

Crimean-Congo Hemorrhagic Fever

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

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Importance

Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic viral disease that is asymptomatic in infected animals, but a serious threat to humans. Human infections begin with nonspecific febrile symptoms, but progress to a serious hemorrhagic syndrome with a high case fatality rate. Although the causative virus is often transmitted by ticks, animal-to-human and human-to-human transmission also occur. This disease is a particular threat to farmers and other agricultural workers, veterinarians, laboratory workers and hospital personnel.

Crimean-Congo hemorrhagic fever is one of the most widely distributed viral hemorrhagic fevers. This disease occurs in much of Africa, the Middle East and Asia, as well as parts of Europe. Changes in climatic conditions could expand the range of its tick vectors, and increase the incidence of disease. The CCHF virus is also a potential bioterrorist agent; it has been listed in the U.S. as a CDC/NIAID Category C priority pathogen.

Etiology

Crimean-Congo hemorrhagic fever is caused by Crimean-Congo hemorrhagic fever virus (CCHFV). This virus is a member of the genus *Nairovirus* in the family Bunyaviridae. It belongs to the CCHF serogroup.

Although early serological studies revealed very few differences between strains of CCHFV, nucleic acid sequence analysis has demonstrated extensive genetic diversity, particularly between viruses from different geographic regions.

Geographic Distribution

CCHFV is widespread in Africa, the Middle East and Asia. It has also been found in parts of Europe including southern portions of the former USSR (Crimea, Astrakhan, Rostov, Uzbekistan, Kazakhstan, Tajikistan), Turkey, Bulgaria, Greece, Albania and Kosovo province of the former Yugoslavia. Limited serological evidence suggests that CCHFV might also occur in parts of Hungary, France and Portugal. The occurrence of this virus is correlated with the distribution of *Hyalomma* spp., the principal tick vectors.

Transmission

CCHFV usually circulates between asymptomatic animals and ticks in an enzootic cycle. This virus has been found in at least 31 species of ticks, including seven genera of the family Ixodidae (hard ticks). Members of the genus *Hyalomma* seem to be the principal vectors. Transovarial, transstadial and venereal transmission occur in this genus. *Hyalomma marginatum marginatum* is particularly important as a vector in Europe, but CCHFV is also found in *Hyalomma anatolicum anatolicum* and other *Hyalomma* spp. Other ixodid ticks including members of the genera *Rhipicephalus*, *Boophilus*, *Dermacentor* and *Ixodes* may also transmit the virus locally. Although CCHFV has been reported in other families of invertebrates, these species may not be biological vectors; the virus may have been ingested in a recent blood meal. In one study, CCHFV was reported from a biting midge (*Culicoides* spp.). It has also been found in two species of Argasidae (soft ticks); however, experimental infections suggest that CCHFV does not replicate in this family of ticks.

Many species of mammals can transmit CCHFV to ticks when they are viremic. Small vertebrates such as hares and hedgehogs, which are infested by immature ticks, may be particularly important as amplifying hosts. With a few exceptions, birds seem to be refractory to infection; however, they may act as mechanical vectors by transporting infected ticks. Migratory birds might spread the virus between distant geographic areas.

Humans become infected through the skin and by ingestion. Aerosol transmission was suspected in a few cases in Russia. Sources of exposure include being bitten by a tick, crushing an infected tick with bare skin, contacting animal blood or tissues and drinking unpasteurized milk. Human-to-human transmission occurs, particularly when skin or mucous membranes are exposed to blood during hemorrhages or tissues during surgery. CCHFV is stable for up to 10 days in blood kept at 40°C (104°F). Possible horizontal transmission has been reported from a mother to her child.

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Disinfection

CCHFV can be inactivated by disinfectants including 1% hypochlorite and 2% glutaraldehyde. It is also destroyed by heating at 56°C (133°F) for 30 min.

Infections in Humans

Incubation Period

The incubation period is influenced by the route of exposure. Infections acquired via tick bites usually become apparent after 1 to 3 days; the longest incubation period reported by this route is nine days. Exposure to blood or tissues usually results in a longer incubation period. Current estimates suggest that these infections become apparent, on average, after 5 to 6 days, but incubation periods up to 13 days are known.

Clinical Signs

The first sign of Crimean-Congo hemorrhagic fever is a sudden onset of fever and other nonspecific symptoms including chills, severe headache, dizziness, photophobia, neck pain, myalgia and arthralgia. The fever may be very high. Gastrointestinal symptoms including nausea, vomiting, non-bloody diarrhea and abdominal pain are also common. Sharp mood changes, confusion and aggression have been reported in some cases. Cardiovascular changes such as bradycardia and low blood pressure can also occur. This early stage of disease is called the prehemorrhagic phase. It is followed, after several days, by the hemorrhagic phase.

The hemorrhagic phase develops suddenly. It is usually short, lasting on average 2 to 3 days. A petechial rash may be the first symptom. The rash is followed by petechiae, ecchymoses and large bruises on the skin and mucous membranes. Hematemesis, melena, epistaxis, hematuria, hemoptysis and bleeding from venipuncture sites are also common. Bleeding can occur in other locations, including the brain. In one case, internal bleeding mimicked acute appendicitis. Hepatitis occurs in some patients, and may result in jaundice and hepatomegaly. Splenomegaly can also be seen. Some patients die from hemorrhages, hemorrhagic pneumonia or cardiovascular disturbances.

In patients who survive, recovery begins 10 to 20 days after the onset of illness. The convalescent phase is characterized by generalized weakness, a weak pulse and tachycardia. Other symptoms including sweating, dryness of the mouth, headache, dizziness, nausea, poor appetite, labored breathing, polyneuritis, poor vision, loss of hearing, and memory loss have also been seen. Some patients temporarily lose all of their hair. Hepatorenal insufficiency has been reported in some countries but not others. Recovery is usually complete but slow, and can take up to a year. Subclinical infections can occur, but are thought to be uncommon. Mild febrile cases without hemorrhages are also seen.

Communicability

CCHFV is present in blood, body fluids and tissues from affected patients; hemorrhages are an important source of exposure for other people, particularly family members and healthcare workers. Possible horizontal transmission has been reported from a mother to her child.

Diagnostic Tests

Crimean-Congo hemorrhagic fever can be diagnosed by isolating CCHFV from blood, plasma or tissues. At autopsy, the virus is most likely to be found in the lung, liver, spleen, bone marrow, kidney and brain. CCHFV can be isolated in a variety of cell lines including SW-13, Vero, LLC-MK2 and BHK-21 cells. Cell cultures can only detect high concentrations of the virus, and this technique is most useful during the first five days of illness. Animal inoculation into newborn mice is more sensitive than culture, and can detect the virus for a longer period. CCHFV is identified by indirect immunofluorescence or reverse transcription-polymerase chain reaction (RT-PCR) assays. Virus isolation must be carried out in maximum biocontainment laboratories (BSL-4).

Crimean-Congo hemorrhagic fever is often diagnosed by RT-PCR on blood samples. This technique is highly sensitive. However, due to the genetic variability in CCHFV strains, a single set of primers cannot detect all virus variants, and most RT-PCR assays are either designed to detect local variants or lack sensitivity. A real-time RT-PCR assay that can detect numerous variants has recently been published. Viral antigens can be identified with enzyme-linked immunoassay (ELISA) or immunofluorescence, but this test is less sensitive than PCR.

Crimean-Congo hemorrhagic fever can also be diagnosed by serology. Tests detect CCHFV-specific IgM, or a rise in IgG titers in paired acute and convalescent sera. IgG and IgM can usually be found with indirect immunofluorescence or ELISA after 7-9 days of illness. Other serologic tests such as complement fixation and hemagglutination inhibition were used to diagnose Crimean-Congo hemorrhagic fever in the past, but lacked sensitivity. In fatal cases, patients generally die without developing antibodies.

Treatment

Treatment is mainly supportive. Ribavirin is used in some cases. Observational studies in humans and studies in experimentally infected mice support the use of this drug; however, no randomized human clinical trials have been published. Passive immunotherapy with hyperimmune serum has been tested in a few cases, but the value of this treatment is controversial.

Prevention

In endemic regions, prevention depends on avoiding bites from infected ticks and contact with infected blood or tissues.

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Measures to avoid tick bites include tick repellents, environmental modification (brush removal, insecticides), avoidance of tick habitat and regular examination of clothing and skin for ticks. Clothing should be chosen to prevent tick attachment; long pants tucked into boots and long-sleeved shirts are recommended. Acaricides can be used on livestock and other domesticated animals to control ticks, particularly before slaughter or export.

Protective clothing and gloves should be worn whenever skin or mucous membranes could be exposed to viremic animals, particularly when blood and tissues are handled. Unpasteurized milk should not be drunk. In meat, CCHFV is usually inactivated by post-slaughter acidification. It is also killed by cooking.

Strict universal precautions are necessary when caring for human patients. These recommendations include barrier nursing, isolation and the use of gloves, gowns, face-shields and goggles with side shields. Prophylactic treatment with ribavirin has occasionally been used after high-risk exposures. Safe burial practices, including the use of 1:10 liquid bleach solution as a disinfectant, have been published. Laboratory workers must follow stringent biosafety precautions.

An inactivated vaccine from mouse brains has been used in the former Soviet Union and Bulgaria. In most countries, no vaccine is available.

Morbidity and Mortality

Climatic factors can influence the numbers of ticks in the environment and the incidence of disease. In some countries, Crimean-Congo hemorrhagic fever tends to be seasonal. This disease is most common in Iran during August and September, and in Pakistan from March to May and August to October.

Most cases are the result of occupational exposure. CCHF is particularly common in farmers, shepherds, veterinarians, abattoir workers and laboratory workers. Healthcare workers are also at high risk, particularly after exposure to patients' blood. During one nosocomial outbreak at a hospital in South Africa, 33% of medical personnel exposed via needlestick injuries became ill. Approximately 9% of those who had other forms of contact with infected blood also developed CCHF. In the general public, activities that increase tick exposure such as hiking and camping increase the risk of infection.

The average case fatality rate is 30-50%, but mortality rates from 10% to 80% have been reported in various outbreaks. The mortality rate is usually higher for nosocomial infections than after tick bites; this may be related to the virus dose. Geographic location also seems to influence the death rate. Particularly high mortality rates have been reported in some outbreaks from the United Arab Emirates (73%) and China (80%). Geographic differences in viral virulence have been suggested, but are unproven. The mortality rate may also be influenced by the availability of rigorous supportive treatment in area hospitals.

Infections in Animals

Species Affected

CCHFV can be found in many species of wild and domesticated mammals including small animals that serve as hosts for immature ticks, and large herbivores that act as hosts for mature ticks. CCHFV has been isolated from a number of species including cattle, sheep, goats, hares, hedgehogs, dogs and mice (*Mastomys* spp.). Antibodies have been reported in horses, donkeys, pigs, rhinoceroses, giraffes, buffalo and other mammalian species. Most species of birds are seronegative and are thought to be resistant to infection; however, antibodies can be found in ostriches, and these animals become viremic after experimental inoculation. Low CCHFV viremia was also reported from an experimentally infected blue-helmeted guinea fowl (*Numidia meleagris*), and antibodies have been reported in a magpie. A red-beaked hornbill and a glossy starling became seropositive after experimental infection, but viremia did not occur. Although immature *Hyalomma anatolicum* ticks sometimes feed on reptiles, antibodies to CCHFV have only been reported from one reptile, a tortoise from Tadjikistan.

Incubation Period/ Clinical Signs

CCHFV infections are asymptomatic in animals other than experimentally inoculated newborn rodents (laboratory mice, rats and Syrian hamsters). The only symptom in experimentally infected sheep and cattle was a transient, mild elevation in body temperature.

Communicability

Mammals become viremic and can transmit CCHFV in their blood and tissues. Domesticated ruminants including cattle, sheep and goats are viremic for one week after experimental infection. Most species of birds seem to be resistant to infection, but in ostriches, CCHFV can be found in blood for 1 to 4 days and in visceral organs for up to five days after experimental infection.

Post Mortem Lesions

No lesions have been reported except in newborn rodents.

Diagnostic Tests

Serology can identify animals that have been infected or exposed to CCHFV. An IgG ELISA can detect antibodies for the remainder of the animal's life; other tests, including complement fixation and indirect fluorescent antibody, usually detect antibodies for shorter periods. Viremia can be recognized by virus isolation and other techniques (see 'Diagnostic Tests' section under Human Infections), but these tests are not used diagnostically.

Prevention

Acaricides can be used on animals to control ticks, particularly before slaughter or export. Human outbreaks have occurred after exposure to infected ostriches during

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slaughter; these infections seem to be preventable by keeping the birds free of ticks for 14 days before slaughter. In some countries, ostriches are subject to a 30-day pre-slaughter quarantine period at export facilities.

Morbidity and Mortality

Large herbivores have the highest seroprevalence to CCHFV. Seroprevalence rates of 13–36% have been reported in some studies, while others suggest that more than 50% of adult livestock in endemic regions have antibodies. Animals carry CCHFV asymptotically. Deaths occur only in newborn rodents.

Internet Resources

- Centers for Disease Control and Prevention (CDC). Crimean-Congo Hemorrhagic Fever
<http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/cchf.htm>
- Medical Microbiology
<http://www.gsbs.utmb.edu/microbook>
- Public Health Agency of Canada. Material Safety Data Sheets
<http://www.phac-aspc.gc.ca/msds-ftss/index.html>
- The Merck Manual
<http://www.merck.com/pubs/mmanual/>
- The Merck Veterinary Manual
<http://www.merckvetmanual.com/mvm/index.jsp>
- World Health Organization. Crimean-Congo Haemorrhagic Fever Fact Sheet
<http://www.who.int/mediacentre/factsheets/fs208/en/>

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