**MORE THAN *E. CANIS*: THE INCREASINGLY COMPLICATED STORY OF EHRLICHIOSIS**

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**Ehrlichia canis** *(Canine Monocytic Erhlichiosis)*

*Rhipicephalus sanguineus* (the brown dog tick) is the principle vector for *Ehrlichia canis*. This tick can be found throughout the entire United States. It appears to prefer warmer climates. However, it can survive indoors throughout its entire life cycle, unlike other tick species. It is the tick most implicated in home and kennel infestations. This is one of the few tick species with a world-wide distribution.

In addition to *Ehrlichia canis*, the brown dog tick is also the vector for *Babesia canis* and *Anaplasma platys* (*R. sanguineus* is the suspected vector for A. platys in the U.S., confirmed in Japan)

**Clinical Signs**

*Ehrlichia canis* is the causative agent of canine monocytotropic ehrlichiosis. The course of infection may present in three clinical phases: acute, subclinical and chronic. The acute phase of infection typically manifests in transient illness that largely goes unrecognized. Many infected dogs recover spontaneously without medical attention. However, depending on the virulence of the strain and the health status of the dog, clinical signs might result in presentation to the veterinarian. Some clinical observations might include: fever, anorexia, lethargy, ocuonalosal discharge, and petechiation. In about 20% of cases, lymphadenomegaly and splenomegaly have been observed. If clinical signs during the acute phase of disease go undetected, the infection will progress into the subclinical phase of infection, where the patient will appear clinically healthy. Some animals will eventually progress to the chronic phase of infection wherein clinical signs reemerge. Again, the clinical presentation and severity of disease varies among patients. As in many tick-borne diseases, circulating immune-complexes produced by antibodies reactive to soluble antigens in the blood stream deposit in tissues where there is specialized vasculature. Such locations include the glomeruli, the synovial membranes and the meninges. For this reason, many dogs chronically infected with tick-borne pathogens develop glomerulonephritis, polyarthritis and meningitis. Other clinical findings may include weakness, anorexia, weight loss, fever, pallor lymphadenopathy, hepatomegaly, splenomegaly, retinal lesions and edema. There is up to a 25% mortality rate in animals that develop chronic ehrlichiosis.

**Onset**

The acute stage of the disease typically occurs 2 to 4 weeks after infection. As previously stated, this stage is transient and often goes undetected. Subsequently, if clinical signs resolve spontaneously the result will be the development of the subclinical phase of infection. The subclinical phase may persist for months or even years. Healthy, young dogs may be able to clear the infection at this phase on their own. However, *E. canis* can evade the host immune system. In as many as three or more years after initial infection, the chronic phase of the disease may
develop. In cases where the chronic phase of disease does not occur, the agent may persist throughout the life of the animal.

-Clinical pathology: During the acute phase of infection, common laboratories findings include thrombocytopenia, mild leukopenia and mild anemia (usually nonregenerative). During subclinical infection, otherwise clinically healthy dogs may have thrombocytopenia or mild nonregenerative anemia. The most common hematologic abnormality observed in chronic disease is thrombocytopenia. In severe cases, pancytopenia may develop as a result of severe, typically irreversible bone marrow damage. The prognosis for dogs with this form of the disease is grave. Other common laboratory abnormalities seen with chronic ehrlichiosis include granular lymphocytosis, elevated liver enzymes and hyperglobulinemia.

**Diagnostic Tests**

**Microscopic Evaluation:** *E. canis* - The detection of morula in leukocytes is so infrequent that it is not a reliable means of diagnosis. Even in animals seen during the acute phase of infection, the detection of morula is difficult. Detection can be optimized by performing buffy coat smears of peripheral blood or by evaluating tissue aspirates taken from the spleen or lymph nodes which typically harbor the organism.

**Serology:** Detection of antibodies to *E. canis* is the most reliable and frequently used method for confirming a diagnosis. Serum antibodies to *E. canis* can develop as soon as 7 days after infection but typically peak at 80 days post-infection in untreated animals. A negative antibody response in animals suspected to be acutely infected should be repeated in 2-3 weeks. As with other vector-borne infections, a positive serology by any method could indicate active infection, latent infection or previous exposure. The in-house ELISA assay (SNAP 4Dx Plus, IDEXX Laboratories, Westbrook, ME) is arguably the method most frequently used by most veterinarians since it is a point-of-care test. This test has one spot for antibodies to *Ehrlichia* species. It will detect antibodies to *E. canis*, *E. chaffeensis* and *E. ewingii*. It is currently the only serological assay that will detect antibodies to *E. ewingii*. In a recent study (Beall et al., 2012), over 8,000 dogs were tested for antibodies to *Ehrlichia* species. The test population was from a region extending from Oklahoma to the eastern seaboard. In this study 7.1% of the dogs tested had antibodies to an *Ehrlichia* species. Of that group only 0.8% had antibodies to *E. canis*, 2.8% had antibodies to *E. chaffeensis* and 5.1% had antibodies to *E. ewingii*. *E. chaffeensis* and *E. ewingii* are zoonotic pathogens and exposure of dogs to these pathogens warrants discussions with owners regarding the potential for exposure to family members. Direct transmission from an infected dog is highly unlikely, however, family members are often exposed to the same environmental risks as their pets and this should prompt discussions regarding practicing good tick control, effective and safe tick removal, and awareness of clinical signs associated with tick-borne diseases in people and pets.

The SNAP 4DX Plus test is a qualitative assay so if quantification of antibody levels is desired, the IFA test can be used. IFA tests for *E. canis* are offered at most commercial diagnostic laboratories. This assay is highly sensitive in detecting antibodies to *E. canis* and *E. chaffeensis* but false positive reactions can occur due to cross-reactive antibodies and/or nonspecific binding. The IFA for *E. canis* will not detect antibodies to *E. ewingii*. To confirm a diagnosis of monocytotropic ehrlichiosis it is necessary to have a reciprocal titer of 80 and clinical or laboratory findings consistent with the disease.
PCR: Nucleic acid detection is rarely performed in the diagnosis of *E. canis* infection, but it can be used to differentiate between organisms of the genus *Ehrlichia*. Dogs in the acute phase of clinical disease may be PCR positive, even prior to seroconversion. However, PCR analysis is not reliable in detecting subclinical, seropositive persistently infected carriers or animals in the chronic phase of the disease. PCR testing for *E. canis* is available at commercial and state diagnostic laboratories.

**Treatment**

Early treatment of *Ehrlichia canis* is imperative. Doxycycline or Minocycline at a dose of 5-10 mg/kg BID, PO is currently the drug of choice. The standard length of therapy in naturally infected animals is 28 days. Usually, rapid remission of clinical signs occurs within 2-3 days after initiation of antimicrobial therapy in dogs with acute or mild chronic illness.3 Dogs with severe chronic disease or those with aplastic anemia may not respond to antimicrobial therapy.

*Ehrlichia ewingii* and *Ehrlichia chaffeensis*

*Amblyomma americanum* (the lone star tick) is the principle vector for the other *Ehrlichia* spp. The lone star tick is found throughout the Eastern United States, from central and eastern Texas, north into Missouri and southern Minnesota and Wisconsin, spreading east to the coast in a broad, sweeping belt. A northern expansion of the tick is occurring up to the coastal areas of Maine. It is an “aggressive” tick species and feeds on multiple wild and domestic species, including dogs as well as humans. This tick is also the vector for the Panola Mountain *Ehrlichia*, *Cytauxzoon felis*, *Rickettsia* spp. and the Heartland virus (humans). It has also been the cause of food allergies to red meat in sensitized individuals.

**Illness and clinical signs in dogs**

*Ehrlichia ewingii* is the causative agent of canine granulocytotropic ehrlichiosis, but this agent can also infect humans.

- Clinical Signs: Dogs present with polyarthritis and/or nonspecific clinical signs including fever, lethargy, anorexia, vomiting, or diarrhea. Signs develop one to three weeks after the bite. Laboratory abnormalities include nonregenerative anemia, thrombocytopenia, lymphopenia, and eosinopenia.

*Ehrlichia chaffeensis* is the causative agent of Human Monocytic Ehrlichiosis (HME) but also infects dogs. Clinical manifestations of this disease in dogs are not completely defined. Dogs may present with nonspecific clinical signs of anorexia, fever, lethargy or lymphadenopathy. Clinically, infections in the dog may be indistinguishable from infections of *E. canis*. However, adequate documentation in experimentally infected animals is limited and has only resulted in hematological abnormalities without evidence of clinical disease.

- Onset: The incubation period for this infection is not clearly defined but expected to be 1 to 3 weeks if similar to other related agents. Thrombocytopenia has been documented in experimentally infected dogs.

**Diagnostic Tests**

Microscopic Evaluation of blood smear and/or synovial fluid: Morula: often observed for *E. ewingii* (in circulating neutrophils and neutrophils in synovial fluid, Figure right). Morula are rarely observed in circulating monocytes, lymphocytes or in lymph node aspirates in dogs.
acutely infected with *E. canis*. The same may be suspected of dogs infected with *E. chaffeensis*. Serology is most often used as an initial diagnostic assay to confirm infection in animals suspected of having a tick-borne disease. See above under *E. canis*. PCR analysis can confirm the presence of either pathogen in clinically ill patients. Most commercial laboratories can perform these assays on whole blood samples collected in EDTA.

**Therapy:**
Therapy with doxycycline continued for 3-4 weeks has proven efficacious in treating clinical disease in humans. Doxycycline typically causes rapid remission of clinical signs in dogs infected with *E. ewingii*. However, there is no well-established protocol for dose or length of therapy at this time for infection with *E. chaffeensis* or *E. ewingii* in dogs. Extrapolations from work done with *E. canis* would indicate that 5-10 mg/kg PO, BID is also effective for treatment of infections with these *Ehrlichia* spp.

**Important Pathogens of the Lone Star Tick (LST)**
The Lone star tick (*Amblyomma americanum*) is an aggressive tick accounting for more tick bites in humans than any other tick species (Figure 1). It has a wide, ever expanding geographic distribution that covers over half of the US and has extended its distribution into northern Mexico. The tick is a major public health concern since it has the ability to transmit multiple pathogens that affect people and pets and can even result in food allergies to red meat. The following is a list of pathogens known to be carried and transmitted by the LST.

*Ehrlichia ewingii* - Canine and human granulocytic ehrlichiosis
*Ehrlichia chaffeensis* - Human monocytic ehrlichiosis (also affects dogs)
Panola Mountain Ehrlichia (goats, humans, dogs)
*Rickettsia amblyommii* – reportedly less pathogenic that R. rickettsia, but may result in death in children
*R. rickettsii* – single reported case of transmission
*Borrelia lonestari*: Southern Tick Associated Rash Illness
*Cytauxzoon felis* – feline intraerythrocytic parasite
Viruses: Heartland virus, Bourbon, Tacaribe, others?
Allergies and anaphylaxis to red meat (beef, lamb or pork)

Alpha-gal carbohydrate in saliva □ hives to anaphylaxis

Recently, we identified as many as 60% or more of LSTs in Florida carry *R. amblyommii*. Last year a report was published that indicated an increase in the cases of Rocky Mountain spotted fever (RMSF), but that disease symptoms were milder and did not result in rapid death as was typical of the disease ([http://www.npr.org/sections/health-shots/2015/10/28/451990557/the-lone-star-tick-may-be-spreading-a-new-disease-across-america](http://www.npr.org/sections/health-shots/2015/10/28/451990557/the-lone-star-tick-may-be-spreading-a-new-disease-across-america)). However, it was reported in Senora, Mexico that 20.2% of the 104 children who were hospitalized for the disease died from the infection (Pediatric Infectious Disease Journal: February 2015 - Volume 34 - Issue 2 - p 125–130).

**Seroprevalence of Ehrlichia canis, Ehrlichia chaffeensis and Ehrlichia ewingii in dogs in North America** (Beall, Alleman, Breitschwerdt, et al., 2012 Parasites and Vectors, 5:29)
In this multi-institutional study we tested 8,662 dogs for antibodies to each of these three *Ehrlichia* sp. Samples were collected from locations within the broad geographic distribution of the LST. Overall, 7.1% of dogs tested positive for one or more *Ehrlichia* spp. Of this population only 0.8% were positive for antibodies to *E. canis* while 2.8% were seropositive for *E. chaffeensis* and 5.1% for *E. ewingii*. An alarming 1.6% of the dogs were positive for both *E. ewingii* and *E. chaffeensis* organisms carried by the LST.

These findings support the conclusion that most Ehrlichia infections in dogs within the geographic distribution of the LST are the result of infections with either *E. chaffeensis*, *E. ewingii* or both. This is a public health concern since both of these pathogens may result in human illness as well as canine disease.
Figures

Figure 1: Three lone star ticks, two adults (male and female) and one nymph. The female is easily recognized by the prominent white spot on the dorsum.

Figure 2: The geographic distribution of the lone star tick in the US. This tick has now expanded its region into Northern Mexico.