Heartwater

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

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Importance

Heartwater, a tick-borne bacterial disease of domestic ruminants caused by *Ehrlichia ruminantium*, is one of the most important diseases of livestock in Africa. This disease can significantly decrease productivity in endemic areas, and it can cause severe outbreaks in young unvaccinated animals or newly introduced non-indigenous livestock, which often die if they are not treated with antibiotics soon after the illness starts. Wild ungulates contribute to the organism's maintenance and sometimes also become ill.

E. ruminantium can enter new regions in infected animals or ticks, including ticks on hosts that are not susceptible to heartwater itself, such as people, reptiles or migrating birds. On at least one occasion, tortoises imported into Florida were found to be carrying infected ticks, and cattle egrets (*Bubulcus ibis*) were probably involved in spreading *A. variegatum* between some islands in the Caribbean. Once a population of infected ticks becomes established in an area, eradication may become difficult or impossible. The presence of heartwater in the Caribbean, the only region outside Africa where this disease has become endemic, increases the risk that it could enter North or South America.

Etiology

Heartwater is caused by the obligate intracellular bacterium *Ehrlichia* (formerly *Cowdria) ruminantium*, a small, Gram negative, pleomorphic coccus in the family Anaplasmataceae and order Rickettsiales. Strains of *E. ruminantium* are very diverse and can vary significantly in their virulence.

Closely related species of *Ehrlichia*, such as the Panola Mountain *Ehrlichia* in the U.S., can complicate the detection of heartwater in some areas, as these organisms can cross-react in serological tests and false positives have been reported in some PCR assays, depending on the primers used.

Species Affected

E. ruminantium affects cattle, sheep, goats and water buffalo. This organism was also proposed to be the cause of a heartwater-like disease reported in camels in Africa; however, some evidence suggests that this disease is more likely to be caused by another agent. Wildlife known to be susceptible to *E. ruminantium* include antelopes such as blesbok (*Damaliscus pygargus*), sable antelope (*Hippotragus niger*), springbok (*Antidorcas marsupialis*), greater kudu (*Tragelaphus strepsiceros*), wildebeest (*Connochaetes gnou, C. taurinus*), eland (*Taurotragus oryx*), lechwe (*Kobus leche kafuensis*), steenbok (*Raphicerus campestris*) and sitatunga (*Tragelaphus spekii*); certain other African ungulates such as African buffalo (*Syncerus caffer*) and giraffes (*Giraffa camelopardalis*); and some cervids including naturally infected Timor deer (*Cervus timorensis*) and chital (*Axis axis*) and experimentally infected white-tailed deer (*Odocoileus virginianus*). Bison (*Bison* spp.), and wild relatives of sheep and goats, including Arabian tahrs (*Arabitragus jayakari*), are also thought to be susceptible, though definitive confirmation is lacking. A report of possible fatal heartwater in an African elephant (*Loxodonta africana*), which was co-infected with *Bacillus anthracis*, the agent of anthrax, is unproven.

E. ruminantium has been reported occasionally in animals other than ungulates. Nucleic acids of this or a related species were detected by PCR in both healthy dogs and dogs with symptoms suggestive of ehrlichiosis in Africa, and dogs experimentally infected with one isolate of *E. ruminantium* were PCR positive for up to 3 weeks, though they remained asymptomatic. Experimental infections have been established in ferrets, laboratory mice and some wild rodents (e.g., the four-striped grass mouse, *Rhabdomys pumilio* and the southern multimammate mouse, *Mastomys coucha*), but these species are not thought to be natural hosts for heartwater. Other animals that have been proposed as hosts include the scrub hare (*Lepus saxatilis*), leopard tortoise (*Geochelone pardalis*) and helmeted guinea fowl (*Numida meleagris*); however, subsequent studies could not confirm the initial reports of susceptibility in leopard tortoises and guinea fowl.

Zoonotic potential

Currently, the only indication that *E. ruminantium* might be zoonotic is a report, published in 2005, of positive PCR results for this organism in three fatal human illnesses in Africa. Two were children with encephalitis, vasculitis of the brain and pulmonary edema. Clinical details were not available for the other case, in an adult. Definitive evidence for a causative role was lacking, and there have been no reports of possible human cases since that time.

Geographic Distribution

Heartwater is endemic in most of sub-SaharanAfrica and surrounding islands such as Madagascar, Mauritius, Reunion, the Comores and Mascarenes, as well as in some islands in the Caribbean.

Reports of possible *E. ruminantium* or a related organism in Asia include the PCR-based detection of a single *E. ruminantium* gene in ticks and cattle blood in China and one report of *E. ruminantium*-like organisms on visual examination of the brains of two Arabian tahrs with a fatal illness resembling heartwater in Oman in 2018. The tahrs were housed with other exotic species, which were apparently not examined for possible carrier status, and there was no isolation of the organism or genetic confirmation of its identity.

Transmission

E. ruminantium is transmitted by ticks in the genus *Amblyomma*, especially *A. hebraeum* (the South African bont tick) and *A. variegatum* (the tropical bont tick). The latter is its sole vector in the Caribbean. It can also be acquired from other *Amblyomma* species, such as *A. lepidum*, *A. gemma*, *A. astrion* and *A. pomposum*, though they are more limited in their distribution or less likely to infest livestock, and certain species found outside endemic areas (e.g., the three North American species *A. maculatum*, *A. mixtum* and *A. dissimile*) are competent vectors in the laboratory. This organism can be transmitted transstadially in *Amblyomma* ticks, which can remain infected for at least 15 months, but transovarial transmission is not thought to be significant in this genus. Other tick genera were historically not considered to be vectors for *E. ruminantium*; however, *Rhipicephalus microplus* can infect sheep under laboratory conditions and can also transmit the organism transovarially, though the sheep infected via tick bites in one study had only mild clinical signs.

Cattle, sheep, goats and some wild ungulates (e.g., African buffalo, giraffes and some antelope) can carry *E. ruminantium* at low levels for several weeks to almost a year after recovery, and are capable of infecting ticks during this time. This organism has also been detected in colostrum, and vertical transmission has been demonstrated in calves, though these experiments could not distinguish transplacental transmission from acquisition in colostrum or milk. *E. ruminantium* can spread between animals iatrogenically in blood, for instance when unsterilized needles are reused; however, significant transmission on fomites is otherwise considered unlikely in the field, as the organism does not survive outside a host for more than a few hours at room temperature, and blood exposed to sunlight loses its infectivity in less than 5 minutes. *E. ruminantium* has been reported to persist for as long as 72 hours at 4°C (39°F).

Disinfection

E. ruminantium is an obligate intracellular organism and does not survive long outside the host, but agents employed against other Gram negative bacteria would probably be effective if disinfection is warranted.

Incubation Period

The incubation period is usually around 1-3 weeks, but some infections can become apparent as early as 5 days or as late as 4-5 weeks.

Clinical Signs

Heartwater ranges in severity from a mild or subclinical disease known as heartwater fever to a peracute, rapidly fatal illness.

The classical acute form usually begins with a sudden fever and nonspecific signs of illness such as anorexia, listlessness and congested mucous membranes, with most affected animals also developing respiratory signs (e.g., moist cough, bronchial rales, rapid breathing), which may progress to dyspnea and, in the terminal stage, frothing at the mouth. Some animals also have diarrhea, which is sometimes profuse and/or hemorrhagic; however, this is inconsistent and diarrhea has not been reported in some experimentally infected animals. Neurological signs are common and become more severe as the illness progresses. Convulsions, lateral recumbency with paddling or galloping movements, opisthotonos, hyperesthesia and nystagmus may be seen terminally. Animals that become recumbent usually die. Sudden death is the primary finding in peracute cases, which occur most often in non-native breeds of cattle and small ruminants. It is sometimes preceded by a brief interval of fever, severe respiratory distress, hyperesthesia, lacrimation and possibly diarrhea, and convulsions may be seen in the terminal stage.

Heartwater can also present as a milder subacute illness with a prolonged fever, coughing and death or recovery within 1-2 weeks. Neurological signs are inconsistent in this form, and deaths are often due to complications such as pneumonia. A transient fever may be the only clinical sign in heartwater fever, which is a mild or subclinical infection most often seen in neonatal lambs and goats, young calves, partially immune older animals, some indigenous breeds and resistant wildlife in endemic regions.

Post Mortem Lesions

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Animals with heartwater often have pulmonary and mediastinal edema with congestion in the lungs, froth in the trachea and hydrothorax, as well as ascites, perirenal edema, and edema of the mediastinal and bronchial lymph nodes. Hydropericardium with straw–colored to reddish pericardial fluid, the lesion that gives heartwater its name, is more

consistently found in sheep and goats than cattle. Congestion and/or edema may also be noted in other organs. In the gastrointestinal tract, it is most often seen in the abomasal mucosa of cattle. The heart often contains subendocardial petechiae, and submucosal and subserosal hemorrhages may be found in various other organs. Splenomegaly may also be apparent, particularly in sheep and goats, though the enlargement may not be marked. Gross lesions are usually subtle or absent in the CNS, except for occasional cases with congestion of the meningeal vessels and/or meningeal edema. Animals that die suddenly may have few or no gross lesions.

Diagnostic Tests

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. The specificity of PCR assays varies and some tests may cross-react with some other *Ehrlichia*, especially closely related organisms such as the Panola Mountain *Ehrlichia*. Loop-mediated isothermal amplification (LAMP) assays to detect *E. ruminantium* have also been published.

In endemic areas, heartwater is often diagnosed at necropsy by observing *E. ruminantium* colonies in stained (e.g., Giemsa) smears from the brain, especially in well-vascularized areas such as the cerebrum, cerebellum or hippocampus, or in the intima of blood vessels. This technique can also be used in live animals if tissue samples are collected via biopsy, though this is often impractical. *E. ruminantium* colonies appear as clumps of reddish-purple to blue, coccoid to pleomorphic organisms inside capillary endothelial cells, are often found close to the nucleus, and may be in a ring or horseshoe. Experience is necessary for identification of the organisms, as they can resemble other agents such as *Babesia bovis*, stain precipitates, and certain subcellular structures or blood cells. Immunoperoxidase techniques, including combined immunostaining and counterstaining with hematoxylin, can also be employed, and are more likely to detect small numbers of organisms than tissue stains alone. Colonies can be difficult or impossible to find in the tissues of some animals that have been treated with antibiotics, and only a few colonies may be detected in peracute cases.

Culture of *E. ruminantium* is not usually used for routine diagnosis in endemic regions, as it is labor-intensive and slow. This organism can be isolated (e.g., from blood samples) in many primary ruminant endothelial cells, endothelial cell lines and some tick cell lines such as IDE8. Recovered organisms have traditionally been identified by microscopic examination and/or immunostaining. Heartwater may also be diagnosed by inoculating fresh blood from a suspected case into a susceptible sheep or goat, though this is generally discouraged for animal welfare reasons.

Serology can be employed on a herd basis, but is of limited value for identifying clinical cases in individual animals, as seropositive animals are common in endemic regions, sick animals may die before developing antibodies, and tests can cross-react with other ehrlichiae. Some of the available tests include indirect immunofluorescence, ELISAs and immunoblotting (Western blotting).

Heartwater carriers are difficult to identify. These animals are sometimes seronegative, colonies are difficult to find in their tissues, and while PCR may sometimes identify nucleic acids in the blood or bone marrow, this is inconsistent. Some carriers have been identified by feeding ticks on the animal and testing the ticks by PCR. Animal inoculation may also be successful during the first few weeks after recovery from a clinical case.

Treatment

E. ruminantium is resistant to most antibiotics but can be treated with a few drugs, such as tetracyclines, combined with supportive care as needed. Early treatment is important, as antibiotics are often ineffective once neurological signs appear. Animals should be kept comfortable, quiet and undisturbed, as stimuli may elicit fatal convulsions. Treated animals can remain carriers.

Control

Disease reporting

Veterinarians who encounter or suspect heartwater 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

In endemic regions, clinical cases are prevented by prophylactic treatment of newly introduced animals with tetracyclines, tick control and/or immunization. Although intensive tick control can be used, there may be serious losses if there is any break in acaricide applications or effectiveness, as the treated animals will have little or no immunity to heartwater. For this reason, tick control is often employed strategically, 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. The only currently available commercial vaccine contains a live, moderately virulent *E. ruminantium* strain, which can either be administered to neonatal animals, which tend to be inherently resistant to heartwater, or to older animals which are treated with antibiotics once they develop a fever but before they become significantly ill.

E. ruminantium is usually introduced into a heartwater-free region in infected animals, including asymptomatic carriers, or in ticks. During import testing, the World Organization for Animal Health (WOAH) recommends that animals be repeatedly tested by PCR and that the epidemiology of the importing herd also be studied to determine that the animals and their resident ticks are free of this organism. Animals that may carry *Amblyomma* ticks but are not susceptible to heartwater, including reptiles, should also be inspected for ticks before entry.

Outbreaks in heartwater-free regions are usually controlled with quarantines and movement controls, euthanasia of infected animals, and treatment with acaricides to prevent the establishment of an infected tick population in the area. While it is theoretically possible to eradicate heartwater by eliminating its vectors, *Amblyomma* ticks are difficult to eliminate 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 conducted in the Caribbean between 1994 and 2008 were ultimately unsuccessful, though they succeeded in reducing the numbers of ticks on some islands and eradicating them from others.

Morbidity and Mortality

The mortality rate in untreated livestock ranges from <10% to 90%, depending on the animal's species, breed and previous exposures, as well as the virulence and dose of the infecting strain. Newborn lambs and kids are innately resistant to clinical signs, regardless of the immune status of their dams, during the first week of life. Innate resistance appears to last for about 3-4 weeks after birth in calves; however, many calves do not seem to develop severe disease for up to 6-9 weeks of age, possibly due to additional contributions from maternal immunity.

While serious illnesses are possible in all susceptible livestock, clinical cases are often particularly severe in sheep and goats. Breeds imported from regions free of heartwater (e.g., Merino sheep, Angora or Saanen goats) may have morbidity and mortality rates up to 80% or higher, while indigenous breeds in heartwater areas, such as Afrikander sheep or Creole goats, usually have milder signs. One estimate indicated a mortality rate of about 10% among indigenous goats in Guadalupe. Whether resistance is an innate characteristic of a breed or the result of natural selection among resident animals in heartwater areas is unclear; however, there appears to be a genetic component, as some animals can pass their resistance to offspring when cross-bred with susceptible breeds. Cattle can sometimes have mortality rates as high as 60-80%, with *Bos taurus* breeds often more severely affected than *Bos indicus*. Coinfections and the general health of the animal may also be important: in one study, all experimentally infected sheep in the U.S. recovered without treatment, after a clinical course of 2 days to 2 weeks.

Most infections among wildlife in endemic regions appear to be subclinical or mild. Nevertheless, clinical cases can be seen occasionally, and high mortality rates have sometimes been reported in previously unexposed animals (e.g., lechwe) introduced into endemic areas. Many cases in experimentally infected white-tailed deer from North America were also fatal.

Internet Resources

The Merck Veterinary Manual

United States Animal Health Association. Foreign Animal Diseases

Heartwater Disease: Potential Worldwide Threats for Livestock. Gap Analysis Workshop Report. 2018. Agricultural Research Service, Washington, D.C

World Organization for Animal Health (WOAH)

WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

WOAH Terrestrial Animal Health Code

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*Link defunct