*Review*
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# Canine Granulocytic Anaplasmosis: A Review

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*Anaplasma phagocytophilum* is an emerging pathogen of humans, horses, and dogs worldwide that is transmitted by Ixodid ticks and maintained in a variety of small wild mammal species. Recent studies suggest that multiple strains of *A. phagocytophilum* may be circulating in wild and domestic animal populations, and these strains may have differential host tropisms and pathogenicity. The organism infects and survives within neutrophils by disabling key neutrophil functions, including neutrophil motility, phagocytosis, the oxidative burst mechanism, and neutrophil-endothelial cell interactions, as well as interfering with neutrophil apoptosis. Coinfections with other tick-borne pathogens may occur, especially *Borrelia burgdorferi*. *A. phagocytophilum* causes an acute febrile illness in dogs with lethargy and inappetence. Less frequent signs include lameness, coughing, polydipsia, intermittent vomiting, and hemorrhages. Diagnosis is based on finding morulae within granulocytes in the peripheral blood, the combination of acute and convalescent serology using immunofluorescent antibody techniques, and detection of the DNA of *A. phagocytophilum* using specific polymerase chain reaction assays. Whether persistent infection or reinfection with *A. phagocytophilum* occurs after natural infection requires additional study, with most reports suggesting that anaplasmosis is a self-limiting disease in dogs that responds well to a 2-week course of doxycycline therapy.

**Key words:** *Anaplasma phagocytophilum*; Dog; Tick-borne disease.

*Anaplasma phagocytophilum* (formerly *Ehrlichia equi*, *Ehrlichia phagocytophila*, and in humans, the human granulocytic ehrlichiosis [HGE] agent) is an obligate, intracytoplasmic coccus that belongs to the family Anaplasmataceae (Fig 1).[1] The outer cell wall structure of the bacterium ultrastructurally resembles that of Gram-negative bacteria. It infects granulocytes, predominantly neutrophils but also eosinophils, where it exists and reproduces in membrane-bound vesicles, forming microcolonies called morulae (Latin for mulberry) (Fig 2A). *A. phagocytophilum* is transmitted by ticks, which include *Ixodes pacificus* in the western United States, *Ixodes scapularis* in the upper midwestern and northeastern United States, *Ixodes ricinus* in Europe, and *Ixodes persulcatus* and *Dermacentor silvarum* in Asia and Russia.[2–4] Other *Ixodes* spp. ticks also have been implicated in transmission, including *Ixodes trianguliceps*, *Ixodes hexagonus*, and *Ixodes ventalloi* in Europe.[5–7] The organism was first described as a veterinary pathogen, after its identification in the cytoplasm of leukocytes of sheep in Scotland.[8,9] The disease in domestic ruminants, which occurs in Europe, is also known as tick-borne fever, and has been reported in sheep, cattle, goats, and deer. Reports of equine granulocytic anaplasmosis occurred as early as 1968 in California.[10] Dogs were first identified with *A. phagocytophilum* infection in California in 1982.[11] The 1st reports of granulocytic infections in humans in the United States came from the upper midwest in 1993,[12] and since then, human granulocytic anaplasmosis has been increasingly recognized in the United States, Europe, and Asia.

**Abbreviations:**

| | |
|---|---|
| DNA | deoxyribonucleic acid |
| GMP | guanosine monophosphate |
| HGE | human granulocytic ehrlichiosis |
| IFA | immunofluorescent antibody |
| IFN | interferon |
| IL | interleukin |
| NADPH | nicotinamide adenine dinucleotide phosphate |
| PCR | polymerase chain reaction |
| PSGL-1 | P-selectin glycoprotein ligand-1 |
| RNA | ribonucleic acid |

Cases of canine granulocytic anaplasmosis in North America have been reported from California, Washington, Illinois, Minnesota, Wisconsin, Missouri, and British Columbia.[11,13–20] In Europe, infected dogs have been reported from Austria, Italy, Sweden, Switzerland, Germany, Poland, and the United Kingdom.[21–28] Evidence of possible exposure of dogs to *A. phagocytophilum* has been detected in at least 39 US states, with the highest seroprevalence being reported in dogs from the upper midwestern, northeastern, and western states.[19,29–33] This documented canine *A. phagocytophilum* exposure parallels the geographic distribution of human cases, which most commonly occur in the Northeast, upper Midwest, and northern California. In addition to horses, cattle, sheep, goats, and humans, serological cross-reactivity with other *Anaplasma* spp. such as *Anaplasma platys* can occur, potentially overestimating the true distribution of *A. phagocytophilum* infection. *A. phagocytophilum* infection has been reported, albeit less commonly, in camelids and domestic cats.[34–37] The renaming of *E. equi*, *E. phagocytophilum*, and the HGE agent as *A. phagocytophilum* based on sequence results of the 16S rRNA genes has been controversial because these organisms differ from previously named *Anaplasma* species, such as *Anaplasma marginale*, in their host cell tropism.[38] In addition, the former *Ehrlichia* species differed in their virulence and in their ability to cause disease

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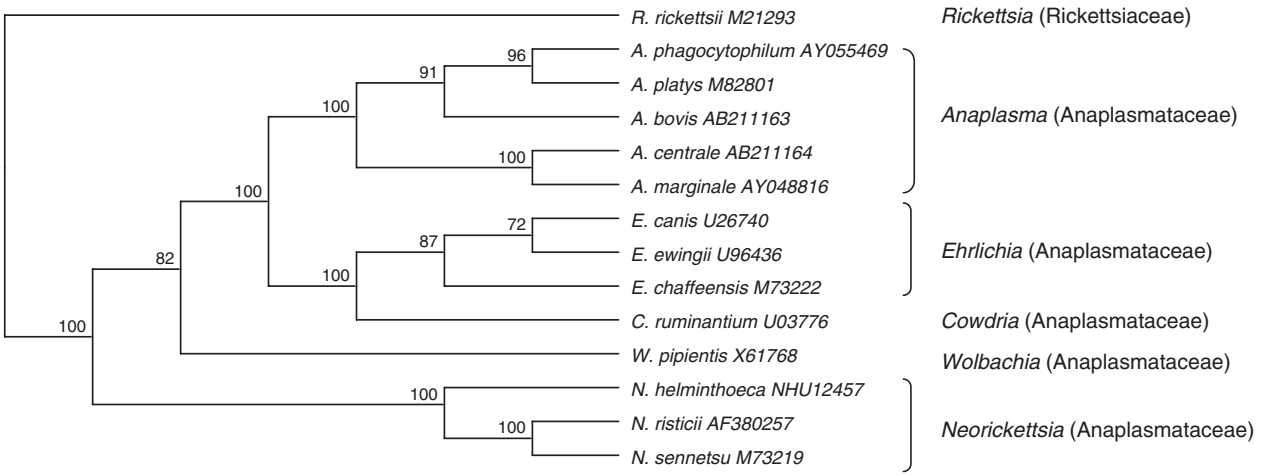



**Fig. 1.** Phylogenetic tree, based on 16S rRNA gene sequences, showing relationships between α-proteobacteria belonging to the order Rickettsiales. The dataset was resampled 1,000 times and bootstrap percentages are given at the nodes of the tree. Bar, 10 substitutions per 100 nucleotides. Species and family names (in parentheses) are given on the right.

in different host species, with cross-transmission experiments showing failure of European *E. phagocytophila* to cause disease in horses, and failure of the HGE agent isolated from humans in the United States to cause disease in cattle.[39] These are now considered to represent phenotypic variations among *A. phagocytophilum* strains in different geographical locations. Other than llamas, domestic ruminants in the United States have not been reported to be infected with *A. phagocytophilum*. Strains infecting domestic ruminants in Europe and white-tailed deer in the United States (Ap-V1) appear to be distinct from those infecting horses, humans, and dogs on the basis of sequence results of major surface protein genes.[40,41]

## Ecology and Epidemiology

*A. phagocytophilum* is transmitted primarily by ticks in the *I. persulcatus*-complex. Experimental transmission after *I. pacificus* and *I. scapularis* bites has been demonstrated.[3,4,42] In a recent study, tick exposure was reported for 14 of 18 dogs with granulocytic anaplasmosis in Europe.[26] Depending on geographical location, a variety of small wild mammals, including mice, woodrats, chipmunks, voles, and shrew, as well as deer and possibly birds act as reservoir hosts for *A. phagocytophilum*. For the midwestern and eastern United States, white-footed mice (*Peromyscus leucopus*) and eastern chipmunks likely act as reservoirs,[4,43] whereas in the western states, dusky-footed woodrats, gray squirrels, and chipmunks have been implicated.[44–47] Evidence is accumulating that some strains circulating in the rodent population may not infect other species, such as horses.[48] Larger wild animal species including mountain lions and coyotes also act as hosts, but function primarily as sentinels, as they do not develop chronic infection and are unlikely to infect juvenile ticks.[47] Dogs and humans are accidental hosts. Bacteremia appears to be of short duration (<28 days), and as such dogs and humans are not important in transmission to other host species.[49] A study in Slovenia showed that approximately 15.4% of the human sample population had antibodies for *A. phagocytophilum*, although there was no difference in antibody prevalence of those people with exposure to dogs and those without exposure.[50]

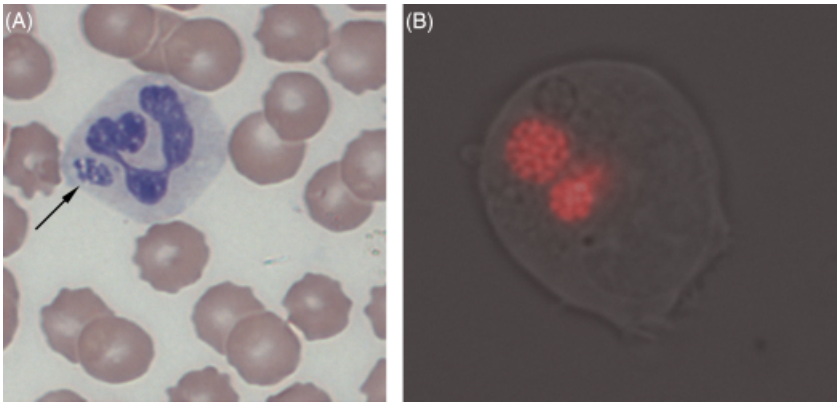



**Fig. 2.** (**A**) Canine neutrophil containing an *Anaplasma phagocytophilum* morula. Wright's stain, ×100 oil magnification. (**B**) HL-60 cell infected with *A. phagocytophilum* that has been transformed genetically to express mCherry, a red fluorescent protein (Image generously provided by MJ Herron, University of Minnesota).

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Rarely, transmission of *A. phagocytophilum* has been reported in the absence of a tick vector. Nosocomial transmission of the organism was recently reported in China.[51] An outbreak investigation suggested that transmission occurred through direct, close contact with blood and respiratory secretions of a patient who died of human granulocytic anaplasmosis. In a report from the upper Midwest, 3 adults who had each butchered over 250 deer and gave no report of tick bites developed granulocytic anaplasmosis, possibly after exposure to deer blood.[52] More recent studies, however, suggest that the *A. phagocytophilum* strain infecting deer in the United States is distinct from that infecting humans,[40,41] so it was suggested that the individuals may have been unwittingly bitten by ticks.[53] Rare case reports also describe possible transmission of *A. phagocytophilum* to humans transplacentally[54] and after blood transfusion.[55] Perinatal infection with *A. phagocytophilum* was described in a bitch from Wisconsin with a retained, mummified fetus. No evidence of infection was documented in the surviving puppies from the litter.[56]

The seroprevalence of *A. phagocytophilum* in dogs has been evaluated worldwide (Table 1), although neither molecular evidence nor culture positive cases of *A. phagocytophilum* have been documented in the southern hemisphere.[19,20,29–33,58–74] The prevalence of seropositive test results depends on whether the dog population sampled was sick or healthy, whether clinical suspicion existed for the presence of a vector-borne infectious disease, and geographical variation in exposure to tick vectors and reservoir hosts. In addition, because antibodies to *A. phagocytophilum* cross-react with other *Anaplasma* species, such as *A. platys*, seropositivity may not necessarily reflect previous exposure to *A. phagocytophilum*. For example, a recent study examining 233 dogs from northern Arizona showed moderate agreement between positive ELISA serology and polymerase chain reaction (PCR) positivity to *A. platys*, whereas no dog tested PCR positive for *A. phagocytophilum*.[70] Reported seroprevalences in dogs from regions of North America and Europe are as high as 55 and 50%, respectively.[20,57] A recent large study that used a commercially available recombinant p44/MSP2 ELISA assay[a] to determine the prevalence of seroreactivity to *A. phagocytophilum* in over 400,000 dogs from the United States also revealed wide variation in seroprevalence, with some counties in the upper midwestern and northeastern United States having seroprevalence of $>40\%$, although the overall seroprevalence in these regions was 6.7 and 5.5%, respectively.[33] In northern California, between 0 and 50% of the dogs in 8 small towns were seropositive for *A. phagocytophilum*, showing wide variation in the extent of exposure even over relatively small geographic areas.[75] Among 996 serum samples collected from Swiss dogs between March 1991 and March 1998, 7.5% were positive for *A. phagocytophilum* antibodies, with seroprevalence significantly higher in the southern part of the Swiss Alps.[67] Although *A. phagocytophilum* has been detected in ticks from China and Russia, no prevalence studies in dogs have been reported from these countries to date.[2,76,77] Although molecular evidence of *A. phagocytophilum* infection in dogs was detected in Venezuela and Thailand using PCR, it was subsequently determined that these dogs were in fact infected with *A. platys*, and false PCR priming had occurred as a result of high organism loads within the blood.[78,79] Evidence of *A. phagocytophilum* exposure and infection in dogs recently was detected in Tunisia,[74] and a bacterium closely related to *A. phagocytophilum* was detected in dogs in South Africa.[80]

Five genetic variants of *A. phagocytophilum* have been identified in dogs, with 1–2 nucleotide differences in the 16S rRNA gene sequences at nucleotide positions 54, 84, 86, and 120.[17] Organisms detected in 2 dogs from Switzerland had 16S rRNA gene sequences that were identical, and these sequences were found to be identical to the 16S rRNA gene sequences found in human granulocytic *Anaplasma* species.[23] DNA sequencing of Swedish canine isolates also showed 100% homology with human isolates.[81] The degree to which genetic variation contributes to altered pathogenicity of different strains of *A. phagocytophilum* currently is poorly understood.

Risk factors for *A. phagocytophilum* infection in dogs include season of the year, coinfection with other tick-borne pathogens, and signalment. In the western United States, infection with *A. phagocytophilum* has been diagnosed most frequently in dogs between April and July, with some infections occurring in October.[17] For the states of Minnesota and Wisconsin, a bimodal seasonal distribution of illness has been reported that reflects the activity of the *I. scapularis* tick, in late spring (May, June) and fall (October, November).[13,20] In Berlin, 17 of 18 cases were reported between the months of April and September, with the remaining case occurring in November.[26] The seasonal distribution of disease most likely reflects periods of peak nymphal and adult tick activities, as well as periods when humans and their dogs are engaged in increased outdoor activities. The proportion of seropositive dogs increased with the age of the dog population in the Swedish study,[66] reflecting an increased likelihood of exposure over time. The median age of clinically affected dogs has been approximately 6–8 years (range, 6 months to 14 years).[13,17,26,82] Golden Retrievers comprised almost half of affected dogs in 1 study, possibly reflecting the popularity of these dogs for outdoor activities,[82] although other studies have reported disease in a variety of different breeds.[13,17,26]

Because of shared arthropod vectors, concurrent exposure to multiple vector ticks, or both, coinfections with *A. phagocytophilum* and other arthropod-borne pathogens may occur and complicate the clinical picture. Conversely, the presence of antibodies to other tick-borne pathogens may represent a risk factor for *A. phagocytophilum* infection. A kennel of Walker Hounds in southeastern North Carolina showed a high degree of coinfection with *Ehrlichia* spp., *Bartonella* spp., *Rickettsia* spp., and *Babesia* spp.[83] Of the 27 dogs screened, 26 were *Ehrlichia* or *Anaplasma* spp. seropositive, 16 *Babesia canis* seropositive, 25 *Bartonella vinsonii* seropositive, 22 *Rickettsia rickettsii* seropositive, and 3 had antibodies that reacted to *A. phagocytophilum*. PCR results from the

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**Table 1.** Prevalence of antibodies reacting to *Anaplasma phagocytophilum*, and the DNA of *A. phagocytophilum*, in blood samples collected from dogs worldwide.

| Location | Number of Dogs | Population | Method | Prevalence (%) | Reference |
|---|---|---|---|---|---|
| Europe | | | | | |
| Germany | 563 | Sick dogs, suspected to have anaplasmosis | IFA serology | 50.1 | Barutzki et al[57] |
| Germany | 111 | Healthy and sick dogs | IFA serology | 43.2 | Jensen et al[58] |
| | | | PCR | 6.3 | |
| Central Italy | 1,232 | Not stated | IFA serology | 8.8 | Ebani et al[59] |
| Italy | 460 | Dogs suspected to have tick-borne illness | PCR | 0 | Solano-Gallego et al[60] |
| Sicily, Italy | 342 | Not stated | IFA serology | 32.8 | Torina et al[61] |
| Sicily, Italy | 344 | Pet dogs, pound dogs, hunting dogs | PCR | 0 | de la Fuente et al[62] |
| Northwest Poland | 192 | Dogs from a region with endemic Lyme borreliosis | PCR | 1.0 | Skotarczak et al[24] |
| Portugal | 55 | Dogs suspected to have tick-borne illness | IFA serology | 55 | Santos et al[63] |
| | | | PCR | 0 | |
| Spain | 466 | Sick and healthy dogs | IFA serology | 11.5 | Solano-Gallego et al[64] |
| Northwest Spain | 479 | Dogs presenting to veterinary clinics | IFA serology | 5 | Amusategui et al[65] |
| Sweden | 611 | Dogs suspected to have sarcoptic mange | IFA serology | 17.7 | Egenvall et al[66] |
| Switzerland | 996 | Sick and healthy dogs | IFA serology | 7.5 | Pusterla et al[67] |
| United Kingdom | 120 | Dogs suspected to have tick-borne illness | PCR | 0.8 | Shaw et al[68] |
| North America | | | | | |
| South Ontario and Quebec, Canada | 53 | Dogs suspected to have tick-borne illness | IFA serology | 0 | Gary et al[69] |
| Northern Arizona (Hopi Reservation), USA | 233 | Pet and stray dogs | ELISA serology | 11.6 | Diniz et al[68] |
| | | | PCR | 0 | |
| Connecticut and New York, USA | 106 | Sick, privately owned dogs | IFA serology, Western immunoblotting | 9.4 | Magnarelli et al[29] |
| Oklahoma, USA | 259 | Dogs suspected to have tick-borne illness | IFA serology | 33 | Rodgers et al[30] |
| Baxter, Minnesota, USA | 731 | Sick and healthy pet dogs | IFA serology | 55.4 | Beall et al[20] |
| | 273 | | PCR | 9.5 | |
| North Carolina and Virginia, USA | 1,845 | Sick dogs presenting to a referral hospital | IFA serology | 1.1 | Suksawat et al[31] |
| Hoopa, Humboldt County, California, USA | 182 | Sick and healthy pet dogs | IFA serology | 40 | Henn et al[19] |
| | | | PCR | 7.6 | |
| California, USA | 1,082 | Clinically healthy dogs | IFA serology | 8.7 | Foley et al[32] |
| Missouri, USA | 88 | Sick dogs and dogs suspected to have ehrlichiosis | PCR | 1.1 | Liddell et al[14] |
| USA | 479,640 | Sick and healthy dogs presenting to veterinary clinics | ELISA serology | 4.8 | Bowman et al[33] |
| South America | | | | | |
| Southeastern Brazil | 198 | Dogs suspected to have tick-borne illness | PCR | 0 | de Paiva Diniz et al[71] |
| Asia | | | | | |
| Israel | 195 | Apparently healthy pet dogs, stray and shelter dogs | IFA serology | 9 | Levi et al[72] |
| Yamaguchi and Okinawa, Japan | 154 | Sick and healthy dogs presenting to a teaching hospital | PCR | 0 | Inokuma et al[73] |
| Africa | | | | | |
| Tunisia | 286 | Healthy and sick pet and kenneled dogs | IFA serology | 25.2 | M'ghirbi et al[74] |

IFA, immunofluorescent antibody; PCR, polymerase chain reaction.

[Correction added after online publication <16 Sept 2009>: Reference details corrected throughout table.]

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27 dogs showed 15 infected with *Ehrlichia canis*, 9 with *Ehrlichia chaffeensis*, 8 with *Ehrlichia ewingii*, 3 with *A. phagocytophilum*, and 9 with *A. platys*. Because *Borrelia burgdorferi* is transmitted by the same Ixodid tick species and maintained in sylvatic cycles with the same rodent reservoirs, evidence of coinfection with *B. burgdorferi* and *A. phagocytophilum* frequently is detected, and the 2 organisms may enhance one another's pathogenicity.[84,85] Across the United States, antibodies to both *B. burgdorferi* and *A. phagocytophilum* were most commonly found in dogs from the Midwest (2.0%), followed by the Northeast (1.4%).[33] In a study of 731 naturally exposed dogs from 1 veterinary practice in Baxter, Minnesota, 29% of dogs had antibodies to *A. phagocytophilum*, 11% had antibodies to *B. burgdorferi*, and 25% of dogs had antibodies to both.[20] Of 89 suspected ill dogs, antibodies to *A. phagocytophilum* were found in 25%, antibodies to *B. burgdorferi* in 9%, and antibodies to both pathogens in 43% of dogs. In a study from northern California, dogs that were seropositive for *A. phagocytophilum* were 18.2 times more likely to be seropositive for *B. vinsonii* subspecies *berkhoffii* than dogs that were *Anaplasma* seronegative.[75]

## Pathogenesis

*A. phagocytophilum* is transmitted transtadially within the tick and the tick must attach for 36–48 hours for transmission to occur.[86,87] The organism may alternate between 2 forms, small dense-cored cells, which bind to host cellular targets, and reticulate cells, which multiply intracellularly and then mature into dense-cored cells that are released upon cell lysis.[88–90] Studies using human neutrophils have shown that the bacterium attaches to sialylated ligands on the surface of the neutrophil, such as P-selectin glycoprotein ligand-1 (PSGL-1) and the tetrasaccharide sialyl Lewis X, and enters host neutrophils through caveolae-mediated endocytosis (Fig 3).[91–93] Caveolae are specialized lipid rafts enriched in proteins and lipids, which perform a number of signaling functions. Use of this port of entry allows the organism to bypass phagolysosomal pathways.[93] Recent work sug-

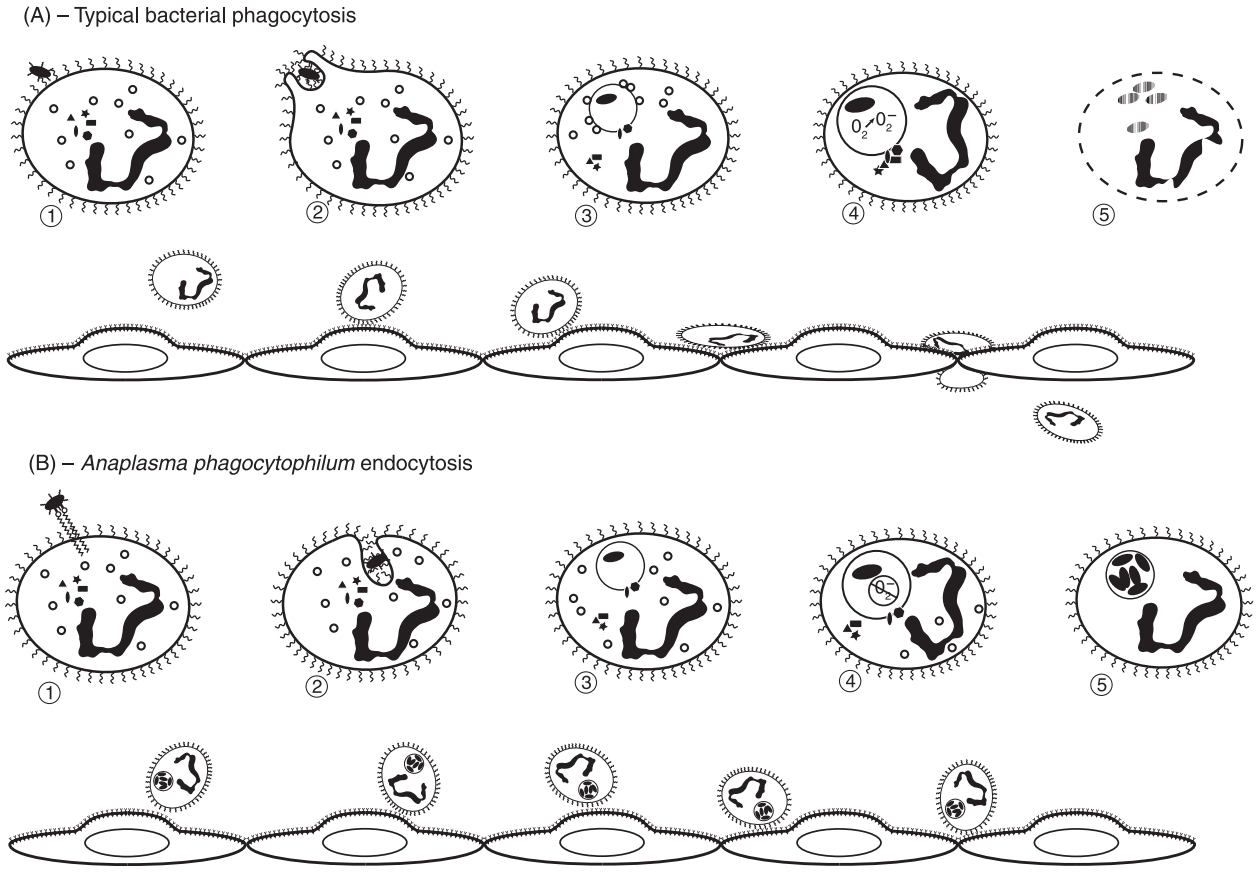



**Fig. 3.** (**A**) Typical neutrophil response to a bacterial pathogen. (1) Bacteria bind immunoglobulin or LPS-type receptors on the neutrophil surface. (2) Bacteria enter through phagocytosis. (3) Lysosomes fuse with phagosome. (4) Bacteria are killed by activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system and generation of superoxide anions. (5) PMNs undergo apoptotic cell death and inflammation resolves. (6) Neutrophils interact with endothelial cells through rolling, attachment, and diapedesis. (**B**). Impaired neutrophil response to *Anaplasma phagocytophilum*. (1) *A. phagocytophilum* binds neutrophils using fucosylated ligands on the neutrophil surface. (2) The organism enters through receptor-mediated caveolae endocytosis. (3) Endosomes modified to prevent lysosome fusion. (4) *A. phagocytophilum* inhibits production of superoxide anion, as well as formation of NADPH complex. (5) *A. phagocytophilum* delays neutrophil apoptosis by delaying expression of apoptosis-associated genes. (6) *A. phagocytophilum* infection results in decreased neutrophil adherence to endothelial cells, which may help to maintain an intravascular presence of the organism so it is more accessible to feeding ticks.

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gests that *A. phagocytophilum* possesses a bacterial 2-component system utilizing the signal transducer cyclic di-GMP that is essential for infection of, and adaptation to, the host cell environment.[90] In order to ensure its intracellular survival and replication, *A. phagocytophilum* actively dysregulates key neutrophil bactericidal functions. Of major importance, the bacterium is capable of inhibiting neutrophil superoxide production, by blocking the assembly of the multicomponent NADPH oxidase system on the inclusion membrane, and detoxifying superoxide anion.[93,94] The bacterial protein AnkA apparently enters the nucleus and interacts with gene regulatory regions, downregulating expression of host defense genes including $gp91^{phox}$, a component of NADPH oxidase.[95] *A. phagocytophilum* has been shown to decrease neutrophil motility and phagocytosis,[96] and decreases endothelial adherence and transmigration of neutrophils, which normally occurs through selectin-mediated rolling, cellular activation, and binding via surface integrin molecules. In contrast, research evaluating neutrophil function in dogs experimentally infected with a Swedish isolate of *A. phagocytophilum* showed normal phagocytosis with enhancement of the respiratory burst.[97] The decreased neutrophil adherence to endothelial cells appears to result from loss of PSGL-1 and L-selectin ligands by infected neutrophils, at a time when $\beta_2$-integrin, immunoglobulin superfamily adhesion molecule, and intercellular adhesion molecule are upregulated.[98] The latter may promote pathogen survival in peripheral blood.

Typically, neutrophils circulate for 10–12 hours before they enter tissues and undergo death through apoptosis, and as such make an unfavorable home for most pathogens. Remarkably, *A. phagocytophilum* is able to delay neutrophil apoptosis in vitro and in vivo, allowing it to survive and form morulae within a normally short-lived, terminally differentiated leukocyte.[93,94,99–101]

Although the mechanism for cell-to-cell bacterial transfer is not known, the organism induces interleukin-8 (IL-8) release in infected humans, as well as increasing the surface expression of CXCR2, an IL-8 receptor that may lead to further recruitment of susceptible neutrophils for infection by the pathogen and subsequent uptake by uninfected ticks.[102,103] In addition, *A. phagocytophilum* can infect human CD34+ bone marrow cells,[104] endothelial cells,[105] and cells of the megakaryocyte lineage.[106] These cells may also serve as potential cell reservoirs for cell-to-cell transfer of infection to peripheral blood neutrophils. Recently *A. phagocytophilum* has been transformed in the laboratory such that it is capable of expressing fluorescent proteins, permitting direct visualization of the organism within cells with fluorescence microscopy (Fig 2B).[107] This tool should facilitate further understanding of the tissue distribution, cellular binding, entry, and intracellular replication of *A. phagocytophilum* in vivo.

*A. phagocytophilum* infection is associated most commonly with the development of mild to moderate thrombocytopenia, although other cytopenias also may occur, including neutropenia, lymphopenia, and mild anemia. The mechanism of these hematologic abnormalities remains unclear. *A. phagocytophilum* can enter cells of the megakaryocyte lineage, which also express PSGL-1, although such infection does not appear to impair the ability of megakaryocytes to produce platelets.[106] Antiplatelet antibodies have been detected in serum from humans[108] and dogs[26] with granulocytic anaplasmosis, and immune-mediated mechanisms may contribute to thrombocytopenia. However, thrombocytopenia occurs in acute disease, before antibodies are detected, and in mice with no B or T cells (severe combined immune deficiency), suggesting other mechanisms may be important.[109]

Impaired neutrophil function and leukopenia as a result of *A. phagocytophilum* infection may predispose to the development of secondary opportunistic infections. These have been best documented in sheep and cattle with tick-borne fever in Europe. *A. phagocytophilum* may predispose lambs to tick pyemia, which is characterized by lameness and paralysis caused by *Staphylococcus aureus*,[110] *Pasteurella* spp.,[111,112] and *Listeria monocytogenes*.[113] Opportunistic infections also have been documented and suggested as a potential cause of mortality in humans and dogs with granulocytic anaplasmosis,[49,94,114] but are less well described than those in ruminants. Impaired neutrophil function in humans infected with *A. phagocytophilum* may impact the outcome of infection with *B. burgdorferi*.[85]

Because granulocytic anaplasmosis is largely a self-limiting infection in dogs, a paucity of information is available regarding the pathology of *A. phagocytophilum* infection. Tissue injury appears to result from the host inflammatory response, rather than the bacterial infection itself.[115] Information regarding the pathology of human infection also is limited, although splenic lymphoid depletion, macrophage aggregates and apoptosis within the liver, paracortical lymphoid hyperplasia, and hemophagocytic cells within tissues of the reticuloendothelial system have been described.[114] One report described the death of a horse after experimental infection with a Swedish isolate of *A. phagocytophilum*.[116] At necropsy, widespread petechial, ecchymotic, and intrathoracic hemorrhages were documented. Microscopic pathology consisted of necrotizing vasculitis and hyaline thrombosis, with perivascular mononuclear cell infiltration. Within the liver, there were scattered aggregates of inflammatory cells within the hepatic sinusoids and evidence of hepatocyte apoptosis. The vascular changes in this case were suggestive of disseminated intravascular coagulation, which also has been reported in humans with granulocytic anaplasmosis.[49] It was hypothesized that tissue damage might result from substances released by infected neutrophils, or through induction of monocyte tissue factor procoagulant activity.[117] Macrophage activation during human granulocytic anaplasmosis is evidenced by high serum ferritin, IL-10, IL-12 p70, and interferon $\gamma$ (IFN-$\gamma$) concentrations, as well as evidence of hemophagocytosis in infected individuals.[115]

The immune response to *A. phagocytophilum* infection is not fully characterized. IFN-$\gamma$ production is thought to play an important role in the initial control of *A. phagocytophilum* infection,[118,119] although it may also

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contribute to the inflammatory process associated with the disease.[120] The production of IFN-γ may be triggered by IL-12 and IL-18 production.[121,122] Natural killer T-lymphocytes may be the primary source of IFN-γ, with dendritic cells producing IL-12 and IL-18. In a mouse model of infection, ultimate bacterial clearance appeared to be dependent on CD4+ T cells, and did not depend on major Th1 cytokines such as IL-12 and IFN-γ.[119] Although T-cell-mediated immunity generally is considered to be the most important arm of the immune system for clearance of intracellular pathogens, data generated from mouse models suggest a substantial role for humoral immunity in clearance of the ehrlichiae, including *A. phagocytophilum*.[123,124] Antibodies may develop after exposure to bacteria during extracellular phases of infection. Antibodies may access intracellular components containing ehrlichiae or enhance phagocytic activity.[123] Both B and T cells are needed to clear infection, because mice with severe combined immunodeficiency, which lack both B and T cells, remain persistently infected. In contrast, mice with isolated T-cell deficiencies can clear infection.[119] In lambs, *A. phagocytophilum* is capable of evading the host immune response through differential expression of MSP2, an outer surface protein involved in immune recognition, as has been documented for *A. marginale* infections in cattle.[125,126] Additional research is required to document whether persistence occurs through similar mechanisms in other host species.

## Clinical Disease in Dogs

Most dogs naturally infected with *A. phagocytophilum* probably remain healthy, as indicated by widespread serological evidence of exposure in endemic areas in the absence of a history of clinical illness.[20,32] To date, there are no case reports documenting fatalities in dogs. Four large case series have been reported describing the clinical features of natural infection in dogs examined in Germany (18),[26] Scandinavia (14),[82] Washington state (8),[17] and the upper Midwest of the United States (17),[13] together with several reports including 3 or fewer dogs from the United States, Italy, British Columbia, Switzerland, Austria, and the United Kingdom.[11,15,16,22,23,25,27,28,56] Other reports describing illness in dogs associated with morulae within granulocytes have not distinguished between *E. ewingii* and *A. phagocytophilum*.[127–131] Some of these were from areas within the United States where *A. phagocytophilum* infection is not endemic. One report from the southeastern United States described molecular detection of *E. ewingii* in 2 of 6 dogs with granulocytic morulae, and detection of an organism resembling *E. canis* in another, with PCR assays for *A. phagocytophilum* being negative in the 3 dogs tested.[130]

The most common clinical signs in dogs infected with *A. phagocytophilum* that develop illness are lethargy and fever, which occur after an incubation period of 1–2 weeks. Lethargy has been reported in almost all dogs affected.[13,17,26,82] Three of the 4 larger case series reported fever in approximately 90% of affected dogs.[13,17,82] The remaining case series reported fever in 66% of affected dogs.[26] Reported rectal temperatures in febrile dogs have ranged in magnitude from 102.6 to 106.5°F (39.2–41.4°C). Inappetence or anorexia has been reported in 47–88% of dogs.[13,17,26] Musculoskeletal signs, such as reluctance to move and lameness, also have been commonly reported. Lameness was reported in 1 of 17 dogs from the upper Midwest,[13] 5 of 8 dogs from Washington state,[17] and 2 of 18 dogs from Europe.[24] In some dogs, lameness may result from a neutrophilic polyarthritis.[24,132]

Infrequent coughing may be noted, which is typically soft and nonproductive (J.E. Sykes, unpublished data)[17,56] as well as scleral injection (J.E. Sykes, unpublished data). The presence of a cough was associated with interstitial infiltrates on thoracic radiographs in 1 case report, with a focal area of alveolar infiltrates, and large numbers of neutrophils containing morulae were recovered from a tracheal wash.[56]

Less commonly, polydipsia, pale mucous membranes, gastrointestinal signs including vomiting and diarrhea, and hemorrhage, manifested as mucosal petechiae, melena, or epistaxis, have been reported.[13,17,26] Protracted vomiting, hypersalivation, and fever was the presenting complaint in a dog that recently presented to our hospital that had morulae within granulocytes and PCR confirmation of infection. Splenomegaly and mild lymphadenopathy, detected during physical examination or after radiographic or ultrasonographic imaging, may also be present.[13,26] In canine and murine models of infection, splenomegaly and lymphadenopathy are because of reactive lymphoid hyperplasia and, in the spleen, concurrent extramedullary hematopoiesis.[133,134]

Neurologic manifestations have been uncommonly described in people with human granulocytic anaplasmosis, and the organism has been detected in cerebrospinal fluid.[135] Neurologic signs consisting of seizures and proprioceptive deficits were reported in 2 of 17 dogs from the upper midwest with granulocytic anaplasmosis, respectively, but the dog with seizures had a history of idiopathic epilepsy.[13] An association between neurological signs and infection in dogs was not apparent in 1 retrospective study of 248 dogs with disorders of the nervous system.[136] A granulocytic morula was detected using cytology in the CSF of a dog with meningitis from California. The reciprocal serum antibody titers in this dog were highest for *E. canis* (40,960), followed by *R. rickettsii* (5,120) and *A. phagocytophilum* (40).[129] Further molecular studies were not carried out, so it was possible that this organism was *E. ewingii*.

Infection with *A. phagocytophilum* appears to be self-limiting in dogs, and dogs with chronic disease have not been described. The extent to which *A. phagocytophilum* can persist in tissues and contribute to chronic disease manifestations in human and canine patients is the subject of ongoing investigations. In 1 report, treatment of dogs that had been experimentally infected with *A. phagocytophilum* with prednisolone up to 6 months after infection was associated with development of positive PCR results for the organism, and in some dogs, reappearance of morulae on blood smears and thrombocytopenia.[137] In another report, persistent infection was

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thought to occur in dogs despite treatment with doxycycline, because dogs developed positive PCR results after treatment with prednisolone 5 weeks after doxycycline therapy.[b] However, it is unknown whether viable organisms were present as determined using culture or animal inoculation studies.

The most consistent laboratory abnormality is thrombocytopenia, which occurs in approximately 90% of dogs.[13,17,26] The platelet count in thrombocytopenic dogs has been reported to range from 5,000 to 164,000 platelets/μL.[13,17,26,82] The bone marrow of infected dogs contains increased absolute numbers of megakaryocytes and immature megakaryocytes, suggesting that thrombocytopenia may occur due to platelet destruction.[138] The majority of affected dogs have had lymphopenia, with lymphocytosis being reported rarely.[13,17,26] Anemia was reported in 3/8 dogs from Washington and 2/15 dogs from the upper Midwest, and was typically mild and nonregenerative. In contrast, 11 of 18 dogs from Germany were anemic, with hematocrits that ranged from 19 to 39% (median, 32%).[26] The anemia was found to be regenerative in 3 of 8 of these anemic dogs. Both neutrophilia and neutropenia have been reported, although the majority of affected dogs have had neutrophil counts in the lower half of the reference range.[13,17,82] Monocytopenia has been reported in approximately one-third of infected dogs from the United States,[13,17] whereas several dogs from Germany had monocytosis.[26] Mild hypoalbuminemia, hyperglobulinemia, and a mild increase in hepatic enzyme activity (especially alkaline phosphatase) are most commonly observed on serum biochemistry bio-profile.[13,17,22,82] High alkaline phosphatase activity was reported in 88% of affected dogs from North America, and 61% of dogs in the German study. Hyperbilirubinemia was present in 5 of 22 dogs with granulocytic anaplasmosis in Europe[26] but has not been reported in dogs from North America. The differences in clinical presentation that have been reported from Europe and North America may be a reflection of strain differences in *A. phagocytophilum*, as has been reported in cattle and sheep.[39,139]

## Diagnosis

The diagnostic criteria for confirmed human granulocytic anaplasmosis are clinical signs and laboratory findings suggestive of granulocytic anaplasmosis together with (1) detection of morulae within neutrophils combined with a single positive reciprocal antibody titer to *A. phagocytophilum* of $\geq$80; (2) a 4-fold increase or decrease in the antibody titer within 4 weeks; (3) a positive PCR test result using specific *A. phagocytophilum* primers; or (4) isolation of *A. phagocytophilum* from blood.[49] These criteria also could be applied to dogs, although isolation is not used routinely for diagnosis.

Morulae may be seen within neutrophils during cytologic examination of Romanowsky-stained peripheral blood smears. Although the finding of morulae within neutrophils in peripheral blood from a dog in an endemic area is highly suggestive of infection with *A. phagocytophilum*, the morulae cannot be distinguished from those of *Ehrlichia* spp. such as *E. ewingii*, and serology or PCR are needed to confirm that the organism is *A. phagocytophilum*. Morulae were detected within neutrophils from 36, 56, 67, and 100% of dogs in each of the 4 larger case series reported.[13,17,26,82] The percentage of neutrophils containing morulae during acute infection has ranged from 7 to 32%.[13,17,82] In experimentally infected dogs, morulae appear as early as 4 days after inoculation, and persist for 4–8 days.[133]

Several conventional and real-time PCR assays have been developed for detection of *A. phagocytophilum* DNA in peripheral blood, buffy coat, bone marrow, or splenic tissue specimens. Some of these assays amplify DNA from other rickettsial species, and sequencing of the PCR product is required to determine whether *A. phagocytophilum* is the infecting species. Other assays only amplify the DNA of *A. phagocytophilum*. The targets of the majority of the assays used have been either the 16S rRNA gene or the outer surface protein gene *msp2* (p44). Assays based on the *msp2* gene are usually specific for *A. phagocytophilum*, whereas assays based on the 16S rRNA gene may detect other *Anaplasma* species, and even other bacteria such as *Bartonella henselae*.[137] Other reported assays have targeted the *msp4*, *groEL*, *rrs*, *epank1*, or *ankA* genes of *A. phagocytophilum*.[140–143] One real-time assay was designed to amplify DNA from the *msp2* gene over a wide variety of strains isolated from varying locations.[18] *A. phagocytophilum* DNA was amplified in 1 study using PCR from 3% of healthy dogs and 37% of clinically ill dogs.[20] After treatment, all dogs in 1 study became PCR negative,[26] supporting an association between positive PCR results and clinical illness. In experimentally infected dogs, the results of PCR on whole blood were positive for 6–8 days before and 3 days after morulae appeared on blood smears.[133,137]

Diagnosis also can be accomplished using paired, acute, and convalescent serology. Most veterinary laboratories perform serologic testing using immunofluorescent antibody (IFA) techniques. IgG class antibodies are 1st detectable approximately 8 days after initial exposure, 2–5 days after the appearance of morulae. As a result, during acute illness, antibodies may be inapparent, so PCR may be more useful for diagnosis of acute infection when morulae are not present. Because positive titers may reflect previous exposure, demonstration of a 4-fold rise in titer is required. Antibody titers may persist for several months[21,137] with 1 study showing seropositivity as long as 12 months after resolution of acute illness.[17] In humans, persistent antibody titers lasting as long as 3 years have been described.[49] A polyvalent ELISA using a recombinant p44 antigen has been developed that is suitable for testing serum from both dogs and horses.[144] A point-of-care lateral flow ELISA device,[a] which also uses a recombinant Msp2/p44 protein, is also available for the detection of antibodies to *A. phagocytophilum* in dog serum. Positive test results using this assay do not imply that *A. phagocytophilum* is the cause of a dog's illness, and as with IFA testing, negative results may occur in dogs presenting with acute illness because

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of the lag in antibody production relative to the onset of clinical signs.

Serologic cross-reactivity among different *Anaplasma* species occurs. Using monoclonal antibodies directed at the highly conserved major surface protein 5 (Msp5), 100% serologic cross-reactivity was documented between *A. phagocytophilum* and *A. marginale* by an indirect ELISA assay, but no cross-reactivity was documented using a competitive ELISA.[145] Dogs infected with *A. platys* also test positive using serologic assays for *A. phagocytophilum*, including the widely used recombinant Msp2 assay.[33] Serological cross-reactivity between *A. phagocytophilum* and *E. canis* also has been reported, but appears to be uncommon and minor.[17,56,146] Dogs presenting to the authors' teaching hospital that have antibodies to *A. phagocytophilum* generally lack antibodies that react to *E. canis* using IFA testing.

In a comparative study, blood samples taken from dogs suspected of being infected with *A. phagocytophilum* were tested by IFA, 16S rRNA gene-based PCR, and by blood smear examination.[147] A total of 73% of animals that were positive using PCR and cytologic examination for inclusions also had positive antibody titers, whereas 34 of 36 samples (94%) that were positive using cytologic examination of blood smears were also PCR positive. Thus, use of multiple diagnostic modalities may be needed to confirm the diagnosis of granulocytic anaplasmosis in some cases.

*A. phagocytophilum* isolates from dogs and humans can be readily cultivated in human promyelocytic leukemia cell lines (HL-60) and tick embryo cell lines. Although culture may be the most sensitive diagnostic modality for detection of acute infection in human patients,[148] this method is not routinely used in dogs for diagnostic purposes.

## Treatment and Prevention

The treatment of choice for granulocytic anaplasmosis in dogs is doxycycline (5 mg/kg PO q12h for 2 weeks). Most dogs show clinical improvement within 24–48 hours of initial antibiotic treatment, with 1 study documenting that 2 of 8 infected dogs required up to 6 days of tetracycline treatment for full resolution of clinical signs.[17] Infection may be prevented by keeping ticks from attaching to the host, and prompt removal of ticks. Ticks should be removed by gently grasping the tick close to the skin with tweezers, forceps, or a commercially available tick removal device and retraction using constant pressure. Combinations of imidacloprid and permethrin[c] and fipronil and (S)-methoprene[d] have been shown to prevent the transmission of *A. phagocytophilum* to dogs from infected ticks for up to 25 days after initial treatment.[149] Nevertheless, infections have been documented in dogs apparently receiving monthly tick preventatives.[26]

Reinfection has not been reported in dogs. In the human literature, reinfection has been documented in 1 patient.[150] Horses have been shown to resist reinfection after recovery from initial infection with *A. phagocytophilum*.[151] Natural infection may confer long-term protection against development of new disease.

## Human Granulocytic Anaplasmosis and Public Health Significance

Human granulocytic anaplasmosis is a nonspecific febrile illness of varying severity that closely resembles the disease in dogs, and has been described as an "influenza-like illness after a tick bite."[152] Men are affected slightly more frequently than women,[153] and up to 75% of affected humans report a history of a tick bite.[49] As in dogs, coinfections with *B. burgdorferi* can occur. The overall seroprevalence in individuals bitten by ticks in the United States is 8.9–36%,[49] with disease incidence being highest in humans from the upper midwestern and northeastern United States. In Europe, the disease has been most commonly reported in humans from Sweden and Slovenia, where it was first reported in 1997.[154,155] Morulae may be observed less frequently in humans with granulocytic anaplasmosis in Europe and the disease may be somewhat milder than the North American counterpart.[156]

The most common clinical signs reported in human patients are myalgia, often severe headache, malaise, and shaking chills, but anorexia, nausea, arthralgias, and coughing also may occur.[49,152,153] The disease typically is mild and self-limiting. In the absence of adequate antimicrobial therapy, active clinical illness beyond 2 months has not been reported.[49] Occasionally, more severe disease may occur, with up to 17% of affected humans requiring admission to an intensive care unit in 1 study.[152] Death occurs in $\leq$1% of clinically affected humans, usually as a result of complications such as a septic or toxic shock-like syndrome, respiratory insufficiency, opportunistic fungal or viral infections, rhabdomyolysis, acute renal failure, hemorrhage, and neurologic diseases.[49] Severe illness tends to occur in humans of advanced age or in those with concurrent immunosuppressive illness or drug therapy. Laboratory testing of peripheral blood typically reveals normal or slightly decreased white blood cell and platelet counts, sometimes with a neutrophilic left shift, and mild to moderate increases in hepatic transaminase activities.[49,152,153] In the United States, the disease is reportable to the Centers for Disease Control and Prevention. Dogs act as sentinels for human exposure, and have the potential to be a source of infection by bringing infected ticks in to contact with humans.

## Footnotes

[a] 4Dx SNAP test, IDEXX Corporation, Westbrook, ME

[b] Alleman A, Chandrashekar M, Beall M, et al. Experimental inoculation of dogs with a human isolate (NY18) of *Anaplasma phagocytophilum* and demonstration of persistent infection following doxycycline therapy. J Vet Intern Med 2006;20:763 (abstract)

[c] K9 Advantix, Bayer, Shawnee Mission, KS

[d] Frontline Plus, Merial, Duluth, GA

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