Diseases Caused by the Epizootic Hemorrhagic Disease Virus Serogroup

Epizootic Hemorrhagic Disease, Hemorrhagic Disease, Ibaraki Disease, Bovine Influenza, Bovine Epizootic Fever, Bluetongue-like Disease

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Importance

Epizootic hemorrhagic disease is an important disease of cervids, especially white-tailed deer. The causative virus is widespread among wild cervids in North America, where white-tailed deer are endemic, and periodically causes serious epidemics in wild and/or captive populations. Sporadic clinical cases and outbreaks have also been reported in other cervids, cattle, bison, yaks and other animals, although most infections in these species seem to be subclinical. In Japan, the illness in cattle is called Ibaraki disease, and there have been several outbreaks of varying severity, with mortality rates as high as 10%. Since 2004, other serotypes of epizootic hemorrhagic disease virus (EHDV) have caused outbreaks in cattle and some other ruminants in the Middle East, the Caribbean and North America. Some of these outbreaks were extensive, although the illness was generally milder than in white-tailed deer. In addition to occasional deaths, these epidemics resulted in significant economic losses from decreased productivity, including reduced milk yield. Disease control is difficult, as EHDV is spread by *Culicoides* midges, and commercial vaccines for cattle are only produced in Japan.

Etiology

Epizootic hemorrhagic disease virus (EHDV) belongs to the genus *Orbivirus*, family *Reoviridae.* Seven serotypes (1, 2 and 4-8) are currently recognized. The former serotype 3 viruses now belong to serotype 1 (EHDV-1), and EHDV-318 has been incorporated into EHDV-6. Ibaraki disease, which occurs in parts of Asia, is caused by the Ibaraki strain of EHDV-2 (formerly Ibaraki virus). One outbreak of Ibaraki disease, in 1997-1998, is now attributed to a serotype 7 virus.

Like some other viruses, epizootic hemorrhagic disease viruses can reassort and recombine to produce new variants. Many, or perhaps all, of the serotype 6 viruses in North America are reassortants between serotype 2 and serotype 6 viruses.

EHDV is closely related to bluetongue virus, a factor that can influence the development and/or selection of some diagnostic tests.

Species Affected

Many cervids can be infected with EHDV, and clinical cases have been reported in some species. White tailed deer (*Odocoileus virginianus*) are highly susceptible, and are known to become ill after infection with serotypes 1, 2, 6 and 7. They are probably susceptible to all 7 serotypes. Clinical cases have also been reported occasionally in other species including mule deer (*O. hemionus*), pronghorn (*Antilocapra americana*), North American elk (*Cervus elaphus nelsoni*) and pygmy brocket deer (*Mazama nana*). Probable but unconfirmed fatal cases were documented in a captive gray brocket deer (*M. gouazoubira*) and several wild marsh deer (*Blastocerus dichotomus*). Serological and/or virological evidence of infection has been reported in naturally infected, asymptomatic marsh deer, black-tailed deer (*O. hemionus columbianus*), goitered gazelle (*Gazella subgutturosa subgutturosa*), rusa deer (*C. timorensis rusa*) and other cervids. Red deer (*C. elaphus elaphus*), fallow deer (*Dama dama*), roe deer (*Capreolus capreolus*) and Muntjac deer (*Muntiacus muntjac*) can be infected experimentally, although no clinical cases have been reported.

Outbreaks and sporadic cases caused by various serotypes, including EHDV-1, EHDV-2, EHDV-6 and EHDV-7, have been reported in cattle, although subclinical infections seem to be much more common. Clinical cases have also been seen in a few yaks (*Bos grunniens*), American bison (*Bison bison*), and bighorn sheep (*Ovis canadensis*), and rarely in sheep and alpacas. Antibodies have been found in a few goats, although viruses could not be recovered from experimentally infected animals. Some other species reported to have serological and/or virological evidence of infection include water buffalo, Arabian oryx (*Oryx leucoryxoryx*) black rhinoceros (*Diceros bicornis*), white rhinoceros (*Ceratotherium simum*) and black bears (*Ursus americanus floridanus*). EHDV did not seem to replicate in experimentally infected pigs, and one survey found no evidence of infection in dogs.

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Zoonotic potential

There is no evidence that epizootic hemorrhagic disease virus infects humans.

Geographic Distribution

The distribution of competent vectors for EHDV predicts that these viruses could theoretically be maintained between latitudes 35°S and 49°N. To date, EHDV has been reported from North and South America, the Caribbean, Australia, Asia, Africa and the Middle East, with seropositive animals detected as far north in Eurasia as Turkey. Serotypes 1, 2 and 6 are currently endemic in North America. Viruses of these serotypes have also been reported from the Caribbean, although only serotype 6 has been identified to date in South America. Serotypes 1, 2, 5, 6, 7 and 8 are known to occur in Australia; serotypes 1,4 and 6 have been identified in Africa; serotypes 6 and 7 caused outbreaks in the Middle East, and serotypes 2, 5 and 6 have been reported from parts of Asia. The form of disease in cattle known as Ibaraki disease has been seen in Japan, Korea and Taiwan.

Some areas where EHDV circulates, including Australia, have reported few or no clinical cases. EHDV has not been found in Europe, but there has been only limited surveillance for subclinical infections in wild cervids.

Transmission

EHDV is transmitted by biting midges in the genus *Culicoides*, which act as biological vectors. These midges can fly short distances of 1- 2 km, but they can be blown much farther by wind. Relatively little is known about which species of *Culicoides* are the primary vectors in each area, although some (e.g., the North American species *C. sonorensis*) are proven to be competent vectors in the laboratory. While mosquitoes or other blood-sucking insects might theoretically be able to transmit this virus mechanically, and there is one report of virus isolation (EHDV-4) from two *Anopheles* mosquitoes in Asia, such insects are thought to have little or no role in the epidemiology of this disease. Iatrogenic transmission has not been reported, but it is also theoretically possible.

Infected animals can remain viremic for varying periods. A few white-tailed deer were viremic for up to 2 months in laboratory experiments, although most seem to clear the virus by 3 weeks. Australian EHD viruses were isolated from experimentally infected cattle for a mean of 1-4 weeks, with a maximum of 2-8 weeks depending on the serotype. Experimentally infected deer can also shed EHDV in oral secretions and feces; however, this is not thought to be significant in transmission, except possibly where animal densities are high in captive populations.

The Ibaraki strain of EHDV-2 has been found in the internal organs of aborted fetuses. Probable vertical transmission of EHDV was also reported in one calf in the U.S. This calf was born to a symptomatic cow with a confirmed diagnosis, and had clinical signs consistent with infection *in utero*, but no diagnostic samples were collected.

Disinfection

Effective disinfectants for EHDV include acids, oxidizing agents such as sodium or calcium hypochlorite at 20,000-30,000 ppm (2-3%), alkalis such as 2% sodium hydroxide, glutaraldehyde, beta-propiolactone, iodophors and phenolic compounds. most nonenveloped viruses, EHDV is resistant to lipid solvents (e.g., ether, chloroform). It can be inactivated by heat treatment at 50°C for 3 hours, 60°C for 15 minutes, or 121° C for 15 minutes.

Incubation Period

The incubation period for epizootic hemorrhagic disease in deer is estimated to be 5-10 days.

Clinical Signs

Deer

Clinical cases in white-tailed deer range from peracute illness, with death often occurring within 36 hours, to a more chronic course with animals remaining ill for several weeks. Some deer are found dead with few or no clinical signs. In other cases, there may be fever, anorexia, lethargy, weakness, stiffness/ lameness, respiratory distress, and severe and rapid edema of the head and neck. Swelling of the mucous membranes of the oral cavity, and swelling and hyperemia of the conjunctiva, are common. Ulcers and erosions in the oral cavity can result in excessive salivation and nasal discharge, which may both be blood-tinged. Diarrhea and dehydration have also been seen. Some animals develop progressive abnormalities in blood clotting, with extensive hemorrhages in many tissues including the skin and gastrointestinal tract. Deaths are common during the acute stage of the disease. Surviving animals may have ulcers, erosions, scars and other damage to the lining of the rumen and omasum, resulting in prolonged lethargy and inappetence, and some animals become emaciated. There may also be breaks or rings in the hooves caused by growth interruptions, resulting in lameness. In severe cases, animals slough the hoof wall or toe; some of these deer may be found crawling on their knees or chest.

Similar signs, including sudden death, have been reported in some other cervids (e.g., brocket deer). Few clinical cases have been described in naturally infected mule deer. One animal was found dead; another deer in the same location had clinical signs of lethargy, emaciation, ataxia, and opaque nasal and oral discharge, and died soon after capture. Farmers have reported illnesses in elk during outbreaks, and infection was confirmed in one herd with clinical signs during the 2012 outbreaks in the U.S. However, descriptions of these illnesses have not been published. One naturally-infected elk, housed in a facility that had sick white-tailed deer, had an episode of lethargy that may have been associated with the infection.

Cattle and yaks

Most infections in cattle, including infections with the viruses causing Ibaraki disease, are thought to be subclinical.

Ibaraki disease, which occurs among cattle in parts of Asia, is the best-known syndrome in cattle. Common clinical signs of Ibaraki disease include fever, anorexia, conjunctival injection with lachrymation, nasal discharge and foamy salivation. Infected animals may develop edema, hemorrhages, erosions and/or ulcerations in the mouth, on the lips, and around the coronets. They can also be stiff and lame, and the skin may be thickened and edematous. Swallowing disorders, which are considered to be the pathognomonic sign of Ibaraki disease, occur in 20-30% of affected animals. They are caused by damage to the striated muscles of the pharynx, larynx, esophagus and tongue, and may lead to dehydration, emaciation and aspiration pneumonia. Abortions, fetal malformations and stillbirths were reported during the 1997-1998 Ibaraki disease outbreak in Japan, which was caused by a serotype 7 virus (most other outbreaks have been caused by serotype 2 viruses). Some affected cattle die, often due to complications from dysphagia and aspiration pneumonia.

There were few descriptions of epizootic hemorrhagic disease in cattle outside Asia until 2004, when outbreaks were reported on Reunion Island, followed by further outbreaks in the Middle East in 2006, the Caribbean in 2011, and the U.S. in 2012. The clinical signs in these and earlier outbreaks included fever, oral lesions (erosions, ulcers, necrotic lesions, erythema and swelling), excessive salivation, nasal discharge and crusting of the muzzle, inappetence or difficulty eating, ocular signs (conjunctival edema, palpebral swelling and ocular discharge), stiffness, lameness associated with coronitis, mammary gland lesions (teat erythema, red-to-purple udder discoloration) and weight loss. Mild yield dropped significantly during some outbreaks. Hemorrhagic lesions were described on some farms: some cattle in Israel had petechiae in the oral cavity and edema and ecchymoses on the hooves, and some animals in the U.S. had diarrhea with tarry feces or frank undigested blood in the feces. Respiratory signs, including respiratory distress, and neurological signs were also reported, though rarely, and abortions occurred in some animals. One premature calf born to an infected cow had signs consistent with epizootic hemorrhagic disease at birth, but recovered. In pregnant cows experimentally infected with EHDV, the fetus may be resorbed or develop hydranencephaly if it is infected between 70 and 120 days of gestation. Deaths have been reported occasionally in cattle, but most animals seem to recover in 3-30 days. Some animals may remain lame and unthrifty for a prolonged period.

Oral, nasal and ocular signs and lameness, similar to the clinical signs in cattle, were reported in yaks during the outbreaks in the U.S. One animal had scant, dark black, watery feces with fresh blood. This animal, which died, also developed neurological signs consisting of intermittent focal facial tremors and excessive lip smacking. An acute, fatal hemorrhagic disease, which may have been epizootic hemorrhagic disease, was described in a yak at a U.S. zoo in 1970. In this case, the clinical signs included acute depression and anorexia, with blood in the feces, sanguineous ocular secretions, and hemorrhagic sclera.

American bison may either remain asymptomatic or develop clinical signs that resemble the illness in cattle.

Other species

One herd of sheep was reported to be affected during outbreaks in the U.S. in 2012, but no details are currently available. However, illnesses attributed to EHDV were recently described in two herds of sheep in Turkey. The clinical signs in one herd were high fever, edema of the head, which was especially prominent under the chin, and mouth and nose lesions including hyperemia and foamy saliva. In the second herd, the signs included anorexia, lethargy, edema of the head, lameness, abdominal distension and oral lesions including oral hyperemia and mild cyanosis of the tongue. A few affected sheep died, including two ewes in the late stages of pregnancy. Experimentally infected sheep have remained asymptomatic or had clinical signs limited to a rise in body temperature, mild buccal hyperemia and/or ulceration. However, epizootic hemorrhagic disease has been difficult to reproduce in other ruminants, including cattle, for unknown reasons, and these experiments do not preclude the possibility that some naturally infected sheep might have more severe signs.

Most bighorn sheep affected by epizootic hemorrhagic disease have been found dead, or the clinical signs were not described. However, the signs that have been mentioned (e.g., lethargy and swelling of the head, face and lips) resemble the illness in other species.

Post Mortem Lesions

The lesions in white-tailed deer are characterized by hemorrhages and edema of varying severity and extent. Petechiae, ecchymoses and hemorrhages can be found in various organs and tissues, and may be widespread. Commonly affected sites include the oral mucous membranes, skin, subcutaneous tissues and viscera, especially the heart, aorta, base of the pulmonary artery, gastrointestinal tract, lymph nodes, urinary bladder, and serosal surfaces of the pleural and peritoneal cavities. Areas of discoloration suggestive of erosions and ulcerations maybe found in the gastrointestinal tract, including the mouth, rumen and omasum. Pulmonary edema and pericardial effusion, which may be severe, can be seen in some cases. Dry, gray-white necrotic lesions may sometimes be detected in the hard palate, tongue, dental pads, esophagus, larynx, rumen and abomasum. Some animals may have rings or breaks on the hooves, or sloughing of the tips or walls of the hooves.

Lesions reported from fatal cases in other species, including yaks, brocket deer and bighorn sheep, have been similar. There are few description of fatal cases in cattle;

however, some animals with Ibaraki disease have degeneration of the striated muscles in the esophagus, larynx, pharynx, tongue, and skeletal muscles, in addition to edema and hemorrhagic lesions of the oral cavity, abomasum and coronets. Signs of aspiration pneumonia may also be present.

Diagnostic Tests

Virological evidence of EHDV can be found in the blood of viremic animals or in tissue samples (especially spleen, lymph nodes, lung) collected at necropsy. EHDV can be isolated in various cell lines including Vero, BHK21 or variants of KC (*Culicoides variipennis*) cells, or in embryonated chicken eggs. The virus can be identified with techniques such as immunofluorescence, serogroup-specific sandwich ELISAs or reverse transcriptase polymerase chain reaction (RT-PCR) assays. Methods to identify the viral serotype include virus neutralization or plaque inhibition tests with reference antisera, or serotype-specific RT-PCR assays. Serogroup-specific RT-PCR tests can be used to detect viral RNA directly in blood or tissues. (Other molecular techniques, such as dot blot assays or *in situ* hybridization, have also been described.) Viral RNA can sometimes be found for prolonged periods (e.g., for up to 160 days in deer tissues) and may still be present after the animal has cleared the virus and recovered. Viral antigens can be detected in tissues by immunofluorescence or ELISAs (antigen capture c-ELISA or sandwich ELISA). Rapid, penside antigen detection tests such as lateral flow assays have also been developed, and may be commercially available in some areas.

Currently available serological tests include ELISAs, virus neutralization and agar gel immunodiffusion (AGID). Virus neutralization is labor-intensive and takes 3-5 days to perform, and the World Organization for Animal Health (OIE) recommends a monoclonal antibody-based competitive ELISA (C-ELISA). AGID and some ELISAs cannot distinguish EHDV from bluetongue or other orbiviruses. Antibodies to EHDV can usually be found 10-14 days after the animal was exposed, and neutralizing antibodies and viruses may be found concurrently in infected animals. Many deer and cattle have pre-existing antibodies to EHDV, and a rising titer should be diagnosed with paired serum samples.

Treatment

There is no specific treatment for epizootic hemorrhagic disease, other than supportive care.

Control

Disease reporting

Epizootic hemorrhagic disease is difficult to control once it has been transmitted to its vectors. Infections should be reported quickly in countries where EHDV is not endemic. Veterinarians who encounter or suspect this disease should follow their national and/or local guidelines for reporting.

Epizootic hemorrhagic disease is endemic in the U.S.; however, this disease has sometimes been reportable in certain states. State authorities should be consulted for current information.

Prevention

Live attenuated and inactivated Ibaraki disease vaccines are used in cattle in Japan, but commercial vaccines for domesticated ruminants are not available outside this area, at present. Autogenous inactivated vaccines are employed in some captive cervid herds in U.S., but their efficacy has not been published.

Measures to reduce exposure to the *Culicoides* vectors might be helpful during outbreaks, although they are unlikely to be effective as the sole control measure. Such measures can include avoidance of environments where midges are more prevalent (e.g., low-lying, damp pastures), stabling animals from dusk to dawn, and/or the use of insecticides or insect repellents (e.g., insecticide-impregnated nets in stables) to help protect groups of animals. Effective vector control is challenging, due to factors such as the extensive breeding sites and large populations of *Culicoides*, and there are also environmental concerns with widespread use of pesticides. Stabling may vary in efficacy, as some species of *Culicoides* are now known to enter barns and stables, especially late in the season when temperatures are becoming colder.

Some countries affected by outbreaks in the Middle East have implemented vector controls on infected premises, quarantined herds, and established surveillance programs in cattle and monitoring programs for wildlife reservoirs.

There is no known means of prevention in wild cervids.

Morbidity and Mortality

Deer

White-tailed deer are very susceptible to epizootic hemorrhagic disease, with morbidity and mortality rates that can be as high as 90% in captive animals. Data in wild deer are limited, however, mortality rates were estimated to be 6-20% during some outbreaks among EHDV-naive populations in the U.S. Surviving deer develop long-lived neutralizing antibodies. The clinical signs are thought to be much less severe in mule deer and pronghorn, which also reside in areas where white-tailed deer are affected.

In North America, most outbreaks are seen in late summer or early autumn, and new cases usually end with the onset of freezing weather, due to the death of the *Culicoides* vectors. The patterns of disease can differ between regions. In the southeastern U.S., most cases in animals native to the area are mild, and the mortality rates are low. In the Midwest and Northeast, this disease typically recurs most years, but its extent ranges from a few scattered cases to severe epizootics with high mortality rates. This variability is thought to be caused by many factors including the abundance and distribution of the insect vectors, the EHDV serotype, existing herd immunity, and genetic variations in

the susceptibility of the host. Outbreaks are often associated with wet weather, which provides breeding areas for these insects. However, some outbreaks may be linked with droughts, which can concentrate animals and vectors around diminishing water sources. Epizootic hemorrhagic disease is uncommon in Canada, and outbreaks have occurred in limited locations (i.e., the southern portions of Alberta, Saskatchewan and British Columbia).

Little is known about the patterns of disease (if any) in wild species in South America, Africa or the Middle East. However, infections may be common in some cervids. In Brazil, 74% of marsh deer were seropositive for EHDV.

Cattle

Although most cattle seem to be infected subclinically with EHDV, outbreaks and clinical cases have been reported sporadically in endemic regions. Ibaraki disease outbreaks of varying severity have been seen at approximately 5-20 year intervals in Japan. One of the most severe epidemics affected more than 43,000 cattle, with a mortality rate of approximately 10%. Clinical cases have been reported sporadically at other times in unvaccinated herds.

There were few descriptions of epizootic hemorrhagic disease in cattle outside Asia until 2004, when outbreaks were reported on Reunion Island, followed by further outbreaks in several Middle Eastern countries in 2006, the Caribbean in 2011, and the U.S. in 2012. Most of these outbreaks involved a single serotype, while viruses of serotype 2 predominated but did not cause all of the recognized cases in the North American outbreak (a few herds were affected by EHDV-6 or EHDV-1). Some of the recent epidemics were extensive, affecting at least 130 herds in the U.S. and more than 100 dairy and beef herds in Israel. Reported overall morbidity rates in cattle populations ranged from 1% to 19%. However, only a proportion of the cattle in any herd seems to become ill. The reported within-herd morbidity rate ranged from < 0.5% to > 80%, often differing between herds in the same outbreak. Most clinical cases seem to occur in adults; however, some dairy calves < 1 year of age were confirmed to have this disease in the U.S. Clinical cases are generally less severe in cattle than in white-tailed deer, and most animals recover. Reported overall mortality rates up to 2%, and case fatality rates ranging from 2% to 26% were reported during the recent outbreaks.

Seroprevalence rates among cattle in endemic regions can vary from 1% to > 60%, depending on the region and year. Because few or no clinical cases are usually reported, these antibodies are thought to result from subclinical infections. However, some cases might be missed due to lack of awareness and diagnostic testing. Although there was no extensive outbreak among North American cattle in 2013, epizootic hemorrhagic disease was diagnosed in three pregnant cows in a North American herd of 35 animals, and one animal in a nearby herd. Increased awareness resulting from the 2012 outbreak contributed to the recognition of these cases. In North America, clinical cases seem to occur in conjunction with outbreaks in wild cervids.

Other domesticated animals

Cattle were the only domesticated animals affected during the outbreaks in the Caribbean and the Middle East. However, 8 herds of bison, 6 herds of yaks, one herd of elk and one sheep flock developed clinical signs during the 2012 outbreaks in the U.S. The case fatality rates in most species are unknown, but deaths have been reported in bison and yaks.

Very low seroprevalence rates have been reported in sheep and goats during outbreaks among cattle, and small ruminants are not thought to be involved in the epidemiology of epizootic hemorrhagic disease. There is currently only one published description of clinical cases in sheep, from Turkey, Six of 36 sheep were affected in one herd, and 8 of 50 animals in a second herd. Three animals, including two ewes in the late stages of pregnancy, became severely ill and died. Although viral RNA was detected in the sick sheep, antibodies were not found.

Internet Resources

Australia and New Zealand Standard Diagnostic Procedure. Epizootic Haemorrhagic Disease
www.scahls.org.au/Procedures/Documents/ANZSDP/ehd-april2015.pdf

European Food Safety Authority (EFSA). Scientific Opinion on Epizootic Hemorrhagic Disease
http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1418/abstract

United States Geological Survey (USGS) Hemorrhagic Disease in Wild Ruminants
https://www.nwhc.usgs.gov/publications/wildlife_health_bulletins/WHB_2012-05_Hemorrhagic.pdf

USGS National Wildlife Health Center (report or request assistance for wildlife mortality events or health issues)
http://www.nwhc.usgs.gov/mortality_events/reporting.jsp

International Veterinary Information Service (IVIS)
http://www.ivis.org

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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