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STANDARDS of CARE
EMERGENCY AND CRITICAL CARE MEDICINE®
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LYME DISEASE IN DOGS

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Lyme disease is caused by the spirochete *Borrelia burgdorferi*, transmitted by the bite of an ixodid tick after 2 to 4 days of tick attachment. In the United States in 2002, 95% of the human cases of Lyme disease occurred in just 12 states (listed in order of incidence of cases): New York, Connecticut, Pennsylvania, New Jersey, Massachusetts, Wisconsin, Minnesota, Rhode Island, Maryland, New Hampshire, Maine, and Delaware. Although only 10% of humans exposed to the agent of Lyme disease show no signs of illness, most dogs (approximately 95%) remain asymptomatic carriers after exposure. In some Lyme-endemic areas, 90% of healthy dogs have positive Lyme titers. A positive titer may not be a significant finding and may not prove whether a dog is currently sick because of Lyme disease or predict whether it will become ill from Lyme disease in the future.

Ixodid ticks in Lyme-endemic areas may transmit other organisms that may cause signs mimicking those of Lyme disease, or coinfections may increase the likelihood of signs. Such agents include *Anaplasma phagocytophilum* (formerly *Ehrlichia equi;* the agent of human granulocytic ehrlichiosis), *Babesia microti, Bartonella* spp, and tick-borne encephalitis virus. In one Lyme-endemic area, 40% of Lyme-positive dogs also had positive titers for *A. phagocytophilum*.

The clinical manifestations most commonly attributed to Lyme disease in dogs include Lyme arthritis (LA), a lameness/fever/anorexia syndrome generally responsive to a short course of antibiotics in the tetracycline or penicillin family, and Lyme nephropathy (LN), a more serious protein-losing nephropathy (PLN) syndrome associated with positive Lyme titers. LN is not seen in the experimental model of Lyme disease and has not satisfied Koch's postulates. Cardiac, neurologic, ophthalmic, or dermal manifestations in dogs are not as commonly seen or well documented. The tick exposure experimental model of Lyme disease in dogs shows that adult beagles develop positive Lyme titers but remain asymptomatic carriers. Young (6 to 12 weeks of age) beagle puppies develop positive titers and may show several 4-day, self-limiting episodes of lameness/fever/anorexia beginning 2 to 5 months after exposure to ixodid ticks from Lyme-endemic areas.

Controversy still remains concerning the extent of morbidity and/or mortality related to Lyme disease in dogs, whether treatment of asymptomatic positive dogs is necessary, whether vaccination against this disease is warranted, and whether vaccination might cause sensitization or increase the risk for enhanced antigen–antibody deposition in glomeruli or synovia in genetically predisposed dogs. Lyme vaccine for humans was withdrawn because of poor sales in 2002, because Lyme antigens were found to have molecular mimicry with human self-antigens, and because physicians feared using a vaccine that might cause immune-mediated sequelae in some genetically predisposed people. Despite the ongoing controversies, the following guidelines are given as helpful standards of care at this time.

DIAGNOSTIC CRITERIA

Historical Information

Gender Predisposition: None.

Age Predisposition

- **LA**—Often young to middle-aged dogs.

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- **LN**—On average, dogs with PLN associated with Lyme disease are younger than dogs with other glomerulopathies (5.5 years versus 7 to 8 years).

Breed Predisposition

- **LA**—Often large-breed dogs with a history of outdoor (tick) exposure in Lyme-endemic regions of the East and Midwest.
- **LN**—Labrador retrievers, golden retrievers, and possibly Shetland sheepdogs appear to be at increased risk, but individuals of any breed may be affected.

Owner Observations

- Owners may or may not have seen ticks on their dogs.
- **LA**—Lameness, reluctance to move, joint swelling/pain, anorexia, lethargy.
  - — Acute onset is most common, with one or only a few joints involved, especially the carpi and hocks.
  - — Chronic, intermittent, and possibly shifting leg lameness is less common.
- **LN**—Anorexia, vomiting, lethargy, weight loss, polyuria/polydipsia, urinary accidents, edema/ascites, dyspnea, sudden collapse/death, sudden blindness, seizure, nystagmus.
  - — Only 30% of dogs with LN had a previous or concurrent history of lameness.

Other Historical Considerations/Predispositions

- Because of the lengthy incubation, there may not be a seasonal presentation; however, one study suggested that dogs with LN presented more often during tick season.
- A postvaccinal Lyme-like arthritis has been described but is not well documented.
- About 30% of dogs with LN had previously received Lyme vaccinations.
- Lyme-endemic areas may also be endemic for anaplasmosis, ehrlichiosis, babesiosis, bartonellosis, Rocky Mountain spotted fever, and leptospirosis. Consider a Lyme-positive test result as a marker for exposure to ticks and wildlife. Coinfections may cause more serious illness.

Physical Examination Findings

- **LA**—Joint swelling/pain in one or more joints (often carpi and hocks), fever, ± lymphadenopathy.
- **LN**—Findings may be related to:
  - — **Renal failure:** Dehydration, oral ulcers, weight loss/muscle wasting.
  - — **Vasculitis** and **hypoalbuminemia:** Peripheral edema, pleural effusion and/or ascites, dyspnea, muffled heart sounds.
  - — **Hypertensive damage:** Retinal hemorrhage and/or detachment, heart murmur.
  - — **Thromboembolic (TE) events:** Dyspnea caused by pulmonary thromboembolism, hindlimb weakness with decreased femoral pulses as a result of saddle thrombus.
  - — **Neurologic changes** caused by vasculitis, hypertension, or TE events.
- **Lyme myocarditis** may cause complete heart block.

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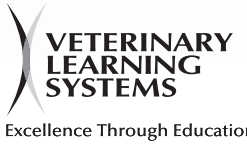

Laboratory Findings

- A positive Lyme titer. The author recommends the Canine SNAP 3Dx Test (Idexx Laboratories, Westbrook, ME) rather than the two-tiered ELISA or indirect fluorescent antibody (IFA) titer followed by Western blot if the dog has been exposed to Lyme vaccine. The SNAP 3Dx test is sensitive and specific for antibodies acquired via natural exposure to the organism.
  - — Positive Lyme titers neither prove nor predict illness related to Lyme disease because 4.8% of seropositive dogs show signs of lameness/fever/anorexia but so do 4.6% of seronegative dogs. Positive titers are a marker for tick/wildlife exposure.
  - — There is no acute phase of Lyme disease in dogs manifested in the experimental model. By the time a dog is sick because of Lyme disease, the Lyme titer should be positive and paired titers are not helpful. Antigenic variation during chronic infection causes new IgM production, and thus IgG versus IgM titers do not help determine time of initial exposure.
- **LA:**
  - — Complete blood count (CBC)/chemistry screen findings are unremarkable. Anemia, leukopenia, and/or thrombocytopenia are generally not seen in dogs with LA and, if present, may indicate other tick-borne or immune-mediated disease.
  - — Urinalysis findings are generally unremarkable, but the author recommends checking all Lyme-positive dogs for proteinuria via a urinalysis and a urine protein/creatinine (Up/c) ratio (normal: <0.4) or E.R.D.-HealthScreen Canine Urine Test (Heska, Ft. Collins, CO) for microalbuminuria. Dogs with low-positive results should be monitored every few months for a possible rising trend. When E.R.D. results are high-positive or Up/c ratio is 1.0 or higher, the dog should be tested for possible LN and to rule out other causes of proteinuria.
- **LN:**
  - — Urinalysis may reveal proteinuria, casts, and possible hemoglobulinuria/hematuria. Dogs with tubular involvement may have glucosuria and/or low urine specific gravity. There may be an active sediment with negative urine culture.
  - — Chemistry profile findings include hypoalbuminemia, hypercholesterolemia, possible azotemia, hyperphosphatemia, hyperkalemia, hyperglobulinemia, and/or hyperbilirubinemia.
  - — CBC shows nonregenerative anemia, thrombocytopenia, stress leukogram.

CHECKPOINTS

- Controversy exists concerning how long to treat LA (2 to 4 weeks).
- Controversy exists concerning how long to treat LN with antibiotics (1 month to long-term). No one knows how long is long enough to clear all dogs of the Lyme organism. (See Initial Treatment, page 5)
- In vitro studies suggest that two forms of the spirochete may need to be treated. Use doxycycline or amoxicillin for the motile form and metronidazole for a resistant L-form or spheroplast.
- Controversy exists about whether asymptomatic Lyme-positive dogs (i.e., those with neither arthritis nor proteinuria) should be treated with antibiotics or vaccinated. There is no indication that vaccination helps in treating Lyme-positive dogs, and the antigens in Lyme vaccines may even cause more antigen–antibody deposition in glomeruli or synovia.
- Controversy exists concerning vaccination of seronegative dogs for prevention of Lyme disease. Most dogs do not become ill from exposure to Lyme antigens (from vaccine or natural exposure). Most infected dogs remain asymptomatic carriers, have self-limiting arthritis, or respond rapidly to inexpensive, safe oral antibiotics for LA. Dogs that do not respond as readily to antibiotics may be genetically predisposed to have immune-mediated sequelae after exposure to Lyme antigens. There is concern that Lyme vaccine may sensitize them and that annual booster vaccines may cause harm. Whether you choose to use Lyme vaccines or not, multiple tick-borne agents in Lyme-endemic regions make excellent tick control imperative.

  - — Renal biopsy findings include glomerulonephritis, tubular necrosis/regeneration, and lymphoplasmacytic interstitial nephritis. Earlier changes associated with LN are unknown because there is no experimental model.

Other Diagnostic Findings

- **LA:**
  - — Joint tap shows neutrophilic (suppurative), nonseptic inflammation.
  - — Radiographs of affected joint(s) reveal soft tissue swelling ± nonerosive arthritis.

- **LN:**
  - — Possible hypertension.
  - — Ultrasonography/radiography of kidneys is often unremarkable.
  - — Dogs in a hypercoagulable state may have low antithrombin III level, elevated D-dimer test, and/or abnormal thromboelastography curve.

Summary of Diagnostic Criteria

- History of exposure to ticks in Lyme-endemic area.
- **LA**—Acute or intermittent fever/anorexia/arthritis in one or more joints.
- **LN**—PLN with possible nephrotic syndrome, renal failure, hypertension, and/or thromboembolic complications. Early LN may have occult proteinuria.
- Positive Lyme titer on SNAP 3Dx test (or ELISA/IFA/Western blot indicating natural exposure).
- Rule out other differentials (see below).
- Fast response to treatment (1 to 2 days) is generally seen with LA, but remember:
  - — Response may be due to the antiinflammatory properties of doxycycline.
  - — Response may be due to treatment of another doxycycline-responsive illness.
  - — Response may be due to spontaneous remission (trauma/degenerative joint disease).
- Response to treatment for LN is not necessarily fast if it occurs at all.

Diagnostic Differentials

In Lyme-endemic regions, consider testing for other tick-borne infectious diseases that can mimic LA or LN. Unlike Lyme disease, these may present during an acute phase with negative titers; therefore, paired or convalescent titers are needed. Antigen may be sought in acute cases by specific polymerase chain reaction (PCR) testing, but samples must be taken before starting antibiotic therapy to avoid false-negative results.

- ***Ehrlichia canis, Ehrlichia ewingii, Ehrlichia chaffeensis*** (mimics LA or LN)—*E. canis* titers (antibodies cross-react, but the test for *E. canis* may not detect all infections. For instance, only about 50% of dogs with *E. ewingii* test positive on an *E. canis* test); *Ehrlichia* spp PCR.
- ***A. phagocytophilum*** (mimics LA or LN)—Antibodies do not cross-react with *E. canis* tests; conduct separate *A. phagocytophilum* (*E. equi)* titers or *Ehrlichia* spp PCR.
- ***Babesia canis*** and/or ***Babesia gibsoni*** (mimics LN)—Serology or PCR.
- ***B. microti*** (mimics LN)—Antibodies do not cross-react with other *Babesia* spp antigens; conduct separate *B. microti* titers or *Babesia* spp PCR.

ON THE NEWS FRONT

Nadelman and colleagues showed that for adult humans living in Lyme-endemic areas, taking one dose (200 mg PO) of doxycycline within 72 hours of removal of an engorged *Ixodes* tick prevented any manifestations of Lyme disease and prevented seroconversion.

- ***Bartonella* spp** (mimic LA or LN)—Serology for *B. vinsonii, B. henselae*; blood culture or PCR.
- **Rocky Mountain spotted fever** (mimics acute LN)—*Rickettsia rickettsii* serology or PCR; direct fluorescent antibody test on skin biopsies before starting antibiotics.
- ***Mycoplasma* spp** (mimics LA)—Joint tap culture.

Other causes of lameness/stiffness/weakness:

- **Immune-mediated polyarthropathy** (mimics LA)—Generally responds promptly to steroids if added 1 to 2 days after seeing little response to doxycycline.
- **Reactive arthritis**—Occurs secondary to drug administration (e.g., sulfa/trimethoprim), allergies, *Campylobacter* (?).
- **Systemic lupus erythematosus**—Antinuclear antibody test (ANA); evidence of other target organ damage.
- **Rheumatoid arthritis**—Rheumatoid factor; radiographs may show erosive arthritis.
- **Septic arthritis**—Positive joint tap culture.
- **Trauma** or **degenerative joint disease.**
- **Other pain/swelling near joint**—Panosteitis, osteomyelitis, hypertrophic osteodystrophy, hypertrophic osteopathy, polymyositis, and neoplasia.
- **Inability to rise**—Neuromuscular, metabolic, cardiopulmonary, or vascular disease.

Other causes of PLN (renal biopsy may be helpful):

- **Immune-mediated glomerulonephritis**—Primary or secondary to infections listed above as well as heartworm, *Brucella, Hepatozoon, Leishmania,* adenoviral infection, neoplasia, drugs (sulfa–trimethoprim), allergies, vaccines (?).
- **Systemic lupus erythematosus**—ANA, Coombs' test.
- **Hereditary nephritis.**
- **Amyloidosis.**
- **Glomerulosclerosis, other glomerulopathies.**
- **Proteinuria**—Urine culture, chest radiographs, abdominal ultrasound, and lymph node and/or bone marrow aspirates may help rule out other causes of proteinuria. Mild proteinuria without hypoalbuminemia may be due to early PLN, fever, hypertension, steroids, or infectious/inflammatory conditions.

TREATMENT RECOMMENDATIONS

Initial Treatment

- **LA**—Doxycycline: 10 mg/kg PO sid–bid for 2–4 weeks.
- **LN**—Doxycycline: 10 mg/kg PO sid–bid given long-term.

  And

  Angiotensin-converting enzyme (ACE) inhibitor treatment: enalapril (0.5 mg/kg PO sid–bid) or benazepril (0.25 mg/kg PO sid–bid) to decrease proteinuria; given long-term.

  And

  In hypoalbuminemic dogs, low-dose aspirin therapy (0.5–5.0 mg/kg PO sid) to decrease the risk for thromboembolic events; given long-term.
- It is unknown how long it takes to clear Lyme infection.
  - Skin cultures were still positive for *Borrelia* organisms in three of 24 infected dogs after 1 month of antibiotic therapy.
  - Because of the poor prognosis for LN, the author uses doxycycline long-term until either the Lyme titer has waned or Up/c, albumin, creatinine, and blood urea nitrogen (BUN) have normalized.
  - Treatment of experimental dogs infected several months before treatment showed that the SNAP 3Dx titer waned 4 to 5 months after treatment. But it is suspected that carriers or dogs with chronic infections may not become seronegative as fast and may have positive SNAP 3Dx titers for years, as occurs in successfully treated humans. A positive SNAP 3Dx titer after treatment does not necessarily indicate that treatment has failed to clear a carrier state.
  - Recently available, the new Lyme Quantitative C6 Antibody Test (Idexx Laboratories) can help monitor for a quantitative decline in C6 antibodies after treatment. Finding a marked decline in quantitative C6 antibody 6 months after treatment (compared with pretreatment values) would indicate a good response to treatment and perhaps clearance of the carrier state.
- Use tick control to avoid further antigenic exposure and prevent exposure to other tick-borne infectious agents.

Alternative/Optional Treatments/Therapy

- Doxycycline is the first-choice agent because it has antiinflammatory properties and may treat other doxycycline-responsive diseases, such as ehrlichiosis. If doxycycline is not tolerated orally, it may be given intravenously. Less common choices include amoxicillin (20 mg/kg PO bid–tid), azithromycin (25 mg/kg PO sid), or ceftriaxone (25 mg/kg IV sid). Antibiotics are given for 2 to 4 weeks for LA and long-term for LN. No one knows how long is long enough to clear all dogs from the carrier state.
- Steroids (prednisone, 2.2 mg/kg/day PO, weaning to 0.5 mg/kg PO every other day) may be added for suspected immune-mediated arthritis if the response to antibiotics is inadequate or slow (after 1 to 2 days). Beware of gastric ulceration if using steroids in conjunction with low-dose aspirin in dogs with LN. Steroids are weaned slowly as for other immune-mediated diseases.
- Amlodipine (0.05–0.1 mg/kg PO sid) may be added if hypertension (systolic blood pressure > 170 mm Hg) still exists with high-dose ACE inhibitor therapy in dogs with LN.
- Hemodialysis may be indicated in dogs that are oliguric/anuric, hyperkalemic, fluid overloaded, and nonresponsive to medical efforts to increase glomerular filtration rate (e.g., mannitol, furosemide, dopamine).
- Other immunosuppressive therapies for PLN (e.g., steroids, cyclophosphamide, azathioprine, chlorambucil, mycophenolate) need more study. Cyclosporine was not found to be helpful in one study of canine glomerulonephritis.

Supportive Treatment

- Omega-3 fatty acids for LA and LN.
- Isotonic and colloidal fluid support as necessary.
- Antiemetics and gastrointestinal protectants as necessary (e.g., for vomiting, melena).
- Aluminum hydroxide for hyperphosphatemia. Do not give within 1 to 2 hours of doxycycline.
- Modified-protein/restricted-phosphorus diet as necessary for renal failure with PLN.

Patient Monitoring

- **LA**—Check for proteinuria every 3 to 6 months. (See Diagnostic Differentials, page 4.)
- **LN**—Monitor blood pressure, Up/c, creatinine, BUN, albumin, phosphorus, and CBC/platelet count every 1 to 2 weeks, then less frequently if the dog is stable. Continue ACE inhibitor therapy as long as proteinuria is found. Continue low-dose aspirin therapy as long as hypoalbuminemia exists. Continue antihypertensive therapy if needed.
- Conduct Lyme quantitative C6 antibody testing and compare the pretreatment and 6-month posttreatment values. Chronic infections may have qualitatively positive SNAP 3Dx titers for years, even after

successful clearance of the organism, but quantitative C6 antibody testing can hopefully show a marked decline in antibodies after treatment. A stable low-positive result posttreatment is probably due to immune cell memory.

Home Management

- Continue medications, supplements, and special diet at home.
- Tick control:
  - A tight amitraz collar (e.g., Preventic, Virbac Animal Health, Fort Worth, TX) is highly recommended to prevent tick attachment.
  - For dogs that swim: Fipronil (Frontline Top Spot Plus, Merial, Duluth, GA), permethrins—use with caution around cats—(K9 Advantix, Bayer Animal Health, Shawnee Mission, KS; Defend EXspot, Schering-Plough Animal Health, Union, NJ), or phenothrin (Hartz Advanced Care Brand, Hartz Mountain, Secaucus, NJ).
  - Products that repel ticks or thwart attachment help prevent diseases from organisms that are transmitted early during attachment (e.g., Rocky Mountain spotted fever, ehrlichiosis).

Milestones/Recovery Time Frames

- **LA**—Response is generally rapid (days). Most dogs fully recover without developing LN.
- **LN**—Generally poor prognosis if dog presents very ill with anorexia, vomiting, and dehydration. If LN is picked up earlier, look for response to therapy, including increased appetite, decreased vomiting, and closer to normal Up/c, serum albumin, phosphorus, BUN, creatinine, cholesterol, and CBC/platelet count parameters.

Treatment Contraindications

- Vaccination for Lyme disease with bacterin or subunit ospA vaccines may be contraindicated because vaccine antigens may cause further antigen–antibody immune-complex deposition in glomeruli or synovia.
- Steroids plus NSAIDs increase the risk for gastric ulceration, especially in azotemic patients.
- Cystocentesis is not recommended in patients with thrombocytopenia.

PROGNOSIS

Favorable Criteria

- **LA**—Prognosis is good for acute presentation. Dogs with chronic polyarthropathy and a positive Lyme titer may not respond to doxycycline alone but often respond when steroids are added.
- Occult proteinuria may be found early in some asymptomatic Lyme-positive dogs with no evidence of anorexia, vomiting, hypoalbuminemia, or azotemia; these dogs have a better prognosis than dogs presented with anorexia/vomiting and LN. (See Diagnostic Differentials, page 4.)

Unfavorable Criteria

- **LN**—Patients with PLN and dehydration, vomiting, anorexia, hypoalbuminemia, and azotemia often succumb within days or weeks. These cases are predisposed to effusions (especially after rehydration with crystalloids), thromboembolic events, hypertension, and anuric renal failure.
- **LA**—Chronic arthritis that does not respond to doxycycline and/or steroids is probably degenerative joint disease, and chronic NSAIDS or stronger immunosuppressive therapy may be needed.

RECOMMENDED READING

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