

Fighting Lyme: The Latest on Diagnosis, Treatment and Prevention

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INTRODUCTION

Canine Lyme and the causative agent *Borrelia burgdorferi* have become a huge problem in many areas of the United States and Europe over the last 20 years. Over the last 5 years the disease has spread considerably and the incidence has risen considerably, even in areas of the Northeast that previously only had sporadic cases. The dilemmas facing practitioners regarding this disease are many. Regarding clinical Lyme cases the first dilemma is how to diagnose the disease. How to verify that a dog that is sick, and serologically positive – actually has Lyme disease. What diagnostics are appropriate in a case like this? The second, and often easier decision the practitioner must make is regarding treatment – with what? How much? and for how long. Often the harder question are regarding non-clinical dogs. When and then how to monitor non-clinical dogs for evidence of *Borrelia burgdorferi* infection? And, most importantly, how to prevent Lyme disease? How good is tick control? Should we or should we not vaccinate? Who should we vaccinate and do vaccines prevent or promote the most severe manifestation of Lyme disease – Lyme nephritis? This talk will briefly review the most updated information regarding the practical aspects of the diagnosis and treatment of canine Lyme disease. It will then focus on prevention of clinical Lyme disease. Should we monitor non-clinical dogs for *Borrelia burgdorferi* infection? And if we do - what do we do with a positive result? Does treatment prevent clinical disease? Should all dogs be treated or are there ways to pick and choose? And then should we vaccinate? What vaccines are there? Do the vaccines work? How do they work? Are there risks to vaccinating Lyme negative dogs? Lyme positive dogs? Using new data this talk will revolve around the ways that veterinarians can answer those questions best in their practice.

LYME DISEASE: CLINICAL SIGNS

The lack or apparent lack of clinical signs in most dogs with active Lyme infection makes both the diagnosis and the study of this disease very difficult. In dogs, clinical signs are observed only in approximately 10% of infected cases. These signs tend to occur 2 – 5 months after the infection and include lameness – mono or polyarthritis, lymphadenopathy, lethargy, and fever. Skin lesions are uncommon in dogs. These signs typically resolve within approximately 3 days, in some case only with antibiotic therapy. Some questions remain regarding more serious, less common syndromes that have been associated with Lyme infection in dogs including: Renal disease (Lyme nephritis), Cardiac disease (myocarditis) and neurological disease. Another question yet to be answered is whether some dogs get the devastating chronic recurrent disease as seen in some infected humans.

DIAGNOSIS

What diagnostic tools are available?

1. Bacterial culture or PCR. This is very difficult in the case of *Borrelia* due to the small number of infecting organisms and the complicated techniques involved in their successful culturing. Blood PCR testing is not recommended as a screening test for this organism as many infected dogs will have a negative PCR result.
2. Serology. Clinically today we must rely on serology in conjunction with clinical signs to diagnose this disease. There are currently 3 types of serological testing commercially available:
 - a. Non-specific ELISA. This is a very sensitive test aimed at identifying any antibodies produced against *Borrelia* whole cell antigen. It does NOT differentiate between antibodies produced in reaction to Lyme infection vs. Lyme vaccination and will be positive in both instances. Since we can usually never be sure of infection status and many times of vaccination status a positive non-specific ELISA should ideally be followed up with an additional test that would confirm infection like a Western blot or a C₆ antibody test
 - b. C₆ antibody testing. There are currently two commercially available tests for canine antibodies against the Lyme C₆ protein. This protein is expressed only during infection, therefore these tests are meant to be positive only in the event of natural exposure and negative in naive dogs or dogs vaccinated for Lyme. These tests include the in-house 3Dx

or 4Dx SNAP tests and the quantitative C₆ antibody test available through IDEXX.

Logical use of these tests:

- i. The SNAP 4Dx is an excellent test for screening dogs for Lyme infection. This can be done as part of a screening program for asymptomatic dogs or when Lyme disease is suspected. A positive result is indicative of active Lyme infection.
- ii. The quantitative C₆ antibody test tests for similar antibodies as the 4Dx but in a quantitative fashion. The value of knowing the quantitative C₆ titer is still unproven at this time, but we have shown that the titer correlated very well with circulating anti-Lyme immune complexes and is likely a very useful tool in treatment decisions of non-clinical dogs. The practical questions of when and how to use this tool will be addressed using new data. Briefly, it appears that the pre-treatment serum quantitative C₆ antibody concentration does predict immune complex load and can be used to assess value of therapy or possibly risk of vaccination. A follow up C₆ antibody concentration does suggest successful treatment.
- c. Western blot. This technique involves a blot smeared with Lyme antigens located in known locations. This is a relatively expensive and labor intensive type of test and its interpretation requires expertise. Therefore this will never be in-house technology. As we have learned more about the 4Dx and quantitative C₆ assays, they have taken some of the role of the Western blot as a confirmatory assay. At this time I would recommend using the Western blot only in dogs where the vaccinal status is important to the veterinarian.

LYME PREVENTION

Tick removal: It takes time for an infected tick to transmit *Borrelia* to a dog, this typically can happen no sooner than 48 hours from the beginning of the blood meal. Therefore daily tick removal especially immediately after possible tick exposure is beneficial. People should handle possible infected ticks with care though, since there is the potential for transmission to the person from the tick. Daily tick removal and tick control should be seen and the base of the Lyme prevention pyramid, and are crucial as part of the prevention strategy. Tick control should be used even in low incidence areas. Without concurrent tick control it is likely that the success of our prevention will decrease even if vaccines are appropriately used as well.

Should We Vaccinate??

Whenever contemplating the use of a vaccine one needs to take weigh the pros and cons. These are the considerations that should be evaluated in such cases in my opinion:

How common is the pathogen? How common is the disease? How severe is the disease? How treatable is the disease? How good is the natural immunity? How expensive, reliable, and safe is the vaccine? Is there a zoonotic potential? Now all that has to be done is to answer the above questions for the vaccine we are considering.

1. Common? The disease is very common. Even though most dogs are asymptomatic the infection rate is so high in the Northeast that it is a very common disease. 10% clinical signs of 50-75% of the dogs in some areas is a lot!
2. Severity? Maybe not that bad in some cases, although the pain associated with acute clinical signs can be quite severe. What we do not know is the prevalence of more severe syndromes such as Lyme nephritis and chronic recurrent disease. We do know that Lyme nephritis does occur; it is associated with *Borrelia burgdorferi* infection and is often fatal, with young healthy dogs dying within a few weeks of showing signs of clinical disease. Once you have seen one of these, I believe the severity issue takes on a whole new meaning.
3. Treatable? Acute arthritic and febrile Lyme are pretty treatable in most cases in terms of eliminating clinical signs. But in many if not most dogs we think based on experimental studies we never get rid of the bacteria even with antibiotic therapy. So maybe not that treatable. And then of course there is Lyme nephritis which at best seems very hard to treat.
4. Natural immunity? Not very good. Since the immune response appears to dampen over time. This is likely a result of the bacteria hiding themselves from the immune system by "hiding" in synovium and down-regulating their immunogenic surface proteins.

5. How expensive, reliable, and safe is the vaccine? There are 3 kinds of commercially available vaccines. All are relatively inexpensive. Two are whole cell bacterin based vaccines and the other a recombinant outer surface protein A (OspA) single antigen vaccine. There is some company generated published safety data, but it is limited and mostly relates to acute reactions in relatively small numbers of dogs. All 3 vaccines are approved for dogs and so had to go through USDA required safety testing. All 3 types of vaccine are likely to be effective. How do they work? We know that all 3 vaccines primarily work by providing dogs with outer surface protein A (OspA) antigen. Subsequently the dogs develop antibodies against OspA. These antibodies are taken up by the tick, during the blood meal and actually work in the gut of the tick to bind the bacteria during the blood meal. Once the bacteria have reached the body of the dog then the anti-OspA vaccination antibodies are not effective as the surface proteins covering the bacteria change they enter the mammalian body. OspC is the main immunogenic protein exhibited by the tick in the dog's body during natural infection. A new vaccine that has just been released (Nobivac[®] Lyme) also includes OspC antigens that are generated in culture by a unique strain of *Borrelia burgdorferi*, in addition to OspA antigen from a more conventional strain also found in the vaccine. To date though, there is no published data regarding the added benefit of the OspC antigen content of the vaccine.
6. Zoonosis? Not really, although there is some risk from infected ticks that are removed before finishing the blood meal. When given a choice the ticks tend to only feed on one species at a time.

The safety of Lyme vaccines

There are different aspects to this question:

1. Regarding acute vaccine reactions: Simplistically one could say: All the dogs in the vaccine studies seemed fine so the vaccine must be safe. Obviously that is not good enough. The vaccine studies are too small to pick up uncommon reactions, are too short in duration, are invariably conducted by the vaccine companies themselves and most of them are never published. There are actually also safety studies conducted on every vaccine that are much larger, but also typically looking for acute reactions and most often not published.
2. The more pressing question is: Do vaccines contribute to clinical signs associated with Lyme disease or to the syndrome known as Lyme nephritis? A large amount of new and exciting data will be presented to try to answer this question. And it is a good question because we now know that Lyme nephritis is not caused by an inflammatory response to renal invasion of *Borrelia burgdorferi* organisms. Lyme nephritis is a condition associated with an accumulation of immune complexes in the kidney. We have shown that all Lyme positive dogs have a measurable level of Lyme specific circulating immune complexes in their blood. More recently we have been able to purify renal immune complexes from kidneys of dogs that died of Lyme nephritis and to identify Lyme specific antibodies are present within those immune complexes. Studies are still ongoing regarding possible co-infections or other antigen-antibody complexes in those kidneys. We have recently concluded a series of studies assessing the possible contribution of vaccination to circulating immune complexes. Briefly we can say that the effect of Lyme vaccines on immune complexes in Lyme negative dogs is very transient and likely of little to no clinical significance. In Lyme positive dogs the story may be different and strategies to treat first and then vaccinate will be discussed. Possible differences between the different types of vaccines regarding their safety and potential contribution to immune complexes will be demonstrated
- 3.

My recommendations (based on the above criteria):

1. Vaccinate in endemic areas? Yes - To prevent infection from ticks. What defines an endemic area? That is a good question. Through screening the prevalence should be determined in each practice. In an area with high prevalence (over 20%?) It may be logical to vaccinate all dogs. In an area with less prevalence possibly identifying dogs at increased risk is the wise way to do it. This should be IN ADDITION to good tick control!
2. Vaccinate Lyme negative dogs? Yes.
3. Vaccinate positive dogs? Yes - To prevent reinfection from the tick as the immune system may or may not be able to prevent active disease even if the dog is Lyme positive. Here is the most relevant place for the concern over the immune complex issue Studies are currently ongoing that will hopefully aid in providing data to enable more precise recommendations in the near future.

4. How often to vaccinate? Annually at this time with the currently available vaccines.
5. Even in vaccinated dogs TICK CONTROL must be stressed to the owners since a very heavy Lyme burden may override vaccinal protection.

LYME TREATMENT

I believe there is little question about treating Lyme positive dogs with clinical signs. What should we use? There is no proven benefit in vaccinating a dog with clinical Lyme disease from a therapeutic standpoint. So we are left with antibiotics. Amoxicillin and doxycycline both work well although there is some evidence that doxycycline may be better, and should be used for 4-6 weeks. Doxycycline will also likely be better at treating additional organisms that may have co-infected our patient along with Lyme disease. The harder question is what about the non-clinical majority. Why not treat them all? Although it is hard to look the concerned owner of a young Lyme positive Golden Retriever in the eye and refuse to treat a possibly fatal disease, theoretically we should approach the treatment question from a risk-cost-benefit standpoint. At this time I am not sure we have enough information to make an informed choice in this matter. What do we know?

1. Lyme positive dogs may remain infected with Lyme at low numbers with or without treatment.
2. There is some evidence to show that in many cases treatment tends to lower Lyme titers faster than they would decline without treatment. This may be true for bacterial load as well as serological titers.
3. Based on experimental and a growing number of field studies data IDEXX laboratories is currently recommending treatment above a certain C₆ quantitative titer and then rechecking titers 6 months later to evaluate treatment afterwards. As we gain experience with this approach and controlled field studies are published we will have a clearer understanding of the question to treat or not to treat?

LYME NEPHRITIS

Current Recommendations for Screening and Treatment of Dogs with Suspected Lyme Nephritis.

(These are based on limited experience, theory and not yet on strong clinical data!).

1. Monitor dogs in endemic areas for Lyme infection
2. Screen all positive dogs for signs of proteinuria or microalbuminuria.
3. Screen all dogs that present with proteinuria or microalbuminuria for Lyme.
4. Consider treating any dogs positive for both Lyme and proteinuria or microalbuminuria with 4-6 weeks of doxycycline.
5. If proteinuria persists or worsens (based on urine protein/creatinine ratio):
 - a. Continue doxycycline
 - b. Consider low protein diet and an ACE inhibitor
 - c. Consider renal biopsy
6. If the renal biopsy is consistent with immune mediated GN consider immunosuppression with drugs like mycophenolate, azathioprine, chlorambucil, or cyclosporine.

References available upon request