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 infected humans over 90% have clinical signs.

The clinical signs in humans are typically divided into 3 stages:
Early: days – weeks. ECM (erythema chronicum migrans), then flu-like symptoms
Late: weeks – months. These signs can occur if untreated. They are typically musculoskeletal pain, cardiac abnormalities, and neurologic signs.
Late: months – years. Similar to the late signs these commonly include arthritis, and neurologic signs. Especially worrisome in people is the episodic recurrence of clinical disease in some cases months to years after the initial infection despite appropriate therapy.

In dogs, on the other hand, (no pun intended) 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
The lack of clinical signs in most cases obviously affects our ability to accurately diagnose this disease. Therefore we need to base our diagnosis when presented with a sick dog on wide criteria – not just one serological test – as accurate as that test may be in correctly identifying infection. First we should ask: Do dogs with clinical disease due to lyme invariably have antibody titer? And as far as we know the answer to that question is yes. Since the onset of clinical signs takes at least 2 months, we should have antibody production by then and at least in acute disease should not have serologically negative clinical cases of Lyme disease.

What diagnostic tools are available?
1. Bacterial culture or identification. 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. The ideal place to obtain a culture is from the skin adjacent to the area the tick was feeding on. PCR (polymerase chain reaction) for Borrelia can also be performed on tissue from this region but is not offered for commercial clinical testing.

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. Logical use of this test:
      i. To screen for lyme infection in dogs that were definitely not vaccinated.
      ii. To check vaccination status assuming the dogs has definitely not been infected as well as vaccinated.

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 conform 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 SNAP test and the quantitative C₆ antibody test available through Idexx. Logical use of these tests:
   i. The SNAP 3Dx appears to be a very good test for screening dogs for lyme exposure. This can be done as part of a screening program for asymptomatic dogs or when Lyme disease is suspected. A positive result is good evidence for lyme exposure. There appears to be little to no cross reactivity with vaccinational antibodies therefore a vaccinated (but not infected) dog would have a negative test result. The 3Dx test is semi-quantitative but for a more accurate quantitative result Idexx recommends the quantitative assay.
   ii. The quantitative C₆ antibody test tests for similar antibodies as the 3Dx but in a quantitative fashion. The value of knowing the quantitative C₆ titer is still unclear at this time, although results of small experimental studies of Lyme disease in dogs suggest that a drop in C₆ titers correlates to a positive clinical outcome. This is a very new test and I believe that its true value will become apparent in the future. New studies will be presented showing a correlation between quantitative C₆ titers and circulating immune complexes.

c. Western blot. This technique involves a blot smeared with lyme antigens located in known locations. When a patient’s serum is placed on the blot the specific antibodies will recognize the antigens and bind to them. A marker is then used to identify the presence of the canine antibodies. This technique recognizes the presence of antibodies induced by exposure to the bacteria as well as antibodies produced in response to a vaccine and therefore gives us the maximum information possible. When should this test be used? 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 3Dx 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 18-24 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. Tick control is probably one of the best ways to prevent Lyme disease. A recent study demonstrated that the use of tick control alone with fipronil (Frontline®) was successful in preventing Lyme infection in most dogs when exposed to infected ticks compared to none in non-treated control dogs

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? Not that bad in most cases. What we do not know is the prevalence and significance of more severe syndromes such as Lyme nephritis and chronic recurrent disease.

3. Treatable? Pretty treatable in most cases in terms of eliminating clinical signs. But in many 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 cartilage and down-regulating their immunogenic surface proteins.

5. How expensive, reliable, and safe is the vaccine? There are two kinds of commercially available vaccines. Both appear to be relatively inexpensive. One is a whole cell bacterin and the other a recombinant outer surface protein A (OspA) single antigen vaccine. There is very little published safety data. Both vaccines are approved for dogs and so had to go through safety testing. Both types of vaccine are likely to be effective. Studies performed at Cornell using the recombinant OspA (Merial) vaccine showed very high protection rates when challenged with infected ticks 1 month and one year after vaccination. Both vaccines actually work in a similar way. This is by providing the dog with antibodies against OspA. These antibodies 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 vaccinational antibodies (from either vaccine) 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.

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.

My recommendations (based on the above criteria):
1. Vaccinate in endemic areas? Yes - To prevent infection from ticks.
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.

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
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:


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?
1. With special stains (Silver Stain) a single spirochete was thought to be identified in 2 kidneys evaluated.
2. 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.
3. 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:
1. Is it really Lyme or something else? Is Lyme the whole story?
2. What does a live dog or an early case look like?
3. What is the real time frame of the disease?
4. What does a mild case look like?
5. Can some of them resolve?
6. Does treating these dogs early post infection lower the risk of the disease?
7. Can the disease be induced by an immune response to one of the vaccines?

We do not have answers to any of those questions at this time. Studies currently underway may eventually yield answers to some. At this time I can report on the result of one study that showed that there is no correlation between Lyme status and the prevalence of microalbuminuria in a large group healthy asymptomatic Labrador Retrievers.

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!)
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 azathioprine, chlorambucil, or cyclosporine.

Additional references available upon request