LOGISTICS OF LYME: DIAGNOSIS, TREATMENT AND PREVENTION

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ETIOLOGY AND EPIDEMIOLOGY

Lyme disease is the most common vector borne disease of humans. It is estimated that approximately 30000 to 40000 cases are reported to the CDC each year, but based on insurance claim data, the total number of cases annually is estimated to be closer to half a million. There has been a progressive rise in reported case numbers over the last few decades. The cost of diagnosis and treatment of Lyme disease each year is estimated to be over US$1.3 billion dollars/annum.[1] The main species causing human disease in the US is *Borrelia burgdorferi* sensu stricto (with recently suggested controversial name change to *Borreliella*).[2] Most (90%) of human Lyme cases in the US still occur in the northeast, with most remaining cases from the upper Midwest. There are scattered cases in northern California. This geographic distribution reflects the distribution of *Ixodes scapularis* and *Ixodes pacificus*, which belong to the *Ixodes persulcatus* complex. *Ixodes scapularis* is responsible for transmission in the upper midwest and northeast, and *Ixodes pacificus* in the west. Even though *I. scapularis* and *I. pacificus* look identical, they have different behaviors and preferred reservoir hosts, so the epidemiology of Lyme disease differs on the east coast and west coast. The spatial distribution of *Ixodes* ticks in the US does not match the distribution of Lyme borreliosis in humans and dogs. This reflects the density of the tick population and the distribution and density of the reservoir host population. The primary reservoir for *Ixodes scapularis* ticks in the upper Midwest and the northeast is *Peromyscus leucopus*, the white-footed mouse. These mice subclinically harbor large numbers of the spirochete. However, southern *I. scapularis* ticks prefer to feed on lizards (skinks) than mammals. Lizards are poor reservoir hosts for *B. burgdorferi*, and this explains why the prevalence of Lyme is low in the southeast.[3] In the west, the western gray squirrel is thought to be the most important reservoir, but the preferred hosts for *I. pacificus* are also lizards. The distribution of Lyme disease has been expanding in southeastern and midwestern Canada, northern California, and into the southeastern United States.[4-6]

Pathogenesis

Ixodes scapularis ticks have a 2 to 4 year, 3-stage life cycle. The eggs hatch into uninfected larvae in the spring. They acquire infection with the spirochete in the summer when they feed primarily on small rodents, which are reservoir hosts for the spirochete. The larvae then overwinter and molt into nymphs the following spring. The nymphs further feed on small rodents, deer, and humans and molt into adults, which subsequently mate and lay 1000-3000 eggs on the forest floor, which are uninfected.

Spirochetes attach to the tick midgut using OspA, which binds to the tick gut receptor protein TROSPA. When the tick feeds, the spirochete migrates through the tick hemolymph to the salivary glands. Although initial studies suggested that the expression of OspA is downregulated and OspC is upregulated during this process, recent studies have shown

maintenance of OspA expression throughout feeding, with a decrease in OspA expression only in the mammalian host.[7]

Transmission of European *Borrelia* species occurs after 24 hours of feeding, but for North American species, transmission requires a minimum of 36 hours. In contrast, *Ehrlichia* takes about 2 hours and *Anaplasma* about 8 hours; the human pathogen Powassan virus can be transmitted in 15 minutes. Tick saliva contains more than 100 molecules, some of which can actually help to protect *B. burgdorferi* from immune destruction because they inhibit inflammation. This is known as *saliva-assisted transmission (SAT)*.[8]

Clinical Manifestations

Humans. Erythema migrans (EM) occurs in 80-90% of humans with Lyme disease in the United States, typically 7 to 14 days after a tick bite. The characteristic bull's eye shaped rash results from an initial reaction to tick saliva at the site of the tick bite, and then an inflammatory response to spirochetes as they migrate outwards through connective tissue. The rash may reach 35 cm in diameter, and may be pruritic or painful, and sometimes is associated with malaise. Bacteremia is not a major feature of infection, so tests for *B. burgdoferi* DNA in blood are not very sensitive. Of Lyme disease cases reported to the CDC, the most common clinical manifestation is erythema migrans, in over 70% of cases, followed by arthritis. Neurologic manifestations, especially Bell's palsy, are next, followed by rare cardiac disease (www.cdc.gov).

Dogs. When dogs are infected, more than 95% show no signs. Dogs do not develop EM, and instead show late manifestations of Lyme disease. These consist either of a neutrophilic polyarthritis, which is often accompanied by thrombocytopenia, or Lyme nephritis. Lyme polyarthritis occurs when the spirochetes migrate through connective tissues to the joints.[9-11] Thrombocytopenia in association with protein-losing nephropathy may also raise suspicion for Lyme nephritis.[9]

Diagnosis

Because most dogs that are exposed to *B. burgdorferi* do not show signs, diagnosis of Lyme borreliosis requires the presence of consistent clinical signs. Some veterinary diagnostic laboratories offer PCR assays for detection of *B. burgdorferi* DNA. The best specimen for PCR is a skin biopsy closest to the tick bite site, but the site of tick attachment is usually not known. In dogs with polyarthritis, synovial fluid may be the best specimen for PCR testing, but negative results do not rule out Lyme disease because of the paucity of organisms that are often present.

Antibody-detection assays offer greater sensitivity for diagnosis, but lack etiologic predictive value (association between positive test results and disease). ELISA and lateral flow assays detect antibodies to specific outer surface proteins, such as OspA, OspC, OspF, and VlsE. Although antibodies to OspA are more likely to be associated with vaccination than with natural infection, some naturally-infected dogs may mount an early antibody response to OspA, so the detection of antibodies to OspA is not specific for vaccination. OspF is typically not expressed until 6 to 9 weeks after infection, so antibodies to this outer surface protein suggest more chronic infection. C6 is a component of the VlsE outer surface protein, which is only expressed during natural infection. Therefore, antibodies to the C6 peptide (a

component of the IDEXX SNAP 4Dx Plus and Antech Accuplex assays) indicate natural infection; because dogs are seropositive by the time they develop clinical signs, negative results rule out Lyme disease. False positive antibody test results can occur with the VETSCAN and Accuplex assays (but not the IDEXX C6 assay) in dogs infected with the relapsing fever *Borrelia* species *Borrelia turicatae*, which has been identified in dogs in Florida and Texas.[12]

Four Lyme vaccines are available for dogs. The first is a recombinant nonadjuvanted lapidated OspA vaccine that elicits a strong antibody response to OspA (Boehringer Ingelheim). There are two bacterins that are mixed bacterial cell lysates of two strains that express OspA and OspC (Merck and Elanco). The fourth is a subunit chimeric non-lipidated vaccine that contains recombinant OspA and a recombinant construct of 7 different OspC types (Zoetis). The latter vaccine was designed following studies that showed that dogs experimentally infected with ticks from Rhode Island were co-infected with > 10 different OspC types.[13] There are > 30 different OspC genotypes, and antibodies to one OspC genotype may not cross-protect against others. Lyme vaccines exert their effect within the tick rather than in the host, which gives them the ability to prevent infection of the host. Vaccine-induced antibodies are ingested by the tick during acquisition of the blood meal. These bind to the spirochetes in the tick and induce complement-mediated bacterial lysis. Anti-OspA antibodies are most critical and all vaccines stimulate a response to OspA.[14] The new experimental human Lyme vaccine, VLA15, currently in Phase 2 clinical trials, is a recombinant OspA vaccine that contains a spectrum of OspA types in order to induce protection against both European and US *Borreliella* species.[15] Whether vaccines that stimulate antibodies to a variety of OspC types provide additional protection is not clear. Because reinfections can occur with different strains of *B. burgdorferi* following natural infection,[16] there is potentially rationale to vaccinate even seropositive individuals with vaccines that stimulate a stronger immune response to OspA than occurs with natural infection.

Treatment

The recommended treatment for dogs with Lyme borreliosis is doxycycline, 5 mg/kg PO q12h, for 4 weeks; amoxicillin is an alternative for dogs that do not tolerate doxycycline. The goal should be resolution of clinical signs. Dogs can retain high quantitative C6 titers (IDEXX Laboratories) after treatment, and some dogs have titers boostered by reinfections, even with good tick control. Dogs with advanced Lyme nephritis do not typically respond to antibiotics. Immunosuppressive drugs such as mycophenolate may result in clinical improvement. There is no evidence that treatment of healthy seropositive dogs eliminates infection, and it has the potential to contribute to antibiotic resistance. Identification of healthy seropositive dogs is an opportunity to emphasize ectoparasite control and discuss vaccination, and the possibility that humans in the household might have been exposed to vector-borne pathogens. Whether healthy seropositive dogs should be examined for proteinuria is controversial.

Prevention

In addition to vaccination, prevention of Lyme disease can be accomplished by use of parasiticides. Even though *B. burgdorferi* is transmitted after 36 hours, other pathogens, such as *Anaplasma* and *Ehrlichia*, are transmitted more rapidly, and so products should be

chosen that work as rapidly as possible. Those products include pyrethroids and isoxazolines. Pyrethroids include type I pyrethroids, such as permethrin, and type II pyrethroids, such as cyphenothrin, deltamethrin and flumethrin. Unlike other pyrethroids, flumethrin is safe for use on cats, safe to use on dogs that live with cats, and has potent tick preventative activity (with imidacloprid). Selamectin is available as a topical monthly product for cats; and there are oral isoxazolines for dogs and topical products for cats. Several studies have demonstrated the ability of some these products to prevent transmission of *B. burgdorferi* and *Anaplasma phagocytophilum*.[17-19]

References available on request