

# Identifying tick-borne diseases

*Regular testing and clear client communication are essential elements of successfully managing tick-borne diseases.*



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A 46-year-old woman was evaluated at an emergency room in Mississippi for severe headache, back pain, an inability to walk unassisted, nausea, vomiting and lethargy. She was diagnosed with a lower back sprain and cystitis, and muscle relaxants and trimethoprim-sulfamethoxazole were prescribed. Her condition worsened, and three days later she was admitted to the hospital, where she was noted to have fever, headache and vomiting. She also had a pinpoint rash all over her body, which had originated on her palms, soles, face and arms. The patient was started on oral doxycycline and intravenous vancomycin therapy. Her condition further worsened, and she required multiple transfusions due to severe thrombocytopenia.

On the second day of hospitalization, she was pronounced brain dead from cerebral edema. She was diagnosed with Rocky Mountain spotted fever (RMSF) post-mortem. What these physicians did not know is that three weeks earlier, one of the woman's dogs had been seen by a veterinar-

ian for an inability to stand, petechiae of the gums and lethargy; severe thrombocytopenia was also noted. This dog died two days after being admitted to the veterinary hospital, and tests to identify infectious agents were not performed.<sup>1</sup>

Tick migration and the various tick-borne diseases are becoming more prevalent. The Lone Star tick (*Amblyomma americanum*), a known carrier of *Ehrlichia*, *Rickettsia rickettsii* (the cause of RMSF) and *Babesia*, was historically found only in the southeast and Texas but recently has been found as far north as Canada.<sup>2</sup> In North America, ixodid (hard-bodied) ticks are the predominant vectors of tick-borne pathogens, including *Anaplasma*, *Babesia*, *Bartonella*, *Borrelia*, *Coxiella*, *Ehrlichia*, *Hepatozoon* and *Rickettsia* species. *Ixodes*, *Amblyomma*, *Dermacentor* and *Rhipicephalus* are the predominant genera of ixodid ticks.

Four commonly discussed tick-transmitted diseases in both veterinary and human literature are Lyme disease, ehrlichiosis, anaplasmosis and RMSF. Veterinarians serve a unique role in communicating the potential health problems ticks and other parasites

can transmit to people and their Pets. This article will help identify the most common tick-borne diseases and discuss why it's important to have a solid understanding of these diseases and their affect on both Pets and people.

### Lyme disease

Lyme disease results when the bacterium *Borrelia burgdorferi* is transmitted to a dog or person by the tick *Ixodes pacificus* or *Ixodes scapularis*. *B. burgdorferi* is a spiral-shaped, gram-negative bacterium that multiplies in the skin and then disseminates to other tissues. In 2005, the Center for Disease Control reported that 23,305 Lyme disease cases were found in people; the incidence of this disease has increased remarkably in people, up from 9,896 reported cases in 1992. While previously Lyme disease was thought to exist only in geographically circumscribed areas, cases have been reported in 49 states and the District of Columbia.

### Clinical characteristics in dogs

Ninety to 95 percent of dogs that have antibodies to *Borrelia* will not show clinical signs.<sup>3</sup> Patients that are symptomatic most commonly show signs of Lyme arthritis. These patients have a sudden onset of lameness, fever, lethargy and swelling of one or more joints, often accompanied by pre-scapular and/or popliteal lymphadenopathy.

Lyme nephropathy is another manifestation of Lyme disease. This form is uncommon but typically carries a poor prognosis. Patients present with vomiting, diarrhea, weight loss, polyuria, polydipsia, peripheral edema and/or ascites. Diagnostic testing reveals uremia, hyperphosphatemia, hypoalbuminemia, hypercholesterolemia and proteinuria. Recent research has shown that this disease may be a sterile immune com-

plex disease.<sup>4</sup> Golden Retrievers, Labrador Retrievers and Shetland Sheepdogs seem to be overrepresented in some of the studies.<sup>5</sup>

### Clinical characteristics in people

Ninety percent of people who are positive for Lyme disease will show clinical signs.<sup>3</sup>

Most people, unlike dogs, show acute illness with erythema migrans (bull's eye rash) and flu-like signs. Arthritis manifests later, along with cardiac, neurologic and dermatologic changes.<sup>5</sup> There is no naturally acquired immunity; people and Pets who have had Lyme disease can be reinfected.

### Ehrlichiosis and anaplasmosis

*Ehrlichia* and *Anaplasma* are small, gram-negative, coccobacillary obligate intracellular parasites that primarily invade the white blood cells; indeed, the two types of bacteria were previously categorized with reference to the type of white blood cell infected—that is, whether they infected monocytic or granulocytic cells. The two genera are also transmitted by different vectors. *Ehrlichia* is transmitted primarily by the brown dog tick, *Rhipicephalus sanguineus*, while *Anaplasma* is transmitted by *Ixodes scapularis* and *I. pacificus*.<sup>6,7</sup> Although infection is more common in dogs, cats have also been documented with *Ehrlichia* infections.<sup>8</sup>

*Ehrlichia* and *Anaplasma* are now categorized in three separate groupings based on the 16 sRNA gene:

- **Group 1:** *Ehrlichia canis*, *Ehrlichia ewingii* (emerging pathogen in south central Midwest) and *Ehrlichia chaffeensis* (causes human monocytic ehrlichiosis, which is primarily transmitted by the Lone Star tick).
- **Group 2:** *Anaplasma platys* and *Anaplasma phagocytophilum* (causes human

granulocytic anaplasmosis, which is primarily transmitted by *Ixodes*). Between 1990 and December 2004, thirteen states reported 2,871 cases of human granulocytic anaplasmosis to the CDC.<sup>9</sup> This disease is thought to be underdiagnosed.

■ **Group 3:** *Ehrlichia risticii*, *Ehrlichia sensu* and *Neorickettsia helminthoeca* (cause of salmon poisoning disease).

In early stages of ehrlichiosis or anaplasmosis, the patient presents with lethargy, anorexia and weight loss. Lymphadenopathy, fever, splenomegaly, epistaxis, melena and other signs of bleeding occur later in the disease process.<sup>6,9</sup>

The most commonly found clinical laboratory abnormalities are thrombocytopenia, nonregenerative anemia, hyperglobulinemia, hypoalbuminemia, elevated alkaline phosphatase and elevated alanine transaminase. There is no naturally acquired immunity; individuals who have had ehrlichiosis or anaplasmosis can become reinfected.

### Rocky Mountain spotted fever

RMSF is caused by the bacteria *R. rickettsii*, small, gram-negative, coccobacillary obligate intracellular parasites that multiply within the vascular endothelium and smooth muscle. During the past 50 years, the CDC has received reports of 200 to 1,120 human cases of RMSF each year, from all 48 states except Vermont and Maine. Roughly 95 percent of cases occur between the months of April and September.<sup>10</sup>

Affected patients present with fever (102.5°F to 104.9°F) beginning four to five days after the tick bite. Petechiae and ecchymoses, when present, are typically located in the oral, ocular and genital mucous membranes. Retinal hemorrhages may be noted. Edema of the extremities, lips, pinnae, penile sheath and scrotum may be noted.<sup>10</sup>

The most commonly found clinical laboratory abnormalities are hypoalbuminemia (from vascular endothelial damage and leakage), thrombocytopenia and moderate leukocytosis. Radiographic examination of the thorax has documented diffuse interstitial densities or pneumonitis. Naturally acquired immunity does occur with RMSF.

### Diagnosis of tick-borne diseases

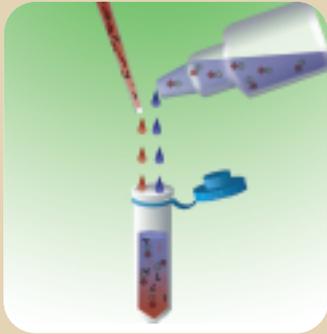
Diagnosis of these conditions is based on history, clinical signs, elimination of other diagnoses, laboratory data and response to antibiotic therapy. *B. burgdorferi*, *Ehrlichia*, *Anaplasma* and *R. rickettsii* infection typically cause seroconversion, which means that antibody testing may be useful.

### Antibody tests

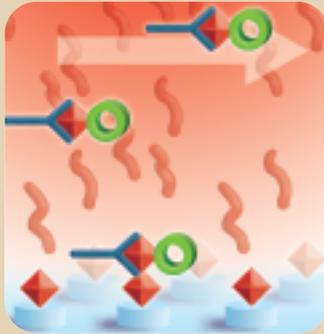
**ELISA.** This lab technique is able to detect *B. burgdorferi*, *Ehrlichia*, *Anaplasma* and *R. rickettsii*. The in-clinic SNAP® 3Dx® ELISA (IDEXX) can test for *B. burgdorferi* and *E. canis* antibodies as well as the *Dirofilaria immitis* antigen. This test has been shown to be highly sensitive and specific. Cross-reactivity between *E. canis* and *E. chaffeensis* can occur with this test, but *A. phagocytophilum* will not be detected.

The recently introduced SNAP® 4Dx® ELISA additionally tests for *A. phagocytophilum* antibody. Cross reactivity with *A. platys* can occur with the SNAP® 4Dx®. The Lyme portion of the test detects antibodies against C<sub>6</sub> peptides, which are not expressed in the tick, tissue culture or Lyme vaccines. Therefore, cross-reaction does not occur with this test in previously vaccinated dogs. Since the 3Dx® and 4Dx® tests give only a qualitative (positive or negative) answer regarding infection with *B. burgdorferi*, a quantitative C<sub>6</sub> test has been developed. This test

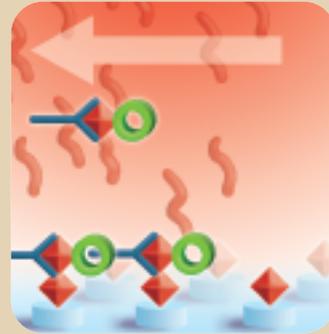
## ELISA Antibody Testing



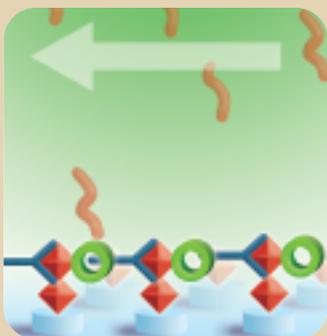
**Figure 1.** Mixing of conjugate (enzyme + antigen) and patient sample. The enzyme-antigen conjugate combines with sample antibodies, if present, to form conjugate-antibody complexes.



**Figure 2.** Application to matrix. The sample tube contents are poured across an antigen-containing matrix. If conjugate-antibody complexes are present, they bind to antigens in the matrix.



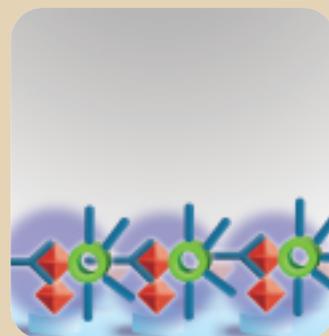
**Figure 3.** Bidirectional flow. The sample flows across the matrix in the opposite direction, providing a second chance for the conjugate-antibody complexes to bond with antigens in the matrix.



**Figure 4.** Rinsing. The matrix is rinsed with a cleaning solution to remove materials not bonded to the test matrix.



**Figure 5.** Substrate solution. This solution interacts with the enzymes in the conjugate.



**Figure 6.** Test results indicator. With a positive test, the conjugate enzymes convert substrate molecules from colorless to blue.

quantifies the level of antibodies. Quantification can help determine whether to treat subclinical patients and to monitor response to therapy, but further field research is needed before the clinical significance of this test is truly defined.<sup>5</sup> It is important to remember that, as with other antibody tests, the test may be positive for some time after infections have been resolved. Dogs may remain positive for months to years following successful treatment.

**Western blot.** This lab technique has historically been used as a first-line diagnostic

test for Lyme disease but is subjective and cannot reliably distinguish vaccinal antibodies from those induced by actual bacteremia.

**IFA.** This lab technique is able to detect *B. burgdorferi*, *Ehrlichia*, *Anaplasma* and *Rickettsia* antibodies. Paired serum samples are essential in determining acute infection. This procedure has high sensitivity but poor specificity.

### Other tests

**Polymerase chain reaction (PCR).** This test is able to amplify the DNA of *Borrelia*,

*Ehrlichia*, *Anaplasma* and *Rickettsia* species but is unable to determine whether DNA is from a viable whole organism or a nonviable fragment of the organism that is no longer pathogenic.<sup>4,5</sup>

**Urine protein/creatinine ratio.** This test is used to detect proteinuria secondary to Lyme nephropathy. The test should be performed in conjunction with a complete urinalysis, since an active urinary tract infection can falsely elevate the ratio.

### Treatment

For treatment of these diseases in both people and Pets, doxycycline is the antibiotic of choice. Dosages in dogs are:

- **Lyme disease:** 10 mg/kg administered orally, once daily for three to four weeks<sup>5</sup>
- **Ehrlichiosis/anaplasmosis:** 10 to 20

mg/kg administered orally, once daily for three to four weeks<sup>9</sup>

- **RMSF:** 10 to 20 mg/kg administered orally, once every 12 hours for seven to 10 days<sup>11</sup>

Side effects of doxycycline administration include vomiting and diarrhea and, less commonly, photosensitivity and hepatotoxicity. Esophageal strictures have been documented in cats when dry-pilling occurs; it is recommended to follow oral administration with a minimum of 6 mL of water in the cat.<sup>11</sup>

The question that arises in both the human and veterinary literature is whether antibiotic therapy truly resolves these infections, specifically *Borrelia* infections. The inability to determine organism clearance is most likely attributable to shortcomings in current diagnostic tools. Positive PCR tests are unable to distinguish between live

organisms and DNA fragments from dead organisms.<sup>4,5</sup> Antibodies may be present for months to years after the infection has cleared; therefore, tests that detect antibodies may remain positive for the same length of time.<sup>5</sup> The Infectious Diseases Society of America has critically examined human studies documenting the persistence of *Borrelia* organisms after the use of known effective antibiotics. They have determined that “there is no convincing evidence for the persistence of *Borrelia* in humans after treatment with antibiotic regimens known to be active against *Borrelia*.”<sup>12</sup>

Treatment of asymptomatic Pets with positive Lyme ELISAs remains controversial. Treatment of asymptomatic Pets with positive ELISAs has largely been based on a study indicating that arthritis is reduced in antibiotic-treated dogs and chronic silent infection with *B. burgdorferi* can be converted into active disease with the administration of immunosuppressive doses of corticosteroids.<sup>13</sup> Depending on the Pet's clinical status, other appropriate adjunctive treatment should be administered, including but not limited to nutritional supplementation, corticosteroids, fluid therapy and blood transfusions. Alternative antibiotics for organisms nonresponsive to doxycycline are also available and are determined by the disease being treated. Patients with proteinuria secondary to Lyme disease may be treated with angiotensin-converting enzyme inhibitors, omega-3 fatty acid supplements and low-dose aspirin. Immunosuppressive treatment, fluid therapy and additional antihypertensive administration may be necessary for Lyme nephropathy.

### Prevention

Currently, the best method for preventing infection with *B. burgdorferi* and other

pathogens transmitted by ixodid species is to avoid exposure to vector ticks. If exposure is unavoidable, K9 Advantix® (Bayer) and Frontline® Top Spot or Plus (Merial) work extremely well as topical acaricides, although 100 percent kills should not be expected in areas with high tick burden. I have had success in using both a topical acaricide and Preventic® collars in areas with high tick numbers. K9 Advantix® and Preventic® (Virbac) collars should not be used on cats due to potentially toxic and/or lethal effects. It is vital to stress the importance of tick control with clients because preventing the initial attachment and subsequent feeding is the best defense against tick-borne infections. *Borrelia* is typically found in the midgut of unfed ticks and takes about 24 to 48 hours to migrate to the salivary glands, so it is possible to remove the ticks before they infect their host. The issue arises when a tick is only able to take a partial blood meal. Partially fed *I. scapularis* ticks that have been interrupted from feeding can transmit *B. burgdorferi* before 24 hours upon reattachment to a second host.<sup>14</sup> Ticks have also been documented to transmit *Ehrlichia*, *Anaplasma* and *Rickettsia* species within 24 hours of attachment, so removal soon after attachment aids in reducing possible transmission of disease but does not guarantee it.<sup>14</sup>

Vaccination for Lyme disease has created dissension among practitioners because it is not considered a core vaccine and they are concerned that the vaccine may be involved in the immunopathogenesis of Lyme arthritis and nephropathy. Vaccination against Lyme disease in areas where the disease is endemic has been shown to significantly reduce infection rates.<sup>4,15</sup>

There are currently two types of Lyme disease vaccines available for dogs: whole-cell

killed bacterin (LymeVax®—Fort Dodge Animal Health) and recombinant OspA vaccine (Recombitek® Lyme—Merial; Continuum® Lyme—Intervet). Bacterin vaccines stimulate anti-OspC antibodies as well as OspA antibodies.<sup>5</sup> There is no vaccine currently available for *Ehrlichia* or *Anaplasma* infection in Pets. Because natural infection with *B. burgdorferi* does not impart any protective immunity, infected Pets should continue to receive immunizations with Lyme vaccines along with topical acaricides.

### Summary

There is controversy in the veterinary community regarding whether testing for Lyme disease, ehrlichiosis or anaplasmosis is warranted in presumptively healthy dogs. Our job as veterinarians is to protect Pet health and promote public health. There is concern that chronic, subclinical Lyme disease, if undiagnosed and untreated, may promote degenerative joint disease. Of even greater concern is the possibility that dogs can act as a reservoir for *Ehrlichia* and *Anaplasma* species, thus increasing exposure to people.<sup>6</sup>

Just as horses are sentinels for mosquito-transmitted encephalitides, dogs and cats should be considered sentinels for tick-borne diseases. Human infection with tick-borne pathogens can be serious, even fatal. Regular testing and treatment of Pets should allow us to catch disease early. Positive tests should dictate conversations with clients about tick-borne diseases, signs, prevention and treatment both in their Pets and themselves. As veterinarians, we not only have the ability to improve the health of Pets but can also contribute to the well-being of the people who share their home with Pets. 

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