Crimean-Congo Hemorrhagic Fever

Congo Fever,
Central Asian Hemorrhagic Fever,
Uzbekistan hemorrhagic fever
Hungribta (blood taking),
Khunymuny (nose bleeding),
Karakhalak (black death)

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Importance

Crimean-Congo hemorrhagic fever (CCHF) is caused by a zoonotic virus that seems to be carried asymptomatically in animals but can be a serious threat to humans. This disease typically begins as a nonspecific flu-like illness, but some cases progress to a severe, life-threatening hemorrhagic syndrome. Intensive supportive care is required in serious cases, and the value of antiviral agents such as ribavirin is still unclear. Crimean-Congo hemorrhagic fever virus (CCHFV) is widely distributed in the Eastern Hemisphere. However, it can circulate for years without being recognized, as subclinical infections and mild cases seem to be relatively common, and sporadic severe cases can be misdiagnosed as hemorrhagic illnesses caused by other organisms. In recent years, the presence of CCHFV has been recognized in a number of countries for the first time.

Etiology

Crimean-Congo hemorrhagic fever is caused by Crimean-Congo hemorrhagic fever virus (CCHFV), a member of the genus *Orthonairovirus* in the family Nairoviridae and order Bunyavirales. CCHFV belongs to the CCHF serogroup, which also includes viruses such as Tofla virus and Hazara virus. Six or seven major genetic clades of CCHFV have been recognized. Some strains, such as the AP92 strain in Greece and related viruses in Turkey, might be less virulent than others.

Species Affected

CCHFV has been isolated from domesticated and wild mammals including cattle, sheep, goats, water buffalo, hares (e.g., the European hare, *Lepus europaeus*), African hedgehogs (*Erinaceus albiventris*) and multimammate mice (*Mastomys* spp.). Serological evidence of exposure has been reported in many additional species, such as horses, donkeys, camels, water buffalo, dogs, red foxes (*Vulpes vulpes*), wild dogs (*Lycaon pictus*), Pallas cats (*Felis manul*), genets (*Genetta genetta*), a number of African ungulates (e.g., rhinoceros - *Diceros bicornis, Ceratotherium simum*; giraffe, *Giraffa camelopardalis*; African buffalo, *Syncerus caffer*), hedgehogs (*Erinaceus europaeus, Hemiechinus auritus*), various rodents and bats. Among seropositive species, susceptibility has been confirmed by experimental infection in equids (horses, donkeys), European hares, scrub hares (*Lepus saxatilis*), and some wild rodents. However, some mammals may be resistant to this virus. For instance, one group was able to recover CCHFV from the blood of experimentally infected long-eared hedgehogs (*Hemiechinus auritus*) but not European hedgehogs (*Erinaceus europaeus*). It should be noted that many studies on animal susceptibility were done in the 1970s or earlier, and there has been little research since then.

Serological surveys in birds have mostly found no evidence for infection. However, ostriches are susceptible to CCHFV and are sometimes infected in nature. A low level of viremia was also reported in an experimentally infected guinea fowl (*Numidia meleagris*), and antibodies were found in one naturally infected magpie (*Pica pica*), although pooled sera from several groups of magpies were seronegative. Experimentally infected chickens, laughing doves (*Spilopelia senegalensis*), pigeons (*Columba livia*), rooks (*Corvus frugilegus*) and a red-beaked hornbill (*Tockus* sp.) did not become viremic, and the chickens, laughing doves, rooks and pigeons remained seronegative. However, the hornbill and a glossy starling (*Lamprotornis* sp.) developed antibodies to CCHFV, and ticks fed on these birds apparently acquired the virus and transmitted it to rabbits. There is very little information about reptiles, but one tortoise from Tadzhikistan was seropositive.

Significant clinical signs have only been reported in animal models for human disease, which include newborn rodents and certain immunodeficient mouse strains, as well as experimentally infected cynomolgus macaques (*Macaca fascicularis*) injected with high doses of one particular CCHFV strain. Other attempts to infect nonhuman primates caused few or no clinical signs, although one baboon (*Papio papio*) developed cutaneous lesions.

Zoonotic potential

CCHFV is zoonotic.

Geographic Distribution

CCHFV appears to be widespread in Africa, the Middle East and Asia, and also occurs in parts of southern and eastern Europe. Different clades and strains circulate in different regions. This virus seems to be maintained only where ticks of the genus *Hyalomma* are established. Within Europe and Asia, evidence for its presence has been reported as far north as Spain, Portugal, Hungary, Romania, Bulgaria, Ukraine, Kosovo, Albania, Macedonia, southern Russia, Mongolia, Kazakhstan and Uzbekistan, although human clinical cases have not been documented in all of these countries. While *Hyalomma* ticks are found occasionally in northern Europe and Asia, probably after transport on migrating birds, these regions are considered inhospitable for the permanent establishment of *Hyalomma* species. Recent surveys found no evidence that CCHFV circulates in Poland, Germany, Italy or central France. The situation in southern France is unclear. One old review mentions unspecified serological evidence for its presence, and *Hyalomma* ticks seem to be established in some regions; however no surveys for CCHFV have been done recently in southern France and no indigenous human cases have ever been reported.

Transmission

Humans usually become infected in tick bites or by contact with blood and tissues from infected animals or humans. Ticks in the genus *Hyalomma* seem to be the principal vectors for CCHFV and are thought to be critical for maintaining it in endemic areas. *Hyalomma marginatum* and *H. asiaticum* are important in Europe and Asia, respectively, but the virus also occurs in other members of this genus, including some species that infest reptiles (e.g., *H. aegyptium*). Transovarial and transstadial passage, venereal transmission and cofeeding (transmission from infected ticks to uninfected ticks feeding simultaneously on an uninfected host) have been demonstrated in *Hyalomma*. CCHFV can overwinter in unfed *Hyalomma* ticks, which can survive milder winters. It has also been found in a number of species in the genera *Rhipicephalus*, *Boophilus*, *Dermacentor* and *Ixodes*. How many of these ticks are competent vectors is uncertain, but some might transmit the virus locally. CCHFV has been reported infrequently in other blood-feeding invertebrates, such as biting midges (*Culicoides* spp.) and argasid (soft) ticks, but they are not thought to play any role in its epidemiology. Experimental infections indicate that it does not replicate in argasid ticks. Migratory birds might spread infected ticks between distant regions.

CCHFV in blood, tissues or crushed ticks can enter the body after contaminating mucous membranes or skin. Infections acquired through skin contact probably occur via broken skin. Some cases appeared to be caused by drinking unpasteurized milk, and a few were reported in people who had recently eaten raw liver or raw meat from freshly slaughtered animals. Person-to-person transmission can occur, especially during close contact. Hemorrhages from severely ill patients are an important source of exposure for relatives and healthcare workers. Viral RNA has also been detected in saliva and urine, and intermittently and in low amounts in conjunctival, nasal and rectal swabs. However, some studies suggest that skin contact with secretions and excretions that do not contain blood might have a relatively low risk of transmission. Sexual transmission was proposed to be the source of the illness in a few cases, including one instance where a man probably transmitted the virus to his wife during convalescence. Airborne transmission has been reported rarely after laboratory accidents or medical procedures that generated droplets or aerosols. In one unusual outbreak, clinical cases occurred in several people who visited the room of a severely ill patient who was on a respirator, but had no direct contact with the patient.

In utero transmission has been reported in humans, but its frequency is unclear. Whether CCHFV can be transmitted in milk is still uncertain, although no viral RNA was detected in the milk of two mothers who breastfed until diagnosis, and their infants did not become infected. Possible contamination of milk with blood (e.g., in skin lesions) is a concern even if the virus is not secreted directly into milk. How long CCHFV persists during convalescence is unclear. Nucleic acids have been found in urine for up to 25 days after the onset of clinical signs, and in blood for up to 36 days, but the presence of live virus was not demonstrated in either case.

How animals acquire CCHFV is still poorly understood, although ticks are thought to play an important role.

CCHFV can survive for a short time in the environment, especially in some organic material. Infectious virus was found for up to 10 days, and occasionally longer, in blood kept at 4°C (39°F). Viral RNA was detected for as long as 30 days in serum at 4°C, but infectivity was not assessed in this study. CCHFV was also reported to remain infectious in serum for at least a few days at unspecified ambient temperatures, and to be stable "under wet conditions" for 15 days at 4°C, 11 days at 20°C (68°F) and 7 hours at 37°C (99°F). Dried virus was found to remain infectious for less than 24 hours.

Disinfection

CCHFV can be inactivated by many disinfectants including 1% hypochlorite, 70% alcohol, hydrogen peroxide, peracetic acid, iodophors, glutaraldehyde and formalin. It can also be destroyed by UV light or pH < 6. One study found that heating at 56°C (133°F) for 30 minutes inactivated the virus, while another reported that 60°C (140°F) for 60 minutes was more effective. A recent report indicated that CCHFV in culture fluid was no longer infectious after 15 minutes at either 56°C or 60°C.

Infections in Animals

Clinical Signs/ Postmortem Lesions

CCHFV is thought to infect animals with few or no clinical signs. No illnesses have been attributed to this virus in naturally infected animals. Most experimentally infected livestock (cattle, sheep, goats, horses, donkeys) and wild species (e.g., hares, hedgehogs) also remained asymptomatic, although a transient mild fever was seen in some individuals, and two calves were lethargic, with a reduced appetite, for a few days. One virus was isolated from a febrile cow during an outbreak of abortions, but whether other agents also occurred in the herd is unclear. Of the five pregnant sheep included in one study, four gave birth to healthy lambs, while one aborted for unknown reasons. CCHFV was not isolated from the fetus.

Attempts to establish animal models for human CCHF were, until recently, unsuccessful except in newborn rodents or immunodeficient mice. In recent unpublished studies, inoculating cynomolgus macaques with high doses of one particular CCHFV strain resulted in a range of outcomes from asymptomatic infections to severe, lethal cases. The most severe signs and the only deaths occurred after intravenous inoculation; subcutaneous inoculation alone was not fatal. In addition to nonspecific signs such as inappetence, some animals developed oliguria, edema of the face and body, and various hemorrhagic signs. There is, however, no indication that this model is applicable to naturally infected nonhuman primates. Other experimentally infected nonhuman primates, as well as cynomolgus macaques inoculated with another strain, have generally remained asymptomatic or had only a few mild signs such as a transient fever. One baboon developed pruritus and a rash on the extremities, with histological lesions of vasculitis and hemorrhages at these sites.

Diagnostic Tests

Laboratory tests for CCHFV are not employed for diagnostic purposes in animals. Serology is mainly used to identify regions where animals have been exposed to this virus and humans may be at risk. Most surveys use various ELISAs. Other serological tests, including complement fixation and indirect fluorescent antibody tests, have also been described. Viremia can be recognized by virus isolation, RT-PCR and other techniques (see 'Diagnostic Tests' section under Human Infections). It is reported to last about a week in experimentally infected livestock and 2-15 days in experimentally infected small mammals.

Control

Disease reporting

Veterinarians who encounter an animal infected with CCHFV should follow their national and/or local guidelines for disease reporting. In the U.S., infected animals should be reported immediately to state or federal authorities. They are unlikely to be found except incidentally, as there is usually no clinical reason to test an animal for Crimean-Congo hemorrhagic fever.

Prevention

Preventive measures in animals are usually intended to reduce the risk of virus transmission to humans or to avoid transporting CCHFV to a region where it is not endemic. Currently, acaricides and/or other tick control measures seem to be the only practical means of control. However, complete prevention of tick bites is unlikely, and control measures are sometimes targeted especially to the period around slaughter, when people are most likely to be exposed to CCHFV in animal blood or tissues. Human infections caused by ostriches at abattoirs seem to be prevented by keeping these birds free of ticks for 14 days before slaughter. In some countries, ostriches are also subject to a 30-day pre-slaughter quarantine period at export facilities.

Morbidity and Mortality

No illnesses or deaths seem to be associated with CCHFV in animals, with the exception of animal models, which are artificial systems designed to mimic human disease and can have high case fatality rates (e.g., 75% in intravenously inoculated cynomolgus macaques). Seroprevalence rates in livestock vary widely in endemic regions, with some areas reporting only low seroprevalence but other regions with rates of 50% or more, and focally sometimes much higher. Changes in animal populations have been associated with some human outbreaks, either because the animals amplified the virus or because they served as food sources that allowed tick populations to expand.

Infections in Humans

Incubation Period

The incubation period is reported to range from 1 to 13 days, although the possibility of longer periods has been suggested. Most cases seem to appear within a week.

Clinical Signs

Some infections with CCHFV seem to be asymptomatic, while others result in mild to severe illnesses. Clinical cases usually begin as a febrile flu-like syndrome, with symptoms such as chills, headache, dizziness, photophobia, sore throat, neck pain, myalgia and arthralgia. The fever can sometimes be very high. Gastrointestinal signs including nausea, vomiting and diarrhea, as well as abdominal pain, are also common. Some patients have a maculopapular rash or cutaneous flushing, and there are occasional reports of other symptoms such as neurological signs (sharp mood changes, confusion, aggression) and cardiovascular changes (e.g., bradycardia, low blood pressure). One patient presented with fever and epididymo-orchitis. Some people may experience a brief (e.g. 24-48 hour) remission. Patients can recover completely after the flu-like stage or progress to a hemorrhagic syndrome of varying severity.

The hemorrhagic stage develops suddenly and usually lasts for a few days; however, it may be as short as a day or persist for more than a week. A petechial rash on the skin and mucous membranes can be the first sign. It may be followed

by ecchymoses and bruises. Ecchymoses may be very large in this disease, with some involving most of a limb. Hematemesis, melena, epistaxis, hematuria, hemoptysis and bleeding from venipuncture sites are also common, and bleeding can occur in other locations, including the eye (subconjunctival and retinal hemorrhages) or brain. In one case, internal bleeding mimicked acute appendicitis. Hepatomegaly and splenomegaly are common, and hepatitis or jaundice may be seen. Deaths are usually the result of hemorrhages, shock or multiorgan failure.

Some survivors may have a prolonged convalescence, especially when the illness was severe. Older reports from South Africa described a number of issues during convalescence, especially marked generalized weakness. Other symptoms in these reports included dryness of the mouth, headache, nausea, poor appetite, polyneuritis, impaired vision, loss of hearing, memory loss, temporary hair loss and hepatorenal insufficiency. Recently published cases and descriptions of CCHF generally do not mention similar signs. The effects of the illness on pregnancy are incompletely understood. Some pregnant women have aborted, while others gave birth to healthy uninfected infants, especially when their illness was relatively mild.

Diagnostic Tests

Crimean-Congo hemorrhagic fever can be diagnosed by isolating the virus or detecting its nucleic acids and antigens in blood samples or tissues. Urine, saliva and other secretions and excretions may also contain nucleic acids, but the suitability of these samples for diagnosis has not been fully investigated. At autopsy, CCHFV can be found in a variety of tissues, such as liver, spleen, lung, bone marrow, kidney and brain. The biosafety measures for safe handling of diagnostic samples from CCHF patients have recently been re-examined (Weidmann et al, 2016); current safety guidelines should be consulted for specific recommendations.

Clinical cases are often diagnosed with a combination of reverse transcription-polymerase chain reaction (RT-PCR) tests and serology. CCHFV strains are highly variable, and many RT-PCR tests only recognize local variants or a subset of viruses. However, tests that can detect most or all known variants, including the highly divergent AP92 strain, have also been developed. Other published assays to detect nucleic acids include microarray and macroarray-based techniques and loop-mediated isothermal amplification. In fatal cases, viral RNA tends to increase as the disease progresses.

Virus isolation is generally most useful during the first week of illness, especially the first 5-6 days, although high virus concentrations may persist longer in severely ill patients. CCHFV can be isolated in a variety of cell lines including SW-13, Vero, CER, LLC-MK2 and BHK-21 cells, but titers may be low. Recovered viruses can be identified by immunofluorescence or genetic tests such as RT-PCR. Animal inoculation into newborn or immunodeficient mice is more sensitive than cell culture, and has been used occasionally in clinical cases, though it is generally discouraged if there are alternatives. ELISAs can identify viral antigens in blood samples, but these antigens may no longer be detectable once a serological response has developed. Immunohistochemistry can be used on tissues collected at autopsy.

Antibodies to CCHFV are usually detected with ELISAs or indirect immunofluorescence. Other serological tests such as complement fixation and hemagglutination inhibition were sometimes used in the past, but were less sensitive. Antibody titers can usually be detected by 7-9 days after the onset of the clinical signs, and sometimes sooner, but they are often absent or low in fatal cases. Either specific IgM or rising titers should be seen. Virus neutralization is rarely employed, due to the hazards of handling live CCHFV.

Treatment

Treatment is mainly supportive. Seriously ill patients require intensive care. Ribavirin has been widely used to help treat Crimean-Congo hemorrhagic fever, but its efficacy has not been conclusively demonstrated and is questioned by some authors. This drug appears to be most effective when it is given very soon after the onset of clinical signs (e.g., during the first 48 hours). There is little information about anti-CCHFV hyperimmune serum, although it is reported to be administered routinely to patients in Bulgaria. Favipiravir, alone or in combination with ribavirin, appears to be promising in animal models but had not been tested in humans.

Prevention

The risk of acquiring Crimean-Congo hemorrhagic fever from ticks can be decreased with repellents such as DEET, clothing that minimizes skin exposure (e.g., long-sleeved shirts, long pants tucked into boots) and avoidance of tick habitats. Environmental modification around dwellings (e.g., removal of brush and long grass, insecticides) might be appropriate in some circumstances. Clothing and skin should be examined regularly for ticks, which should be removed. Whenever possible, this should be done without touching the tick with bare hands.

Protective clothing and gloves should be worn during exposure to viremic animals, particularly when blood and tissues are handled, and the hands should be washed immediately afterward. Because this virus does not cause clinical signs in animals, this generally means that these measures should be employed routinely in endemic areas. Unpasteurized milk should not be drunk. CCHFV is thought to be inactivated in meat by post-slaughter acidification; however, some conditions such as chronic stress may reduce acidification, and two recent cases were associated with eating freshly slaughtered raw meat acquired from a butcher. Holding meat at 4-8ºC for 24 hours after slaughter has been recommended. It is safest to always cook meat and other animal tissues thoroughly, and to use good hygiene (e.g., hand washing, avoidance of mucous membrane contact) when preparing them for cooking.

Standard barrier nursing precautions should be employed, at a minimum, when caring for human patients. Some countries may recommend higher standards. The use of a N95 or equivalent respirator, eye protection, and single airborne precaution room or well-ventilated setting has been advised during any medical procedure that may produce aerosols or droplets. Safe burial practices have been published for fatal cases. Laboratory workers must follow stringent biosafety precautions. People who have had high-risk exposures are often treated prophylactically with ribavirin, and a recent retrospective analysis suggests it has been effective in preventing illnesses. Postexposure prophylaxis with hyperimmune serum is reportedly used in Bulgaria.

No vaccine is available in most countries, although an inactivated vaccine derived from mouse brains has been used to immunize people in the former Soviet Union and Bulgaria. There is limited information about this vaccine.

Morbidity and Mortality

Sporadic clinical cases or outbreaks occur regularly in some endemic regions. In other areas, they seem to emerge unexpectedly after long periods with no apparent human illnesses. Changes in animal populations, tick numbers or human exposure may account for the latter situation. Underdiagnosis, especially of milder cases, is also possible, and immunity might sometimes play a role: in one outbreak, clinical cases mainly occurred in people who had recently moved to an endemic region.

Occupational groups with an elevated risk of Crimean-Congo hemorrhagic fever include farmers, shepherds, veterinarians, abattoir workers, healthcare personnel and laboratory workers, as well as anyone at elevated risk of exposure to ticks. Seasonality can result from seasonal changes in tick numbers or increased human exposure to slaughtered livestock, such as at the Muslim festival of Eid-al-Adha. The case fatality rate is thought to be approximately 5-30% in most instances, although rates as high as 80% have been reported occasionally in limited outbreaks. Factors such as the availability and quality of healthcare, virus dose, route of exposure, coinfections, and possibly the viral strain, are thought to influence mortality. In the past, nearly all cases of Crimean-Congo hemorrhagic fever were thought to be severe. However, serological surveys have revealed the existence of milder illnesses or subclinical infections in < 2% to 30% of the population in some endemic regions. In Turkey, where more than 10,0000 clinical cases have been reported since 2002, antibodies have been found in 10-15% of the population, and most infections are thought to be asymptomatic or mild. Up to 15% of the population in Greece is also seropositive, although very few clinical cases are reported, and the predominant strain might be of low virulence. Crimean-Congo hemorrhagic fever seems to be milder in children than adults in Turkey, where the overall case fatality rate in all age groups is ≤ 5%. However, this might not be true for all regions. A study from Iran reported a high percentage of severe illnesses in children, with a case fatality rate of 26%, and a study from the former USSR found no difference in disease severity between children and adults. It should be noted that the latter study was done before mild and asymptomatic cases were known to occur, and some cases might have been missed.

Internet Resources

Centers for Disease Control and Prevention (CDC). Crimean-Congo Hemorrhagic Fever

European Centre for Disease Prevention and Control. Crimean-Congo Hemorrhagic Fever

Public Health Agency of Canada. Pathogen Safety Data Sheets

The Merck Manual

The Merck Veterinary Manual

World Health Organization (WHO). Crimean-Congo Haemorrhagic Fever

World Organization for Animal Health (WOAH)

WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

Acknowledgements

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