

# Ehrlichiosis in Dogs

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## **P** Profile

### DEFINITION

Caused by small, pleomorphic, gram-negative, coccoid bacteria that are obligate intracellular parasites (**Table**). Bacteria appear intracytoplasmically in clusters called morulae (**Figure 1**) and can be divided into three classes based on whether they infect mononuclear cells, granulocytes, or thrombocytes. *Ehrlichia canis* is the species most often associated with canine ehrlichiosis, but other species also cause natural infection. Molecular technology has resulted in reclassification of *Ehrlichia* species, and terminology is always changing:<sup>1</sup> e.g., *E. equi*, human granulocytic ehrlichiosis, and *E. phagocytophila* are now collectively recognized as *Anaplasma phagocytophila*.

**Systems.** Lymphoreticular, neuromuscular, ophthalmic, joint, and hematopoietic systems can be affected, therefore making diagnosis a challenge (**Signs**).

**Incidence/prevalence/geographic distribution.** Depend largely on prevalence and geographic distribution of vector and reservoir hosts for specific *Ehrlichia* species (**Table**). Practitioners must know prevalence

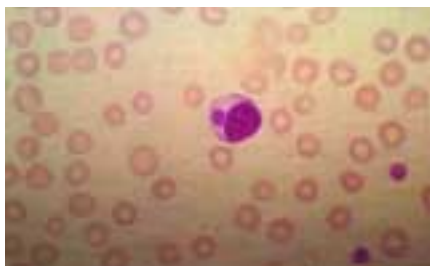


Figure 1. Morulae of an *Ehrlichia canis* organism in a mononuclear cell

in their own regions. In regions enzootic for *E. canis*, up to 25% of asymptomatic dogs may have serum antibodies.<sup>2</sup> True incidence for all ehrlichiosis is not known.

### SIGNALMENT/RISK FACTORS

All dogs are potentially susceptible to *Ehrlichia* infection. Reinfection can occur. Dogs receiving blood transfusions from unscreened donors may have increased risk, especially if donors reside in enzootic regions. No breed, age, or sex predilection exists, although German shepherds may be more susceptible than other breeds, especially for the severe chronic pancytopenia form.<sup>3</sup>

### PATHOPHYSIOLOGY

Infection occurs when an infected tick ingests a blood meal and salivary secretions contaminate the feeding site. The incubation period is 8 to 20 days. Vasculitis and immune mechanisms are involved in the pathogenesis of ehrlichiosis.<sup>4</sup>

### SIGNS

**History.** Depression, lethargy, mild weight loss, and anorexia with or without bleeding are common. Owners may notice dermal petechiae and/or ecchymoses. Bleeding can occur from any mucosal surface, but epistaxis is most frequent. Change in eye color, blindness, lameness, stiff-stilted gait, and neck pain may also be present. Course can be divided into acute, subclinical, and chronic phases, but accurate staging is difficult. Two- to 4-week acute phase often goes unnoticed but is characterized by fever, ocular discharge, anorexia, depression, petechiae, ecchymoses, and lymphadenomegaly/splenomegaly. Thrombocytopenia may persist in subclinical phase, which can

last for months/years. Dogs may eliminate rickettsia or may remain carriers for life or enter chronic phase, which in severe form results in pancytopenia with grave prognosis.

**Physical examination.** One or all of the following may be found: petechiae/ecchymoses (50%); polyarthropathy with multiple painful joints/effusion (more likely with granulocytic species and may be as high as 90%); lymphadenomegaly/splenomegaly (20% to 25%); pale mucous membranes (45%); stiff-stilted gait with neck/muscle pain (rare); anterior uveitis (8%); and retinal hemorrhage with or without detachment (8%). Thus, tick-borne diseases can be "great imitators" of other diseases.

### DIFFERENTIAL DIAGNOSIS

Because of its multisystemic nature, the list is long. As a general rule, infectious, immune-mediated, and neoplastic diseases are those that are usually mistaken for ehrlichiosis. See algorithm on page 30 for diagnostic approach to petechiae/ecchymoses.

### LABORATORY FINDINGS/DIAGNOSIS








Usually based on a combination of clinical signs, hematologic abnormalities, thrombocytopenia, and serologic findings (**Clinicopathologic Findings**). There is no "gold standard" definitive test.

Thrombocytopenia has often been used for ehrlichiosis screening; thus, the percentage could be overestimated. **Ehrlichiosis should never be ruled out because platelet count is normal.** Also, in the author's experience, ehrlichiosis is rarely found in conjunction with platelet counts less than 20 to 30 thousand/ $\mu$ l. If count is



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## GEOGRAPHIC DISTRIBUTION OF *EHRlichia* AND PROVEN OR SUSPECTED VECTORS OF EHRlichIOSIS

<i>Ehrlichia</i> Species	Geographic Distribution	Tick Vector
 <i>E. canis</i> (monocytic)	Worldwide, primarily tropical/temperate; in chronic disease, signs may develop years after tick transmission and after dog has moved to nonenzootic region where disease might not be considered	<i>Rhipicephalus sanguineus</i>
 <i>E. chaffeensis</i> (monocytic)	United States, primarily midsouth to southern region	<i>Amblyomma americanum</i> , <i>Dermacentor variabilis</i>
 <i>Neorickettsia risticii</i> ( <i>E. risticii</i> ) (monocytic)	United States, Canada	Unknown; possibly trematodes in aquatic snails and various insects
<i>N. risticii</i> subspecies <i>atypicalis</i>	Western United States	
 <i>E. ewingii</i> (granulocytic)	United States, primarily southern/lower mideastern regions, including Missouri	<i>A. americanum</i> , <i>Otobius megnini</i> , <i>Ixodes?</i>
 <i>E. equi</i> * (granulocytic)	United States, primarily west coast, Wisconsin, Minnesota, and northeastern/north-central regions	<i>Ixodes pacificus</i> , <i>I. scapularis</i> , <i>I. ricinus</i>
Human granulocytic <i>Ehrlichia</i> *	United States, upper Midwest (Minnesota, Wisconsin) and northeastern regions, Europe	
<i>E. phagocytophila</i> *	United Kingdom, Africa, Asia, Europe (Sweden, Switzerland)	
 <i>Anaplasma platys</i> ( <i>E. platys</i> ) (platelets)	Southeastern United States, southern Europe (Greece, Italy, France), Israel, South America	<i>R. sanguineus?</i>
 Species known to cause ehrlichiosis in dogs * Now classified as <i>Anaplasma phagocytophila</i>		

extremely low, other causes should be strongly considered. Granular lymphocytosis, monoclonal gammopathies, and plasmacytosis of bone marrow are more common with neoplastic diseases, but in a region enzootic for ehrlichiosis, further tests should be done if these disorders are present. Cytologic studies showing morulae in white blood cells of blood smear, CSF, or joint fluid (Figure 2) may provide definitive diagnosis, but this is unusual.



Figure 2. Morulae of an *Ehrlichia ewingii* organism found in a neutrophil from joint fluid

**Serologic testing/PCR/immunoblotting.** IFA or ELISA is used. Seroconversion usually occurs 7 days after exposure but may take 28 days. In the natural setting, almost all

clinically ill dogs seroconvert by that time. Species-specific antibody testing is necessary. One *Ehrlichia* antibody test does not react with all *Ehrlichia* antibodies. In enzootic areas, although serologic tests may be positive the clinical signs may be due to another condition. Be aware of the test's limitations. Also, successfully treated dogs can retain positive and even high titers for years. A recently marketed "point-of-care" in-clinic ELISA test for *E. canis* antibodies (SNAP 3Dx—IDEXX Laboratories Inc., Westbrook, ME) yielded positive results at a dilution of 1:100 or greater. A similar in-house ELISA has been developed in Israel (Immunocomb—Biogal, Kibbutz Gal'ed, Israel). These tests have good specificity and sensitivity. Their primary utility, in the author's opinion, is screening dogs for which the practitioner has a strong suspicion of *E. canis* infection.<sup>5</sup> If a dog has active clinical ehrlichiosis, it is unlikely the test would be negative. Thus, negative results probably rule out *E. canis* infection in most cases (although infection with other *Ehrlichia* species would still be possible).

### CLINICOPATHOLOGIC FINDINGS

- Thrombocytopenia (82%)
- Anemia (82%—usually nonregenerative)
- Leukopenia (32%)
- Pancytopenia (18% of chronic cases)
- Granular lymphocytosis (has been reported)
- Polyclonal gammopathies (occasionally monoclonal)
- Bone marrow aspirates: plasmacytosis
- Proteinuria, hematuria
- Lymphocytic pleocytosis of cerebrospinal fluid (rare)
- Neutrophilic inflammation of joint fluid (rare with *E. canis*; common with granulocytic species)
- Prolonged buccal mucosal bleeding times (rare)

PCR and western immunoblotting have been used in research to characterize and distinguish between species of *Ehrlichia* but have not provided "significant" benefit in the clinical setting. The western blot yields

CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay; IFA = indirect fluorescent antibody; PCR = polymerase chain reaction; PCV = packed cell volume.

results in the same time frame as IFA or ELISA, and the PCR on blood has not proven to be very sensitive. In one study, only 13 of 49 (27%) naturally infected IFA-positive dogs had positive results for *E. canis* on PCR.<sup>6</sup> In summary, diagnosis is still based on a combination of clinical signs, clinicopathologic abnormalities, and serologic testing.

**Postmortem findings.** Characteristic histopathologic findings are perivascular plasma cells or lymphoplasmacytic infiltrates in multiple organs (lungs, brain, meninges, kidney, lymph nodes, bone marrow, spleen, and skin). Morulae are infrequently observed in tissue at necropsy.



## Treatment

Most dogs can be treated as outpatients. Effective drugs include tetracyclines, doxycycline, chloramphenicol, and imidocarb dipropionate. Doxycycline is the most commonly used agent. The current recommendation is to treat for 3 to 4 weeks (**Tx at a glance**). The sooner treatment is initiated, the more favorable the prognosis. It is difficult if not impossible to cure dogs in the severe chronic stage (bone marrow suppression). The fluoroquinolones, which are effective against Rocky Mountain spotted fever and some species of *Ehrlichia*, do not seem to be effective against *E. canis* infection.<sup>7</sup> In addition, recent evidence has also questioned the clinical effectiveness of imidocarb dipropionate.<sup>8</sup>

Supportive therapy with fluids for dehydration and blood transfusion if the dog is severely anemic (PCV < 20%) may be justified, but routine transfusion will not significantly increase the platelet or neutrophil count. Data on use of such growth factors as erythropoietin (Epogen—Amgen, Thousand Oaks, CA) or granulocyte colony-stimulating factor (Neupogen—Amgen,

Thousand Oaks, CA) as adjunctive therapy are limited. However, a single case report suggests they might be useful for severe chronic ehrlichiosis.<sup>9</sup> Short-term treatment (2 to 7 days) with glucocorticoids may be beneficial early in treatment because immune-mediated mechanisms may be involved. Such treatment may be more important for dogs with polyarthropathy, meningitis, and/or vasculitis.



## Follow-up

**Patient monitoring.** Most dogs with acute ehrlichiosis begin to respond within 48 to 96 hours. Within 7 to 14 days, platelet count generally is normal. If not, another cause should be considered (e.g., immune-mediated thrombocytopenia). Coinfection with other tick-borne agents is increasing and should be considered.<sup>6</sup> Platelet count should be performed at end of therapy and, in the author's opinion, again in 6 months. We have had a few research dogs in a tick-free environment that, after apparent successful therapy with doxycycline, developed recurrent thrombocytopenia and positive results on blood and splenic aspirate PCR 6 months later. Others have reported suboptimum long-term results with doxycycline.<sup>10</sup> Serologic testing and blood PCR are not effective methods to assess therapy. In contrast to Rocky Mountain spotted fever, long-term immunity does not develop secondary to "successful" treatment or natural exposure, so reinfection is possible.<sup>11</sup>

**Prevention.** No vaccine is currently available; chemoprophylaxis and tick-control measures are primary means of prevention. Tetracycline is effective when administered daily at 6.6 mg/kg Q 24 H to dogs in enzootic or tick-infested areas. To date, the author is unaware that any *Ehrlichia* species has developed resistance to doxycycline.

CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay; IFA = indirect fluorescent antibody; PCR = polymerase chain reaction; PCV = packed cell volume.



## at a glance

- **Doxycycline:** 5–10 mg/kg PO Q 12–24 H x 30 days
- **Tetracycline:** 22 mg/kg PO Q 8 H x 30 days
- **Oxytetracycline:** 25 mg/kg PO Q 8 H x 30 days
- **Minocycline:** 10 mg/kg PO Q 12 H x 30 days
- **Chloramphenicol:** 15–25 mg/kg PO Q 8 H x 30 days
- **Imidocarb dipropionate (Imizol—Schering-Plough, Kenilworth, NJ):** 5 mg/kg IM once, repeat in 2–3 weeks.

Maintaining strict tick-control programs for the dog and its environment is very important. The most effective products include fipronil<sup>a</sup>, imidacloprid/permethrin combination<sup>b</sup>, and amitraz<sup>c</sup>.

### RELATIVE COST OF TREATMENT

#### Uncomplicated \$\$\$

Includes examination, diagnostic evaluation, treatment, and follow-up platelet counts.

#### Complicated (bone marrow disease, severe anemia requiring blood transfusions) \$\$\$\$



## Prognosis/Future Considerations

The question persists whether *Ehrlichia* is eliminated from the dog by treatment. In the natural setting, it is difficult to separate recrudescence from reinfection. As a general rule, the "straightforward" *Ehrlichia* patient (if there is such a thing) should have a positive response to doxycycline approximately 65% to 70% of the time without future problems unless reinfection occurs. Owners need to realize that reinfection is possible and measures to decrease exposure are extremely important. ■

See Aids & Resources, back page, for references, further reading, and contacts.