Summary

- Main clinical presentation: Febrile disease, haemorrhagic symptoms, neurological syndrome (FD, HS (NS))
- Transmission via ticks (esp. Hyalomma marginatum marginatum) and direct contact with infected animals
- Human to human transmission occurs; CAVE nosocomial infection
- High mortality (up to 40%)

Transmission

Crimean-Congo Haemorrhagic Fever (CCHF) occurs throughout Africa, in Asia, in the former USSR and in Eastern Europe, the Balkans (Kosovo, Albania), the Middle East (including Oman and the United Emirates), Pakistan and the Maghreb, including Egypt. The virus was originally isolated in 1944-45 in the Crimean Peninsula in the north of the Black Sea, during an outbreak in Soviet military personnel. In 1956 it was found in Kinshasa, Congo, first in a patient and shortly afterwards in a scientist who acquired a subsequent laboratory infection. In 1967 it was shown by Chumakov and Casals that both viruses were virtually identical, so now it is referred to as Crimean-Congo Haemorrhagic Fever Virus.

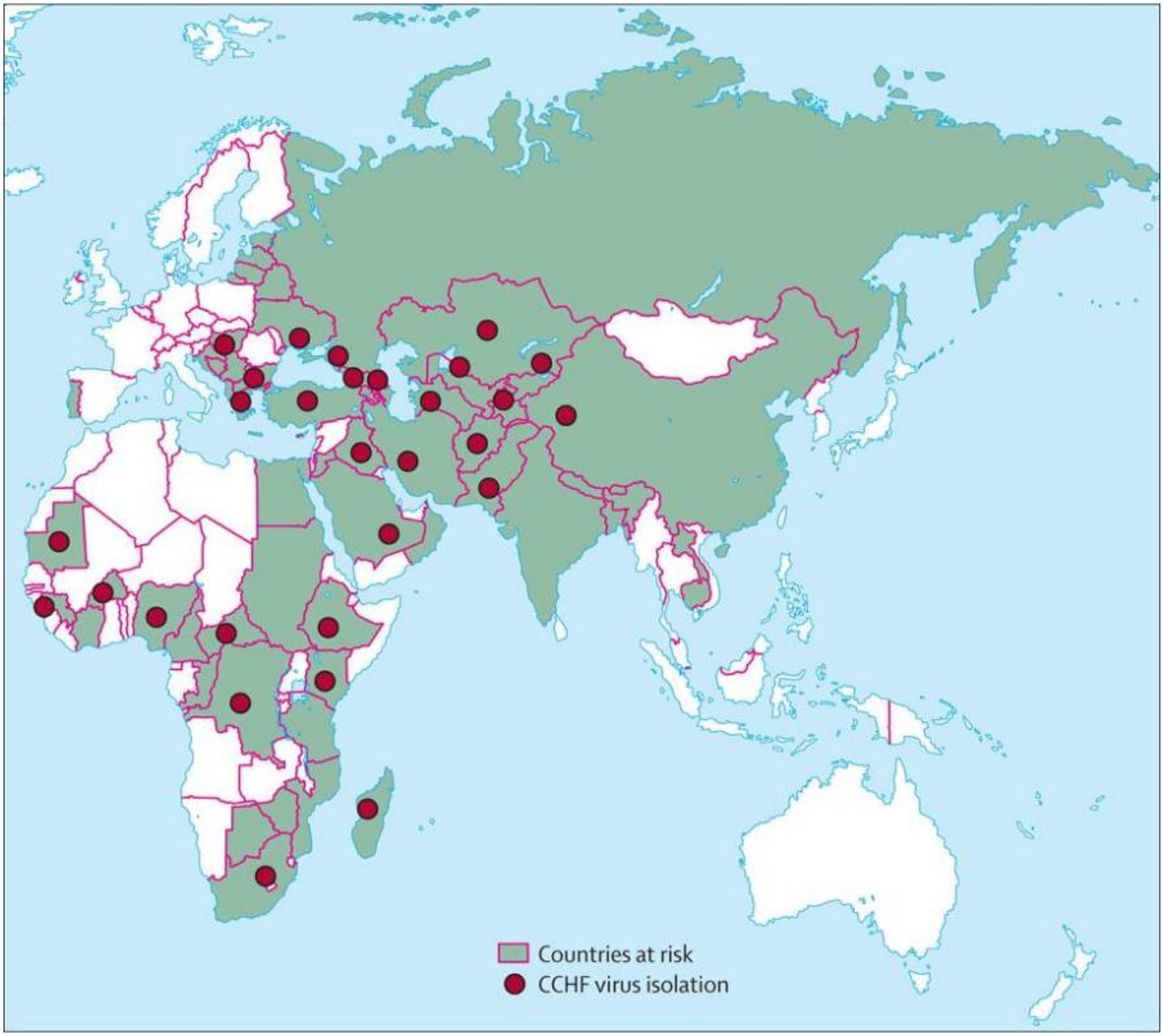


Figure: Distribution of Crimean-Congo Haemorrhagic Fever (Ergönül et al, Lancet Infect Dis)

Man can be infected by the bite of ticks, especially Hyalomma ticks, although sometimes many other tick species are involved. The virus can survive in a tick population because it is transmitted both by the transovarial and the transstadial route. The larvae and nymphs of the ticks become infected when they suck blood from viremic small mammals and birds. Adult ticks infect themselves through the blood of infected wild or domesticated ruminants. Man can be also infected by direct contact with infected animal tissue or blood (goats, cattle,

sheep, hares, ostriches) and during shearing of tick-infested sheep. In sheep and goats, the viraemia lasts a week. When these animals are slaughtered or die from their babesiosis/anaplasmosis, they can still be viraemic. The people who looks after the animal or deals with the carcass can therefore become infected. Herdsmen, farmers, veterinary surgeons and slaughterhouse workers have an increased risk of infection. Human to human transmission is well documented, and nosocomial transmission also occurs. A classic scenario is a patient with bleeding who requires surgery after which the virus spreads to medical staff and/or members of the family.

Virus

CCHF virus that causes Crimean-Congo Haemorrhagic Fever belongs to the family of the Bunyaviridae, genus Nairovirus. Other genera within the family include Orthobunyavirus, Hantavirus, Phlebovirus, and Tospovirus. CCHF is a tripartite, negative-sense, single-stranded RNA genome that comprises Large (L), Medium (M) and Small (S) segments. The three genome segments encode four structural proteins—the RNA-dependent RNA polymerase (L protein) is encoded by the large (L) segment, the glycoproteins (GN and GC) are encoded by the medium (M) segment, and the nucleocapsid protein (N) is encoded by the small (S) segment.

Clinical aspects

After an incubation period of 3 days after a tick bite and up to 6 days after contact with infected animal tissues, the disease starts with a sudden onset of fever. Clinical features commonly show a dramatic progression characterised by haemorrhage and myalgia, headache and vomiting. A discrete exanthema/enanthema can be seen, mainly on the palate. On the 4th day petechiae and extensive ecchymoses appear, followed by severe systemic bleeding including melaena, haematemesis, epistaxis and haematuria. There is no direct effect on the central nervous system, although confusion, lethargy and aggressive behaviour can occur.

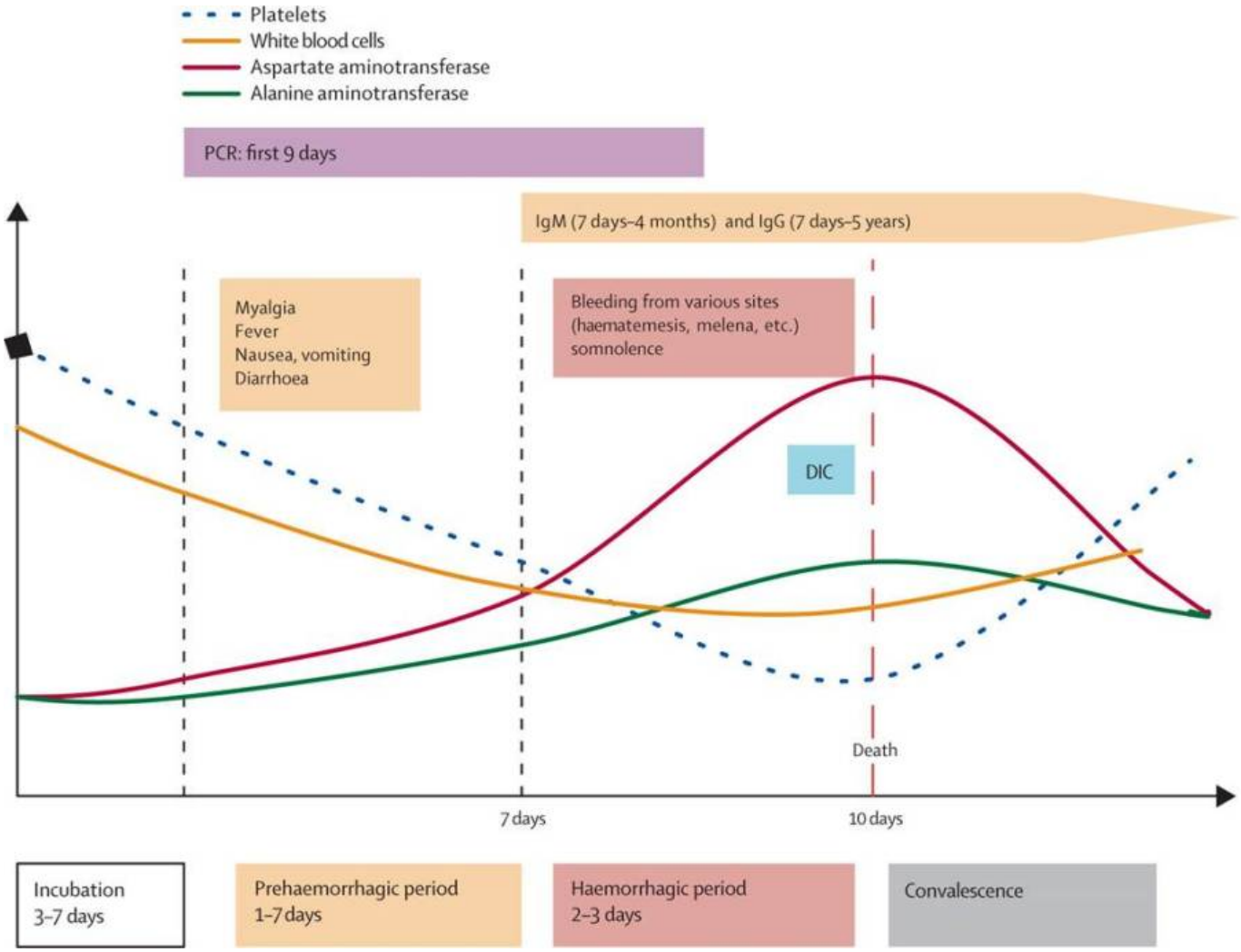


Figure: Clinical course of Crimean-Congo Haemorrhagic Fever (Ergönül et al, Lancet Infect Dis).
DIC: Disseminated Intravascular Coagulation

Haematology results frequently show leukopenia and thrombocytopenia. The levels of liver enzymes, creatinine phosphokinase, and lactate dehydrogenase are raised and coagulation markers are prolonged. Infection of the endothelium has a major pathogenic role. Besides direct infection of the endothelium, indirect damage by viral factors or virus-mediated host-derived soluble factors that cause endothelial activations and dysfunction are thought to occur.

Mortality is high (15-40%), especially during an epidemic but mild cases and spontaneous

recovery also occurs.

Diagnosis

Early diagnosis is critical both for patient management and for the prevention of human to human transmission. The diagnosis is made by demonstrating the presence of the virus in viraemic phase plasma either by culturing or RT-PCR or by detecting a seroconversion. RT-PCR is highly sensitive and specific.

IgM and IgG antibodies are detectable by ELISA and immunofluorescence assays from about 7 days after the onset of disease. Specific IgM declines to undetectable levels by 4 months post-infection, but IgG remains detectable for at least 5 years.

Treatment

General supportive measures and symptomatic therapy. People who are infected should be treated in strict isolation since airborne transmission can occur. Barrier-Nursing should be in place for infection control.

Ribavirin (Virazole®) was used to treat CCHF. There is no evidence from randomised clinical trials for the use of ribavirin to treat human CCHF — its effectiveness has only been described in observational studies. Patients should be treated for 10 days (30 mg/kg as an initial loading dose, then 15 mg/kg every 6 hours for 4 days, and then 7·5 mg/kg every 8 hours for 6 days).

Another study suggested treatment using passive immunotherapy, transferring the plasma of convalescing survivors to infected patients However the study had no control groups and was limited to seven patients, therefore conclusions cannot be made.

Prevention

Vector control

In endemic areas ticks should be eliminated from animals two weeks before they are

slaughtered (e.g. with a pyrethroid acaricide). The virus is sensitive to heat and is not resistant to an acid environment. This explains why transmission by eating infected meat is rrare.

Vaccination

There is no commercial vaccine.

Kyasanur Forest disease

Kyasanur forest disease is caused by Kyasanur forest disease virus, a flavivirus. It occurs principally in the Shimoga and Kanara district of Karnataka (formerly Mysore), India. The geographic distribution of this virus is not restricted to Karnataka, e.g. 22 percent of persons living in the Andaman and Nicobar Islands were found to be seropositive for KFD in 2002. Human infection by closely related viruses is known in Saudi Arabia (Alkhurma virus) and China (Nanjianyin virus).

The virus was identified in 1957 when it was isolated from a sick monkey from the Kyasanur forest in Karnataka state. This happened during a fatal epizootic among wild monkeys. The main hosts of this virus are small rodents, but shrews, bats, and monkeys may also carry the virus. Transmission is via the bite of an infected tick, mainly *Haemaphysalis spinigera*. Apart from tick bite, humans can also get infected by contact with an infected animal, such as a sick or recently dead monkey. Goats, cows, and sheep may become infected with KFD, but they do not have a role in the transmission of the disease. There is no evidence of the disease being transmitted via the unpasteurized milk of any of these animals.

The incubation period is not well known, some state 3-8 days, others 1-2 weeks. The patient develops sudden onset fever, severe headache, followed by back pain, muscle pain in the extremities, inflammation of the eyes, dehydration, gastrointestinal symptoms with or without gastrointestinal bleeding. Hypotension and pancytopenia can ensue. Some patients develop cough due to bronchopneumonia prior to coma and death. Some patients recover without complications after this first phase. However in most patients, the illness is biphasic, and the patient begins experiencing a 2nd wave of symptoms at the beginning of the 3rd

week. These symptoms include fever and signs of encephalitis. The diagnosis is made by virus isolation from blood or by serologic testing using ELISA. There are approximately 400-500 symptomatic cases of KFD per year with a case fatality rate of 3-5 percent.

There was an important outbreak in May and June 2003. Forest workers are particularly at risk. There is a safe, effective formalin-inactivated vaccine available for control of Kyasanur Forest disease since 1990. More than 80,000 people were immunized in trials during 1990 to 1992, with no report of adverse effects. The vaccine is prepared from tissue culture and administered at a dose of 1.0 ml subcutaneously (0.5 ml below age 6), with a booster dose after 4 weeks.