Ehrlichiosis and Anaplasmosis: An Update

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KEYWORDS

• Anaplasma • Ehrlichia • Dog • Cat • PCR • Serology • Doxycycline • Zoonosis

KEY POINTS

- A growing number of *Ehrlichia* and *Anaplasma* species have been detected in dogs and cats.
- The incidence of these diseases is expanding into new geographic areas.
- Broader availability of in-clinic diagnostic tests targeting multiple pathogens has supported better and more timely medical decision-making.
- Doxycycline remains the best therapeutic option; however, proper protocols should be used to optimize outcomes and help avoid antimicrobial resistance.
- Tick prevention is key to avoiding infection, even in urban areas.

CANINE EHRLICHIOSIS

Etiology

Ehrlichia spp are tick-borne intracellular gram-negative α-proteobacteria that multiply in microcolonies known as morulae.[1,2] They mainly infect leukocytes (monocytes, macrophages, and neutrophils) of mammals and cells of the intestine, hemocoel, and salivary glands of ticks.[3–5] Currently, the genus *Ehrlichia* is composed of six species: *Ehrlichia canis*, *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, *Ehrlichia muris eauclarensis*, *Ehrlichia ruminantium*, and *Ehrlichia minasensis* (**Fig. 1**).[2,6] *Ehrlichia canis* is the most frequently documented species infecting dogs worldwide. It is transmitted by the brown dog tick *Rhipicephalus sanguineus*, and causes a syndrome called canine monocytotropic ehrlichiosis (CME, also known as canine monocytic ehrlichiosis).[4,7] In North America, other species of *Ehrlichia* have been documented in geographic regions that follow the distribution of their confirmed or suspected tick vectors. *Ehrlichia chaffeensis* and *E. ewingii* are frequently identified in the southeastern and south-

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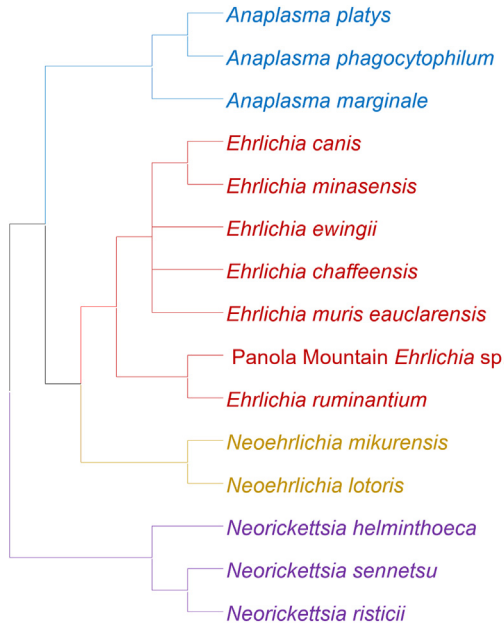

Fig. 1. Phylogenetic tree of *Anaplasma* and *Ehrlichia* spp and closely related bacteria from the Alphaproteobacteria family based on the 16S rRNA gene. (*Courtesy of* Pedro Diniz, USA.)

central United States, from the East Coast extending westward to Texas, areas where their vector *Amblyomma americanum* (the Lone Star tick) and their main reservoir host, the white-tailed deer, are frequently present.[8,9] *Ehrlichia chaffeensis* causes monocytotropic ehrlichiosis, whereas *E. ewingii* causes granulocytotropic ehrlichiosis in dogs and people. A large survey showed that *E. ewingii* is the most seroprevalent *Ehrlichia* species in dogs in the United States.[10] Dogs may serve as reservoir hosts for this species, because chronic infection for more than 1 year has been documented experimentally.[11] Sporadic infections with *E. muris eauclarensis*, which is most likely transmitted by the black-legged tick *Ixodes scapularis*, have also been reported in dogs and people in the Upper Midwestern United States.[12,13] Similarly, a species phylogenetically close to *E. ruminantium* named Panola Mountain *Ehrlichia* sp, which was found in *A. americanum* and *Amblyomma maculatum* (the Gulf Coast tick), was documented in a sick goat, a dog, and a person in the Southeastern United States.[14–17] Recent serologic evidence indicates that dogs in the Central-West region of Brazil are also exposed to *E. minasensis*, a species originally detected from cattle, horses, and cervids, and transmitted by several ticks.[6,18–20]

Epidemiology

CME has been documented in all continents, mainly in tropical and subtropical regions where environmental conditions are favorable for the survival of *R. sanguineus* ticks (Fig. 2). Because no transovarial transmission of *E. canis* occurs, *R. sanguineus* larvae do not transmit the infection but they can become infected after feeding. Transstadial transmission does occur, with nymphs and adult ticks capable of transmitting *E. canis* to dogs for up to 155 days postmolting.[21] The prevalence of *E. canis* infection in *R. sanguineus* ticks ranges from 2.5% to 6% in tropical areas.[22] The existence of two distinct

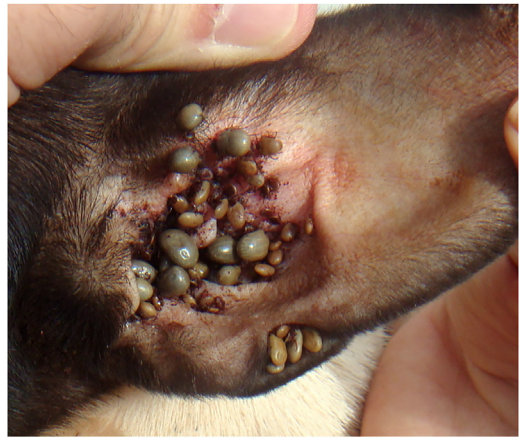

Fig. 2. Severe *Rhipicephalus sanguineus* infestation in a dog. (*Courtesy of* Daniel Moura de Aguiar, Brazil.)

lineages of *R. sanguineus* (temperate and tropical) impacts the distribution of CME because the tropical lineage is a more competent vector for *E. canis*.[23,24] The geographic distribution of the tropical lineage ranges from Brazil to Mexico and Southern parts of the United States including Florida and Southern Texas, where high *E. canis* seroprevalence is reported.[25–28] *Dermacentor variabilis* (the American dog tick) may also be a vector for *E. canis* and *E. chaffeensis*, but with a less significant role.[29] Dogs are considered the main reservoir for *E. canis* because prolonged bacteremia occurs, which facilitates the acquisition of this pathogen by ticks.[25,26] *Amblyomma* sp and *Ixodes* sp ticks are more active during the spring and summer months. In contrast, *R. sanguineus* ticks can survive indoors in homes or kennels, and be active year-round, especially in subtropical areas, such as the coastal Southern United States.[30]

In the United States, *E. canis* exposure in dogs is estimated to be 1.8%, whereas the seroprevalence of *E. chaffeensis* and *E. ewingii* ranges between 3.1% and 3.8%. *Ehrlichia canis* exposure is more frequent in the South and Western regions of the United States, whereas exposure to *E. chaffeensis* and *E. ewingii* is more frequent in the South and Mid-Atlantic regions.[27] In Central and South America, reported molecular prevalence ranges from 18% in Colombia,[31] 29% in Mexico,[32] and 64% in Panama,[33] to 88% in Brazil.[34] In Europe, Asia, and Africa reported molecular prevalence ranges from less than 3.0% to 23%.[35]

Ehrlichia sp can survive and remain infectious in preserved and refrigerated whole blood for up to 11 days.[36,37] Therefore, they are transmitted by transfusion of blood or blood components or contaminated needles especially in endemic areas, potentially causing disease in transfusion recipients.[38] Conversely, perinatal transmission has not been documented in dogs.[39,40] Dogs of all breeds and ages are susceptible to CME, with German shepherd dogs and Siberian huskies predisposed to developing more severe clinical manifestations.[41] In some endemic regions, *E. canis* infection is more frequently observed among young dogs,[42,43] whereas seroreactivity is more frequent in adult dogs.[44] This observation may be caused by a higher probability of exposure to *E. canis* over time, rather than an increase in susceptibility with age.

Infection, Clinical Presentation, and Relevance

CME caused by *E. canis* is a multisystemic disease with variable severity depending on the clinical stage. The pathogenesis involves an incubation period of 8 to

20 days followed by acute, subclinical (asymptomatic), and chronic phases. The definition of each clinical phase in naturally infected dogs is difficult because clinical and laboratory findings are similar, with variable duration and severity.[45] The most common clinical signs during acute or chronic phases in naturally infected dogs are lethargy, inappetence, anorexia, weight loss, fever, epistaxis, petechiation, lymphadenopathy, and splenomegaly (**Fig. 3**, **Table 1**). Clinical manifestations vary depending on the strain of *E. canis,* host susceptibility, and the immune response, with acute disease in some dogs manifesting with moderate to severe signs and even death, whereas other dogs tolerate the infection with limited signs of illness.[46–48] In general, *Ehrlichia* sp subvert the host innate immune system, allowing the pathogens to perpetuate within macrophages (in the case of monocytic ehrlichiosis) or granulocytes (in the case of granulocytic ehrlichiosis) causing lymphadenomegaly and lymphoreticular hyperplasia in the spleen and liver. These immunologic and inflammatory changes result in leukocyte infiltration of parenchymal organs and perivascular cuffs in several locations, such as kidneys, spleen, meninges, lungs, eyes, and spleen.[45,49] Hypergammaglobulinemia is frequently documented in severe cases, including polyclonal or monoclonal (in the case of *E. canis*) expansion. This antibody production does not confer adequate protective immunity.[50] Thrombocytopenia is the most common finding during all three phases of CME because of increased consumption, immune-mediated destruction, sequestration of platelets in the spleen, and decreased production from hypoplastic bone marrow. Cytokine-mediated thrombocytopathia also occurs.[51,52] Once the acute phase subsides, there is an apparent

Fig. 3. Dog with severe epistaxis caused by canine ehrlichiosis. (*Courtesy of* Daniel Moura de Aguiar, Brazil.)

Table 1
Common clinical presentations and laboratory abnormalities in canine ehrlichiosis or anaplasmosis

Organism	*Anaplasma phagocytophilum*[a]	*Anaplasma platys*[b]	*Ehrlichia canis*[c]	*Ehrlichia chaffeensis*[d]	*Ehrlichia ewingii*[e]
Syndrome	Granulocytotropic anaplasmosis	Infectious cyclic thrombocytopenia	Monocytotropic ehrlichiosis	Monocytotropic ehrlichiosis	Granulocytotropic ehrlichiosis
Disease course	Acute or subclinical	Acute or subclinical	Acute, subclinical, or chronic	Acute or subclinical	Acute or subclinical
Clinical severity	Generally mild to moderate	Generally mild to moderate	From mild to life-threatening	Asymptomatic to mild	Asymptomatic to moderate
Main historical finding	Lethargy, inappetence, anorexia, lameness, weakness, stiffness, weight loss, rarely vomiting or diarrhea	No clinical abnormalities in most cases in the United States When present, lethargy, inappetence, anorexia, weight loss, epistaxis can occur	Lethargy, inappetence, anorexia, vomiting, diarrhea, weight loss, epistaxis, melena	No manifestations in most cases	Lameness, join pain, reluctance to move, stiffness, rarely vomiting or diarrhea It can be asymptomatic
Main signs	Fever, lymphadenopathy, splenomegaly, joint swelling, rarely epistaxis, and CNS signs	Fever, lymphadenopathy, petechiae, ecchymosis, pale mucous membranes	Fever, lymphadenopathy, splenomegaly, petechiae, ecchymosis, pale mucous membranes, melena, ocular and nasal discharge, scleral congestion, hyphema, uveitis, retinal detachment, CNS signs, cardiac arrhythmias	Fever, lymphadenopathy, petechiae	Fever, painful or swollen joints, ataxia, paresis, lymphadenopathy, splenomegaly, CNS signs

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Table 1
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Organism	*Anaplasma phagocytophilum*[a]	*Anaplasma platys*[b]	*Ehrlichia canis*[c]	*Ehrlichia chaffeensis*[d]	*Ehrlichia ewingii*[e]
Main laboratory findings	Thrombocytopenia, neutrophilic polyarthritis, leukocytosis, neutrophilia, lymphopenia, eosinopenia, mild to moderate nonregenerative anemia, hypoalbuminemia, hyperglobulinemia, elevated ALP and ALT activities, hyperbilirubinemia, proteinuria	Thrombocytopenia, leukocytosis with neutrophilia, lymphocytosis, and monocytosis	Thrombocytopenia, neutropenia, monocytosis, eosinophilia, nonregenerative anemia, pancytopenia, polyclonal or monoclonal hyperglobulinemia, increased ALT and ALP activities, proteinuria, increased SDMA	Mild thrombocytopenia, anemia, and/or leukopenia	Thrombocytopenia, neutrophilic polyarthritis, leukocytosis, neutrophilia, monocytosis, anemia, elevated ALP and ALT activities, increased SDMA
Differential diagnoses	Other vector-borne diseases (Lyme disease, ehrlichiosis, among others), immune-mediated polyarthritis, immune-mediated hemolytic anemia, systemic lupus erythematosus	Other vector-borne diseases (anaplasmosis, ehrlichiosis, among others), immune thrombocytopenia	Other vector-borne diseases (anaplasmosis, Rocky Mountain spotted fever, leishmaniasis, among others), coccidioidomycosis, immune-mediated polyarthritis, immune-mediated hemolytic anemia, immune thrombocytopenia, systemic lupus erythematosus	Other vector-borne diseases (anaplasmosis, ehrlichiosis by E. canis or E. ewingii among others), idiopathic immune thrombocytopenia	Lyme disease, idiopathic immune-mediated polyarthritis, immune-mediated hemolytic anemia, immune thrombocytopenia, systemic lupus erythematosus

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; CNS, central nervous system; SDMA, symmetric dimethylarginine.

[a] Refs.[46,58–65]
[b] Refs.[46,47,66–70]
[c] Refs.[46,58,71–74]
[d] Refs.[46,58,71,72,75–77]
[e] Refs.[55–58,72,78,79]

clinical recovery with the disease becoming subclinical or asymptomatic for 6 to 9 weeks or persisting for years.[53] These dogs may have mild thrombocytopenia but without clinical signs of disease.[54] Chronic CME may develop in some dogs, with weight loss, myalgia, bleeding tendencies, ocular lesions, neurologic signs, cardiac arrhythmias, and a grave prognosis (**Figs. 3–7**). Complications from chronic infection include glomerulonephritis and nephrotic syndrome because of the deposition of immune complexes, and bone marrow suppression resulting in pancytopenia and secondary infections. At this stage, *E. canis* is hardly detected in circulation but may be detected in the spleen, lymph nodes, and bone marrow.[53]

Clinical manifestations of *E. ewingii* include fever and lameness associated with neutrophilic polyarthritis, but infected dogs may be asymptomatic.[55,56] Rarely, more severe neurologic signs, such as paresis, proprioceptive deficits, anisocoria, intention tremor, and head tilt, may be present.[57] Renal disease, immune-mediated hemolytic anemia, proteinuria, neutrophilia, abnormal lymphocytes, and increased liver enzyme activities were the most frequent abnormalities reported in dogs naturally infected with *E. ewingii*, although cause and effect was not established.[56] In contrast, *E. chaffeensis* infection in dogs is generally asymptomatic, or only mild signs are reported (see **Table 1**). A dog infected with *E. muris* was presented with fever, lethargy, and lameness,[13] whereas Panola Mountain *Ehrlichia* spp was reported as asymptomatic in a dog.[15]

CANINE ANAPLASMOSIS

Etiology

Canine anaplasmosis is caused by two distinct pathogens. *Anaplasma phagocytophilum* is the causative agent of granulocytotropic (also called granulocytic) anaplasmosis in domestic animals and people because it mainly targets peripheral neutrophils and eosinophils. This pathogen was previously named *Ehrlichia equi*, *Ehrlichia phagocytophila*, and in humans, the human granulocytotropic ehrlichiosis agent, but based on DNA sequencing these organisms were subsequently grouped under the genus *Anaplasma*.[2] This organism was first described in 1932 in a Scottish sheep as "a granulocytotropic ehrlichial disease."[80] In the United States, it was first identified in horses from California in 1969[81] and subsequently in dogs from California in 1982.[82] In Europe, cases were likely seen in dogs and horses in Sweden in 1989.[83] In people,

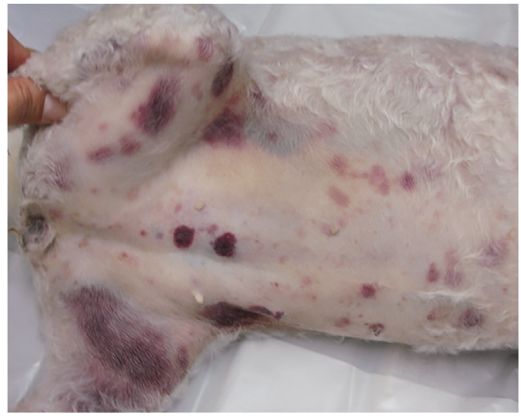

Fig. 4. Petechiae and ecchymoses caused by canine ehrlichiosis. (*Courtesy of* Ana Silvia Dagnone, Brazil.)

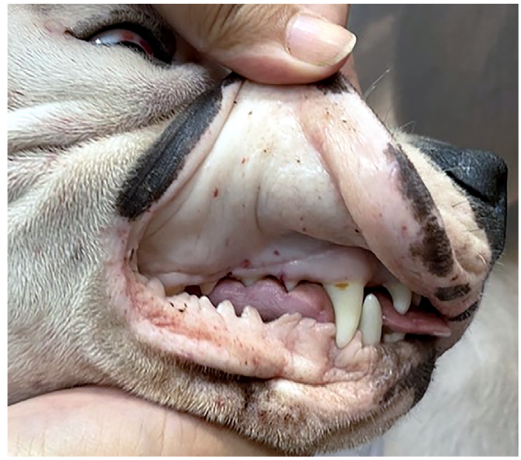

Fig. 5. Pale mucous membranes and petechiae in a dog with chronic ehrlichiosis. (*Courtesy of* Ana Silvia Dagnone, Brazil.)

A. phagocytophilum infection was first detected in Minnesota and Wisconsin between 1990 and 1993,[84,85] with canine cases identified simultaneously from those states.[86] Human anaplasmosis is an emerging disease, with more than 5000 human cases reported annually in the United States.[87]

Anaplasma platys is the causative agent of thrombocytotropic anaplasmosis (also called infectious cyclic thrombocytopenia). This pathogen was first described as basophilic inclusion bodies in platelets of thrombocytopenic dogs in the United States in 1978.[88] Since then, this organism has been detected in other domestic animals, such as cats, horses, cattle, goats, and people.[89–91] This pathogen was previously

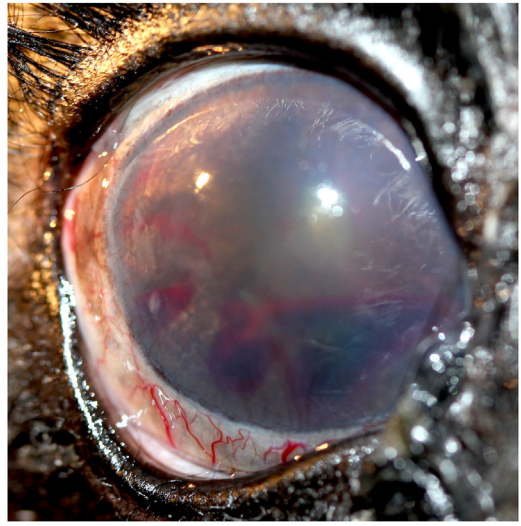

Fig. 6. Hyphema, corneal fibrosis, and evident scleral vessels in a dog with uveitis caused by ehrlichiosis. (*Courtesy of* Nathalie M. B. Dower, Brazil.)

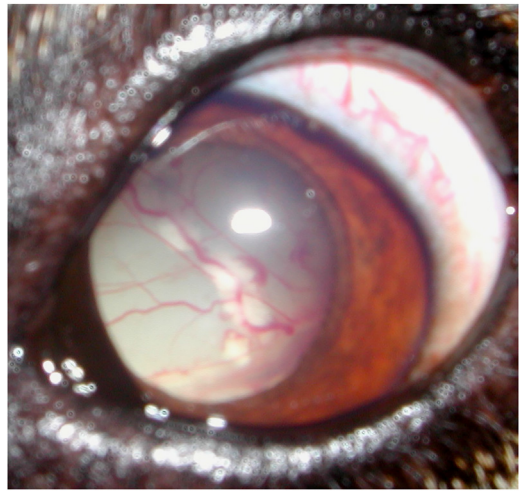

Fig. 7. Retinal detachment in a dog caused by ehrlichiosis. (*Courtesy of* José L. Laus and Ivan R. Martinez Padua, Brazil.)

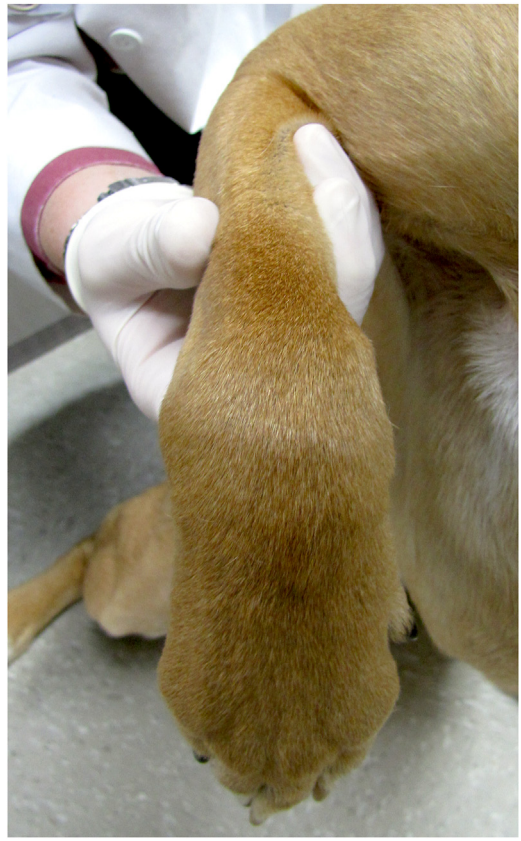

Fig. 8. Swollen carpal joint caused by canine anaplasmosis. (*Courtesy of* Matt Eberts, USA.)

named *Ehrlichia platys* but was subsequently found to belong to the genus *Anaplasma* based on DNA sequencing.[2]

Epidemiology

Anaplasma phagocytophilum has a worldwide distribution. Endemic areas follow the distribution of the *Ixodes* sp ticks.[92] *Ixodes scapularis* (black-legged tick) is the main vector in Eastern regions of United States and Canada,[93,94] where a 213% increase in the number of counties with established tick populations was documented between 1996 and 2015.[95] *Ixodes pacificus* (the Western black-legged tick) is the vector in the west coast of the United States.[96] This tick has expanded its geographic distribution to include southwest Canada and Alaska in recent years.[97,98] In Europe, *Ixodes ricinus* (the castor bean tick) is the main vector for *A. phagocytophilum*[99]; its geographic distribution is also expanding, and now includes northwestern areas of Europe.[100–102] *Ixodes persulcatus* (the taiga tick) is the main vector in eastern Europe and southeast Asia (China, Mongolia, Korea, and Russia), although several other *Ixodes* species have been implicated in carrying and transmitting *A. phagocytophilum*.[103–105] Several genetic variants of *A. phagocytophilum* from a large number of domestic and wild animals have been described worldwide.[64,106] In the United States, the white-footed mouse, the redwood chipmunk, and woodrats are the main reservoir for an *A. phagocytophilum* variant capable of causing disease in people, dogs, and horses.[107–110] In Europe, hedgehogs and red squirrels may be the main reservoir of *A. phagocytophilum* variants commonly detected in dogs and people.[111] It is estimated that 1 in every 30 dogs in the United States and 1 in every 240 dogs in Canada screened have been exposed to *Anaplasma* sp (presumably *A. phagocytophilum* for the most part), with higher frequencies in the Northeastern, upper Midwestern, and Pacific Northwestern United States, and southern regions of Canada, especially Alberta, British Columbia, and Nova Scotia provinces.[112,113] In Europe, *A. phagocytophilum* is more frequently detected in northern and central regions, especially in Hungary, Romania, and Poland, whereas in Asia it was more frequently reported in China and Malaysia. A molecular prevalence of 40% to 57% was reported from Jordan and Iran, respectively, but estimates were based on testing of a limited number of dogs. This pathogen is rarely reported from dogs in South America or Africa.[64]

Anaplasma platys also has a worldwide distribution, with infections frequently found in the same geographic regions as *E. canis*, because they share the same vector *R. sanguineus*.[114,115] *Anaplasma platys* has also been less frequently detected in other ticks, such as *Rhipicephalus turanicus*,[116] *I. persulcatus*,[117] *I. ricinus*,[118] and *Dermacentor nuttalli*.[117] Canine infections with *A. platys* are more frequently detected in southern parts of the United States, especially in Arizona and New Mexico.[119] In Europe, it is more frequently diagnosed in dogs from countries in the Mediterranean basin, including Italy, Spain, Portugal, France, Turkey, Greece, Croatia, and Romania.[41,66] This pathogen is also frequently detected in dogs from Central and South America (Brazil, Colombia, Paraguay, Uruguay, among others),[114,120–123] the Caribbean,[68,124] Africa,[125–127] Middle East,[128,129] and Asia.[130–132]

Infection, Clinical Presentation, and Relevance

Dogs with granulocytotropic anaplasmosis are generally present with lethargy, fever, inappetence or anorexia, musculoskeletal pain, reluctance to walk, and lameness (see **Table 1**), although asymptomatic dogs have been documented after natural or experimental infection.[46,62,64] Lameness, weakness, or stiffness (**Fig. 8**) are frequently reported as a consequence of monoarthropathy or polyarthropathy, secondary to the

immune response triggered by the infection.[63,64] Exactly how *A. phagocytophilum* causes disease remains unknown, but proposed mechanisms include cytokine-mediated myelosuppression; the development of autoantibodies; infection of hematopoietic precursors; and consumption of blood cells, especially platelets.[133] Thrombocytopenia is the most common laboratory abnormality detected, followed by anemia, increased liver enzymes, and hyperbilirubinemia.[46,58–65] Joint aspirates may reveal turbid synovial fluid with a high neutrophil count, where intracellular inclusions may be visualized. However, *A. phagocytophilum* morulae are morphologically indistinguishable from *E. ewingii* inclusions, so molecular methods such as polymerase chain reaction (PCR) and/or DNA sequencing are required to distinguish these organisms.[133] The morulae may also be confused with stain artifacts or basophilic precipitates. Although granulocytotropic anaplasmosis is considered an acute disease (generally with 1–2 weeks of duration),[63] persistent infections in dogs from several months to a year have been documented experimentally.[46,134–136] Therefore, if antimicrobial treatment is not administered, subclinical infection with acute flare-ups could possibly develop.[136,137] Dogs may develop secondary immune-mediated diseases, such as immune-mediated hemolytic anemia, immune-mediated thrombocytopenia (ITP), and polyarthritis.[65] Fatal cases have been reported, with immune-mediated hemolytic anemia and disseminated intravascular coagulation being the most frequent cause of death.[64]

Infection with *A. platys* in the dog is characterized by recurrent thrombocytopenia that waxes and wanes on approximately a 10- to 14-day cycle during acute infection.[47,88] Thrombocytopenia is believed to be a consequence of platelet phagocytosis by macrophages, either because of injury to platelets by the organism or opsonization by platelet-antibody.[138] Dogs can remain asymptomatic during the acute phase, although clinical manifestations, such as lethargy, inappetence, anorexia, weight loss, and epistaxis, have been reported (see **Table 1**). When present, the physical examination may reveal fever, lymphadenopathy, and petechiae. Apparently, clinical manifestations from strains in the United States are generally mild or asymptomatic,[46,47,70] whereas strains in Europe and South America are associated with more severe manifestations.[67,69,139,140] Nonetheless, subclinical carriers have been frequently reported from the United States and abroad.[124,141–143] Infectious cyclic thrombocytopenia is life-threatening especially if the patient is subjected to surgery or blunt trauma.

FELINE EHRLICHIOSIS AND ANAPLASMOSIS

Etiology

Infections of cats with *Ehrlichia* or *Anaplasma* species are much less frequent than in dogs. Worldwide, the most frequently reported species are *E. canis* and *A. phagocytophilum,* with *A. platys*, *Anaplasma bovis*, *E. chaffeensis*, *E. ewingii*, and others rarely reported.[144–148] The same vectors responsible for infections in dogs are suspected to transmit them to cats.[149,150]

Epidemiology, Clinical Presentation, and Relevance

The frequency of cats infected with or exposed to *E. canis* or *A. phagocytophilum* also varies according to the geographic region, population tested, and diagnostic method used. The seroprevalence of *E. canis* exposure in cats was reported to be 0.14% in the United States,[148] from 6% to 18% in Europe,[151] and 33% in Brazil.[152] For *A. phagocytophilum*, reported seroprevalences ranged from 1.8% to 38% in the United States and 2% to 33% in Europe.[148,151,153] Molecular prevalence for *A. phagocytophilum* in

peripheral blood varied from 0% to 23% in Europe and 0% to 7% in the United States.[154]

Not all infected cats present with clinical disease, which is characterized by nonspecific signs, such as intermittent fever, anorexia, lethargy, dehydration, joint pain, and epistaxis. Similarly, hematologic findings are variable and may include nonregenerative anemia, thrombocytopenia, lymphopenia, monocytosis, or hyperglobulinemia. In contrast to dogs infected with *A. phagocytophilum*, polyarthropathy is infrequently documented in infected cats.[155,156]

DIAGNOSIS OF EHRLICHIOSIS AND ANAPLASMOSIS

The combination of more than one diagnostic assay, especially one serology-based and one molecular-based assay, is recommended to optimize the diagnosis of ehrlichiosis and anaplasmosis across the different stages of infection.[157,158] Because every assay has strengths and limitations, a negative result from cytology, serology, or PCR does not necessarily rule out infection. A summary of the most frequently used diagnostic assays is provided in **Table 2**, but no in-clinic serology or molecular-based test for these diseases in cats is currently available. Clinical and laboratory abnormalities must be taken into consideration when evaluating a suspected case (see **Table 1**), because no single diagnostic test is capable of accurately detecting *Anaplasma* or *Ehrlichia* infection in all cases.[159]

Microscopic Examination

Microscopic examination of peripheral blood is always indicated in patients with thrombocytopenia or anemia to verify cell counts and review red blood cell and platelet morphology. However, microscopic evaluation of peripheral blood, buffy coat, or aspirates from lymph nodes or bone marrow is time consuming and have overall limited sensitivity and specificity for detecting *E. canis*, *E. chaffeensis*, *E. ewingii*, and *A. platys* when compared with other diagnostic assays.[160] For the diagnosis of *A. phagocytophilum*, review of peripheral blood smears yields moderate to high sensitivity, probably caused by the acute nature of the infection.[63,161] Morphologic features of the morulae do not allow species identification and the cell type infected (monocyte or granulocyte) does not always correlate directly with the species of *Ehrlichia* or *Anaplasma* involved (eg, *E. canis* can infect granulocytes or lymphocytes, **Figs. 9–11**).[3,162] The exception is when morulae are detected in platelets, which suggests *A. platys* infection (**Fig. 12**).[88] In summary, cytologic examination of peripheral blood and other samples may be most sensitive in cases with acute illness, when circulating numbers of organisms are highest, but not visualizing an organism does not rule out infection. More sensitive diagnostic tools should be used when ehrlichiosis and anaplasmosis is suspected.

Serology

Several assays are available for the detection of antibodies against *Anaplasma* and *Ehrlichia* species. Most in-clinic tests are based on enzyme-linked immunosorbent assays, whereas laboratory-based assays are either based on enzyme-linked immunosorbent assays or microimmunofluorescence (immunofluorescence assay [IFA]). These rely on the patient's ability to mount a detectable antibody response; consequently, most serologic assays yield negative results during early phases, generally 1 to 2 weeks postinfection.[157,163,164] Of note, after the infection is managed with antimicrobials, antibodies can remain elevated for several months to years, especially for *E. canis*.[165] In-clinic serologic assays are a valuable tool to clinicians to quickly

Table 2
Most common diagnostic assays for anaplasmosis and ehrlichiosis in dogs and cats

Assay	Specimen	Setting	Organism Detected	Advantage	Limitation
Cytology	Peripheral blood Buffy coat Lymph node Bone marrow	Point of care	*Anaplasma phagocytophilum* *Anaplasma platys* *Ehrlichia canis* *Ehrlichia chaffeensis* *Ehrlichia ewingii*	Cost-effective The assay is performed on-site or at a diagnostic laboratory Feline samples can be tested	Cannot determine bacterial species (except for *A platys*) Time-consuming when scanning a large number of oil immersion fields (500–1000) needed to increase sensitivity[160] Low to moderate specificity, depending on the operator's training level (lymphocytic azurophilic granules, lymphoglandular bodies, and phagocytosed material may resemble ehrlichial inclusions)[175] *E. canis*, *E. ewingii*, and *A. platys*: Low sensitivity when compared with other methods (from 0% to 10% in peripheral blood of infected dogs, but moderate sensitivity for buffy coat, bone marrow, or lymph node with *E. canis*)[63,160,176–178] *A. phagocytophilum*: moderate to high sensitivity (40%–94%), but cannot be differentiated from *E. ewingii*[63,161]

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Table 2
(*continued*)

Assay	Specimen	Setting	Organism Detected	Advantage	Limitation
Serology: SNAP 4Dx Plus (IDEXX)	Serum, plasma, or anticoagulated whole blood	Point of care	*A. phagocytophilum* *A. platys* *Borrelia burgdorferi* *E. canis* *E. chaffeensis* *E. ewingii* *Dirofilaria immitis* (antigen)	Results in 8 min Cost-effective and easy to perform at the clinic Stored at room temperature for 90 d Reported sensitivity of 97% for *E. canis*, 98% for *E. ewingii*, 85% for *A. phagocytophilum*, and 83% for *A. platys* when compared with IFA, Western immunoblot, and/or species-specific ELISA[179] The manufacturer claims better performance than other lateral-flow ELISA assays[180] Available worldwide	Does not quantify antibody levels, therefore cannot detect a 4-fold increase between paired samples Cannot differentiate between antibodies against *A. phagocytophilum* and *A. platys*, or between *E. canis* and *E. ewingii*[181] Limited sensitivity for *E. chaffeensis*[181] Not approved for cats
Serology: VetScan Flex4 (Zoetis)	Serum, plasma, or anticoagulated whole blood	Point of care	*A. phagocytophilum* *A. platys* *B. burgdorferi* *E. canis* *E. chaffeensis* *E. ewingii* *D. immitis* (antigen)	Results in 8 min Cost-effective and easy to perform at the clinic Stored at room temperature Available in the United States and several countries across Europe and Asia	Does not quantify antibody levels, therefore cannot detect a 4-fold increase between paired samples Cannot differentiate between antibodies against *A. phagocytophilum* and *A. platys*, or among *E. canis*, *E. chaffeensis*, or *E. ewingii*

					Reported sensitivity of 61% for *E. canis*, 59% for *E. ewingii*, 13% for *A. phagocytophilum*, and 33% for *A. platys* when compared with IFA, Western immunoblot, and/or species-specific ELISA[179] Limited peer-reviewed literature Not approved for cats
Serology: ImmunoComb (Biogal)	Serum	Point of care	*E. canis*	Results in 20 min Cost-effective and easy to perform at the clinic Results provide semiquantification of antibodies, based on the color tone of the test spot Reported sensitivity of 86% for *E. canis* when compared with IFA[182]	Not available in the United States or Canada but available in several countries in Europe, the Americas, and Asia Requires refrigeration Limited peer-reviewed literature Not approved for cats
PCRun (Biogal)	Anticoagulated whole blood	Point of care	*A. platys* *E. canis*	Based on PCR assay, so can detect active infection Results within 1 h One study reported 100% sensitivity and specificity[183] Marketed for *A. platys* and *E. canis* detection, but reported to detect *A. phagocytophilum*, *E. chaffeensis*, and *E. ewingii*	Not available in the United States, Canada, and most of Europe, but available in several countries in the Americas, Middle East, and Asia Requires specific equipment (heat block) Time-consuming when compared with other point-of-care assays One study reported sensitivity of 75%[184]

(*continued on next page*)

Table 2
(*continued*)

Assay	Specimen	Setting	Organism Detected	Advantage	Limitation
					Limited peer-reviewed literature Not approved for cats
Serology: Immunofluorescent assay	Serum	Diagnostic laboratory (many private or university-based laboratories)	*A. phagocytophilum* *E. canis*	Provides quantification of antibody response (titer) A 4-fold increase in titers confirmed active infection Continuous decrease in titers may indicate treatment success Feline samples can be tested	Tests must be performed at a diagnostic laboratory Results may take days to be available Acute infection may yield negative results Dogs with chronic infection may not seroconvert Not yet available for *A. platys*, *E. chaffeensis*, or *E. ewingii* Cannot determine species involved in the infection because cross reactivity may occur Lack of standardization among laboratories
Serology: Accuplex4 (Antech)	Serum	Diagnostic laboratory	*A. phagocytophilum* *E. canis* *B. burgdorferi* *D. immitis* (antigen)	In one experimental study, antibodies against *E. canis* were detected earlier than IFA or SNAP[185] Reported sensitivity of 100% for *E. canis* when compared with IFA[186]	Only available in the United States and Canada Tests must be performed at a diagnostic laboratory Reported sensitivity of 75% for *A. phagocytophilum* when compared with IFA[187] Limited peer-reviewed literature Not approved for cats

PCR: Single test or tick-borne panel	Anticoagulated whole blood Buffy coat Lymph node Bone marrow Other tissues	Diagnostic laboratory (many private or university-based laboratories)	*A. phagocytophilum* *A. platys* *E. canis* *E. chaffeensis* *E. ewingii* Other organisms (panels vary among laboratories)	Can detect active infection High analytical sensitivity and specificity Species/strain present is identified with specific PCR assays and/or DNA sequencing Panels can detect coinfections with other vector-borne pathogens Feline samples can be tested	Tests must be performed at a diagnostic laboratory Results may take days to be available Limited sensitivity in case of subclinical or chronic infection Prone to false-positive because of cross-contamination if laboratory best practices are not properly followed Lack of standardization among laboratories

Abbreviations: ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay.

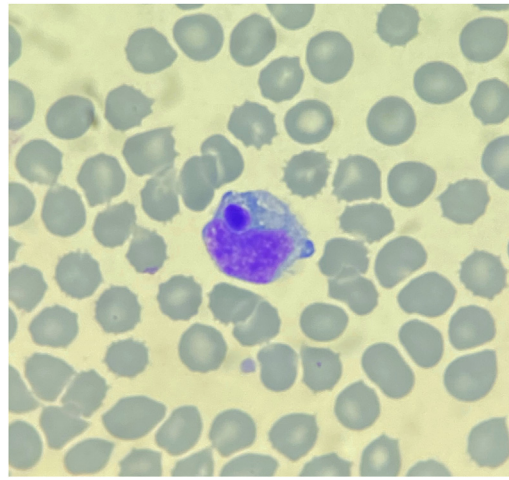

Fig. 9. Morulae of *Ehrlichia canis* in a monocyte (note that it cannot be distinguished from morulae of *Ehrlichia chaffeensis*). (*Courtesy of* Arnon Falcão Calábria, Brazil.)

document exposure to vector-borne pathogens. However, the presence of specific antibodies against *Anaplasma* and/or *Ehrlichia* spp only indicates exposure to the organisms, and should not be used alone to make a diagnosis without taking into consideration clinical and laboratory abnormalities and other case context.[166] In general, a seroreactive dog with no signs or laboratory abnormalities and negative PCR testing does not require antibiotic therapy but should be monitored to rule out subclinical infection (**Table 2**). The presence of long-lasting antibodies levels is particularly relevant in areas endemic for vector-borne pathogens, where a positive serologic test may be caused by past exposure and not necessarily associated with the current

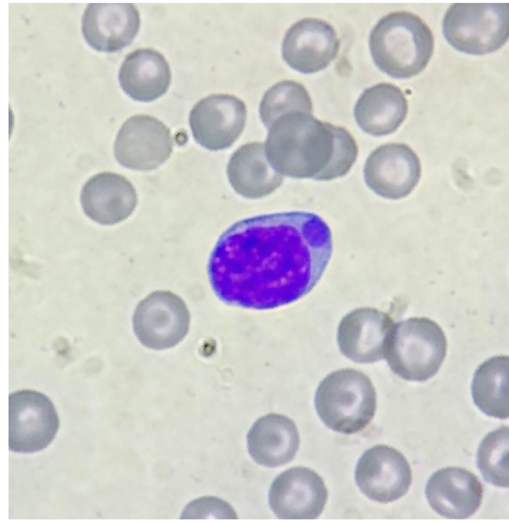

Fig. 10. Morulae of *Ehrlichia canis* in a lymphocyte. (*Courtesy of* Jeniffer Ariane de Morais, Brazil.)

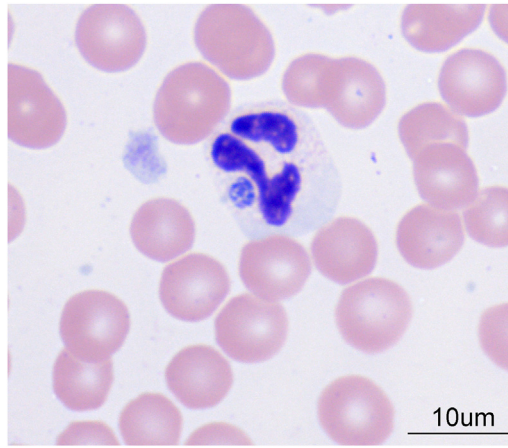

Fig. 11. Morulae of *Anaplasma phagocytophilum* on a neutrophil (note that it cannot be distinguished from morulae of *Ehrlichia ewingii*). (*Courtesy of* Kristin Nunez, USA.)

disease.[166] Chronically infected dogs generally have high titers, although some dogs may be seronegative because of the ability of the pathogen to evade the immune system.[47,56,62,89,167]

Most in-clinic serologic assays do not provide quantification of antibodies (titers), whereas laboratory-based assays can quantify specific antibody concentration and support the detection of a four-fold increase in titers between acute and convalescent samples, which confirms active infection. Therefore, clinicians should establish a routine of banking frozen specimens at the initial presentation to allow such analysis during follow-up visits.[157] The sensitivity and specificity are high for most available serology assays, but vary across reports, with no peer-reviewed studies for some tests (see **Table 2**). Serologic cross reactivity among *Anaplasma* and *Ehrlichia* species within their respective genus in some assays prevent the determination of the bacterial species involved, but it does not prevent the clinician from reaching a diagnosis and establishing appropriate antimicrobial therapy, because these infections generally

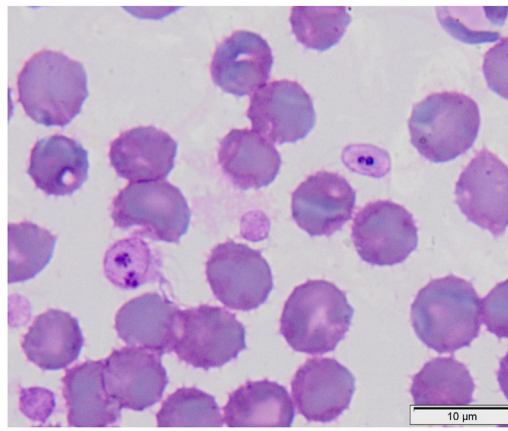

Fig. 12. Morulae of *Anaplasma platys* in platelets. (*Courtesy of* Charalampos Attipa, UK.)

respond well to doxycycline therapy.[41,168] The presence of other vector-borne agents should always be considered, given that the same vector may be capable of transmitting more than one pathogen (eg, *A. phagocytophilum* and *Borrelia burgdorferi* by *Ixodes* ticks).[169,170]

Polymerase Chain Reaction

In recent decades, PCR assays have become widely available for the diagnosis of anaplasmosis and ehrlichiosis because of a significant reduction in the cost of reagents and equipment. PCR assays have several advantages over serology, including the detection of acute infection with high levels of analytical sensitivity and specificity, the opportunity to test different specimens (eg, fine-needle aspirate or biopsy samples),[171] the ability to determine the bacterial species involved, and to screen for multiple pathogens by the use of PCR panels.[158] Tissue samples, such as the spleen, lymph nodes, or bone marrow aspirates, are more sensitive for the molecular detection of *Anaplasma* and *Ehrlichia* spp than peripheral blood, especially during subclinical/chronic phases of infection or after antibiotic therapy.[171–173] However, anticoagulated whole-blood samples are more practical to obtain and if collected during the acute phase, achieve good clinical sensitivity using PCR. Well-designed and validated PCR assays can detect few organisms in clinical specimens, at concentrations that cannot be visualized by microscopic examination.[160] In addition, these assays are paired with DNA sequencing, for the further identification of species, strains, or variants, providing valuable epidemiologic data about animal and human health.[89] However, despite advances in chemistry and equipment, PCR assays are not widely available at the point of care (see **Table 2**). In addition, results may take days to become available, limiting the clinician's ability to reach quick medical decisions. Most importantly, a negative PCR result never rules out infection, because low levels of bacteremia (seen in subclinical or chronic infections) may be lower than the level of detection of the assay or not be present in the specimen tested.[171,174] Because the phase of infection is generally unknown, PCR-based results should be interpreted in combination with serologic testing (**Table 3**).[157,158] Similar to serologic assays, clinicians should routinely bank frozen EDTA-blood samples of patients suspected of a tick-borne disease during the initial consultation and before antibiotic therapy. These samples are later used for repeat PCR testing in a highrisk patient with a negative initial result, and analyzed for additional known pathogens or novel organisms if needed.[157]

TREATMENT AND PREVENTION OF EHRLICHIOSIS AND ANAPLASMOSIS

The decision to start antimicrobial therapy depends on several factors including clinical manifestations, the results of specific diagnostic testing, and predictive values for positive and negative tests in the region. Clinicians should also consider other noninfectious differentials, and veterinary antibiotic stewardship guidelines. **Table 3** summarizes the most common clinical scenarios and treatment recommendations. Among all etiologic pathogens of anaplasmosis and ehrlichiosis, *E. canis* infection in dogs is more frequently associated with severe to life-threatening manifestations, requiring more comprehensive therapy. Conversely, *A. phagocytohilum* infection generally responds quickly to proper antimicrobial therapy. Tetracyclines remain the antibiotic class of choice to control ehrlichial infections in companion animals but their indiscriminate use increases the risk of antimicrobial resistance.[188,189] Doxycycline remains the recommended antibiotic, with other tetracyclines also being effective for dogs and cats (**Table 4**). Doxycycline treatment in dogs during the acute phase of *E. canis* infection reduces oxidative stress and promotes resolution of clinical and

Table 3
Potential clinical scenarios of suspected anaplasmosis or ehrlichiosis and treatment recommendations[a]

Compatible Clinical and/or Laboratory Findings	In-Clinic Serology	IFA[b]	PCR	Diagnosis	Treatment	Recommendations, Treatment Response, and Other Considerations
No	Positive for *Ehrlichia canis*	Negative to low titer for *E. canis*	Negative	Possible subclinical ehrlichiosis	No	Low titers may indicate past exposure with resolution of infection Repeat serologic testing after 2–3 wk because increasing titers indicate active infection Repeat CBC in 2–3 wk; consider monitoring chemistry and urinalysis Consider repeating PCR assay after a few days, because bacteria levels vary in circulation
		High titer for *E. canis*	Negative	Possible subclinical ehrlichiosis	No	High titers may indicate active infection but can persist following previous exposure Follow the recommendations above for CBC, chemistry, urinalysis, and PCR testing
	Positive for *Anaplasma*	Negative or positive for *Anaplasma*	Negative	Suspected chronic anaplasmosis	No	*Anaplasma platys* frequently cause chronic infection, whereas *Anaplasma phagocytophilum* is generally acute

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Table 3
(*continued*)

Compatible Clinical and/or Laboratory Findings	In-Clinic Serology	IFA[b]	PCR	Diagnosis	Treatment	Recommendations, Treatment Response, and Other Considerations
						Repeat CBC for cyclic thrombocytopenia, which supports *A. platys* infection Consider repeating PCR assay after a few days, because bacteria levels vary in circulation
Yes	Negative	Negative for *E. canis*	Positive for *E. canis*	Acute ehrlichiosis	Yes	An increase in antibody titers after 2–3 wk confirms acute infection Expected rapid clinical response to treatment in 2–3 d, with improvement of laboratory abnormalities in 1–3 wk
		Negative for *Anaplasma*	Positive for *Anaplasma*	Acute anaplasmosis	Yes	Same as above
	Positive for *Anaplasma*	Negative or low titers for *Anaplasma*	Negative	Possible acute anaplasmosis	Yes	Detected antibodies may be caused by past exposure An increase in antibody titers after 2–3 wk confirms acute infection If acute presentation, consider repeating PCR after a few days

					A. platys frequently cause chronic infection and more difficult to treat, whereas *A. phagocytophilum* is generally acute and responds quickly to antibiotic therapy Consider repeating PCR assay after a few days, because bacteria levels vary in circulation Consider infection with other vector-borne pathogens and other underlying diseases
Positive for *E canis*	Negative to low titer for *E. canis*	Negative	Possible acute ehrlichiosis	Yes	Same as above
	High titer for *E. canis*	Negative or positive	Suspected chronic ehrlichiosis	Yes	If blood PCR is negative, consider PCR of lymph node aspirates (especially if enlarged) Antibody titers may remain elevated for several months after therapy Variable response to treatment, with poor prognosis in dogs with bone marrow suppression

Abbreviations: CBC, complete blood count; IFA, immunofluorescence assay.

[a] Not meant to be a comprehensive list of all possible diagnostic scenarios.

[b] IFA assays for *A. platys*, *E. chaffeensis*, or *E. ewingii* are not currently available in veterinary medicine.

Table 4
Recommended antimicrobial drugs for the treatment of anaplasmosis and ehrlichiosis in dogs and cats

Drug	Dose and Interval	Route	Minimum duration[a]	Considerations
Doxycycline	5 mg/kg every 12 h or 10 mg/kg every 24 h	PO[b], IV	28 d [166,168,202]	Consider liquid formulation for cats or small dogs to avoid esophageal damage
Minocycline	Dogs: 5–10 mg/kg every 12 h Cats: 5–12.5 mg/kg every 12 h	PO[b]	28 d	Recommended if doxycycline is not available
Oxytetracycline	7.5–10 mg/kg every 12 h	IV	Until the patient can tolerate oral doxycycline	Used if oral antibiotics are not tolerated because of gastrointestinal signs

Abbreviation: IV, intravenous.
[a] Extended duration may be necessary in chronic cases.
[b] If available, IV preparations of doxycycline or minocycline are preferred when the patient cannot tolerate oral medication; however, it should be diluted in 100 to 1000 mL of lactated Ringer solution or 5% dextrose and be administered over 1 to 2 hours.

hematologic abnormalities.[74,190] In these authors' experience, a dose of 5 mg/kg orally every 12 hours is associated with fewer gastrointestinal adverse effects, such as vomiting and anorexia, while remaining as effective as the dose of 10 mg/kg orally every 24 hours. Esophageal strictures caused by tablet-induced focal esophagitis have been well described in cats and may also happen in small dogs.[191–193] Thus, at least 6 mL of liquid should be given orally after each tablet,[194] or liquid formulations could be considered. Of note, if liquid doxycycline is compounded from tablets, the preparation should be used within 7 days, because a 14% to 18% decrease in doxycycline concentration has been documented in liquid formulations stored from 14 to 28 days.[195] In addition, the pharmacokinetics of tetracyclines in the gastrointestinal tract is affected by chelation by calcium (from foods, such as dairy products, or certain oral antacids), causing a decrease in absorption, bioavailability, and efficacy. Among all tetracyclines, doxycycline is the least affected by the ingestion of calcium-rich foods.[196] However, in humans, simultaneous ingestion of milk diminished the peak plasma concentration of doxycycline by 24% and absorption by 9% to 53% (mean, 30%).[197] Anecdotal evidence supports a potentially similar effect in dogs who received doxycycline with milk or cheese, where the rate of clinical improvement was delayed. Therefore, it is prudent to avoid calcium-rich foods when administering oral tetracyclines, if possible.

Minocycline may be used if doxycycline is not available (see **Table 4**).[198] If the patient cannot tolerate oral antibiotics because of gastrointestinal signs, intravenous doxycycline or oxytetracycline is used until the patient can receive oral doxycycline.[159,166,199] One study also reported clinical and hematologic recovery of dogs with CME treated with rifampicin (10 mg/kg PO, once daily for 21 days), but three out of five infected dogs remained PCR positive from blood samples.[200] Given the limited clinical experience in conjunction with a few experimental studies and drug

safety profile, rifampicin may be an alternative antibiotic for CME[168] but should not be used as monotherapy or as the first line of treatment until more data are reviewed. Clinical improvement to doxycycline therapy for acute and subclinical cases of ehrlichiosis or anaplasmosis is generally rapid in dogs and cats (within 24–48 hours), with platelet count and other laboratory abnormalities returning to normal within 2 weeks.[168,201–203] However, because of this rapid improvement, some clients may consider early termination of antibiotics. In one study of *A. phagocytophilum*–infected cats without comorbidities, three out of seven did not recover clinically after 3 weeks of doxycycline treatment.[204] Clinicians should highlight the importance of the minimum recommended duration of antibiotics to avoid potential chronic infection and the development of microbial antibiotic resistance. Antibody titers decline and generally become negative within 6 to 9 months after the introduction of antibiotics, but may remain elevated for years in some cases.[166] In acute cases presented with mild to moderate manifestation, if clinical improvement is absent after 3 days of adequate antimicrobial therapy, clinicians should investigate the presence of other vector-borne diseases (babesiosis, bartonellosis, and leishmaniasis in endemic areas or for patients with a travel history), other infectious causes (coccidioidomycosis), or noninfectious underlying disease.

Because tetracyclines and rifampicin are bacteriostatic,[205] the duration of therapy necessary to control the infection remains unknown. Several studies were unable to detect *E. canis*, *A. phagocytophilum*, or *A. platys* in canine blood or tissues after 4 weeks of doxycycline treatment of acute or subclinical disease, even after immunosuppression.[47,74,202,206] However, elimination of the *E. canis* infection is not achieved in all cases, especially during chronic infection. In one study, persistent infection with *E. canis* was detected after 28 days of doxycycline when naive ticks fed on chronically infected dogs.[201] In cats, *A. phagocytophilum* PCR-positive results were also reported from 8 days, 37 days, 120 days, 150 days, to 2 years after doxycycline treatment of varying duration.[154,204] These differences in susceptibility to treatment may be caused by distinct strains of organisms, differences in host immunity, variations in dosing regimens, or reinfection.[168] Chronic CME cases with severe manifestation are challenging and have a poor prognosis because of myelosuppression and consequent pancytopenia and bleeding disorders.

The use of glucocorticoid therapy in canine ehrlichiosis and anaplasmosis remains controversial. Despite being advocated for CME by some clinicians, studies have not documented significant clinical or prognostic benefits of glucocorticoids as an adjunct to doxycycline.[207,208] Therefore, glucocorticoids are not recommended in the first line of treatment because resolution of clinical and hematologic abnormalities after administration of doxycycline is usually rapid, and they may theoretically predispose to secondary infections and the inability to clear the infection, even with antibiotic therapy.[41,168,199] Doxycycline and minocycline also have anti-inflammatory and immunomodulatory properties,[209] which may be associated with the rapid response during the first days of treatment. In cases where improvement of clinical and/or hematologic abnormalities are not documented after the first week of antibiotic therapy, anti-inflammatory doses of glucocorticoids may be considered. For uveitis, topical anti-inflammatory medications (glucocorticoids or nonsteroidal anti-inflammatory drugs) and mydriatic drugs to improve comfort and prevent pupil adhesions are also frequently used in combination with oral prednisolone at 1 mg/kg every 24 hours for 1 to 2 weeks.[210] For antibody-mediated syndromes, such as ITP, the use of higher immunosuppressive doses of glucocorticoids has been suggested for up to 7 days in addition to ongoing therapy with doxycycline if no response is documented with doxycycline alone. Glucocorticoids are not recommended in the case of *E canis*–

induced myelosuppression because the pancytopenia is not believed to be immune-mediated.[168] A few case reports have described the use of erythropoietin (100 IU/kg subcutaneously every 3 days), ferrous sulfate (100 mg/kg orally every 24 hours), and folate (5 mg/kg orally every 24 hours) for anemia; filgrastim (50 μg/kg subcutaneously every 48 hours for up to three doses) for neutropenia; and desmopressin (1 μg/kg subcutaneously every 24 hours for 3 days) for bleeding disorders.[168,211,212]

In addition to antibiotics, supportive therapy is essential for survival and may include fluid therapy with electrolyte management, appropriate blood products in the presence of severe anemia or thrombocytopenia or life-threatening hemorrhage, control of vomiting with antiemetics (maropitant, ondansetron), and prevention or treatment of gastroduodenal ulceration and erosion (proton-pump inhibitors such as omeprazole).[213] Appetite stimulants and nutritional support should be implemented in patients who are persistently anorexic. Dogs with severe thrombocytopenia with acute infection may benefit from a single intravenous injection of 0.02 mg/kg of vincristine, which is hypothesized to stimulate thrombopoiesis, accelerate fragmentation of megakaryocytes, reduce phagocytosis of platelets by macrophages, and interfere with antiplatelet antibody formation and binding.[214] The use of a single dose of levamisole at 0.5 to 2 mg/kg subcutaneously as immunostimulant in dogs receiving doxycycline therapy for *E canis* infection was evaluated in one study where a significant increase in leukocyte, lymphocyte, and monocyte counts was documented within a 5-day period without adverse effects.[215] Imidocarb dipropionate is no longer recommended for the treatment of *E. canis* infection because of a lack of documented efficacy,[216] but its use is recommended when coinfection with *Babesia canis* or *Babesia vogeli* is suspected or confirmed.[168] Enrofloxacin is not effective against *Ehrlichia* spp and therefore should not be used.

ZOONOTIC IMPLICATIONS

All *Ehrlichia* and *Anaplasma* species listed in this review have been reported to infect people. Direct transmission of ehrlichial species from dogs or cats to humans has not been documented. However, infection in companion animals suggests the presence of the vector in the same environment to which human companions may also be exposed. Therefore, avoiding tick bites is the most effective measure to prevent disease in humans. *Ixodes* and *Amblyomma* ticks aggressively feed on people. *R. sanguineus* has also been documented to attach and feed on humans, especially when exposed to high temperatures.[217] For example, this tick species was responsible for an outbreak of Rocky Mountain spotted fever in people in Arizona.[218] Although not confirmed for *Ehrlichia* or *Anaplasma* spp, accidental needle sticks or tick removal using bare hands are important modes of transmission for other tick-borne pathogens, especially to veterinarians, veterinary technicians, and animal caretakers.[219–221] The case fatality rate (ie, the proportion of anaplasmosis or ehrlichiosis patients that reportedly died as a result of infection) in people is roughly 1% to 3% of ehrlichiosis cases and 0.3% of anaplasmosis cases in the United States.[222–224] Fatalities have been rarely reported in Europe.[225,226]

PREVENTION STRATEGIES

Exposure to *Ehrlichia* or *Anaplasma* species does not confer full protective immunity. Dogs and cats remain susceptible to reinfection and subsequent clinical disease if reexposed to vectors. Protective vaccines for dogs or cats are not commercially available. Therefore, vector control is the most effective prophylactic measure, and should be based on decreasing exposure to vectors by restricting access to tick-infested

areas, year-round use of acaricides, and prompt removal of ticks with forceps or gloves. Ticks spend a significant amount of their life cycle not attached to their host, with approximately 5% on dogs and the remainder (~95%) in the environment.[227] Thus successful strategies incorporate tick control for the host and the environment, especially for *R. sanguineus*, which can thrive in urban settings.[217,227] In addition, landscaping the areas where dogs and cats have access can also decrease the risk of tick infestations, by clearing tall grasses and brushes, creating a 3-foot wide barrier of wood chips or gravel between play areas and surrounding wooded areas, frequently mowing the lawn, and maintaining the area clutter free.[228,229] For dog and cat breeders, where animals travel to shows or competitions, periodic antibody screening, PCR testing, and adequate treatment of positive animals should also be considered beyond vector control.

SUMMARY

In the last decade, the understanding of the epidemiology of vector-borne diseases has significantly expanded. These diseases continue to expand in geographic distribution because of enhanced vector activity from climate change. Broader use of accurate diagnostic tests provides clinicians with timely information to support better medical decision making. Doxycycline remains the therapy of choice for *Ehrlichia* or *Anaplasma* infections, and clinical resolution is achieved in most acute and subclinical cases. Clearance of infection may not be achieved in all cases, especially in chronic presentations. With the absence of effective vaccines for ehrlichiosis or anaplasmosis in dogs or cats, continuous tick prevention is the only effective strategy to avoid these diseases.

CLINICS CARE POINTS

- PCR testing of blood or tissue samples (spleen, lymph node, and bone marrow) is a sensitive and specific diagnostic tool, but a negative PCR result never rules out infection.
- For organisms where serologic testing is possible, combining PCR with serology increases overall diagnostic sensitivity. Acute and convalescent serologic testing and repeat testing using PCR can facilitate diagnosis.
- Doxycycline or minocycline for at least 4 weeks is the treatment of choice for dogs and cats but longer treatment durations may be necessary in complex cases.
- In acute cases, rapid clinical improvement and an increase in platelet count is observed within the first week of treatment, but antibiotic therapy should not be discontinued.
- Supportive therapy not only accelerates recovery but also is essential in complicated cases, when clinical response may take more than 4 weeks.
- Decreasing antibody titers and normalization of platelet counts after antibiotic therapy supports resolution of infection, but titers can remain elevated for several months in some cases.
- No vaccine is yet available, so a robust tick control program must be implemented to avoid infection or reinfection after antibiotic treatment.

DISCLOSURE

The authors have nothing to disclose.

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