmatians and bull terriers.

Familial renal amyloidosis in Shar pei, beagles, English foxhounds, and Abyssinian and Siamese cats is often primarily medullary without gross proteinuria but progresses to renal failure. Medullary renal biopsies are not recommended because of the risk of hemorrhage. Familial amyloidosis in Shar pei has earlier onset than reactive amyloidosis (mean age 4.1 years, M/F = 1:2.5); only 25% to 43% have proteinuria but 64% had some glomerular involvement, thus renal cortical biopsies are still helpful (amyloid stains with Congo Red). Recurrent fever/swollen hock syndrome/increased interleukin (IL)-6 is seen in Shar pei, similar to familial Mediterranean fever.

Several hereditary types of collagenofibrotic nephropathies (type I, type III, periodic acid-Schiff [PAS] negative) and fibronectin glomerulopathies (PAS positive) have been

described in humans with PLN associated with massive infiltration of collagen or fibronectin fibrils in the mesangium and subendothelium.[100] Collagenofibrotic glomerulonephropathy (collagen III) has been described in 2 unrelated young dogs with PLN[101,102] and nonamyloid fibrillary glomerulonephritis in a nephrotic cat and a young dog.[103,104] Without special stains and EM, these biopsies would have been misread as other forms of glomerular disease.

Many dog breeds[98] are predisposed to juvenile renal disease (renal dysplasia), polycystic renal disease, Fanconi syndrome, and so forth, which are not primary glomerulopathies but in some dogs cause proteinuria, possibly hypoalbuminemia, and/or hypercholesterolemia, mimicking changes seen with primary glomerular disease. Breeds predisposed to primary glomerulopathies as well as other familial renal diseases that need to be differentiated include the bull terrier, golden retriever, and soft-coated wheaten terrier (SCWT) (see **Table 1**). Also listed are breeds with higher risk for immune-mediated glomerular disease, possibly triggered by infection (eg, Lyme nephritis in retrievers, leishmaniasis in American foxhounds, ehrlichiosis in German shepherds), by drugs (eg, sulfa in Doberman pinschers), or by other hypersensitivities (possibly food allergies in SCWT).

ACQUIRED CAUSES OF GLOMERULAR LEAKAGE OF PROTEIN

Acquired PLN is sporadically seen in any breed and is often caused by IMGN, reactive amyloidosis, or glomerulosclerosis (GS). Comprehensive descriptions (TEM and/or IF in addition to LM analysis) of renal lesions in several hundred clinical cases of PLN were described 17 to 40 years ago.[1–3,105–114] Because newly emerging infectious diseases (especially tick-borne) and new genetic predispositions may change the spectrum of disease with time, comprehensive examinations of renal cortical biopsies on our current patients with PLN need to be done so that predominant types of glomerular lesions as presented to veterinarians in various locations are known, treatment protocols for properly identified subsets of PLN can be investigated, and individuals treated appropriately.

In general, glomerular lesions are common. In dogs with and without clinical signs of renal disease, 90% had glomerular lesions in 1 study.[107] Among dogs with renal disease, 52% had glomerular lesions in another study.[106] The population at risk for PLN was middle-aged to older dogs, with slightly more males represented. Glomerulonephritis and amyloidosis were described more often than other types of glomerular lesions in dogs and cats.[1–3,105–116] Membranoproliferative glomerulonephritis (MPGN) was common in dogs (presumably immune-mediated, and possibly postinfectious, as is seen in people in developing countries). Membranous nephropathy (MN) was the most common lesion in cats with PLN, but in general, PLN is not common in cats.[113,114]

IMGN

Pathologists describe lesions depending on how much of each glomerulus is involved (eg, segmental, global), how many glomeruli are involved in the sample (eg, focal, diffuse), and whether there is inflammatory cell infiltration or mesangial cellular proliferation. Immune complex (antigen-antibody) deposits can involve immunoglobulin (Ig) A, IgG, and/or IgM, with or without complement (C3). The complexes can be CIC or be formed in situ as antigens are caught and bind antibody secondarily. The antigens involved are rarely identified but are sought indirectly by history, clinical presentation, by serologic tests for antibodies, by using culture, cytology, and PCR for antigens associated with infections, and by searching for inflammatory disease and neoplasia.

The true cause is often unproved because immunohistochemistry or elution studies on the glomerular complexes are rarely done. Immune complex deposition causes inflammation (glomerulonephritis) through a variety of mediators, inflammatory cells, complement and platelet activation, renin-angiotensin-aldosterone (RAA) system activation, and numerous humoral and cellular responses that influence the progression versus resolution by mesangial phagocytosis.[1,3,117]

MPGN is the most common form of IMGN in dogs with a mean age of 10.5 years and no sex predilection.[110] It is uncommon in the cat.[118] Most common in dogs is type 1 MPGN with immune complexes seen as lumpy-bumpy deposits by EM and IF on the subendothelial side of the GBM (mesangiocapillary GN) and/or in the mesangium. Linear deposits that would indicate true autoimmune disease (systemic lupus erythematosus) have not been described in dogs and cats. The granular deposits of IMGN may stain positive for complement and IgA, IgG, and/or IgM combinations. By LM, the complexes make the GBM appear thickened or duplicated (railroad) but if tissue sections are cut thickly at 5 to 6 μm, MPGN may be overdiagnosed.

MPGN has been associated with sulfa drugs (mostly in Dobermans[40–42]), neoplasia, inflammatory diseases, and with many types of infectious diseases, such as chronic bacterial infection (endocarditis, bartonellosis,[119] brucellosis[120]), arthropod-borne (anaplasmosis [suspected],[121] babesiosis,[122–126] Lyme borreliosis,[53–57] ehrlichiosis,[49–52] hepatozoonosis,[127,128] leishmaniasis,[16–19] Rocky Mountain spotted fever (RMSF)[129]), viral diseases (canine adenovirus I,[130] feline leukemia virus,[131] feline immunodeficiency virus [suspected],[132–134] feline infectious peritonitis [FIP][135]) or parasitic diseases (*Dirofilaria/Wolbachia*,[136–140] heterobilharziasis [schistosomiasis],[141] trypanosomiasis[1,3]) in which carrier status and chronic immune stimulation from antigenic variation occurs. In leishmaniasis, high antihistone antibodies are present and associated with MPGN[142]; histones are cationic and are implicated in binding the CIC to the GBM, perhaps as a planted antigen. Some diseases may cause proteinuria as a result of vasculitis (RMSF, anaplasmosis, bartonellosis, ehrlichiosis, greyhound vasculopathy, leptospirosis, FIP) or renal infiltration (toxoplasmosis, cryptococcosis, systemic fungal infections, neoplasia), and not necessarily IMGN.

Although dogs seropositive for leptospirosis were described as having IMGN,[143] coinfections (eg, heartworms, leishmaniasis, and so forth) may have played a role; leptospirosis is generally considered to cause tubular rather than glomerular proteinuria, or vasculitis.[144–146] Another spirochetal disease, Lyme borreliosis, has been associated with MPGN involving Lyme-specific immune complexes, accompanied by tubular necrosis/regeneration and interstitial nephritis, sometimes with glycosuria caused by tubular disease.[53–56] Lyme nephritis may be seen in any breed but mostly in Labrador and golden retrievers and Shetland sheepdogs, and has a younger onset at 5.6 ± 2.6 years compared with other dogs with PLN at 7.1 ± 3.6 years. There may be specific *Borrelia* strains or genetic predispositions for this form of Lyme disease because most Lyme-positive dogs (even retrievers) remain asymptomatic and do not show proteinuria or PLN.[57] Thus, when a dog with PLN happens to be Lyme positive, it should be checked for coinfections and other causes of PLN, because Lyme seropositivity indicates tick exposure and not necessarily a diagnosis of Lyme nephritis.[54]

Bernese mountain dogs have a genetic predisposition (see **Table 1**) for MPGN that is no longer believed to be associated with Lyme seropositivity. The mode of inheritance is autosomal recessive, possibly with an X-linked modifier (M/F ratio = 1:4).[24–27] Another type of MPGN is seen in congenital complement deficiency in Brittany spaniels[29]; normal complement levels were found in 49 other dogs with acquired PLN.[147]

Treatment of type I MPGN involves treating the underlying infectious, inflammatory, or neoplastic disease process. Antiplatelet drugs may also be tried to decrease platelet activation, which seems to be involved in the inflammatory cascade. Sometimes IMGN is also treated with immunosuppressive protocols (see later discussion).

Membranous nephropathy (MN) is a form of IMGN characterized by severe proteinuria (similar to that seen with reactive amyloidosis) and seen more often in males. The glomerular damage is caused by complement-dependent mechanisms and not inflammatory cell infiltration because the immune complexes are found on the subepithelial (podocyte) side of the GBM, away from the capillaries. Unbound circulating antibody may react to antigens that are fixed on the urinary side of the GBM. It may be a true autoimmune disease; in humans it is associated with underlying immunologic defects. It is the second most common lesion in dogs (M/F = 1.75:1, mean age 8 years, range 1–14 years). Because of the severe proteinuria, it is often accompanied by the nephrotic syndrome, identified in 14 (30%) of 46 proteinuric dogs (mean 6.5 years). Survival times for dogs with MN ranged from 4 days to 3 years. In cats with PLN, MN is the most common lesion (M/F = 6:1, mean age 3.6 years, range 1–7 years). In a study of 24 cats with MN, 46% died or were euthanized shortly after diagnosis; 17% survived 4 to 10 months, 33% survived 2.5 to 6 years (3/8 of the long-term survivors were given steroids). Cats with only IgG and/or C3 deposits had longer survival than those that had IgA or IgM deposits. Spontaneous remissions have been reported but more study needs to be done to validate treatment regimes and prognostic factors. In MN in human patients, immunosuppressive treatment with pulse or alternate-day steroids and alkylating agents (cyclophosphamide, chlorambucil) for 6 months helps, although relapses are common. Cyclosporine also helps in two-thirds of cases.[1,112–114]

Familial MN is seen in Doberman pinschers (<3 years old). By LM the GBM looks thickened, possibly showing spikes on the epithelial side that do not take up silver stain. Deposits are seen by IF and TEM and the granularity may be so intense that the beaded pattern almost seems linear. Mesangia may also stain for IgG and C3, which are more common than IgM and/or IgA in dogs. TEM can stage the engulfment and resolution process.

Proliferative glomerulonephritis (PGN), also known as endocapillary or mesangial PGN, has been described in 2% to 16% of dogs with PLN (mean 7–9 years).[1] It is seen in humans with lupus, IgA nephropathy, or as a postinfectious GN (eg, after streptococcal or staphylococcal infection) in which GN follows an infection without a carrier status, which may be why there is no membranous component. The mesangial proliferation is defined as 4 or more mesangial or mononuclear cells per area, often with increased mesangial matrix seen. By IF and TEM there are fine granular deposits of IgG and/or IgM, subepithelial in the BM and in the mesangium. Treatment is to remove the source antigen.

IgA nephropathy may appear just as mesangial proliferative GN by LM but the immune deposits are seen by TEM and stain for IgA (more than for IgG or IgM) by IF.[148] Because IgA is dimeric in dogs, it may be trapped nonspecifically in the mesangium in 47% to 85% of normal dogs.[109,149,150] IgA nephropathy may be associated with hepatic and gastrointestinal disease[149]; treatment may depend on removing the underlying cause. IgA positivity (and less so IgM) was seen in some glomeruli in SCWT with protein-losing enteropathy (PLE)/PLN and food allergies,[87] but it is not yet proved whether the glomerular lesions in that breed are primarily immune mediated or sclerotic (FSGS) with secondary deposition of immune complexes.

Minimal change disease (MCD) is common in children (often steroid responsive but relapses are common) but rarely described in veterinary literature.[151] Ehrlichiosis and the drug masitinib were shown to cause MCD.[49,152] This nil disease shows no

morphologic lesions by LM, but there is foot process effacement seen by TEM examination, and increased vimentin staining by IF. Loss of the anionic charge at the GBM causes massive proteinuria and often nephrotic syndrome.

Reactive Amyloidosis

Reactive amyloidosis may be seen in any breed (dog > cat) and is often associated with glomerular deposition and severe proteinuria caused by extracellular deposition of polymerized serum amyloid A protein (SAA, an acute phase reactant made by the liver) into β-pleated sheets, seen as homogeneous eosinophilic thickening at the GBM and mesangium, staining red with Congo Red stain. This is 1 subset of PLN that can be diagnosed by LM. Other organs may be affected (eg, liver and spleen), becoming friable and hemorrhage easily (biopsy is not recommended). Among dogs with PLN, 23% had amyloidosis in 1 study.[116] Chronic infectious, inflammatory, or neoplastic disease was found in 32% to 53% of cases (mean age 9.2 years, M/F = 1:1.7) with beagles, collies, and Walker hounds predisposed.[153] Nephrotic syndrome is common because proteinuria is severe. Prognosis is poor; 58% of dogs were euthanized or died soon after diagnosis and only 8.5% survived for 1 year or more.[154] Colchicine (0.01–0.03 mg/kg by mouth every 24 hours) may help decrease hepatic production of SAA but may cause gastrointestinal upset. Dimethylsulfoxide (DMSO, 90 mg/kg by mouth 3 times a week or subcutaneous injections diluted 1:4 with sterile water) is antiinflammatory, decreases interstitial fibrosis, and may improve renal function and decrease proteinuria, but it causes garlic breath and may cause nausea/anorexia.[155]

The odorless and tasteless metabolite of DMSO, methylsulfonylmethane (MSM), may be used in place of DMSO.

Glomerulosclerosis

The prevalence of glomerulosclerosis (GS) increases with age.[1] It may be a primary (genetic) disease as in some forms of FSGS or it may be secondary to hypertension (eg, as a result of hyperadrenocorticism or steroid use) or any glomerular injury, such as an end-stage lesion. It may be underdiagnosed and misdiagnosed as MPGN. Nonspecific trapping of complexes in sclerotic/fibrotic areas may be seen by IF. In humans there are 5 subtypes, each with different prognoses, but these are poorly characterized in dogs and cats. Genetic structural defects of the SD or circulating permeability factors may functionally alter the permselectivity of the GBM, and predispose for indolent immune complex deposition, damage, and sclerosis. Glomerulosclerosis secondary to hyperadrenocorticism or hypertension rarely causes severe enough proteinuria to cause hypoalbuminemia.

DETECTING PROTEINURIA, THE HALLMARK OF PLN

Annual screening for proteinuria is recommended in healthy dogs as part of annual health care.[7] In particular, breeds with genetic risks for PLN should be screened early and often, especially if used for breeding. The earliest warning of glomerular disease is microalbuminuria (MA), defined as 1 to 30 mg albumin/dL, which can be detected by species-specific enzyme-linked immunosorbent assays for albuminuria such as the in-house semi-quantitative E.R.D. (HESKA) test or by quantitative MA by a reference laboratory. The sensitive MA test is useful as a first-line screening agent for genetic PLN (eg, SCWT,[89] Samoyeds[74]) or acquired glomerular damage (eg, in Lyme- or heartworm-positive dogs[57,139]).

Microalbuminuria is often associated with age and with systemic diseases.[156,157] In older dogs, MA may be too sensitive to be helpful compared with the UPC test.

Looking for persistence as well as trend of progression or stability is important before assigning clinical significance to MA, because many if not most older dogs have low to moderate positive MA, possibly as a result of normal aging of the kidney or infectious/inflammatory/neoplastic/vascular insults.

Urinary dipstick tests for protein are less sensitive than MA, picking up more than 30 mg/dL, and are less specific for albuminuria, showing false-negative and false-positive results compared with MA. Dipstick false-positive readings may occur with high pH, hematuria, pyuria, and/or bacteriuria, and more often with feline than canine samples.[158] In 1 study, when dipstick and urine specific gravity (USG) were used together, dogs with a USG greater than 1.012 and +1 by dipstick were likely nonproteinuric; but for those with +1 dipstick and USG less than or equal to 1.012, proteinuria should be further assessed by use of the UPC ratio.[159] Both dipstick and urine turbidity with sulfasalicylic acid (SSA) testing for proteinuria were less specific and gave false-positive results, whereas UPC testing showed higher specificity but less sensitivity, with some false-negative results.[160] Multistix PRO dipsticks, read by a Clinitek 50 analyzer (Bayer Corporation), were more sensitive but less specific than SSA testing for proteinuria in dogs (but not a good alternative for cats); manual calculation of the UPC is done with the dipstick's estimated urinary creatinine level.[161] Another in-house analyzer, the IDEXX VetTest, showed strong association for UPC results with the reference Vitros 50 instrument,[162] however not all laboratories use similar methodology, and inter-laboratory comparisons may be difficult.[163] Any UPC test may be increased by Bence Jones and other nonalbumin proteins in the urine. A urine albumin/creatinine ratio can also be done.[164]

Macroproteinuria is generally defined using UPC measurements. Borderline UPC values in nonazotemic animals (0.5–1.0 in dogs and 0.4–1.0 in cats) should be monitored for persistence and trend of progression. Larger amounts (UPC of >1.0) should be investigated and localized as to the source (prerenal, renal, or postrenal); renal proteinuria is then categorized as functional or pathologic (glomerular, tubular, or interstitial).[2,7] Investigation of macroproteinuria is always recommended if azotemia exists. Therapeutic intervention is recommended for nonazotemic animals at UPC greater than or equal to 2.0, but is often started at lower values if a breed-associated cause is suspected and progression is expected without early intervention. For azotemic animals, intervention is recommended at UPC greater than or equal to 0.5 (dogs) and UPC greater than or equal to 0.4 (cats).

Once macroproteinuria is found, UPC is the standard test for quantitation, monitoring, and for comparisons. There was no statistical difference found in the measurement of UPC between free-catch and cystocentesis samples.[165] Day-to-day variation of the UPC was seen in female dogs with stable glomerular proteinuria caused by X-linked hereditary nephropathy.[166] This study showed that significant differences in UPC to indicate progression of disease or failure of intervention would have to be greater than 35% variance at high UPC near 12, and greater than 80% variance at a low UPC near 0.5. This may be true for other forms of PLN (not just mosaics). To minimize costs of averaging results from 3 samples, equal pooling of 3 urine samples for 1 determination was found to be as valid as averaging results from 3 samples ($\pm$ 20%).[167]

Moderate exercise does not cause MA to increase.[168] Contrary to what was seen with another inflammatory marker (C-reactive protein), degree of MA showed no correlation with degree of periodontal disease, and there was no change in USG, MA, or UPC before and after dental treatment[169]; positive MA in 12.4% of dogs needing dental work may be related to their age.

Because whole ejaculate (not just sperm) physically added to urine may increase dipstick proteinuria,[170] it is not recommended to collect urine samples for MA testing

immediately after collecting semen. In 1 study, whole blood physically added to urine did not cause UPC greater than 0.4, and abnormal MA greater than 1 mg/dL did not occur until the urine was grossly pink.[171] In experimental dogs, UPC was less than 2.0 even on days 1 to 2 after cystotomy.[172] In dogs with induced bacterial cystitis, UPC ranged from 1.5 to 40.8 but did not correlate with sediment findings.[172] In dogs with spontaneous pyuria, 67% had normal MA and 81% had normal UPC; abnormal MA (but not UPC) was more often seen if pyuria was accompanied by hematuria and bacteriuria.[171]

Cushing's disease,[173–175] exogenous steroids[75,176,177] and hypertension[178] are associated with increased proteinuria. Glomerular damage (glomerulosclerosis) may eventually occur if exposure is severe or prolonged, but the proteinuria is usually mild (UPC <2) and generally not accompanied by hypoalbuminemia. Blood pressure measurements and MA or UPC should be monitored when giving steroids or phenylpropanolamine. Dogs with diabetes mellitus[175,179] may also have proteinuria but these are often accompanied by Cushing's disease and/or hypertension.

Once pre- and postrenal causes for proteinuria are ruled out, renal proteinuria can be further differentiated (glomerular and/or tubular) with the help of sodium dodecyl sulfate-agarose gel electrophoresis (SDS-PAGE) methodology applied to urine samples. High molecular weight proteins (such as albumin at 69,000 Da) indicate glomerular leakage, whereas lower molecular weight proteins are found in urine when tubular cells are not working properly.[17,144,180]

CLINICAL PRESENTATIONS OF PLN: DIAGNOSTIC CLUES

History, physical examination, laboratory tests, imaging, and renal cortical biopsy are used to identify pathologic glomerular proteinuria, search for underlying causes, stage PLN, and classify the subtype of PLN to select specific, supportive, and symptomatic treatments (**Box 1**). The clinicopathologic signs of PLN are initially different from those of whole nephron or primary tubular (interstitial nephritis) causes of renal failure. The mean age at presentation is 5 to 8 years with no sex or slight male predominance.[86,94] Classic signs include proteinuria, hypoalbuminemia and hypercholesterolemia.[1,3,84,105,110–112,116]

The author proposes the following 4 stages of PLN progression.

Stage 1

Persistent glomerular proteinuria (microalbuminuria progressing to macroalbuminuria) begins without other renal signs, but there may be signs from an underlying infectious, inflammatory, immune-mediated, neoplastic, endocrine, or hypertensive disease. For instance, fever, polyarthropathy, vasculitis, uveitis, cytopenias (commonly thrombocytopenia), and/or allergies/hypersensitivities suggest an infectious or immune-mediated cause. Diagnostic clues to identify causes and complications of PLN in the author's geographic area are given in **Box 1**. Because many healthy dogs are Lyme seropositive, finding Lyme seropositivity is not necessarily diagnostic for Lyme nephropathy and a thorough work-up is recommended lest a coinfection go unrecognized (eg, with babesiosis).[125] Depending on geographic area and travel history, tests for additional agents that affect the kidney via vasculitis, immune-mediated mechanisms, or renal invasion may be warranted.[181]

Stage 2

UPC is persistently increased causing serum albumin level to drop. Serum cholesterol level increases as a result of urinary loss of lecithin-cholesterol acyltransferase.

Box 1
Clues to find causes and complications for a dog with PLN in a Lyme-endemic area; treatment ideas

History should include

- Signalment, pedigree, family history, coat or color type (eg, coloring for Labradors: black, yellow, chocolate)
- Travel history, tick exposure
- History of prior treatment of tick-borne disease such as Lyme disease
- Medication exposure (sulfa, masitinib), vaccination exposure
- Polyuria/polydypsia? Vomiting? Appetite? Weight loss?
- History of lower urinary tract signs (pollakiuria, stranguria, accidents)
- History of lameness, dyspnea, blindness, effusions/edema, neurologic events
- History of allergies, inflammatory bowel disease, PLE, Addison disease (SCWT)

Physical examination should include

- Body weight, body condition score, hydration status
- Temperature, femoral pulses, respiration
- Mucous membranes: check for anemia, petechiation
- Ophthalmologic examination including fundic examination
- Peripheral edema? Ascites?
- Ausculation for murmur, dyspnea, muffling
- Lymphadenopathy?
- Abdominal palpation, organomegaly?
- Neurologic examination
- If lameness: joint swelling/effusion? Which joints? Pulses?
- Blood pressure measurements (multiple)

Clinical pathology, microbiology, parasitology, immunology samples

- Blood samples for
  - Complete blood count (CBC)
  - Biochemical profile
  - Coagulation profile, thromboelastography
  - Blood cultures if indicated
  - SNAP-4Dx (IDEXX) for heartworm antigen and antibodies against *Borrelia burgdorferi* (C6 quantitation if positive), *Ehrlichia canis/chaffeensis*, *Anaplasma phagocytophilum/platys*; do additional SNAP test (convalescent) 2 weeks into the illness if the history is acute; get quantitative titers if positive (0 and 6 months after treatment)
  - *Ehrlichia* PCR to check for *Ehrlichia ewingii* antigen, if indicated
  - *Bartonella* Western blot, culture/PCR, titers
  - *Babesia* spp PCR (for novel spp), titers (*B canis*, *B gibsoni*, *B microti*); get additional titers (convalescent) 2 weeks into the illness if the history is acute
  - Rocky Mountain spotted fever acute/convalescent titers (if the history is acute; RMSF does not cause a carrier status)

- *Leptospira titers* (get additional titer [convalescent] 2 weeks into the illness if the history is acute)
- *Brucella, Leishmania, Trypanosoma* tests, and so forth as indicated
- Coombs, antinuclear antibody titer, rheumatoid factor, perinuclear antineutrophil cytoplasmic antibody, and so forth as indicated.
- Save additional EDTA whole blood for future PCR testing and for DNA banking or DNA test, if available
- Consider samples for antithrombin III, C3, CIC levels, and so forth

Urine samples for

- Urinalysis
- Urine culture
- Urine protein/creatinine ratio (UPC)
- Urine SDS-PAGE

Cytology of

- Joint fluid cytology/culture
- Lymph node aspirate
- Bone marrow aspirate
- Effusions

Imaging studies

- Chest radiographs
- Abdominal ultrasound
- Echocardiogram if indicated
- Radiographs of joints if lameness present

Renal cortical biopsy for TEM, IF, and thin-section LM (via percutaneous ultrasound-guided Tru-cut needle)

- Control hypertension if present; discontinue antithrombotics 3–7 days before biopsy
- Contact Dr George Lees (email glees@cvm.tamu.edu, tel. 979-845-2351, fax 979-845-6978) at the Texas Veterinary Renal Pathology Service before planning sample collection to get the renal biopsy kit with its special fixatives, tools, and shipment label (if you already have a kit, check that the fixatives are still in date), packing and return shipping instructions, and to coordinate the best date for the procedure to be done because the samples must be received on ice by overnight shipment. Dr George Lees, Building 508, Room 120, Veterinary Teaching Hospital, Texas A&M University, College Station, TX 77843
- Consider saving a frozen kidney sample for future elution studies

Therapeutic considerations

Standard therapy

- Doxycycline 10 mg/kg/d, pending infectious disease results (1 month; longer for Lyme nephritis)
- Angiotensin-converting enzyme (ACE) inhibition: enalapril (Enacard) 0.5–1.0 mg/kg every 12 to 24 hours, or benazepril (Lotensin) 0.25–0.5 mg/kg every 12 to 24 hours
- Low antithrombotic dose of aspirin if albumin $\leq$2.5 g/dL, 1.0 mg/kg every 24 hours
- Omega-3 fatty acid supplement
- Antihypertensives are added to ACE inhibitor if dog is still hypertensive (eg, amlodipine [Norvasc] 0.2–0.4 mg/kg every 12 hours)

Other therapies for renal disease (eg, dietary modification, phosphate binder, gastroprotectant, antiemetic, and so forth)

Immunosuppressive therapy

If biopsy results (TEM, IF, thin-section LM) show compelling evidence of active immune complex deposition and inflammation, then immunosuppressive medications should be considered

As a rule-of-thumb, if <50% of the glomeruli are open and/or >50% show glomerular obsolescence, and if the tubulointerstitial lesion is characterized by diffuse fibrotic changes (as opposed to cellular inflammatory changes), immunosuppressive protocols may be ineffective and possibly contraindicated

If the patient is decompensating rapidly, consider starting a protocol while renal biopsy results are pending

There are no blinded treatment studies; the following protocols are offered anecdotally depending on owner considerations, patient tolerance, and so forth. Continue to monitor blood pressure, UPC, CBC, chemistry panel, and so forth. every 1–4 weeks, depending on the severity/stability of clinical signs, and continue to look for an underlying cause that may present itself with time or as a result of immunosuppression

Protocol 1: Methylprednisolone sodium succinate (Solu-Medrol) 5 mg/kg intravenously every 24 hours × 2 days; cyclophosphamide (Cytoxan) 200 mg/m^2 intravenous bolus first day. Check white blood cells in 1 week; cyclophosphamide is repeated every 2 weeks for a maximum of 6 cycles; Solu-Medrol is only used when the first cycle of cyclophosphamide is given

Protocol 2 (barring financial constraints): Methylprednisolone sodium succinate as protocol 1; mycophenolate mofetil (CellCept) 10 mg/kg intravenously or by mouth every 12 hours long-term

Protocol 3: Methylprednisolone sodium succinate as protocols 1 and 2; azathioprine (Imuran) 2 mg/kg by mouth every 24 hours × 7 days, then every 48 hours long-term

With thanks, **Box 1** is derived from discussions with Drs Nicola Mason, Reid Groman, and Tabitha Hutton at the University of Pennsylvania School of Veterinary Medicine.

The dyslipidemia occurring with hypoalbuminemia also includes increased hepatic activity of several enzymes leading to decreased high-density lipoprotein and increased low-density lipoprotein and triglycerides.[182] Serious events caused by complications of PLN can occur before azotemia or polyuria/polydipsia exist and are more common in Stage 2 than Stage 1 PLN (eg, hypertension, thromboembolic events, and/or nephrotic syndrome with ascites/edema).

Causes of hypertension are multifactorial and include activation of the RAA system, abnormal salt and water handling, decreased renal production of vasodilatory prostaglandins and kinins, and increased arteriolar sensitivity to circulating vasoconstrictors.[183] Hypertensive target organ damage may be the reason for presentation to the veterinarian. Damage includes blindness caused by retinal hemorrhage/detachment, cardiovascular disease (left ventricular hypertrophy, epistaxis, arteriosclerosis/atherosclerosis), neurologic abnormalities (cerebrovascular accidents or stroke), and renal changes (glomerulosclerosis, proteinuria, pressure diuresis). Self-perpetuation of hypertension is caused by glomerulosclerosis and increased total peripheral resistance as a result of vascular damage (arteriosclerosis/atherosclerosis). Risk for hypertensive target organ damage increases as blood pressure increases; severe risk is seen at blood pressure measurements (BPM) greater than or equal to 180/120 mm Hg, moderate risk at 160 to 179/100 to 119 mmHg, mild risk at 150 to 159/95 to 99 mm Hg, and minimal risk at less than 150/95 mm Hg.[183] Roughly 60%

to 90% of dogs and cats with renal disease are hypertensive and it is associated with poor outcome.[5,183,184]

The risk for thromboembolic events in patients with PLN is well recognized.[1,3,84,116] Mechanisms causing hypercoagulability in patients with PLN include urinary loss of antithrombin (AT, which has similar size and charge as albumin) and platelet hypersensitivity as a result of hypoalbuminemia.[185–188] Spontaneous vascular damage caused by hypertension or vasculitis and iatrogenic damage caused by venipuncture and catheter placement may initiate thrombus formation. Both arterial and venous thromboembolic (TE) events have been associated with PLN. Life-threatening TE events may affect the heart, central nervous system, lung, aortic bifurcation (saddle thrombus), portal/mesenteric/splenic veins, and so forth, causing dyspnea, lameness, abdominal distress, collapse, or sudden death. One report found 22% of dogs with PLN had TE events.[116] In SCWT, 10/84 dogs (12%) with PLN and 11/62 dogs (18%) with combined PLE/PLN were believed to have TE events.[84]

The drop in plasma colloid oncotic pressure caused by hypoalbuminemia allows vascular fluid to be lost to the interstitium (as a result of Starling forces), perhaps leading to peripheral edema and signs of third spacing (dyspnea from pleural effusion; ascites from abdominal effusion; tamponade from pericardial effusion). Arterial hypertension and/or vasculitis from associated infectious, inflammatory, or immune-mediated disease may increase the risk for edema/effusions. Nephrotic syndrome (proteinuria, hypoalbuminemia, hypercholesterolemia, and edema/effusions)[1,3,105,112] may be seen in cases of Stage 2 PLN, and although dramatic, has not been associated with decreased survival compared with cases of non-nephrotic canine PLN.[189] In SCWT, 9/67 dogs (13%) with PLN and 23/58 (40%) of dogs with PLE/PLN had effusions.[84]

Stage 3

Risks continue as in Stage 2, but now azotemia begins. As a result of glomerulotubular imbalance, there may be little or no concentrating defect and therefore no perceived polyuria/polydipsia (PU/PD). In SCWT dogs with PLN (or PLE/PLN), average biochemical findings were serum creatinine = 5.4 ± 4.1 mg/dL (4.6 ± 3.3), BUN = 95 ± 73 mg/dL (86 ± 61), albumin = 2.2 ± 0.4 g/dL (1.8 ± 0.4), cholesterol = 399 ± 126 mg/dL (311 ± 128), phosphorus = 8.9 ± 6.3 mg/dL (8.4 ± 4.6), UPC = 5.3 ± 3.1 (7.1 ± 4.7), and the average USG was 1.023 ±.011 (1.022 ± 0.012).[84] The UPC may decrease with increasing azotemia, but this is not necessarily a good sign, because there are fewer working nephrons leaking protein.

Stage 4

ESRD now includes isosthenuria and PU/PD, vomiting, weight loss, and other signs of chronic renal failure, or in some acute cases (eg, Lyme nephritis), possibly oliguria/anuria. The UPC may drop further because of fewer working nephrons. Serum albumin may normalize or hypoalbuminemia may be masked by dehydration. There may be glycosuria and/or renal tubular acidosis as a result of tubular damage and decreased reabsorption of glucose and bicarbonate from the glomerular filtrate.

RENAL CORTICAL BIOPSY

To characterize the type of glomerular damage causing PLN, it is recommended to take renal cortical samples early in the process, before fibrosis or end-stage changes obscure the original lesion. By TEM examination, glomerular basement membrane ultrastructural (hereditary) defects can be seen and not misdiagnosed as acquired

MN or MPGN. With TEM, immune complex deposits can be seen and localized as subendothelial versus subepithelial versus mesangial. With IF and special stains, complexes can be associated with C3 or immunoglobulin subtypes IgA, IgG, and/or IgM. Without knowing what types of subsets are being treated, which protocols work for which disease cannot be studied. Perhaps various subtypes of glomerular disease can be associated with specific prognoses and response to treatments; for example, IMGN and MCD may respond to steroids and/or immunosuppressives, whereas hereditary nephritis and FSGS may not. In human adults, although complete and partial remissions were seen with advocated alternate-day steroid/alkylating agents, a Cochrane systematic review of 18 randomized trials with 1025 patients showed no long-term benefit for the use of immunosuppressives for idiopathic MN[190] but found that immunosuppressives (especially steroids) helped decrease progression to renal failure in 13 studies with 623 people with IgA nephropathy.[191] Such information is not yet available in veterinary medicine. Only 1 controlled study (with cyclosporine) has been done, and the statistics were unable to show a response in dogs with PLN to cyclosporine probably because subtypes were not differentiated adequately or in high enough numbers.[9] Pathologists often disagree about light microscopic evaluations, especially when sections are cut too thickly as they are for other routine histopathology. For breeds with inherited forms of PLN, characterization of phenotype subtype is important to decrease the risk that sporadic (nongenetic) PLN cases are admixed into genome-wide association studies. The challenge for progress in veterinary medicine demands that comprehensive diagnostic testing is done to fully characterize and classify PLN subtypes, and to validate or negate the use of specific treatment protocols for specific entities.[192]

The when, why, and how of procuring renal cortical biopsies are described in detail elsewhere.[193–199] The procedure involves planning several days beforehand. Hypertension should be controlled and antithrombotics should be stopped at least a few days, preferably a week, before to avoid hemorrhage. Contact the Texas Veterinary Renal Pathology Service (glees@cvm.tamu.edu, tel 979-845-2351, fax 979-845-6978) to receive instructions and special materials (see **Box 1**). With anesthesia and ultrasound guidance, 2 to 4 Tru-cut renal cortical biopsies are taken percutaneously, checked by magnification for evidence of glomeruli, and prepared properly for TEM (1-mm cubes in chilled 3% glutaraldehyde), IF (1-mm cubes in chilled Michel transport medium), and for thin-section LM (longer core in 10% formalin). As more information is obtained and shared, more will be learned about PLN subtypes and their response to various treatment protocols. Until then, results will help us make logical choices based on what is known in other species.

MANAGEMENT OF PLN

Specific therapy may include antibiotics for bacterial or rickettsial infections, antiprotozoals for babesiosis, treatment of heartworm infection, chemotherapy or debulking for neoplasia, and so forth (if the underlying cause of PLN is known), and avoidance of possible trigger antigens (eg, sulfa in Dobes, food allergies in SCWT) (see **Box 1**). In our area, doxycycline 10 mg/kg/d is often given for 1 month even without firm cause; Lyme-positive dogs may be given doxycycline much longer (because only 85%–90% are cleared in 1 month).

Nonspecific but standard of care for all patients with PLN includes use of an ACE inhibitor to decrease proteinuria[77,200–204] and a low antithrombotic dose of aspirin[205–207] to help lower the risk of serious TE events and perhaps decrease inflammation and progression to renal failure.

An ACE inhibitor such as enalapril (Enacard) or benazepril (Lotensin) decreases proteinuria by dilating both the efferent as well as afferent arterioles at the glomerulus, thereby lowering the glomerular filtration pressure. The ACE inhibitor therapy should be given to all cases of PLN, whether they are hypertensive or not. If the animal is also hypertensive, the ACE inhibitor may also help decrease the blood pressure a bit, but if needed, a calcium channel blocker (eg, amlodipine [Norvasc]) may be added to further lower BPM. When ACE inhibitors are used for cardiac patients, there is concern that increased azotemia may occur; this is because cardiac patients often have low cardiac output and poor renal perfusion, which can drop further with ACE inhibitor drugs. However, in cases of PLN, when cardiac output is normal and blood pressure is normal or often high, the use of ACE inhibitors is actually renoprotective, and even higher doses of ACE inhibitors can be used without impairing GFR. Another past question was whether to avoid enalapril in cases of azotemic PLN because it is cleared by the kidney, and whether to use benazepril instead which is cleared by the liver. There seems to be no clinical advantage; having an increased blood level and activity of enalapril may be a good thing for these cases. Other drugs that might be added if proteinuria is not responding include angiotensin II receptor blockers (ARB) such as losartan (Cozaar) or telmisartan (Micardis), an aldosterone receptor antagonist such as spironolactone (Aldactone), or a renin inhibitor such as aliskiren (Tekturna).[204] Although these inhibitors of the RAA system may help the kidney by decreasing proteinuria as well as by decreasing inflammation and fibrosis,[3,204] they may increase the serum potassium level, which in 50% of renal cases may already be increased when eating renal diets. If potassium levels do not lower after changing to another renal diet formulation then a home-prepared reduced-potassium diet may be useful, especially for patients needing these drugs.[205]

An antithrombotic dose of aspirin is important for all animals with hypoalbuminemia because of the risk for thromboembolism. Aspirin decreases production of thromboxane A2, which not only helps inhibit platelet aggregation to decrease the risk of thromboembolism[206–208] but because platelet activation is part of the inflammatory process that increases renal damage, aspirin may help decrease proteinuria and fibrosis, as did a thromboxane synthase inhibitor in studies of heartworm-induced PLN.[209–211] The lowest dose for inhibition of platelet function in dogs seems to be 1.0 mg/kg/d.[207,208] The recommended dose for cats is 5 mg per cat every 72 hours.[212] Other TE preventive drugs to be studied include clopidogrel (Plavix) and the anticoagulant warfarin (Coumadin). Heparin (fractionated or unfractionated) is less useful in patients with PLN because heparin works by binding to AT, which is low in cases of PLN because of urinary loss. Thrombolytics that have been used when TE events occur include streptokinase (Streptase)[213] and tissue plasminogen activator.[214]

Samoyed dogs with X-linked hereditary PLN lived 53% longer when fed a diet restricted in protein, lipid, calcium, and phosphorus.[78] Sodium restriction is recommended because dogs with PLN are at risk for hypertension and may be salt sensitive.[3] Omega-3 fatty acids are antiinflammatory and were found to be renoprotective, decreasing the progression of renal failure.[215] Anecdotally, the immunomodulating Chinese herb *Astragalus membranaceus* (*Astragalus propinquus* or huang qi) helped 2 people with idiopathic MN and nephrotic syndrome achieve complete remission, after little or no response for years trying more standard treatments (ACE inhibitors, ARB, spironolactone, aliskiren, prednisone, cyclosporine, mycophenolate).[216,217] In 1 patient, nephrosis returned on stopping the herb, and complete remission was achieved again on its reintroduction.[216] She took the herb for 1 year and has remained in remission for 4 years. This herb warrants further investigation.

Especially before and during intravenous therapy and anesthesia to get renal cortical biopsy samples, an animal with low colloid osmotic pressure may require crystalloid therapy for dehydration and also colloid therapy, such as hydroxyethyl starch (Hetastarch), to decrease risk of edema/effusions. Other therapies for renal disease (phosphate binder, gastroprotectant, antiemetic, appetite stimulant, and so forth) are used as needed (see articles by Linda Ross; and David J. Polzin elsewhere in this issue for further exploration of this topic). Recently the use of sodium bicarbonate was shown to slow progression of hypertensive nephropathy, even if the patient was not acidotic.[218] Studies in veterinary medicine need to be done.

Perhaps the most controversial topic is whether (and when) to use immunosuppressive therapy for dogs and cats with PLN. There are no controlled studies that show benefit; there is only 1 randomized study done in canine field cases (and none in cats) that actually showed decreased survival in the cyclosporine-treated group (11 months) compared with placebo (16 months).[9] However, side effects, small numbers, and incomplete subtyping of phenotypes may have played a role, so perhaps cyclosporine could be of benefit in some cases. The immunosuppressants cyclosporine (Neoral, Sandimmune, Atopica) and tacrolimus (FK506 or Prograf) are calcineurin inhibitors that inhibit T-lymphocyte signal transduction and the transcription of IL-2 and related cytokines. Cyclosporine slowed disease progression in hereditary X-linked PLN in Samoyeds.[76] This is possible because in addition to its immunosuppressive properties, calcineurin inhibitors act to stabilize the actin cytoskeleton of the podocyte via synaptopodin and TRPC6 regulation.[10,11] Other drugs used for nephrotic syndrome may also have actions at the podocyte level (eg, corticoids, ACE inhibitors, COX2 inhibitors, and mizoribine).[10] A case report did show benefit of use of mycophenolate (CellCept) in a dog with IMGN.[219] Mycophenolate, a product of the fungus *Penicillium*, is an immunosuppressant (not a calcineurin inhibitor) that acts by reducing guanine nucleotides in lymphocytes, thereby inhibiting DNA synthesis and guanosine triphosphate-dependent metabolism.

The most commonly used immunosuppressant/antiinflammatory combinations in veterinary medicine are corticosteroids, which suppress T- and B-cell proliferation, cell-mediated/humoral immunity, inflammatory mediator/cytokine production, phagocytosis, respiratory burst, and neutrophil/macrophage emigration and function. Steroids are beneficial for human patients with IgA nephropathy,[191] MCD,[1] and children with MPGN,[220,221] however, solid evidence is lacking for the use of steroids for adults with MN.[190] If renal biopsy shows active inflammation and immune-mediated disease, steroids may have a role in veterinary patients with PLN. However, the blind use of steroids for PLN cannot be recommended, because steroids increase proteinuria,[75,173–177] and increase the risk for TE events, hypertension, glomerulosclerosis, and gastric ulceration, all of which may already exist in the patient with PLN. Controlled studies of steroid use in patients with known subtypes of PLN need to be done.

Immunosuppressive alkylating agents such as cyclophosphamide (Cytoxan) and chlorambucil (Leukeran) are used for humans with IgA nephropathy[191] and pulse therapy with steroids for MPGN,[221] lupus, and MN.[1] Alkylating agents interfere with DNA/RNA replication/transcription. They decrease white blood cells and antibody production, but the exact mechanisms are still unclear.

Other immunosuppressive medications such as azathioprine (Imuran, a purine antagonist), sirolimus (Rapamune), methotrexate (MTX), interferon, tumor necrosis factor α antibodies such as inflixamab (Remicade) or etanercept (Enbrel), IV-IgG, and monoclonal antibodies (eg, directed against IL-2) are not generally used for human patients with PLN and have not been studied in veterinary cases of PLN.

Apheresis or plasmapheresis has been advocated to remove antibodies, CIC, and circulating permeability factors that may cause PLN, for instance, in MCD.[222]

Although colchicine and DMSO may be suggested for treatment of amyloidosis, there are no veterinary studies to support their benefit.[155]

If dogs with PLN have renal transplants, they may need 1 or both kidneys removed to help lessen loss of proteins. They could have relapse disease in the transplanted kidney, or if they have an inherited SD defect, they may produce antibodies to the new antigens they are not tolerant to (eg, nephrin if they did not make nephrin before).[10] Patients with PLN having hemodialysis require higher doses of heparin because of their low antithrombin levels.

Monitoring of blood pressure, UPC, CBC, and biochemical parameters is important every 1 to 4 weeks, depending on the severity or stability of signs. With time, or because of immunosuppressive therapy, infectious/inflammatory/neoplastic diseases may reveal themselves and the clinician needs to be watchful for the underlying cause to be unmasked or for an additional diagnosis (eg, urinary tract infection) while on immunosuppressive therapy. If the dog has been treated for an infectious disease such as Lyme disease, C6 antibody quantitation at 6 months is done to compare with the previous baseline, and to get a new baseline for comparison in the future should the dog show lameness or recurrence of signs. If relapse or reinfection is suspected based on an increase in C6 Quant, then doxycycline may need to be repeated.

PREVENTION

As genetic predispositions are discovered for early or late-onset PLN, breeding questions will arise. DNA banking will be helpful along with classification of PLN subtypes, to find genetic marker tests by GWA studies and avoid breeding carriers with one another (for recessive traits). Even without knowing the mode of inheritance, early detection by frequent screening of dogs (by MA or UPC) before breeding is most important. In some cases DNA tests are already available (see **Table 1**). In SCWT dogs, annual screening tests are recommended whether bred or not, including at least MA and serum albumin, and if the owners can afford it, more thorough screening of CBC, Chemscreen, urinalysis, UPC, ± fecal alpha-1 protease inhibitor testing (for PLE). Starting ACE inhibitors early is recommended if the MA or UPC is found with an inactive urinary sediment. Tick control is advocated for all dogs that live or travel to areas with tick-borne diseases that can cause illness.

SUMMARY

Genetic and acquired defects of glomerular permselectivity allow for proteinuria and may lead to PLN. The clinicopathologic abnormalities (proteinuria, hypoalbuminemia, hypercholesterolemia) seen with this type of nephron dysfunction are initially different from those seen with whole nephron loss or primary tubular disease. Morbidity and mortality from complications of PLN may be severe even before progression to azotemia and renal failure occur, including thromboembolic events, nephrotic syndrome with edema/effusions, and hypertensive target organ damage. Leakage of plasma proteins into the glomerular filtrate can damage tubular cells and eventually affect the function of the entire nephron. Detection, localization, and treatment of proteinuria are important to decrease the clinical signs and complications of PLN and to decrease the likelihood of progression to renal failure. Thorough diagnostic work-ups to characterize the underlying causes and to comprehensively describe glomerular lesions by transmission electron microscopy, immunofluorescence, and

thin-section light microscopy help to identify subsets of glomerular disease and study their response to specific treatment protocols.

REFERENCES

1. Vaden SL. Glomerular diseases. In: Ettinger SJ, Feldman EC, editors. Textbook of veterinary internal medicine. 7th edition. St. Louis (MO): Saunders (Elsevier); 2010. p. 2021–36.
2. Vaden SL, Brown CA. Glomerular disease. In: Bonagura JD, Twedt DC, editors. Kirk's current veterinary therapy XIV. St. Louis (MO): Saunders (Elsevier); 2009. p. 863–8.
3. Grauer GF. Glomerulonephropathies. In: Nelson RW, Couto CG, editors. Small animal internal medicine. 4th edition. St. Louis (MO): Mosby (Elsevier); 2009. p. 637–44.
4. Jacob F, Polzin DJ, Osborne CA, et al. Evaluation of the association between initial proteinuria and morbidity rate or death in dogs with naturally occurring chronic renal failure. J Am Vet Med Assoc 2005;226(3):393–400.
5. Wehner A, Hartmann K, Hirschberger J. Associations between proteinuria, systemic hypertension and glomerular filtration rate in dogs with renal and non-renal diseases. Vet Rec 2008;162(5):141–7.
6. Syme HM, Markwell PJ, Pfeiffer D, et al. Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. J Vet Intern Med 2006; 29(3):528–35.
7. Lees GE, Brown SA, Elliott J, et al. Assessment and management of proteinuria in dogs and cats: 2004 ACVIM Forum Consensus Statement (Small Animal). J Vet Intern Med 2005;19(3):377–85.
8. Heska Corporation data. Prevalence of microalbumuminuria in veterinary clinic staff-owned dogs, 2003. Available at: http://www.heska.com/Documents/RenalHealthScreen/erd_data.aspx; Prevalence of microalbuminuria in cats, 2003. Available at: http://www.heska.com/Documents/RenalHealthScreen/erd_datacat.aspx. Accessed July 24, 2010.
9. Vaden SL, Breitschwerdt EB, Armstrong PJ, et al. The effects of cyclosporine versus standard care in dogs with naturally occurring glomerulonephritis. J Vet Intern Med 1995;9(4):259–66.
10. Lowik MM, Groenen PJ, Levtchenko EN, et al. Molecular genetic analysis of podocyte genes in focal segmental glomerulosclerosis – a review. Eur J Pediatr 2009;168(11):1291–304.
11. Zenker M, Machuca E, Antignac C. Genetics of nephrotic syndrome: new insights into molecules acting at the glomerular filtration barrier. J Mol Med 2009;87(9):849–57.
12. Russo LM, Bakris GL, Comper WD, et al. Renal handling of albumin: a critical review of basic concepts and perspective. Am J Kidney Dis 2002;39(5):899–919.
13. Schoeb DS, Chernin G, Heeringa SF, et al. Nineteen novel NPHS1 mutations in a worldwide cohort of patients with congenital nephrotic syndrome (CNS). Nephrol Dial Transplant 2010;25(9):2970–6.
14. Caridi G, Trivelli A, Sanna-Cherchi S, et al. Familial forms of nephrotic syndrome. Pediatr Nephrol 2010;25(2):241–52.
15. Santin S, Garcia-Maset R, Ruiz P, et al. Nephrin mutations cause childhood- and adult-onset focal segmental glomerulosclerosis. Kidney Int 2009;76(12):1268–76.
16. Gaskin AA, Schantz P, Jackson J, et al. Visceral leishmaniasis in a New York foxhound kennel. J Vet Intern Med 2002;16(1):34–44.

17. Zatelli A, Borgarelli M, Santilli R, et al. Glomerular lesions in dogs infected with *Leishmania* organisms. Am J Vet Res 2003;64(5):558–61.
18. Poli A, Abramo F, Mancianti F, et al. Renal involvement in canine leishmaniasis. A light microscopic, immunohistochemical and electron-microscopy study. Nephron 1991;57(4):444–52.
19. Costa FAL, Goto H, Saldanha LCB, et al. Histopathologic patterns of nephropathy in naturally acquired canine visceral leishmaniasis. Vet Pathol 2003; 49(6):677–84.
20. Breitschwerdt EB. Immunoproliferative enteropathy of Basenjis. Semin Vet Med Surg (Small Anim) 1992;7(2):153–61.
21. Bartges JW. Gee – It's GN: proteinuria. In: Proceedings of the Atlantic Coast Veterinary Conference. Available at: http://www.vin.com/Members/Proceedings/Proceedings.plx?CID=ACVC2006&PID=pr14336&Print=1&O=VIN. Accessed July 14, 2010.
22. Rha JY, Labato MA, Ross LA, et al. Familial glomerulonephropathy in a litter of beagles. J Am Vet Med Assoc 2000;216(1):46–50.
23. Bowles MH, Mosier DA. Renal amyloidosis in a family of beagles. J Am Vet Med Assoc 1992;201(4):569–74.
24. Reusch C, Hoerauf A, Lechner J, et al. A new familial glomerulonephropathy in Bernese mountain dogs. Vet Rec 1994;134(16):411–5.
25. Minkus G, Breuer W, Wanke R, et al. Familial nephropathy in Bernese Mountain Dogs. Vet Pathol 1994;31(4):421–8.
26. Gerber B, Eichenberger S, Haug K, et al. Association of urine protein excretion and infection with *Borrelia burgdorferi* sensu lato in Bernese Mountain dogs. Vet J 2009;182(3):487–8.
27. Gerber B, Haug K, Eichenberger S, et al. Follow up of Bernese Mountain dogs and other dogs with serologically diagnosed *Borrelia burgdorferi* infection: what happens to seropositive animals? BMC Vet Res 2009;5:18.
28. Chandler ML, Elwood C, Murphy KF, et al. Juvenile nephropathy in 37 boxer dogs. J Small Anim Pract 2007;48(12):690–4.
29. Cork LC, Morris JM, Olson JL, et al. Membranoproliferative glomerulonephritis in dogs with a genetically determined deficiency of the third component of complement. Clin Immunol Immunopathol 1991;60(3):455–70.
30. Hood JC, Savige J, Hendtlass A, et al. Bull terrier hereditary nephritis: a model for autosomal dominant Alport syndrome. Kidney Int 1995;47:758–65.
31. Hood JC, Robinson WF, Clark WF, et al. Proteinuria as an indicator of early renal disease in bull terriers with hereditary nephritis. J Small Anim Pract 1991;32(5): 241–8.
32. Hood JC, Savige JA, Dowling J, et al. Ultrastructural appearance of renal and other basement membranes in the bull terrier model of autosomal dominant hereditary nephritis. Am J Kidney Dis 2000;36(2):378–91.
33. Hood JC, Dawling J, Bertram JF, et al. Correlation of histopathological features and renal impairment in autosomal dominant Alport syndrome in Bull terriers. Nephrol Dial Transplant 2002;17(11):1897–908.
34. Burrows AK, Malik R, Hunt GB, et al. Familial polycystic kidney disease in bull terriers. J Small Anim Pract 1994;35(7):364–9.
35. O'Leary CA, MacKay BM, Malik R, et al. Polycystic kidney disease in Bull Terriers: an autosomal dominant inherited disorder. Aust Vet J 1999;77(6): 361–6.
36. Casal ML, Dambach DM, Meister T, et al. Familial glomerulonephropathy in the Bullmastiff. Vet Pathol 2004;41(4):319–25.

37. Hood JC, Huxtable C, Naito I, et al. A novel model of autosomal dominant Alport syndrome in Dalmatian dogs. Nephrol Dial Transplant 2002;17(12):2094–8.
38. Wilcock BP, Patterson JM. Familial glomerulonephritis in Doberman Pinscher dogs. Can Vet J 1979;20(9):244–9.
39. Picut CA, Lewis RM. Juvenile renal disease in the Doberman pinscher: ultrastructural changes of the glomerular basement membrane. J Comp Pathol 1987;97(5):587–96.
40. Giger U, Werner LL, Millichamp NJ, et al. Sulfadiazine-induced allergy in six Doberman Pinschers. J Am Vet Med Assoc 1985;186(5):479–84.
41. Vasilopulos RJ, Mackin A, Lavergne SN, et al. Nephrotic syndrome associated with administration of sulfadimethoxine/ormetoprim in a dobermann. J Small Anim Pract 2005;46(5):232–6.
42. Trepanier LA. Idiosyncratic toxicity associated with potentiated sulfonamides in the dog. J Vet Pharmacol Ther 2004;27(3):129–38.
43. Lees GE, Wilson PD, Helman RG, et al. Glomerular ultrastructural findings similar to hereditary nephritis in four English cocker spaniels. J Vet Intern Med 1997;11(2):80–5.
44. Lees GE, Helman RG, Homco LD, et al. Early diagnosis of familial nephropathy in English cocker spaniels. J Am Anim Hosp Assoc 1998;34(3):189–95.
45. Lees GE, Helman RG, Kashtan CE, et al. A model of autosomal recessive Alport syndrome in English cocker spaniel dogs. Kidney Int 1998;54(3):706–19.
46. Davidson AG, Bell RJ, Lees GE, et al. Genetic cause of autosomal recessive hereditary nephropathy in the English cocker spaniel. J Vet Intern Med 2007; 21(3):394–401.
47. Mason NJ, Day MJ. Renal amyloidosis in related English foxhounds. J Small Anim Pract 1996;37(6):255–60.
48. Lavoue R, van der Lugt JJ, Day MJ, et al. Progressive juvenile glomerulonephropathy in 16 related French Mastiff (Bordeaux) dogs. J Vet Intern Med 2010; 24(2):314–22.
49. Codner EC, Caceci T, Saunders GK, et al. Investigation of glomerular lesions in dogs with acute experimentally induced *Ehrlichia canis* infection. Am J Vet Res 1992;53(12):2286–91.
50. Codner EC, Maslim WR. Investigation of renal protein loss in dogs with acute experimentally induced *Ehrlichia canis* infection. Am J Vet Res 1992; 53(3):294–9.
51. Nyindo M, Huxsoll DL, Ristic M, et al. Cell-mediated and humoral immune responses of German shepherd dogs and beagles to experimental infection with *Ehrlichia canis*. Am J Vet Res 1980;41(2):250–4.
52. de Castro MB, Machado RZ, de Aquino LP, et al. Experimental acute canine monocytic ehrlichiosis: clinicopathological and immunopathological findings. Vet Parasitol 2004;119(1):73–86.
53. Dambach DM, Smith CA, Lewis RM, et al. Morphologic, immunohistochemical, and ultrastructural characteristics of a distinctive renal lesion in dogs putatively associated with *Borrelia burgdorferi* infection: 49 cases (1987–1992). Vet Pathol 1997;34(2):85–96.
54. Littman MP, Goldstein RE, Labato MA, et al. ACVIM small animal consensus statement on Lyme disease in dogs: diagnosis, treatment, and prevention. J Vet Intern Med 2006;20(2):422–34.
55. Chou J, Wunschmann A, Hodzic E, et al. Detection of *Borrelia burdorferi* DNA in tissues from dogs with presumptive Lyme borreliosis. J Am Vet Med Assoc 2006;229(8):1260–5.

56. Sanders NA. Canine Lyme nephritis. In: Proceedings of the 18th ACVIM Forum. Seattle (WA), May 25–28, 2000. p. 627–8.
57. Goldstein RE, Cordner AP, Sandler JL, et al. Microalbuminuria and comparison of serologic testing for exposure to *Borrelia burgdorferi* in nonclinical Labrador and Golden Retrievers. J Vet Diagn Invest 2007;19(3):294–7.
58. Kerlin RL, Van Winkle TJ. Renal dysplasia in golden retrievers. Vet Pathol 1995; 32(3):327–9.
59. de Morais HS, DiBartola SP, Chew DJ. Juvenile renal disease in golden retrievers: 12 cases (1984–1994). J Am Vet Med Assoc 1996;209(4):792–7.
60. Reilly CM, Munson L, Bell JS. Progressive juvenile nephropathy in Gordon Setters. Vet Pathol 2007;44(5):740.
61. Carpenter JL, Andelman NC, Moore FM, et al. Idiopathic cutaneous and renal glomerular vasculopathy of greyhounds. Vet Pathol 1988;25(6):401–7.
62. Hertzke DM, Cowan LA, Schoning P, et al. Glomerular ultrastructural lesions of idiopathic cutaneous and renal glomerular vasculopathy of greyhounds. Vet Pathol 1995;32(5):451–9.
63. Cowan LA, Hertzke DM, Fenwick BW, et al. Clinical and clinicopathologic abnormalities in greyhounds with cutaneous and renal glomerular vasculopathy: 18 cases (1992–1994). J Am Vet Med Assoc 1997;210(6):789–93.
64. Bjotvedt G, Hendricks GM, Brandon TA. Hemodynamic basis of renal arteriosclerosis in young greyhounds. Lab Anim Sci 1988;38(1):62–7.
65. Cox ML, Lees GE, Kashtan CE, et al. Genetic cause of X-linked Alport syndrome in a family of domestic dogs. Mamm Genome 2003;14(6):396–403.
66. Lees GE, Helman RG, Kashtan CE, et al. New form of X-linked dominant hereditary nephritis in dogs. Am J Vet Res 1999;60(3):373–83.
67. Koeman JP, Biewenga WJ, Gruys E. Proteinuria associated with glomerulosclerosis and glomerular collagen formation in three Newfoundland dog littermates. Vet Pathol 1994;31(2):188–93.
68. Finco DR. Familial renal disease in Norwegian elkhound dogs: physiologic and biochemical examinations. Am J Vet Res 1976;37(1):87–91.
69. Finco DR, Duncan JD, Crowell WA, et al. Familial renal disease in Norwegian elkhound dogs: morphologic examinations. Am J Vet Res 1977;38(7):941–7.
70. McKay LW, Seguin MA, Ritchey JW, et al. Juvenile nephropathy in two related Pembroke Welsh corgi puppies. J Small Anim Pract 2004;45(11):568–71.
71. Cook SM, Dean DF, Golden DL, et al. Renal failure attributable to atrophic glomerulopathy in four related rottweilers. J Am Vet Med Assoc 1993;202(1): 107–9.
72. Zheng K, Thorner PS, Marrano P, et al. Canine X chromosome-linked hereditary nephritis: a genetic model for human X-linked hereditary nephritis resulting from a single base mutation in the gene encoding the α5 chain of collagen type IV. Proc Natl Acad Sci U S A 1994;91(9):3989–93.
73. Jansen B, Valli VE, Thorner P, et al. Samoyed hereditary glomerulonephropathy: serial clinical and laboratory (urine, serum biochemistry and hematology) studies. Can J Vet Res 1987;51(3):387–93.
74. Lees GE, Jensen WA, Simpson DF, et al. Persistent albuminuria precedes onset of overt proteinuria in male dogs with X-linked hereditary nephropathy. J Vet Intern Med 2002;16(3):353.
75. Lees GE, Willard MD, Dziezyc J. Glomerular proteinuria is rapidly but reversibly increased by short-term prednisone administration in heterozygous (carrier) female dogs with X-linked hereditary nephropathy. J Vet Intern Med 2002; 16(3):352.

76. Chen D, Jefferson B, Harvey SJ, et al. Cyclosporine A slows the progressive renal disease of Alport syndrome (X-linked hereditary nephritis): results from a canine model. J Am Soc Nephrol 2003;14(3):690–8.
77. Grodecki KM, Gains MJ, Baumal R, et al. Treatment of X-linked hereditary nephritis in Samoyed dogs with angiotensin-converting enzyme (ACE) inhibitor. J Comp Pathol 1997;117(3):209–25.
78. Valli VE, Baumal R, Thorner P, et al. Dietary modification reduces splitting of glomerular basement membranes and delays death due to renal failure in canine X-linked hereditary nephritis. Lab Invest 1991;65(1):67–73.
79. DiBartola SP, Tarr MJ, Webb DM, et al. Familial renal amyloidosis in Chinese Shar Pei dogs. J Am Vet Med Assoc 1990;197(4):483–7.
80. May C, Hammill J, Bennett D. Chinese Shar Pei fever syndrome: a preliminary report. Vet Rec 1992;131(25–26):586–7.
81. Rivas AL, Tintle L, Kimball ES, et al. A canine febrile disorder associated with elevated interleukin-6. Clin Immunol Immunopathol 1992;64(1):36–45.
82. Rivas AL, Tintle L, Meyers-Wallen V, et al. Inheritance of renal amyloidosis in Chinese Shar Pei dogs. J Hered 1993;84(6):438–42.
83. Johnson KH, Sletten K, Hayden DW, et al. AA amyloidosis in Chinese Shar Pei dogs: immunohistochemical and amino acid sequence analysis. Int J Exp Clin Invest 1995;2(2):92–9.
84. Littman MP, Dambach DM, Vaden SL, et al. Familial protein-losing enteropathy and protein-losing nephropathy in soft-coated wheaten terriers: 222 cases (1983–1997). J Vet Intern Med 2000;14(1):68–80.
85. Vaden SL, Hammerberg B, Davenport DJ, et al. Food hypersensitivity reactions in soft-coated wheaten terriers with protein-losing enteropathy or protein-losing nephropathy or both: gastroscopic food sensitivity testing, dietary provocation, and fecal immunoglobulin E. J Vet Intern Med 2000;14(1):60–7.
86. Vaden SL, Sellon RK, Melgarejo LT, et al. Evaluation of intestinal permeability and gluten sensitivity in soft-coated wheaten terriers with familial protein-losing enteropathy, protein-losing nephropathy, or both. Am J Vet Res 2000;61(5): 518–24.
87. Afrouzian M, Vaden SL, Harris T, et al. Immune complex mediated proliferative and sclerosing glomerulonephritis in Soft Coated Wheaten Terriers (SCWT): is this an animal model of IgA nephropathy or IgM mesangial nephropathy? J Am Soc Nephrol 2001;12:670A.
88. Allenspach K, Lomas B, Wieland B, et al. Evaluation of perinuclear anti-neutrophilic cytoplasmic autoantibodies as an early marker of protein-losing enteropathy and protein-losing nephropathy in Soft Coated Wheaten Terriers. Am J Vet Res 2008;69(10):1301–4.
89. Vaden SL, Jensen W, Longhofer S, et al. Longitudinal study of microalbuminuria in soft-coated wheaten terriers. J Vet Intern Med 2001;15(3):300.
90. Nash AS, Kelly DF, Gaskell CJ. Progressive renal disease in soft-coated wheaten terriers: possible familial nephropathy. J Small Anim Pract 1984;25(8):479–87.
91. Eriksen K, Grondalen J. Familial renal disease in soft-coated wheaten terriers. J Small Anim Pract 1984;25(8):489–500.
92. Chew DJ, DiBartola SP, Boyce JT, et al. Renal amyloidosis in related Abyssinian cats. J Am Vet Med Assoc 1982;181(2):139–42.
93. DiBartola SP, Benson MD, Dwulet FE, et al. Isolation and characterization of amyloid protein AA in the Abyssinian cat. Lab Invest 1985;52(5):485–9.
94. DiBartola SP, Tarr MJ, Benson MD. Tissue distribution of amyloid deposits in Abyssinian cats with familial amyloidosis. J Comp Pathol 1986;96(4):387–98.

95. Boyce JT, DiBartola SP, Chew DJ, et al. Familial renal amyloidosis in Abyssinian cats. Vet Pathol 1984;21(1):33–8.
96. Niewold TA, van der Linde-Sipman JS, Murphy C, et al. Familial amyloidosis in cats: Siamese and Abyssinian AA proteins differ in primary sequence and pattern of deposition. Amyloid 1999;6(3):205–9.
97. Godfrey DR, Day MJ. Generalised amyloidosis in two Siamese cats: spontaneous liver haemorrhage and chronic renal failure. J Small Anim Pract 1998; 39(9):442–7.
98. Lees GE. Familial renal disease in dogs. In: Ettinger SJ, Feldman EC, editors. Textbook of veterinary internal medicine. 7th edition. St. Louis (MO): Saunders (Elsevier); 2010. p. 2058–62.
99. Pescucci C, Mari F, Longo I, et al. Autosomal-dominant Alport syndrome: natural history of a disease due to COL4A3 or COL4A4 gene. Kidney Int 2004;65(5): 1598–603.
100. Herrera GA, Turbat-Herrera EA. Renal diseases with organized deposits: an algorithmic approach to classification and clinicopathologic diagnosis. Arch Pathol Lab Med 2010;134(4):512–31.
101. Kamile J, Yasuno K, Ogihara K, et al. Collagenofibrotic glomerulonephropathy with fibronectin deposition in a dog. Vet Pathol 2009;46(4):688–92.
102. Kobayashi R, Yasuno K, Ogihara K, et al. Pathological characterization of collagenofibrotic glomerulonephropathy in a young dog. J Vet Med Sci 2009;71(8): 1137–41.
103. Cavana P, Capucchio MT, Bovero A, et al. Noncongophilic fibrillary glomerulonephritis in a cat. Vet Pathol 2008;45(3):347–51.
104. Brown PJ, Skuse AM, Tappin SW. Pulmonary haemorrhage and fibrillary glomerulonephritis (pulmonary-renal syndrome) in a dog. Vet Rec 2008;162(4):486–7.
105. Center SA, Smith CA, Wilkinson E, et al. Clinicopathologic, renal immunofluorescent, and light microscopic features of glomerulonephritis in the dog: 41 cases (1975–1985). J Am Vet Med Assoc 1987;190(1):81–90.
106. Macdougall DF, Cook T, Steward AP, et al. Canine chronic renal disease: prevalence and types of glomerulonephritis in the dog. Kidney Int 1986;29(6): 1144–51.
107. Muller-Peddinghaus R, Trautwein G. Spontaneous glomerulonephritis in dogs. I. Classification and immunopathology. Vet Pathol 1977;14(1):1–13.
108. Muller-Peddinghaus R, Trautwein G. Spontaneous glomerulonephritis in dogs. II. Correlation of glomerulonephritis with age, chronic interstitial nephritis and extrarenal lesions. Vet Pathol 1977;14(2):121–7.
109. Koeman JP, Biewenga WJ, Gruys E. Proteinuria in the dog: a pathomorphological study of 51 proteinuric dogs. Res Vet Sci 1987;43(3):367–78.
110. Vilafranca M, Wohlsein P, Trautwein G, et al. Histological and immunohistological classification of canine glomerular disease. Zentralbl Veterinarmed A 1994; 41(8):599–610.
111. Biewenga WJ, Gruys E. Proteinuria in the dog: a clinicopathological study in 51 proteinuric dogs. Res Vet Sci 1986;41(2):257–64.
112. Jaenke RS, Allen TA. Membranous nephropathy in the dog. Vet Pathol 1986; 23(6):718–33.
113. Nash AS, Wright NG, Spencer AJ, et al. Membranous nephropathy in the cat: a clinical and pathological study. Vet Rec 1979;105(4):71–7.
114. Wright NG, Nash AS, Thompson H, et al. Membranous nephropathy in the cat and dog: a renal biopsy and follow-up study of sixteen cases. Lab Invest 1981;45(3):269–77.

115. Grauer GF. Canine glomerulonephritis: new thoughts on proteinuria and treatment. J Small Anim Pract 2005;46(10):469–78.
116. Cook AK, Cowgill LD. Clinical and pathological features of protein-losing glomerular disease in the dog: a review of 137 cases (1985–1992). J Am Anim Hosp Assoc 1996;32(4):313–22.
117. Nangaku M, Couser WG. Mechanisms of immune-deposit formation and the mediation of immune renal injury. Clin Exp Nephrol 2005;9(3):183–91.
118. Asano T, Tsukamoto A, Ohno K, et al. Membranoproliferative glomerulonephritis in a young cat. J Vet Med Sci 2008;70(12):1373–5.
119. Breitschwerdt EB, Maggi RG, Chomel BB, et al. Bartonellosis: an emerging infectious disease of zoonotic importance to animals and human beings. J Vet Emerg Crit Care 2010;20(1):8–30.
120. Margolis G, Forbus WD, Kerby GP, et al. Glomerulonephritis occurring in experimental brucellosis in dogs. Am J Pathol 1947;23(6):983–93.
121. Granick JL, Armstrong PJ, Bender JB. *Anaplasma phagocytophilum* infection in dogs: 34 cases (2000–2007). J Am Vet Med Assoc 2009;234(12): 1559–65.
122. Pomianowski A, Lew S, Kuleta Z, et al. Peritoneal dialysis in a dog with acute renal failure caused by the infection with *Babesia canis*. Pol J Natur Sc 2008; 23(1):257–67.
123. Cavalcante LFH, Neuwald EB, Mello FP, et al. Nephrotic syndrome in dog associated *Babesia canis*. Acta Scientiae Veterinariae 2006;34(3):335–8.
124. Camacho AT, Guitian FJ, Pallas E, et al. Azotemia and mortality among *Babesia microti*-like infected dogs. J Vet Intern Med 2004;18(2):141–6.
125. Slade DJ, Lees GE, Berridge BR, et al. Resolution of a proteinuric nephropathy associated with *Babesia gibsoni* infection in a dog. J Am Anim Hosp Assoc, in press.
126. Kim HJ, Park C, Jung DI, et al. A case of protein losing nephropathy in a dog infected with canine *Babesia gibsoni*. Korean J Vet Res 2006;46(1):77–81.
127. Baneth G, Weigler B. Retrospective case-control study of hepatozoonosis in dogs in Israel. J Vet Intern Med 1997;11(6):365–70.
128. Macintire DK, Vincent-Johnson N, Dillon AR, et al. Hepatozoonosis in dogs: 22 cases (1989–1994). J Am Vet Med Assoc 1997;210(7):916–22.
129. Quigg RJ, Gaines R, Wakely PE Jr, et al. Acute glomerulonephritis in a patient with Rocky Mountain Spotted Fever. Am J Kidney Dis 1991;17(3):339–42.
130. Hervas J, Gomez-Villamandos JC, Perez J, et al. Focal mesangial-sclerosing glomerulonephritis and acute-spontaneous infectious canine hepatitis; structural, immunohistochemical and subcellular studies. Vet Immunol Immunopathol 1997;57(1/2):25–32.
131. Glick AD, Horn RG, Holscher M. Characterization of feline glomerulonephritis associated with viral-induced hematopoietic neoplasms. Am J Pathol 1978; 92(2):321–32.
132. Poli A, Abramo F, Taccini E, et al. Renal involvement in feline immunodeficiency virus infection: a clinicopathological study. Nephron 1993;64(2):282–8.
133. Baxter KJ, Levy JK, Edinboro CH, et al. Renal disease in cats infected with feline immunodeficiency virus. J Vet Intern Med 2010;24(3):677.
134. Avila A, Reche A Jr, Kogika MM, et al. Occurrence of chronic kidney disease in cats naturally infected with immunodeficiency virus. J Vet Intern Med 2010; 24(3):760.
135. Hayashi T, Ishida T, Fujiwara K. Glomerulonephritis associated with feline infectious peritonitis. Nippon Juigaku Zasshi 1982;44(6):909–16.

136. Grauer GF, Culham CA, Cooley AJ, et al. Clinicopathologic and histologic evaluation of *Dirofilaria immitis*-induced nephropathy in dogs. Am J Trop Med Hyg 1987;37(3):588–96.
137. Kramer L, Simon F, Tamarozzi F, et al. Is *Wolbachia* complicating the pathological effects of *Dirofilaria immitis* infections? Vet Parasitol 2005;133(2/3):133–6.
138. Ludders JW, Grauer GF, Dubielzig RR, et al. Renal microcirculatory and correlated histologic changes associated with dirofilariasis in dogs. Am J Vet Res 1988;49(6):826–30.
139. Grauer GF, Oberhauser EB, Basaraba RJ, et al. Development of microalbuminuria in dogs with heartworm disease. J Vet Intern Med 2002;16(3):352.
140. Casey HW, Splitter GA. Membranous glomerulonephritis in dogs infected with *Dirofilaria immitis*. Vet Pathol 1975;12(2):111–7.
141. Ruth J. *Heterobilharzia americana* infection and glomerulonephritis in a dog. J Am Anim Hosp Assoc 2010;46(3):203–8.
142. Ginel PJ, Camacho S, Lucena R. Anti-histone antibodies in dogs with leishmaniasis and glomerulonephritis. Res Vet Sci 2008;85(3):510–4.
143. Ortega-Pacheco A, Colin-Flores RF, Gutierrez-Blanco E, et al. Frequency and type of renal lesions in dogs naturally infected with *Leptospira* species. Ann N Y Acad Sci 2008;1149:270–4.
144. Zaragoza C, Barrera R, Centeno F, et al. Characterization of renal damage in canine leptospirosis by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and Western blotting of the urinary proteins. J Comp Pathol 2003;129(2–3):169–78.
145. Mastrorilli C, Dondi F, Agnoli C, et al. Clinicopathologic features and outcome predictors of *Leptospira interrogans* Australis serogroup infection in dogs: a retrospective study of 20 cases (2001–2004). J Vet Intern Med 2007;21(1):3–10.
146. Sykes JE, Hartmann K, Lunn KF, et al. 2010 ACVIM/ISCAID Small Animal consensus statement on leptospirosis: diagnosis, epidemiology, treatment, and prevention. Draft is currently on the ACVIM. Available at: http://www.acvim.org/websites/acvim/File/Resources/Lepto_consensus_draft_July11_forcomment_2010.pdf. Accessed July 25, 2010, to be published J Vet Intern Med 2011.
147. Acierno MJ, Labato MA, Stern LC, et al. Serum concentrations of the third component of complement in healthy dogs and dogs with protein-losing nephropathy. Am J Vet Res 2006;67(7):1105–9.
148. Harris CH, Krawiec DR, Gelberg HB, et al. Canine IgA glomerulonephropathy. Vet Immunol Immunopathol 1993;36(1):1–16.
149. Miyauchi Y, Nakayama H, Uchida K, et al. Glomerulopathy with IgA deposition in the dog. J Vet Med Sci 1992;54(5):969–75.
150. Biewenga WJ, Gruys E, Hendriks HG. Urinary protein loss in the dog: nephrological study of 29 dogs without signs of renal disease. Res Vet Sci 1982; 33(3):366–74.
151. Vilafranca M, Wohlsein P, Leopold-Temmler B, et al. A canine nephropathy resembling minimal change nephrotic syndrome in man. J Comp Pathol 1993; 109(3):271–80.
152. Sum SO, Hensel P, Rios L, et al. Drug-induced minimal change nephropathy in a dog. J Vet Intern Med 2010;24(2):431–5.
153. DiBartola SP, Tarr MJ, Parker AT, et al. Clinicopathologic findings in dogs with renal amyloidosis: 59 cases (1976–1986). J Am Vet Med Assoc 1989;195(3): 358–64.

154. DiBartola SP, Benson MD. The pathogenesis of reactive systemic amyloidosis. J Vet Intern Med 1989;3(1):31–41.
155. Pressler BM, Vaden SL. Managing renal amyloidosis in dogs and cats. Vet Med 2003;98(4):320–33.
156. Whittemore JC, Gill VL, Jensen WA, et al. Evaluation of the association between microalbuminuria and the urine albumin-creatinine ratio and systemic disease in dogs. J Am Vet Med Assoc 2006;229(6):958–63.
157. Whittemore JC, Miyoshi Z, Jensen WA, et al. Association of microalbuminuria and the urine albumin-to-creatinine ratio with systemic disease in cats. J Am Vet Med Assoc 2007;230(8):1165–9.
158. Grauer GF, Moore LE, Smith AR, et al. Comparison of conventional urine protein test strip method and quantitative ELISA for the detection of canine and feline albuminuria. J Vet Intern Med 2004;18(3):418–9.
159. Zatelli A, Paltrinieri S, Nizi F, et al. Evaluation of a urine dipstick test for confirmation or exclusion of proteinuria in dogs. Am J Vet Res 2010;7(2):235–40.
160. Lyon SD, Sanderson MW, Vaden SL, et al. Comparison of urine dipstick, sulfosalicylic acid, urine protein-to-creatinine ratio, and species-specific ELISA methods for detection of albumin in urine samples of cats and dogs. J Am Vet Med Assoc 2010;236(8):874–9.
161. Welles EG, Whatley EM, Hall AS, et al. Comparison of Multistix PRO dipsticks with other biochemical assays for determining urine protein (UP), urine creatinine (UC), and UP:UC ratio in dogs and cats. Vet Clin Pathol 2006;35(1): 31–6.
162. Kahn M, Fernandes P, Jensen M, et al. Comparison of the Vitros 250 and the IDEXX VetTest chemistry analyzer for urine protein:creatinine ratios in dogs and cats. J Vet Intern Med 2005;19(3):431.
163. Fernandes P, Kahn M, Yang V, et al. Comparison of methods used for determining urine protein-to-creatinine ratio in dogs and cats. J Vet Intern Med 2005;19(3):431.
164. Kuwahar Y, Nishii N, Takasu M, et al. Use of urine albumin/creatinine ratio for estimation of proteinuria in cats and dogs. J Vet Med Sci 2008;70(8):865–7.
165. Beatrice L, Nizi F, Callegari D, et al. Comparison of urine protein-to-creatinine ratio in urine samples collected by cystocentesis versus free catch in dogs. J Am Vet Med Assoc 2010;236(11):1221–4.
166. Nabity MB, Boggess MM, Kashtan CE, et al. Day-to-day variation of the urine protein:creatinine ratio in female dogs with stable glomerular proteinuria caused by X-linked hereditary nephropathy. J Vet Intern Med 2007;21(3):425–30.
167. LeVine DN, Zhang DW, Harris T, et al. The use of pooled vs. serial urine samples to measure urine protein:creatinine ratios. Vet Clin Pathol 2010;39(1):53–6.
168. Gary AT, Cohn LA, Kerl ME, et al. The effects of exercise on urinary albumin excretion in dogs. J Vet Intern Med 2004;18(1):52–5.
169. Rawlinson JE, Goldstein RE, Erb HN, et al. Tracking inflammatory and renal parameters in dogs pre- and post-treatment for periodontal disease. J Vet Intern Med 2005;19(3):430–1.
170. Prober LG, Johnson CA, Olivier NB, et al. Effect of semen in urine specimens on urine protein concentration determined by means of dipstick analysis. Am J Vet Res 2010;71(3):288–92.
171. Vaden SL, Pressler BM, Lappin MR, et al. Effects of urinary tract inflammation and sample blood contamination on urine albumin and total protein concentrations in canine urine samples. Vet Clin Pathol 2004;33(1):14–9.

172. Bagley RS, Center SA, Lewis RM, et al. The effect of experimental cystitis and iatrogenic blood contamination on the urine protein/creatinine ratio in the dog. J Vet Intern Med 1991;5(2):66–70.
173. Ortega TM, Feldman EC, Nelson RW, et al. Systemic arterial blood pressure and urine protein/creatinine ratio in dogs with hyperadrenocorticism. J Am Vet Med Assoc 1996;209(10):1724–9.
174. Hurley KG, Vaden SL. Evaluation of urine protein content in dogs with pituitary-dependent hyperadrenocorticism. J Am Vet Med Assoc 1998;212(3):369–73.
175. Mazzi A, Fracassi F, Dondi F, et al. Ratio of urinary protein to creatinine and albumin to creatinine in dogs with diabetes mellitus and hyperadrenocorticism. Vet Res Commun 2008;32(Suppl 1):S299–301.
176. Waters CB, Adams LG, Scott-Moncrieff JC, et al. Effects of glucocorticoid therapy on urine protein-to-creatinine ratios and renal morphology in dogs. J Vet Intern Med 1997;11(3):172–7.
177. Schellenberg S, Mettler M, Gentillini F, et al. The effects of hydrocortisone on systemic arterial blood pressure and urinary protein excretion in dogs. J Vet Intern Med 2008;22(2):273–81.
178. Bacic A, Kogika MM, Barbaro KC, et al. Evaluation of albuminuria and its relationship with blood pressure in dogs with chronic kidney disease. Vet Clin Pathol 2010;39(2):203–9.
179. Struble AL, Feldman EC, Nelson RW, et al. Systemic hypertension and proteinuria in dogs with diabetes mellitus. J Am Vet Med Assoc 1998;213(6):822–5.
180. Zini E, Bonfanti U, Zatelli A. Diagnostic relevance of qualitative proteinuria evaluated by use of sodium dodecyl sulphate-agarose gel electrophoresis and comparison with renal histologic findings in dogs. Am J Vet Res 2004;65(7):964–71.
181. Littman MP. Diagnosis of infectious diseases of the urinary tract. In: Bartges JW, Polzin DJ, editors. Nephrology and urology of small animals. Ames (IA): Blackwell; 2011. p. 241–52.
182. Laquaniti A, Bolignano D, Donato V, et al. Alterations in lipid metabolism in chronic nephropathies: mechanisms, diagnosis and treatment. Kidney Blood Press Res 2010;33(2):100–10.
183. Brown S, Atkins C, Bagley R, et al. ACVIM consensus statement: guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. J Vet Intern Med 2007;21(3):542–58.
184. Finco DR. Association of systemic hypertension with renal injury in dogs with induced renal failure. J Vet Intern Med 2004;18(3):289–94.
185. Green RA, Russo EA, Greene RT, et al. Hypoalbuminemia-related platelet hypersensitivity in two dogs with nephrotic syndrome. J Am Vet Med Assoc 1985; 186(5):485–8.
186. Palmer KG, King LG, Van Winkle TJ. Clinical manifestations and associated disease syndromes in dogs with cranial vena cava thrombosis: 17 cases (1989–1996). J Am Vet Med Assoc 1998;213(2):220–4.
187. Greco DS, Green RA. Coagulation abnormalities associated with thrombosis in a dog with nephrotic syndrome. Compend Cont Educ Pract Vet 1987;9(6):653–8.
188. Goncalves R, Penderis J, Chang YP, et al. Clinical and neurological characteristics of aortic thromboembolism in dogs. J Small Anim Pract 2008;49(4):178–84.
189. Klosterman ES, Moore GE, deBrito Galvao JF, et al. A case-control study of nephrotic syndrome in dogs: 78 cases. J Vet Intern Med 2010;24(3):678.
190. Schieppati A, Perna A, Zamora J, et al. Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. Cochrane Database Syst Rev 2004;4:CD004293.

191. Barakat R, Molony DA, Samuels JA. Immunosuppressive agents for treating IgA nephropathy. Cochrane Database Syst Rev 2003;4:CD003965.
192. Cowgill LD. Diagnostic assessment of proteinuric renal disease: the 21st century vision. In: ACVIM Forum Proceedings. 2009. Available at: http://www.vin.com/Members/proceedings/Proceedings.plx?CID=ACVIM2009&Category=&PID=51528&O=VIN. Accessed October 20, 2010.
193. Lees GE, Berridge BR. Renal biopsy – when and why. NAVC Clinician's Brief 2009;7(10):26–8.
194. Lees GE, Berridge BR, Clubb FJ. Evaluation of renal biopsy samples. NAVC Clinician's Brief 2009;7(10):67–9.
195. Lees GE, Berridge BR, Cianciolo RE. Renal biopsy stains. NAVC Clinician's Brief 2010;8(1):27–30.
196. Lees GE, Bahr A, Sanders MH. Performing renal biopsy. NAVC Clinician's Brief 2010;8(4):67–72.
197. Vaden SL, Levine JP, Lees GE, et al. Renal biopsy: a retrospective study of methods and complications in 283 dogs and 65 cats. J Vet Intern Med 2005; 19(6):794–801.
198. Vaden SL. Renal biopsy of dogs and cats. Clin Tech Small Anim Pract 2005; 20(1):11–22.
199. Vaden SL. Renal biopsy: methods and interpretation. Vet Clin North Am Small Anim Pract 2004;34(4):887–908.
200. Brown SA, Finco DR, Brown CA, et al. Evaluation of the effects of inhibition of angiotensin converting enzyme with enalapril in dogs with induced chronic renal insufficiency. Am J Vet Res 2003;64(3):321–7.
201. Lefebvre HP, Laroute V, Concordet D, et al. Effects of renal impairment on the disposition of orally administered enalapril, benazepril, and their active metabolites. J Vet Intern Med 1999;13(1):21–7.
202. Tenhundfeld J, Wefstaedt P, Nolte IJA. A randomized controlled clinical trial of the use of benazepril and heparin for the treatment of chronic kidney disease in dogs. J Am Vet Med Assoc 2009;234(8):1031–7.
203. Grauer GF, Greco DS, Getzy DM, et al. Effects of enalapril versus placebo as a treatment for canine idiopathic glomerulonephritis. J Vet Intern Med 2000; 14(5):526–33.
204. Vaden SL. What's on the horizon for management of proteinuria renal diseases? In: ACVIM Forum Proceedings. 2009. Available at: http://www.vin.com/Members/Proceedings/Proceedings.plx?CID=acvim2009&PID=pr51531&O=VIN. Accessed October 20, 2010.
205. Segev G, Fascetti AJ, Weeth LP, et al. Correction of hyperkalemia in dogs with chronic kidney disease consuming commercial renal diets by potassium-reduced home-prepared diet. J Vet Intern Med 2010;24(3):546–50.
206. Grauer GF, Rose BJ, Toolan LA, et al. Effects of low-dose aspirin and specific thromboxane synthetase inhibition on whole blood platelet aggregation and adenosine triphosphate secretion in healthy dogs. Am J Vet Res 1992;53(9): 1631–5.
207. Rackear D, Feldman B, Farver T, et al. The effect of three different dosages of acetylsalicylic acid on canine platelet aggregation. J Am Anim Hosp Assoc 1988;24(1):23–6.
208. Shearer L, Kruth SA, Wood D. Effects of aspirin and clopidogrel on platelet function in healthy dogs. In: Proceedings of the 19th ECVIM-CA Congress. Available at: http://www.vin.com/Members/Proceedings/Proceedings.plx?CID=ecvim2009&PID=pr52275&O=VIN. Accessed July 10, 2010.

209. Longhofer SL, Frisbie DD, Johnson HC, et al. Effects of thromboxane synthetase inhibition on immune complex glomerulonephritis. Am J Vet Res 1991;52(3): 480–7.
210. Grauer GF, Frisbie DD, Longhofer SL, et al. Effects of a thromboxane synthetase inhibitor on established immune complex glomerulonephritis in dogs. Am J Vet Res 1992;53(5):808–13.
211. Grauer GF, Frisbie DD, Snyder PS, et al. Treatment of membranoproliferative glomerulonephritis and nephrotic syndrome in a dog with a thromboxane synthetase inhibitor. J Vet Intern Med 1992;6(2):77–81.
212. Smith SA, Tobias AH, Jacob KA, et al. Arterial thromboembolism in cats: acute crisis in 127 cases (1992–2001) and long-term management with low-dose aspirin in 24 cases. J Vet Intern Med 2003;17(1):73–83.
213. Ramsey CC, Burney DP, Macintire DK, et al. Use of streptokinase in four dogs with thrombosis. J Am Vet Med Assoc 1996;209(4):780–5.
214. Clare AC, Kraje BJ. Use of recombinant tissue-plasminogen activator for aortic thrombolysis in a hypoproteinemic dog. J Am Vet Med Assoc 1998;212(4): 539–43.
215. Brown SA, Brown CA, Crowell WA, et al. Beneficial effects of chronic administration of dietary omega-3 polyunsaturated fatty acids in dogs with renal insufficiency. J Lab Clin Med 1998;131(5):447–55.
216. Ahmed MS, Hou SH, Battaglia MC, et al. Treatment of idiopathic membranous nephropathy with the herb *Astragalus membranaceus*. Am J Kidney Dis 2007; 50(6):1028–32.
217. Leehey DJ, Casini T, Massey D. Remission of membranous nephropathy after therapy with *Astragalus membranaceus*. Am J Kidney Dis 2010;55(4):772.
218. Mahajan A, Simoni J, Sheather SJ, et al. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int 2010;78(3):303–9.
219. Banyard MRC, Hassett RS. The use of mycophenolate mofetil in the treatment of a case of immune-mediated glomerulonephritis in a dog. Aust Vet Pract 2001; 31(3):103–6.
220. Alchi B, Jayne D. Membranoproliferative glomerulonephritis. Pediatr Nephrol 2010;25(8):1409–18.
221. Yagi K, Yanagida H, Sugimoto K, et al. Clinicopathologic features, outcome, and therapeutic interventions in four children with isolated C3 mesangial proliferative glomerulonephritis. Pediatr Nephrol 2005;20(9):1273–8.
222. Yokoyama H, Wada T, Zhang W, et al. Advances in apheresis therapy for glomerular diseases. Clin Exp Nephrol 2007;11(2):122–7.