Reference Point

Recognition of the threat of *Ehrlichia ruminantium* infection in domestic and wild ruminants in the continental United States

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Disease attributable to *Ehrlichia ruminantium* (formerly *Cowdria ruminantium*) infection was first described in South Africa in 1838 as a nervous condition of sheep that developed after a substantial infestation of ticks.\(^1\) It is an infectious but noncontagious tick-borne disease (ie, heartwater) that affects domestic and wild ruminants. Infection often causes the death of clinically affected ruminants. In 2009, many sub-Saharan African countries and the island of Guadeloupe in the Caribbean reported clinical cases of heartwater in their domestic ruminant populations.\(^2\) Additionally, livestock have died of heartwater on the islands of Marie-Galante and Antigua in the Caribbean.\(^3\)

On the basis of the proximity of the United States mainland to the Caribbean islands, the ultimate concern for animal health officials, members of the livestock industry, and other stakeholders may not be what should be done to keep heartwater from being introduced into the continental United States, but rather what can be done to limit the extent of an outbreak when this incursion transpires. A key element to controlling the extent of a disease outbreak is early recognition of the disease in an animal population. Therefore, the purpose of the information reported here is to describe the salient features of heartwater and to promote increased disease awareness among veterinarians, livestock owners, wildlife biologists, and other stakeholders. It is our hope that this awareness will translate into a more rapid detection of disease and the ability to limit the extent of an outbreak should it occur in the continental United States.

**Pathogen Characteristics**

*Ehrlichia ruminantium* is an aerobic, gram-negative, nonmotile, coccoid- to ellipsoidal-shaped organism in the order Rickettsiales and family Anaplasmataceae.\(^4\) This organism is typically transmitted to a susceptible host through infective blood.\(^5\) Once inside the host, this obligate intracellular agent typically resides inside intracytoplasmic inclusions (diameter, ≤4.0 µm) in neutrophils and endothelial cells and replicates by binary fission and, less frequently, by budding. The number of replicated organisms inside these cells can range from 1 to several thousand.\(^6,8\)

Different strains of *E ruminantium* may not induce homologous or heterologous cross-protection, with this lack of immune induction potentially attributable to antigenic diversity.\(^7,8\) Antigenic diversity also impacts the degree of pathogenicity of various strains of *E ruminantium* in Africa and the Caribbean islands. Whereas some strains are highly virulent, others appear to be non-pathogenic.\(^7,8\) Remarkably, a less pathogenic strain of *E ruminantium*, which is referred to as Panola Mountain *Ehrlichia*, may exist in the central, southeastern, and eastern United States; preliminary characterization of this pathogen by investigators indicates that this strain is genetically and antigenically more closely related to *E ruminantium* than to any other *Ehrlichia* spp.\(^9,10\) In a goat with experimentally induced disease,\(^9\) the Panola Mountain *Ehrlichia* bacteria caused a transient illness with a mild febrile condition that was followed by a chronic latent infection. The lack of reports of heartwater or heartwaterlike disease in domestic or wild ruminants from areas in which Panola Mountain *Ehrlichia* organisms have been detected provides further indirect support that this bacterium has low pathogenicity in infected animals.\(^10\)

*Ehrlichia ruminantium* does not survive for long periods outside of a host. Blood exposed to sunlight will lose infectivity in ≤5 minutes.\(^11\) In a dead animal, the organism will typically begin to die in ≤6 hours.\(^12\) However, infectivity may be prolonged for as long as 72 hours under cold conditions (\(4°C\ [39.2°F]\)).\(^13\) *Ehrlichia ruminantium* is also susceptible to treatment with antimicrobials,\(^7\) particularly tetracycline derivatives.

**Epidemiology**

Tick vector—*Amblyomma* spp ticks must be present in a geographic area to transmit *E* ruminantium to susceptible ruminant hosts during and after an outbreak of heartwater. This tick species is categorized as a 3-host tick; therefore, each life stage of the tick (ie, larva, nymph, and adult) feeds on a different host and...
may require as few as 5 months or up to 4 years to complete the tick life cycle.\textsuperscript{18,13} Infection can be transmitted by each life stage of the tick.\textsuperscript{16} Infective organisms can endure in these various life stages for an extended period (eg, 5 to 15 months).\textsuperscript{15,17}

In Africa, there are 5 native species of \textit{Amblyomma} spp ticks (\textit{Amblyomma variegatum}, \textit{Amblyomma hebraeum}, \textit{Amblyomma lepidum}, \textit{Amblyomma astrion}, and \textit{Amblyomma pomposum}) considered natural vectors of heartwater. These 5 species have transmitted \textit{E ruminantium} under field conditions to susceptible animal species, and transmission has caused clinical signs of disease.\textsuperscript{30,14} In experimental conditions, 5 other species of \textit{Amblyomma} spp ticks (\textit{Amblyomma cohaerens}, \textit{Amblyomma gemma}, \textit{Amblyomma tholloni}, \textit{Amblyomma sparsum}, and \textit{Amblyomma marmoreum}) indigenous to Africa are capable of transmitting \textit{E ruminantium} to ruminants.\textsuperscript{18} Three \textit{Amblyomma} spp ticks (\textit{Amblyomma maculatum}, \textit{Amblyomma cajennense}, and \textit{Amblyomma americanum}) indigenous to North America are susceptible to infection with \textit{E ruminantium}.\textsuperscript{19,20} But only \textit{A maculatum} appears to be efficient at transmitting heartwater to susceptible ruminants.\textsuperscript{19,20} \textit{Amblyomma americanum} also serves as a natural vector for the \textit{E ruminantium}–like Panola Mountain \textit{Ehrlichia} organisms\textsuperscript{9,10} initially identified in the southeastern United States.\textsuperscript{9} \textit{Amblyomma dissimile}, which was introduced into Florida and typically parasitizes reptiles and amphibians,\textsuperscript{31,32} has also transmitted \textit{E ruminantium} to goats in experimental conditions.\textsuperscript{23} Despite being found occasionally on cattle in natural conditions, researchers\textsuperscript{23} believe it is unlikely that \textit{A dissimile} plays a substantial role in the transmission of heartwater among ruminants.

The tropical bont tick (\textit{A variegatum}) and bont tick (\textit{A hebraeum}) are considered to be the most important vectors of heartwater because of their adaptation to domestic ruminant livestock, ease with which they transmit \textit{E ruminantium} among ruminants, and geographic distribution.\textsuperscript{14,33} However, given the widespread distribution of the tropical bont tick in the Caribbean islands, this tick may be the arthropod vector that is eventually responsible for the first outbreak of heartwater in the United States. Consequently, veterinarians, livestock owners, and wildlife biologists should be familiar with the phenotypic characteristics of this tick and be on alert for infestations on domestic and wild ruminants (Figure 1).

Other tick species (\textit{Rhipicephalus evertsi}, \textit{Boophilus decoloratus}, \textit{Ornithodoros savignyi}, \textit{Rhipicephalus appendiculatus}, \textit{Hyalomma truncatum}, \textit{Amblyomma nuttalli}, \textit{A americanum}, \textit{Amblyomma neumanni}, and \textit{Amblyomma imitator}) are not capable of transmitting \textit{E ruminantium}.\textsuperscript{16,19} Mechanical transmission of \textit{E ruminantium} by arthropods has not been confirmed or verified.\textsuperscript{16}

Ruminant host susceptibility—Domestic cattle (\textit{Bos taurus} and \textit{Bos indicus}), sheep (\textit{Ovis aries}), and goats (\textit{Capra hircus}) are target species for heartwater, but other less familiar domestic ruminants in the family Bovidae (eg, Asian water buffalo [\textit{Bubalus bubalis}]) are also susceptible to disease.\textsuperscript{26} Sheep and goats typically have more severe clinical disease than do cattle. \textit{Bos indicus} breeds of cattle typically are more resistant to infection than are \textit{B taurus} breeds.\textsuperscript{27} Similarly, indigenous breeds of goats and sheep in heartwater-endemic areas appear to be more resistant to disease, compared with resistance of other nonindigenous breeds of goats and sheep.\textsuperscript{27} Additionally, young lambs and kids during the first week after birth and calves during the first month after birth typically have resistance to overt clinical disease after infection.\textsuperscript{26–30}

Although heartwater has been the suspected cause of death in many species of ungulate ruminant wildlife, only 12 species indigenous to Africa and 3 non–African-origin species are proven to be susceptible to infection by \textit{E ruminantium}\textsuperscript{33–37} (Table 1). All 15 species are present in the continental United States as captive (eg, farmed) or free-ranging populations.\textsuperscript{33–35} Although these species can function as a sentinel species for heartwater, this disease is likely to be observed first in white-tailed deer (\textit{Odocoileus virginianus}) or axis deer (\textit{Axis axis}). White-tailed deer are an important sentinel species because of their ubiquitous geographic distribution\textsuperscript{36} and potential interaction with heartwater-infected domestic ruminants. Although they lack the extensive range of white-tailed deer, there are free-ranging populations of axis deer in Texas, California, and Washington\textsuperscript{37–39}, axis deer are a popular farmed species in many southern and midwestern states.\textsuperscript{35–33,37} Several other ungulate ruminant wildlife species have been introduced into the continental United States as captive and free-ranging populations\textsuperscript{33–35,37–42} and are suspected to be susceptible to \textit{E ruminantium} infection.\textsuperscript{31,32} However, studies are needed to confirm the susceptibility of these introduced species to \textit{E ruminantium} infection.

**Transmission**—The typical life cycle of \textit{E ruminantium} includes a phase in which the organism is transmitted between successive life stages of \textit{Amblyomma} spp ticks before transmission to a susceptible vertebrate host. Additionally, the organism may be transmitted iatrogenically.

**Tick-to-tick transmission**

Miniscule amounts of \textit{E ruminantium}–infected blood (0.001 to 0.02 mL) from a febrile animal are nec-
A variegatum are frequently found on migratory and Venezuela (43) during feeding. Thus, the potential for interaction be to a susceptible host.

Experimentally

<table>
<thead>
<tr>
<th>Ruminant</th>
<th>Experimentally induced infection*</th>
<th>Natural infection†</th>
<th>Population type</th>
</tr>
</thead>
<tbody>
<tr>
<td>African buffalo (Syncerus caffer)</td>
<td>Yes</td>
<td>—</td>
<td>Captive</td>
</tr>
<tr>
<td>Axis deer (Axis axis)</td>
<td>—</td>
<td>Yes</td>
<td>Free-ranging, captive</td>
</tr>
<tr>
<td>Barbary sheep (Ammotragus lervia)</td>
<td>—</td>
<td>Suspected</td>
<td>Free-ranging, captive</td>
</tr>
<tr>
<td>Bison (Bison spp)</td>
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<td>Suspected</td>
<td>Free-ranging, captive</td>
</tr>
<tr>
<td>Black wildebeest (Connochaetes gnu)</td>
<td>Yes</td>
<td>—</td>
<td>Captive</td>
</tr>
<tr>
<td>Blackbuck antelope (Antilope cervicapra)</td>
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<td>Suspected</td>
<td>Free-ranging, captive</td>
</tr>
<tr>
<td>Blesbok (Damaliscus dorcas philips)</td>
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<td>—</td>
<td>Captive</td>
</tr>
<tr>
<td>Blue wildebeest (Connochaetes taurinus)</td>
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<td>—</td>
<td>Captive</td>
</tr>
<tr>
<td>Eland (Taurotragus oryx)</td>
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<td>Captive</td>
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<tr>
<td>Fallow deer (Dama dama)</td>
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<tr>
<td>Giraffe (Giraffa camelopardalis)</td>
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<td>—</td>
<td>Captive</td>
</tr>
<tr>
<td>Greater kudu (Tragelaphus strepsiceros)</td>
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<td>—</td>
<td>Captive</td>
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<tr>
<td>Himalayan tahr (Hemitragus jemlahicus)</td>
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<td>Suspected</td>
<td>Captive</td>
</tr>
<tr>
<td>Lechwe (Kobus leche kaluensis)</td>
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<td>Moufflon (Ovis aries)</td>
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<td>Rusa (Timor) dear (Canvus timorensis)</td>
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<td>Springbok (Antidorcas marsupialis)</td>
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<tr>
<td>Steenbok (Raphicerus campestris)</td>
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<td>Yes</td>
<td>Captive</td>
</tr>
<tr>
<td>White-tailed deer (Odocoileus virginianus)</td>
<td>Yes</td>
<td>—</td>
<td>Free-ranging, captive</td>
</tr>
</tbody>
</table>

* A yes response for experimental heartwater infection indicates infection as a result of ticks or inoculation of infected blood or infected cell culture material into these species; infection was confirmed by simultaneous control infections in small ruminants or evaluation of brain smears or supportive evidence of disease on the basis of pathological or epidemiological (or both) findings. A suspected response indicates that the clinical signs of disease were compatible with heartwater in these species, but no diagnostic tests were performed to confirm E ruminantium infection.

† Refractory response indicates that no clinical signs of disease were observed in this species after exposure to E ruminantium; however, no follow-up diagnostic tests were performed to detect rickettsemia to exclude the potential for subclinical infection. A yes response for natural infection indicates that natural infection was confirmed via examination of brain or tunica intima smears and supportive evidence of disease on the basis of pathological or epidemiological (or both) findings. A suspected response indicates that natural infection was confirmed via examination of brain or other migratory bird species.

Essary to initially infect an Amblyomma spp tick with E ruminantium. Then, development of the bacteria begins in the intestinal epithelial cells and continues in the hemolymph and salivary glands of infected ticks. Infections render the tick as an infected carrier for the entirety of its life stage. Whether during molting of the tick from a larva to a nymph or from a nymph to an adult, the organism is typically transferred between life stages (ie, transstadial transmission) because of the persistence of infection in the tissues and fluids of the E ruminantium–infected ticks. Transovarial transmission, which is characterized by a disease agent being transferred from an infected female to her eggs, may rarely occur, but this has been reported only in bont ticks.

In field settings, the proportion of Amblyomma spp ticks that become infected with E ruminantium varies. This variability is a consequence of the carrier state of ruminant hosts, carrier state of wild hosts, inherent differences between Amblyomma spp and E ruminantium strains, and concurrent infection of a batch of newly hatched tick larvae by an E ruminantium–infected ruminant. For example, only 1% to 4% of adult A variegatum ticks on the Guadeloupe islands were infected with E ruminantium. In another study, E ruminantium infection rates were 0% to 91%.

Some evidence suggests that Ehrlichia spp can also be transmitted among ticks that are cofeeding on migratory birds. Immature A variegatum, A maculatum, and A cajennense are frequently found on migratory birds. Although birds may be resistant to clinical infections, infections among these tick species are possibly caused by cofeeding on infected birds. These 3 tick species exist within the Caribbean islands (A variegatum and A cajennense) and Venezuela (A maculatum and A cajennense). Thus, the potential for interaction between these tick species is plausible, particularly if the geographic distribution of A variegatum continues to expand into South America via the migration of egrets or other migratory bird species.

**Tick-to-vertebrate host transmission**

Six to 12 weeks may pass before an infected tick is able to transmit E ruminantium to a susceptible host. However, only a portion of infected ticks will transmit E ruminantium during feeding. Furthermore, tick transmission of E ruminantium to a susceptible host during feeding is not instantaneous and requires 2 to 3 days for nymphs and ≤ 4 days for adults.

In heartwater-endemic areas, the prevalence of subclinical vertebrate carriers predominates over hosts with clinical disease, which may be attributable to the reproduction of E ruminantium in capillary endothelial cells with intermittent release of organisms into the bloodstream. Consequently, the amount of rickettsemia in carrier animals is generally less than that of clinically.
Vertebrate host-to-vertebrate host transmission

Vertical transmission of *E. ruminantium* from cows to neonatal calves purportedly occurs under natural conditions. Transmission is thought to be caused by ingestion of *E. ruminantium*-infected leukocytes in colostrum produced by the infected dam.  

Iatrogenic transmission

The SC, IM, and IP inoculation of infective blood into susceptible animals can also initiate infection. Therefore, it is important to recognize management procedures that involve the use of blood-contaminated hypodermic needles or other instruments that may be fomites for the transmission of this disease to susceptible ruminants.

Geographic distribution—Heartwater can exist only where tick vectors are present. The geographic distribution of *Amblyomma* spp ticks is predicated on a suitable habitat for tick survival.

Traditional range

*Amblyomma* spp ticks are generally found at elevations from sea level to 2,590 m (8,497 feet). These species are more abundant during the rainy season and in environments typified by continuous high relative humidity. However, *Amblyomma* spp ticks cannot survive when rainfall is < 25.0 cm/y (9.8 inches/y) or > 280.0 cm/y (110 inches/y). Because the seasonal reproductive activity of these ticks is regulated by rainfall and warm temperatures, heartwater-endemic regions are found in a variety of habitats in sub-Saharan Africa and from wooded savanna to bushland to wooded grassland that comprise tropical, humid temperate, dry subhumid, semiarid, and arid climates. Outside of Africa, suitable habitat for *A. variegatum* ticks can be found in the Caribbean islands, southeastern United States, and Latin America.  

Introduction to new geographic regions

Because *E. ruminantium* cannot persist outside a host for more than a few hours, the principal mode of release of *E. ruminantium* into a new geographic location is via carrier animals, transport on a host, or both. Cattle transported from Senegal to Guadeloupe were believed to have introduced *A. variegatum* ticks into the Caribbean islands in 1828.  

This tick has slowly spread to at least 16 of the 27 Caribbean islands or island groups in this region after introduction (Figure 2).  

Subsequently, heartwater has been diagnosed in domestic ruminants on 3 of these islands (ie, Guadeloupe, Marie-Galante, and Antigua) and perhaps as many as 7 other islands as determined on the basis of serologic evidence of infection.

Trade of live ruminants between heartwater-endemic countries and the United States appears to have been curtailed. Therefore, animals and birds that are otherwise resistant to *E. ruminantium* infection are likely to increase in importance as transporters of infected ticks into the United States from endemic countries. Support for this belief is provided in a review in which the importation of exotic ticks into the United States on reptiles (eg, alligators, iguanas, monitor lizards, snakes, tortoises, and turtles), wild animals (eg, Cape buffalo, elephants, rhinoceroses, and zebras) or their skins, birds (eg, ostrich), and humans is summarized. Six heartwater-susceptible *Amblyomma* spp ticks (ie, *A. dissimile*, *A. gemma*, *A. hebraeum*, *A. lepidum*, *A. marmoreum*, *A. sparsum*, *A. tholloni*, and *A. variegatum*) were described as among these imported ticks, and some ticks were infected with *E. ruminantium*.

Given their susceptibility to infestation by *A. variegatum* ticks and the adaptation of their feeding biology almost exclusively to ungulate hosts, the cattle egret (*Bubulcus ibis*) may have the most potential for the transport and introduction of *A. variegatum* ticks into new geographic regions of the United States. The cattle egret is firmly established in the Caribbean islands and, because of their tendency to migrate extensively, is thought to be partly responsible for the dissemination of *A. variegatum* ticks to many of the Caribbean islands.

Additionally, populations consisting of 750,000 to 1.5 million cattle egrets are established in the United States. Year-round breeding colonies exist in Florida, and these birds frequently migrate to the Greater Caribbean Basin, including Guadeloupe. Seasonally variable populations of cattle egrets are also found in every state in the continental United States, and breeding colonies exist in every state except Montana, New Hampshire, Washington, and West Virginia. As native vegetation is converted into grazing lands, these birds are expected to continue to colonize new areas.
Cattle egrets use 3 distinct spring and fall migration corridors in North America (Figure 3). These corridors include an eastern route from Newfoundland that follows the Atlantic coast states to Florida and Mississippi, through the Greater Caribbean Basin to the southern portion of Mexico, and then through Central America and into Colombia; a central route from Kansas east to Alabama and then south to Panama; and a Pacific Coast route from southern Arkansas to west-central Mexico.

Records of the US Geological Survey Bird Banding Laboratory for North American and Caribbean adult cattle egret populations have revealed migrations > 3,100 km (1,926 miles). Juvenile birds will also migrate over great distances (eg, ≤ 5,000 km [3,107 miles]) from their birthplace. These distances are critical because the feeding periods for *A variegatum* larvae and nymphs on cattle egrets are 6 to 13 days and 5 to 10 days, respectively. Thus, these ticks may survive long enough on cattle egrets that migrate from the Greater Caribbean Basin to North America that they could eventually feed on a susceptible population of domestic or wild ruminants in the United States.

The high probability of tick-ruminant interaction is attributable to the feeding characteristics of cattle egrets; these birds forage almost exclusively in close association with cattle or other ruminants. Additionally, cattle egrets synchronize their feeding and resting periods with those of cattle and oftentimes are found on or near resting cattle. Consequently, this close association to both feeding and resting cattle may provide the opportunity for mechanical transport of ticks from cattle egrets to other hosts and to resting cattle may provide the opportunity for introduced ticks to find new hosts.

Unquestionably, *A variegatum* is the most important vector for introducing heartwater into the United States. However, given the presence of 3 indigenous *Amblyomma* spp (*A maculatum* [Gulf Coast tick], *A cajennense* [Cayennenne tick]), and *A americanum* [Lone Star tick]) that feed on ruminants, it may not be necessary for *A variegatum* ticks to become established in some areas of the United States to sustain an outbreak of this disease. For example, transstadial transmission of *E ruminantium* from larva to nymph and from larva to nymph to adult has been confirmed. More importantly, that same study revealed that *A maculatum* nymphs and adults that were infected in the larval stage transmitted *E ruminantium* to susceptible goats. Another study has also shown that *E ruminantium*-infected *A maculatum* nymphs were able to successfully transmit this pathogen to susceptible sheep. The efficiency of *A maculatum* as a vector was similar to that of *A variegatum*, the most important natural vector of heartwater. Thus, *A maculatum* has the potential to play a future role in the establishment and maintenance of heartwater, if the disease were to be introduced into the United States. In contrast, *A cajennense* and *A americanum* appear to be of less concern as a potential indigenous vector of heartwater. These same studies verified the inability of *E ruminantium*-infected *A cajennense* and *A americanum* nymphs to transmit infection when allowed to feed on susceptible goats and sheep. Transstadial transmission of *E ruminantium* from larva to nymph and from larva to nymph to adult also does not appear to be important in *A cajennense*. Another *Amblyomma* spp found in the United States, *A dissimile* (American reptile tick) has transmitted *E ruminantium* to a goat in experimental conditions. However, because this tick species usually feeds on snakes, iguanas, and lizards, it is not considered to have a major role in the transmission of heartwater between ruminants.

Larvae and nymphs of *A maculatum* feed on small rodents and ground-dwelling birds. Nymphs also readily feed on cattle, whereas adults primarily feed on larger mammals (eg, cattle, horses, and white-tailed deer). The original distribution of this tick seldom exceeded > 161 km (100 miles) inland along the Gulf coast and on the Atlantic coast in Florida, Georgia, and the southern portion of South Carolina. Currently, *A maculatum* can be found in Alabama, Arizona, Arkansas, Florida, Georgia, Indiana, Kansas, Kentucky, Louisiana, Mississippi, Missouri, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia. This expansion in geographic distribution is hypothesized to be caused, in part, because this tick feeds on many bird species.

**Disease Characteristics**

**Incubation period**—After transmission of *E ruminantium* to a susceptible ruminant host, the organism is seques-
tered in regional lymph nodes where replication begins. A febrile stage develops between 3 and 10 days after transmission, at which time organisms are located in plasma cells, neutrophils, and, occasionally, other granulocytes. After *E. ruminantium* transmission by infected ticks during feeding under field conditions, susceptible animals typically have overt clinical signs within 1 to 5 weeks (mean, 2 weeks).

**Immunity and carrier state**—In heartwater-endemic areas, populations of indigenous cattle (particularly *B. indicus*-type breeds), goats, and sheep typically are more resistant to infection than are nonindigenous breeds. This suggests that genetic factors are important in these ruminants for the development of immunity against heartwater. Immunity is probably maintained best in sheep; in contrast, immunity is of the shortest duration in cattle. Calves, kids, and lambs also have natural resistance against heartwater during the neonatal period, and resistance appears to be unrelated to the immune status of the respective dam.

Following recovery from clinical disease, some domestic ruminants can become reinfected with *E. ruminantium*, resulting in another bout of clinical disease or even death. Some animals may also have a transient carrier state. For example, in a report, *E. ruminantium* was recovered from the blood of cattle, goats, and sheep for up to 40 days following spontaneous or drug-induced (oxytetracycline) recovery from clinical disease. In another study, cattle and sheep maintained a carrier state for 5 to almost 9 months after recovery from clinical disease. In the Caribbean islands, cattle and Creole goats were transient carriers of *E. ruminantium* for 2 and 11 months, respectively.

A carrier state has been detected in both clinically normal wild ungulate ruminants that are free-ranging in Africa and in eland (*Taurotragus oryx*), giraffe (*Giraffa camelopardalis*), greater kudu (*Tragelaphus strepsiceros*), blue wildebeest (*Connochaetes taurinus*), and African buffalo (*Syncerus caffer*) with experimentally induced disease. The latter 5 species with experimentally induced disease are located in the continental United States as part of captive populations. If infected with *E. ruminantium*, there is the possibility that these 5 and perhaps other wild ungulate ruminants could become a reservoir for *E. ruminantium* infection and contribute to the spread of heartwater.

**Morbidity and mortality rate**—In heartwater-endemic areas, morbidity varies considerably and is dependent on the strain of *E. ruminantium* that causes the outbreak and the intensity of management practices (eg, tick control and vaccination). Mortality rate in clinically affected animals also varies considerably; this is particularly dependent on when treatment is initiated during the course of the disease. Mortality rate in indigenous breeds may be 5% to 10%, but is typically greater in nonnative populations. For example, mortality rates of 40%, 60%, and 90% have been observed in calves, adult cattle, and Angora goats, respectively.

**Clinical signs**—Clinical signs depend on the stage of disease of the animal at the time of examination (ie, peracute, acute, subacute, or subclinical form). The peracute form is relatively rare and has usually been observed in European breeds of cattle (*B. taurus*), goats, and sheep introduced into heartwater-endemic areas of Africa. Furthermore, sudden death is a characteristic of the peracute form. However, livestock owners that closely and frequently observe their animals may find that high fever, respiratory distress, terminal convulsions, and diarrhea may precede death during the peracute form.

The acute form is most often detected and is typified by a fever (up to 42°C [107°F]) that will subside after 1 or 2 days but will recur and persist for an additional 3 to 6 days. Inappetance, signs of depression, listlessness, moist cough, and bronchial rales typically accompany fever. Cyanosis of mucous membranes and dyspnea may be observed. In most animals with acute disease, clinical signs of CNS disease (eg, rapid blinking of the eyes, protrusion of the tongue, twitching of muscles, hypersensitivity to touch, a staggering and often high-stepping gait, circling, abnormal postures, and aggression) are next to appear. Signs of CNS disease typically increase in severity and end with the animal in lateral recumbency, with opisthotonus, nystagmus, galloping movements, chewing movements, frothing at the mouth, and convulsions shortly before death. In instances in which marked clinical signs of CNS disease are absent, a profuse and often hemorrhagic diarrhea is observed. The acute form of disease is typically fatal in < 1 week from the onset of clinical signs.

The subacute form of disease is rarely encountered in animals with heartwater and is characterized by prolonged fever, coughing, and mild incoordination. Affected animals recover or die within 1 to 2 weeks after the onset of the subacute form of disease. A mild or subclinical form of heartwater is characterized by transient fever and can develop in partially immune cattle or sheep, calves < 3 weeks old, antelope, and some indigenous breeds of cattle and sheep with natural resistance to the disease. Similarly, susceptible wild ruminants may have inapparent and transient infections or overt signs of clinical disease and may subsequently die.

**Pathophysiologic and clinicopathologic changes**—The tropism of *E. ruminantium* for endothelial cells results in damage to capillaries of the host. Thus, the resulting increased capillary permeability caused by damage to epithelial cells is particularly detrimental to cardiac and respiratory function. In severely affected animals and animals with advanced stages of disease, a substantial decrease in cardiac output is observed in addition to a decrease in diastolic blood pressure. Changes in lung function are variable and are dependent on the stage of disease. Respiratory alkalosis that is evident during the early febrile stage of disease may transform to respiratory acidosis during more advanced disease stages. Furthermore, endotoxin release may cause a portion of these observed changes in cardiac and respiratory function.

Primary clinicopathologic changes include progressive anemia, fluctuations in total and differential WBC counts (ie, neutropenia, eosinopenia, and lymphocytosis), hyperbilirubinemia, a decrease in concentrations of serum total proteins (hypoalbuminemia), and
azotemia. Effusion into body cavities is commonly detected in most fatal instances of disease and is characterized by a transparent or slightly turbid light yellow fluid that will often coagulate after exposure to air because of high albumin and globulin concentrations. Hypocalcemia may also develop because of the effects of hypoalbuminemia.

Postmortem lesions—Gross lesions attributable to endothelial damage are typically observed in cattle, goats, and sheep that die as a result of heartwater; however, there are instances in which no discernible lesions are detected. Effusion of body cavities is an extremely common finding in most fatal cases of the disease. Hydropericardium is a common lesion, particularly in goats and sheep, which prompts the use of the term heartwater to describe this disease. In some cases, hydrothorax, which consists of several liters of fluid in cattle, 0.5 L in sheep, and rarely > 20 mL in goats, with minimal hydropericardium may be the most prominent finding detected during necropsy. Additionally, ascites, pulmonary edema, perirenal edema, cerebral edema, and splenomegaly are typically evident elsewhere in the body.

Reports on the pathological changes in wild ruminants that have died are limited, but findings appear similar to those observed in domestic ruminants. Generalized congestion, hydrothorax, hydropericardium, ascites, lung edema, and splenomegaly are the most commonly observed gross postmortem findings. Histopathologic lesions appear similar to the changes described in domestic ruminants.

**Diagnosis**

Detection of the previously described diverse range of characteristic clinical signs of disease and postmortem lesions in domestic and wild ruminants and the presence of *Amblyomma* spp ticks on an animal or a history of tick exposure provide support for a presumptive diagnosis of heartwater. A definitive diagnosis of heartwater can be established in animals that died of the disease by use of light microscopy to detect the characteristic *E ruminantium* organisms in the cytoplasm of cerebral cortical or hippocampal capillary endothelium (Figure 4). A small piece (5 x 5 mm) of cerebral cortex or hippocampus should be crushed between 2 microscope slides until the tissue has a soft, pasty consistency. The tissue should then be moved to the end of the horizontally oriented bottom slide. Next, the top slide, angled at approximately 45° to the bottom slide, is used to drag the tissue along the bottom slide in a manner to produce both a thick and thin smear. This procedure stretches the capillaries linearly and facilitates microscopical detection. The slide is allowed to air-dry, then fixed in absolute methanol or ethanol, stained with a Romanowsky-type stain (eg, giemsa), and examined via light microscopy by use of oil immersion at 100X magnification. If present, the cytoplasmic vacuoles of *E ruminantium* will have a dark blue appearance, as opposed to the violet color of the nucleus of the host cell. In other instances, homogeneous purple masses of initial bodies that are 1 to 2 µm in diameter may be observed in the cytoplasm of affected cells. Apart from cocci and initial bodies, bulky dark blue forms with diameters of up to 2 to 4 µm can be evident in the shape of horseshoes, rods, irregular masses, and rings.

Heartwater can also be diagnosed in ruminants via the testing of tissues (eg, blood; brain, lung, and kidney tissues; and thoracic fluid) with a PCR assay or the isolation of *E ruminantium* in cultured endothelial cells inoculated with infected blood. Isolation of *E ruminantium* from *Amblyomma* spp ticks that were retrieved from animals with clinical signs of heartwater would also provide supportive evidence for a diagnosis of heartwater.

Unfortunately, available serologic tests cross-react with antibodies against related *Ehrlichia* and *Anaplasma* spp, as well as *Rickettsia* spp, *Neorickettsia*, and *Coxiella burnetii*, resulting in many false-positive results. Thus, serologic tests should not be used as the sole method for the establishment of a definitive diagnosis of heartwater in areas endemic for these other pathogens.

**Treatment**

In outbreaks of heartwater, tetracycline antimicrobials (ie, chlorotetracycline, doxycycline, oxytetracycline, and tetracycline) have been used to successfully treat heartwater in clinically affected domestic ruminants and white-tailed deer. Sulfonamide antimicrobials (ie, sulfadiazine, sulfadimidine, sulfanilamide, sulfapyridine, sulfaguanidine, and sulfathiazole) are also effective, but they often are not used because of the superior effectiveness of tetracycline antimicrobials.

For tetracycline antimicrobials to be effective against heartwater, it is important to initiate treatment during the early stages of infection when the only clinical sign is fever. If signs of CNS disease are evident at the time of treatment, prognosis is poor. Typically, the minimum therapeutic dose for short-acting tetracycline antimicrobials is between 10 and 20
mg/kg (22 and 44 mg/lb) administered as a single IM injection; alternatively, half of the dose can be administered IV and the remaining half administered IM. Experience has shown that a single-treatment is not reliable and a second injection is often needed to bring about a return of normal body temperature and to prevent death. Consequently, treatment is typically repeated 24 hours later. During the advanced stages of heartwater, larger dosages, multiple injections, or both may be necessary. Long-acting formulations of oxytetracycline can also be used, but they do not appear to be any more effective than the aforementioned short-acting tetracycline antimicrobials as a treatment for heartwater.

Other treatments to counteract or treat peripheral vascular collapse and increased capillary permeability should be considered when treating animals with heartwater. Furthermore, the administration of drugs that are active for reducing edema (eg, diuretics), stabilizing membranes (eg, corticosteroids), and blocking vasoactive compounds (eg, corticosteroids and NSAIDs) may be beneficial. Additionally, IV administration of fluids and electrolytes and provision of nutritional support should be considered.

Prevention and Control

After a viable population of E ruminantium—infected Amblyomma spp ticks becomes established in a geographic area, prevention of heartwater through the eradication of tick vectors is likely to be a challenging process. Consequently, livestock owners in heartwater-endemic areas have implemented strategic tick control practices and vaccination to control this disease. Routine administration of oxytetracycline is also used as a metaphylactic control strategy to protect susceptible animals that are to be introduced into endemic areas. Strategic tick control practices are more effective in cattle than in goats or sheep; the objective of these practices is to minimize tick burden without drastically interfering with natural transmission of heartwater, which is responsible for the development of immunity in infected neonates and for the maintenance of immunity against heartwater in older herdmates. In field conditions, animals vaccinated with inactivated or preferably live-attenuated vaccines have been protected after exposure to E ruminantium. Recombinant DNA vaccines do not appear to be as effective in protecting susceptible animals against heartwater under field conditions.

Public Health Implications

Despite the ability of E ruminantium to infect human endothelial cells in vitro, humans are thought to be resistant to E ruminantium infection. However, fatal E ruminantium infection has been reported in humans in South Africa. All 4 of these people initially had clinical signs consistent with viral encephalitis. Ehrlichia ruminantium infection was strongly suggested on the basis of DNA-sequence evidence for this organism obtained from all 4 people and the presence of brain lesions that are typical of those seen in domestic animals infected with this rickettsia. Panola Mountain Ehrlichia, which may yet be proven to be another strain of E ruminantium, might also emerge as a cause of zoonotic disease in the United States within the geographic distribution of its tick vector, A americanum. Recently, a human was infected with this disease agent after a tick bite.

Vigilance for the Detection of FADs

Animals and animal by-products are being transported globally at record rates. Therefore, an incursion of an FAD into the United States is more plausible than ever. Consequently, veterinarians, livestock producers, or anyone involved with wildlife must not discount the possibility that an FAD could be encountered in their locality. Education about which FADs can affect these animals must be a priority.

Everyone in the agriculture and wildlife industries must gain knowledge of the clinical signs of FADs and vigilantly monitor for their emergence. The 3 hallmark signs of heartwater are clinical signs compatible with a CNS disorder in multiple animals, high mortality rate in clinically affected animals, and postmortem findings related to increased vascular permeability (ie, hydropericardium, hydrothorax, pulmonary edema, and splenomegaly); all 3 emerge concurrently among a group of ruminants infected with E ruminantium. For anyone that has not observed an outbreak of heartwater, it is conceivable that the aforementioned 3 hallmark signs of heartwater may be attributed to more common diseases of domestic animals, such as oak poisoning, hemochoria, Clostridium perfringens type D enterotoxemia, and ionophore toxicity. Additionally, it should be mentioned that theileriasis (East Coast Fever), Babesia bovis, and trypanosomiasis are 3 FADs with clinical signs and postmortem and histologic lesions similar to those of heartwater in infected animals.

A comprehensive list of differential diagnoses for endemic diseases should also include FADs that induce similar clinical signs. This preparation will keep the clinical signs and characteristics of FADs at the top of a diagnostician’s list of causes when an FAD may be encountered. Enhanced awareness of these diseases by veterinarians and producers should lead to early recognition of an incursion and reduce the economic and biological impact of the disease. If a veterinarian suspects that domestic ruminants are affected by heartwater or any other FAD, the state veterinarian or federal area veterinarian in charge should be contacted immediately; it is the responsibility of these animal health authorities or their designee to initiate all FAD investigations. Live-stock owners can also contact these officials directly or defer this responsibility to their attending veterinarian. The USDA-APHIS Veterinary Services, Wildlife Services National Wildlife Disease Program operates a surveillance and emergency response system. If heartwater or any other FAD is suspected in wildlife, veterinarians and others may contact local wildlife disease biologists; alternatively, they may also contact the APHIS National Wildlife Disease Surveillance and Emergency Response Program. If an FAD is observed in wildlife, coordinators of the national wildlife disease surveillance and emergency response system will send wildlife biologists to evaluate this type of emergency situation.
Conclusions

The introduction of heartwater into a nonendemic area is a considerable threat to the United States mainland. Despite operations to eradicate this tick and, thus, this disease from the Western Hemisphere through the Caribbean Amblyomma Program, A variegatum ticks and E ruminantium continue to be found in the Caribbean islands. Consequently, surveillance of domestic ruminants for the early detection of heartwater must be conducted by veterinarians and livestock owners. Scrutiny at the local level is the first line of defense against heartwater becoming an established disease in the United States. If heartwater is introduced into the continental United States, all critical factors are present (ie, tick vectors, environmental factors, and domestic and wild ruminant hosts) to sustain this disease after an outbreak. Environmental conditions in the southern United States are favorable for the long-term survival of A variegatum ticks and currently support populations of domestic A maculatum ticks. Because this tick species is also a competent vector for ruminants for the early detection of heartwater must be conducted by veterinarians and livestock owners.

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