Heartwater

Cowdriosis,
Malkopsiekte,
Péricardite Exsudative Infectieuse,
Hidrocarditis Infecciosa,
Idropericardite dei Ruminanti

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Importance

Heartwater, a rickettsial disease of ruminants, is one of the most important diseases of livestock in Africa. This tick-borne illness can significantly decrease productivity in regions where it is endemic. It is particularly serious in non-indigenous livestock that are moved into heartwater areas; many of these animals may die. Wild ruminants can also be infected. Most wildlife species appear to carry the organism asymptomatically, but serious illness has been reported in lechwe moved into endemic areas, as well as in experimentally infected white-tailed deer.

Heartwater is readily introduced into new regions in infected animals or ticks. Known and potential host ticks are widely distributed, and can be found on a variety of animals including reptiles. On at least one occasion, leopard tortoises and African spurred tortoises imported into Florida were found to be carrying infected ticks. Once the tick vector becomes established, eradication of heartwater is difficult. One host tick, *Amblyomma variegatum*, was introduced into the Caribbean early in the 19th century. During the 1970s and early 1980s, this tick spread rapidly from island to island; in some cases, it may have been carried by cattle egrets. The presence of heartwater in the Caribbean increases the risk of introducing this disease into the Americas.

Etiology

Heartwater results from infection by *Ehrlichia* (formerly *Cowdria) ruminantium*, a small, Gram negative, pleomorphic coccus in the family Anaplasmataceae and order Rickettsiales. This organism is an obligate intracellular parasite. Strains of *E. ruminantium* are very diverse: while some strains are highly virulent, others appear to be non-pathogenic. Several different genotypes can co-exist in a geographic area, and may recombine to form new strains.

Closely related species of *Ehrlichia* (e.g., the Panola mountain *Ehrlichia*) exist in some areas. These organisms can complicate the diagnosis of heartwater, as cross-reactions occur in all serological tests, and false positives have been reported in some PCR assays, depending on the primers used. This has implications for various aspects of heartwater, including its geographic distribution and the species affected.

Species Affected

E. ruminantium affects cattle, sheep, goats and water buffalo. It can also infect some wild ungulates, with or without clinical signs. Wild species proven to be susceptible to natural and/or experimental infection include blesbok (*Damaliscus pygargus*), wildebeest (*Connochaetes gnou* and *C. taurinus*), African buffalo (*Syncerus caffer*), eland (*Taurotragus oryx*), giraffes (*Giraffa camelopardalis*), greater kudu (*Tragelaphus strepsiceros*), sable antelope (*Hippotragus niger*), lechwe (*Kobus leche kafuensis*), steenbok (*Raphicerus campestris*), springbok (*Antidorcas marsupialis*), sitatunga (*Tragelaphus spekii*), Timor deer (*Cervus timorensis*), chital (*Axis axis*) and white-tailed deer (*Odocoileus virginianus*). Some other ungulates, including various cervids, bison (*Bison* spp.), and wild relatives of sheep and goats are also thought to be susceptible, but confirmation is lacking. Reports of possible fatal heartwater in an African elephant (*Loxodonta africana*) and a dromedary camel are unproven, and could have occurred from other causes. The elephant was also infected with *Bacillus anthracis*, the agent of anthrax.

E. ruminantium nucleic acids were recently detected by PCR in a dog in Africa, but the susceptibility of this species remains to be confirmed. Experimental infections have been established in ferrets, laboratory mice, the four-striped grass mouse (*Rhabdomys pumilio*) and the southern multimammate mouse (*Mastomys coucha*). There is no evidence that any of these animals are important in the epidemiology of heartwater. Leopard tortoises (*Geochelone pardalis*) and helmeted guinea fowl (*Numida meleagris*) were reported to be susceptible in earlier studies, but this was not confirmed in a later report, and they are no longer considered to be hosts. The scrub hare (*Lepus saxatilis*) may be a host, but this has not been proven.

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Zoonotic potential

Currently, the evidence that *E. ruminantium* may be zoonotic is limited to findings published in 2005, which reported positive PCR results for this organism in three fatal cases of human ehrlichiosis in Africa. Two cases occurred in children with encephalitis, vasculitis of the brain, and pulmonary edema. Clinical details were not available for the other case, an adult. *E. ruminantium* was not proven to be the cause of death in any of these three individuals, and it remains to be determined whether this organism can cause illnesses in humans. As of 2015, there appear to be no additional reports of possible zoonotic infections.

Geographic Distribution

Heartwater is endemic in most of Africa south of the Sahara desert, as well as in surrounding islands such as Madagascar, and in some islands in the Caribbean (currently thought to be limited to Guadeloupe, Antigua and Marie Galante).

Transmission

Heartwater is transmitted by ticks in the genus *Amblyomma*. Transstadial transmission occurs in these ticks, which can remain infected for at least 15 months. Transovarial transmission is not thought to be epidemiologically significant in nature, although it has been demonstrated in the laboratory. *A. variegatum* (the tropical bont tick) is the major vector in Africa and the Caribbean. Other known vectors are *A. hebraeum* (the bont tick) in southern Africa, *A. lepidum* and *A. gemma* in East Africa, Somalia and the Sudan; and *A. astrion* and *A. pomposum*. Species demonstrated to be capable of transmitting *E. ruminantium* in the laboratory include *A. sparsum*, *A. cohaerans*, *A. marmoreum*, *A. tholloni*, and three North American ticks, *A. maculatum* (the Gulf Coast tick), *A. cajennense* and *A. dissimile*. *A. maculatum* is the most likely of the latter three species to act as a significant vector if *E. ruminantium* is introduced into North America. Based on PCR results, *E. ruminantium* might infect members of some other tick genera; however, these ticks are not thought to be capable of transmitting this organism to animals.

Ticks become infected with *E. ruminantium* by feeding on acutely ill or subclinically infected animals. Cattle, sheep, goats and some wild ungulates (e.g., blesbok, wildebeest, African buffalo, eland, giraffe, greater kudu, sable antelope) can continue to carry the organism at low levels for a time after recovery; reports of the carrier state after natural or experimental infections range from a month or two to almost a year. Vertical transmission is thought to occur, and *E. ruminantium* has been detected in colostrum. Iatrogenic transmission is possible (e.g., when unsterilized needles are reused between animals); however, significant transmission on fomites is otherwise considered unlikely in the field. *E. ruminantium* is very fragile and does not survive outside a host for more than a few hours at room temperature, although it has been reported to persist for as long as 72 hours at 4°C. Blood exposed to sunlight loses infectivity in less than 5 minutes.

Disinfection

There has been little or no research on the disinfectant susceptibility of *Ehrlichia* organisms.

Incubation Period

The mean incubation period in natural infections is approximately 2-3 weeks (14 days in small ruminants and 18 days in cattle). Some infections can become apparent as late as 4-5 weeks after exposure.

Clinical Signs

Peracute cases of heartwater can be seen, although they are reported to be relatively rare, and are usually seen in non–native breeds of sheep, cattle and goats. This form of heartwater is characterized by sudden death, which may be accompanied by terminal convulsions, and preceded by a brief interval of fever, severe respiratory distress, hyperesthesia and lacrimation. Diarrhea has also been reported in some animals.

Acute disease is the most common form of heartwater in domesticated ruminants. The initial signs may include sudden fever, anorexia, listlessness, congested mucous membranes and respiratory signs (e.g., moist cough, bronchial rales, rapid breathing), which can progress to dyspnea. Some animals have diarrhea, which may be profuse and/or hemorrhagic. Neurological signs often develop in affected animals; commonly reported signs include chewing movements, protrusion of the tongue, twitching of the eyelids and circling, often with a high-stepping gait. Animals sometimes stand rigidly with muscle tremors. Some may become aggressive or anxious. As the disease progresses, the neurological signs become more severe, and the animal goes into convulsions. In the terminal stages, lateral recumbency with paddling or galloping movements, opisthotonos, hyperesthesia, nystagmus and frothing at the mouth are common. Animals with the acute form of heartwater usually die within a week. Heartwater can also present as a subacute disease with milder signs such as a prolonged fever, coughing and mild incoordination. CNS signs are inconsistent in this form. Subacute cases are reported to be infrequent (although some cases might not be recognized if diagnostic testing is not done). In this form, the animal either recovers or dies within 1 to 2 weeks.

Mild or subclinical infections may be seen in young calves, lambs or kids; partially immune livestock; some indigenous breeds; and some wild ruminants. Transient fever may be the only clinical sign in this form, which is known as “heartwater fever.”

Post Mortem Lesions

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Hydropericardium, with straw–colored to reddish pericardial fluid, gives heartwater its name; this lesion is

more consistently found in sheep and goats than in cattle. Other common lesions include pulmonary and mediastinal edema, froth in the trachea (due to pulmonary edema and terminal dyspnea), hydrothorax, ascites, perirenal edema, and edema of the mediastinal and bronchial lymph nodes. There may also be congestion and/or edema in the gastrointestinal tract, especially in the abomasal mucosa of cattle. Subendocardial petechial hemorrhages are common, and submucosal and subserosal hemorrhages may also be seen in other organs. Splenomegaly may be noted, particularly in sheep and goats. Congestion and meningeal edema are sometimes found in the brain; however, gross lesions are usually subtle or absent in the CNS. Minimal or no lesions have also been reported in some cases.

Similar lesions have been reported in wild ruminants, with the most common lesions reported to be hydrothorax, hydropericardium, lung edema, ascites, splenomegaly and generalized congestion.

Diagnostic Tests

Polymerase chain reaction (PCR) tests can identify *E. ruminantium* in tissues at necropsy, or in the blood of live animals from just before the onset of the fever to a few days after recovery. Nucleic acids may sometimes be detected in the blood or bone marrow of carrier animals, but this is inconsistent. Some PCR tests for *E. ruminantium* can react with some other *Ehrlichia*, including *E. chaffeensis*, *E. canis* and the Panola Mountain *Ehrlichia*, although there is usually lower reactivity to these organisms if the test is correctly calibrated. A PCR assay that can distinguish *E. ruminantium* and the Panola Mountain *Ehrlichia* was recently described. Loop-mediated isothermal amplification (LAMP) assays to detect *E. ruminantium* have also been published. Other DNA techniques may also be available, but are uncommonly used for clinical diagnosis.

Heartwater can also be diagnosed by observing *E. ruminantium* colonies in stained (Giemsa) smears from the brain or intima of blood vessels at necropsy. The best samples to collect from the brain are well-vascularized portions such as the cerebrum, cerebellum or hippocampus. *E. ruminantium* occurs as clumps of reddish-purple to blue, coccoid to pleomorphic organisms inside capillary endothelial cells. These organisms are often found close to the nucleus, and may be in a ring or horseshoe. *E. ruminantium* can also be detected in formalin-fixed brain sections using immunoperoxidase techniques, including combined immunostaining and counterstaining with hematoxylin. These techniques are more likely to detect small numbers of organisms than the use of tissue stains alone. Colonies can be difficult or impossible to find in some animals that have been treated with antibiotics. Only a few colonies may be found in peracute cases.

E. ruminantium can be isolated (e.g., from blood samples) in many primary ruminant endothelial cells or endothelial cell lines. The cultured organism is identified by microscopic examination or immunofluorescence/immunoperoxidase staining. Heartwater may also be diagnosed by inoculating fresh blood from a suspected case into a susceptible sheep or goat. However, this technique is generally discouraged for animal welfare reasons.

Various serological tests for heartwater are available, including indirect immunofluorescence, enzyme-linked immunosorbent assays (ELISAs) and immunoblotting (Western blotting). Serology may be used to check the immune status of vaccinated animals, or as part of diagnosis on a herd basis; however, cross-reactions occur with various *Ehrlichia* species and other related organisms, such as some members of the genus *Anaplasma*. False negative results can also be seen, especially in cattle. Furthermore, infected animals typically seroconvert after recovery, and many animals die, making serology of limited use for clinical diagnosis in individual animals.

Heartwater carriers are difficult to detect. Rickettsial colonies are difficult to find in these animals, and animal inoculation may be unsuccessful except during the first few weeks after recovery. Carriers may sometimes be found by PCR, or by feeding ticks on the animal and testing the ticks by PCR. Some carriers can be seronegative.

Treatment

Tetracyclines are reported to be effective in the early stage of the disease. Prolonged treatment and/or larger doses may be needed if treatment is started later, and antibiotics are often ineffective once neurological signs appear. Sulfonamides also have activity against *E. ruminantium* but are less effective. Treated animals can remain carriers.

Supportive treatment (fluids, nutritional support) may also be needed. and additional drugs may be indicated to treat or mitigate conditions such as peripheral vascular collapse, increased capillary permeability, edema and convulsions. Animals should be kept quiet and undisturbed, in comfortable surroundings; stimuli may elicit fatal convulsions.

Control

Disease reporting

A quick response is vital for containing outbreaks in regions free of heartwater, particularly where potential tick vectors exist. Veterinarians who encounter or suspect this disease should follow their national and/or local guidelines for disease reporting. In the U.S., state or federal veterinary authorities should be informed immediately.

Prevention

E. ruminantium cannot survive outside a living host for more than a few hours at room temperature. For this reason, heartwater is usually introduced in infected animals, including asymptomatic carriers, or in ticks. In heartwater-free countries, susceptible ruminants from endemic regions are tested before importation. Because serology is

unreliable, the World Organization for Animal Health (OIE) currently recommends that the epidemiology of the importing herd be studied to determine that the animals and their resident ticks are free of *E. ruminantium*, and that the animals also be repeatedly tested by PCR. In addition, all animals that may carry *Amblyomma*, including species not susceptible to heartwater, must be inspected for ticks before entry. Wild animals such as birds may also be an issue. Cattle egrets (*Bubulcus ibis*) have been implicated in the dispersal of *Amblyomma* ticks in the Caribbean. Outbreaks occurring outside endemic regions are usually controlled with quarantines, euthanasia of infected animals and tick control. It is important to prevent ticks from feeding on infected animals, or the disease may be impossible to eradicate.

In endemic regions, clinical cases are prevented by prophylactic treatment of newly introduced animals with tetracyclines, strategic tick control and/or immunization. Tick control is usually employed at levels that prevent animals from being exposed to high doses of *E. ruminantium*, but allow continuous low level exposure. This helps establish immunity in young animals and maintains it in older members of the herd. Intensive tick control is no longer recommended in endemic regions, as it eliminates this immune boosting effect, and there can be serious losses if there is a break in tick control. Potential issues with tick control include the development of acaricide resistance, as well as seasonal increases in tick numbers and other problems that can make it difficult to control heartwater with this method alone.

Immunization currently consists of infecting animals with a commercial "vaccine" that contains a live, moderately virulent, *E. ruminantium* strain, then treating them with antibiotics when a fever develops. Alternatively, this vaccine may be given to young kids or lambs during their first week of life, or to calves during the first month. Such young animals are resistant to heartwater, and usually do not require treatment. (However, more valuable animals may still need to be monitored.) This vaccine does not protect animals from all field strains, and revaccination is risky due to the possibility of anaphylactic reactions. Other types of vaccines are in development, and some experimental vaccines have been tested in field trials.

It might be possible to eradicate heartwater from some regions by eliminating its vectors. However, *Amblyomma* ticks are difficult to eradicate due to their high rate of reproduction, the wide variety of hosts they infest, and the development of acaricide resistance. Regional *Amblyomma variegatum* eradication programs (the Caribbean *Amblyomma* Program and the POSEIDOM Vétérinaire Programme) were conducted in the Caribbean between 1994 and 2008. These programs succeeded in reducing the numbers of ticks on some islands and eradicating them from others, but complete eradication throughout the Caribbean was not achieved.

Morbidity and Mortality

The mortality rate in susceptible livestock ranges from <10% to 90%, depending on the animal's species, breed and previous exposures. Morbidity and mortality rates are normally higher in non-native than indigenous breeds, and sheep and goats are usually affected more severely than cattle. For example, up to 80% of merino sheep may die, but the mortality rate can be only 6% in Persian or Afrikander sheep. Angora and Saanen goats are also very susceptible to heartwater, while Creole goats in Guadeloupe are resistant. In cattle, reported mortality rates can be as high as 60-80%, and *Bos indicus* breeds tend to be less severely affected than *Bos taurus*. Genetic resistance has been demonstrated in some breeds. Young ruminants are resistant to heartwater. Sheep and goats are reported to be resistant during the first week of life, while immunity can last up to 6-9 weeks in some calves. At least in calves, there appears to be a maternally-derived component in addition to innate immunity. Early resistance might be shortened in calves from heartwater-naïve dams.

Most infections in wild ruminants appear to be subclinical or mild, but high mortality rates have been reported in lechwe introduced into endemic areas, and in experimentally infected white-tailed deer. Occasional cases of heartwater have also been reported in other wild ruminants in Africa.

Internet Resources

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

United States Animal Health Association.
Foreign Animal Diseases
http://www.aphis.usda.gov/emergency_response/downloads/nahems/fad.pdf

World Organization for Animal Health (OIE)
http://www.oie.int

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/

OIE Terrestrial Animal Health Code
http://www.oie.int/international-standard-setting/terrestrial-code/access-online/

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*Link defunct as of 2015.