LYME DISEASE: TREATMENT OF ACUTE AND CHRONIC MANIFESTATIONS

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Lyme disease, caused by the spirochete *Borrelia burgdorferi (Bb)*, is one of the most common tick-borne diseases in the world. The Centers for Disease Control and Prevention (CDC) reported a dramatic increase in the number of diagnosed human infection cases, increasing from 30,000 to 300,000 recently.[1] According to the CDC, 95% of human Lyme disease cases came from the following 13 states: CT, DE, ME, MD, MA, MN, NH, NJ, NY, PA, VT, VA, WI.[2]

Are we seeing this increase in our canine population? In the United States, more than 90% of the canine cases occur in the northeast and Midwest.[3] That said, only 5% of seropositive dogs in endemic areas develop infection or show clinical signs.[3-5] With the Idexx 3D or 4D SNAP test, there is likely an over-diagnosis of Lyme disease. How do we interpret a positive test, and more importantly, how do we treat acute and chronic manifestations of Lyme disease?

Transmission

While *Bb* can be transmitted by urine, milk, and blood, the most common transmission is likely via tick infestation by hard-shell deer ticks (e.g., *Ixodes scapularis* or other related *Ixodes* species). Ixodes ticks have a 2-year life cycle,[3,4] and hatch in the spring (into larvae). A female tick lays approximately 2000 eggs.[3] Larvae become infected with *Bb* when feeding on white-footed mice, which are persistently infected, but often remain unaffected or asymptomatic.[3] The larvae molt into nymphs that feed on new hosts. While nymphs are less effective vectors than adult ticks, they can still infect their hosts within the four-day feeding period.[6] Likewise, nymphs can become infected when feeding on an infected animal. In the fall, nymphs molt to adults, with 50% of adult ticks in the Northeast estimated to be carrying *Bb*.[6] Once the tick attaches and feeds, the spirochetes (which live in the midgut of the tick) begin to migrate to the salivary gland and enter the host. Risk of infection is believed to be minimal during the first 12 hours of feeding.[6] Typically, transmission of *Bb* occurs during prolonged feeding periods (typically > 48 hours).[3,6]

Pathophysiology

While in the tick, Outer Surface Protein A (OspA) allows *Bb* to remain anchored in the midgut. During feeding, a trigger signals down-regulation of OspA protein and up-regulation of OspC expression (e.g., this may be due to a temperature increase by the host). OspC allows *Bb* to become established within the host and avoid detection by the immune system.

Following a tick bite, local skin infestation occurs, progressing to infection within the joint capsules, muscles, connective tissue, and lymph nodes. Experimentally, incubation of *Bb* takes anywhere between 2-5 months.[3,4] *Bb* persists in the body for a long duration, and can be found in the joints, skin, connective tissue, muscle, lymph nodes, and kidneys. Less commonly, *Bb* can be found in the blood, synovial fluid, or CSF, but this is rare.[3]

Testing
Historically, testing for Lyme was done based on antibodies against *Bb* via enzyme-linked immunosorbent assays (ELISA) and indirect fluorescent antibody (IFA) techniques.[4,7] Culture and PCR can potentially be performed, but are typically very difficult (due to low number of organisms) or complicated.[8] With certain tests, false positive results may be seen due to vaccination or cross-reaction to similar organisms.[9] Positive tests can be confirmed with Western blot or ELISA looking specifically against certain proteins (recombinant Osp C or C6).[9] Western blot can be used to differentiate seropositive dogs from vaccine. This technology is not commonly utilized as compared to a decade ago; this is typically only recommended if the vaccinal status is important to the veterinarian.[8]

Currently, the most common commercially available tests for Lyme test for antibodies against Lyme C6 peptide. These include: SNAP 3Dx and 4Dx and the quantitative C6 antibody test (both available through Idexx Laboratories). As C6 is expressed only during infection, a positive result is consistent with nature exposure or ongoing infection. While quantitative C6 levels are beneficial, they are still unspecific. The elevation in C6 levels does appear to correlate with circulating anti-Lyme immune complexes, and quantitative C6 levels is thought to decrease with antibiotic therapy.[1,7,8]

Newer serologic testing may become more utilized, including Cornell's newest multiplex Multiplex assay (a quantitative serologic test which includes a Western blot and quantitation of antibodies directed against OspA, OspC, and OspF during acute or chronic infection),[b,1] Antech's newest serologic test AccuPlex4 (which identifies antibodies to 5 antigens)[1] and Abaxis ELISA quantitative Lyme test. For further information on testing, the reader is referred to additional resources.[7,8]

Clinical signs
The manifestation of Lyme disease varies between humans and dogs. In humans, clinical signs of acute illness include erythema migrans rash and flu-like signs. More chronic signs include arthritis, possible skin changes, neurologic signs (e.g., meningitis), and cardiac signs.

In dogs, three states of Lyme disease can be seen. With acute Lyme disease, dogs typically develop transient fever, lethargy, depression, hesitance to move, anorexia, pain, lymphadenopathy, and acute arthritis (seen as a mono- or polyarthropathy). Joints may be inflamed and warm to the touch. Sub-acute signs may also be seen, where lameness can last several weeks. While clinical arthritis may be transient, inflammatory changes to the synovial fluid may be ongoing and potentially persistent. Typically, lameness in dogs occurs months after tick exposure. Chronic signs include cardiac changes (e.g., bradyarrhythmias such as heart block, etc.), neurologic signs, arthritis and changes related to Lyme nephritis (estimated to occur in 1-2% of dogs affected by Lyme disease).[10]

Lyme nephritis is a rare but fatal complication seen with *Bb*. Lyme nephritis is not caused by an inflammatory response to renal invasion of Bb organisms, but rather thought to be a condition due to accumulation of immune complexes in the kidney. Unique histopathologic changes to the kidneys have been identified with Lyme nephritis and include immune-mediated glomerulonephritis, lymphocytic-plasmacytic interstitial nephritis, and diffuse tubular necrosis

and regeneration. Chronic signs of Lyme nephritis include inappetance, vomiting, muscle wasting, weight loss, lethargy, and malaise, and can progress to halitosis, azotemia, edema, and death. Certain breeds including golden retrievers and Labrador retrievers seem to be over-represented.[3,11] Even with aggressive treatment, long-term prognosis is guarded to grave, with one study showing that 49/49 dogs diagnosed with Lyme nephritis were all euthanized within 1-8 weeks of diagnosis.[11]

To treat or not to treat

In canine patients suspected of having Lyme disease based on a positive 3DX or 4DX SNAP test, the decision to treat should be based on the presence of clinical signs, breeds at risk for developing life-threatening chronic effects (e.g., breeds predisposed to Lyme nephritis), and presence of proteinuria or microalbuminuria.

In Lyme-positive dogs that are asymptomatic and without evidence of proteinuria, treatment is generally not recommended. Risks of treatment with antibiotic therapy (e.g., doxycycline) include increased liver enzymes, gastrointestinal signs (e.g., anorexia, vomiting, diarrhea, esophagitis, esophageal strictures, etc.), and antibiotic resistance. That said, thorough discussion with the owner should include preventative care (see Prevention below), follow up monitoring (e.g., quantitative C6, proteinuria, etc.), and rare but potentially deadly risks (e.g., Lyme nephritis) in breeds at risk.

In positive dogs that are symptomatic, treatment should be initiated and the patient monitored for proteinuria. Typically, clinical signs should resolve within 2-3 days after the initiation of antibiotic therapy. Vaccination is not currently recommended in positive, symptomatic dogs. If antibiotic treatment does not result in clinical improvement within several days, then the patient should be assessed and worked up for potential other diseases. In one study, non-Lyme-related causes of clinical signs were found in 40% of dogs that were originally diagnosed with Lyme disease.[12] Other differentials should include:

- Rocky Mountain spotted fever
- Canine ehrlichiosis
- Orthopedic disease (e.g., panosteitis, osteoarthritis, degenerative joint disease, cruciate injury, etc.)
- Immune-mediated disease (rheumatoid arthritis, lupus erythematosis, etc.)
- Neoplasia

For this reason, in a symptomatic, Lyme-positive dog (tentatively diagnosed with acute Lyme disease), the use of corticosteroids and NSAIDs isn't typically recommended, as it may mask the diagnostic value of antibiotic therapy (or mask other underlying diseases), warranting additional work-up.

Treatment

Acute Lyme disease should be treated with doxycycline at 5 mg/kg per os (PO) every 12 hours, amoxicillin at 20 mg/kg every 8-12 hours, minocycline at 10 mg/kg PO every 12 hours, or Convenia injection 2 doses, 2 weeks apart, subcutaneously.[1] Currently, it is debated how long to treat with antibiotic therapy for, due to the long duration of *Bb* harboring within the body. In

general, if treatment is initiated, it should be continued for 4-6 weeks. Again, patients should be monitored for acute improvement; if immediate improvement is not seen within 2-3 days, further diagnostic workup should be performed.

For chronic Lyme disease, appropriate monitoring for proteinuria or microalbuminuria should be performed q. 3-6 months. In patients that have continued proteinuria (after 4-6 weeks of antibiotic therapy), a renal biopsy should be considered (to rule out an immune-mediated glomerulonephritis), along with a low-protein diet, angiotensin-converting enzyme inhibitor (ACEi) therapy, and an additional course of antibiotic therapy. If evidence of immune-mediated glomerulonephritis is seen, the use of immunosuppressive therapy is warranted (e.g., azathioprine, cyclosporine, mycophenolate, etc.).

For dogs with Lyme nephritis, treatment is aimed at preserving quality of life, improving azotemia, minimizing clinical signs and adverse effects, minimizing proteinuria, and treating hypertension and hypercoagulable states. Treatment should focus specifically on the following:

Fluid therapy

Treatment includes the judicious use of fluid therapy. As many patients with Lyme nephritis are hypoalbuminemic, conservative crystalloid fluid therapy is warranted. While many crystalloid choices exist, any balanced crystalloid may be used based on the patient's requirements for a buffered vs. non-buffered solution, electrolyte needs, or osmolality. Unfortunately, due to the lowered colloid osmotic pressure (COP; normal range 16-20 mm Hg) secondary to hypoalbuminemia, volume overload, overhydration, and edema are commonly seen secondary to crystalloid therapy.

The use of colloidal support may be beneficial in patients with Lyme nephritis to help increase COP. Colloids expand plasma volume and should be used for the maldistribution of extracellular water and expansion of the interstitial space. Colloidal molecules are distributed to the extracellular fluid (ECF) and remain in the intravascular space for a longer duration than crystalloids. Colloids currently used in veterinary medicine include hydroxyethyl starches such as:

- Hetastarch (e.g., Hespan, Hextend) which has a molecular weight of approximately 450,000 Daltons)
- Tetrastarch (e.g., VetStarch, Voluven at 130,000 Daltons)
- Pentastarch (e.g., PentaLyte, HAESteril at 240,000 Daltons)

Other choices include Dextran-40 (40-80,000 Daltons), Dextran 70 (40-100,000 Daltons; average weight 70,000 Daltons), human serum albumin (HSA) 5%, and canine serum albumin. Currently, the use of HSA is not recommended (based on the author's opinions), due to the potential risks of antigenic stimulation and secondary immune complex formation with chronic or repetitive use; the administration of HSA in dogs has been associated with anaphylactic shock, immune-mediated joint disease, and glomerulonephritis. Canine serum albumin is a safer alternative; however, this can be costly and is not always readily available. The use of fresh frozen plasma (FFP) is typically not recommended as a replacement of albumin in these hypoproteinemic patients, as it requires a large volume (which is often cost prohibitive).

Typically, FFP is used to provide clotting factors, Vitamin K-dependent factors (e.g., II, VII, IX, X), alpha-macroglobulins, and low amounts of albumin. Higher doses of FFP (typically 45 ml/kg) are necessary to increase albumin by 1 g/dL (1.4 liters in a 30 kg dog); hence, FFP is not routinely used to increase albumin when safer, less expensive colloids can be used.

With Lyme nephritis, it is imperative to carefully monitor patients for hydration status. This can be done based on serial physical examination —checking for return of skin turgor, appropriate weight gain, and moisture of mucous membranes. However, physical examination findings are subjective, and <5% dehydration is difficult to assess. The concurrent use of evaluation of PCV/TS (aiming for hemodilution), blood glucose, blood urea nitrogen (BUN or AZO), weight, urine output, urine specific gravity (USG), and thirst can be used in conjunction with physical examination findings to better assess hydration status. Note that in patients with underlying renal insufficiency, urine will be isosthenuria and USG cannot be used to adequately assess hydration.

Gastrointestinal support

Azotemic patients should be treated with phosphate binders (e.g., aluminum hydroxide) if hyperphosphatemic, along with gastrointestinal protectants (e.g., omeprazole, pantoprazole, famotidine, sucralfate, etc.) for presumptive uremic gastritis. Anti-emetics (e.g., maropitant, ondansetron, dolasetron) should be implemented for patient comfort and to treat nausea.

Anti-hypertensives

Hypertension is often seen in patients with Lyme nephritis and kidney disease. The use of anti-hypertensives are warranted if a systolic blood pressure (BP) is persistently > 160-180 mm Hg.[13] Long-term management of hypertension requires serial BP monitoring and *gradual/sustained* reduction in BP (versus an acute, sudden decrease).[13] Typically, hypertension can initially be managed with the use of ACEI therapy (See Proteinuria treatment below). Persistent hypertension may require higher doses of ACEI or combination therapy with vasodilatory drugs (e.g., hydralazine), calcium channel blockers (e.g., amlodipine), or even angiotensin II receptor antagonists (e.g., losartan). While hospitalized, the use of intravenous vasodilators can be used (e.g., nitroprusside) for *severe* hypertension (e.g., systolic > 190 mm Hg); however, these require a constant rate infusion (CRI) and frequent blood pressure monitoring (e.g., continuous or q. 1 hour) while administering.

Proteinuria treatment

The use of ACEi is warranted in dogs with Lyme nephritis. Not only does the use of ACEi improve renal function and potentially prolong survival,[14] but it also helps reduce glomerular transcapillary hydraulic pressure, proteinuria, and glomerular cell hypertrophy.[14] Treatment with ACEi is thought to decrease proteinuria and preserve renal function by decreasing cellular proliferation and intraglomerular hypertension, along with decreasing the size of glomerular capillary endothelial cell pores.[14] In rats, ACEi work by preventing the loss of glomerular heparan sulfate which can occur with glomerular disease.[14] [Heparan sulfate is a glocyosaminoglycan-proteoglycan that adds to the negative charge of the glomerular capillary wall, minimizing filtration of negatively charged proteins (e.g., albumin)].[14] Enalapril or benazapril can be used; as enalapril (0.5 mg/kg PO q 12-24 hours) is renally-excreted, the author prefers benazepril (0.25 – 1 mg/kg PO q 12-24 hours).

Nutrition
Ideally, a low-protein, low sodium diet should be fed. Low-sodium diets are beneficial as they decrease glomerular hyperfiltration, improve the efficacy of ACEi treatment, and delay the progression of glomerular disease.[14] However, as the prognosis for Lyme nephritis is grave, focus should be on maintaining appetite in anorexic dogs. Feeding omega-3 polyunsaturated fatty acids (e.g., Nordic Naturals Pet-Omega3) may be beneficial in dogs with Lyme nephritis, as it may help enhance prostacyclin activity, while decreasing thromboxanes and leukotriene production; this may help attenuate glomerular disease.[14]

Hypercoagulability: Anticoagulant therapy
The use of anticoagulant therapy is indicated in Lyme nephritis patients that are hypercoagulable secondary to antithrombin III loss. Dogs with AT III levels < 70% of normal should ideally be started on anticoagulant therapy to minimize the risks of thromboembolic disease.[14] There are numerous options for anticoagulant therapy, including warfarin, heparin, coumadin, and low-dose aspirin.[14] Due to the ease of therapy, ability to be administered on an outpatient basis, and lack of requirement for intensive monitoring, the author prefers low-dose aspirin therapy at 0.5 to 5 mg/kg orally once a day in dogs).

Miscellaneous treatment
There are a few other miscellaneous treatments recommended for Lyme nephritis. The novel use of mycophenolate has been anecdotally used with success long term in dogs with Lyme nephritis; this appears to mediate the immune response to *Bb* antibody and may improve urine protein: creatinine ratios in dogs. Currently, there is little published veterinary literature regarding the use of mycophenolate in Lyme nephritis, but it appears to be potentially promising. Side effects of mycophenolate include gastrointestinal signs (e.g., anorexia, vomiting, diarrhea), lethargy, lymphopenia, and increased rate of infection (secondary to immunosuppression).

Prevention
As the prognosis for chronic Lyme disease is grave, the goal of Lyme disease should be focused on preventive medicine. A Lyme prevention package should be initiated with the following:

- Monthly tick control with parasiticides (including one that provide a tick repellant)
- Daily tick removal (training pet owners to tick check immediately after hiking etc.)
- Vaccination. The decision to vaccinate should be based on an endemic area, exposure of the dog, and risk factors (e.g., breeds at risk for Lyme nephritis).[4,11] Positive, symptomatic dogs should not be vaccinated; rather, asymptomatic, high-risk dogs should be considered for vaccination (e.g., hunting dogs, Golden retrievers, Labrador retrievers, etc. in high-risk areas). Currently, there are four companies producing Lyme vaccines, all of which product anti-OspA *borreliacidal* antibodies that kill *Bb* within the tick. One vaccine[a] also contains a unique isolate that induces anti-OspC *borreliacidal* antibodies, providing a wider margin of coverage; this vaccine also provides protection against subclinical arthritis.

Prognosis
The decision to treat a positive dog should be based on clinical signs, breeds at risk, owner concerns, and evidence of proteinuria. The prognosis for *acute* Lyme disease is excellent, and

most patients respond within 2-3 days of antibiotic therapy. Even recurrent clinical signs appear to respond to additional courses of antibiotic therapy (as compared to response in humans with recurrence). Some dogs may also spontaneously recover from Lyme disease without therapy at all. That said, the prognosis for *chronic* manifestations of Lyme disease (e.g., Lyme nephritis) is grave. Again, preventive care is imperative to help minimize the incidence of clinically symptomatic Lyme infection. As dogs act as sentinels for human borreliosis, preventative care is of utmost importance.

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Footnotes:

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b. https://ahdc.vet.cornell.edu/docs/Lyme_Disease_Multiplex_Testing_for_Dogs.pdf