Slide 1

Crimean-Congo Hemorrhagic Fever

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

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Overview

- Organism
- History
- Epidemiology
- Transmission
- Disease in Humans
- Disease in Animals
- Prevention and Control

In today's presentation we will cover information regarding the organism that causes Crimean-Congo hemorrhagic fever and its epidemiology. We will also talk about the history of the disease, how it is transmitted, species that it affects (including humans), and clinical and necropsy signs observed. Finally, we will address prevention and control measures, as well as actions to take if Crimean-Congo hemorrhagic fever is suspected.

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THE ORGANISM

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The Organism

- Crimean-Congo hemorrhagic fever virus (CCHFV)
  - Genus *Nairovirus*
  - CCHF serogroup
- Extensive genetic diversity
  - Viruses from different geographic regions

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.

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HISTORY

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History

- 1944
  - First described in Crimea
  - Soviet military personnel
- 1969
  - Also detected in Congo
- Outbreaks continue to occur
- Potential bioterrorist agent
  - CDC/NIAID Category C pathogen

The disease was first characterized in the Crimea in 1944 and given the name Crimean hemorrhagic fever. Illness was detected in about 200 Soviet military personnel assisting peasants in the area following the Nazi invasion. It was then later recognized in 1969 as the cause of illness in the Congo, thus resulting in the current name of the disease. New outbreaks have occurred in recent years. 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. Sources: CDC and Curr Opin Virol. 2012 Apr;2(2):215-20. doi: 10.1016/j.coviro.2012.03.001.

[Photo: Crimea (depicted in dark green) shown in relation to Ukraine (light green). Source: Wikimedia Commons]

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EPIDEMIOLOGY

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Geographic Distribution

- Africa
- Middle East
- Asia
- Parts of Europe
  - Southern parts of former USSR
  - Turkey
  - Bulgaria
  - Greece
  - Albania

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.

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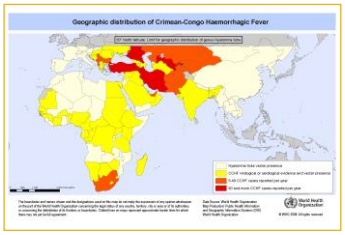
Geographic Distribution



[Photo: Map showing the geographic distribution of Crimean-Congo Hemorrhagic Fever. Pale yellow indicates areas with *Hyalomma* tick vector presence; dark yellow indicates areas with CCHF virological or serological evidence and vector presence; orange indicates areas where 5-49 cases of CCHF are reported per year; and red indicates areas where 50 or more cases of CCHF are reported each year. Source: World Health Organization at http://www.who.int/csr/disease/crimean_congoHF/Global_CCHFRisk_20080918.png]

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Morbidity and Mortality: Humans

- Seasonal trends
- Occupational exposures
  - Farmers, shepherds, veterinarians, abattoir workers, laboratory workers
  - Healthcare workers
- Recreational exposures
  - Hiking
  - Camping

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. In the general public, activities that increase tick exposure such as hiking and camping increase the risk of infection.

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Morbidity and Mortality: Humans

- Case fatality rate: 30-50%
- Mortality rate: 10-80%
  - Highest after tick bites
  - Higher in some geographic areas
    - Geographic differences in viral virulence suggested but unproven
  - Also affected by availability of supportive treatment in hospitals

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.

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Morbidity and Mortality: Animals

- Large herbivores
  - Highest seroprevalence
- Seroprevalence rates
  - 13-36%
  - More than 50%
- Animals asymptomatic

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 asymptomatically.

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TRANSMISSION

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Vectors

- Transmitted by ticks
  - *Hyalomma* spp. are principal vectors
    - Transovarial
    - Transstadial
    - Venereal
  - Other ixodid ticks
  - Biting midges?
  - Soft ticks?

CCHFV usually circulates between asymptomatic animals and ticks in an enzootic cycle. 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. [Photo: *Hyalomma marginatum* tick. Source: Adam Cuerden/Wikimedia Commons]

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Transmission in Humans

- Tick bites
- Contact with infected, crushed ticks
- Contact with infected animal tissues
- Ingestion of unpasteurized milk
- Contact with infected people
  - Blood, tissues
- Horizontal transmission?
- Aerosol?

Humans become infected through the skin and by ingestion. 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. Aerosol transmission was suspected in a few cases in Russia.

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Transmission in Animals

- Viremic mammals can transmit CCHFV to ticks
  - Hares
  - Hedgehogs
- Birds resistant to infection
  - May act as mechanical vectors, transporting infected ticks
  - Might spread virus between regions

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.

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DISEASE IN HUMANS

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Incubation in Humans

- Varies by route of exposure
  - Tick bites
    - 1-3 days (up to 9 days)
  - Blood or tissues
    - 5-6 days (up to 13 days)

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.

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Disease in Humans

- Pre-hemorrhagic phase
  - Sudden onset fever
  - Chills, headache, dizziness
  - Dizziness, photophobia, neck pain
  - Myalgia, arthralgia
  - Nausea, vomiting
  - Non-bloody diarrhea
  - Bradycardia
  - Low blood pressure

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 pre-hemorrhagic phase. It is followed, after several days, by the hemorrhagic phase.

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Disease in Humans

- Hemorrhagic phase
  - Petechial rash
  - Ecchymoses and large bruises
  - Hematemesis
  - Melena
  - Epistaxis
  - Hematuria
  - Hemoptysis
  - Bleeding from other sites

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. [Photo: Male patient with Crimean-Congo hemorrhagic fever. Source: BE Henderson/CDC Public Health Image Library]

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Disease in Humans

- Convalescent phase
  - 10-20 days after illness onset
  - Generalized weakness
  - Tachycardia
  - Other nonspecific symptoms
- Recovery usually complete but slow
  - May take up to one year
- Subclinical infections uncommon

In patients who survive, recovery begins 10 to20 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 be 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.

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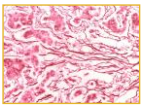
Diagnosis in Humans

- Virus isolation and identification
  - Blood, plasma, tissues
  - Cell culture or animal inoculation
  - BSL-4 required
- RT-PCR
  - Blood
  - Highly sensitive
  - Used for local variants



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. 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.

[Photo: Under a high magnification of 400X, this Wilder's reticulin-stained photomicrograph depicts the cytoarchitectural changes found in a liver tissue specimen extracted from a Congo/Crimean hemorrhagic fever patient. This particular view reveals a "thickening and a disassociation between the fibers of the reticular network." Source: CDC Public Health Image Library]

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Diagnosis in Humans

- Serology
  - Tests detect IgM or IgG (paired titers)
  - Indirect immunofluorescence
  - ELISA
- Past serologic tests
  - Complement fixation
  - Hemagglutination

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

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Treatment in Humans

- Supportive
- Ribavirin
  - No randomized human clinical trials to support this therapy
- Passive immunotherapy
  - Hyperimmune serum
  - Value of treatment controversial

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.

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DISEASE IN ANIMALS

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Species Affected

- Many species of wild and domesticated mammals
  - Hosts for immature ticks
    - Small mammals
  - Hosts for mature ticks
    - Large herbivores
- Other potential hosts
  - Birds mostly seronegative
  - Reptiles rarely 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.). Most species of birds are seronegative and are thought to be resistant to infection. Although immature *Hyalomma anatolicum* ticks sometimes feed on reptiles, antibodies to CCHFV have only been reported from one reptile, a tortoise from Tadzhikistan. [Photo: Large herbivores, such as cattle, can serve as hosts for mature ticks. Source: USDA ARS]

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Disease in Animals

- CCHFV infections usually asymptomatic in animals
- Mild clinical signs possible in experimentally infected animals
  - Newborn rodents
  - Sheep and cattle

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. No lesions have been reported except in newborn rodents.

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Diagnosis

- Serology
  - IgG ELISA
  - Complement fixation
  - Indirect fluorescent antibody
- Virus isolation and other techniques
  - Can detect viremia
  - Not used diagnostically

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.

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PREVENTION AND CONTROL

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Prevention and Control

- Avoid tick bites
  - Tick repellents
  - Environmental modification
  - Avoidance of tick habitat
  - Examination of skin and clothing for ticks
  - Clothing to prevent tick attachment
- Acaricides (animals)

In endemic regions, prevention depends on avoiding bites from infected ticks. 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.

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Prevention and Control

- Avoid contact with infected blood or tissues
  - Wear protective clothing and gloves
- Food safety
  - Do not consume unpasteurized milk
  - Virus usually inactivated in meat by post-slaughter acidification
  - Virus also killed by cooking

Contact with infected blood or tissues should also be avoided. 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.

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Prevention and Control

- Strict universal precautions
  - Use when caring for human patients
    - Barrier nursing
    - Isolation
    - Use of gloves, face-shields and goggles
- Prophylactic treatment
  - Ribavirin
- Stringent biosafety precautions

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.

[Photo: Depicted here in this 2007 photograph, was a Centers for Disease Control microbiologist, and Special Pathogens Branch (SPB) staff member in the process of inserting a rack of boxes containing biological stocks into a liquid nitrogen freezer where they would be stored. Source: CDC Public Health Image Library]

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Disinfection

- 1% hypochlorite
- 2% glutaraldehyde
- Heat
  - 56°C (133°F) for 30 min

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. [Photo: Disinfectants. Source: Danelle Bickett-Weddle/CFSPH]

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Additional Resources

- Center for Food Security and Public Health
  - www.cfsph.iastate.edu
- CDC
  - www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/cchf.htm
- World Health Organization
  - www.who.int/mediacentre/factsheets/fs208/en/

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Acknowledgments

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