Rabbit Hemorrhagic Disease

Viral Hemorrhagic Disease of Rabbits, Rabbit Calicivirus Disease

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Importance

Rabbit hemorrhagic disease is an extremely contagious and often fatal viral disease of domesticated and wild rabbits. This disease affects only rabbits of the species *Oryctolagus cuniculus*. Severe losses are common in unvaccinated animals; on some farms, most or all of the rabbits may die. This disease has also caused dramatic declines in some wild rabbit populations, particularly when it is first introduced. Rabbit hemorrhagic disease spreads very readily. The causative virus is very resistant to inactivation if it is protected by organic material; it may persist in chilled or frozen rabbit meat, as well as in decomposing carcasses in the environment, for months.

Rabbit hemorrhagic disease was first seen in the 1980s, but its origins are not completely understood. It may have emerged from avirulent caliciviruses circulating asymptomatically in European rabbit populations. The first known outbreak occurred in China in 1984, spread by angora rabbits that had been imported from Europe. Within nine months, this disease had killed 14 million domesticated rabbits in China. By the late 1990s, outbreaks had been reported from forty countries, and rabbit hemorrhagic disease had become endemic in wild rabbit populations in Europe, Australia and New Zealand. Other parts of the world including the Americas have experienced periodic outbreaks in domesticated rabbits. However, the species of wild rabbits found in North America are not susceptible to rabbit hemorrhagic disease, and this disease has been eradicated from domesticated rabbits each time.

Etiology

Rabbit hemorrhagic disease is caused by the rabbit hemorrhagic disease virus (RHDV), a member of the genus *Lagovirus* and family Caliciviridae. Many strains of RHDV appear to circulate in rabbit populations; these viruses can have distinct epidemiological and genetic characteristics. Only a single serotype is known, but two major subtypes exist: RHDV and the antigenic variant RHDVa. Nonpathogenic strains of RHDV have been identified in wild rabbits. One recent study suggests that different lineages of RHDV may have repeatedly emerged as epidemic viruses.

Species Affected

Rabbit hemorrhagic disease affects wild and domesticated members of the species *Oryctolagus cuniculus*. Other rabbit species including cottontails (*Sylvilagus floridanus*), black-tailed jackrabbits (*Lepus californicus)* and volcano rabbits (*Romerolagus diazzi*) do not seem to be susceptible. Similarly, European brown hares (*Lepus europaeus*) and varying (snowshoe) hares (*Lepus americanus*) are not affected by RHDV, although they are susceptible to a rabbit disease caused by a different calicivirus (European brown hare syndrome). Virus replication has not been reported in other mammals, including rabbit predators, although seroconversion can occur.

Geographic Distribution

Rabbit hemorrhagic disease is endemic in Australia, New Zealand, Cuba, parts of Asia and Africa, and most of Europe. Outbreaks have also been reported from domesticated rabbits in the Middle East and the Americas. Rabbit hemorrhagic disease was endemic in domesticated rabbits in Mexico from the late 1980s to 1991, and limited, independent outbreaks were reported from the U.S. in 2000 (Iowa), 2001 (Utah, Illinois, New York) and 2005 (Indiana). However, the disease was eradicated in each case, and rabbit hemorrhagic disease is not currently endemic in North America.

Transmission

Rabbit hemorrhagic disease is transmitted by direct contact with infected animals, as well as on fomites. Rabbits can acquire this disease through the oral, nasal or conjunctival routes. Most or all excretions including urine, feces and respiratory secretions are thought to contain virus. Animals may remain infectious for up to a month. RHDV can also be acquired by exposure to an infected carcass or hair from an infected animal. Long-term, persistent or latent infections have recently been recognized in rabbits. Whether viral RNA becomes reactivated in these carriers, and under what conditions, is unknown.

RHDV is readily spread on fomites including contaminated food, bedding and water. Flies and other insects are very efficient mechanical vectors; only a few virions are needed to infect a rabbit by the conjunctival route. Wild animals can transmit the virus mechanically. Although virus replication does not seem to occur in predators or scavengers, these animals can excrete RHDV in feces after eating infected rabbits.

RHDV is very resistant to inactivation when it is protected within tissues. This virus can survive for 7.5 months in tissue suspensions stored at 4°C (39°F), and for more than three months at 20°C (68°F) in dried organ homogenates. In one study, RHDV remained viable in decomposing rabbit carcasses at 22°C (72°F) for up to 20 days, but only seroconversion was reported at 26 or 30 days. However, virus-inoculated bovine liver left to decompose in New Zealand fields (to simulate infected carcasses) remained infectious for at least three months. Unprotected viruses shed in excretions are not thought to remain viable for more than a few weeks, and may lose some of their infectivity within one to two weeks. RHDV is also reported to survive exposure to pH 3.0, heat of 50°C (122°F) for an hour, and freeze-thaw cycles.

Incubation Period

The incubation period is one to three days.

Clinical Signs

All rabbits can become infected with RHDV, but young animals are resistant to disease. Typically, symptoms occur only in animals that are more than eight weeks old. Peracute or acute disease is described most often in domesticated rabbits, but subacute and chronic disease can also be seen. In peracute infections, infected rabbits develop a fever and die suddenly within 12 to 36 hours of its onset. The only symptoms may be terminal squeals followed rapidly by collapse and death. In acute disease, dullness, anorexia, congestion of the palpebral conjunctiva, or prostration may be seen. Animals with acute disease can also develop neurologic signs including incoordination, excitement, opisthotonos and paddling. Some rabbits turn and flip quickly in their cages; this can resemble convulsions or mania. Respiratory symptoms, including dyspnea, cyanosis and a terminal, bloodstained, frothy nasal discharge, sometimes occur. Lacrimation, ocular hemorrhages or epistaxis may also be seen. Some animals that recover from acute disease develop severe jaundice, with weight loss and lethargy, and die in a few weeks. In these animals, there may be diarrhea or constipation and abdominal dilatation just before death. Similar but milder symptoms are seen in the subacute form, and most of the rabbits may survive. Chronic, persistent infections are thought to be asymptomatic.

Post Mortem Lesions

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Rabbits that die of rabbit hemorrhagic fever are usually in good condition. The primary lesion is hepatic necrosis, and the most consistent post-mortem lesions are hepatic necrosis and splenomegaly. The liver may be pale, with a fine reticular pattern of necrosis outlining each lobule. In cases with extensive necrosis, the liver can be diffusely pale. It may also be yellow, gray, friable or congested. The spleen is usually black and engorged, with rounded edges. The kidneys may be very dark brown. Disseminated intravascular coagulation (DIC) is common in the terminal stages of disease, and results in hemorrhages in a variety of organs and tissues. The trachea is often hyperemic and contains frothy, bloodstained mucus. Congestion and multifocal hemorrhages may be seen in the lungs. Hemorrhages are also common in the thymus, and petechiae may be found on the serosal membranes or viscera. Infarcts may be seen in most organs. Hemorrhages are not necessarily present in rabbits euthanized before the terminal stage. In subacute disease, catarrhal enteritis of the small intestine and jaundice may also be seen. Congestion of the meninges has been reported.

Morbidity and Mortality

The morbidity rate varies from 30% to 100%, and the mortality rate is 40-100%. The highest morbidity and mortality rates are seen in adult rabbits from naïve populations. Young rabbits less than eight weeks old are less likely to become ill or die. In some experiments, 40% of 5 to 8 week old rabbits survived when 90% of adult rabbits were killed by the same dose. Rabbits four weeks of age and younger are unaffected. The age-related resistance in very young rabbits is still poorly understood, but maternal antibodies have been suggested as one possible explanation for survival in older kittens. Surviving rabbits develop immunity and become resistant to related strains of RHDV. Some animals may be persistently infected.

In wild rabbits, outbreaks can be seasonal. In some populations, they have been associated with the breeding season. The morbidity and mortality rates vary between populations. In Europe, rabbit hemorrhagic disease has caused dramatic declines in wild rabbit populations in Spain, Portugal and France, but wild rabbits in the U.K. and some other Northern European countries have been less severely affected. In some areas, rabbit populations may recover, and initial high morbidity and mortality rates may be followed by sporadic, less virulent outbreaks.

Nonpathogenic strains of RHDV have recently been identified in wild rabbits. These viruses may be responsible for disease resistance in some populations. An alternatively hypothesis is that the virulence of an RHDV strain is determined by its behavior in each population (e.g., the dose of virus each rabbit typically receives).

Diagnosis

Clinical

Rabbit hemorrhagic fever should be suspected when several animals die suddenly after a brief period of lethargy and fever. Hepatic necrosis at necropsy supports the diagnosis. This disease can be more difficult to diagnose when it occurs in an isolated rabbit.

Differential diagnosis

Rabbit hemorrhagic disease should be differentiated from acute pasteurellosis, atypical myxomatosis, poisoning, heat exhaustion, enterotoxemia due to *E. coli* or *Clostridium perfringens* Type E, and other causes of severe septicemia with secondary DIC. Some of these diseases can be ruled out at necropsy.

Laboratory tests

The rabbit hemorrhagic disease virus has not been grown in cell cultures. This virus is usually recognized by concentrating it from the liver, blood, spleen or other organs, and identifying it with reverse transcription polymerase chain reaction (RT-PCR) tests, immunoblotting (Western blotting), negative-staining immunoelectron microscopy, immunostaining or enzyme-linked immunosorbent assays (ELISAs). A hemagglutination test was also used in the past, but it is less sensitive and specific than other assays. *In situ* hybridization can detect RHDV as early as 6-8 hours after infection, but this technique is mainly used in research.

Antibodies can be found in convalescent rabbits by hemagglutination inhibition or ELISA tests. Where rabbit hemorrhagic disease is not endemic, inoculation into rabbits can confirm the first diagnosis. Animal inoculation can also help to identify cases that have not been definitively diagnosed by other tests.

Samples to collect

Before collecting or sending any samples from animals with a suspected foreign animal disease, the proper authorities should be contacted. Samples should only be sent under secure conditions and to authorized laboratories to prevent the spread of the disease.

The liver contains the highest viral titers in acute or peracute disease, and is the best organ to submit for virus identification. Serum and spleen may also contain high levels of virus. In rabbits with chronic or subacute disease, RHDV may be easier to find in the spleen than the liver. RT-PCR can detect viral RNA in a many organs, urine, feces or serum. Serum should be collected for serology.

Recommended actions if rabbit hemorrhagic disease is suspected

Notification of authorities

Rabbit hemorrhagic disease must be reported to state or federal authorities immediately upon diagnosis or suspicion of the disease.

Federal Area Veterinarians in Charge (AVIC):

http://www.aphis.usda.gov/vs/area_offices.htm

State Veterinarians:

http://www.aphis.usda.gov/vs/sregs/official.html

Control

Uninfected countries may place restrictions on the importation of rabbits, meat and angora wool from endemic areas. In an outbreak, strict quarantine is necessary. RHDV is extremely contagious; it can be transmitted on fomites and by insects, birds and scavenging mammals. Eradication can be accomplished by depopulation, disinfection, surveillance and quarantines. RHDV can be inactivated with 10% sodium hydroxide or 1-2% formalin. Other suggested disinfectants include 2% One-stroke Environ® (Vestal Lab Inc., St. Louis, MO) and 0.5% sodium hypochlorite (10% household bleach). This virus resists degradation by ether or chloroform. Carcasses must be removed immediately and disposed of safely. Infected farms should not be restocked immediately, as RHDV can persist for a time in the environment, particularly when it is protected in tissues. Sentinel rabbits can be used to monitor premises for persistent viruses.

In regions where RHDV circulates in wild rabbits, eradication is not feasible. Instead, this disease is controlled in domesticated rabbits with biosecurity measures including sanitation and disinfection, the maintenance of closed colonies, and vaccination. Vaccination may be limited to breeding animals if rabbit hemorrhagic disease has not been reported on a farm, but all animals should be vaccinated if an outbreak has occurred. Even with strict sanitation and other control measures, the likelihood of reinfection is high after an outbreak. Vaccination can interfere with eradication by masking infections. Sentinel animals can be used to monitor for the persistent viruses on vaccinated farms. Immune serum has also been used to provide short-term protection in an outbreak.

Public Health

There is no indication that the rabbit hemorrhagic disease virus infects humans.

Internet Resources

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

United States Animal Health Association. Foreign Animal Diseases
http://www.vet.uga.edu/vpp/gray_book02/fad/index.php

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

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/eng/normes/mmanual/a_summry.htm

OIE Terrestrial Animal Health Code
http://www.oie.int/eng/normes/mcode/A_summry.htm

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*Link defunct as of 2007