Rift Valley Fever

Infectious Enzootic Hepatitis of Sheep and Cattle

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Importance

Rift Valley fever (RVF) is a zoonotic viral disease that can affect a variety of species, including ruminants and camels, causing high mortality in young animals and/or abortions in adults. The RVF virus is endemic mainly in sub-Saharan Africa, but it has also been seen in North Africa, and may have become established in Egypt. There are concerns that this virus might be spreading, after outbreaks were reported in Saudi Arabia and Yemen in 2000. Rift Valley fever tends to occur in periodic epidemics, which typically occur after heavy rainfalls and may be devastating to domesticated livestock. These outbreaks are thought to begin when dormant, infected mosquito eggs hatch in flooded areas. However, the epidemiology of Rift Valley fever is incompletely understood, and low levels of infection have now been identified during interepidemic periods.

Rift Valley fever outbreaks in domesticated animals are often accompanied by human disease. Many human cases are caused by occupational exposure to blood and tissues from infected animals, but mosquito-borne transmission can also occur. The most common form of the disease is a self-limiting, flu-like illness. Complications in a minority of cases include ocular disease, neurological signs, kidney dysfunction and a life-threatening hemorrhagic syndrome with hepatic dysfunction. Although overall case fatality rates are thought to be low (≤ 2%), there may be very large number of cases during some epidemics, resulting in hundreds of serious cases and significant numbers of deaths.

Etiology

Rift Valley fever results from infection by the Rift Valley fever virus, an RNA virus in the genus *Phlebovirus* in the family Bunyaviridae. There are several genetic lineages of this virus, some of which may co-circulate, in endemic regions. Some viral isolates differ in virulence in laboratory rodents and possibly other species.

Species Affected

Rift Valley fever can affect many species of animals including sheep, cattle, goats, African buffalo (*Syncerus caffer*), water buffalo (*Bubalus bubalis*), camels, some species of monkeys, and a number of rodents (various wild African rodents, rats [*Rattus rattus*], nonnative gray squirrels [*Sciurus carolinensis*] and laboratory rodents including hamsters, gerbils, rats and mice, but not guinea pigs. Severe disease can be seen in newborn puppies and kittens, although adult dogs and cats seem to be unaffected. Some experimentally infected ferrets developed febrile reactions. Limited information suggests that some wild ruminants other than African buffalo are also susceptible to disease.

Sheep, goats and cattle are thought to be the primary amplifying hosts among domesticated animals, although other species such as camels could also be involved. The role of wildlife is still being investigated, but some animals might amplify the virus, or help maintain it during interepidemic periods. In addition to African buffalo, serological evidence of infection has been reported in other wild ruminants (e.g., Thomson’s gazelle [*Gazella thomsonii*], lesser kudu [*Tragelaphus strepsiceros*], impala [*Aepyceros melampus*] and waterbuck [*Kobus ellipsiprymnus*]), as well as in black rhinoceros (*Diceros bicornis*), African elephant (*Loxodonta africana*) and warthog (*Phacochoerus aethiopicus*). Some wild species, such as giraffe, seem to become infected mainly during outbreaks in domesticated animals, and may be unlikely to maintain the virus. Wild rodents have been proposed as possible hosts for RVF virus, but their role (if any) is currently uncertain. There is also evidence for infection in other species including bats. Birds do not become infected in laboratory experiments, and surveillance has not detected any evidence of infection in nature.

Zoonotic potential

Humans are susceptible to infection with Rift Valley fever virus, and can develop clinical signs. The viremia may be sufficient to infect mosquitoes.
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Geographic Distribution

The Rift Valley fever virus is endemic in Africa south of the Sahara desert. Although outbreaks are most common in southern and eastern Africa, they also occur in other regions. Outbreaks or infections have been reported sporadically in Egypt and various islands off the coast of Africa (e.g., Madagascar, Mayotte), and a major outbreak occurred on the Arabian peninsula (Saudi Arabia and Yemen) in 2000-2001. Rift Valley fever might have become endemic in some of these regions, including Egypt; however, this can be difficult to determine, both because the virus is not necessarily found during interepidemic periods, and because some reported infections may result from illegal animal importation.

Transmission

Rift Valley fever is transmitted by mosquitoes, which act as biological vectors. This virus has been detected in many genera of mosquitoes in endemic regions; however, laboratory experiments suggest that some of these species are not competent vectors for transmission. At present, the major hosts appear to be members of the genera Aedes, Culex and Anopheles. Other biting insects might also be able to transmit this virus from viremic animals, although their role (if any) in nature is still uncertain. Potential mechanical and/or biological vectors include stable flies (Stomoxys spp.), tsetse flies (Glossina morsitans), sandflies (Lutzomyia longipalpis), biting midges (Culicoides variipennis), blackflies and ticks. RVF virus was not detected in approximately 1000 ticks collected from livestock during one recent outbreak.

The mechanisms that maintain RVF virus in nature and cause it to emerge in epidemic form are incompletely understood, and might differ between areas. Transmission cycles are best understood in savannah regions, where the virus is thought to survive between outbreaks in the dried eggs of Aedes mosquitoes found in shallow depressions in the soil (dambos). Infected mosquitoes are thought to hatch when the dambos fill after heavy rainfall, and initiate transmission cycles involving additional mosquito species, and animals that act as amplifying hosts. The vertebrate amplifying hosts are thought to be critical in propagating epidemics. Virus transmission has also been demonstrated at low levels in livestock, wildlife and humans during interepidemic periods. Infection cycles in some other climates, such as forested regions, are poorly understood and might differ from this pattern.

RVF virus can be transmitted in utero to the fetus of ruminants, camels and other species. This virus may also infect other animals exposed to abortion or birth products, which contain large amounts of virus; however, the importance of this route is controversial. Although RVF virus can enter the body through mucous membranes, and might occur in milk, one attempt to inoculate puppies, kittens and lambs with virus-spiked milk was unsuccessful. Virus shedding in secretions and excretions from infected ruminants is poorly understood, although it is not thought to be important in spreading Rift Valley fever. Some studies have, nevertheless, detected small amounts of virus in oral fluids and nasal discharge, as well as in semen, and sentinel sheep were infected by unknown route(s) during 2 laboratory experiments. There was evidence for horizontal transmission during experiments in cats and dogs, and virus was detected in the saliva of puppies. RVF virus has not been reported in the urine or feces of any species except when these excretions are contaminated by blood.

Humans can acquire RVF virus by direct contact with infected tissues, contact with aerosolized viruses generated in laboratories or during slaughter, or from mosquitoes. The relative importance of mosquito-borne exposure and exposure to infected animal tissues continues to be debated. Drinking raw (unpasteurized) milk is a significant risk factor for human infection, although definitive proof for this route is lacking. Vertical transmission to human infants has been demonstrated in at least 2 cases. Person-to-person (horizontal) transmission does not seem to occur, but the blood and tissues of patients might be sources of exposure for medical personnel.

In vitro experiments suggest that RVF virus can persist for a few days in some protein-rich environments such as tissues. In a neutral or alkaline pH, mixed with serum or other proteins, the virus may survive for as long as four months at 4°C (40°F) and eight years below 0°C (32°F). It is quickly destroyed by pH changes in decomposing carcasses. Under optimal conditions, RVF virus remained viable in aerosols for more than an hour at 25°C (77°F).

Disinfection

The Rift Valley fever virus is susceptible to low pH (≤ 6.2), lipid solvents and detergents, and solutions of sodium or calcium hypochlorite with residual chlorine content greater than 5000 ppm.

Infections in Animals

Incubation Period

The incubation period in sheep, goats and cattle is thought to be approximately 1-3 days, based on laboratory experiments. Young ruminants and puppies can develop clinical signs as early as 12 hours after inoculation.

Clinical Signs

In endemic regions, epidemics of Rift Valley fever are characterized by high mortality rates in newborn animals and abortions in adults. Between epidemics, this virus can circulate without apparent clinical signs in susceptible species, or there may be sporadic abortions that could be confused with other diseases.

Rift Valley fever is usually most severe in young animals. Nonspecific signs of fever, anorexia, weakness and lymphadenopathy are common in lambs. Hemorrhagic or
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characteristic sign in adult sheep, goats and other species in some species of nonhuman primates, while some other species seem to be unaffected or minimally affected.

Post Mortem Lesions

The most consistent lesion in all species is hepatic necrosis, which tends to be more extensive and severe in younger animals. In aborted fetuses and newborn lambs, the liver may be very large, yellowish-brown to dark reddish-brown, soft and friable, with irregular patches of congestion. Multiple gray to white necrotic foci are usually present, but may not be grossly visible. The liver lesions are often less severe and more localized in calves and adult animals, and may consist of numerous pinpoint reddish to grayish-white necrotic foci. The walls of the gallbladder may be edematous, and can contain visible hemorrhages. Hepatic necrosis is also the most prominent and consistent microscopic lesion, and eosinophilic oval or rod-shaped intranuclear inclusion bodies may be found in the liver in up to 50% of cases.

Additional gross lesions may include jaundice, widespread subcutaneous hemorrhages, petechial and/or ecchymotic hemorrhages on the surface of other internal organs (including the serosa of the heart in experimentally infected puppies and kittens), and fluid in the body cavities. The peripheral lymph nodes and spleen are typically enlarged, congested and/or edematous to some degree, and may contain petechiae. A variable degree of inflammation or hemorrhagic enteritis can sometimes be found in the intestines of ruminants and experimentally infected puppies and kittens. Ruminants may have hemorrhages and edema in the abomasal folds, sometimes with blood in lumen of the intestine. The hemorrhagic syndrome reported in 7-11-month-old, experimentally infected Yansaka sheep included unusual lesions of pulmonary edema/hemorrhage, and thrombosis in the heart, kidneys and brain. Aborted fetuses are often autolyzed.

Diagnostic Tests

Rift Valley fever can be diagnosed by detecting the virus in the blood of febrile animals, or the tissues of dead animals and aborted fetuses. Some recommended tissues for sampling include the liver (the major site of replication), spleen and brain, with some sources also recommending kidney and lymph nodes; however, the virus may also be found at other sites.
Several RT-PCR tests including loop-mediated isothermal amplification (LAMP) techniques can detect Rift Valley fever viral RNA. Virus isolation is also possible, although this virus is a hazard to laboratory personnel, and biosecure facilities are required. Rift Valley fever virus can be grown in numerous cell lines including baby hamster kidney cells, monkey kidney (Vero) cells, chicken embryo–related (CER) cells and AP61 mosquito cell lines, as well as in primary kidney or testis cultures from calves or lambs. Although animal inoculation is avoided whenever possible, hamsters, adult or suckling mice, embryonated chicken eggs or two-day-old lambs can also be used. Viral antigens can be detected by immunostaining or with enzyme immunoassays (ELISAs, lateral flow assays). Some ELISAs are commercially available. In addition, the high viral titers in some samples (e.g., tissues from aborted fetuses or blood) may allow a rapid diagnosis to be made with serological tests such as virus neutralization, using organ suspensions as the antigen. The latter test should be supplemented with other, more definitive, assays.

ELISAs and virus neutralization can detect antibodies to RVF virus. Virus neutralization tests that require live virus are generally not recommended outside endemic regions or in laboratories not capable of biocontainment, but alternative neutralization tests that do not require highly virulent viruses are in development. Indirect immunofluorescence is used less frequently, while other serological assays employed in the past (hemagglutination inhibition, complement fixation, agar gel immunodiffusion) are generally no longer used. Cross-reactions with other phleboviruses can occur in serologic tests other than virus neutralization; however, the latter test has few or no issues with cross-reactivity.

**Treatment**

No specific treatment, other than supportive care, is available.

**Control**

**Disease reporting**

Animals that may be infected with Rift Valley fever virus must be reported immediately, to protect humans who may be exposed and aid in controlling the outbreak. In endemic areas, animal cases also act as a warning that human outbreaks may be imminent, and public health messages and prevention advice should be issued.

**Prevention**

Vaccines are generally used to protect animals from Rift Valley fever in endemic regions. Vaccination of susceptible animals may protect people as well as animals by reducing amplification of the virus. Attenuated and inactivated Rift Valley fever vaccines are both available. An advantage to inactivated vaccines is their safety; however, they are less immunogenic than attenuated vaccines, and if quality control fails, an incompletely inactivated vaccine could introduce the virus to livestock. Attenuated RVF vaccines produce better immunity, but vaccine viruses might reassort with wild type RVF viruses, contributing to viral diversity. Attenuated RVF vaccines can also cause abortions and birth defects in pregnant animals. A newer inactivated vaccine, called Clone 13, did not cause abortions or fetal deformities in pregnant ewes vaccinated at 15 days of gestation. Vaccination campaigns conducted in resource-poor areas face additional challenges such as mechanical transmission from already infected animals when needles are reused. For this reason, some sources including the World Health Organization do not recommend that vaccination campaigns be initiated once an epidemic has begun.

Because epidemics typically follow heavy rainfall, weather prediction models may give some advance warning when conditions are favorable for outbreaks. Sentinel herds have also been used as part of early warning systems in some areas. Movement bans or restrictions, and the closure of livestock markets during outbreaks, may help prevent virus transmission to unaffected regions. Larvicides are the most effective form of vector control, if mosquito breeding sites can be identified and are limited in size. However, breeding sites are usually extensive, making vector control impractical.

**Morbidity and Mortality**

Epidemics of Rift Valley fever tend to occur at intervals, when heavy rainfalls cause infected mosquito eggs to hatch and a susceptible animal population is present. In Africa, outbreaks typically occur in savannah regions every 3 to 15 years, and less frequently in some other areas. Low levels of infection can also be seen in livestock and wildlife during interepidemic periods. Some regions may mainly experience low-level virus activity during each rainy season, without explosive epidemics.

The morbidity rate varies between outbreaks, and is influenced by factors such as pre-existing immunity, pregnancy status, and the age of the animals. In some cases, illnesses are widespread in herds throughout the country, and most of the animals in infected herds are affected. Among domesticated animals, infections seem to be most severe in sheep and goats. Abortion rates in sheep range from 5% to nearly 100%, but they are generally lower in cattle (e.g., < 10%). Widespread abortions have also been reported sometimes in camels; 10% of camels aborted in one outbreak.

The case fatality rate can be very high in young animals, with fatalities decreasing in older age groups. The mortality rate may reach 70% to 100% in newborn lambs and kids, while estimated mortality in calves, and older lambs and kids, varies from 10% to 70%. Overall, the mortality rate is estimated to be 10-30% in adult sheep and < 10% in adult cattle, but higher rates have been reported in some outbreaks or herds. Deaths are most common in pregnant ewes that abort. Some experiments suggest that there may be breed-
specific differences in the severity of clinical signs; however, naive sheep of breeds not indigenous to Africa (e.g., European breeds) do not necessarily become severely ill. Mortality rates were 81% in experimentally infected young kittens (≤2 weeks of age), and 50-100% in young puppies (≤1 week of age), but no adult cats or dogs 2 weeks of age or older died.

Infections in Humans

Incubation Period

In humans, the incubation period is estimated to be 3 to 6 days. This is based on a limited number of cases, almost all acquired in the laboratory or by contact with the tissues of infected animals, rather than after exposure to mosquitoes.

Clinical Signs

Most people are infected subclinically with RVF virus or develop a mild to moderate, non-fatal, febrile flu-like illness with liver abnormalities. The symptoms of uncomplicated infections are usually nonspecific and may include fever, headache, generalized weakness, dizziness, weight loss, myalgia and back pain. Some patients also have stiffness of the neck, photophobia and vomiting or diarrhea. Most people recover spontaneously within a week.

A clinical syndrome that appears to be characteristic of severe Rift Valley fever was described in several patients during the 2006-2007 epidemic in Kenya, and included nonspecific signs of fever, malaise and headaches, together with arthralgia in the large joints (elbows, knees and shoulders), gastrointestinal signs (nausea, vomiting, mid-epigastric pain), progressing to tender hepatomegaly, jaundice and delirium. Lymphadenopathy and diarrhea appeared to be absent in these patients.

Complications including renal dysfunction, meningoencephalitis, ocular disease, or a hemorrhagic syndrome with liver involvement occur in a small percentage of patients. The hemorrhagic syndrome is the most serious form, and may be seen in up to 1% of patients, with symptoms usually developing 2-4 days after the initial signs. Jaundice may be the first indication of this syndrome, followed by signs such as hematemesis, melena, menorrhagia, a macular or purpuric rash, petechiae and bleeding from the gums. These patients often progress to frank hemorrhages, shock and death within 3-6 days. Acute kidney dysfunction is a new complication reported in severe cases during recent outbreaks, and can also lead to death. Whether the kidney dysfunction is caused directly by the virus or a consequence of complications such as shock is still unclear. Survivors of this syndrome did not develop chronic kidney disease.

Ocular disease and meningoencephalitis can be late complications of Rift Valley fever. The ocular form is estimated to occur in up to 2% of patients, typically begins 1-3 weeks after the initial symptoms, and is characterized by retinal lesions and blurred vision. While ocular lesions disappear after 10-12 weeks in some patients, others experience some degree of permanent visual impairment, which may include blindness. Encephalitic signs are seen in less than 1%, and usually begin 1-4 weeks (but occasionally later) after the initial signs. The symptoms can include intense headache, memory loss, vertigo, hallucinations, confusion, disorientation, coma or seizures. Some patients have permanent neurological damage, which may be severe, but deaths are uncommon.

Some authors indicate that increased mortality or abortions in pregnant women have not been seen during outbreaks. However, there are at least two reports of maternal transmission to the fetus. One infant, whose mother was also ill with malaria, was born with a rash and jaundice. The infant in the other case died soon after birth.

Diagnostic Tests

Rift Valley fever virus can be detected in the blood, brain, liver or other tissues, but viremia usually occurs only during the first three days of fever. There are also reports of virus detection in other samples, such as throat swabs, cerebrospinal fluid, pericardial and peritoneal fluid. Tests to detect RVF virus in humans are similar to those used in animals, and can include PCR assays, virus isolation, and various antigen detection assays. During some outbreaks, RT-PCR was able to identify people with high levels of viremia in the blood, who were more likely to progress to severe illness. ELISAs and other serological tests can detect specific IgM or rising titers.

Treatment

No specific treatment, other than supportive care, is available. Some animal studies have suggested that antiviral drugs or other therapies such as passive antibodies might be effective; however, these treatments have not been tested in humans. Most cases of Rift Valley fever are thought to be relatively mild, brief illnesses and resolve on their own.

Prevention

Public education about transmission methods can help reduce infections during outbreaks. Milk should be pasteurized or boiled, and all other animal tissues including blood and meat should be cooked, and not consumed raw. Home slaughter of livestock is not recommended during outbreaks.

Barrier precautions should be used whenever contact may occur with infectious tissues or blood from animals; recommended measures include gloves and other barriers to prevent direct contact with tissues and/or aerosols. The precautions can depend on the form of exposure, with necropsies considered high risk procedures. Diagnostic tissue samples should be processed by trained staff in appropriately equipped laboratories. An inactivated vaccine has been used in some at-risk individuals (e.g., laboratory workers), but has had limited availability, and is no longer manufactured by one former supplier. Although person-to-
person transmission has not been reported, there is a risk of transmission by contact with viruses in human blood and tissues. Standard (universal) precautions (e.g., barriers to prevent direct contact with blood and other potential sources of virus) have been recommended for healthcare workers who care for patients with confirmed or suspected Rift Valley fever.

Mosquito repellents, long shirts and trousers, bednets, and other arthropod control measures should be used to prevent transmission by mosquitoes and other potential insect vectors. Outdoor activities should be avoided, if possible, during periods of peak mosquito activity.

Morbidity and Mortality

Humans are highly susceptible to Rift Valley fever. Specific risk factors include assisting in animal births, having contact with tissues (e.g., slaughtering or skinning an animal, preparing meat for cooking, handling abortion products, conducting necropsies), drinking raw (unpasteurized) milk, and sheltering animals within the home. Clinical cases are often seen in veterinarians, abattoir workers and others who work closely with blood and tissue samples from animals. Laboratory workers are also at risk. Human infections tend to occur mainly during Rift Valley fever epidemics in livestock, and are typically preceded by cases in animals; however, illnesses were first diagnosed in people during some outbreaks. Sporadic cases may also be seen during interepidemic periods.

The vast majority of human infections appear to be asymptomatic or mild. However, the number of infections in some epidemics can be very large (e.g., possibly more than 180,000 infections in Kenya in 2006-2007), resulting in hundreds of serious cases and significant numbers of deaths. The overall case fatality rate for all patients with Rift Valley fever is estimated to be between 0.5% and 2%, but case fatality rates in hospitalized patients with more severe symptoms may be much higher (e.g., 31% of 747 hospitalized patients in Sudan in 2006-2007). Case fatality rates up to 50% have been reported in the hemorrhagic syndrome, and the case fatality rate in people with acute renal dysfunction was 40% during an outbreak in Sudan.

Internet Resources

Centers for Disease Control and Prevention (CDC). Rift Valley Fever
http://www.cdc.gov/vfhr/vf/

European Food Safety Authority (EFSA)

http://www.fao.org/DOCREP/005/Y4140E/y4140e00.htm#

References


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