HEMOPARASITES OF THE DOG AND CAT

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EHRlicHOSES
Several different Ehrlichia species are known to infect dogs (E. canis, E. ewingii, Anaplasma platys (formerly E. platys), Neorickettsia risticii (formerly E. risticii), E. chaffeensis, and Anaplasma. phagocytophilum, (formerly E. equi and the human granulocytic ehrlichia, HGE)), and the clinical presentations may differ, depending on the organism involved. Although any of these agents can be transmitted by blood transfusions from infected animals, but, most infections are tick-transmitted.

Monocytic Ehrlichioses

Transmission and Pathogenesis
*E. canis* is transmitted by the brown dog tick, *Rhipicephalus sanguineus*, and the primary vector for *E. chaffeensis* is the Lone Star tick, *Amblyomma americanum*. The organisms invade the monocytes and lymphocytes in the blood, liver, spleen, bone marrow, lymph nodes, lung, kidney, and central nervous system. Once inside the monocytes, the organisms form membrane-bound morulae that may contain from up to 50 or more bacteria.

Clinical Findings
Natural infections with *E. canis* or *E. chaffeensis* cause diseases that can be clinically similar. Current serological assays cannot distinguish infections due to cross-reactive antigens. The clinical course of disease is well characterized for infections with *E. cans*. There are three phases of disease seen with CME: acute, subclinical, and chronic. Clinical findings usually occur 1 to 3 weeks after infection, and during the acute phase of the disease, are typically mild and consist of fever, depression, anorexia +/- hemorrhage. The most consistent laboratory finding is thrombocytopenia but anemia and leukopenia may also occur. During the subclinical phase there are few if any clinical signs observed. Even so, many animals experience mild thrombocytopenia, hyperglobulinemia, and high antibody titer against *E. canis*. This phase may last for months to years. The chronic phase of the disease may be mild or severe. In mild cases, dogs remain infected but little evidence of illness is recognized. Animals are often febrile with outward signs of illness that may include weakness, depression, anorexia, weight loss, bleeding disorders and pale mucous membranes. Less frequent signs include peripheral lymphadenopathy, edema, retinal lesions, ataxia, hepatomegaly, splenomegaly and possibly death. Laboratory findings include severe thrombocytopenia (> 80% of cases), nonregenerative anemia, and/or leukopenia, hyperglobulinemia, and elevated liver enzymes. Some animals with chronic ehrlichiosis develop marked lymphocytosis with most of the cells being granular lymphocytes. The severity of disease varies with the pathogenicity of specific strains of the organism and individual differences in host defensive mechanisms (e.g., pups generally are affected more severely than adults).

Diagnosis
It is rare to diagnosis canine monocytic ehrlichiosis by recognition of morulae in blood lymphocytes or monocytes. The diagnosis is generally suspected based on clinical and routine laboratory findings and confirmed using serology. The serological assays most widely used are the indirect fluorescent antibody (IFA) test, which is available at most commercial laboratories,
and the SNAP®3Dx® or SNAP 4Dx Plus assays (IDEXX Laboratories, Inc., Maine, USA) for clinic use.

**Treatment**

Doxycycline or Minocycline (5 mg/kg PO bid) treatment for 3 to 4 weeks is generally effective in eliminating clinical signs, but titers (especially high titers) may persist, suggesting that many animals remain persistently infected after treatment. However a recent publication (Eddlestone et al. J Vet Intern Med. 21:1237-1242) 3 to 4 weeks of doxycycline at 5 mg/kg BID cleared infection in experimentally inoculated dogs.

**Granulocytic Ehrlichiosis/Anaplasmosis**

Granulocytic Ehrlichiosis and Anaplasmosis are caused by organisms that have a tropism for neutrophils. There are two main organisms that are known to infect dogs, *Ehrlichia ewingii*, and *Anaplasma phagocytophilum*. These organisms are morphologically indistinguishable and produce very similar clinical disease in the dog.

*Anaplasma phagocytophilum* (AP) is a tick-transmitted, obligate intracellular bacterium. Infection with AP has been recognized in a wide variety of hosts including, humans, dogs, cats, horses, ruminants and many wild-life species such as white-tailed deer, dusky-footed woodrat, mountain lions and bears. *E. ewingii* has been reported in dogs in central, eastern and southeastern U.S. Human infections have been reported from Missouri, Oklahoma, and Tennessee. The only confirmed tick vector is *Amblyomma americanum*. The White-tailed deer suspected to be an important reservoir for infection, similar to *E. chaffeensis*.

**Clinical Disease**

Infections, as with most tick-borne disease go through an acute, a subclinical and a chronic phase of the disease. Clinical features of the infection with *A. phagocytophilum* and *E. ewingii* are identical.

**Acute phase of infection**

Most clinical cases, typically 1 to 3 weeks after tick inoculation. Subclinical carrier states do exist in dogs, but there is debate whether or not these subclinical carriers may progress to chronic disease or not. Clinical signs, include fever, lethargy, malaise, anorexia, reluctance to move. The predominant characteristic clinical finding is polyarthritis, although occasionally, CNS disease and respiratory disease, cough and labored breathing, has also been reported with canine anaplasmosis. These diseases produce clinical findings indistinguishable from those seen in Lyme disease.

Laboratory findings include a mild to moderate nonregenerative anemia, thrombocytopenia, and lymphopenia +/- neutropenia. The most frequent hematological abnormality is thrombocytopenia and is seen if over 80% of clinical cases.

**Diagnosis of Acute Infection**

Diagnosis can often be made by microscopic identification of AP or EW morulae in circulating neutrophils in the peripheral blood or synovial fluid. These are most often found during acute phase of the disease (1 to 10 wks PI), and they may be seen in 1% - 15% or more of circulating neutrophils. In animals presenting with polyarthritis, organisms can usually be found in a small percent of neutrophils in synovial fluid.
Acute cases of AP infection may be negative on serological assays, and PCR assays have been designed to amplify various specific genes of this organism. The SNAP 4Dx Plus assay can be used to identify antibodies in infected animals. It is the only commercially available to diagnose infection with Ehrlichia ewingii.

Treatment
The treatment for the granulocytic forms of Ehrlichiosis / Anaplasmosis is the same as for Ehrlichia canis. Resolution of clinical signs typically occurs shortly after institution of therapy.

Anaplasma platys (Infectious Cyclic Thrombocytopenia)

Anaplasma platys causes infectious cyclic thrombocytopenia in dogs. This agent is unique in that it is the only intracellular infectious agent described to specifically infect platelets. It produces cyclic parasitemias and concomitant thrombocytopenia occurring at 1 to 2 week intervals. Parasitized platelets are easily found during the initial parasitemia, but subsequent parasitemias have decreasing percentages of parasitized platelets. Platelet counts usually remain below 20,000/µl for only 1 or 2 days, before rapidly increasing. Infected dogs usually do not exhibit evidence of illness, but mild fever may occur at the time of the initial parasitemia. Minimal or no evidence of hemorrhage is present in most cases, but epistaxis, petechia and ecchymosis of mucous membranes have been reported. Diagnosis of infection with this agent can be made by observing organisms within platelets. Serological diagnosis is not available for A. platys infection, but there is often cross reaction on 4Dx Plus diagnostic assay that will detect infection with Anaplasma phagocytophilum. Therefore, many animals infected with A. platys will test positive for A. phagocytophilum on the SNAP test. Anaplasma platys can be specifically identified using PCR technology. Doxycycline at the dose described above is effective in treating this infectious agent.

BABESIOSIS

Babesia canis

Etiology and Epidemiology
Babesia species are intracellular protozoan parasites of RBCs that cause increased RBC destruction and anemia. Babesiosis occurs in dogs in many countries, including the United States. Babesia canis is a large (4-7 µm in length) pear-shaped parasite. Strains present in the U.S. generally cause mild or unapparent disease in adults (unless immunosuppressed), but severe disease in pups. South African strains can cause severe disease and death in adult dogs.

Transmission
In the US, B. canis is transmitted the brown dog tick, (R. sanguineus) and Dermacentor spp. Inoculation with contaminated blood may also result in transmission of the disease.

Clinical Findings
The severity of the disease varies with age of the animal and strain of Babesia. The course of disease may be acute, subclinical or chronic. Clinical signs include lethargy, anorexia, pale mucous membranes, fever, splenomegaly and icterus. The anemia results primarily from intravascular hemolysis although extravascular destruction of erythrocytes also occurs. A
regenerative response is seen in most cases. Mild to severe thrombocytopenia is frequently seen. Most infected dogs will test positive on Coombs’ test.

**Diagnosis**
A definitive diagnosis of *B. canis* infection is made by identification of the organisms in stained-blood films. Serological diagnosis can be made using Indirect fluorescent antibody (IFA) tests, but some cross-reactivity occurs between babesial species. IFA tests may be negative in acutely infected animals, especially puppies. If parasites are not recognized in the blood, it is difficult to differentiate babesiosis from autoimmune hemolytic anemia, because both disorders may be Coombs’ positive.

**Treatment**
Infected adult animals are often carriers and reservoirs but do not require therapy. Imidocarb dipropionate (Imizol) (6.6 mg/kg SQ or IM, single injection, repeat dose in two weeks) is the treatment of choice of clinical ill patients. Treated and untreated dogs often remain carriers of disease.

*Babesia gibsoni*

**Etiology and Epidemiology**
*Babesia gibsoni* is considered to be a small Babesia (1 to 3 µm), similar to *B. microti*, the etiological agent of human and rodent babesiosis. The organism is endemic in Africa, the Middle East and Asia. The first report in the US was in 1968, however, the infected Bull Terrier likely contracted the agent while in Malaysia. In 1979 the organism was isolated from a dog that lived in Connecticut and never traveled outside the US. Since 1998 there has been a rapid increase in the number of cases reported, predominantly in Pit Bull breeds.

**Transmission and Pathogenesis**
The brown dog tick *Rhipicephalus sanguineus* is the suspected vector in the US, but definitive transmission studies have not been done. However, transplacental transmission and inadvertent inoculation with contaminated blood appears to be the primary mechanism of transfer in the Pit Bull breeds and other dogs.

**Clinical Findings**
Commonly reported clinical abnormalities in dogs include fever, lethargy, pale mucus membranes, lymphadenopathy, splenomegaly, regenerative anemia with intravascular hemolysis, hemoglobinuria and and thrombocytopenia. Mild anemia and thrombocytopenia can be seen in subclinically infected animals.

**Diagnosis**
The clinical diagnosis is often made by microscopic examination of a peripheral blood film. Species identification is accomplished by PCR analysis of whole blood. PCR analysis in conjunction with IFA is the preferred method for identifying subclinical carriers. In subclinical carriers, the parasitemia is too low to be detected microscopically and PCR analysis must be done to confirm a carrier state.

**Treatment and Prognosis**
The current recommended treatment is azithromycin 10mg/kg once a day for 10 days, and atovaquone 13.5 mg/kg TID for 10 days, given with a fatty meal. Using this treatment, approximately 80% of the infected animals will be PCR negative in 6 weeks.

*Mycoplasma haemocanis*
*Mycoplasma haemocanis* is the causative agent of hemotrophic mycoplasmosis in dogs. It has been considered to be a distinctly different organism from *M. haemofelis*, but the sequence analysis indicates 95% to 99% sequence identity to *M. haemofelis*. A small hemoplasma, similar to *M. haemominutum* in cats, "Candidatus Mycoplasma haemoparvum" has recently been identified in dogs.

**Transmission**
*M. haemocanis* is suspected to be transmitted by the brown dog tick.

**Clinical Signs**
Clinical signs are typically only seen in splenectomized or immunosuppressed dogs. Immunocompetent dogs are typically carriers that may relapse with clinical disease if immunocompromised. Signs included fever, anemia and sometimes icterus.

**Diagnosis**
The diagnosis of animals with clinical disease can be made by finding chains of parasites on the surface of infected erythrocytes. PCR analysis can be used to confirm the diagnosis or to diagnose subclinically infected carrier animals.

**Treatment**
The treatment of choice is Doxycycline (5 mg/kg PO q12h) or tetracycline/oxytetracycline (20 mg/kg PO q8h) given for 3 weeks.

**FELINE HEMOPARASITES**

*Ehrlichia canis* and *Anaplasma phagocytophilum* may also infect cats and cause clinical disease (see above for details).

*Mycoplasma haemofelis*
*Mycoplasma haemofelis* is the causative agent of hemotropic mycoplasma in the cat.

**Transmission**
Transmission is primarily through the bite of infected fleas. Blood transfusions may also be a source of infection. The organism can also be transmitted from mother to offspring, but the exact mechanism is not clearly understood.

**Clinical Signs**
Clinical signs may appear in adult or young immunocompetent animals. Fever, weakness and anemia are predominant findings. Splenomegaly is common. The anemia in uncomplicated infections is typically associated with extravascular destruction of erythrocytes and icterus may be seen. However, nonregenerative anemia may be seen in animals co-infected with FeLV or FIV.
**Routine Laboratory Findings**
Parasites may or may not be visualized in blood even when animals are markedly anemic. Organisms appear during cyclic parasitemic episodes and then rapidly disappear from circulation. When visualized on the surface of infected erythrocytes they appear as small dots, chains or ringlets. The anemia may appear nonregenerative if a precipitous decrease in hematocrit has occurred early in the disease or if other concurrent disorders (e.g., FeLV or FIV infections in cats) are present. Many infected animals are Coombs’ test positive.

**Diagnosis**
Diagnosis may be made by microscopic visualization of organisms on the surface of infected erythrocytes but cyclic parasitemias may result in circulating numbers of organisms that are too low for microscopic visualization. PCR analysis can be used to detect organism DNA in these animals or to identify carrier cats.

**Treatment**
The recommended treatment is Doxycycline (5 mg/kg PO q12h) or tetracycline/oxytetracycline (20 mg/kg PO q8h) antibiotics administered for a 3 week period.

**CYTAUXZOOONOSIS**

*Cytauxzoon felis* is a protozoal parasite and the causative agent of feline cytauxzoonosis. It is a tick-transmitted, intraerythrocytic parasite transmitted by the Lone star tick. Wild cats, panthers, mountain lions and bobcats, are thought to be the natural reservoir and unapparent carriers. The infection is often fatal to domestic cats. Infected cats are most often seen in rural areas where the reservoir and tick vector is present.

**Clinical Signs**
Clinical findings include fever, anorexia, depression, anemia icterus and often lateral recumbency. The anemia is often significant, but due to the rapid nature of the disease, it often appears nonregenerative even though it is hemolytic in nature. Cats become thrombocytopenic during late stages of disease. Nearly all untreated cases in domestic cats are fatal, although a less virulent strain has been reported in a restricted area of northwestern Arkansas and northeastern Oklahoma.

**Diagnosis**
Parasitemia occurs late in the disease but organisms are often identified on blood films when cats present with clinical infection. The parasites appear as "signet ring" bodies 1 to 1.5 microns in diameter or as bipolar, oval or "safety pin" bodies 1 by 2 microns. The cytoplasm of the protozoan stains a light blue, while the nucleus appears red to purple. PCR analysis is of little value in clinical cases since the disease course is rapid and therapy must be initiated promptly.

**Treatment**
Therapy using atovaquone (15 mg/kg orally three times daily) and azithromycin (10 mg/kg orally once daily) for a period of 10 days had a 60% survival rate. This is compared to a 25% survival
rate using imidocarb dipropionate [Imizol] (3.5 mg/kg IM given twice at a 14 day interval) and Atropine (0.04 mg/kg IV, IM, or SC) is given 15 minutes prior to each imidocarb treatment.