LYME DISEASE: A GROWING CONCERN
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BORRELIA LIFE CYCLE AND OUTER SURFACE PROTEINS (OSP)

The causative agent of Lyme disease is the bacteria *Borrelia burgdorferi*, which is transmitted by black legged ticks. *Ixodes scapularis* (or deer tick) acts as the vector for *B. burgdorferi* in the northeastern, mid-Atlantic, and north-central USA, while *Ixodes pacificus* is the vector on the Pacific coast. All stages of *Ixodes* ticks feed on *Borrelia*-infected animals and birds and can transmit disease. There are 16 strains of *B. burgdorferi* in the USA, but clinical differences between strains are unknown.

*B. burgdorferi* transmission occurs approximately 24-53 hours after initial tick attachment, but transmission can occasionally occur in less than 24 hours. Co-infections from the same tick vector can be transmitted earlier than *B. burgdorferi*. The outer membrane of *B. burgdorferi* is composed of outer surface proteins (Osp). Osp are expressed by *B. burgdorferi* at different stages of the life cycle. Outer surface protein A (OspA) is required for the tick vector to become infected and is expressed during the part of the *Borrelia* life cycle that occurs in the midgut of the tick. The next stage of the *Borrelia* life cycle occurs when the bacteria move from the midgut of the tick to the salivary glands. At this stage, outer surface protein expression moves from Osp A to OspC. Once *B. burgdorferi* has been transmitted to a susceptible mammal, expression of OspA is minimal or absent and another outer surface protein, OspC, dominates. OspC is required for *B. burgdorferi* to infect mammals. Anti-Osp C antibodies are capable of killing *Borrelia*, while anti-Osp A antibodies can only prevent transmission.

*B. burgdorferi* travels interstitially rather than hematogenously and lives in interstitial tissue near collagen and fibroblasts. Since *Borrelia* localizes in infected tissues, it is rarely detectable by culture/PCR on blood samples. For this reason, diagnostics are based on antibody testing rather than antigen testing.

BORRELIOSIS - DIAGNOSIS

*B. burgdorferi* – Initial Screening
Point-of-care ELISA (IDEXX SNAP™ 4Dx® Plus) or BioCD (Antech™ Accuplex™) tests are antibody tests used for screening dogs. Experimental studies indicate that anti-*B. burgdorferi* antibodies are detectable 3-12 weeks after exposure and persist for weeks to months to years. Annual screening using point-of-care tests can act as important tools, serving as a marker for tick exposure and comorbid tick-borne infections in individual dogs and therefore an assessment of the success of prevention strategies such as Lyme vaccination and tick control. Additionally, since dogs are more likely to be infected with *B. burgdorferi* than humans, canine screening provides a guide to the local risk of infection for dogs and humans. If a dog has been vaccinated against *B. burgdorferi*, screening test results should be interpreted with caution. If the Antech™ Accuplex™ 4 is used, early stage infection and vaccination can produce positive results, so vaccination records are required to differentiate between infected and vaccinated dogs. However, the IDEXX SNAP™ 4Dx® Plus test detects antibodies against Lyme C6 peptide, expressed only during infection, not vaccination, so vaccination against Lyme disease does not interfere with test results.

Lyte Quant C6 Test
This test provides a quantitative assessment of antibodies against the *B. burgdorferi* C6 peptide, so is not affected by recent vaccination against Lyme disease. A titer of ≥30 U/mL supports a positive infection status. While the Quant C6 titer correlates with levels of circulating immune complexes, it does not correlate with severity of clinical disease. However, a reduction in C6 antibody titer should be
demonstrated during successful treatment, so serial Quant C6 titers can be used as part of a treatment/management protocol in infected dogs.

LYME DISEASE – CLINICAL PRESENTATION

Infection with B. burgdorferi has no acute stage and clinical signs appear 2-5 months after infection. Because B. burgdorferi localizes in tissues, infection can recrudesce, producing intermittent clinical signs. It is important to rule out other important causes of clinical signs in the diagnostic process for clinical Lyme disease, as prevalence of clinical Lyme disease is low. However, local exposure can be very high (70-90% in some areas), so canine Lyme disease is regularly diagnosed. Dogs co-infected with other tick-borne infections (e.g. Anaplasma) are more likely to show clinical signs.

There are only two clinical syndromes known to occur in canine Lyme disease -

1. **Polyarthritis** – This has a point prevalence of approximately 3% seropositive dogs, meaning that at any one time, 3% of seropositive dogs show clinical signs, although the overall prevalence of clinical signs for untreated infected dogs is likely to be higher. The incubation period for Lyme arthropathy can be prolonged, with a median incubation period of 68 days reported for one experimental study (Straubinger et al., 1998 *Wiener Klinische Wochenschrift* 110(24):874-81). Lyme polyarthritis was also reported to be self-limiting in a published experimental infection model.

2. **Protein-Losing Nephropathy** – This has a reported point prevalence of approximately 2% seropositive dogs. Again, overall prevalence of clinical signs for untreated infected dogs is likely to be higher. Lyme nephropathy is an immune-mediated glomerulonephritis caused by circulating immune complex deposition in the glomeruli, rather than a direct inflammatory effect of *B. burgdorferi* on the nephrons. Proteinuria is the hallmark of protein-losing nephropathy and azotemia can occur later in the disease process. Labradors and Golden Retrievers are at increased risk of Lyme nephritis, probably because of impaired removal of immune complexes from the glomeruli.

LYME DISEASE TREATMENT

The antimicrobial of choice for treatment of *B. burgdorferi* infections is doxycycline or minocycline (10mg/kg q24h). A 4-week course is standard for Lyme arthropathy, although course length should be guided by response to therapy and some cases required more prolonged therapy. In Lyme nephropathy, a 2-6 months course of doxycycline or minocycline (10mg/kg q24h) is usually required, although clinicians should be guided by response to therapy. Ancillary therapy such as ACE-inhibitors, a low-protein diet, anti-thrombotic drugs, anti-hypertensive drugs, and omega-3 fatty acid supplements, to treat the associated renal failure is usually instituted.

The response to treatment for Lyme disease should be dramatic, occurring in 1-2 days, if the diagnosis is correct. If there is no response to therapy for arthritis in 2 days, the differential diagnosis list should be reviewed. The most common differential for Lyme arthropathy is immune-mediated polyarthritis, which should respond to glucocorticoid therapy at immunosuppressive doses.

The Lyme C6 Quant antibody titer can be used to track the efficacy of treatment. If the original level was >100, there should be at least a 50% decline in titer after 6 months treatment, if treatment was successful and tick prevention to prevent re-exposure to *B. burgdorferi* is effective.

PREVENTION STRATEGIES

1. **Tick Control**

To prevent tick-borne disease, the active ingredients in topical products and collars should prevent attachment or kill ticks soon after attachment. Even Lyme-vaccinated dogs need tick control because of tick-borne co-infections. Topical permethrin, collars containing permethrin or amitraz and oral isoxazoline compounds should achieve this goal. However, it should be remembered that collars need to
be worn tightly enough to make contact with the skin to be effective. Also, permethrin is deadly to cats, so households with both dogs and cats might choose other products.

Ancillary methods to prevent tick exposure, such as landscaping to clear brush and other areas that are likely to harbor ticks and the avoidance of tick habitats during dog walking etc. should also be used.

2. Vaccination Against Lyme Disease

Natural infection with *B. burgdorferi* does not induce long-lasting protective immunity. Vaccination provides protection against infection by inducing antibodies against *Borrelia* outer surface proteins. Anti-Osp C antibodies are capable of killing *Borrelia*, while anti-Osp A antibodies can only prevent transmission of infection to mammals.

**Outer surface protein A (Osp A)**

All current vaccines induce antibodies against outer surface protein A (OspA). OspA expression is required for *Borrelia* to infect ticks and is found in *Borrelia* that are located in the midgut of the tick. OspA expression is reduced soon after tick attachment to mammals and OspA immunity appears to be effective only during a narrow window at the beginning of a blood meal, but it helps prevent further transmission of *B. burgdorferi* from ticks feeding on vaccinated dogs.

**Outer surface protein C (Osp C)**

OspC expression is required for *Borrelia* to infect mammals. This is the main immunogenic protein of *B. burgdorferi* and is located in the tick salivary glands and in the dog’s body during natural infection. There are approximately 15 OspC types in the USA and 30 OspC types have been identified worldwide. Until recently, it was thought that a single ‘universal’ OspC type could induce antibodies that would cross-protect against the other OspC types. This has recently been disproven (Oliver et al., 2016), emphasizing the importance of inducing antibodies against a number of different OspC types to help provide optimal protection from *Borrelia* infection in mammals. Broader protection is provided if both antibodies against both OspA and OspC are induced. Vaccination can induce a clinically insignificant rise in Lyme disease specific circulating immune complexes. However, studies have not linked canine Lyme nephritis with vaccination against Lyme disease.

**MANAGEMENT STRATEGIES**

Dogs can be classified for Lyme disease management purposes into the following categories -

1. **Lyme-Negative Dogs**

   Even if an individual dog is *Borrelia*-negative, tick removal and control could potentially be incomplete, so effective tick control should be discussed/instituted. Screening for possible co-infections, such as *Anaplasma, Rickettsia rickettsii, and Babesia* should be performed.

2. **Lyme-Positive Dogs without Clinical Signs**

   Effective tick control should be instituted and a thorough physical exam and urinalysis, including UP:UC, should be performed. If UP:UC is elevated, 4-6 weeks doxycycline treatment should be considered, as Lyme disease can have a prolonged incubation period. After antibiotic therapy is concluded, vaccination should be considered, since lifestyle factors for the infected dog led to Lyme-positive antibody status in the first place.

3. **Lyme-Positive Dogs with Clinical Signs**

   Effective tick control should be instituted and a thorough physical exam, CBC, serum biochemistry and urinalysis, including UP:UC, should be performed. A Quant C6 titer should be performed to serve as a baseline and further C6 tests can be used as a guide to the efficacy of therapy. Antimicrobial therapy with doxycycline and tick control should be commenced. After antibiotic therapy is concluded, vaccination should be considered, since lifestyle factors for the infected dog led to Lyme-positive antibody status in the first place.
Suggested Reading:


