ACVIM consensus update on Lyme borreliosis in dogs and cats

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Abstract

An update of the 2006 American College of Veterinary Internal Medicine (ACVIM) Small Animal Consensus Statement on Lyme Disease in Dogs: Diagnosis, Treatment, and Prevention was presented at the 2016 ACVIM Forum in Denver, CO, followed by panel and audience discussion and a drafted consensus statement distributed online to diplomates for comment. The updated consensus statement is presented below. The consensus statement aims to provide guidance on the diagnosis, treatment, and prevention of Lyme borreliosis in dogs and cats.

Abbreviations

- **Bb**
  - *Borrelia burgdorferi* sensu stricto
- **Bb–sl**
  - *Borrelia burgdorferi* sensu lato
- **BMDs**
  - Bernese Mountain Dogs
- **CIC**
  - circulating immune–complexes
- **EBM**
  - evidence–based medicine classification
- **ICGN**
  - immune–complex glomerulonephritis
- **LB**
  - Lyme borreliosis

- **Osp**
  - outer surface protein (eg, OspA, OspC, OspF)
- **PLN**
  - protein–losing nephropathy
- **TBD**
  - tickborne disease(s)
- **UPC**
  - urine protein/creatinine ratio
- **VlsE**
  - variable major protein–like sequence, expressed

1 INTRODUCTION

Over the past decade, since the first ACVIM Small Animal Lyme Consensus Statement was written, a broader understanding of the large number of *Borrelia* species that exist, the variability of strains of *Borrelia burgdorferi* sensu stricto (Bb), and the diversity of other pathogens carried by *Ixodes* and other ticks has been gained. The geographic distribution of infected ticks has expanded because of bird migration, suburban sprawl, and climate changes. Additional diagnostic tests are available to help rule out coinfections and other causes of clinical signs potentially attributable to Lyme borreliosis (LB), help differentiate vaccinal from natural acute or chronic exposure anti–Bb antibodies, and follow those antibodies that may wane post–treatment. Guidelines are offered for management of nonclinical nonproteinuric Bb–seropositive dogs and those with suspected clinical Lyme arthritis, Lyme nephritis, or both. Prevention updates include discussion of acaricide products provided as collars, topicals, or chewables that may facilitate owner compliance as well as new vaccination updates.

What has not changed is the finding that most Bb–seropositive dogs and cats show no clinical signs of illness, neither experimentally (using the natural tick exposure model) nor in the field. Signs of Lyme arthritis, seen in a small subset of infected dogs, are transient or respond quickly to PO

antibiotics. Signs of dermatologic, neurologic, or cardiac manifestations as seen in human patients are rare and not well–documented in dogs or cats. The most serious (putatively associated) form of LB in dogs, Lyme nephritis, is less common than Lyme arthritis. No experimental model to study its pathogenesis, treatment, and prevention in over–represented (retriever) breeds has been developed, and no validated staining techniques are available to prove that glomerular immune–complexes are Lyme–specific in kidney biopsy specimens from living dogs. Despite these limitations, strategies for empirical management of Lyme nephritis are given, as recently offered by the International Renal Interest Society (IRIS) Glomerular Disease Study Group.2-5

The objectives of this consensus statement are to review the evidence and provide findings and recommendations that address these topics regarding *Borrelia* spp. infection in dogs or cats:

1. What species are most common and where are the endemic areas?
2. What are the most common clinical manifestations of LB?
3. What diagnostic tests to confirm Bb exposure are recommended for clinically ill animals?
4. What treatments are recommended for clinically ill animals?
5. What testing is recommended for healthy animals?
6. Should treatments be offered for nonclinical, nonproteinuric seropositive dogs?
7. What prevention modalities are recommended?

This Lyme consensus update is best read in conjunction with the previous one, which includes many of the references for the original experimental and field studies. The update initially was discussed during a Special Interest Group presentation at the ACVIM National Forum in 2015. The authors conversed by phone and community emails with draft findings presented at the ACVIM National Forum in 2016. The 6 authors each voted whether or not to support the summary statements in the update. If a vote

is not recorded with a statement, then the vote of support was unanimous. For statements about which a consensus could not be reached, the vote of the committee members is listed and a brief explanation given for the dissenting votes. The update then was provided to the general ACVIM and ECVIM memberships and the Companion Animal Parasite Council and comments considered before submission for publication. The evidence–based medicine (EBM) scale for references, comments, and recommendations was used as data was obtained from the following:

> 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: Nonrandomized 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.

2 TOPIC 1: WHAT SPECIES ARE MOST COMMON AND WHERE ARE THE ENDEMIC AREAS?

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

There are at least 52 *Borrelia* species, including 21 in the LB group (*B. burgdorferi* sensu lato; Bb–sl; these gram–negative spirochetes generally migrate within the host interstitially), 29 in the relapsing fever group (migrating hematogenously), and 2 undetermined members. In dogs residing in North America, LB has only been associated with *B. burgdorferi* sensu stricto (Bb), of which at least 30 subtypes or strains exist, based on outer surface protein C (OspC) genotyping. The strains appear host–specific; different strains are more common in people as compared with dogs.7, 8 In Europe, coinfections of Bb with other Bb–sl strains (ie, *B.*

garinii) may predispose dogs to illness. Other Bb–sl species causing human LB (ie, *B. mayonii* in upper Midwestern states; *B. afzelii, B. bavariensis, B. garinii,* and *B. spielmanni* in Europe) are not known to cause illness in dogs. The main tick vector for Bb is the 3–host tick *Ixodes scapularis* in Northeastern, Mid–Atlantic, upper Midwestern states, and adjacent areas of Canada11, 12 (http://www.capcvet.org/parasite-prevalence-maps. Accessed January 5, 2018); *I. pacificus* in the Pacific states and Canada; and, *I. ricinus* in Europe. *Ixodes scapularis* also may transmit *B. mayonii* in the upper Midwest and adjacent Canada causing LB signs (with unusually high spirochetemia) and *B. miyamotoi*13, 14 in the Northeastern, Mid–Atlantic, upper Midwestern US and adjacent areas of Canada is a cause of tickborne relapsing fever (TBRF) in humans but is not yet known in dogs. Similarly, *B. lonestari*15, 16 transmitted by *Amblyomma* and other ticks, once thought to cause southern tick–associated rash infection (STARI) in humans, has not been associated with illness in dogs. Relapsing fever *Borrelia* species (*B. hermsii* in Northwestern states and adjacent Canada; *B. turicatae* in Southern states;18, 19 *B. persica* in the Middle East and Asia20, 21) have been described in sick dogs (*B. persica* also is described in sick cats), and are transmitted by *Ornithodorus* soft argasid ticks, which only feed for 15–90 minutes.

Most *Borrelia* species are transmitted transstadially within the tick; some in the relapsing fever group (eg, *B. miyamotoi*) also are transmitted transovarially. *Ixodes* larvae acquire Bb during their first meal, usually in the summer, from a small mammal or bird. The spirochete has numerous outer surface proteins (osp), and during feeding, OspA, expressed by Bb and acting as a hook to the tick's midgut, is down–regulated as OspC expression increases, allowing spirochetes to migrate from the midgut and enter the host, usually after 36–48 hours of tick attachment. More than 30 OspC genotypes or strains are found in nature (not all are pathogenic). Among 16 strains found in New England, the most common ones in humans were types A, B, I, K, and N, whereas the most common ones in dogs were A, B, F, I, and N. This finding impacts vaccine development for humans and

dogs.

Other organisms transmitted by *I. scapularis* and potentially associated with clinical illness in humans, dogs, and cats (some agents) include *Anaplasma phagocytophilum, Ehrlichia muris,* tickborne encephalitis (Powassan) virus, *F. tularensis*, and possibly *Bartonella* spp.29, 30 These infections can mimic LB and if coinfections occur, may be associated with increased morbidity. Additional *Ixodid* organisms causing illness in humans (eg, *Babesia microti*, *Babesia duncani*, *B. miyamotoi*, and *B. mayonii*) have not yet been associated with disease manifestations in dogs or cats. A *Babesia microti*–like organism causes protein–losing nephropathy (PLN) in dogs in Spain and Portugal and has been found in foxes in North America.32, 33

> Statement: The panel recommends further research to evaluate disease manifestations in dogs and cats because of non–Bb *Borrelia* spp. [EBM–D] Coinfections must be considered in those with suspected LB [EBM–C].

2.2 Topic 1b: Geographic distribution and epidemiology of Bb infection

The geographical persistence and spread of Bb is related to the 2–year, 3–stage (larva, nymph, and adult) life cycle of its *Ixodes* spp. vector, which feeds on a variety of hosts. One blood meal occurs per stage, and uninfected tick larvae hatch to feed on *Borrelia*–infected reservoir hosts, principally mice, squirrels, shrews, birds (*I. scapularis*) and lizards (*I. pacificus*). Within endemic geographical areas, the prevalence of *B. burgdorferi* in nymphal or adult ticks can reach approximately 50%.34-36 Although nymphs are likely responsible for the majority of Bb transmission to humans and dogs because the small size of this stage allows them to feed on the host undetected, dogs may be less susceptible to transmission of Bb from infected nymph versus adult infected ticks.37, 38 *Borrelia* infection often occurs in the warmer months as a result of the questing

behavior of ticks and the recreational habits of humans (owners) and their dogs. Later the same summer, nymphs molt to adults which feed on large mammals, preferentially deer, but also dogs and humans. Adult *Ixodes* ticks can be active in the fall, winter, and early spring when ambient air temperatures exceed 4°C (40°F). Deer are important for the maintenance, amplification, and spread of the tick population because adult ticks mate on them. Thus, *Borrelia*–infected ticks may first spread large distances by bird travel but then spread in a local area by deer or other reservoir movement. With suitable vegetation and ample reservoir hosts, Bb–infested ticks gradually will become established in an area. Similarly, decreases in vegetation and reservoir hosts, particularly deer, will result in a gradual decrease in disease.

Prevalence estimates of LB in dogs are hindered by a lack of demonstrative clinical signs and no national surveillance system for companion animal diseases. However, screening tests for Bb antibodies are widely used, and estimated canine Bb seroprevalence data at the US state and county and Canadian province and territory levels are available based on input from commercial diagnostic laboratories through the Companion Animal Parasite Council (CAPC; http://www.capcvet.org/parasite-prevalence-maps. Accessed on January 5, 2018; Table 1). Lyme disease in humans has been a notifiable disease in the US for many years although not every case is reported to the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention. CDC provides estimate of Americans diagnosed with LB each year. http://www.cdc.gov/media/releases/2013/p0819-lyme-disease.html. Press release August 19, 2013. Accessed on January 5, 2018. Reported cases of LB by state or locality, 2006–2016. Available at www.cdc.gov/lyme/stats/chartstables/reportedcases_statelocality.html. Accessed on January 5, 2018.) and surveillance summaries lag behind disease reporting. Underreporting of cases in humans is more likely in highly endemic areas, whereas misclassification (overreporting) is more likely in nonendemic areas. The same may be true for dogs. Travel history of

sick or seropositive dogs is an important historical question because cases in nonendemic areas may occur after travel to or importation from endemic disease areas.

Table 1. Bb antibody seroprevalence totals in dogs in North America, 2017 (http://www.capcvet.org/parasite-prevalence-maps. Accessed on January 5, 2018)

State	#Positive/#tested; %	State	#Positive/#tested; %	State	#Positive/#te %
AL	122/37,125; 0.33	KY	666/50,644; 1.32	ND	591/12,804; 4
AK	3/59; 5.08	LA	33/17,017; 0.19	OH	2,687/214,195
AZ	208/42,740; 0.49	ME	11,856/84,812;13.98	OK	118/36,923; 0.
AR	41/19,657; 0.21	MD[a]	11,832/172,014; 6.88	OR	129/12,862; 1.
CA	1,389/156,151; 0.89	MA[a]	38,448/248,335; 15.48	PA[a]	44,475/318,94 13.94
CO	188/21,876; 0.86	MI	3,477/238,240; 1.46	RI[a]	2,782/21,696; 12.82
CT[a]	22,132/135,483; 16.34	MN[a]	11,524/137,235; 8.40	SC	748/61,934; 1.
DE[a]	1,600/29,289; 5.46	MS	27/10,498; 0.26	SD	59/6,809; 0.8
DC[a]	1,069/11,496; 9.30	MO	204/61,677; 0.33	TN	455/59,693; 0
FL	1,548/209,288; 0.74	MT	13/1,038; 1.25	TX	584/221,599;
GA	349/95,670; 0.36	NE	43/7,465; 0.58	UT	11/640; 1.72
HI	22/7,869; 0.28	NV	16/3,345; 0.48	VT	4,724/32,657; 14.47
ID	5/632; 0.79	NH[a]	10,405/78,309; 13.29	VA[a]	21,141/270,52 7.81
IL	7,003/232,469; 3.01	NJ[a]	16,017/154,178; 10.39	WA	37/4,957; 0.75
IN	3,432/102,541; 3.35	NM	39/9,620; 0.41	WV	2,870/35,058;
			35,955/326,326;		13,922/162,77

IA	2,606/64,430; 4.04	NY[a]	11.02	WI[a]	8.55
KS	80/31,354; 0.26	NC	5,818/253,695; 2.29	WY	8/426; 1.88
Canada, available province/territory data					
AB	1/533; 0.19	NB	61/857; 7.12	ON	1,915/82,886;
BC	0/180; 0.00	NF	1/146; 0.68	QC	865/22,847; 3
MB	621/17,824; 3.48	NS	302/1,523; 19.8	SK	1/36; 2.78

Highlighted states–2017 areas of interest. Also check maps (http://www.capcvet.org/parasite-prevalence-maps. Accessed on January 5, 2018) of adjacent states for high seropositivity in contiguous counties.
[a]Twelve states reported in 2003 to account for 95% of cases.[1]

The main vector for Bb–sl in Europe is *I. ricinus* and the distribution of LB follows its expansion. The highest prevalence was found in central Europe with an increase of the infection rate of adult ticks from west to east. At least 5 species (*B. afzelii*, *B. garinii*, *B. burgdorferi* s.s., *B. spielmanii*, and *B. bavariensis*) cause disease in humans. Different species are found in questing ticks in different parts of Europe. These different species lead to a wider variety of clinical signs in infected humans in Europe compared with North America; whether or not this is true for dogs is unknown.

> Statement: 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].

3 TOPIC 2: WHAT ARE THE MOST COMMON CLINICAL MANIFESTATIONS OF LB?

3.1 Topic 2a: Considerations for dogs in North America

Most Bb–seropositive dogs show no clinical signs. The 2 main clinical manifestations of Bb infection in dogs, Lyme arthritis (in the field and experimentally) and Lyme nephritis (only in the field), were extensively reviewed previously and are not presented in detail here.1, 45-47 Subclinical histologic evidence of mild–to–moderate synovial changes and tick bite site perivasculitis and perineuritis are consistent findings in dogs experimentally infected with Bb after tick exposure; the changes seen are milder in 18–week old versus 6–week old exposed puppies.38, 48-50 Although neurologic signs were described in a few seropositive dogs in the past, recent field studies showed no association of neurologic signs in seropositive dogs, thus neuroborreliosis as seen in human and equine patients is not well–documented in dogs.53-56 Fatal myocarditis was described in Boxer pups with Bb–positive immunohistochemistry, for which no other cause was found; there may be a genetic (breed) predisposition for autoimmune myocarditis triggered by a Lyme antigen which mimics cardiac myosin. Lyme carditis, although uncommon in people, typically is manifested as atrioventricular block; this disease presentation also is poorly documented in dogs. Orbital myositis is a rare finding in infected people and has been reported in 1 dog.

> Statement: Neurologic and cardiologic manifestations of LB in dogs are not well–documented [EBM–D].

3.2 Topic 2b: European considerations; Bernese Mountain Dogs in Europe

In Europe, numerous serosurveys in dogs from different countries show a wide range of differences in seroprevalence. This is not surprising, considering the unequal distribution of ticks carrying Bb–sl. Little information is available regarding clinical disease in dogs caused by these organisms in Europe. Most studies show no association of seropositivity with clinical signs.60-64 One clinical study described 98 dogs with clinical signs possibly attributable to LB (history of tick infestation, lameness,

neurological signs, nephropathy, lethargy, anorexia, fever). Of these, 21 dogs (21%) were Bb–sl–seropositive (higher seroprevalence than in healthy dogs and dogs showing non–LB clinical signs). In 13 of the 21 dogs, no other cause of illness was found after extensive diagnostic evaluation, indicating a relationship between Bb–sl–seropositivity and disease. However in none of the 13 dogs could spirochetal DNA or viable spirochetes be detected.

> Statement: It is not proven that European LB causes clinical signs in dogs [EBM–D].

Interestingly, Bernese Mountain Dogs (BMDs) in Europe are more often Bb–sl–seropositive compared to dogs of other breeds.60, 66 In 1 study, 58% of 160 healthy BMDs were seropositive, compared with 15% seropositivity in healthy dogs of other large breeds with long hair living in the same region. No reason was found as to why the BMDs would be more prone to Bb–sl infection compared to other dogs in the region with similar risk of exposure. In another study of 200 randomly selected dogs admitted to 1 hospital, 13 were BMDs and, of these, 12 (92%) were Bb–sl–seropositive, compared with only 13 (7%) seropositive dogs of the remaining 187 dogs. In this study, BMDs were more often coinfected with *A. phagocytophilum* but the risk of infection with *A. phagocytophilum* alone was not higher than in other dogs. This finding indicates that a higher exposure of BMDs to ticks could not be the reason for the high Bb–sl–seroprevalence. In both studies, there may have been a breed predisposition of BMDs for Bb–sl infections. Furthermore, it is interesting that both of the studies showing higher Bb–sl–seroprevalence were performed in close proximity to each other in central Europe (Switzerland and southern Germany), the region where the highest prevalence of Bb–sl infested ticks was found. One might speculate about a regional effect, a close genetic relationship among the positive dogs, a genetic predisposition for infection (as was found in Beagles) or a unique infectious species of Bb–sl in the area.

> Statement: Although not associated with illness, BMDs in central Europe are more often Bb–sl–seropositive than other breeds [EBM–C].

3.3 Topic 2c: Considerations in cats

Cats living in Bb–endemic areas are sometimes seropositive.1, 69-73 Cats infested with *I. scapularis* containing Bb develop serum antibodies against the organism and DNA of Bb has been amplified from skin biopsy specimens taken from tick attachment sites.74-76 Ticks removed from cats in endemic areas have been positive for Bb. These studies suggest that cats can be infected by Bb and that *Ixodes* spp. are the likely vectors for Bb in cats in the United States.

Cats experimentally infested with *Ixodes* spp. have not developed detectable clinical signs of disease, even if infested twice.74-76 Cats in Bb–endemic areas may have clinical signs potentially referable to Bb infection but to date, no published studies document the organism as the cause of illness. It is difficult to prove causation of illness associated with Bb in cats because *Ixodes* spp. also are the vector for *A. phagocytophilum*. Anaplasmosis has been documented in cats in 2 studies in a Bb–endemic region.77, 78 Clinical signs of anaplasmosis and borreliosis are similar to each other in dogs and people, and this may be the case for cats as well.

It is proposed by some that cats fail to develop borreliosis because they are more efficient at removing infected ticks. However, seroconversion occurs in naturally exposed and experimentally infested cats suggesting that infection occurs, which should be blocked if ticks were promptly removed. At this time, evidence excluding borreliosis as a cause of clinical illness in cats is as weak as the data indicating causation.

> Statement: Although cats may be Bb–seropositive, it is unknown if Bb infection causes illness in cats [EBM–D].

4 TOPIC 3: WHAT DIAGNOSTIC TESTS TO

CONFIRM Bb EXPOSURE ARE RECOMMENDED FOR CLINICALLY ILL ANIMALS?

4.1 Topic 3a

In dogs, serology is the only recommended modality to evaluate for exposure to Bb (Table 2). Validated serologic tests for Bb exposure in North America include in–house and reference laboratory C_6–based testing (SNAP4Dx and SNAP4DxPlus [IDEXX Laboratories, Westbrook, Maine]; Lyme Quant C6 [IDEXX Laboratories, Westbrook, Maine]),79-81 the VetScan Canine Lyme Rapid assay (Abaxis North America, Union City, California), the AccuPlex4 test (Antech Diagnostics, Irvine, California),82, 83 and the Multiplex test (Cornell University Animal Health Diagnostic Center, Ithaca, New York).84, 85 Few studies compare different Bb antibody assay performance. In 1 study using Western blot as the gold standard, a commercially available kit based on the C_6 antigen was found to be more accurate than a commercially available multiplex fluorescence (AccuPlex4 [Antech Diagnostics, Irvine, California]) assay. In other studies of dogs experimentally infected with Bb, anti–OspC antibodies were detected before those against other peptides, suggesting that the multiplex assay may be more sensitive in acute cases of LB.83-85 This may not be clinically relevant because infected dogs do not typically present acutely.

Table 2. Bb antibody tests available

	Commonly used	**Differentiates vaccinal versus natural exposure antibody**	**Qualitative**	**Quantitative**	**Bedsi**
Whole cell IFA or ELISA		No		X	
IgM and IgG		No		X	

Western Blot		Possibly	X	Semi	
SNAP4DxPlus (IDEXX)	X	Yes, VlsE (C_6)	X		X
Quant C_6[a] (IDEXX)	X	Yes, VlsE (C_6)		X	
VetScan Rapid (Abaxis)	X	Possibly; VlsE, OspC, Flagellin	X		X
AccuPlex4 (Antech)	X	Possibly; OspA, OspC, OspF, p39, SLP	X		
Multiplex (Cornell)	X	Possibly; OspA, OspC, OspF		X	

[a]The Quant C_6 is not considered a screening test (see text).

Quantitative Bb antibody assays are available for C_6 (Lyme Quant C6 [IDEXX Laboratories, Westbrook, Maine]), and OspA, OspC, and Osp F antibodies (Multiplex [Cornell University Animal Health Diagnostic Center, Ithaca, New York]). Only 1 panelist recommends the routine use of a quantitative C_6 test for healthy nonclinical, nonproteinuric qualitatively seropositive dogs. The dissenting panelists stated that there is insufficient published evidence that higher titers predict illness or are associated with future illness to advocate routine recommendation of this test in healthy dogs.

Antibodies against C_6, VlsE (variable major protein–like sequence, expressed), and OspF indicate natural exposure because these antigens are not present in any Bb vaccines. Vaccines that induce OspC antibodies interfere with this marker of natural exposure on Western blot, AccuPlex4, VetScan and Multiplex tests. After experimental natural exposure, OspC antibodies increase by 2–3 weeks, and wane in 3–5 months (without re–

exposure), whereas OspF antibodies increase by 6–8 weeks and remain increased in untreated carriers.83-85, 87 The OspC antibodies probably increase again in field conditions (ie, re–exposure is a natural booster), thus finding OspC antibodies in a nonvaccinated dog may indicate recent exposure or re–exposure, without specifying when the dog was first infected in its life. The OspA antibodies usually are a marker for vaccination, but they may develop transiently in early infection,83, 85 or possibly later during chronic infections, as seen in infected humans, because Bb displays antigenic variation, and expresses its antigenic repertoire over time to avoid host immunity.88-91 The C_6 result has been shown to wane after treatment;92-94 OspF antibodies also may wane. Determination of quantitative titers to C_6 (or potentially OspF), pre– and 3 to 6 months post–treatment, were recommended by 4/6 panelists to check for a decrease after treatment as an indicator of decreased antigenic load, and to establish a new baseline for future comparison, because qualitative tests may stay positive a long time after treatment. An increased result over baseline may indicate re–exposure or relapse. The dissenting panelists state there is no published evidence that quantitative test results predict current illness, the potential for development of chronic disease, or differentiate reinfection from reactivation of a chronic infection.

Panelists did not recommend whole cell ELISA, immunofluorescent antibody (IFA) testing, or Western blot testing because of possible cross–reactions with other spirochetal infections, or the IgM versus IgG antibody testing because dogs do not present with acute illness before seroconversion.

> Statement: Panelists agreed that the presence of antibodies against C_6, VlsE, Osp C (in nonvaccinates), 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].

4.2 Topic 3b

In cats, several studies document antibodies against Bb occur in the serum of cats that are naturally exposed or infected with Bb after being experimentally infested with *I. scapularis*.70-76 Recent studies measured antibodies against the C_6 peptide using kits labeled for use with dog serum, which do not use species–specific reagents (SNAP4Dx and SNAP4DxPlus [IDEXX Laboratories, Westbrook, Maine]).75, 76 In 2 recent studies in which cats were experimentally infested with wild caught *I. scapularis*, 8 of 13 cats seroconverted.75, 76 Duration of positive test results varied, but was as short as 1 week in 1 cat. In 1 of the studies, skin biopsy specimens also were tested for Bb DNA by PCR assay and 3 of 9 cats were PCR positive but remained C_6 antibody negative over the 84–day study.

> Statement: The panel believes that further optimization experiments should be performed before this kit (SNAP4Dx and SNAP4DxPlus [IDEXX Laboratories, Westbrook, Maine]) can be recommended for routine use with cat serum [EBM–D].

5 TOPIC 4: WHAT TREATMENTS ARE RECOMMENDED FOR CLINICALLY ILL ANIMALS?

5.1 Topic 4a: Treatment of lyme arthritis in dogs

The classical presentation of LB is an acute monoarticular or polyarticular lameness with joint swelling, fever, lethargy, and mild local lymphadenopathy, usually in young, often large breed dogs with an active/outdoor lifestyle, but depending upon geographical location, is seen in other types of dogs. Treatment is based on treating infection and managing pain. Experimentally, the illness is self–limiting, and in the field typically a rapid response to antibiotics occurs within 1–2 days.

Many antibiotics, used both parenterally and PO, show efficacy in treating LB (Table 3).69, 98 Beta–lactams and tetracyclines have been shown to be effective for lessening clinical signs of LB in dogs. Because of the

protracted biological behavior of *Borrelia,* a long course of antibiotics (4 weeks) is indicated.95, 99-102 The best drug, dosage, and duration of treatment for affected dogs are unknown. Panelists recommend doxycycline as the first choice in most sick dogs with suspected LB because of the ease of administration, efficacy against coinfections (eg, *Anaplasma*, *Ehrlichia, Leptospira* spp.), and purported antiarthritic, anti–inflammatory properties.1, 103 Doxycycline was not associated with dental staining in children and is labeled for use in puppies and kittens as early as 4 weeks of age in some countries. However, although not a recommendation of the panelists, some veterinarians in the field recommend use of amoxicillin for doxycycline–sensitive or growing dogs. Recently, cefovecin (2 injections, 14 days apart) was shown to be as efficacious as 4 weeks of doxycycline or amoxicillin. Panelists agreed that this option could be considered for dogs intolerant of tetracyclines. Despite reports that 4 weeks of high dose treatment (10 mg/kg doxycycline q12h) did not clear all organisms in all dogs,101, 102 most veterinarians treat for 4 weeks[1] and many use a lower dosage of 10 mg/kg doxycycline q24h or divided q12h. Relapse seen in both dogs and humans101, 102, 106-108 may be caused by coinfection or reinfection, especially with other Bb strains.

Table 3. Antibiotics used in the treatment of LB

Antibiotic	Duration of Use	Frequency	Route	Dosage
Doxycycline or minocycline[a]	30 days	1–2 times daily	PO or IV	10 mg/kg
Amoxicillin	30 days	3 times daily	PO	20 mg/kg
Azithromycin	10–20 days	Once daily	PO	25 mg/kg
Clarithromycin	30 days	2 times daily	PO	7.5–12.5 mg/kg
Erythromycin	30 days	2–3 times daily	PO	25 mg/kg
Cefotaxime	14–30 days	3 times daily	IV	20 mg/kg
Ceftriaxone	14–30 days	Once daily	IV or SC	25 mg/kg

Cefovecin	28 days	2 times, 14 days apart	SC	8 mg/kg

[a]Doxycycline or minocycline are favored choices; minocycline is absorbed better without food.

Chronic Lyme arthritis is not well–documented in dogs and there is no evidence to support treatment beyond 1 month. In humans, the treatment of persistent clinical signs attributed to LB remains controversial (CDC website: http://www.cdc.gov/lyme/. Accessed on January 5, 2018; IDSA website: http://www.idsociety.org/Lyme/. Accessed on January 5, 2018; ILADS website: http://www.ilads.org/. Accessed on January 5, 2018).91, 98, 106, 108, 110, 111 A recent randomized, double–blind, placebo–controlled trial in Europe showed no difference in quality of life in those treated short–term versus long–term.

Response to antibiotic treatment in dogs presenting with signs of acute arthritis should be rapid (1–3 days) if the clinical signs are a consequence of LB. Analgesics should be considered (eg, gabapentin for neuropathic pain) as needed. Nonsteroidal anti–inflammatory drugs may be less preferable, so as to avoid a necessary "wash–out" period to decrease risk of gastrointestinal ulceration, should subsequent treatment with glucocorticosteroids be indicated for suspected immune–mediated polyarthropathy in nonresponsive dogs. If relapse occurs before or after completion of antibiotic treatment, additional diagnoses should include other infectious disease agents, immune–mediated disease, soft tissue trauma (eg, ligamental or meniscal tears), septic arthritis, or degenerative joint disease.

> Statement: Panelists agreed that Lyme arthritis be treated for 4 weeks with antibiotics (doxycycline preferred) [EBM–D].

5.2 Topic 4b: Treatment for Bb–seropositive dogs with

PLN

The nephropathy putatively associated with borreliosis is an immune–complex glomerulonephritis (ICGN).112-115 No validated staining techniques are available to prove that glomerular immune complexes found in kidney biopsy specimens are Lyme–specific in the living dog, and diagnosis depends on Bb–seropositivity in a dog with PLN for which no other cause is found. No experimental model for Lyme nephritis is available, and it is difficult to study treatment protocols. Recommendations are based on antimicrobial treatment and standard diagnostic and treatment protocols for ICGN and PLN, as recommended by the IRIS Canine Glomerulonephritis Study Group.2-5, 116-118 Proteinuria concurrent with seropositivity for an infectious agent with the potential to incite glomerular disease does not necessarily document a cause and effect relationship, even if clinical signs (eg, lameness) are seen. Only < 30% of dogs with Lyme nephritis have a history of past or concurrent Lyme arthritis.2, 5, 51, 112 Proteinuria is an uncommon finding, seen in <2% of Bb–seropositive dogs. Antibodies against Bb may be coincidental and a marker for wildlife exposure, because clinical signs (eg, lameness, proteinuria) attributed to LB may be caused by coinfection (eg, *Ehrlichia*, *Anaplasma*, *Babesia*, *Bartonella,* other *Borrelia* spp., Rocky Mountain spotted fever, heartworm, leptospirosis) or tick paralysis. Response to antibiotic treatment also is not proof of causation (eg, doxycycline may treat coinfections and has anti–inflammatory and antiarthritic properties sufficient to cause resolution of clinical signs).92, 99, 100, 106 Besides infectious causes, PLN may be associated with neoplasia, amyloidosis, as well as genetic, toxic, or other causes. Thus, a thorough diagnostic evaluation still is warranted to rule out other diseases, and to stage and to characterize possible complications of PLN (eg, hypertension, thromboembolic events, nephrotic syndrome, and renal failure).2, 116

For clinically stable seropositive dogs with mild changes of PLN (ie, uncomplicated nonprogressive renal proteinuria or mild hypoalbuminemia,

without azotemia) recommendations include antimicrobial treatment, evaluation for evidence of other possible causes of proteinuria (eg, coinfections, neoplasia, genetic diseases), and management of proteinuria, hypertension, and hypercoagulopathy based on established standard–of–care guidelines including a renin–angiotensin–aldosterone system inhibitor (angiotensin–converting enzyme inhibitor or aldosterone receptor (RAAS) blocker), antithrombotics, protein– and phosphorus–restricted diets based on IRIS staging, omega–3 fatty acids, and antihypertensives if needed.2, 3, 117 For dogs with more severe, persistent, or progressive glomerular disease, or complications such as vomiting, dehydration, edema, effusions, or worsening azotemia, additional recommendations include antiemetics, crystalloids or colloids, aldosterone antagonist diuretics, phosphate binders, and treatments for chronic kidney disease as needed.2, 3, 117 In addition, immunosuppressive agents are indicated if there is biopsy–confirmed evidence of an active immune–mediated pathogenesis (eg, electron–dense deposits by transmission electron microscopy, unequivocal immunofluorescent staining in the glomeruli),4, 120 or even without biopsy confirmation in nonresponders or those with rapid progression, severe azotemia (serum creatinine concentration > 5 mg/dL) or severe hypoalbuminemia (serum albumin concentration < 2.0 g/dL).2, 5, 121

For ICGN with profound proteinuria, hypoalbuminemia, nephrotic syndrome, or rapidly progressive azotemia, single drug or combination treatment consisting of rapidly acting immunosuppressive agents (Table 4) is recommended in addition to antimicrobials and standard PLN treatments and diets.2-5, 117, 122, 123 Immunosuppressive treatment is not without risk, especially in cases with concurrent diabetes mellitus, pancreatitis, active or latent bacterial or fungal infections, uncontrolled hypertension, hepatic dysfunction, or bone marrow suppression. Another relative contraindication is a breed with known inherited glomerulopathy.

Table 4. Recommended dosages and adverse effects of representative immunosuppressive drugs for management of immune–complex glomerular

disease

Drug	Dosage	Main adverse effects	Mode of action
Mycophenolate[a]	5 mg/kg q12h PO and increase to 10 mg/kg if no GI upset	Gastrointestinal upset	Antagonizes guanosine metabolism
Prednisolone[a]	1mg/kg q12h PO for 4–5 days then taper as soon as possible	Polyuria, polydipsia, polyphagia, thromboembolism, muscle wasting, induction of liver enzymes, panting, adrenal suppression, gastric ulceration	Inhibition of phospholipase A2, reduction in cytokine release, inhibition of neutrophil migration, down regulation of Fc receptor
Azathioprine	2 mg/kg q24h PO for 2 weeks, then 1–2 mg/kg q48h	Gastrointestinal upset, myelosuppression, acute pancreatitis, hepatotoxicity, GI disorders, infection, malignancy	Antagonizes purine metabolism
Cyclosporine	5–20 mg/kg q12h PO (taper dose upward from low to high to avoid GI complications)	Gastrointestinal upset, gingival hyperplasia	Calcineurin inhibitor
Chlorambucil	0.2 mg/kg q24–48h PO	Gastrointestinal upset, myelosuppression	Alkylating agent
Cyclophosphamide	50 mg/m^2 4 days/week PO, or as pulse treatment 200–250	Myelosuppression, GI upset, hemorrhagic cystitis, infection	Alkylating agent

	mg/m^2 every 3 weeks		

[a]Mycophenolate is a favored choice, with or without corticosteroids (see text).

The IRIS Study Group recommended mycophenolate as the first immunosuppressive employed, perhaps with a tapering dose of prednisolone in dogs with acute rapidly progressive glomerular disease. To minimize adverse effects of glucocorticoids, they should not be the sole agent and should be tapered as quickly as possible. Other immunosuppressive drugs (Table 4) are also anecdotally deemed efficacious for ICGN. Experiential evidence suggests that mycophenolate results in more remissions and long–term survival in dogs with ICGN. For stable or slowly progressive glomerular diseases, the Study Group recommended mycophenolate or chlorambucil alone or in combination with azathioprine on alternating days. For mycophenolate–intolerant dogs, consensus was lacking for the next preferred agent. Individual case variation and cost of medication may influence choice of treatment. For situations with extreme financial constraints, a short course of prednisone was suggested (1 mg/kg q12h for 4 days with a 2–week taper).

For both rapidly or slowly progressive forms of ICGN, therapeutic efficacy is assessed serially by monitoring proteinuria, blood pressure, serum albumin concentration, and kidney function tests. In the absence of overt adverse effects, at least 12 weeks of immunosuppressive (nonsteroidal) drug treatment should be undertaken before altering or abandoning an immunosuppressive trial. Panelists did not agree on the duration of antibiotic treatment, which ranged from 1 to 3 months, or longer if subsequent Quant C_6 antibody concentrations did not wane appropriately.

> Statement: 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 [EBM–D].

5.3 Topic 4c

Because borreliosis in cats has never been confirmed in a single cat, the optimal treatment plan is unknown. In cats with suspected anaplasmosis, clinical signs rapidly resolve after doxycycline is administered at 5 mg/kg q12h or 10 mg/kg PO q24h for 14–28 days.77, 78 Whether or not these cats also were infected with Bb cannot be determined. Based on studies of acute borreliosis in dogs, these doxycycline protocols are likely to be effective in cats as well.

6 TOPIC 5: WHAT TESTING IS RECOMMENDED FOR HEALTHY ANIMALS?

Panelists (5/5) recommended that a qualitative Bb antibody assay be included with annual wellness and preventive care for healthy dogs living in or near endemic areas in North America (there is no evidence to support screening healthy cats for Bb antibodies). Screening for Bb antibodies allows: (1) follow–up proteinuria screening for all seropositive dogs and early intervention for possible Lyme nephritis (see treatment), (2) follow–up minimal data base including CBC and serum biochemistry to identify cytopenias and kidney disease associated with tick and wildlife exposure, (3) identification of seropositive dogs (sentinels) that may indicate risk of exposure of humans, horses, cats or other dogs in the area and the need for modification of preventive protocols; and, (4) recognition of successful preventive strategies in high risk areas. Panelists identified potential pitfalls when screening healthy dogs, including the potential for overuse of antibiotics in rare dogs with false positive assay results, overuse of antibiotics in healthy dogs that would never develop LB, assay expense, induction of anxiety in the owner, and the additional time necessary for

owner education.

> Statement: 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].

7 TOPIC 6: SHOULD TREATMENTS BE OFFERED FOR NONCLINICAL, NONPROTEINURIC SEROPOSITIVE DOGS?

This topic is still controversial; 4/6 panelists do not routinely recommend treatment for such dogs (Table 5),96, 124 stating that: (1) this practice potentially promotes overuse of antibiotics; (2) no data exists proving treatment of healthy dogs is associated with decreased risk of illness; (3) Bb may not be cleared from all tissues with treatment; and, (4) reinfection may commonly occur in dogs in endemic areas. Seropositivity indicates tick and wildlife exposure and possible coinfection(s). Tick control and possible vaccination should be readdressed (see below). Panelists in North America (5/5) recommend reevaluation for proteinuria at least 2–3 times per year, even if the dog is treated with antibiotics, because clearance may not occur, and because the pathogenesis of Lyme nephritis is unknown.

Table 5. Some pros and cons of treatment of all nonproteinuric, nonclinical seropositive dogs

Pros	Cons
Treatment of possible Bb–associated periarticular inflammation	Treatment is not needed if periarticular inflammation is not present; older (18 week old) infected puppies showed milder histologic changes than younger (6 week old) infected puppies
Treatment of possible coinfections	Treatment is not needed if coinfection is not present
Possible prevention	

of future Lyme arthritis or Lyme nephritis	There is no ability to monitor the response to treatment if the dog is truly nonclinical; the vast majority of Bb–seropositive dogs never become ill nor proteinuric
	Unnecessary owner cost
	Overuse of antibiotics may cause microbial resistance in the environment at large
	Possible adverse effects of treatment
	Possible laxity in checking for proteinuria in carriers, even though they may not all be cleared with treatment
	Theoretically, a subclinically infected dog may be in a premunitive state that could be protective, at least for that particular strain

If a seropositive dog is nonclinical and nonproteinuric, there is no current evidence–based data that a quantitative C_6 antibody test (Lyme Quant C6 [IDEXX Laboratories, Westbrook, Maine]) result helps decision–making regarding whether antimicrobial treatment is warranted. The magnitude of Quant C_6 is not predictive of illness. A majority of untreated nonclinical nonproteinuric seropositive dogs probably have high concentrations, as do experimentally infected dogs, which all remain nonclinical. In the absence of clinical signs increased Quant C_6 may indicate exposure and a robust immune response to the organism.96, 124 Some dogs may eventually either clear the organism or remain nonclinical carriers, as did experimental dogs.

Dogs that show clinical signs of illness are a small subset of those with high Quant C_6 results. Correlation exists between the magnitude of quantitative C_6 and circulating immune–complex concentration. One panelist recommends that nonclinical dogs with high C_6 results be given a therapeutic course of doxycycline, possibly with a repeat quantitative C_6 performed in 3–6 months to document a new baseline result for comparisons if indicated in the future. Response to treatment is associated with a decrease in Quant C_6. Evidence is lacking as to what degree of reduction is considered acceptable as compared with being indication for

continued treatment in the absence of clinical signs. The argument for treating until Quant C_6 results wane by at least 50% is that the organism may never be cleared as it enters "protected" collagen tissue, and may develop into a latent cystic or L–form. Clinicians who treat believe treatment may lessen the likelihood of future development of immune–complex disease such as ICGN or nonclinical histologic changes found in experimental dogs (eg, arthritis, perivasculitis, and perineuritis), although this has never been confirmed by a controlled study.

Although anecdotally owners have reported improved well–being after antibiotic treatment in nonclinical dogs, without randomized placebo–controlled clinical trials it is unknown if the perceived improvement is related to decreased subclinical disease from Bb, anti–inflammatory properties, treatment of other subclinical disease, or is merely a placebo effect.

> Statement: Most (4/6) panelists do not routinely recommend antimicrobial treatment for nonclinical nonproteinuric Bb–seropositive dogs [EBM–D].

8 TOPIC 7: WHAT PREVENTION MODALITIES ARE RECOMMENDED?

8.1 Topic 7a: Tick control

Prevention of Bb infection and development of LB is multifaceted. The simplest and yet the most difficult step to achieve is tick prevention. Ticks and the wildlife that carry ticks are in ever increasing proximity to dogs and people. Frequent tick checks and removing ticks as soon as they are identified is of utmost importance, although difficult in pets with long or dark hair. Perimeter control is equally important. *Ixodes scapularis* preferentially live under hardwood forest canopy and in the underlying leaf litter.125-128 At least in the home environment, minimizing chances for tick inhabitation means keeping lawns cut short, cleaning areas of brush and

weeds, and using wood chips in gardens. Improved landscaping helps pets avoid ticks questing in vegetation and brush (Centers for Disease Control and Prevention National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) Division of Vector–Borne Diseases (DVBD). Preventing ticks in the yard. https://www.cdc.gov/lyme/prev/in_the_yard.html. Accessed on January 5, 2018). Daily tick checks provide timely removal with a hemostat, tweezers, or tick removal device, by grasping the tick close to its attachment on the skin, and retracting slowly but steadily. Kennels should be monitored and treated for *Rhipicephalus* infestations to decrease risk of infection with other tickborne diseases (TBDs). Tick type may be identified by checking for the anal groove of *Ixodes* or with images available on–line (University of Rhode Island at http://www.tickencounter.org/tick_identification. Accessed on January 5, 2018). In Bb–endemic areas, if a person removes an engorged *Ixodes* tick, it is recommended that person take a 1–day dose of doxycycline within 72 hours to help prevent LB. No such study has been done in dogs regarding prevention of LB or other TBDs that are sensitive to doxycycline.

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 the many other TBDs in Bb–endemic areas for which there are no vaccines available. Because ticks can become active even during the winter if temperature increases above 40°F (4°C), year–round tick prevention is advocated. Many products both topical and oral are available that have label claim against *I. scapularis* and currently are on the market. This panel does not recommend any individual product, but those that quickly kill or prevent attachment and feeding by the tick are preferable. *Borrelia burgdorferi* generally is not transmitted until at least 36–48 hours after tick attachment, but other TBDs may be transmitted more rapidly, and prevention of tick attachment (eg, with amitraz or permethrins130-134) or a relatively fast kill after attachment (eg, with isoxazoline products135-139) is preferred over use of fipronil, which does not kill the tick until after it has been attached for 24 hours. Fluralaner killed almost 90% of ticks by 4 hours, 98% by 8 hours, and 100%

at 12 hours after application. Tick collars should be applied tightly enough to have contact with skin, not just hair. Topical permethrins should not be used on or near cats. The new PO (hydrolysate chewable) isoxazoline products, which kill at least some of the tick species studied to date within 8 hours of attachment by binding to tick–specific neurotransmitter gamma–aminobutyric acid–gated chloride channels which mammals do not have, are easy to administer, increase compliance, and may help coverage for dogs that swim or get bathed often.140, 141 Combinations of products with different mechanisms also may be used. See Table 6 for a comparison of some commonly used tick control products.

Table 6. Examples of tick control products in the United States

Products[a]	T, F	Swim	Cats	Prevents attachment	Age, BW	Pregnancy lactation	Fre
Topicals							
Fipronil							
Frontline	T, F	Yes	Yes	No	≥8 week	Consult vet	Mor
Permethrins	T, F, M	Yes	No	Yes		Consult vet	Mor
Activyl T+					≥8 week, 4#		
Advantix II					≥7 week, 4#		
Parastar+							
Vectra 3D							
Revolution	Does not kill *Ixodes*, therefore Revolution is not recommended for tic control						
Collars							
Amitraz	T only	No	No	Yes			2–3
Preventic					≥12	Consult vet	

					week		
Permethrins	T, F, M	No				Consult vet	
Scalibor			No	Yes	≥12 week		6 m (2–3 lag)
Seresto			Yes	≥ 10 week cats	≥7 week, 4#		8 m
Chewables							
Isoxazolines	T, F	Yes		No, but relatively fast kill			
NexGard			No		≥8 week, 4#	Consult vet	1 m
Simparica			No				1 m
Bravecto[b]			Topical available		≥6 months	Yes	3 m but 2 m for *Amb*

BW: body weight; F: fleas; M: mosquitos; T: ticks; wk: weeks; #: pounds. [a]Products, ingredients, and manufacturers: Activyl Tick Plus (indoxacarb, permethrin; Merck Animal Health, Intervet Inc, Roseland, NJ 07068). Bravecto (fluralaner; Merck Animal Health, Intervet Inc, Summit, NJ 07901). [b]Bravecto topical is available for cats and dogs; oral chewable Bravecto is only available for dogs. Frontline Plus (fipronil, S–methoprene; Merial Limited, Duluth, Georgia 30096). Preventic collar (amitraz; Virbac Corporation, Fort Worth, Texas 76137). K9 Advantix II (imidacloprid, permethrin, pyriproxyfen; Bayer Healthcare LLC, Animal Health Division, Shawnee Mission, Kansas 66201). NexGard (afoxolaner; Frontline Vet Labs, Division of Merial Limited, Athens, Georgia 30601). Parastar Plus for Dogs

(fipronil, cyphenothrin; Novartis Animal Health US, Inc, Greensboro North Carolina 27408). Revolution (does not kill *Ixodes*; selamectin; Zoetis Inc, Kalamazoo, Michigan 49007). Scalibor Protector Band (deltamethrin; Merck Animal Health, Intervet Inc, Roseland, New Jersey 07068). Seresto (flumethrin, imidoclopramid; Bayer HealthCare LLC, Animal Health Division, Shawnee Mission, Kansas 66201). Simparica (sarolaner; Zoetis Inc, Kalamazoo, Michigan 49007). Vectra 3D (dinotefuran, permethrin, pyriproxyfen; CEVA US, Lenexa, Kansas 66215).

In 1 study of 9 cats infested with wild–caught *I. scapularis* twice, 2 cats seroconverted after the first infestation, became seronegative, and then seroconverted again after the second infestation suggesting a new primary infection. Thus, it appears that Bb infection does not induce preventive immunity in cats and repeated infection can occur without tick control. In another study of naturally exposed cats with and without clinical signs referable to borreliosis, whether or not the owner purchased a tick control product was recorded. When serum antibodies against Bb and *A. phagocytophilum* were measured, it was shown that purchase of a tick control product did not lessen the likelihood of detecting serum antibodies. Whether this finding related to lack of efficacy or failure of compliance could not be determined from the study. In dogs, use of tick control products appropriately can lessen the risk of developing antibodies against Bb and *A. phagocytophilum*, and this is likely to occur in cats as well if the products are used as directed.135, 137, 143

> Statement: Whether Bb vaccines are used or not, there is strong consensus that tick control must be used not only to help prevent LB but also to prevent many other TBDs for which there are no vaccines available [EBM–C].

8.2 Topic 7b: Bb vaccination

The efficacy of tick control products is excellent, as proven by prevention of

seroconversion after tick exposure challenge.135, 137, 143 However, compliance for using these products properly is an ongoing problem, and many veterinarians in Bb–endemic areas also recommend Bb vaccinations, although the latter are not as efficacious when used alone. In the United States, all currently available Bb vaccines (Recombitek Lyme. Merial Limited. Duluth, Georgia; Lymevax Zoetis, Florham Park, New Jersey 07932; Duramune Lyme Boehringer Ingelheim Vetmedica, Inc, St. Joseph, Missouri 64506; Nobivac Lyme, Merck Animal Health, Summit, New Jersey 07901; Vanguard crLyme, Zoetis, Florham Park, New Jersey 07932; Table 7) induce anti–OspA antibodies, which when imbibed by a feeding tick will attack spirochetes which express OspA wihin the tick's midgut, halting transmission. Anti–OspA titers are however not boosted by natural exposure and wane in vaccinates, allowing infection of the host. Anti–OspC antibodies induced by bivalent bacterin vaccines (Lymevax Zoetis, Florham Park, New Jersey 07932; Duramune Lyme Boehringer Ingelheim Vetmedica, Inc, St. Joseph, Missouri 64506; Nobivac Lyme, Merck Animal Health, Summit, New Jersey 07901) or the chimeric recombinant vaccine (Vanguard crLyme, Zoetis, Florham Park, New Jersey 07932), and boosted by natural exposure, can eliminate transmitted organisms that express OspC. Panelists who routinely recommend Bb vaccines for dogs (in addition to tick control) cite high efficacy, safety, and good duration of immunity (Jody Sandler, DVM, Director of Veterinary Services. Guiding Eyes for the Blind, Yorktown New York. Personal communication).144-150 Vaccinal duration of immunity however appears inconsistent and less than ideal for some vaccines studied.83, 151 Six–month boosters have been proposed147, 151 during the initial year (although no safety studies are available) and it is unknown whether or not to suggest 6–month versus annual boosters thereafter. Vaccine failures were found only 22 weeks after OspA subunit or bacterin vaccination. The most recently licensed Bb vaccine (Vanguard crLyme, Zoetis, Florham Park, New Jersey 07932) was shown in prerelease studies to induce OspA and OspC antibodies against 7 Bb strains, which may afford broader protection. In a 15–month duration–

of–immunity study completed by the manufacturer, vaccinated dogs were less likely (7/16 dogs seroconverted) than control dogs (14/16 dogs seroconverted) to develop evidence of Bb infection after tick challenge (Zoetis Study B864R–US–12–037).

Table 7. Available Bb vaccines in North America

Vaccine type	Name of vaccine	Adjuvant
Recombinant OspA (monovalent)	Recombitek Lyme (Merial)	No
Bivalent whole–cell inactivated bacterin (contains one Osp A containing strain, one unique OspC–producing strain, as well as other antigens)	LymeVax (Zoetis)	Yes
	Duramune Lyme (Elanco, formerly licensed to Boehringer Ingelheim)	Yes
	Nobivac Lyme (Merck)	Yes
Chimeric recombinant (contains monovalent OspA and 7 types of OspC from North American strains)	Vanguard crLyme (Zoetis)	Yes

The routine use of Bb vaccinations in Bb–endemic areas in North America was recommended by 3/6 panelists, for seronegative as well as healthy nonclinical, nonproteinuric seropositive dogs, because no natural immunity occurs from previous infection, partly because of the ability of the spirochete to “hide” from the immune system in synovial membranes, down–regulating their immunogenic surface proteins, and because of the existence of many strains for which there is no cross–reacting immunity.

The 3/6 panelists who dissented cited inconsistent efficacy and duration of immunity (see above), cost, need for proper tick control, lack of controlled studies with respect to tick control when assessing vaccines in the field,

theoretical concerns for immune–mediated sequelae,1, 153 and because most Bb–seropositive dogs remain nonclinical, nonproteinuric carriers. The theoretical concerns regarding future sensitization or aggravation of ICGN by Bb vaccinal antigen–antibody circulating immune complexes (CIC), proinflammatory OspA, or molecular mimicry of other Bb antigens by self–proteins are difficult to study because of the lack of an experimental model of Lyme nephritis, the difficulty in documenting true Lyme nephritis cases in the field, and the probable genetic predisposition whereby Bb immune–complexes are not cleared properly by the kidneys. The evidence for a negative impact of vaccination remains anecdotal at best. It is unknown if there is an underlying genetic podocytopathy, or some other pathogenesis for Lyme nephritis. Fewer than 10% of suspected Lyme nephritis cases had prior Bb vaccination (Richard Goldstein [coauthor]. Personal communication) and their PLN may have been because of other causes (eg, infectious, genetic, amyloidosis, glomerulosclerosis) or vaccine failure. There is no known negative impact of post–vaccinal Lyme–specific CICs, which increase transiently after vaccination (≤8 weeks in vaccinated seronegative dogs; to higher concentrations and longer in vaccinated seropositive dogs).155, 156

> Statement: 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 (nonclinical, nonproteinuric) 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].

9 SUMMARY

Our panel achieved consensus on evaluating all dogs at risk in North America with a qualitative Bb antibody assay, testing all Bb–seropositive dogs for proteinuria, using doxycycline as the first choice for dogs or cats with suspected clinical LB (although the best protocol and duration are unknown), using mycophenolate with or without prednisone in Lyme nephritis suspects that are not responding to standard care, and using tick control for all dogs and cats at risk (Table 8). Consensus was not reached on whether to treat all Bb–seropositive dogs and cats, whether to use quantitative C_6 antibody test results to guide treatment recommendations or to follow treatment responses, how long to use antibiotics for Lyme nephritis cases, and whether or not to use Bb vaccines, even in Bb–endemic areas.

Table 8. Summary of recommendations in consensus and not in consensus

Consensus	Nonconsensus
Screening all dogs in Bb–endemic and emerging areas in North America	Treating healthy nonclinical nonproteinuric Bb–seropositive dogs
Testing all Bb–seropositive dogs for proteinuria in North America (frequency/duration debatable)	Using quantitative titers to decide about treatment
Choosing Doxycycline first choice for sick dogs at 10 mg/kg/dy for 1 month	How long to use antibiotics in Lyme nephritis suspects (1 month versus 3–6 months)
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

CONFLICT OF INTEREST DECLARATION

The authors declare that none of their collaborations influenced their work

on this Consensus. Collaborative Research: Antech Laboratories (MRL), Boehringer Ingelheim Vetmedica, Inc. (REG, MRL, MPL), IDEXX Laboratories (REG, MRL), Zoetis (REG, MRL); Other: AKC–CHF/SCWTCA/SCWTAC (MPL); Grayson–Jockey Club (GEM), Kindy French Foundation (MPL), Maddie's Fund (GEM), NIH (GEM), Shipley Foundation (MAL); Consultant or Sponsored CE events: Aratana (MPL), Boehringer Ingelheim Vetmedica, Inc. (REG, GEM), Heska (MPL), IDEXX Labs (REG, MPL), Merck (REG, GEM), Merial (REG), and Zoetis (REG, MAL, GEM)

OFF–LABEL ANTIMICROBIAL DECLARATION

Authors declare no off–label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

REFERENCES

Citing Literature