Lyme Disease: Treat, vaccinate, or do nothing?
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INTRODUCTION
• In the USA, caused by spirochete *Borrelia burgdorferi* – it is the most common tick-transmitted zoonotic diseases in North America.
• Although 95% of exposed dogs remain asymptomatic, the main clinical features in dogs include recurrent lameness due to arthritis (sometimes accompanied fever, anorexia and depression).
• Rarely, renal failure (due to immune mediated glomerulonephritis) can occur.
• Cardiac, neurologic, and dermatologic disease has also been attributed to Lyme disease but not shown in experimental models.
• Horses, cattle, and cats can be infected – clinical disease in cats has not been reported.

EPIZOOTIOLOGY
• Transmission - by *Ixodes* ticks: *I. scapularis* in the Northeast and Midwest; *I. pacificus* in the West.
• In particularly the coastal regions of Northeastern states (CT, NY, RI), the infection rate of *I. scapularis* ticks with *Borrelia* can be 50-90%.
• Tick larvae and nymphs feed on small mammals (mice); adult ticks feed on deer and larger mammals.
• Infected nymphs and adult ticks attach to dogs and pass on *Borrelia* while feeding.
• Because the bacteria lives in the mid-gut of the tick, and must migrate to the salivary glands of the tick for transfer to the skin of a host, transmission does not occur at least for the first 24 hours after attachment – some suggest this is as long as 36-48 hours.
• The presence of small, flat, non-engorged *Ixodes* ticks on a dog suggests a very low risk of infection.

INCIDENCE/PREVALENCE/Geographic distribution
• Seroprevalence in dogs varies greatly with exposure to infected ticks in endemic areas.
• 70-90% of dogs in highly endemic areas may be sero-positive but less than 5% of these dogs will show clinical signs of Lyme disease (lameness) over nearly a 2 year period.
• Distribution - Northeast (Maine to Maryland - >90% of cases occur here), the upper Midwest (Wisconsin, Minnesota) and the far west (mainly northern California).

SIGNALMENT/Breeds/age
• Dogs, occasionally horses and cattle, show signs; cats are exposed but signs not reported.
• Any dog breed exposed may become infected but Shetland Sheepdogs, Labrador and Golden Retrievers have been more likely than other breeds to develop Lyme nephritis.
• Adult dogs experimentally infected with *B. burgdorferi* did not develop clinical signs; 6-26 week-old-puppies were more likely to develop disease experimentally. Any age dog may be infected after natural exposure. No gender differences have been reported.

PATHOPHYSIOLOGY
• Arthritis – although not completely clear, the immune (both cellular and humoral) response to the migrating spirochetes is involved.
• After a tick bite, the organism migrates over weeks and months to produce a generalized infection mainly of connective tissue in joints, tendons, muscles, and lymph nodes.
• Immune-complexes to Borrelia-specific antigens may be deposited in the kidneys but living organisms are not found in the kidneys.
• Incubation period in experimentally infected does: 2–5 months.

**SIGNS**

• Important to remember that 95% of exposed dogs remain asymptomatic.

• Acute form - transient fever (103 – 105F), anorexia, depression, and acute lameness lasting for only 3–4 days; reoccurs days to weeks later in the same or in other limbs (shifting lameness); one or more joints may be swollen and warm; a pain response is elicited on joint manipulation; responds well to antibiotic treatment.

• Chronic non-erosive polyarthritis found in animals with prolonged infection without adequate treatment; may persist despite antimicrobial therapy.

• Superficial lymph nodes close to the infecting tick bite may be enlarged.

• Kidneys – reported glomerulonephritis with immune-complex deposition in the glomeruli leading to fatal renal disease; patients may present with renal failure (vomiting, diarrhea, anorexia, weight loss, polyuria/polydipsia, peripheral edema or ascites); unknown why some dogs develop nephropathy while others do not.

• Cardiac and neurologic complication – rare clinical reports.

**DIFFERENTIAL DIAGNOSIS/COINFECTIONS**

• Fever, lameness, or proteinuria can have many other causes – infectious (bacterial, tick-borne such as ehrlichiosis, anaplasmosis, Rocky Mountain spotted fever, leishmaniasis, and fungal; histoplasmosis, blastomycosis), immune-mediated (idiopathic, lupus, rheumatoid), degenerative, trauma, neoplasia, breed specific (Akita arthritis, Shar Pei fever).

• Ixodes ticks can also be infected with *Anaplasma phagocytophilum*, *Babesia microti*, *Bartonella* spp., and tick borne encephalitis virus (about 40% of dogs sero-positive for Lyme disease are also sero-positive for *A. phagocytophilum*).

• Dogs infected with both *Borrelia* and *A. phagocytophilum* have slightly less than twice the frequency of lameness than dogs infected with *Borrelia* alone (53% compared to 29%).

**DIAGNOSIS**

• Although no individual test result proves that a dogs clinical signs are due to *Borrelia* infection, a presumptive diagnosis can be made based on: 1) evidence of exposure, 2) consistent clinical signs with infection, 3) ruling out other differentials, 4) response to appropriate treatment.

• Evidence of exposure – presence of an engorged Ixodes tick, dog lives or visited an endemic area, or positive test result.

• Routine CBC and serum biochemistry are usually unremarkable unless protein-losing glomerulopathy is present (uremia, proteinuria, hypercholesterolemia, hyperphosphatemia, and hypoalbuminemia).

• Culture of the organism (from the skin site of tick attachment, collagen-rich connective tissues such as muscle fascia and synovium, blood or plasma, CSF, and synovial fluid) requires special media and long incubation times (2-4 weeks); limited by low sensitivity (especially after antibiotic therapy), expense, delayed results, and invasive nature of tissue sampling.

• PCR on similar samples as above - sensitivity depends on the samples (varies from 10 to 80% in human studies); techniques have not been standardized among laboratories: not a widely accepted as a diagnostic tool as not reliable, practical, cost effective, or sensitive.

• ELISA and Western blotting – positive serology indicates previous exposure to *B. burgdorferi* antigens; may indicate disease; regular ELISA cannot be used to differentiate between vaccination and infection, but Western blotting allows differentiation; cross-reaction with antibodies induced by other bacterial infections (e.g. *Leptospira* spp., *Anaplasma* spp.) is minimal.

• Point-of-care tests - SNAP 3Dx or 4Dx, (IDEXX Laboratories, Westbrook, ME) – membrane ELISA test detects a subgroup of antibodies against the outer surface protein VlSE using the C6 peptide; convenient test that only detects infection and does not respond to Lyme vaccine-induced antibodies; in dogs, a positive antibody response
occurs 3-5 weeks after infection and normally drops or may even disappear about 2–6 months after antibiotic therapy.

- A quantitative version of the IDEXX SNAP test exists – Lyme Quant C6 Test (IDEXX Laboratories, Westbrook, ME) – correlates well with Western blotting; test remains positive for at least 69 weeks.
- C6 antibody titers also correlate with Lyme-specific circulating immune complexes, and the level of these immune complexes correlates with the severity of clinical illness of dogs.
- Because serology becomes positive well before the development of disease in infected dogs, paired titers are redundant; also, titer magnitude is not associated with the presence or absence of clinical signs, thus serology is not an accurate indicator of disease status or response to treatment.

TREATMENT

- The most commonly used antibiotic in dogs to treat Lyme disease is doxycycline (10 mg/kg, PO, q24h for at least 4 weeks); also addresses most co-infections.
- Others – amoxicillin (20 mg/kg, PO, q8h), azithromycin (25 mg/kg, PO, q12h), ceftriaxone (25 mg/kg, IV, q24h) for 4 weeks; amoxicillin is indicated in young puppies to avoid teeth staining from doxycycline.
- NOTE: all these therapeutic regimes have failed to clear organisms from the tissues of some dogs.
- The clinical signs of acute arthritis and fever should improve within 1-2 days of starting therapy; titers can remain for months or years although C6 titers may disappear.
- C6 antibody titers and Lyme-specific circulating immune complexes are both decreased 5 months after Lyme-infected dogs (both clinically affected and asymptomatic) are treated for 1 month with doxycycline – implications of this are still unknown.
- Lyme positive but asymptomatic dog – is some studies, neither sero-positivity nor the titer magnitude were correlated with whether the dog would show clinical signs during a 20 month period. Thus, currently, there seems little data to support the treatment of asymptomatic dogs with antibiotics.

MONITORING

- Dogs with Lyme disease should be monitored for proteinuria (complete urinalysis, in-house E.R.D.-HealthScreen Urine Test [Heska Corp, Fribourg, Switzerland], urine protein:creatinine ratio).
- ACVIM consensus statement - monitoring C6 antibody concentrations can not be routinely recommended at this time as there is not enough field data correlating titers with the subsequent development of disease.

PREVENTION

Vaccination

- ACVIM consensus statement – Dogs in non-endemic areas should not need vaccination. The majority of ACVIM diplomats do NOT recommend vaccination in endemic areas also. Such decisions should be made between each owner and vet based on individual case basis.
- 4 vaccines are currently available in the US
  - Monovalent bacterin – Lymevax, Fort Dodge Animal Health, Fort Dodge, IA.
  - Bivalent bacterin – Galaxy Lyme, Schering-Plough Animal Health, Union, NJ.
  - Non-adjuvanted rOsp A vaccine – Recombitek, Merial, Duluth, GA.
  - Adjuvanted rOsp A vaccine – ProLyme, Intervet, Millsborough, DE.
- Bacterin and rOsp A vaccines all work by generating anti-Osp A antibodies in the dog which when ingested by ticks, kill the *Borrelia* bacteria in the mid-gut of the ticks.
- Protocols of use: - ideally administer before exposure at 9 to 12 weeks, booster 2-4 weeks later, followed by annual boosters, preferably in the spring before tick exposure. Duration of immunity is short because there is no natural booster effect.
- Efficacy studies: - Lymevax bacterin resulted in a 78% efficacy against illness. Recombitek has been reported to produce a 100% protection against illness or infection to a 1 year of challenge.
• Bacterins have been suggested to also stimulate anti-Osp C antibodies but few bands to Osp C are seen on Western blots in bacterin-vaccinated dogs. Further, there is no evidence to suggest that anti-Osp C antibodies protect dogs against infection or disease (they don’t appear to in mice).

• Some have suggested that because bacterins contain more types of antigens, there might be more risk for immune-mediated reactions and adverse effects (ACVIM consensus statement).

• Adverse vaccine effects:- estimated to be < 2% overall. There are concerns that vaccination may contribute to the immunopathogenesis of disease in dogs (certainly, Lyme-nephropathy is a immune complex disease). Currently, there is no clear data implicating vaccine antigens in the potentiation of Lyme disease.

• Vaccination of seropositive dogs:- although some have advocated treating Lyme-positive dogs with a month of doxycycline and vaccination with LymeVax at 0 and 14 days, there is no data supporting this recommendation. In fact, there might be untoward immunologic consequences to this approach; further, the indiscriminate use of doxycycline could well lead to resistance developing in Borrelia and other organisms. However, some have suggested that vaccinating a seropositive asymptomatic dog with a non-adjuvanted rOsp A vaccine will prevent further infection from ticks (not supported by the ACVIM consensus statement) – perhaps one alternative to this would be to concentrate on tick control on the dog.

**Tick control**

• Essential not only to prevent Lyme disease but also RMSF, ehrlichiosis, anaplasmosis, babesiosis, bartonellosis etc.

• Avoid tick habitats by careful landscaping – ticks love leaf litter, low-lying vegetation, overhanging branches, wooded areas, and overgrown lawns; consult State health websites.

• Recommended tick control products:
  - Fipronil – Frontline Top Spot, Merial, Duluth, GA. Also provides effective flea control. Not washed off with swimming/bathing. 7 to 28 days protection after application.
  - Amitraz collar – Preventic collar, Virbac, Fort Worth, TX. Not active against fleas. Washed off easily. Toxic if eaten (antidote – yohimbine)
  - Permethrin/imidacloprid – Advantix, Bayer, Shawnee Mission, KS. Also repels fleas. Not washed off with swimming or mild bathing.
  - Permethrin-containing products – Defend EXspot or Proticall, Schering-Plough Animal Health, Union, NJ. Also repels fleas. Not washed off with swimming or mild bathing.

• Often recommended to use Fipronil together with Amitraz collar if infestations are heavy.

• Products that prevent tick attachment (Amitraz) or repel ticks (permethrin-containing products) are needed to decrease transmission of other tick-borne disease.

**ZOONOSIS**

• Dogs can transport unattached ticks, which later attach to humans – however, *Ixodid* ticks are not intermittent feeders and attach quickly; once tick starts feeding on a dog, it feeds to repletion and does not change hosts.

• Although it has been speculated that *Borrelia* in the saliva or urine of affected dogs might be transmissible to humans, experiments have failed to prove this.

**REFERENCES**


