Zoonosis Update

Lyme borreliosis

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In 1976, public health officials investigated a cluster of suspected juvenile rheumatoid arthritis cases that occurred among residents of Lyme, Connecticut, and neighboring communities.[1] More than 50 residents were evaluated for recurrent, usually short-lived (1 to 2 weeks' duration) attacks of swelling and pain in a few large joints. Clinical, laboratory, and epidemiologic evidence failed to substantiate an immune-mediated pathogenesis. An arthropod-transmitted bacterium was suspected as the etiologic agent, as many patients also had an expanding, red, annular rash that resembled erythema chronicum migrans (a lesion identified in Europe in the early 20th century that was associated with tick bites and was responsive to penicillin).[2,3] An infectious cause for the disease was confirmed when spirochetal bacteria isolated from *Ixodes dammini* (now considered *I scapularis*) ticks[4] and blood, CSF, and other tissues of patients were shown to be identical.[5-7] The bacterium was named *Borrelia burgdorferi*, and the multisystemic symptoms associated with infection were called Lyme disease or Lyme borreliosis (distinguishing it from other forms of borreliosis caused by other *Borrelia* spp). Subsequently, *B burgdorferi* was identified in ticks in numerous regions of the United States, and infection was associated with clinical illness in nonhuman animals, including dogs and horses.

Findings of experimental, ecologic, epidemiologic, and clinical research conducted in the last 2 decades have tremendously expanded our scientific understanding of Lyme borreliosis. The genome of the causative spirochete has been sequenced, ecologic dynamics of its maintenance in nature have been described, effective diagnostic and treatment protocols have been established, and vaccines have been developed. However, as coverage by the popular media of this complex disease is often a farrago of fact, fallacy, and opinion, familiarity with the current scientific body of knowledge on Lyme borreliosis is critical to enable practicing veterinarians to appropriately address concerns of their clients and to effectively manage animals with the disease.

Microbiology

The genus *Borrelia* is in the order *Spirochetae*, which contains genera that are pathogenic to humans and other animals, such as *Leptospira* and *Treponema*, to which belong the agents of leptospirosis and syphilis, respectively.[8] Like other spirochetes, *Borrelia* spp are spiral shaped, gram-negative, and have an outer sheath encasing endofibrils.[9] Unique to *Borrelia* spp are a singular linear chromosome (with additional linear and circular plasmids) and life cycles that require both arthropod vectors and mammalian hosts.[10]

Borrelia spp may be generally grouped into those that cause a relapsing fever-type illness (eg, *B hermsii*) and those that cause Lyme borreliosis.[10] Spirochetes in the relapsing fever group typically utilize soft (ie, argasid) ticks as their vector. Some relapsing fever-type *Borrelia* spirochetes have recently been recovered from hard (ie, ixodid) ticks,[11,12] but the pathogenic potential of these isolates remains unknown. The Lyme borreliosis *Borrelia* complex is often divided into ***B burgdorferi* sensu stricto** (***B burgdorferi* ss**; those *Borrelia* genetically identical to the type-strain B31, recovered from an *I scapularis* tick from Long Island, NY[13]) and ***B burgdorferi* sensu lato** (***B burgdorferi* sl**; all other closely related *Borrelia*). *Borrelia burgdorferi* ss, *B afzelii*, and *B garinii* cause Lyme borreliosis in humans and animals in Europe and Japan.[14,15] Only *B burgdorferi* ss is recognized as a cause of Lyme borreliosis in the United States.[16] Recently, *B bissettii* was recovered from a human patient in Slovenia[17]; although *B bissettii* has been identified in ticks in the United States,[18] no infection of mammals with this bacterium has been documented.

A linear chromosome and 21 plasmids comprise the genome of the *B burgdorferi* B31 type strain.[19] The genome codes for over 150 lipoproteins, some of which are key to the spirochete's ability to transfer between the tick vector and mammalian host. Several lipoproteins that localize to the outer surface of the spirochete (**outer surface proteins [Osps]**) are important in the transmission of *Borrelia* spirochetes to a vertebrate host and the host's subsequent immune response. While in the gut of the tick, the spirochete expresses chiefly Osp A.[20] The spirochete switches from Osp A to Osp C expression during a period of accelerated reproduction at the beginning of the tick's blood meal.[20] The **variable major protein-like sequence expressed** (**VlsE**) Osp has an invariable region conserved across many species of *Borrelia* and is highly immunogenic in mice, dogs, and primates.[21-24] An understanding of the kinetics of these and other expressed proteins (eg, decorin binding proteins and flagellin) is important for diagnosis (measurement of mammalian antibody response to

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bacterial proteins) and prevention (identification of potential vaccine candidates) of Lyme borreliosis.

Ecology and Transmission

Borrelia burgdorferi is maintained in nature in a cycle that involves hard ticks of the *Ixodes* genus as vectors and small mammals or birds as reservoir hosts. *Ixodes* spp are 3-host ticks that attach to a host and take a blood meal at each life stage (larva, nymph, and adult), then drop off the host to molt in the environment.[25] Larval and nymphal stages of *Ixodes* spp are found in moist, protected areas, such as under leaf litter in humid hardwood forests. The principal hosts of immature *Ixodes* ticks are small rodents, lizards, and ground-feeding birds. The immature ticks typically require 2 to 4 days of attachment to the host to complete a blood meal. At the adult stage, an *Ixodes* tick climbs to the tips of grasses, where it waits (or quests) for a large mammal host to brush against it. Adult ticks feed typically for 5 to 7 days. The abundance and activity of each life stage differ by season and are dependent on weather, sunlight, and host availability.[26,27]

In the northeastern and upper midwestern United States, *I scapularis* (commonly known as the deer tick or black-legged tick) is the principal vector of *B burgdorferi*. Larval and nymphal *I scapularis* acquire *B burgdorferi* primarily from infected white-footed mice (*Peromyscus leucopus*).[5,28,29] *Borrelia burgdorferi* is transmitted trans-stadially from larva to nymph and from nymph to adult. *Ixodes scapularis* that become infected as larvae or nymphs can subsequently transmit the agent as nymphal and adult ticks when they feed in the summer and fall, respectively.[30] Transovarial transmission (adult female to egg) is rare and inefficient.[25,31,32] White-tailed deer (*Odocoileus virginianus*) are the preferred hosts of adult *I scapularis*; however, because they are poor reservoirs for *B burgdorferi*,[33] they serve chiefly to maintain the population of ticks and not that of *B burgdorferi*. Furthermore, birds may introduce infected *I scapularis* into previously nonendemic areas or serve as reservoir hosts for *B burgdorferi*.[34,35]

The transmission cycle of *B burgdorferi* in the western United States is slightly more complicated. The western black-legged tick, *I pacificus*, is the tick vector, but it is not directly involved in the maintenance cycle. The spirochete is maintained in an independent enzootic cycle involving *I spinipalpis* as the arthropod vector[36,37] and dusky-footed woodrats (*Neotoma fuscipes*) and kangaroo rats (*Dipodomys californicus)* as the rodent reservoirs.[38] Larval and nymphal *I pacificus* can acquire *B burgdorferi* when they occasionally feed on these infected rodents. After molting to nymphs and adults, which feed in the spring and fall, respectively, infected ticks can transmit the bacteria to humans and domestic animals.[39,40] Larval and nymphal *I pacificus* prefer to feed on lizards, particularly the western fence lizard (*Sceloperus occidentalis*). Lizards contain a borreliacidal factor in their blood that effectively purges *B burgdorferi* infections from feeding ticks.[41] This is 1 explanation for the lower percentage of infected adult ticks among *I pacificus* in the western United States (typically 1 to 6%),[42,43] compared with the percentage among *I scapularis* in the eastern United States (typically > 50%).[44] Birds also may play a role in the transmission cycle of *B burgdorferi* in specific habitats in the western United States.[45]

The multiple species of *Borrelia* that exist worldwide and the broad host range of their vector ticks contribute to complex life cycles for agents of Lyme borreliosis in other areas of the world.[46] Each of the *Borrelia* genotypes in Europe is associated with a specific vertebrate host: *B burgdorferi* ss and *B afzelii* with small rodents[47,48] and *B garinii* with birds.[48,49] In Japan, *I persulcatus* is the primary vector tick that maintains *B afzelii*, *B garinii*, and *B burgdorferi* ss in enzootic cycles; this species of tick also transmits these agents to humans and domestic animals.[50] All 3 genospecies of *B burgdorferi* sl have been documented in both rodents and birds.[50-52]

In all vector ticks, the *Borrelia* spirochetes undergo both quantitative and qualitative changes prior to and during an infected tick's blood meal. When a larval or nymphal *Ixodes* tick ingests *B burgdorferi* from an infected host, the spirochetes localize to the gut and multiply until the tick molts, at which time the number of spirochetes decreases greatly, resulting in questing nymphs or adults with few spirochetes.[53,54] Once the infected nymphal or adult tick attaches to a new host, spirochetes multiply rapidly in the lumen of the midgut, and there is a change in Osp expression from Osp A (hypothesized to be an adhesion for spirochete attachment to the midgut)[55] to Osp C.[56] The expression of Osp C is subsequently decreased in spirochetes that are in the salivary glands of ticks.[20] Thus, Osp C is thought to facilitate the transmission step wherein the spirochetes migrate from the midgut to the hemocele and finally to the salivary glands, from which they can be transmitted to the host.[20] The spirochetes' development and migration take approximately 2 to 3 days; therefore, transmission to the mammalian or avian host is relatively inefficient until 48 hours after tick attachment.[57] Feeding by ticks is a dynamic process involving the release of many immunologically active substances from the ticks' salivary glands. The host's initial immune response temporarily delays the spirochetes' migration from the bite site,[58] but subsequent downregulation of proinflammatory factors in the host's skin permits the pathogen to disseminate to other organ systems.[27]

Epidemiology

In 1982, the **Centers for Disease Control and Prevention (CDC)** initiated surveillance for Lyme borreliosis in humans in the United States. In 1991, the Council of State and Territorial Epidemiologists adopted a standardized surveillance case definition and added Lyme borreliosis to the list of nationally notifiable diseases. In 2000, 17,730 cases of Lyme borreliosis were reported nationwide.[59]

Although cases of Lyme borreliosis have been reported from 49 states, the multiple ecologic factors required to maintain an effective enzootic cycle translate to a regional geographic distribution of Lyme borreliosis. In 2000, reported incidence of human Lyme borreliosis ranged from 0 cases/100,000 persons in 6 states (eg, Montana) to 110 cases/100,000 persons in

Connecticut. Between 1995 and 2000, reported incidence of Lyme borreliosis exceeded 10 cases/100,000 person-years in 7 states (Connecticut, Delaware, Maryland, New Jersey, New York, Pennsylvania, and Rhode Island). Each year, > 90% of reported cases occur among residents of the northeastern and upper-central states. In these same areas, serologic evidence of exposure to *B burgdorferi* has been observed in a high proportion of dogs (in some instances > 50%).[60,61] In contrast, seroprevalence estimates among clinically normal dogs in the southern and western United States have been uniformly low (≤ 3.5%) and generally within the margin of error of false-positives for the assays used.[62-64]

Risk of infection with *B burgdorferi* is correlated with the opportunity of being bitten by an infected tick and dependent on the density of vector ticks in an endemic area, the proportion of ticks infected, and the duration and nature of the susceptible host's activities in that area. Most cases of Lyme borreliosis are believed to be acquired from the bites of nymphal ticks, which are most abundant in the late spring and early summer. In 1 study,[65] > 50% of humans reported to have Lyme borreliosis in an endemic county of New York experienced onset of illness in June or July. Residence in or near areas of relatively undisturbed and dense vegetation poses the greatest risk.[65] Outdoor recreational activities in similar vegetated areas can also increase chance of infection.[66] Persons whose occupation places them in wooded areas (eg, forestry or wildlife workers) may occasionally be exposed to infected ticks.[67] Dogs and horses that have ongoing access to densely vegetated areas near their home (peridomestic exposure) or occasional recreational access to these same areas are at equal or greater risk of becoming infected, compared with humans.[68]

Signs and Symptoms

Humans—The signs and symptoms of Lyme borreliosis in humans are commonly categorized as early localized, early disseminated, or late disseminated manifestations.[69,70] Early localized Lyme borreliosis is synonymous with erythema migrans, which is a red, expanding rash that occurs 1 to 36 days following a bite from an infected tick.[71] Erythema migrans appears most often at the site of the tick bite, expands over the course of several days, often clears centrally, and resolves spontaneously without specific treatment. Nonspecific flu-like symptoms such as fever, headache, fatigue, and muscle and joint pain often accompany or follow erythema migrans. As the erythema migrans resolves, spirochetes complete their migration through the skin and enter other organ systems, where they cause symptoms referable to the tissues invaded. Objective manifestations associated with early disseminated Lyme borreliosis include meningitis and cranial nerve deficits (most commonly a unilateral facial nerve palsy)[72] and atrioventricular conduction deficits.[73] If not treated, the disease will progress in some patients to late disseminated symptoms, characterized by large joint oligoarthritis[74] and central nervous dysfunction, commonly encephalopathy and radiculopathies.[75]

Dogs—Surveillance studies have detected serologic evidence of exposure to *B burgdorferi* in a variable but large percentage (25 to 90%) of dogs in endemic areas.[76-80] However, not all infected dogs will develop clinical signs of Lyme borreliosis, and younger dogs are more likely to do so than older dogs.[81] Furthermore, dogs appear to lack the spectrum of clinical signs reported in humans with Lyme borreliosis, despite occasionally extensive systemic dissemination of spirochetes.[82] The clinical manifestations of Lyme borreliosis in dogs have been previously reviewed.[83] Briefly, 2 to 5 months after being infected with *B burgdorferi*, dogs most commonly develop lameness, frequently with accompanying fever and anorexia.[81] Arthritis is usually evident and confined to a single joint, most commonly the carpus or tarsus. In dogs experimentally infected by a single inoculation of *B burgdorferi*, arthritis was self-limited, although recurrent episodes of 3 to 6 days' duration occurred for up to several weeks.[81,84] The potential for progression and persistence of arthritis in naturally or repeatedly exposed dogs is not as well described. A distinctive renal syndrome attributed to *B burgdorferi* infection in dogs has been described.[85,86] Renal manifestations of Lyme borreliosis are histologically characterized by glomerulonephritis, tubular necrosis, and interstitial lymphoplasmacytic inflammation that are associated with a rapidly progressive and frequently fatal glomerular disease. Although *B burgdorferi* spirochetes have been identified in renal tissue,[86] the pathogenesis of *B burgdorferi*-associated renal disease is not well understood. In some dogs, CNS dysfunction[87,88] and heart block secondary to myocarditis[89] have been attributed to *B burgdorferi* infection.

Horses—Antibodies against *B burgdorferi* have been detected in ≥ 20% of horses residing in endemic areas.[90-92] However, clinical illness associated with *B burgdorferi* infection appears to be uncommon in horses. No histologic changes or clinical signs were observed in 7 ponies experimentally infected with *B burgdorferi*, although spirochetes were detected in tissues and specific antibody was detected in serum.[93] Clinical signs attributed to infection with *B burgdorferi* in horses include lethargy, low-grade fever, and stiffness and swelling in distal appendicular joints.[91] *Borrelia burgdorferi* spirochetes were detected in brain tissue from a horse with neurologic signs suggestive of encephalitis[94] and in the anterior chamber of the eye in a pony with uveitis and carpal synovitis.[95]

Other domestic animals—Parasitism by infected *Ixodes* spp and detection of antibody against *B burgdorferi* have been reported in cats,[96] but the clinical significance of exposure to *B burgdorferi* among cats is uncertain. In 1 study in a Lyme borreliosis-endemic area,[96] high titers to *B burgdorferi* were detected in cats with joint lameness; however, the proportion of cats with antibodies against *B burgdorferi* did not differ between cats with lameness only and cats with nonspecific febrile illness.

Serologic evidence of *B burgdorferi* infection has been detected in large and small domestic ruminants,[97,98] but it remains undetermined whether the organism causes clinical disease in these species. Detection of antibody against *B burgdorferi* in serum or synovial fluid was associated with lameness and joint

swelling among cattle in an endemic region.[99,100] Attempts to experimentally infect cattle with *B burgdorferi* suggest they have a low susceptibility.[101]

Diagnosis

Diagnosis of Lyme borreliosis can be made on the basis of history of exposure to *Ixodes* ticks in an endemic area, compatible clinical signs, laboratory evidence of infection, consideration and exclusion of other diseases, and, possibly, response to antimicrobial treatment.[83,102] Laboratory results alone are not prima facie evidence of infection but must be interpreted with regard to the pretest probability of the disease existing in the patient.[103,104] Establishing the prior probability of Lyme borreliosis is particularly important for species such as dogs that lack a pathognomonic sign of infection like the erythema migrans rash in humans.

Given the fastidious growth requirements of *B burgdorferi*, attempts to culture spirochetes from blood or other tissues are difficult and most often unrewarding. Thus, most commercially available clinical laboratory tests rely on detection of antibodies in serum. Serologic assays for IgM, IgG, or combined immunoglobulin against *B burgdorferi* are available through most commercial laboratories. The sensitivity of serologic assays is directly dependent on the kinetics of the immunologic response following infection. In humans, serum concentration of IgM against *B burgdorferi* increases within 2 to 3 weeks of infection, peaks around 3 to 6 weeks, and then gradually decreases.[105] Changes in serum IgG concentration lag that of IgM; IgG concentration begins to increase 4 to 6 weeks after infection, peaks at 6 to 8 weeks or later, and remains high for months to years.[6] In most or all dogs, IgG seroconversion occurs prior to onset of clinical signs, usually within 4 to 6 weeks after exposure.[81,102]

Enzyme immunoassays (**EIAs**) and **immunofluorescent assays** (**IFAs**) are the most commonly available serologic tests; however, despite their high sensitivity, these tests generally have poor specificity.[104] Unstandardized and variable procedures for manufacture and validation of commercial test kits further reduce the reliability of these assays.[106,107] In a laboratory proficiency study[108] in which seroimmunologic tests for 14 different pathogens were evaluated, assays for *B burgdorferi* antibody had the poorest correlation between reference and nonreference laboratories. To improve test reliability for human patients, the CDC currently recommends a 2-step serodiagnostic strategy: an initial EIA or IFA, with specimens that yield positive or equivocal results for *B burgdorferi* further tested by western immunoblotting for IgM or IgG antibody, whichever is appropriate for the patient's stage of illness.[109]

In dogs, the immunoblot band pattern does not merely enhance test reliability but provides indispensable information to differentiate serologic responses induced by natural infection with *B burgdorferi* from those produced by vaccination.[77] Dogs that are vaccinated react most strongly to spirochetal proteins in the 31- to 34-kd range that correspond approximately to the Osp A , whereas naturally infected dogs show minimal reactivity to these proteins.[110,111] Dogs and humans that are naturally exposed have a broad immunologic response to numerous *B burgdorferi* proteins between 15 and 100 kd; the number of immunoblot bands tends to increase with the progression of the disease.[102,112-114] Although uniform interpretation criteria for immunoblots have been determined for diagnosis of Lyme borreliosis in humans,[109,115] various strategies have been proposed for sera from dogs,[102,110,116] but scientific consensus has not been reached.

Recently, an EIA test kit became commercially available for in-office diagnosis of Lyme borreliosis in dogs.[a] This assay uses a synthetic peptide, C6, as the antigen; this peptide is based on the **sixth invariable region** (**IR_6**) in the VlsE Osp of *B burgdorferi*.[117] The IR_6 is greatly conserved among *B burgdorferi* strains and highly immunogenic in dogs.[24] Although this assay shows promise,[118,119] field studies that have validated its performance in large numbers of clinically well-characterized dogs have yet to be reported.

Detection of antibody against *B burgdorferi* is not definitive evidence of active or incipient Lyme borreliosis nor an indication of the need for treatment.[78] Serologically detectable anti-*B burgdorferi* IgG may persist for months, years, or indefinitely following infection and resolution of clinical disease.[79,120] For this reason, although serologic screening of scientifically selected populations may yield useful epidemiologic information, it is generally uninformative for clinically normal individuals (eg, those with a recognized tick bite that have no clinical signs of illness). In highly endemic areas where dogs may be regularly bitten by infected ticks, serologic testing cannot differentiate between dogs with active Lyme borreliosis and those with persistent antibodies from an earlier exposure. One study[79] found that the prevalences of serum antibody against *B burgdorferi* did not differ between healthy dogs (89.6% seropositive) and those with joint or limb disorders compatible with Lyme borreliosis (92.9% seropositive). Serodiagnostic testing should be reserved for dogs with a history and clinical presentation that are highly suggestive of active Lyme borreliosis.

Treatment

Although erythema migrans resolves spontaneously in most humans with Lyme borreliosis,[121] the potential for symptoms to progress from mild flu-like illness to severe neurologic or arthritic disease underscores the need for prompt recognition and appropriate treatment. Even before the bacterial cause of Lyme borreliosis was confirmed, antimicrobials were observed to improve the outcome during all stages of disease.[122] Numerous clinical trials and case series have demonstrated the efficacy of oral administration of doxycycline or amoxicillin for 14 to 21 days for the treatment of eyrthema migrans and other early symptoms.[122-127] Uncomplicated arthritis associated with Lyme borreliosis can be successfully treated with oral or IV administration of doxycycline or amoxicillin for 28 days.[128] Intravenous administration of ceftriaxone for 14 to 28 days is recommended for patients with any neurologic manifestations.[129-131] Response to treatment may be slow and inversely correlated with duration and severity of symptoms.

As in humans with Lyme borreliosis, antimicrobial treatment in dogs can accelerate clinical resolution and

reduce the chance of recrudescent Lyme borreliosis. Following experimental inoculation of dogs with *B burgdorferi*, spirochetes were repeatedly cultured from skin biopsy specimens prior to treatment; after 30 days of azithromycin (25 mg/kg [11.4 mg/lb], PO, q 24 h), ceftriaxone (25 mg/kg, IV, q 24 h), or doxycycline (10 mg/kg [4.5 mg/lb], PO, q 12 h), examination of biopsy specimens from multiple tissues failed to yield any viable spirochetes.[84] In a similar study[132] of experimentally infected dogs, administration of immunosuppresive dosages of corticosteroids led to a recurrence of severe lameness in 2 of 2 dogs that had not received antimicrobial treatment but in none of 12 that received antimicrobial treatment.

Treatment is rarely indicated for dogs with serologic evidence of *B burgdorferi* exposure in the absence of clinical disease. As stated previously, although the number of seropositive dogs in an endemic area can be high, the proportion of these that will develop clinical signs is low. Serologic status determined at a singular point in time is not predictive of future illness; a study[78] of dogs without signs of illness in an endemic area of Connecticut showed that the incidence of signs of Lyme borreliosis over a 20-month observation period did not differ between dogs that were initially seropositive and those that were seronegative. A course of antimicrobials prescribed solely on the basis of arbitrarily timed serologic findings is unlikely to reduce morbidity or to be effective in preventing reexposure in an endemic area.

Prevention and Control

The foundation for preventing Lyme borreliosis in domestic animals and humans is the reduction of the risk of tick bites at the environmental or individual level. Avoiding tick bites prevents not only Lyme borreliosis but also other tick-borne diseases, such as ehrlichiosis and babesiosis, in regions where these pathogens are present. A knowledge of the ecologic requirements for the tick-borne diseases that are present in a given area is critical toward selection and implementation of the most effective integrated prevention strategies.[133] In areas where Lyme borreliosis is a peridomestic risk, tick density may be managed locally by targeting animal hosts or by modifying the environment to decrease the availability of tick habitat. Products that kill or repel ticks can reduce the likelihood that ticks will attach to pets. Induced immunity through vaccination may provide additional protection in some highly endemic areas.

Some of the most effective approaches to environmental control of ticks target the reservoir animals that sustain *I scapularis* populations. The use of permethrin-treated cotton balls as nesting material decreased the load of immature *I scapularis* on white-footed mice.[134] Although the number of ticks that infested rodents appeared to decrease with this method over a 3-year period, the number of questing ticks did not differ between treated and untreated sites.[135] The concept of targeting small mammals for tick control was developed commercially as rodent bait boxes that contain fipronil.[b] The success of this targeted approach depends on limiting access of alternative tick hosts to treated areas; therefore, large-scale implementation may be impractical. Bait boxes have not proven as effective in the reduction of tick numbers in the western United States, probably because *I pacificus* feeds on a wider range of vertebrate hosts, compared with *I scapularis*.[136] White-tailed deer have also been effectively targeted in attempts to control adult *I scapularis*. Feeding stations were designed whereby deer that rub against 4 amitraz-impregnated posts transfer acaracide onto their heads and necks (regions of the body where *I scapularis* ticks most frequently attach on deer).[137] In areas where these feeding stations were deployed, the number of adult *I scapularis* observed on deer carcasses was less than that observed on carcasses in areas without the feeding stations.

Environmental approaches to tick control (eg, pesticide application and landscape modification) are designed to decrease suitable habitat for ticks. Acaracides can be a useful adjunctive treatment on limited spatial scales, but applications must be targeted to specific areas and timed appropriately in order to maximize control and minimize excess pesticide residue in the environment.[138,139] Fencing that excludes deer (ie, > 2 m in height) can be constructed around small areas such as a residential property to decrease the number of adult *Ixodes* ticks deposited and thus reduce the number of tick progeny in the environment.[140] A swath of mulch or other inert material placed between wooded areas and lawns can provide an effective impediment to tick movement into areas where they are likely to encounter people and pets.

Control of ticks on dogs is facilitated by the availability of collars impregnated with permethrin or amitraz and topical solutions containing fipronil,[c] permethrin,[d] or selamectin.[e] The myriad of recently developed ectoparasiticides and their control efficacy have been reviewed.[141] Amitraz-impregnated collars appear to be more effective at interrupting the tick life cycle and longer acting than topical applications of fipronil.[142] The appropriate use of amitraz-impregnated collars on dogs can provide effective tick control and thereby prevent infection with *B burdorferi*.[143] Amitraz is also available as a spray or dip for tick control on domestic livestock; its use is contraindicated in horses, pregnant or nursing bitches, and cats. Selamectin is effective in control of brown dog ticks (*Rhipicephalus sanguineus*) and American dog ticks (*Dermacentor variabilis*) on dogs and is safe to use on cats. However, in a study[144] in Europe, topical application of permethrin was more effective at repelling European *Ixodes* spp, compared with topical application of selamectin. Topical administration of permethrin products is contraindicated for cats.[141]

Ideally, owners should examine their pets after visiting tick-infested areas. Although a thorough inspection may not reveal all ticks, prompt removal of those that are found can prevent most tick-borne diseases because there is often a lag period between the initiation of feeding by the tick and pathogen transmission. *Borrelia burgdorferi* spirochetes are not efficiently transmitted to the host until 24 to 48 hours after the tick begins to feed.[145] Ticks should be removed with fine-pointed forceps by grasping the tick at the mouth-

parts as close to the skin as possible and pulling gently, firmly, and perpendicularly away from the skin. A variety of commercial products[f-h] are available that can be effective in removal of nymphal and adult ticks when used properly.[146] Crushing the tick during the removal procedure does not appear to increase likelihood of transmission of *Borrelia* spirochetes.[145] After the tick's removal, the bite site should be washed with an antiseptic compound. The efficacy of antimicrobial prophylaxis for dogs after tick bites is unknown. When considering a prophylactic course of antimicrobials for a tick bite, veterinarians should carefully weigh the risk of tick-borne disease versus the risk of an adverse drug reaction.

Two whole-cell *B burgdorferi* bacterin vaccines are available for canids.[i,j] An initial efficacy study[147] by 1 of the manufacturers indicated that the vaccine protected laboratory dogs against the development of lameness following syringe-delivered challenge with several different strains of *B burgdorferi*. Results of a large-scale field study[61] indicated that the vaccine was safe and effective at preventing development of Lyme borreliosis in many breeds of dogs. A survey[148] of dogs from a single practice in a Lyme borreliosis-endemic area showed a higher prevalence of seroreactivity to the *B burgdorferi* C6 antigen among unvaccinated dogs (64%), compared with the prevalence among dogs that had received annual vaccination with the whole-cell bacterin (5%). Results of a study[149] involving a model of Lyme borreliosis in hamsters indicated that immunity that develops subsequent to administration of the bacterin is specific to *B burgdorferi* infections (ie, not protective against *B afzelii* or *B garinii*) and short-lived (< 1 year). Findings of a similar study[150] suggested that immune-mediated arthritis was associated with the *B burgdorferi* bacterin; however, it remains uncertain whether there is an association between immune-mediated arthritis in dogs and use of this vaccine.

A recombinant subunit vaccine that contains the highly immunogenic Osp A is the next generation of vaccines available for prevention of Lyme borreliosis in dogs.[k] Because Osp A is expressed by *B burgdorferi* primarily in the gut of ticks prior to feeding, immunity against Osp A is thought to function through complement-mediated lysis of *B burgdorferi* in the tick's gut soon after the tick begins its blood meal.[151] In a study[152] involving use of the subunit vaccine in dogs, protection against *B burgdorferi* transmission by naturally infected *I scapularis* was demonstrated. A recombinant *B burgdorferi* vaccine for horses, also based on the Osp A antigen, has been shown to be safe and protective but is not yet commercially available.[153]

Recommended schedules for both the bacterin and recombinant vaccines require administration of an initial dose, a booster vaccination 2 to 4 weeks later, and annual revaccination.[147,152] The decision to vaccinate against *B burgdorferi* should be based on an assessment of each dog's risk of exposure to *B burgdorferi*, including factors such as the regional endemicity of Lyme borreliosis and the dog's likelihood of contact with *Ixodes* spp.[154] Vaccination should target at-risk dogs prior to exposure to *B burgdorferi*, because limited information is available regarding the safety and efficacy of the vaccine after administration to previously exposed dogs.[61] Clients who choose to have their dogs vaccinated against *B burgdorferi* should be cautioned that the vaccine confers no protection against other tick-borne diseases (eg, ehrlichiosis), and therefore acaracides or other measures for reducing tick bites should nonetheless be adopted. These same factors should be considered for vaccination of horses when a commercial product becomes available.

Public Health Considerations

Recognition of ixodid ticks on pets provides the veterinarian an opportunity to provide a public health service by alerting owners to their own potential exposure to tick-borne diseases. Clients should be assured that dogs with Lyme borreliosis do not serve as a direct or indirect source of infection for humans. Although ticks may rarely acquire *B burgdorferi* from infected dogs,[155] dogs are not efficient maintenance reservoirs of these spirochetes and are only incidental hosts for larval and nymphal *Ixodes* spp that serve as vectors for Lyme borreliosis. However, pets may incidentally acquire ticks from outside and transport them to the peridomestic environment before the ticks have had an opportunity to attach. Detection of a tick on a client's pet should motivate a discussion on appropriate acaracide use.

Similar to strategies for domestic pets, prevention of tick-borne diseases in humans relies on tick-bite avoidance behaviors and practices. Standard recommended precautions to take while in areas inhabited by ticks include the following:

- Avoid areas where ticks are present.
- Wear long pants and long-sleeved shirts when in tick habitats. Tuck pant legs into boots or socks and tuck shirt into pants.
- Wear light-colored clothing so ticks can be easily seen.
- Apply a repellent registered for use against ticks; always follow directions on the product label.
- Inspect oneself and children frequently for ticks while in tick habitat.
- Stay in the middle of the trail; avoid trail margins, brush, and grassy areas.
- Once out of tick habitat, thoroughly check entire body for ticks. Parents should examine their children, especially on the scalp and hairline.

In endemic areas where exposure to ticks is peridomestic (eg, the eastern United States), tick-bite prevention measures must be part of a regular, daily routine. Techniques for removal of ticks are the same for humans and pets. In humans, prophylactic administration of antimicrobials after a tick bite is not warranted in most cases because the risk of adverse reaction to the antimicrobial agent is usually greater than the risk of disease. However, a single 200-mg dose of doxycycline within 72 hours after a documented *I scapularis* tick bite was shown to be effective in preventing Lyme borreliosis among persons in a hyperendemic area in New York.[156] In endemic regions, a recombinant Osp A vaccine approved for use in humans was 76% effective in preventing development

of Lyme borreliosis among study subjects who received the full 3-dose series.[157] However, this vaccine is no longer commercially available.[158]

Summary

Despite more than 25 years' experience with Lyme borreliosis, much remains to be learned about this complex zoonosis. Practicing veterinarians, particularly those in the northeastern and upper midwestern states, where Lyme borreliosis is highly endemic, should be familiar with the ecologic features and typical clinical signs of Lyme borreliosis. Interpretation of signs and serologic test results should be made with consideration of the regional prevalence of Lyme borreliosis and the animal's opportunity for exposure to infected *Ixodes* spp. The availability of recently marketed topical acaracides is a valuable adjunctive measure in prevention of Lyme borreliosis. A maximally effective prevention strategy should include consideration of environmental modification, activity restrictions, routine examinations for ticks, prompt removal of attached ticks, and vaccination. Technologic advances, such as the C6 EIA and the Osp A recombinant vaccine, offer the promise of additional tools for the clinical management and prevention of this tick-borne zoonosis.

[a]SNAP 3Dx, IDEXX Laboratories, Westbrook, Me.
[b]Maxforce Tick Management System, Aventis Environmental Science, Montvale, NJ.
[c]Frontline, Merial, Duluth, Ga.
[d]Biospot, Farnam Pet Products, Phoenix, Ariz.
[e]Revolution, Pfizer Inc, New York, NY.
[f]Ticked-Off, Ticked-Off Inc, Dover, NH.
[g]Tick Plier, Sawyer Products, Safety Harbor, Fla.
[h]Pro-Tick Remedy, SCS Ltd, Stony Point, NY.
[i]Galaxy Lyme, Schering-Plough Animal Health, Union, NJ.
[j]LymeVax, Fort Dodge Animal Health, Overland Park, Kan.
[k]Recombitek Lyme, Merial, Duluth, Ga.

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