

# **CANINE PROTEINURIA AND GLOMERULAR DISEASE INCLUDING LYME NEPHRITIS**

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Proteinuria has been found to be a negative prognostic indicator for survival in dogs and cats with CRD! It appears that all efforts to decrease proteinuria are warranted.

## Measuring Urine Protein

As our understanding of proteinuria and our ability to detect small amounts of protein increases so does our knowledge of its importance. Cats and dogs with renal disease can have proteinuria which is likely detrimental to their kidneys even when the primary insult is tubular and not glomerular. There is recent evidence showing that even a protein creatinine ratio of 0.4 (normal for most laboratories) is a negative prognostic indicator for cats with renal disease. There are problems with relying on a dipstick though to evaluate protein:

1. The amount the dipstick picks up depends on urine concentration therefore it has to be normalized for concentration or urine creatinine (P/C ratio).
2. There are many false negatives and false positives. A more accurate method employed in many labs (not on the dip stick) is the SSA (sulfasalicylic acid) technique.
3. Minute concentrations of albumin (microalbuminuria) measurement require a specific test. The value and clinical use of this test is questionable because of a high percentage of positive dogs and cats that are considered to be clinically normal.

A Urine P/C over 0.5 (canine) and 0.4 (feline) is considered abnormal and should be investigated and possibly treated including:

Causes of proteinuria include pre-glomerular, glomerular and post glomerular causes. Pre-glomerular proteinuria: Exercise, Seizures, Myoglobin, Fever, Stress Hypertension, Glucocorticoids – dogs (?), Hemoglobin, Bence Jones' proteins.

Glomerular proteinuria is caused by either glomerulonephritis or amyloidosis. The magnitude of proteinuria CANNOT differentiate between them. Post glomerular proteinuria includes: Tubular proteinuria, parenchymal inflammation and lower urinary tract inflammation.

Consistent additional minimal data base findings

- Hypoalbuminemia (normal globulin)
- Mild hypercholesterolemia
- Isosthenuria, mild azotemia (advanced cases)
- Hypertension with retinal changes.

The differentials for low albumin can be pretty easily assessed when also looking at globulin!

Cause	Albumin	Globulin
PLE	Low	Low
Blood loss	Low	Low
PLN	Low	Normal
Liver disease	Low	Normal, High
Vasculitis	Low	Low, Normal
Increased COP	Low	High

A Minimal data base in a proteinuric dog should include:

CBC, Chem, UA

ERD(?)

Urine culture

P/C ratio

Blood pressure

Abdominal US/radiographs

The antigen search looking for underlying disease is the next step!

Infectious disease testing, Imaging and Repeat physical examination.

What to do while waiting for serology? The options are:

1. Benign (non-specific) therapy and wait if: Mild to moderate proteinuria, and none to mild azotemia only.
2. Renal biopsy now if severe proteinuria, nephrotic and mild to moderate azotemia.
3. Fluid diuresis therapy first if acute component and moderate to severe azotemia

Not specific therapy includes: Diet, ACE inhibition and possibly omega 3 fatty acid supplementation.

Treat hypertension – Systolic BP>160

Specific therapy based on histopathologic diagnosis. See example of Lyme nephritis

### **LYME NEPHRITIS**

It is amazing that for a topic which is talked about so much in some areas and in some practices appears to be so important – there is very little literature and actually no real proof that the disease exists. The following are the 2 main references currently in the veterinary literature:

1. Grauer GF, Burgess EC, Cooley AJ, Hagee JH. Renal lesions associated with *Borrelia burgdorferi* infection in a dog. J Am Vet Med Assoc 1988 Jul 15;193(2):237-9.

2. Dambach DM, Smith CA, Lewis RM, Van Winkle TJ. Morphologic, immunohistochemical, and ultrastructural characterization of a distinctive renal lesion in dogs putatively associated with *Borrelia burgdorferi* infection: 49 cases (1987-1992). *Vet Pathol.* 1997 Mar;34(2):85-96.

The second is a large histopathological study that really first characterized the syndrome that has become "Lyme nephritis". This study described a common pathological lesion noted in 49 dogs within that 6 year period. The common finding in all of those dogs (these are the criteria that were used to search their data base) were glomerulonephritis (GN) (usually membranoproliferative) uncharacteristically accompanied by tubular necrosis with severe tubular dilation. There was also marked interstitial inflammation. Approximately 50% of these samples were obtained at necropsy and 50% were biopsies of dogs alive at the time. The clinical syndrome of severe glomerular disease progressing to acute renal failure and death, with severe uremia, within a short time appeared to be common to all dogs in the study. 21 dogs were shown to have immune complex GN with IgG, IgM and basement membrane complement (C3) deposition. All dogs evaluated with urinalyses were proteinuric.

#### **So where is the connection to Lyme?**

With special stains (Silver Stain) a single spirochete was thought to be identified in 2 kidneys evaluated.

18 of 18 dogs that were tested serologically for Lyme were positive. How they were tested is unclear, likely non-specific ELISA and at least some were vaccinated according to the medical record. Infection was confirmed in 1 dog with Western blot. 13 had a history of a recent lameness.

What were he affected breeds? Labrador Retrievers: 14/49 or 29%, . Golden Retrievers: 10/49 or 20%, 15 other breeds were represented.

Age and Gender? Younger dogs were affected (mean 5.6 ±0.48 years) with no gender predilection.

#### **So What Do We Know?**

A unique lesion in the kidneys of dogs with a devastating glomerular-tubular disease is described with relatively good circumstantial evidence for a Lyme connection. Importantly there are MANY anecdotal reports of a similar clinical syndrome in Labradors and Golden Retrievers, as well as other breeds, in Lyme endemic areas.

Open questions:

- Is Lyme the whole story?
- What does a live dog or an early case look like?
- What is the real time frame of the disease?
- What does a mild case look like?
- Can some of them resolve?
- Does treating these dogs early post infection lower the risk of the disease?
- Can the disease be induced by an immune response to one of the vaccines?

We do not have answers to all of those questions at this time. Studies will be presented showing that:

There is no invasion of Bb bacteria in the kidneys of dogs with Lyme nephritis

There are immune complexes lodged in those kidneys that include Lyme specific antibodies.

Current Recommendations for Screening and Treatment of Dogs with Suspected Lyme Nephritis. (These are based on limited experience theory and not on strong clinical data!).

Monitor dogs in endemic areas for Lyme infection

Screen all positive dogs for signs of proteinuria or microalbuminuria.

Screen all dogs that present with proteinuria or microalbuminuria for Lyme.

Consider treating any dogs positive for both Lyme and proteinuria or microalbuminuria with 4-6 weeks of doxycycline.

If proteinuria persists or worsens (based on urine protein/creatinine ratio):

Continue doxycycline

Consider low protein diet and an ACE inhibitor

Consider renal biopsy . If the renal biopsy is consistent with immune mediated GN consider immunosuppression with drugs like mycophenolate, azathioprine, chlorambucil, or cyclosporine.

Additional references available upon request