Ehrlichiosis and Anaplasmosis: Zoonotic Species

Canine Monocytic Ehrlichiosis,
Canine Hemorrhagic Fever,
Tropical Canine Pancytopenia,
Tracker Dog Disease,
Canine Tick Typhus,
Nairobi Bleeding Disorder,
Canine Granulocytic Ehrlichiosis,
Canine Granulocytic Anaplasmosis,
Equine Granulocytic Ehrlichiosis,
Equine Granulocytic Anaplasmosis,
Tick-borne Fever,
Pasture Fever,
Human Monocytic Ehrlichiosis,
Human Granulocytic Anaplasmosis,
Human Granulocytic Ehrlichiosis,
Human Ewingii Ehrlichiosis

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Importance

Ehrlichiosis and anaplasmosis are tick-borne diseases caused by obligate intracellular bacteria in the genera *Ehrlichia* and *Anaplasma*. These organisms are widespread in nature; the reservoir hosts include numerous wild animals, as well as some domesticated species. For many years, *Ehrlichia* and *Anaplasma* species have been known to cause illness in pets and livestock. The consequences of exposure vary from asymptomatic infections to severe, potentially fatal illness. Some organisms have also been recognized as human pathogens since the 1980s and 1990s.

Etiology

Ehrlichiosis and anaplasmosis are caused by members of the genera *Ehrlichia* and *Anaplasma*, respectively. Both genera contain small, pleomorphic, Gram negative, obligate intracellular organisms, and belong to the family Anaplasmataceae, order Rickettsiales. They are classified as α-proteobacteria. A number of *Ehrlichia* and *Anaplasma* species affect animals. A limited number of these organisms have also been identified in people.

Recent changes in taxonomy can make the nomenclature of the Anaplasmataceae and their diseases somewhat confusing. At one time, ehrlichiosis was a group of diseases caused by organisms that mostly replicated in membrane-bound cytoplasmic vacuoles of leukocytes, and belonged to the genus *Ehrlichia*, tribe Ehrlichieae and family Rickettsiaceae. The names of the diseases were often based on the host species, together with type of leukocyte most often infected. For example, *Ehrlichia equi* mainly infected neutrophils and caused illness in horses; thus, the name of the disease was equine granulocytic ehrlichiosis. After 2001, some species of *Ehrlichia* were reclassified into the genera *Anaplasma* or *Neorickettsia*, and all three genera were placed in the family Anaplasmataceae. In addition, *Ehrlichia equi*, together with *E. phagocytophila* (which causes disease in ruminants) and "the agent of human granulocytic ehrlichiosis" became the single species *Anaplasma phagocytophilum.* As a result, the names of some diseases also changed. For instance, equine granulocytic ehrlichiosis eventually became known as equine granulocytic anaplasmosis. Additional confusion results from the recognition that more than one pathogenic *Ehrlichia* species may infect granulocytes or monocytes in some hosts.

Currently, the genus *Ehrlichia* contains five recognized species: *E. canis*, *E. chaffeensis*, *E. ewingii*, *E. muris* and *E. ruminantium*. *E. canis* causes canine monocytic ehrlichiosis (CME). This organism has been implicated rarely in human illness. *E. chaffeensis* also infects monocytes, causing illness in both dogs and people. In people, this disease is called human monocytic ehrlichiosis (HME). *E. ewingii* infects granulocytes and is zoonotic. The illness is sometimes known as canine granulocytic ehrlichiosis in dogs; however, human ewingii ehrlichiosis (HEE) is now the preferred name for the disease in people, to avoid confusion with the old name for the illness caused by *A. phagocytophilum. E. muris*, which infects monocytes in rodents, might also be zoonotic. *E. ruminantium* (formerly *Cowdria ruminantium*) is the agent of heartwater in ruminants (see the heartwater factsheet for further information). *E. ruminantium* is not thought to be zoonotic, but a report describing several infected people in South Africa suggests that this might need to be reassessed.

The currently recognized species in the genus *Anaplasma* are *A. phagocytophilum, A. platys* (formerly *E. platys*), *A. marginale* (and *A. marginale* subsp. *centrale*), *A. bovis* (formerly *E. bovis*) and *A. ovis. Anaplasma phagocytophilum* infects humans and many species of animals. The disease is known as human granulocytic anaplasmosis (HGA; formerly human granulocytic ehrlichiosis) in people, canine granulocytic anaplasmosis (previously canine granulocytic ehrlichiosis) in dogs, equine granulocytic anaplasmosis (formerly equine granulocytic ehrlichiosis) in horses, and tick-borne fever in ruminants. *A. phagocytophilum* is a very heterogeneous organism, and genetic variants can differ in their virulence for host species. In addition, the isolates maintained in some animal reservoir hosts might not affect people. The remaining *Anaplasma* species are not thought to be zoonotic. *A. platys* infects platelets and causes cyclic canine thrombocytopenia, while *A. marginale*, *A. bovis* and *A. ovis* infect erythrocytes of

domesticated and wild ruminants. A recent study described *A. ovis* nucleic acids in a person with an ehrlichiosis-like illness in Cyprus, but a causative role remains to be confirmed.

Potential new members of *Ehrlichia* and *Anaplasma* continue to be discovered. An organism related to *E. ruminantium,* and known as "the Panola Mountain *Ehrlichia*," infects deer in North America. Little is known about this organism, but it was recently implicated in a case of human ehrlichiosis in the U.S. It can also cause signs of ehrlichiosis in experimentally infected goats. In 2011, an organism closely related to *E. muris* was identified in 4 patients with confirmed ehrlichiosis in Minnesota and Wisconsin. This organism is currently referred to as "ehrlichia species Wisconsin" or the "*E. muris*-like" organism. Detection of a novel *Ehrlichia* species in North American cattle was reported in 2010, and a novel *E. canis*-related organism might infect felids in South America. Additional *Ehrlichia* and *Anaplasma* species, of unknown pathogenicity for humans or animals, have been identified in ticks worldwide.

Some former *Ehrlichia* species have been reclassified into other genera among the Anaplasmataceae. *Neorickettsia risticii* (formerly *Ehrlichia risticii*) causes Potomac horse fever, which is also known as equine monocytic ehrlichiosis. *N. sennetsu* (previously *E. sennetsu*) also infects monocytes and is the agent of sennetsu fever in humans. *N. elokominica* causes elokomin fluke fever in several species of animals, and *N. helminthoeca* causes salmon poisoning disease in canids. The *Neorickettsia* species, whose life cycles are now known to involve trematodes rather than ticks, will not be discussed further.

Geographic Distribution

E. canis and *A. phagocytophilum* occur worldwide, although their distribution within an area varies with the presence and density of their tick vectors. Within the U.S., infections caused by *A. phagocytophilum* are mainly reported in the Upper Midwest and northeastern and western states.

E. chaffeensis was originally described from North America, but it was recently detected in parts of South America, Asia and Africa. It is possible that some of these reports involve other closely-related organisms. Within the U.S., *E. chaffeensis* infections occur mainly in the southeastern, south-central and mid-Atlantic states, where its major tick vector (*Amblyomma americanum*) is endemic.

E. ewingii is also transmitted by *Am. americanum* in North America, and it has been found in deer, other animals and ticks throughout this tick's range. Only a few human cases have been documented, mainly in Tennessee, Missouri and Oklahoma. *E. ewingii* was recently detected in South America and Cameroon, Africa.

E. muris has been found in *I. persulcatus* complex ticks from Eastern Europe to Japan, and was linked to human illness in Russia. A closely related organism was recently described in human patients in North America.

In some cases, disease syndromes are not reported from an organism's entire geographic range. *Anaplasma phagocytophilum* seems to be especially heterogeneous. Although this organism affects humans, horses, dogs and cats in both Eastern and Western Hemispheres, the variants found in the Americas do not seem to cause illness in ruminants.

Transmission

Ehrlichia and *Anaplasma* are transmitted by ticks in the family Ixodidae. These organisms are usually maintained in cycles between ticks and wild or domesticated animal reservoir hosts, which can sometimes remain infected for long periods.

Rhipicephalus sanguineus, the brown dog tick, is the primary vector for *Ehrlichia canis*. *E. canis* can also be transmitted experimentally by *Dermacentor variabilis*, the American dog tick. Other secondary vectors, such as *Amblyomma cajennense*, have been suggested. *Am. americanum* (the Lone Star tick) is the most important vector for both *E. chaffeensis* and *E. ewingii* in North America. Secondary vectors such as *D. variabilis* and *R. sanguineus* might have a minor role in transmission to humans and domesticated animals. Outside North America, *E. chaffeensis* has been found in ticks in the genera *Amblyomma*, *Haemaphysalis, Dermacentor* and *Ixodes* in Asia, in *R. sanguineus* in Cameroon, and in *Am. parvum* in Argentina. *E. muris* can be transmitted by *Haemaphysalis flava* and *Ixodes persulcatus* complex ticks. *Anaplasma phagocytophilum* is transmitted by *Ixodes* species. The major vectors in North America are *Ixodes scapularis* (the black-legged tick) and *I. pacificus* (the Western black-legged tick or Pacific tick). *I. ricinus* transmits *A. phagocytophilum* in Europe, and *I. persulcatus* is the major vector in Asia. This organism can also be found in other tick vectors, such as *I. trianguliceps* in the U.K. or *I. spinipalpis* in the U.S.; however, they do not seem to be important in transmitting it to people or domesticated animals. Genetic variants of *A. phagocytophilum* might be adapted to different reservoir hosts and/or tick species and maintained in distinct cycles.

Transstadial transmission is thought to be important in the life cycles of *Ehrlichia* and *Anaplasma* spp. It has been experimentally demonstrated for *E. canis* in *R. sanguineus,* and *E. chaffeensis* and *E. ewingii* in *Am. americanum*. Transovarial transmission has never been shown and is not thought to occur (although it remains possible that tick eggs are infected at a very low frequency).

Anaplasma and *Ehrlichia* may occasionally be transmitted by other routes, especially in medical procedures that transfer blood or bone marrow. There are a few reports of human *A. phagocytophilum* infections

acquired in blood transfusions, and *E. chaffeensis* infections were apparently transmitted in solid organ transplants. Some *Ehrlichia* spp. can remain viable for more than a week in preserved, refrigerated whole blood. Transmission on contaminated needles and mechanical transmission by biting insects are also theoretically possible. Three human infections with *A. phagocytophilum* might have acquired from deer blood, while cleaning deer carcasses. However, tick bites could not be ruled out, and there is also some question about the zoonotic potential of the organism carried in deer. Possible nosocomial and person-to-person transmission of *A. phagocytophilum* was reported in China, among relatives and healthcare workers who had contact with a patient with extensive hemorrhages. The organism was thought to have been transmitted by close, direct contact with blood and respiratory secretions. Additional studies are needed to confirm whether person-to-person transmission is possible in blood or other body secretions.

Perinatal transmission of *A. phagocytophilum* has been documented in at least two people. The neonates were probably infected transplacentally or during delivery. Infection in breast milk could not be ruled out in one case. Transplacental transmission of *A. phagocytophilum* has been demonstrated in experimentally infected cattle. This organism was also reported in a retained, mummified canine fetus, but there was no evidence that any of the surviving puppies from the litter were infected.

Disinfection

There appears to be little or no research on the disinfectant susceptibility of these obligate intracellular pathogens.

Infections in Animals

Species Affected

Ehrlichia canis

E. canis can cause illness in dogs and other canids, and these animals are thought to be the reservoir hosts. Evidence of infection with this or a similar organism has also been reported in cats and captive wild felids. An *E. canis*-like organism in South American felids might be a novel species.

Ehrlichia chaffeensis

White-tailed deer (*Odocoileus virginianus*) are probably the major reservoir hosts for *E. chaffeensis* in North America. This organism has also been detected by PCR in other cervids, including spotted deer (*Cervus nippon*) in Korea and Japan, and Brazilian marsh deer (*Blastocerus dichotomus*) in South America. Other wild and domesticated animals can also be infected. Antibodies to *E. chaffeensis* have been reported in raccoons (*Procyon lotor*), Virginia opossums (*Didelphis virginiana*), rabbits and foxes. Raccoons and red foxes (*Vulpes vulpes*) have been

infected experimentally. Nucleic acids of *E. chaffeensis* were found in coyotes (*Canis latrans*) and wild lemurs in the U.S. Some surveys in North America suggest that antibodies are uncommon or absent in wild rodents; however, PCR evidence of an *E. chaffeensis*-like organism was reported from rodents in China and Korea. *E. chaffeensis* DNA was recently detected in a hawk during a survey of carnivorous birds in South America. Whether any of these animals can act as reservoir hosts is uncertain.

Clinical cases have been documented in dogs and captive lemurs. Experimentally infected calves can also develop clinical signs, although there are currently no reports of illness in naturally infected cattle. Infections with *E. chaffeensis* have been reported in asymptomatic goats.

Ehrlichia ewingii

Little is known about *E. ewingii*, except that it can cause illness in dogs. Deer and dogs are proposed reservoir hosts.

Ehrlichia muris

E. muris DNA has been found in the blood of small rodents and deer. Rodents are probably the reservoir hosts

Anaplasma phagocytophilum

A. phagocytophilum can infect many species of wild and domesticated animals, and this organism is probably maintained in more than one cycle in nature. Among wildlife, there is molecular and/or serological evidence of infection in deer, moose (*Alces alces*) and other cervids, chamois (*Rupicapra rupicapra*), European bison (*Bison bonasus*), mountain lions (*Puma concolor*), Eurasian lynx (*Lynx lynx*), bears, red foxes, wild boar (*Sus scrofa*), raccoons, opossums, striped skunks (*Mephitis mephitis*), hares (*Lepus capensis*), rodents and birds. *A. phagocytophilum* has also been detected in lizards; however, these isolates seem to differ significantly from those found in mammals.

Various wild rodents and cervids (while-tailed deer) are thought to act as reservoir hosts for *A. phagocytophilum* in North America. Some animals might maintain variants that are not pathogenic for humans or domesticated animals. In particular, some authors question the virulence of white-tailed deer isolates for people. Both livestock and wild ungulates, as well as wild rodents, might be reservoir hosts in Europe.

There are reports of illnesses caused by *A. phagocytophilum* in many species including dogs, a captive timber wolf (*Canis lupus occidentalis*), cats, horses, cattle, sheep, goats, llamas, roe deer, reindeer and non-human primates. Different species can be affected in different geographic regions. North American strains of *A. phagocytophilum* affect dogs, cats, horses and llamas, but do not seem to cause illness in domesticated ruminants. In contrast, the strains found in continental Europe can affect all of these species.

Incubation Period

Dogs infected with *E. canis* usually develop the acute form of canine monocytic ehrlichiosis within 2 to 4 weeks of the tick bite. The chronic form of this illness can occur months or years after the dog was infected.

In ruminants *A. phagocytophilum* causes tick-borne fever 5 to 14 days after a tick bite, and 2 to 6 days after experimental transmission in blood. The incubation period is reported to be 1 to 3 weeks in horses (equine granulocytic anaplasmosis) and 1 to 2 weeks in dogs (canine granulocytic anaplasmosis).

Clinical Signs

Canine monocytic ehrlichiosis (E. canis)

The outcome of infection with *E. canis* can vary from asymptomatic infection to severe, chronic illness. Three stages of canine monocytic ehrlichiosis (CME) – acute, subclinical and chronic – have been described in experimentally infected dogs. These stages may not be easy to distinguish in naturally infected animals. Concurrent infections with other organisms may increase the severity of disease.

Some dogs, but not all, become acutely ill after infection with *E. canis*. They can develop a wide variety of clinical signs. Some dogs present with nonspecific signs such as fever, lethargy, anorexia, lymphadenopathy, splenomegaly and weight loss. Gastrointestinal signs (vomiting, diarrhea), lameness or stiffness, reluctance to walk, edema in the legs or scrotum, coughing, dyspnea and a serous to purulent oculonasal discharge may also be seen. Bleeding disorders, with petechiae, ecchymoses or mild epistaxis, have been reported. Ocular signs can occur in some dogs; reported syndromes include anterior uveitis, chorioretinitis, papilledema, retinal hemorrhages and perivascular infiltrates. Subretinal hemorrhages may lead to retinal detachment and blindness. Neurological signs, caused by meningitis and/or meningeal bleeding, are possible. Severe hepatitis with fever was the primary syndrome in one unusual case. Common laboratory abnormalities include thrombocytopenia and mildly elevated hepatic enzyme levels in serum, sometimes accompanied by leukopenia, leukocytosis or mild anemia. Although fatal cases are possible, the clinical signs can also resolve spontaneously.

Some dogs that recover from acute illness, as well as some dogs that do not develop early clinical signs, remain subclinically infected for months or years. Mild thrombocytopenia is the most common laboratory abnormality in these animals. Subclinically infected dogs may eventually clear the organism, continue to remain infected but asymptomatic, or develop chronic disease. The conditions leading to the development of chronic illness are unknown.

The clinical signs in chronic CME are similar to those in acute cases, but more severe, and vary with the organs affected. They often include fever, chronic weight loss, anorexia, weakness, lethargy, myalgia and edema. Bleeding disorders occur frequently, and may result in pale mucous membranes, petechiae, ecchymoses, epistaxis, hematuria, melena and ocular lesions. Anterior uveitis, retinal abnormalities and blindness have been reported. Pancytopenia, with variably severe combinations of leukopenia, thrombocytopenia and anemia, is common, and may lead to secondary infections. A minority of dogs develop neurological signs (e.g., ataxia, head tilt, nystagmus, meningitis, seizures, cranial nerve deficits, paraparesis or tetraparesis). Other reported complications include renal failure, interstitial pneumonia, liver disease (especially as a complication of bone marrow aplasia) and polymyositis. Reproductive disorders can include prolonged bleeding during estrus, inability to conceive, abortion and neonatal death. Chronic CME can be fatal.

E. chaffeensis infections in dogs

E. chaffeensis infections appear to be clinically indistinguishable from *E. canis* in dogs, but there is little specific information on this disease. In two reports, experimentally infected dogs developed only mild clinical signs. Fever was the only sign in one study, and thrombocytopenia was not detected. In the second report, dogs developed thrombocytopenia and became persistently infected for 2 to 4 months, but remained asymptomatic. More severe illness was reported in the few published cases reports. The clinical signs included hemorrhagic tendencies (e.g., petechiae, ecchymoses, hematuria, epistaxis), vomiting and lymphadenopathy. In one report, one of two dogs with hemorrhagic signs was coinfected with *Babesia gibsoni*. A dog coinfected with *Leptospira grippotyphosa* and *E. chaffeensis* had anterior uveitis and renal failure; the contribution of *E. chaffeensis* to the clinical signs is uncertain. Healthy dogs in endemic areas can also have antibodies to *E. chaffeensis*.

Canine granulocytic ehrlichiosis (E. ewingii)

Fever is the most common clinical sign in dogs infected with *E ewingii*. Other reported signs and laboratory abnormalities include lameness, neutrophilic polyarthritis, peripheral edema, lymphadenopathy, thrombocytopenia, anemia and elevated hepatic enzyme levels in serum. Some dogs may develop neurological signs. Fever (sometimes intermittent), thrombocytopenia and leukopenia were reported in experimentally infected dogs. Antibodies to *E. ewingii* can be found in healthy dogs in endemic areas.

Canine granulocytic anaplasmosis (A. phagocytophilum)

Many healthy dogs have antibodies to *A. phagocytophilum*, suggesting that mild or subclinical infections might be common. In case series and clinical cases from Europe and U.S., lethargy and fever were the most frequently reported clinical signs in canine granulocytic

anaplasmosis (CGA). Inappetence and musculoskeletal signs (lameness, joint pain, reluctance to move) were also common. Lameness is sometimes the result of neutrophilic polyarthritis. Other clinical signs may include infrequent coughing (usually soft and nonproductive), scleral injection, polydipsia, gastrointestinal signs (vomiting, diarrhea), splenomegaly, lymphadenopathy and hemorrhagic signs. Neurological signs seem to be uncommon. Laboratory abnormalities include thrombocytopenia in most dogs, and anemia, lymphopenia, leukopenia or mildly elevated levels of hepatic enzymes in the serum of some dogs. Fatal cases seem to be rare.

A captive timber wolf with CGA developed fever, anorexia, lethargy, thrombocytopenia, lymphopenia and mild anemia, and responded to treatment with doxycycline.

Ehrlichiosis and anaplasmosis in cats

Ehrlichia spp. and *A. phagocytophilum* have been implicated only rarely in feline disease.

Nonspecific signs of fever, lethargy and inappetence are the most commonly reported signs in cats with ehrlichiosis. Some cats also had myalgia, loss of condition, dyspnea, enlarged lymph nodes, polyarthritis, anemia, thrombocytopenia or pancytopenia.

Fever, lethargy and inappetence are also the most common signs in cats infected with *A. phagocytophilum*. Joint pain, lameness, hemorrhagic signs (epistaxis, hematuria, pale mucous membranes), thrombocytopenia and anemia were reported in several cats. Enlarged lymph nodes were seen in some cats, but not others. Some cats also had weight loss, a tender abdomen, conjunctivitis, myalgia, neck rigidity, neurological signs (hyperesthesia, tremors, incoordination), vomiting, pharyngitis, polydipsia, gingivitis or periodontitis. Some clinical signs might have been caused by opportunistic infections associated with *A. phagocytophilum*-mediated immunosuppression.

Equine granulocytic anaplasmosis (A. phagocytophilum)

Equine granulocytic anaplasmosis has an acute onset and varies widely in severity. Young animals typically have mild cases, while adult horses (> 3 years old) tend to develop more severe syndromes. Horses under a year of age may only have a fever. In older animals, common clinical signs include fever, decreased appetite, lethargy, petechiae, icterus, reluctance to move, ataxia and distal limb edema, together with thrombocytopenia and leukopenia. Severe myopathy is possible. Transient ventricular arrhythmias occur on rare occasions, and concurrent infections may be exacerbated. Disseminated intravascular coagulation was reported in one experimentally infected horse. Deaths are uncommon in horses of all ages.

Tick-borne fever (A. phagocytophilum)

Tick-borne fever occurs in domesticated ruminants, particularly sheep and cattle. It has also been documented in goats, deer and reindeer.

In sheep, this disease is mainly seen in young lambs born in tick-infested areas, and in newly introduced older sheep. The primary syndrome is a sudden fever that lasts for 4 to 10 days. Other signs are generally mild and may include inappetence, weight loss or decreased weight gain, listlessness, coughing and increased respiratory and pulse rates. Abortions and stillbirths can occur in pregnant ewes introduced onto infected pastures during the last stages of gestation; abortions are usually seen 2 to 8 days after the onset of the fever. Semen quality can be significantly reduced in rams.

In cattle, tick-borne fever usually occurs in dairy animals recently turned out to pasture. The clinical signs are variable in severity, but may include lethargy, marked anorexia, decreased milk production, coughing, respiratory distress, abortions, stillbirths and reduced semen quality. The two most prominent syndromes are abortions with a drop in milk yield, and respiratory disease.

In uncomplicated cases, animals usually recover within two weeks and deaths are uncommon except in aborting ewes. However, *A. phagocytophilum* increases the animal's susceptibility to other illnesses, which may be serious or fatal. Tick pyemia, caused by *Staphylococcus* spp., is the most frequent and severe complication in young lambs. This illness is characterized by severe lameness, debility and paralysis, and many lambs die. Pasteurellosis and septicemic listeriosis are also common complications.

Ehrlichia chaffeensis in ruminants

Ehrlichiosis due to *E. chaffeensis* has not been reported in naturally infected ruminants. However, some dairy calves that were experimentally infected with this organism developed mild to severe illnesses. In mildly affected animals, the clinical signs included fever, decreased leukocyte numbers and reduced platelet counts. Calves with severe cases had fever and lethargy, followed by progressive muscular weakness in the hind limbs, recumbency and death. Neck twisting was also reported, possibly in response to cervical pain. One calf became recumbent but survived. The authors speculated that ehrlichiosis might not be seen in cattle because subtherapeutic doses of chlortetracycline are used to control other illnesses, such as bovine anaplasmosis, in endemic areas.

No clinical signs, lesions or hematologic abnormalities were reported in deer experimentally infected with *E. chaffeensis*.

Ehrlichiosis in non-human primates

E. chaffeensis caused an outbreak of ehrlichiosis in captive ring-tailed (*Lemur catta*) and red ruffed lemurs (*Varecia variegata rubra*). The clinical signs included fever, anorexia, lethargy, lymphadenopathy, thrombocytopenia and hyperbilirubinemia. Asymptomatic infections were detected in wild lemurs. Rhesus macaques and baboons experimentally infected with *A. phagocytophilum* had fever

and anemia in one study, and fever, lethargy, anemia, thrombocytopenia and neutropenia in another. Severe disease was seen after experimental inoculation of rhesus macaques with *E. canis.*

Communicability

There is a risk of transmitting *A. phagocytophilum,* and possibly *Ehrlichia* spp., between animals in blood transfusions.

Currently, the only published evidence suggesting direct transmission between people or animals consists of two case reports. In China, possible person-to-person transmission of *A. phagocytophilum* was reported in healthcare providers and relatives who were in close, direct contact with blood and respiratory secretions from a hemorrhaging patient. There is also a report of three people in the U.S. who might have become infected with *A. phagocytophilum* while cleaning deer carcasses. Although other sources of exposure (e.g., tick bites) could not be ruled out, the latter case suggests that care should be taken when handling blood and tissues from animals.

Animals can increase human exposure by introducing infected ticks into the home.

Diagnostic Tests

Ehrlichiosis and anaplasmosis can be diagnosed by serology or detection of the organism. Hematologic abnormalities, changes in serum chemistry (e.g., elevated hepatic enzyme levels in serum) and a response to treatment also help support the diagnosis.

Serological tests are often used to diagnose anaplasmosis and ehrlichiosis. Seroconversion or a rising titer is diagnostic. Single titers should be interpreted with caution, as antibodies can often be found in healthy animals. Conversely, antibodies may not be detectable in sick animals, early in the disease. Indirect immunofluorescent antibody tests for *E canis* and *A. phagocytophilum* are widely available at diagnostic laboratories. Because *E. ewingii* has yet not been cultivated *in vitro*, no assays have been developed for this organism; however, sera from dogs infected with *E. ewingii* may react in the *E. canis* IFA. Antibodies to *E canis* and *A. phagocytophilum* can also be detected with ELISA tests. These ELISAs were developed for dogs, but they are not species specific (although they have not necessarily been validated in other animals). Cross-reactions may be seen among bacteria in the genera *Anaplasma*, *Ehrlichia* and *Neorickettsia*. Immunoblotting (Western blotting) can be used to distinguish serological reactions to different species, including *E. ewingii*. This test is mainly used in research.

The detection of intracytoplasmic inclusions (morulae) in leukocytes can support the diagnosis in acutely infected animals. However, this test does not specifically identify *Ehrlichia* and *Anaplasma*. Morulae appear as stippled dark blue or purple inclusions mainly in monocytes (*E. canis, E. chaffeensis* and *E. muris*) or neutrophils (*A.*

phagocytophilum or *E. ewingii*), although they may be found occasionally in other cell types. Wright, Giemsa or Diff-Quik stained peripheral blood, bone marrow smears, lymph node smears or other impression smears from fresh tissues may be used to search for morulae. They are most likely to be found early in the acute illness, and disappear from the blood soon after starting tetracycline treatment. Morulae are rarely detected in chronic CME. The probability of detecting morulae in blood smears also varies with the pathogen and host species. Up to 90% of the granulocytes in ruminants might contain *A. phagocytophilum* morulae during peak bacteremia; however, only 7-32% of the neutrophils in dogs, and up to 30-40% of the granulocytes in horses contain these inclusions. In four case series, *A. phagocytophilum* morulae were detected in blood smears from 36-100% of infected dogs. Inclusions can also be found in significant number of dogs infected with *E. ewingii*. In contrast, *E. canis* and *E. chaffeensis* morulae are uncommon in blood (although the use of buffy coat may be more successful). One estimate suggests that they are found in only 4% of dogs infected with *E. canis.*

PCR assays that detect nucleic acids of *E. canis, E. chaffeensis, E. ewingii* or *A. phagocytophilum* may be available, usually from veterinary schools or research laboratories. Several different assays are used, and they can vary in sensitivity and specificity. Peripheral blood is often tested, but other samples, such as bone marrow or spleen tissue, can also be used. Sequencing of the PCR product may be necessary, as some tests can amplify other organisms. PCR does not always detect very small numbers of organisms, such as *E. canis* in the peripheral blood of subclinically or chronically infected dogs. Blood samples for PCR should be taken before antibiotics are begun, to maximize the chance of finding organisms.

Culture is used mainly in research, and is considered impractical for diagnosing routine clinical cases. It is difficult and time-consuming, and the specialized techniques needed are unavailable at most clinical laboratories. In addition, results may not be available for up to 2–6 weeks. Most *Ehrlichia* and *Anaplasma* species can be isolated in cell cultures. Several cell lines may be employed, but the DH82 canine histiocytic cell line is usually used to isolate *E. chaffeensis*, and human promyelocytic HL-60 cells for *A. phagocytophilum*. Species can be identified by PCR, and by sequencing and analysis of 16S rRNA. Successful *in vitro* cultivation of *E. ewingii* has not yet been reported.

Treatment

Only a limited number of antibiotics are effective for treating ehrlichiosis and granulocytic anaplasmosis. Tetracycline antibiotics, such as oxytetracycline in ruminants and horses, and doxycycline in dogs and cats, are usually the treatment of choice. Rifampin has been used occasionally in dogs, as well as in people. Early treatment is

critical for canine ehrlichiosis caused by *E. canis*; uncomplicated acute cases usually respond promptly, but antibiotics may be less effective in dogs with neurological signs, and treatment of the chronic severe form is difficult. Animals infected with *A. phagocytophilum* usually respond well. Some cases of ehrlichiosis or anaplasmosis require supportive therapy, such as blood or platelet transfusions, or antibiotics for secondary infections.

Some studies document complete clearance of the organisms with doxycycline, while others suggest that they sometimes persist inapparently in animals, including dogs.

Prevention

Tick control is the cornerstone of prevention for ehrlichiosis and anaplasmosis.

Acaricides, including some monthly topical acaricides used for flea and tick control, can decrease the risk of infections in pets. However, no acaricide can entirely eliminate ticks or the risk of illness. Pets that enter tick-infested environments should be inspected frequently, and ticks should be removed promptly with fine-tipped tweezers, forceps, commercial tick removal devices or gloved hands, as for humans. Biological controls and habitat modification (e.g., eliminating brush) can also decrease tick populations. Prophylactic tetracycline antibiotics have been used in dogs in some situations, but some authors consider this to be an impractical method of prevention. In addition, antibiotics can increase the risk of resistance in any bacteria (including non-target organisms) that are exposed. Some authors suggest PCR testing for *A. phagocytophilum* in dogs used as blood donors.

Tick-borne fever is usually controlled by periodic treatment of ruminants with acaricides. One disadvantage of frequent exposure is that ticks may become resistant to these agents. The risk of illness can also be reduced by grazing animals on relatively tick-free pastures. One method to control this disease in lambs is to keep them in tick-free pastures, with their dams, until they are approximately 6-7 weeks old. Occasionally, ruminants that are moved from tick-free environments to infested pastures are treated prophylactically with long-acting tetracyclines. However, this is not a common method of control.

No vaccines are available.

Morbidity and Mortality

Dog and cats

Asymptomatic infections appear to be relatively common in dogs. Antibodies to *A. phagocytophilum* or some species of *Ehrlichia* can be found in up to 50-60% of the dogs in some areas, usually without any evidence of a previous illness. Although cross-reactions can complicate definitive identification in serological surveys, *E ewingii* and *E chaffeensis* are thought to be more common in dogs than *E canis* in some parts of North America. In dogs, anaplasmosis and ehrlichiosis are somewhat seasonal.

Acute cases are more common during warm weather, when tick activity is high and outdoor recreation is more common. However, populations of the tick vector for *E. canis* can become established indoors in houses and kennels, and cases of canine monocytic ehrlichiosis are diagnosed year round. In addition, chronic CME can develop at any time, due to the long and variable incubation period.

Among the organisms known to cause illness in dogs, *E canis* is considered to be the most important agent worldwide, due to the potential severity of the illness and the difficulty in curing chronic cases. German shepherds seem to be particularly susceptible to developing severe CME; however, virulent strains of *E. canis* can cause serious illness in all breeds of dogs. Other organisms can also cause severe anaplasmosis or ehrlichiosis, but overall, infections with *E. chaffeensis* or *A. phagocytophilum* are thought to be milder. However, some organisms that infect dogs are still incompletely understood.

Antibodies to *Ehrlichia* spp. and *A. phagocytophilum* have also been reported among cats in Europe and North and South America, with seroprevalence rates as high as 17% in some locations. Clinical cases seem to be uncommon in this species. It is not known whether these diseases are under-reported, cats are less susceptible to illness, or if they simply remove ticks during self-grooming and thus are infected less often.

Livestock

Equine granulocytic anaplasmosis occurs in both Europe and the Americas. This illness is typically milder in young horses (especially animals under a year of age), but deaths are uncommon at all ages. In some areas, relatively large numbers of horses have antibodies to *A. phagocytophilum*.

Tick-borne fever of ruminants has been reported only from the Eastern Hemisphere. In Europe, this disease usually occurs as a spring and early summer epidemic when dairy cattle are turned out to pasture. In sheep, the illness is seen most often in young lambs born in tick-infested areas, and in older sheep introduced to such areas. Breed-specific differences in susceptibility have been reported in sheep. Tick-borne fever can be a major economic burden in some areas. Although the illness is rarely fatal by itself, secondary infections, especially tick pyemia in lambs, can be serious or fatal. Abortion storms may be seen if pregnant sheep or cattle in the late stages of gestation are introduced to tick-infested pastures. Up to 90% of naive pregnant ewes can be affected. Decreased weight gain in lambs, and reduced milk yield in cattle also cause losses. Although ruminants in endemic areas can develop immunity to *A. phagocytophilum*, it seems to be variable, and may fall quickly if animals are removed from tick-infested areas.

Post Mortem Lesions   ⊡ **Click to view images**

Canine ehrlichiosis and anaplasmosis

The gross lesions are usually nonspecific in acute cases, but typically include enlargement of the spleen. Hemorrhagic lesions in severe canine ehrlichiosis can affect numerous organs including the gastrointestinal tract, heart, bladder, lungs, subcutaneous tissues and eyes. The lymph nodes, particularly the mesenteric nodes, may be enlarged, with red and brown discoloration on cut surface. There may be edema in the legs, as well as ascites and hydropericardium. In chronic CME, splenomegaly and nonspecific lesions may be accompanied by widespread hemorrhages, and microscopically by mononuclear cell infiltration into the perivascular area in multiple organs.

Equine granulocytic anaplasmosis

The characteristic lesions of equine granulocytic anaplasmosis are petechiae, ecchymoses and edema in the subcutaneous tissues and fascia, mainly in the legs. Interstitial pneumonitis has been reported in some animals.

Infections in Humans

Incubation Period

Incubation periods from 5 to 21 days have been reported for ehrlichiosis and anaplasmosis. The U.S. Centers for Disease Control and Prevention (CDC) estimates that symptoms typically appear in 1-2 weeks.

Clinical Signs

In humans, the consequences of infection vary from asymptomatic infections or mild symptoms to a severe, potentially fatal illness. Clinical ehrlichiosis and anaplasmosis have similar symptoms, especially in the early stages; these diseases are all characterized by the acute onset of a nonspecific febrile illness, often (though not always) accompanied by thrombocytopenia, leukopenia and elevated levels of hepatic enzymes in the blood. However, there are some differences in the symptoms and severity of the illnesses.

Human monocytic ehrlichiosis (E. chaffeensis)

Significant numbers of healthy people have antibodies to *E. chaffeensis* in endemic areas, suggesting that unreported asymptomatic or mild infections might be relatively common. The syndromes caused by this organism vary from a mild febrile illness to fulminant disease with multi-organ failure. Fever occurs in almost all patients with documented human monocytic ehrlichiosis (HME), headaches in most, and myalgia and arthralgia in many patients. Less common symptoms include anorexia, coughing, nausea, vomiting, diarrhea and abdominal pain. Gastrointestinal signs are seen more often in children than adults. A skin rash has been reported in up to 66% of pediatric patients, but in less than 30% of adults. The rash is usually nonpruritic, and can be maculopapular, petechial or characterized by diffuse erythroderma. Commonly reported laboratory abnormalities include thrombocytopenia, mild to moderate leukopenia (especially lymphopenia) and elevated serum hepatic enzyme levels. Some patients also have anemia.

Central nervous system (CNS) involvement, including meningitis or meningoencephalitis, is a potential complication in patients with HME. Other reported complications include opportunistic infections, cardiovascular failure, myocarditis, liver dysfunction, acute renal failure, interstitial pneumonia, respiratory distress syndrome, hemorrhages and disseminated intravascular coagulopathy, as well as a multisystemic disease that resembles toxic shock syndrome or septic shock. Complications, severe cases and deaths are more likely to be seen in elderly or immunocompromised patients, or in people with other concurrent illnesses, but fatal cases have been reported even in previously healthy, young patients. The case fatality rate in reported cases of HME is approximately 2-3%.

Human granulocytic anaplasmosis (A. phagocytophilum)

Similarly to HME, there is serological evidence of *A. phagocytophilum* infections in healthy people, and the clinical course in symptomatic cases ranges from mild to severe. Overall, human granulocytic anaplasmosis (HGA) tends to be less severe than HME. Fever, headache and myalgia are the most common signs. Less frequently reported symptoms include nausea, abdominal pain, diarrhea and cough. Rashes occur in less than 10% of patients. CNS involvement is uncommon, although rare cases of meningoencephalitis have been reported. In contrast, peripheral nervous system signs might be more common than in HME. Syndromes that have been described include cranial nerve palsies, brachial plexopathy, demyelinating polyneuropathy and bilateral facial nerve palsy. Neurological signs might result from coinfections with other tick-borne organisms (e.g., *Borrelia burgdorferi*) or opportunistic infections that result from impaired neutrophil function or leukopenia caused by *A. phagocytophilum*. Other reported complications include acute renal failure, acute respiratory distress syndrome, cardiovascular collapse, pancarditis, hemorrhages and a septic or toxic shock-like syndrome. However, complications seem to be less frequent in HGA than HME. Leukopenia, thrombocytopenia and elevated serum levels of hepatic enzymes are the most common laboratory abnormalities. Patients with HGA may recover in 1-2 weeks even without antibiotics; however, treatment is recommended in all symptomatic cases, as some untreated patients can become seriously ill. The case fatality rate is less than 1%, and most deaths are caused by complications from opportunistic infections or other concurrent illnesses.

There have been concerns about the impact of *A. phagocytophilum* on pregnant women, both because the immune system is compromised during pregnancy, and because abortions and stillbirths occur in ruminants infected with this organism. Although little information is available, there is currently no evidence that *A. phagocytophilum* causes reproductive losses or severe sequelae in pregnant women. In one recent case series, no fulminant cases were seen in 6 pregnant women with HGA. Five of the 6 women responded very well to rifampin or doxycycline therapy, and one woman improved clinically without antibiotics and declined treatment. One newborn was infected perinatally, but responded well to treatment. No sequelae were reported in any of the infants, including the infected child, during the first 21 months of life. The report also described 3 similar cases previously reported in the literature. In addition, there is an earlier report of perinatal transmission. That infant (which developed fever and thrombocytopenia) was also treated successfully.

Human ewingii ehrlichiosis (E. ewingii)

Illnesses caused by *E. ewingii* have been reported in only a few patients, and little is known about the clinical signs. Although most documented cases occurred in immunocompromised patients, the symptoms were usually mild. Rash does not seem to be common. Leukopenia, thrombocytopenia and abnormal liver function tests were found in some cases, but not others. Few complications and no deaths have been reported.

Infections with other organisms

Only a few infections with *Ehrlichia canis* have been described in humans. One person with a chronic, asymptomatic infection and six infected people with ehrlichiosis symptoms were reported from Venezuela. In the clinical cases, all patients had a fever, and most had a headache and/or myalgia. Malaise, arthralgia, nausea, vomiting, rash, bone pain, diarrhea or abdominal pain occurred in some patients. Leukopenia was seen in one patient and anemia in another. All of the six patients were young and otherwise healthy, and the *E. canis* strains were identical to those seen in dogs. *E. canis* nucleic acids have also been detected in a small number of stored human serum samples in the U.S.

Infections with an *E. muris*-like organism ("ehrlichia species Wisconsin") in the U.S. were characterized by fever, fatigue and headache in 3 patients, as well as nausea and vomiting in a fourth patient. Laboratory abnormalities included lymphopenia, thrombocytopenia, and in some cases, elevated serum levels of hepatic enzymes. Two of the patients were on immunosuppressive medications for solid organ transplants. The other two were immunocompetent and had relatively mild illnesses. All four patients recovered with doxycycline treatment.

Communicability

A. phagocytophilum has been transmitted directly between people in blood transfusions, and *Ehrlichia* species might also be transmitted by this route. Leukocyte depletion of blood reduces but does not eliminate the risk. Transmission also seems to be possible in solid organ transplants. Perinatal transmission has been reported in two infants.

Nosocomial transmission and possible person-to-person transmission of *A. phagocytophilum* were reported in China. The cases occurred in healthcare workers and relatives in close, direct contact with a severely hemorrhaging patient who also underwent endotracheal intubation. Transmission was thought to have occurred in blood and/or respiratory secretions. The possibility of person-to-person transmission in blood or other body fluids remains to be confirmed.

Diagnostic Tests

The initial, presumptive diagnosis is usually based on the history and clinical signs, together with characteristic changes in platelet and leukocyte numbers and serum chemistry.

Infections with *E. chaffeensis* (HME) or *A. phagocytophilum* (HGA) are confirmed most often by serology. Although antibodies are usually undetectable during the first 7–10 days of illness, these diseases can be diagnosed retrospectively by seroconversion or a 4-fold rise in paired antibody titers. Single positive titers may result from previous exposure. The indirect immunofluorescence assay (IFA) is the most commonly used serological test. Enzyme-linked immunosorbent assays (ELISAs) are also available, but they are qualitative rather than quantitative. There are no serological tests specific for *E. ewingii*; however, there is significant cross-reactivity between this organism and *E. chaffeensis*. Cross-reactions between bacteria in the genera *Anaplasma*, *Ehrlichia* and *Neorickettsia* can complicate definitive identification of some organisms. Some authors also report that early treatment with a tetracycline antibiotic occasionally reduces or eliminates antibody responses to *E. chaffeensis*.

The detection of intracytoplasmic inclusions (morulae) in leukocytes is a quick method that may support the presumptive diagnosis. Morulae appear as stippled dark blue or purple inclusions, and are found mainly in monocytes (*E. chaffeensis*, *E. muris* and *E. canis*) or neutrophils (*A. phagocytophilum* and *E. ewingii*), although they may be detected occasionally in other cell types. Only a small percentage of the cells are infected. Wright, Giemsa or Diff-Quik stained peripheral blood or buffy coat smears may be used to search for morulae, which are most likely to be found during the first week of illness. These structures disappear from the blood within 24–72 hours after starting doxycycline. Morulae are more likely to be found in HGA than HME; they are detected in 25-75% of the clinical cases

caused by *A. phagocytophilum*, but they are usually detected in less than 10% of patients infected with *E. chaffeensis*. Morulae may also be found in the cerebrospinal fluid of patients with HME, but this is rare.

Polymerase chain reaction (PCR) assays on blood or other samples may be the preferred test for definitive diagnosis, early in the disease. Only limited numbers of laboratories may run these assays. PCR is the only test that can identify *E. ewingii* infections. Organisms may also be observed directly in formalin-fixed tissue samples, using immunohistochemistry. This technique can be used on bone marrow biopsies, as well as on various autopsy samples including spleen, lymph node, liver and lung.

Culture is used mainly in research, and is considered impractical for diagnosing routine clinical cases. It is difficult and time-consuming, and the specialized techniques needed are unavailable at most clinical laboratories. In addition, results may not be available for up to 2–6 weeks. Most *Ehrlichia* and *Anaplasma* species can be isolated in cell cultures. Several cell lines may be employed, but the DH82 canine histiocytic cell line is usually used to isolate *E. chaffeensis*, and human promyelocytic HL-60 cells for *A. phagocytophilum*. Species can be identified by PCR, and by sequencing and analysis of 16S rRNA. Successful *in vitro* cultivation of *E. ewingii* has not yet been reported.

Treatment

Ehrlichiosis and anaplasmosis are usually treated with tetracyclines; doxycycline is currently the drug of choice in people. Other antibiotics are occasionally employed, usually in circumstances where there are significant contraindications to the use of tetracyclines. Rifampin has been used successfully in some pregnant women. Early treatment is critical; uncomplicated cases usually respond promptly, but prolonged treatment may be necessary for severe or complicated cases. In suspected cases, antibiotics should be started before diagnostic confirmation is received from the laboratory.

Prevention

Avoidance of tick bites is the most cornerstone of prevention. Protective clothing (e.g., long-sleeved shirts and trousers tucked into socks) and footwear should be used in tick habitats. Ticks may be more visible on light-colored apparel. Clothing can be impregnated with acaricides such as permethrin. Tick repellents such as DEET are also helpful, although it should be kept in mind that they are only effective for a short period against ticks. For example, most tick repellents last less than 2 hours against *Amblyomma* spp. ticks. Clothing should be removed and decontaminated immediately after leaving a tick-infested environment.

People who enter tick habitats should check frequently for ticks and remove them as soon as possible, using fine-tipped tweezers, forceps, commercial tick removal devices or gloved hands. While the minimum attachment time for ticks to transmit *Ehrlichia* and *Anaplasma* is still uncertain, rapid tick removal is likely to reduce the infection risk. Bare hands should not be used to remove ticks, due to the risk of exposure to the tick's fluids or feces; various tick-transmitted disease organisms can enter the body through cuts in the skin or mucous membranes. If gloves are not available, the fingers should be shielded with a barrier, such as a tissue or paper towel. The tick should not be squeezed, crushed or punctured. The CDC warns that tick removal techniques such as the use of hot matches or petroleum jelly may stimulate it to release additional saliva and increase the risk of infection. The tick bite should be disinfected after removal, and the hands washed with soap and water. The tick can be frozen in a plastic bag, for identification in case of illness. Ticks should also be removed from pets, both to prevent them from becoming ill and to prevent ticks from entering the home. Acaricides, biological controls and modification of tick habitats can decrease tick populations.

Prophylactic antibiotic therapy is not recommended after a tick bite, as the risk of infection is relatively low, and antibiotics can have adverse effects (including the development of antibiotic resistance). There is no vaccine for ehrlichiosis or anaplasmosis.

Morbidity and Mortality

Anaplasmosis and ehrlichiosis are more common at times of the year when tick activity is high and people are more likely to be outdoors. In the U.S., most cases of HME (*E. chaffeensis*) are seen from April to September, and the peak incidence of HGA (*A. phagocytophilum*) is in June and July. In Europe, the majority of HGA cases occur between June and August.

Human anaplasmosis and ehrlichiosis are now reportable diseases in the U.S. The number of cases reported to the CDC has generally been increasing, due to increased awareness, new diagnostic tests and other factors. The reported incidence of HGA was 1.4 cases per million persons in 2000 and increased to 6.1 cases per million persons in 2010. During the same period, the incidence of HME from *E. chaffeensis* varied from less than 1 case per million persons (in 2000) to 3.4 cases per million persons (2008). Active surveillance suggests that the true incidence of both diseases may be higher in some areas: the number of HGA cases was as high as 24–58 cases per 100,000 population in Connecticut and the Upper Midwest, while up to 330–414 HME cases per 100,000 population were found in Tennessee and southeastern Missouri. HGA is also increasingly reported in Europe, where it is not a reportable disease. However, fewer cases have been documented than in the U.S., and these cases seem to be less severe. Some authors suggest that this might be caused by the presence of different *A. phagocytophilum* variants in each location. It is also possible that it results from lower physician awareness and decreased frequency of diagnostic testing.

Although *E. chaffeensis* tends to cause more severe illness than *A. phagocytophilum*, asymptomatic or mild infections might be relatively common with both organisms. Serosurveillance suggests that up to 15-36% of the population in endemic areas worldwide has been exposed to *A. phagocytophilum*. Similarly, up to 13% of some populations may have antibodies to *E. chaffeensis*. In one endemic area, 20% of children with no history of HME were seropositive for this organism. The case fatality rate is estimated to be 2-3% for HME, and less than 1% for HGA. Although severe ehrlichiosis or anaplasmosis can be seen in healthy individuals, it is more common in immunocompromised or elderly patients, and in people with other illnesses,

Human ewingii ehrlichiosis (*E. ewingii*) has been reported in only a few patients, most of whom were immunosuppressed. It is uncertain whether the small number of cases is due to the mildness of the condition, or the difficulty in definitive identification of *E. ewingii*. No deaths and few complications have been reported.

Little is currently known about *E. muris* or *E. canis* infections in humans. *E. muris* was implicated in at least 2 PCR-confirmed and 84 serologically diagnosed cases in Russia. In Japan, 1.1% of Tokyo residents had antibodies to this organism (although it is possible that this was due to cross-reactions with other organisms). An *E. muris*-like organism was linked to a few clinical cases in the U.S. Symptomatic cases caused by *E. canis* appear to be uncommon.

Internet Resources

Centers for Disease Control and Prevention (CDC). Ehrlichiosis
http://www.cdc.gov/ehrlichiosis/

CDC. Anaplasmosis
http://www.cdc.gov/anaplasmosis/

International Veterinary Information Service [IVIS]
http://www.ivis.org

The Merck Manual
http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual
http://www.merckvetmanual.com/mvm/index.jsp

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