

CANINE TICK AND FLEA VECTOR BORNE DISEASES

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INTRODUCTION

There are many inflammatory disease syndromes in dogs and cats resulting in clinical signs of disease. Important examples include uveitis, stomatitis, inflammatory bowel disease, bronchitis, hemolytic anemia, thrombocytopenia, and polyarthritis. Each of these syndromes have primary infectious disease causes or primary immune mediated disease causes which can be very hard to differentiate! For each of these syndromes the immune system is ultimately the cause of the inflammation and an infectious disease cause is not always identified.

The Center for Companion Animal Studies actively studies vector borne agents, upper respiratory tract disease agents, gastrointestinal tract infectious disease agents, and vaccines. For this 8 hour lecture series, I have chosen a diverse group of syndromes/agents to discuss in class with emphasis on the things I believe have changed within the last 2 years. During the lectures, we will use case examples and audience response devices to encourage audience participation. Some of these proceedings have been adapted from my other writings including the infectious disease section in the textbook *Small Animal Internal Medicine* (Nelson R and Couto G [eds], Elsevier).

The organisms of the Order Rickettsiales, in the families *Rickettsiaceae* and *Anaplasmataceae*, were reclassified in 2001 following phylogenetic analyses of the 16S rRNA and groESL gene sequences (Dumler and colleagues, 2001). Some *Ehrlichia* spp. were transferred to the *Neorickettsia* genus (including *E. risticii*) and some *Ehrlichia* spp., including *E. phagocytophila* (also called *E. equi* and human granulocytic *Ehrlichia*) and *E. platys*) were placed into the genus *Anaplasma*. The genera *Ehrlichia* and *Neorickettsia* were transferred to the family *Anaplasmataceae*; the genera of *Rickettsia* and *Orientia* remained in the *Rickettsiaceae*. The organisms in the *Ehrlichia*, *Anaplasma*, and *Neorickettsia* are classified genetically and by cell tropism (Monocytotropic, granulocytotropic, or thrombocytotropic).

Vector borne disease diagnostic assay issues. There are many canine and feline vector borne diseases are common. In the United States, *Anaplasma* spp., *Babesia* spp., *Bartonella* spp., *Borrelia* spp., *Ehrlichia* spp., hemoplasmas, and *Rickettsia* spp. are most common. Serological tests are available for some agents but not others (hemoplasmas). PCR assays that amplify the DNA of multiple targets are now commonly available. Multiple laboratories now provide serological assays (some available for in clinic use) and PCR assays for individual agents or panels of agents. With the exception of *B. burgdorferi*, vector borne agents disseminate quickly through the body in infected cells and can lead to illness prior to antibody production, thus, serological tests can be falsely negative in acute vector borne diseases. In these cases, specific DNA can often be amplified from blood samples. In the later stages of vector borne diseases,

PCR assay results can become negative because infection is limited by specific immune responses. Thus, use of antibody tests may be needed to prove evidence of infection if the animal has chronic illness. As each laboratory has specific techniques, results in some tests may not be in agreement. As an example, the following work from our Center was just presented at the American College of Veterinary Internal Medicine meeting in Indianapolis, 2015

COMPARISON OF 2 COMMERCIALY AVAILABLE PCR ASSAYS FOR THE AMPLIFICATION OF *EHRlichia* SPP. DNA FROM BLOOD OF NATURALLY EXPOSED DOGS IN OKLAHOMA

Ehrlichia canis, *E. chaffeensis*, and *E. ewingii* are vector borne pathogens of dogs and people. Amplification of specific DNA is commonly used in the diagnosis of *Ehrlichia* spp., PCR assays for these agents are commonly available commercially, and positive PCR assay results often occur prior to detection of specific antibodies against *Ehrlichia* spp.. The purpose of this study was to compare the results of 2 different commercially available (USA) PCR assays for the amplification of *Ehrlichia* spp. DNA using samples from naturally exposed dogs in an endemic area.

Dogs (n = 72) being sterilized at a low cost clinic in Checotah, OK during July 2014 were selected as those likely to be exposed to *Ambloymma americanum* and so at high risk for *E. ewingii* and *E. chaffeensis* exposure. *Rhipicephalus sanguineus* also is found in the region and so *E. canis* infection was also possible. A total of 1 ml of blood in EDTA collection tubes was stored in a refrigerator overnight, and the next day were sent on cold packs to the first testing laboratory via overnight shipping. On arrival, the samples were split into 2 aliquots with 1 aliquot being frozen at -80C and 1 aliquot being prepared for evaluation in a commercially available conventional *Ehrlichia* spp. PCR assay (www.dlab.colostate.edu). The frozen EDTA blood was shipped to the second PCR laboratory on dry ice for evaluation in a commercially available real time multiplex *Ehrlichia* spp. PCR assay (www.antech.com). Results from samples with sequence confirmation were compared using the kappa statistic.

In the first laboratory, DNA of *E. canis* (1 dog), *E. ewingii* (6 dogs), and *E. chaffeensis* (1 dog) were amplified from some dogs (11.1%). In the second laboratory, DNA of *E. ewingii* was amplified from 9 dogs (12.5%). The agreement between the assays at the genus level was good (kappa = 0.667 [SE 0.139]; 95% CI = 0.395 to 0.938) with an overall percentage agreement of 93.1%. The dog with DNA most homologous with *E. chaffeensis* in the first laboratory showed DNA most homologous with *E. ewingii* in the second laboratory.

Ehrlichia ewingii infection transmitted by *A. americanum* is common in OK. The agreement between the 2 laboratories was good even though some discordant results were detected with the second laboratory appearing to have a higher sensitivity for *E. ewingii* DNA. However, 100% concordance was not expected because the samples were not handled identically and the assays use different technologies. The sequence homology between *E. ewingii* and *E. chaffeensis* is very high and so a different result from 2 different sequencing laboratory can occur. Alternately, dog may have had dual infection.

CANINE GRANULOCYTOTROPIC ANAPLASMOSIS

Etiology and epidemiology. *Anaplasma phagocytophilum* (previously *E. equi*, *E. phagocytophila*, canine granulocytic *Ehrlichia*, and human granulocytic ehrlichiosis agent) is known to infect a variety of animals, including small mammals, mountain lions, coyotes, sheep, cattle, deer, dogs, horses, and people (Dumler et al, 2001). Small mammals and deer are natural reservoirs. The distribution of *A. phagocytophilum* is defined by the range of *Ixodes* ticks and so is most common in California, Wisconsin, Minnesota, and the northeastern states and other areas of the world with this tick genus including Europe, Asia, and Africa. Birds may play a role in spreading infected ticks and may also serve as a reservoir. In endemic areas, seroprevalence can be very high; in one study of healthy dogs in California, 47.3% of the dogs tested in one county were seropositive (Foley and colleagues, 2001). *Borrelia burgdorferi* is also transmitted by *Ixodes* ticks and so co-infections can occur (Jaderlund and colleagues, 2007). The vector needs

to be attached for approximately 24-48 hours in order to transmit the agent. Clinical signs usually develop approximately 1-2 weeks after infection. Neutrophils (and rarely, other leukocytes) phagocytize the organism, and once intracellular, *A. phagocytophilum* prevents phagolysosome fusion. This mechanism allows for multiplication within the phagosome, which gives the appearance of morulae in neutrophils under light microscopy. The exact pathogenesis of disease is still undetermined and it is unclear why some dogs but not others develop clinical signs of disease.

Clinical features. *Anaplasma phagocytophilum* infection appears to be primarily an acute disease in dogs. It has been associated most commonly with non-specific signs of fever, lethargy and inappetence. Stiffness and lameness consistent with musculoskeletal pain are also common and *A. phagocytophilum* has been associated with polyarthritis. Vomiting, diarrhea, difficult breathing, cough, lymphadenopathy, hepatosplenomegaly, and central nervous system signs (seizures and ataxia) have also been reported. Dogs can be chronic, subclinical carriers and so exacerbation of disease could occur in some dogs. However, chronic disease syndromes like those associated with *E. canis* infection have not been documented. In a recent study of dogs with neurological diseases in Sweden, while serological evidence of exposure to *A. phagocytophilum* and *Borrelia burgdorferi* was common, neither organism was linked to the presence of neurological disease (Jaderlund and colleagues, 2007). In one study of valvular endocarditis, all dogs with *Bartonella* spp. associated disease were also seropositive for *A. phagocytophilum* (MacDonald and colleagues, 2004). Whether the coinfection potentiated the *Bartonella* associated disease is unknown.

Diagnosis. Morulae of *A. phagocytophilum* are commonly detected in neutrophils of most clinically affected dogs and so infection is usually confirmed during performance of a complete blood cell count. While thrombocytopenia and lymphopenia are common, neutrophil counts are usually normal. Hemolytic anemia and thrombocytopenia were thought to be from *A. phagocytophilum* infection in one dog in the United Kingdom (Boxfield and colleagues, 2005). Reported biochemical panel and urinalysis abnormalities are mild and nonspecific. The morulae cannot be distinguished from those of *E. ewingii*, but the geographical range of the infections varies between the organisms and so the travel history can aid in ranking the differentials. Serologic test results (IFA and ELISA) can be used if morulae are not identified. A point of care assays that detects antibodies against *A. phagocytophilum* is available (SNAP®4Dx, IDEXX Laboratories, Portland, ME). Antibody assay results can be falsely negative in acute cases and so a convalescent test 2-3 weeks later may be required to confirm exposure. As *A. phagocytophilum* infections are limited geographically, this antibody test result is not needed in the majority of the United States. Polymerase chain reaction assays performed on blood collected in EDTA can be used to confirm infection and differentiate *A. phagocytophilum* infection from other infections, but microbial DNA can also be amplified from healthy dogs (Henn and colleagues, 2007). Most dogs infected by *A. phagocytophilum* have subclinical infections, most infected dogs only have an acute phase, exposure rates in endemic areas are high, and the disease syndromes associated with infection have multiple other causes. Thus, antibody test results and PCR assay results alone cannot be used to prove clinical disease associated with *A. phagocytophilum* infection. For example, while *A. phagocytophilum* is known to cause thrombocytopenia and polyarthritis in some dogs, a recent study failed to show an

association between *A. phagocytophilum* PCR assay or serological test results in dogs with polyarthritis or thrombocytopenia (Foley and colleagues, 2007).

Treatment. Several antibiotics are effective against *A. phagocytophilum* in vitro (Maurin and colleagues, 2003). Doxycycline administered at 5-10 mg/kg, PO, q12-24 hr for at least 10 days is recommended by most clinicians. Whether a 28 day course of doxycycline therapy as recommended for *E. canis* is needed is unknown (Neer and colleagues 2002). If tetracyclines are used, 22 mg/kg, PO, q8hr for 2-3 weeks is recommended. Chloramphenicol administered at 15-25 mg/kg, PO, q 8hr for 14-21 days may be effective in puppies and should be used to avoid dental discoloration. Most dogs respond to therapy within hours to days of initiating therapy.

Zoonotic aspects and prevention. *Anaplasma phagocytophilum* infects people as well as dogs and so the organism is zoonotic. Human infections most likely acquired by direct tick transmission, however, handling infected blood and carcasses can also lead to infection. Care should also be taken when handling ticks. There is currently no vaccine for *A. phagocytophilum* infection. Infection can be avoided by controlling ticks or prophylactic use of tetracyclines when visiting endemic areas. In one study, application of imidacloprid-permethrin prevented transmission of *A. phagocytophilum* from naturally infected *Ixodes scapularis* ticks to dogs (Blackburn and colleagues, 2004). Dogs appear to be susceptible to reinfection and so tick control should be maintained at all times in endemic areas. Dogs used for blood donors that reside in endemic areas should be screened for *A. phagocytophilum* infections by serology or PCR.

CANINE MONOCYTOTROPIC EHRLICHIOSIS

Etiology and epidemiology. Organisms that are associated with monocytotropic ehrlichiosis in naturally-infected dogs include *Ehrlichia canis*, *E. chaffeensis*, and *Neorickettsia risticii* var *atypicalis*. An individual dog can be infected by more than one ehrlichial agent and coinfections with other tick borne pathogens are common (Kordick and colleagues, 1999).

Ehrlichia canis is the most common of these agents and causes the most severe clinical disease; it is maintained in the environment from passage from ticks to dogs. *Rhipicephalus sanguineus* and *Dermacentor variabilis* are the known vectors. The organism is not passed transovarially in the tick, so unexposed ticks must feed on a rickettsemic dog in the acute phase to become infected and perpetuate the disease. Male *R. sanguineus* can take multiple feedings and can both acquire and transmit *E. canis* in the absence of female ticks (Bremer and colleagues, 2005). Dogs seropositive for *E. canis* have been identified in many regions of the world and most of the United States, but the majority of cases occur in areas with high concentrations of *R. sanguineus* such as the Southwest and Gulf Coast.

Ehrlichia chaffeensis is a cause of human mononuclear ehrlichiosis. White tailed deer, voles, coyotes, and opossums are reservoirs and *Amblyomma americanum*, *D. variabilis*, and some *Ixodes* ticks are vectors. Infections by *E. chaffeensis* are detected primarily in the southeastern United States. Clinical manifestations in dogs are currently being detailed (Breitschwerdt and colleagues, 1998; Zhang and colleagues, 2003) and appear to be rare. *Neorickettsia risticii* var *atypicalis* has been detected only in the United States to date and causes similar clinical signs as *E. canis* (Kokoma and colleagues, 1991). Bats and swallows may be the natural reservoirs of

this organism. Trematodes of snails and water insects are thought to be the vectors (Pusterla and colleagues, 2003).

Ehrlichia canis infection causes acute, subclinical, and chronic phases of disease. Infected mononuclear cells marginate in small vessels or migrate into endothelial tissues, inducing vasculitis during the acute phase. The acute phase begins 1 to 3 weeks after infection, and lasts 2 to 4 weeks; most immunocompetent dogs survive. The subclinical phase lasts months to years in naturally infected dogs. Although some dogs clear the organism during the subclinical phase, the organism persists intracellularly in some, leading to the chronic phase of infection. Many of the clinical and clinicopathologic abnormalities that develop during the chronic phase are due to immune reactions against the intracellular organism. The variable duration of the subclinical phase of disease explains why *E. canis* infection does not have a distinct seasonal incidence like Rocky Mountain spotted fever (RMSF). However, acute phase disease is recognized most frequently in the spring and summer when the tick vectors are most active.

Clinical features. Clinical disease from ehrlichial infection can occur in any dog, but its severity varies depending on the organism, host factors, and presence of coinfections. Virulence is thought to vary with different field strains of *E. canis*. Dogs with depressed cell-mediated immunity develop severe disease. However, *E. canis* itself did not cause immunosuppression in young, experimentally infected dogs within the first several months of infection (Hess and colleagues, 2006).

Clinical findings in dogs with *E. canis* infections vary with the timing of infection. The clinical manifestations of acute phase disease are very similar to those of RMSF, owing to the development of vasculitis. Ticks are most commonly found on dogs during the acute phase of infection. Fever can occur in both clinical phases of infection but is more common in dogs with acute ehrlichiosis. Petechiae or other evidence of bleeding noted during the acute phase are generally caused by a combination of mild thrombocytopenia (consumption or immune-mediated destruction) and vasculitis; thrombocytopenia (consumption, immune-mediated destruction, sequestration, decreased production), vasculitis, and platelet function abnormalities (Brandao and colleagues, 2006) occur in the chronic phase. The thrombocytopenia in the acute phase is generally not severe enough to result in spontaneous bleeding and so bleeding may be primarily from vasculitis and decreased platelet function.

Pale mucous membranes usually only occur in the chronic phase during the development of pancytopenia. Hepatomegaly, splenomegaly, and lymphadenopathy are from chronic immune stimulation (i.e. lymphoreticular hyperplasia) and are detected most frequently in dogs in the chronic phase. Interstitial or alveolar edema secondary to vasculitis or to inflammation, pulmonary parenchymal hemorrhage secondary to vasculitis or thrombocytopenia, or secondary infections from neutropenia are mechanisms resulting in dyspnea or cough in some dogs with ehrlichiosis. Polyuria, polydipsia, and proteinuria are reported in some dogs that develop renal insufficiency.

Stiffness, exercise intolerance, and swollen painful joints occur in some dogs with suppurative polyarthritis. Most dogs with polyarthritis from which the organism has been demonstrated have been infected with *E. ewingii* or *A. phagocytophilum*. Ophthalmic manifestations of disease are

common; tortuous retinal vessels, perivascular retinal infiltrates, retinal hemorrhage, anterior uveitis, and exudative retinal detachment occur (Komnenou and colleagues, 2007). CNS signs can include depression, pain, ataxia, paresis, nystagmus, and seizures.

Diagnosis. Neutropenia is common during acute phase vasculitis and after bone marrow suppression in the chronic phase. Chronic immune stimulation causes monocytosis and lymphocytosis; lymphocytes often have cytoplasmic azurophilic granules (i.e., large granular lymphocytes). Regenerative anemia is from blood loss (acute and chronic phases); normocytic, normochromic nonregenerative anemia is from bone marrow suppression or anemia of chronic disease (chronic phase). Thrombocytopenia can occur with either acute or chronic ehrlichiosis, but is generally more severe with chronic phase disease. Thrombocytopathies from hyperglobulinemia potentiate bleeding in some dogs with chronic ehrlichiosis. Chronic ehrlichiosis is classically associated with pancytopenia, but any combination of neutropenia, thrombocytopenia, and anemia can occur. Changes in bone marrow cell lines associated with ehrlichiosis vary from hypercellular (acute phase) to hypocellular (chronic phase). Bone marrow plasmacytosis is common in dogs with subclinical and chronic ehrlichiosis, and the disease can be confused with multiple myeloma, particularly in those dogs with monoclonal gammopathies. Dogs with ehrlichiosis are usually not hypercalcemic and do not have lytic bone lesions.

Hypoalbuminemia in the acute phase is probably caused by third spacing of albumin in tissues because of vasculitis, whereas in chronic phase disease it is due to glomerular loss from immune complex deposition or chronic immunostimulation (i.e., monoclonal or polyclonal gammopathy). Prerenal azotemia can occur with acute or chronic disease; renal azotemia develops in some dogs with severe glomerulonephritis from chronic ehrlichiosis. The combination of hyperglobulinemia and hypoalbuminemia is consistent with subclinical or chronic ehrlichiosis. Polyclonal gammopathies are most common, but monoclonal (e.g., IgG) gammopathies can also occur.

Aspirates of enlarged lymph nodes and spleen reveal reactive lymphoreticular and plasma cell hyperplasia. Nondegenerate neutrophils are the primary cells in synovial fluid from dogs with polyarthritis caused by any *Ehrlichia* spp.; *E. ewingii* and *A. phagocytophilum* morulae can be identified in synovial neutrophils from some dogs. Bone marrow aspirates in dogs with chronic ehrlichiosis typically reveal myeloid, erythroid, and megakaryocytic hypoplasia in association with lymphoid and plasma cell hyperplasia. Morulae from *E. canis* are rarely detected in the cytoplasm of mononuclear cells. Ehrlichiosis generally causes mononuclear pleocytosis and increased protein concentrations in CSF. Antiplatelet antibodies, antinuclear antibodies (ANA), antierythrocyte antibodies (by direct Coombs' test), and rheumatoid factors are detected in some dogs with ehrlichiosis, leading to an inappropriate diagnosis of primary immune-mediated disease (Smith and colleagues, 2004).

No pathognomonic radiographic signs appear in dogs with ehrlichiosis. The polyarthritis is nonerosive, and dogs with respiratory signs most commonly have increased pulmonary interstitial markings, but alveolar patterns can occur. Identification of morulae in cells documents *Ehrlichia* infection, but it is uncommon with monocytotropic strains. Examination of buffy coat smears or blood smears made from blood collected from an ear margin vessel may increase the chances of finding morulae. Some *Ehrlichia* spp. can be cultured, but the procedure is low-yield and expensive and so is not clinically useful.

Most commercial laboratories (using IFAs) and one point-of-care diagnostic test (SNAP®4Dx, IDEXX Laboratories, Portland, Me) use reagents that detect antibodies against *E. canis* in serum. These tests are generally used as the first screening procedures in dogs suspected to have ehrlichiosis. The American College of Veterinary Internal Medicine (ACVIM) Infectious Disease Study Group suggests that *E. canis* IFA antibody titers between 1:10 and 1:80 be rechecked in 2 to 3 weeks because of the potential for false-positive results at these titer levels (Neer and colleagues, 2002). At low titers, agreement between IFA and ELISA can be poor (O'Connor and colleagues, 2006).

If serum antibodies against *E. canis* are detected in a dog with clinical signs consistent with ehrlichiosis, a presumptive diagnosis of canine ehrlichiosis infection should be made and appropriate treatment begun. However, detection of antibodies alone is not diagnostic of ehrlichiosis because of the existence of cross-reactive antibodies between *E. canis*, *Neorickettsia helminthoeca*, and *Cowdria ruminantium*, and because some dogs are subclinically infected.. Additionally, negative test results do not totally exclude ehrlichiosis from the list of differential diagnoses, because clinical disease can be detected before seroconversion and not all *Ehrlichia* spp. induce antibodies that consistently detected in *E. canis* assays.

PCR assays are now available commercially and can be used to detect organism-specific DNA in peripheral blood. It can be performed on joint fluid, aqueous humor, CSF, and tissues. Blood PCR results can be positive before seroconversion in some experimentally inoculated dogs, and positive results document infection, whereas positive serologic tests only document exposure. However, as for serology, no standardization between laboratories currently exists, and insufficient quality control can lead to both false-positive and false-negative results. Until more information is available, the ACVIM Infectious Disease Study Group suggests using PCR with serology, not in lieu of it. Because antibiotic treatment rapidly induces negative blood PCR results, the clinician should draw the blood sample for testing and place it in an EDTA tube before treatment. In one recent study, tissues (lymph nodes, spleen, liver, bone marrow, and blood) from naturally infected dogs were assayed by PCR. Blood and lymph nodes were the most likely to be positive, but were falsely negative in approximately 30% of the samples (Gal and colleagues, 2007).

Treatment. Supportive care should be provided as indicated. Several different tetracycline, doxycycline, chloramphenicol, and imidocarb dipropionate protocols have been used. The ACVIM Infectious Disease Study Group currently recommends doxycycline (10 mg/kg PO q24h for at least 28 days). In one study of experimentally infected dogs, ticks still could acquire *E. canis* from feeding on dogs previously treated with doxycycline for 14 days (Schaefer and colleagues, 2007). Clinical signs and thrombocytopenia should rapidly resolve. If clinical abnormalities are not resolving within 7 days, other differential diagnoses should be considered. Results of studies using imidocarb dipropionate (5 to 7 mg/kg IM or SQ repeated in 14 days) to treat canine ehrlichiosis have been variable. In one recent study, thrombocytopenia persisted and infection was not cleared in experimentally inoculated dogs (Eddlestone and colleagues, 2006). Some patients develop pain at the injection site, salivation, oculonasal discharge, diarrhea, tremors, and dyspnea after administration of this drug. Quinolones are not effective for the treatment of *E. canis* infections in dogs. While coinfections common occur, the presence of

agents like *Anaplasma phagocytophilum*, *Anaplasma platys*, and *L. infantum* did not adversely effect the response to therapy (Mylonakis and colleagues, 2004).

Positive antibody titers have been detected for up to 31 months after therapy in some naturally infected dogs. Dogs with low (<1:1024) antibody titers generally revert to negative within 1 year after therapy. Dogs with antibody titers greater than 1:1024 often maintain positive antibody titers after therapy. It is undetermined whether these dogs are persistent carriers of the organism. Based on these findings, antibody titers are considered to be ineffective for monitoring response to therapy. The ACVIM Infectious Disease Study Group recommends monitoring resolution of thrombocytopenia and of hyperglobulinemia as markers of therapeutic elimination of the organism.

It is currently unknown whether ehrlichial infections are cleared by treatment. If PCR is to be used to monitor treatment, the ACVIM Infectious Disease Study Group recommends the following steps be taken: The PCR test should be repeated 2 weeks after stopping treatment. If still positive, treatment should be reinstated for 4 weeks and retesting performed. If PCR results are still positive after 2 treatment cycles, an alternate antiehrlichia drug should be used. If PCR results are negative, the test should be repeated in 8 weeks, and if still negative it can be assumed therapeutic elimination is likely. In one study, PCR assay performed on splenic aspirates was superior to blood PCR to document elimination of infection (Harrus and colleagues, 2004).

Whether to treat seropositive, healthy dogs is controversial. Arguments for and against testing or treating healthy dogs were reviewed by the ACVIM Infectious Disease Study Group (Neer and colleagues, 2002). The primary reason to treat a seropositive, healthy dog is to try to eliminate infection before development of chronic phase disease. However, treatment of healthy dogs is controversial for at least six reasons: (1) it is unknown whether treatment halts progression to the chronic phase; (2) not all seropositive dogs are infected; (3) not all seropositive dogs progress to the chronic phase; (4) it is unknown whether treatment eliminates infection; (5) even if infection is eliminated, reinfection can occur; and (6) treatment of healthy carriers may result in antimicrobial resistance. Because further data are needed to make definitive recommendations, owners should be given the pros and cons and asked to make treatment decisions.

The prognosis is good for dogs with acute ehrlichiosis, and it is variable to guarded for those with chronic ehrlichiosis. Fever, petechiation, vomiting, diarrhea, epistaxis, and thrombocytopenia often resolve within days after initiation of therapy in acute cases. Bone marrow suppression from chronic phase ehrlichiosis may not respond for weeks to months, if at all. Anabolic steroids and other bone marrow stimulants can be administered but are unlikely to be effective because precursor cells are often lacking. Immune-mediated events resulting in the destruction of red blood cells or platelets are likely to occur with ehrlichiosis, leading to the recommendation to administer antiinflammatory or immunosuppressive doses of glucocorticoids to acutely affected animals. Prednisone (2.2 mg/kg PO divided q12h during the first 3 to 4 days after diagnosis) may be beneficial in some cases.

Zoonotic aspects and prevention. Dogs and people are both infected by *Ehrlichia canis*, *E. ewingii*, and *E. chaffeensis* (Buller and colleagues, 1999). Although people cannot acquire ehrlichiosis from handling an infected dog, dogs may be reservoirs for these agents and may play

a role in the human disease by bringing vectors into the human environment. Ticks should be removed and handled with care.

Tick control should be maintained at all times; administration of fipronil was shown to lessen transmission in one study (Davoust and colleagues, 2003). Because *Ehrlichia canis* is not passed transovarially in the tick, it can be eliminated in the environment by tick control or by treating all dogs through a generation of ticks. *Rhipicephalus* can only transmit *E. canis* for approximately 155 days; if tick control is not feasible, tetracycline can be administered (6.6 mg/kg PO daily for 200 days). During this time, infected dogs will not infect new ticks and previously infected ticks will lose the ability to transmit the organism. Doxycycline given at 100 mg/dog per day was used successfully as a chemopreventative (Davoust and colleagues, 2005). Dogs used as blood donors should be screened serologically yearly and seropositive dogs should not be used.

CANINE GRANULOCYTOTROPIC EHRLICHIOSIS

Etiology and epidemiology. *Ehrlichia ewingii* forms morulae in neutrophils and eosinophils and has been detected in dogs and people that reside in the southern and southeastern United States. While one canine case was reported in New York state, *A. phagocytophilum* is more likely in this region (see sections on canine and feline granulocytotropic anaplasmosis). *E. ewingii* has been detected in a number of ticks, but *Amblyomma americanum* is the only proven vector to date (Murphy and colleagues, 1998). Deer are infected and serve as a reservoir (Yabsley and colleagues, 2002). The incubation period after tick exposure is approximately 13 days. Pathogenesis of disease is unknown, but is likely to be similar to other *Ehrlichia* spp. In general, clinical signs of *E. ewingii* infection are less severe than those of *E. canis*. Concurrent disease or infections may play a significant role in the pathogenesis of *E. ewingii* infection.

Clinical Features. Non-specific signs of *E. ewingii* infection include fever, lethargy, anorexia, depression, and signs consistent with polyarthritis, such as stiffness. Other clinical signs include vomiting, diarrhea, peripheral edema and neurological signs like ataxia, paresis, and vestibular disease. Clinical signs can be mild, self-limited, or inapparent (Goodman and colleagues, 2003). Similar to *R. rickettsii*, acute disease seems to be most common and so *E. ewingii* infection should be highest on the list of differential diagnoses from the spring through autumn when *A. americanum* is most active.

Diagnosis. Suppurative polyarthritis is most common. Other clinicopathologic findings typically associated with acute *E. canis* infection, such as mild to moderate thrombocytopenia and anemia, also occur. Morulae can be detected in neutrophils and eosinophils in peripheral blood and in neutrophils from synovial fluid. However, presence of morulae is transient and so easily missed cytologically. The organism has not been cultured to date and so a specific serological test is not available. However, because the organism is closely related to *E. canis*, antibodies against *E. ewingii* can often be detected in *E. canis* IFA assays. However, *E. ewingii* antibodies do not bind to the *E. canis* peptide used in a point of care diagnostic assay in the United States (SNAP®4Dx, IDEXX Laboratories, Portland, Me) and so this assay cannot be used to screen dogs for *E. canis* infection (Daniluk and colleagues, 2007). PCR assays are now used to differentiate between members of the *Ehrlichia*, *Anaplasma*, and *Neorickettsia* genera and should be performed on blood collected in EDTA before administration of antibiotics.

Treatment. Supportive care should be provided as indicated. The tetracycline, doxycycline, and chloramphenicol protocols recommended for *E. canis* infections are generally effective. The ACVIM Infectious Disease Study Group currently recommends doxycycline (10 mg/kg PO q24h for at least 28 days) for *Ehrlichia* spp. infections of dogs (Neer and colleagues, 2002).

Zoonotic aspects and Prevention. Dogs and people are both infected by *Ehrlichia canis*, *E. ewingii*, and *E. chaffeensis* (Buller and colleagues, 1999). Although people cannot acquire ehrlichiosis from handling an infected dog, dogs may be reservoirs for these agents and may play a role in the human disease by bringing vectors into the human environment. Ticks should be removed and handled with care. Dogs used as blood donors should be screened serologically with *E. canis* IFA tests yearly and seropositive dogs should not be used.

ROCKY MOUNTAIN SPOTTED FEVER

Etiology and epidemiology. Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii*. Other members of the genus also infect dogs in the United States; however, they are not associated with clinical disease but can induce antibodies that cross-react with *R. rickettsii* (see Diagnosis). For example, 17 of 22 canine sera submitted for *R. akari* (rickettsialpox in humans) IFA testing cross-reacted serologically with *R. rickettsii* (Comer and colleagues, 2001). In another study of dogs coinfecting with several tick-borne pathogens, infection with an uncharacterized rickettsial agent commonly induced cross-reacting antibodies to *R. rickettsii* (Kordick and colleagues, 1999). Canine RMSF is recognized predominantly in the southeastern states from April through September when the tick vectors are most active. From 1993 to 1996, 52% of human cases of RMSF were reported from the south Atlantic region (Treadwell and colleagues, 2000). *Dermacentor andersoni* (i.e., American wood tick), *Dermacentor variabilis* (i.e., American dog tick), and *Amblyomma americanum* (i.e., Lone Star tick) are the principal vectors, host, and reservoir of *R. rickettsii*. Recently, there has been a reemergence of RMSF in the southwestern states and *R. sanguineus* ticks are the vector (Demma and colleagues, 2005; Demma and colleagues, 2006; Nicholson and colleagues, 2006). The organism has also been detected in *R. sanguineus* in California (Wikswa and colleagues, 2007). Strains of *R. rickettsii* that infect dogs and humans are closely related genetically (Kidd and colleagues, 2006). Seroprevalence rates are high in endemic areas. In one study of dogs in the southeastern United State, 14.1% and 29.7% of healthy and clinically ill dogs, respectively, had detectable *R. rickettsii* serum antibody titers (Solano-Gallego and colleagues, 2004).

The organism is maintained in nature in a cycle between ticks and small mammals like voles, ground squirrels, and chipmunks, and it is transmitted transovarially in ticks, so nymphs and larvae can be infected without feeding. *R. rickettsii* replicates in endothelial tissues (causing vasculitis) and so can lead to diverse and sometimes severe clinical manifestations of disease as soon as 2 to 3 days after exposure. Antiplatelet antibodies can be detected in many infected dogs, suggesting an immune-mediated component to the thrombocytopenia that is frequently present (Grindem and colleagues, 1999). While seropositive cats have been detected, it is unclear whether clinical illness occurs (Case and colleagues, 2006).

Clinical features. Any dog not previously exposed to *R. rickettsii* can develop RMSF.

Frequently, the tick has fed and left the dog before the development of clinical signs. In one study, only 5 of 30 owners knew their dogs had been infested by ticks (Gasser and colleagues, 2001). After infection, the majority of dogs are subclinical; some develop acute disease with a clinical course of approximately 14 days. No age or sex predilection exists.

Fever and depression are the most common clinical signs. Interstitial pulmonary disease, dyspnea, and cough occur in some dogs and gastrointestinal signs occur in some acutely infected dogs. Because the disease is generally acute, lymphadenopathy and splenomegaly are not as common as in dogs with ehrlichiosis. Petechiae, epistaxis, subconjunctival hemorrhage, hyphema, anterior uveitis, iris hemorrhage, retinal petechiae, and retinal edema occur frequently. Cutaneous manifestations can include hyperemia, petechiae, edema, and dermal necrosis. Hemorrhage results from vasculitis, thrombocytopenia from consumption of platelets at sites of vasculitis, thrombocytopenia from immune destruction, and in some dogs, disseminated intravascular coagulation. Central nervous system (CNS) signs include vestibular lesions (nystagmus, ataxia, head tilt), seizures, paresis, tremors, changes in mentation, and hyperesthesia (Mikszewski and colleagues, 2005). Fatal RMSF is generally secondary to cardiac arrhythmias and shock, pulmonary disease, acute renal failure, or severe CNS disease.

Diagnosis. Clinicopathologic and radiographic abnormalities are common but do not definitively document RMSF. Neutrophilic leukocytosis, with or without a left shift and toxic cells, is found in most clinically affected dogs. Platelet counts are variable, but in one study, 14 of 30 dogs had less than 75,000 platelets/ μ l without evidence of disseminated intravascular coagulation (Gasser, 2001). In other dogs, hemostatic abnormalities consistent with disseminated intravascular coagulation occur. Anemia occurs in some dogs, primarily from blood loss. Increased activities of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, as well as hypoalbuminemia from blood loss or third spacing of albumin in tissues secondary to vasculitis occur frequently. Because *R. rickettsii* does not result in chronic intracellular infection like ehrlichiosis, hyperglobulinemia is rare. Renal insufficiency in some dogs causes azotemia and metabolic acidosis. Serum sodium, chloride, and potassium concentrations decrease in many dogs with gastrointestinal tract signs or renal insufficiency. In contrast to dogs with chronic ehrlichiosis, chronic proteinuria from glomerulonephritis is rare. Positive direct Coombs' test results occur in some dogs.

Nonseptic, suppurative polyarthritis occurs in some dogs. CNS inflammation usually causes increased protein concentrations and neutrophilic pleocytosis in CSF; some dogs may have mononuclear cell pleocytosis or mixed inflammation. No pathognomonic radiographic abnormalities are associated with RMSF, but both experimentally- and naturally- infected dogs commonly develop unstructured pulmonary interstitial patterns.

A presumptive diagnosis of canine RMSF can be based on the combination of appropriate clinical, historical, and clinicopathologic evidence of disease, serologic test results, exclusion of other causes of the clinical abnormalities, and response to anti-rickettsial drugs. Documentation of seroconversion or an increasing titer 2 to 3 weeks after initial serologic testing suggests recent infection. Diagnostic criteria used in one recent study included a fourfold rise in antibody titer or a single titer of greater than 1:1024 if the initial titer was submitted 1 week or more after initial onset of clinical abnormalities (Gasser and colleagues, 2001). Positive serum antibody test

results alone do not prove RMSF because subclinical infection is common. In addition, positive serum antibody tests do not document infection by *R. rickettsii* because infection with nonpathogenic spotted fever group agents can induce cross-reacting antibodies. Demonstration of *R. rickettsii* by inoculating affected tissues or blood into susceptible laboratory animals or by documenting the organism in endothelial cells using direct fluorescent antibody staining leads to a definitive diagnosis of RMSF but are not clinically practical. Polymerase chain reaction (PCR) can be used to document the presence of rickettsial agents in blood, other fluids, or tissues and can be used to document infection. However, some apparently healthy dogs have had *Rickettsia* spp. DNA amplified from blood and so positive PCR assay results may not always correlate to RMSF (Kordick and colleagues, 1999).

Treatment. Supportive care for gastrointestinal tract fluid and electrolyte losses, renal disease, disseminated intravascular coagulation, and anemia should be provided as indicated. Overzealous fluid therapy may worsen respiratory or CNS manifestations of disease if vasculitis is severe.

Tetracycline derivatives, chloramphenicol, and enrofloxacin are the antirickettsial drugs used most frequently. Trovafloxacin and to a lesser extent, azithromycin, were beneficial for treatment of RMSF in experimentally inoculated dogs (Breitschwerdt and colleagues, 1999). Tetracycline (22 mg/kg PO q8h for 14 to 21 days) was commonly used historically. Doxycycline (5 to 10 mg/kg PO q12h for 14 to 21 days) is an alternative to tetracyclines; GI absorption and CNS penetration are superior to tetracycline, owing to increased lipid solubility. Chloramphenicol (22 to 25 mg/kg PO q8h for 14 days) can be used in puppies less than 5 months of age to avoid dental staining associated with tetracyclines. Enrofloxacin (3 mg/kg PO q12h for 7 days) is as effective as tetracycline or chloramphenicol. In one study of 30 dogs with RMSF, all dogs survived and there were no apparent differences in response rate between tetracycline, doxycycline, chloramphenicol, or enrofloxacin (Gasser and colleagues, 2001). Fever, depression, and thrombocytopenia often begin to resolve within 24 to 48 hours after starting therapy.

Administration of prednisolone at antiinflammatory or immunosuppressive doses in combination with doxycycline did not potentiate RMSF in experimentally infected dogs. The prognosis for canine RMSF is fair; death occurs in less than 5% of affected dogs.

Zoonotic aspects and prevention. Because RMSF has not been reported twice in the same dog, permanent immunity is likely. Infection can be prevented by providing strict tick control. It is unlikely that people acquire *R. rickettsii* from contact with dogs, but dogs may increase human exposure to RMSF by bringing ticks into the human environment. People can also be infected when removing ticks with activated *R. rickettsii* from the dog by hand. Two dogs and the owner all died of RMSF in one study (Elchos and Goddard, 2003). As in dogs, RMSF in people is most commonly recognized from April to September when the tick vectors are most active. Untreated RMSF is fatal in approximately 20% of infected people.

OTHER RICKETTSIAL INFECTIONS

Rickettsia felis was originally detected in a commercial cat flea (*Ctenocephalides felis*) colony and has been shown to belong in the spotted fever group. Fever, headache, myalgia, and

macular rash in humans have been attributed to *R. felis* infection in several countries around the world. In addition, one person in Mexico developed neurological symptoms following *R. felis* infection, suggesting that the organism may be the cause of severe debilitating disease in some people. The organism has been detected in *C. felis*, *C. canis*, and *Pulex irritans*; these fleas have a worldwide distribution. *Ctenocephalides felis* is a biological vector for *R. felis*; the organism can be transmitted transovarially and transtadially within the flea. *Rickettsia felis* DNA has been amplified from *C. felis* collected from cats in the United Kingdom, France, Israel, New Zealand, Australia, Thailand, and the United States (Hawley and colleagues, 2006).

In a recent study in our laboratory, we assayed 92 pairs of cat blood and flea extracts from Alabama, Maryland and Texas, using PCR assays that amplify a region of the citrate synthase gene (*gltA*) and the outer membrane protein B gene (*ompB*). Of the 92 pairs, 62 (67.4%) flea extracts and none of the cat blood samples were positive for *R. felis* DNA (Hawley and colleagues, 2006). In another study, we showed *R. felis* and *R. rickettsii* antibody prevalence rates in cats with fever to be 5.6% and 6.6%, respectively, but neither organism was amplified from blood (Bayliss and colleagues, 2007). These results prove that cats are sometimes exposed but further data are needed to determine significance of diseases associations. Because clinical illness in cats has not been documented, optimal treatment is unknown. However, based on results in dogs, doxycycline or a fluoroquinolone would be logical choices. Prevention in cats and people should include flea control.

Neorickettsia helminthoeca (i.e., salmon poisoning) causes enteric signs of disease in dogs from the Pacific Northwest. *Coxiella burnetii* infection is associated with parturient or aborting cats and is primarily a zoonotic disease. *Haemobartonella felis* has been reclassified as a *Mycoplasma*.

CANINE BARTONELLOSIS

Etiology and epidemiology. *Bartonella vinsonii* subsp. *berkhoffii* was initially isolated from a dog with endocarditis in North Carolina (Breitschwerdt and colleagues, 1995). Since that time, dogs in multiple areas of the world have been shown to seroreact with *B. vinsonii* (*berkhoffii*) antigens. *Bartonella vinsonii* (*berkhoffii*) is thought to be tick-borne. Serum of some infected dogs also seroreacts with *B. henselae* and *B. clarridgeiae* antigens; these *Bartonella* species are transmitted by fleas. *Bartonella* species that have been isolated from dogs or from which DNA has been amplified from blood or tissues include *B. vinsonii* (*berkhoffii*), *B. henselae*, *B. clarridgeiae*, *B. washoensis*, *B. quintana*, and *B. elizabethae*. Each of these organisms potentially can induce illness in dogs. Dogs infected with a *Bartonella* species are commonly coinfecting with other agents like *Anaplasma* spp. or *Ehrlichia* spp. which may play a role in the pathogenesis of disease.

Clinical features. Clinical findings or syndromes most frequently attributed to *Bartonella* spp. infections of dogs include endocarditis, fever, arrhythmias, hepatitis, granulomatous lymphadenitis, cutaneous vasculitis, rhinitis, polyarthritis, meningoencephalitis, thrombocytopenia, eosinophilia, monocytosis, immune-mediated hemolytic anemia, epistaxis, and uveitis. *Bartonella vinsonii* (*berkhoffii*) and *B. henselae* seem to be the most likely species to be associated with clinical disease (Breitschwerdt and colleagues, 2004; Goodman and

Breitschwerdt, 2005; Henn and colleagues, 2005). In one study of valvular endocarditis, all dogs with *Bartonella* spp. associated disease were also seropositive for *A. phagocytophilum* (MacDonald and colleagues, 2004). Whether the coinfection potentiated the *Bartonella* associated disease is unknown. Both *B. vinsonii* and *B. henselae* have been associated with endocarditis in dogs in Colorado and Wyoming.

Diagnosis. Serum antibodies can be detected in both healthy and clinically ill dogs, and so the presence of antibodies does not always correlate to illness. Some *Bartonella* species, in particular *Bartonella vinsonii* (*berkhoffii*), can be difficult to culture and so amplification of DNA by PCR assay with or without culture is often needed to confirm infection (Duncan et al, 2007). If positive test results are detected in a clinically ill dog and there is no other obvious explanation for the illness, treatment is indicated.

Treatment. As many cases of bartonellosis in dogs have been apparently resistant to administration of doxycycline, some clinicians believe that azithromycin is the treatment of choice. Fluoroquinolones, alone or in combination with amoxicillin, were apparently effective for the treatment of some dogs with suspected clinical bartonellosis. Rifampin may be required for resistant cases. No matter which drug is used, a minimum of 4-6 weeks of treatment is usually needed. In one study, successfully treated dogs became seronegative (Breitschwerdt and colleagues, 2004).

Zoonotic aspects and prevention. *Bartonella vinsonii* (*berkhoffii*) and *B. henselae* have been detected in both dogs and humans and cat scratch disease has been documented in a human after exposure to a dog (Chen et al, 2007). Care should be taken to avoid bites or scratches while handling or treating infected dogs. Flea and tick control is likely to lessen transmission of *Bartonella* species between dogs and perhaps from dogs to people.

HEPATOZOONOSIS

Agent information. Hepatozoonosis in dogs is caused by the protozoal agents *Hepatozoon canis* and *H. americanum*.¹⁻⁶ In North America, *H. americanum* predominates, is transmitted by *Amblyomma maculatum* (Gulf Coast tick), and is most common in the Texas Gulf Coast.^{1,7,8} In Africa, southern Europe, and Asia, *H. canis* predominates and is transmitted by *Rhipicephalus sanguineus* (brown dog tick). *Hepatozoon canis* DNA is occasionally amplified from samples from dogs in the United States, alone and in combination with *H. americanum*.^{9,10} Other canids like coyotes can be infected by *A. americanum*.¹¹ A *Hepatozoon* species is occasionally found cytologically within blood cells of cats in Europe.^{12,13}

Prevalence rates. The overall prevalence rates for hepatozoonosis in dogs in the United States is unknown. However, all dogs within the range of the tick vectors are potentially at risk. The range of *A. maculatum* is expanding and now hepatozoonosis has been found in other states including Oklahoma, Kansas, and Kentucky.¹

Pathophysiology. After a dog ingests a tick containing sporulated oocysts, sporozoites are released and penetrate the intestinal mucosa. The disseminated sporozoites infect macrophages and replicate asexually in striated muscle cells forming granulomas.¹⁴ Merozoites and gamonts

were detected in circulating macrophages and those in granulomas. Ultimately, the tick ingests the organism circulating in infected leukocytes while taking the blood meal and the sexual cycle is completed in the tick resulting in production of oocysts.

An alternate transmission cycle where dogs are infected by ingestion of *H. americanum* in tissues of prey species has recently been described.^{1,15-19} The infectious stage in tissue is called a cystozoite and has been detected in some rats, mice and rabbits. Vertical transmission has been documented with *H. canis* but not *H. americanum*.

Tissue phases induce pyogranulomatous inflammation resulting in clinical disease which often involves the muscles.²⁰⁻²² Glomerulonephritis, meningoencephalomyelitis, or amyloidosis may occur secondary to chronic inflammation and immune complex disease. Infected dogs can serve as a source of infection for ticks for months to years.²³ However, as *A. maculatum* does not commonly feed on dogs the ticks there are potentially other reservoir hosts for *H. americanum*.

Clinical abnormalities. *Hepatozoon americanum* can be a primary pathogen, resulting in clinical illness without concurrent immune deficiency. Clinically affected dogs have been in all age-groups, but disease is most commonly recognized in puppies. Fever, weight loss, and severe hyperesthesia over the paraspinal regions are common findings. Anorexia, pale mucous membranes from anemia, depression, oculonasal discharge, and bloody diarrhea occur in some dogs. Clinical signs can be intermittent and recurrent. Dogs infected with *H. canis* are often normal or only mildly ill.

In cats, clinical disease associations are currently unclear, but the cats are commonly co-infected with feline leukemia virus or feline immunodeficiency virus.^{12,13}

Laboratory and radiographic abnormalities. Neutrophilic leukocytosis (20,000 to 200,000 cells/ μ l) with a left shift is the most common hematologic finding in dogs with *H. americanum* infection. Thrombocytopenia is unusual unless co-infection with *Ehrlichia canis* or *Anaplasma spp* occurs. Normocytic, normochromic nonregenerative anemia is common and is likely from chronic inflammation. Increased activity of alkaline phosphatase but not creatine kinase occurs in *H. americanum*-infected dogs. Hypoalbuminemia, hypoglycemia, and rarely, polyclonal gammopathy occur in some dogs. Proteinuria from immune complex deposition could occur in some dogs.

Periosteal reactions from the inflammatory reaction directed at tissue phases in muscle can occur in any bone except the skull, are most common in young dogs, do not occur in every case, and are not pathognomonic for hepatozoonosis. Periosteal bone reactions and meningoencephalomyelitis with a mononuclear cell infiltrate were recently documented in a *H. canis*-infected dog in Italy.²¹

Diagnostic tests. Assays to detect antibodies against *Hepatozoon spp.* have been developed but are not routinely used as a diagnostic test for *H. americanum* infection in the United States.^{24,25} The organism can be detected by cytology or histopathology and microbial DNA can be amplified by PCR assay. Dogs with *H. americanum* infection are less likely to be positive for gamonts in blood than are dogs infected with *H. canis*.

Treatment. No therapeutic regimen has been shown to eliminate *H. canis* or *H. americanum* infection from tissues. However, clinical disease resolves rapidly with several drug protocols. For treatment of *H. americanum*, the combination of trimethoprim-sulfadiazine (15 mg/kg PO q12h), pyrimethamine (0.25 mg/kg PO q24h), and clindamycin (10 mg/kg PO q8h) for 14 days is very successful in the acute stage.^{2,22} Use of decoquinatate (10 to 20 mg/kg q12h) with food chronically lessens the likelihood of recurrence of clinical disease and prolongs survival time. Imidocarb dipropionate administered (5 to 6 mg/kg, IM or SC) once or twice 14 days apart is the drug of choice for treatment of *H. canis* and may also be effective for *H. americanum*. Administration of nonsteroidal antiinflammatory agents may lessen discomfort for some dogs but glucocorticoid administration should be avoided in affected dogs since it may exacerbate clinical disease.

Prognosis. The prognosis for dogs infected with *H. americanum* treated in the acute stage and maintained on decoquinatate can be good. The survival rates for these dogs was 84% in one report.

Prevention. Use of tick control products and preventing dogs from eating potentially infected transport hosts are the most important preventative measures for hepatozoonosis.

Zoonotic considerations. Only one person has been shown to be infected by a *Hepatozoon* spp.. Whether infection of people could occur from ingesting under cooked tissues from a transport host is unknown. Care should be taken when removing ticks, ticks should not be ingested by people, and meat should be cooked.

References for this section are available on request to mlappin@colostate.edu