THE 2018 ACVIM LYME CONSENSUS STATEMENT

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INTRODUCTION AND METHODS

The 2018 ACVIM Lyme consensus update[1] includes our current understanding for the diagnosis, treatment, and prevention of Lyme disease in dogs and cats in North America and Europe, and should be read alongside the original consensus of 2006,[2] both available at http://www.acvim.org/Publications/JVIM/Consensus-Statements. The update was written by a panel of 6 diplomates of the ACVIM and ECVIM with infectious and renal disease expertise (MP Littman, B Gerber, RE Goldstein, MA Labato, MA Lappin, and GE Moore) and is summarized below. It includes input from the general memberships of the ACVIM, ECVIM, and CAPC (Companion Animal Parasite Council) via discussion groups at previous ACVIM Forums and comments given after online distribution of the manuscript draft. The revised paper was submitted in January 2018 and published this year. References, comments, and recommendations were graded by the evidence-based medicine (EBM) scale as follows:

EBM-A. Randomized, controlled clinical trials in the target species with spontaneous disease.

EBM-B. Randomized, controlled studies in the target species with disease in an experimental setting.

EBM-C. Non-randomized clinical trials, multiple case series, other experimental studies, and important results from uncontrolled studies.

EBM-D. Expert opinion, case reports, or studies in other species.

TOPICS ADDRESSED

1. What species of *Borrelia* are most common and where are the endemic areas?

1a: Update on *Borrelia* spp. and associated ticks

There are at least 52 *Borrelia* spp. (all gram-negative spirochetes), including 21 in the Lyme borreliosis group [LB; the main culprit of *B. burgdorferi* sensu lato (Bb-sl) is *B. burgdorferi* sensus stricto (Bb-ss or Bb) in Northeastern (NE)/ mid-Atlantic (MA)/upper Midwestern (MW) US, adjacent Canada, and central Europe, with at least 30 strains of Bb based on OspC genotyping] and 29 spp. in the relapsing fever group (RF; e.g., *B. miyamotoi* in the NE/MA/NW US/adjacent Canada; *B. hermsii* in NW/Canada; *B. turicatae* in Southern US; and *B. persica* in the Middle East/Asia). LB generally travels interstitially (exception: *B. mayonii*, a cause of LB in humans in MW/Canada) while the RF group travels hematogenously. *Ixodes* ticks are the main vector for Bb, Bb-sl, *B. miyamotoi*, and *B. mayonii*, and the soft argasid tick *Ornithodorus* (which only feeds 15-90 minutes) is the vector for *B. hermsii*, *B. turicatae*, and *B. persica*. *Ixodes* ticks may also transmit *Anaplasma phagocytophilum*, *Babesia microti*, *B. duncani*, *Ehrlichia muris*, tickborne encephalitis (Powassan) virus, *F. tularensis*, and possibly *Bartonella* spp.

STATEMENT[1]: The panel recommends further research to evaluate disease manifestations in dogs and cats due to non-Bb *Borrelia* spp.[EBM-D] Coinfections must be considered in those with suspected LB. [EBM-C]

1b: Geographic distribution and epidemiology of Bb infection

Transstadial transmission of Bb and the 2-year life cycle of the 3-host Ixodid ticks allows larvae (which feed in the summer on small mammals and birds) to acquire Bb from their first host and transmit Bb as infected nymphs the following spring as they feed on small mammals, birds, and also larger hosts, preferentially deer but also dogs, cats, horses, and humans, and as infected adult ticks the following fall, winter, and early spring, feeding on similar hosts whenever the temperature is greater than 40F (4C). Seroprevalence data for dogs is available for North America by states, counties, provinces, and territories at www.capcvet.org.

STATEMENT[1]: LB is established in geographical areas in North America and Europe, and is spreading, because of persistent tick vectors and reservoir hosts.[EBM-C] The estimated seroprevalence rates in dogs cannot be used as estimates of LB because most dogs that are exposed seroconvert, but do not develop clinical illness.[EBM-C]

2: What are the most common clinical manifestations of Lyme borreliosis?

2a: Considerations for dogs in North America

Experimentally mild-moderate synovial changes and tick bite site perivasculitis and perineuritis are seen (milder in 18-wk old vs. 6-wk old exposed pups); exposed puppies have self-limiting signs and exposed adult dogs remain non-

clinical seropositive carriers. In the field, most exposed dogs remain non-clinical and non-proteinuric. Lyme arthritis, seen in a small percentage of seropositive dogs, is still the only proven clinical manifestation for dogs with Bb. There is no experimental model for 'Lyme nephritis', a protein-losing nephropathy (PLN) putatively associated with Bb-specific antigen-antibody immune-complex glomerulonephritis (ICGN) in dogs and over-represented in retriever breeds (although still uncommon in these breeds) and less common than Lyme arthritis. Coinfections (e.g., other tickborne diseases, heartworm disease, leptospirosis) may mimic signs of LB.

STATEMENT[1]: Neurologic and cardiologic manifestations of LB in dogs are not well-documented. [EBM-D]

2b: European considerations; Bernese Mountain Dogs (BMDs) in Europe

In central Europe at least 5 species of Bb-sl (Bb-ss, *B. garinii*, *B. afzelii*, *B. bavariensis*, and *B. spielmanni*) may cause human illness but are not proven to be associated with canine illness.

STATEMENT[1]: It is not proven that European LB infection causes clinical signs in dogs.[EBM-D] Although not associated with illness, BMDs in central Europe are more often Lyme-seropositive than other breeds. [EBM-C]

2c: Considerations in cats

Although exposed cats may be seropositive and Bb may be isolated from skin biopsy samples from tick bite sites, the association of illness from Bb is not proven. Coinfection with *A. phagocytophilum*, which clinically mimics LB, may confound studies.

STATEMENT[1]: Although cats may be Bb-seropositive, it is unknown if Bb infection causes illness in cats. [EBM-D]

3: What diagnostic tests to confirm Bb exposure are recommended for clinically ill animals?

Because Bb is rarely found in tissues or bodily fluids, serologic tests are more helpful than PCR, culture, or tissue staining. Acute/convalescent or IgM titers are not needed since experimentally dogs do not show clinical signs until 2-5 months after exposure, well after seroconversion. OspA antibodies are likely due to vaccinal antibodies (all current Lyme vaccines contain monovalent OspA) and not usually natural exposure, although there are exceptions. OspC antibodies increase 2-3 weeks after infection, wane in 3-5 months, and once were used as a marker for recent natural exposure or reexposure, however, OspC antibodies may also be induced by current bacterins and the new chimeric recombinant vaccine. Antibodies against C_6 (VlsE) and OspF appear only after natural exposure (at 2-3 wks and 6-8 wks, respectively) and remain increased in untreated carriers. Although the magnitude of exposure titers has not been predictive of current or future illness, 4/6 panelists recommend post-treatment quantitative C_6 or OspF titer testing as a possible indicator of treatment success and to establish a new baseline for future comparisons, indicating reexposure or relapse if high again. Qualitative antibody tests may stay positive for a long time even after successful treatment. The presence of natural exposure Bb-antibodies is a sentinel for possible coinfections from ticks and wildlife, e.g., anaplasmosis, babesiosis, bartonellosis, ehrlichiosis, heartworm disease, leptospirosis, Rocky Mountain Spotted Fever, etc.

STATEMENT[1]: Panelists agreed that the presence of antibodies against C_6, VlsE, OspC, OspF (or some combination of these) indicates exposure to Bb, but is not proof of cause of clinical signs, nor can it be used as a predictor for development of future clinical signs. [EBM-C]

STATEMENT[1]: The panel believes that further optimization experiments should be performed before an in-house kit for the detection of C_6 peptide antibodies (labeled for use with dog serum but without species-specific reagents) can be recommended for routine use with cat serum. [EBM-D]

4: What treatments are recommended for clinically ill animals?

4a: Treatment of Lyme arthritis in dogs

Lyme arthritis (joint swelling, fever, anorexia, local lymphadenopathy), seen in a small subset of infected dogs, is transient or responds quickly to oral antibiotics in 1-2 days. Because of the protracted biological behavior of Bb, a long course (4 weeks) of antibiotics is recommended. The best protocol is unknown. Doxycycline or minocycline are preferred because of possible treatment of coinfections, anti-arthritic/anti-inflammatory properties, and lack of dental staining. Analgesics may be used; non-steroidal anti-inflammatory drugs are not preferred, in order to avoid a needed 'wash out' period (to decrease risk of GI ulceration) should a non-responder subsequently require steroidal treatment for suspected immune disease. In non-responsive cases, other differential diagnoses should be considered, e.g., immune-mediated polyarthropathy, trauma, septic arthritis, or degenerative joint disease. All Bb-seropositive dogs should be tested for proteinuria (see below) and adequate tick prevention should be used year-round.

STATEMENT[1]: Panelists agreed that Lyme arthritis be treated for 4 weeks with antibiotics (doxycycline preferred). [EBM-D]

4b: Treatment for Bb-seropositive dogs with protein-losing nephropathy (PLN)

Seropositive dogs found to have PLN are suspects for Lyme nephritis, although diagnosis of this entity is difficult to prove. There is still no experimental model to study its pathogenesis, best treatment protocol, or prevention in over-represented (retriever) breeds, and still no validated staining techniques to prove that glomerular immune-complexes are Lyme-specific in kidney biopsy samples of living dogs. PLN can be due to Lyme nephritis, coinfections, ICGN, amyloidosis, neoplastic, toxic, genetic, or other causes. Proteinuria and hypoalbuminemia may be seen in leptospirosis cases. Guidelines for the diagnosis and treatment for glomerular diseases are given by the International Renal Interest Society (IRIS) Glomerular Disease Study Group.[3-8] Empiric therapy includes antimicrobials (panelists did not agree on duration; 1-3 months or until C_6 antibody concentrations wane) and standard PLN protocols with renin-angiotensin-aldosterone system inhibitors, renal diet, omega 3-fatty acid supplement, antihypertensives, antithrombotics, crystalloids/colloids, phosphate binders, aldosterone antagonist diuretics, and treatments for chronic kidney disease. If renal biopsy documents ICGN, or even in non-responders with severe disease or rapid progression, immunsuppressives (mycophenolate/prednisone or other protocol) are recommended. Blood pressure, urine protein/creatinine ratio, serum creatinine and albumin concentrations should be monitored. Year-round tick prevention is advocated.

STATEMENT[1]: Panelists agreed that Bb-seropositive dogs with PLN be treated with antimicrobials as advised above and that clinicians follow the guidelines for the standard diagnostic tests and treatments for ICGN and PLN as recommended by the IRIS Canine Glomerulonephritis Study Group.[3-8] [EBM-D]

4c: In cats: If a cat is suspected to have LB, doxycycline is given as above, to treat LB and also the common coinfection anaplasmosis.

5. What testing is recommended for healthy animals?

All panelists recommend routine screening for seropositivity as part of an annual preventive care program for healthy dogs living in or near Lyme endemic areas in North America. Only 1 panelist recommended the routine use of quantitative testing for all qualitatively positive dogs (5/6 panelists stated there is insufficient evidence that the magnitude predicts current or future illness to recommend its use routinely). Seropositivity indicates need for 1) screening for proteinuria, 2) screening for possible occult changes and coinfections from ticks/wildlife, 3) additional preventive protocols, and 4) education of owners regarding risks in their environs.

STATEMENT[1]: It is recommended to screen all healthy dogs that live in, live near, or travel to Bb-endemic areas in North America for Bb antibodies. It is recommended to screen all Bb-seropositive dogs for proteinuria. [EBM-D]

6. Should treatments be offered for non-clinical, non-proteinuric seropositive dogs?

This topic is still controversial.[1,2,9] The magnitude of quantitative testing is not predictive of illness or need for treatment. Most (4/6) panelists do not treat these dogs; 5/5 panelists in North America suggest screening for proteinuria at least 2-3 times/yr whether treatment is given or not, since treatment may not clear all dogs and the pathogenesis of Lyme nephritis is unknown.

STATEMENT[1]: Most (4/6) panelists do not routinely recommend antimicrobial treatment for non-clinical non-proteinuric Bb-seropositive dogs. [EBM-D]

7. What prevention modalities are recommended?

7a: Tick control

Improved landscaping, avoidance of tick habitats, and quick removal of ticks is advocated by all. There are many new products (topicals, collars, and oral chewables) available with strong evidence for prevention of seroconversion if used properly.[1] Bb is generally not transmitted until after 36-48 hrs of tick attachment, but other tickborne microbes may be transmitted much faster, so products which prevent tick attachment or kill them relatively fast are best.

STATEMENT[1]: Whether Bb vaccines are used or not, there is strong consensus (6/6) that tick control must be used not only to help prevent LB but also to prevent many other tickborne diseases for which no vaccines are available. [EBM-C]

7b: Bb vaccination

Half (3/6) panelists do not use Bb vaccines citing inconsistent efficacy and duration of immunity, cost, need for tick control anyway, lack of controlled studies with respect to tick control when assessing vaccines in the field, theoretical concerns for immune-mediated sequelae, and because the vast majority of seropositive dogs remain non-clinical, non-proteinuric carriers.[1,2,10,11] But compliance for tick control is problematic, and vaccination may be useful. Six-month

boostering may improve vaccine efficacy. A chimeric recombinant vaccine with OspC from 7 strains of Bb in addition to monovalent OspA may offer additional coverage.

STATEMENT[1]: Panelists agreed that all dogs in Bb-endemic areas (whether vaccinated or not) should receive adequate tick control year-round, preferably with a product that prevents tick attachment or rapidly kills ticks during early feeding. Consensus for vaccination was not reached. Three of 6 panelists recommend vaccination, stating: 1) healthy Bb-seronegative dogs in North American Bb-endemic regions may be vaccinated with any of the currently available Bb vaccines, and 2) healthy (non-clinical, non-proteinuric) Bb-seropositive dogs in those regions may be vaccinated if the risk of reinfection is high. It is not recommended to vaccinate sick or proteinuric dogs. [EBM-D]

SUMMARY TABLE OF RECOMMENDATIONS IN CONSENSUS AND NOT IN CONSENSUS

CONSENSUS	NON-CONSENSUS
Screening all dogs in Bb-endemic and emerging areas in North America for Bb-antibodies	Treating healthy non-clinical non-proteinuric seropositive dogs
Testing all seropositive dogs in North America for proteinuria (frequency/duration debatable)	Using quantitative titers to decide about treatment
Choosing doxycycline as first choice (10 mg/kg/dy for 1 month; EBM-D)	How long to use antibiotics in Lyme nephritis suspects (1 month, 3-6 months, or until quantitative titer wanes)
Using mycophenolate (± short course prednisone) in Lyme nephritis suspects that are not responding to antibiotics plus standard PLN protocol	Use of Lyme vaccinations
Using tick control for all dogs at risk	6-month boostering of Lyme vaccines

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