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Crimean-Congo haemorrhagic fever

Önder Ergönül

Crimean-Congo haemorrhagic fever (CCHF) is an often fatal viral infection described in about 30 countries, and it has the most extensive geographic distribution of the medically important tickborne viral diseases, closely approximating the known global distribution of *Hyalomma* spp ticks. Human beings become infected through tick bites, by crushing infected ticks, after contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viraemic livestock. Clinical features commonly show a dramatic progression characterised by haemorrhage, myalgia, and fever. The levels of liver enzymes, creatinine phosphokinase, and lactate dehydrogenase are raised, and bleeding 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. In diagnosis, enzyme-linked immunoassay and real-time reverse transcriptase PCR are used. Early diagnosis is critical for patient therapy and prevention of potential nosocomial infections. Supportive therapy is the most essential part of case management. Recent studies suggest that ribavirin is effective against CCHF, although definitive studies are not available. Health-care workers have a serious risk of infection, particularly during care of patients with haemorrhages from the nose, mouth, gums, vagina, and injection sites. Simple barrier precautions have been reported to be effective.

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Introduction

Crimean-Congo haemorrhagic fever (CCHF) is a fatal viral infection described in parts of Africa, Asia, eastern Europe, and the middle east.[1,2] The virus belongs to the genus Nairovirus in the Bunyaviridae family and causes severe diseases in human beings, with a reported mortality rate of 3–30%.[2,3] The geographic range of CCHF virus is the most extensive one among the medically important tickborne viruses (figure 1). Human beings become infected through tick bites, by contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viraemic livestock.[4] The clinical features show common dramatic progression characterised by haemorrhage, myalgia, and fever, with some differences among different regions suggested but not well studied. Treatment with ribavirin has not yet been approved in many countries. However, there are reports that indicate the drug may be beneficial. The widespread geographic distribution of CCHF virus, its ability to produce severe human disease with high mortality rates, and fears about its intentional use as a bioterrorism agent[5] make the virus an important human pathogen. Moreover, ecological complexity of vectorborne diseases, therapeutic controversy, and human-to-human transmission of a zoonotic infection make CCHF an interesting topic for research.

There has been a substantial increase in reports on CCHF virus over the past 5 years. Here I review published work on CCHF, with an emphasis on the recent outbreak in Turkey. CCHF virus-infected cases were first reported in Turkey in 2002,[3,6–8] although epidemics have been reported from neighbouring countries since the 1970s. Between 2002 and 2005, 500 cases were reported to Turkish Ministry of Health, and 26 (5·2%) of these cases died.[9]

Historical background

In the 12th century, a haemorrhagic syndrome was described in present day Tajikistan. The signs were presence of blood in the urine, rectum, gums, vomitus, sputum, and abdominal cavity.[1] The arthropod that caused the disease was said to be tough, small, related to a louse or tick, and normally parasitising a black bird. In the modern era, Crimean haemorrhagic fever was first described as a clinical entity in 1944–45, when about 200 Soviet military personnel were infected while assisting peasants in Crimea in the wake of World War 2.[1,2] The virus was isolated from blood and tissues of patients using intracerebral inoculation of newborn white mice in 1967.[1,2] The virus responsible for Crimean haemorrhagic fever was later shown to be

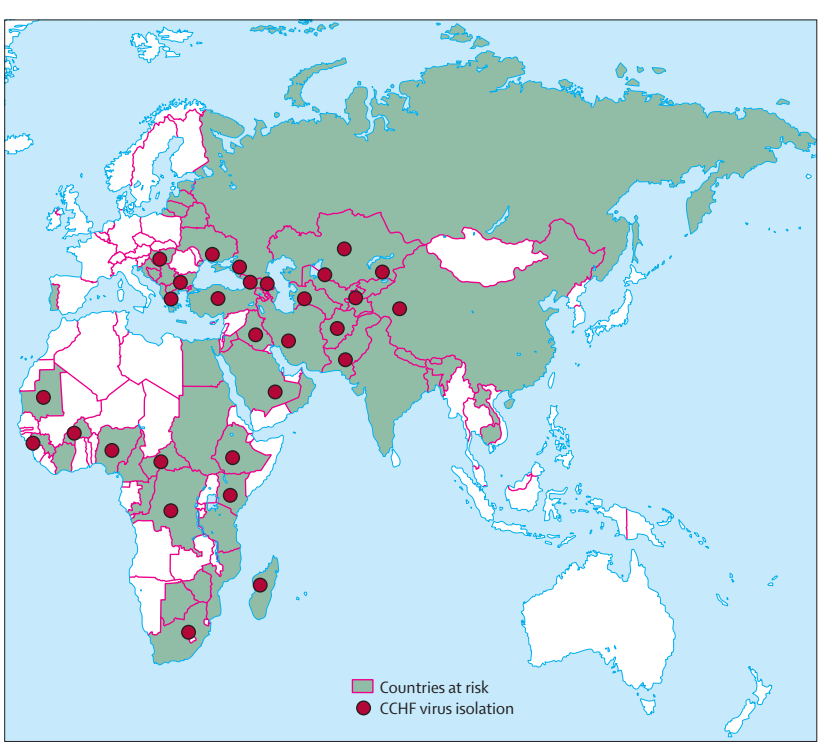

Figure 1: **Worldwide distribution of CCHF virus**

Location	Years	Number of cases*	Case fatality rate (%)	Occupation
Southeast Europe				
Crimea	1944–45[1]	200	10	Military members
Astrakhan	1953–63[1]	104	17	Agricultural workers
Rostov	1963–69[1]	323	15	Agricultural workers
Bulgaria	1953–74[2]	1105	17	Agricultural workers, health-care workers
	1975–96[16]	279	11	Agricultural workers
	1997–03[16]	138	21	Agricultural workers
Albania	2001[17]	7	0	Agricultural workers, health-care workers
Kosovo	2001[18]	18	33	Agricultural workers
Turkey	2002–05[9]	500	5	Agricultural workers
Asia				
China	1965–94[19]	260	21	Agricultural workers
	1997[19]	26	24	Agricultural workers
Kazakhstan	1948–68[1]	75	50	Agricultural workers
Tajikistan	1943–70[1]	97	23	Agricultural and laboratory workers
Pakistan	1976[20]	14	29	Shepherd, health-care workers
	1994[21]	3	Not known	Health-care workers
	2000[22]	9	55	Agricultural workers, health-care workers
Middle east				
United Arab Emirates (UAE)	1979[23,24]	6	50	Health-care workers
	1994–95[24]	11	73	Agricultural workers
Sharjah, UAE	1980[2]	1	0	Storekeeper
Iraq	1979–80[25,26]	55	64	Agricultural workers
Saudi Arabia	1990[27]	7		Agricultural workers
Oman	1995–96[28]	4	Not known	Agricultural workers
Iran	2003[29]	81	18	Agricultural workers
Africa				
Zaire†	1956[1]	2	0	Physician
Uganda	1958–77[1]	12	8	Laboratory workers
Mauritania	1983[2,30]	1	0	Camel herd owner
	2004[31]	38	29	Agricultural workers, health-care workers
Burkina Faso	1983[2]	1	0	..
South Africa	1981–86[2]	32	31	Farmers, health-care workers
Tanzania	1986[2]	1	0	Student
Southwest Africa	1986[2]	1	0	..
Kenya	2000[32]	1	100	Agricultural worker

..=not reported. *The number of the confirmed cases is given if both suspected and confirmed cases were reported. †Present day Democratic Republic of the Congo.

Table 1: **Reported outbreaks of CCHF since 1945**

antigenically indistinguishable from Congo virus, isolated in 1956 from a febrile patient in Belgian Congo (present day Democratic Republic of the Congo).[10] The common antigenic structure among Eurasian Crimean haemorrhagic fever strains[11] and Asian[12] and African strains of Congo virus[9,13,14] led to the virus being called Crimean haemorrhagic fever-Congo virus,[15] and then Crimean-Congo haemorrhagic fever virus.[1]

Epidemiology

The geographic range of CCHF virus is the most extensive among the tickborne viruses that affect human health, and the second most widespread of all medically important arboviruses, after dengue viruses (figure 1).[2]

The history of reported outbreaks is summarised in table 1. Before 1970, most cases were reported from the former Soviet Union (Crimea, Astrakhan, Rostov, Uzbekistan, Kazakhstan, Tajikistan)[1,2] and Bulgaria,[1,2] as well as virus circulation in parts of Africa such as the Democratic Republic of the Congo and Uganda.[10,13] An outbreak in 1965 in China with a case fatality rate of 80% was noted, but not presented in detail.[33] The initial recognition of haemorrhagic cases in Africa occurred in the 1960s, resulting in a series of in-depth studies in South Africa[34–44] and reports of additional outbreaks from Congo,[43] Mauritania,[30] Burkina Faso,[45] Tanzania,[43] and Senegal.[46] A substantial number of cases were also reported from middle eastern countries such as Iraq,[25,26] the United Arab Emirates (UAE),[23,24,47] Saudi Arabia[27] and Oman,[28] and from Pakistan[20] and China.[19] By 2000, new outbreaks had been reported from Pakistan,[21,22,48] Iran,[29] Senegal,[49] Albania,[17] Yugoslavia,[18,50] Bulgaria,[16] Turkey,[3,6,7] Kenya,[32] and Mauritania.[51]

Serological evidence for CCHF virus has been reported from Greece,[31] India,[52] Egypt,[53] Portugal,[54] Hungary,[55] France,[1] and Benin,[1] although the virus was isolated only in Greece and the only reported human case was a Greek laboratory infection. CCHF virus is endemic in the Balkans, including Bulgaria,[16] the former Yugoslavia,[18,50] and Albania.[17] It is of interest that the strain that caused the laboratory-related infection in Greece was exceedingly mild, possibly reflecting chance variation; however, the virus has the greatest phylogenetic difference from other CCHF viruses and Greece is separated from Bulgaria by mountains approximately 1500–2500 m high.[16]

The microbiology and the life cycle of the virus

CCHF is a member of the Nairovirus genus of the family Bunyaviridae. Other genera within the family include Orthobunyavirus, Hantavirus, Phlebovirus, and Tospovirus. The Nairovirus genus includes 34 described viruses and is divided into seven different serogroups.[56] The most important groups are the CCHF group, which includes CCHF virus and Hazara virus, and the Nairobi sheep disease group, which includes the Nairobi sheep disease and Dugbe viruses.[4] CCHF virus, Dugbe virus, and Nairobi sheep disease virus are the only three members of the Nairovirus genus that are known to cause disease among human beings.

Bunyaviruses are enveloped particles with a single-stranded RNA genome of negative polarity (figure 2).[57] 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; previously referred to as G1 and G2) are encoded by the medium (M) segment, and

the nucleocapsid protein (N) is encoded by the small (S) segment.[58,59]

Emerging data on viral replication shows great potential for the development of new drugs. The viral glycoproteins are responsible for the recognition of receptor sites on susceptible cells. Following attachment, viruses are internalised by endocytosis.[4] Replication occurs in the cytoplasm, and the virions mature by budding through the endoplasmic reticulum into cytoplasmic vesicles in the Golgi region.[4] Bunyaviruses are known to bud from Golgi membranes and the budding site seems to be defined by retention of the glycoproteins GN and GC at that particular site.[59] GN is localised to the Golgi compartment, whereas GC is found in the endoplasmic reticulum.[59] Recently, the expression strategy and biosynthesis of the CCHF viral glycoproteins have been studied in more detail, including the identification of precursor cleavage sites and the determination of the exact amino termini of the two major cleavage products, GN and GC.[60] The subtilase SKI-1 has been identified as the cellular protease responsible for the processing step that generates the amino terminus of mature GN.[61,62]

Recent studies of the L RNA genome segment and predicted encoded L polymerase protein of CCHF virus demonstrate that they are approximately twice the size of those found in viruses of other bunyavirus genera. Regions containing ovarian tumour-like cysteine protease and helicase domains were identified in the L segments of CCHF and Dugbe viruses, suggesting an autoproteolytic cleavage process for nairovirus L proteins.[63,64]

Phylogenetic studies and worldwide diversity

In 1970, when the virus was first named as CCHF virus,[15] the antigenic structures of the viruses from various geographic regions were thought to be indistinguishable. However, the development of nucleic acid sequence analysis techniques revealed extensive genetic diversity. Most nucleic acid sequence analyses are based on the S segment of the genome, although some recent studies were done on the M RNA segment. According to these studies, there are eight genetically distinct clades.[15]

Because of their low genetic divergence, the European strains are grouped together, except the Greek strain AP92.[16,17] The strains from southeast Russia are closely related to the European strains.[62,65] Turkish CCHF virus isolates from the recent outbreak are clustered closely with CCHF viral strains from southwest Russia and Kosovo. Bootstrap analysis showed the clade containing the Russian, Balkan, and Turkish CCHF viruses to be well supported (99%), and these viruses are clearly distinct from those in other virus clades, including the clade containing the virus detected in the CCHF outbreak in neighbouring Iran in 2002.[6]

The AP92 strain, isolated from *Rhipicephalus bursa* ticks from Greece, differs from European strains[66] and forms an independent clade. This genetic difference may be attributable to the different species of ticks vector and/or to genetic isolation by adjacent mountain ranges.[16]

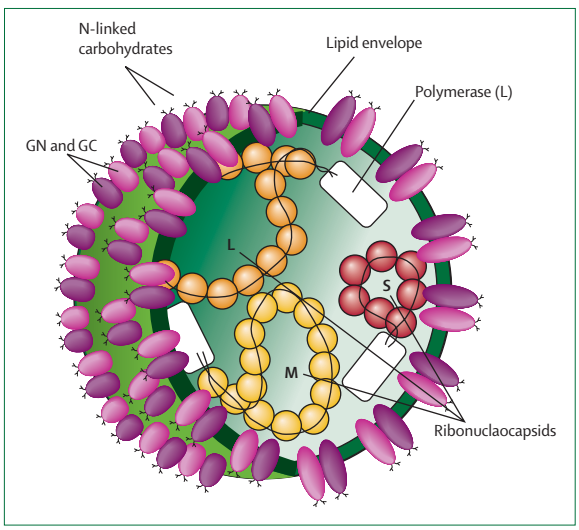

Figure 2: **Schematic presentation of the virus structure**

The third clade is formed from the strains from central Asia—namely Kazahkstan,[67] Tajikistan,[68] Uzbekistan,[68] and China[68]—which are closely related. Phylogenetic analysis of the M segment showed that the Chinese CCHF virus isolates were clustered into three groups, one of which was more closely related to a Nigerian isolate.[69]

Isolates from Iran, Madagascar, and Pakistan were found to be closely related, forming a fourth clade.[16] Partial S-segment nucleotide sequences showed that the Iranian viral isolates clustered along with strains from Pakistan and Madagascar in one distinct lineage.[70] Phylogenetic analysis also demonstrated that the Iranian isolates examined in this study and the CCHF virus strain ArTeh193-3 clustered into different genetic groups, indicating that at least two genetic lineages of CCHF virus could be co-circulating in Iran.[70]

The second group of strains from Iran is closely related to strains from Senegal and Mauritania, which together form a fifth clade.[16]

Finally, there are three distinct clades in Africa: first, strains from Senegal, Mauritania, and South Africa; second, strains from Nigeria and Central African Republic; and third, strains from Uganda.

Ecology

Vertebrate reservoir hosts

CCHF virus circulates in an enzootic tick–vertebrate–tick cycle, and there is no evidence that the virus causes disease in animals. CCHF viral infection has been commonly demonstrated among smaller wildlife species—eg, hares and hedgehogs—that act as hosts for the immature stages of the tick vectors.[1,2] Antibodies against CCHF virus have been detected in the sera of horses, donkeys, goats, cattle, sheep, and pigs in various regions of Europe, Asia, and Africa.[2] It must be borne in

mind that antibody studies, particularly if the prevalence is low, are not as meaningful as obtaining actual virus isolates. Although no ground-feeding birds have shown detectable viraemia,[71] birds may have a role in the transportation of CCHF virus-infected ticks between different countries.

Tick vectors

CCHF viruses are transmitted by *Hyalomma* genus ticks, particularly by *Hyalomma marginatum marginatum*. CCHF virus was isolated from adult *Hyalomma* genus ticks in the 1960s.[1,2] Viral isolates were also obtained from field-collected eggs and unfed immature stages of *H marginatum*, providing evidence of transovarial (ie, from infected mother to egg stage), and transstadial (ie, from larvae to nymph to adult) transmissions.[2]

The known occurrence of CCHF in Europe, Asia, and Africa coincides with the global distribution of hyalomma ticks.[1,2] *H marginatum marginatum* is known as the Mediterranean hyalomma, and it may be the main vector of CCHF virus in Europe. CCHF virus has also been isolated from *Hyalomma anatolicum anatolicum* and other *Hyalomma* spp. Isolates from other tick genera—eg, *Rhipicephalus*, *Ornithodoros*, *Boophilus*, *Dermacentor*, and *Ixodes* spp[1,2]—may be locally important because some have transmitted virus in the laboratory, but viral isolation alone does not incriminate them as vectors without additional laboratory and epidemiological studies.[2]

Climate change

Changes in climatic conditions have been suggested to be one of the factors that has facilitated reproduction of the tick population, and consequently the increased incidence of tick-borne infectious diseases.[72,73] In the northern hemisphere, *H marginatum marginatum* is usually activated by increasing temperature in the spring, particularly in April or May, and the immature stages are active in the summer between May and September.[74] For example, in the Ukrainian steppes in 1963–64, the first adult hyalommas appeared when average daily temperatures reached 5–9°C on April 8 in 1963, and April 20 the following year.[1] Tick densities were reduced by the severe winter of 1968–69 in Astrakhan Oblast (a federal republic of Russia), and consequently the number of the cases of CCHF was drastically reduced.[1] The number of days with a temperature of over 5°C in April, and the daily mean temperature in April in the region of Turkey affected by the recent outbreak were reported to be increased in the years before the outbreak.[75] However, climate change is not necessarily the cause of the marked increased incidence of a variety of tick-borne diseases in many parts of Europe over the past two decades.[76]

In general, CCHF outbreaks have developed against a background of favourable climatic factors and environmental changes beneficial for the survival of large numbers of *Hyalomma* spp ticks and of the hosts of both their immature and adult stages.[1] In the former Soviet Union, environmental changes include wartime neglect of agricultural lands, introduction of susceptible military personnel or new settlers into an infected area, wide scale collectivisation of agriculture, changing pasture patterns, converting floodplains to farmland, and flood control.[1] During World War 2, after the occupation of Crimea (1941–44), normal agricultural activities were disrupted and the common sport of hunting European hares was abandoned. When Soviet troops reoccupied the hilly Crimean steppes in 1944, hares had become excessively abundant and neglected pastures were overgrown with weeds, and the first outbreak of the modern era was documented.[1] Interestingly, a similar explanation was suggested for the outbreak in Turkey:[75] the fields in the affected region had been abandoned from hunting and pasturing between 1995 and 2001 because of terrorist activities in the region; in this period, the numbers of small mammals (eg, hares) and wild animals (eg, boars) increased. After 2001, the fields became available again for hunting and pasturing, and cattle and sheep were exposed to virus-carrying ticks.

The potential roles of migratory birds and the movement of livestock carrying ticks in the spread of the virus over distant geographic areas have been studied.[1,77,78] Birds migrating from the Balkans were suggested to be the cause of the 2002 outbreak in Turkey.[6] However, there is no precise data on CCHF virus in birds and on bird-parasitising ticks.

Location and reference	Year of outbreak	Number of cases	Fatal cases
Bulgaria[2]	1953–65	42	17
Pakistan[20]	1976	11	3
Iraq[25]	1979	2	2
Dubai[23]	1979	5	2
South Africa[38]	1984	8	2
Pakistan[21]	1994	3	Not known
Pakistan[48]	2002	2	1
Albania[50]	2002	1	0
Mauritania[49]	2003	5	5
Turkey (unpublished data)	2005	2	0

Table 2: **Nosocomial infections of health-care workers during outbreaks of CCHF**

Risk factors for infection among human beings

Epidemiologically, CCHF cases are distributed mainly among actively working age groups exposed to tick populations. The major at-risk group are farmers living in endemic areas; most of the affected cases deal with agriculture and/or animal husbandry. Almost 90% of the cases in the recent outbreak in Turkey were farmers.[3,6,7] Although there is no evidence that the virus causes disease in animals, CCHF virus-infected individuals were reported after skin contact with livestock and other animals.[1,2,37,43] Veterinarians and abattoir workers who

work with large domestic animals are also an at-risk group; acquisition of the virus usually takes place while slaughtering animals.[27,32,37,77,79] Viraemic blood from subclinically infected animals was the most likely source of infection, but exposure to ticks during these processes is also likely, at least in some of the cases.[38,79] Meat itself is not a risk because the virus is inactivated by post-slaughter acidification of the tissues and would not survive cooking in any case.

Hiking, camping, and other rural activities are also a risk factor for tick exposure. Gender distribution varies between countries, depending on the participation of women in agricultural work.

Outbreaks have recently been reported in South Africa when heavily tick-infested ostriches were slaughtered.[38,80] Infection was reported to be acquired either by contact with ostrich blood or inadvertently crushing infected ticks while skinning ostriches. Although no antibody was detected among birds during the outbreak,[81,82] ostriches have been experimentally infected, and viraemia was observed for 1–4 days after infection.[80] As a public-health measure, this study suggests that birds should be kept free of ticks for 14 days before slaughtering.

Health-care workers are the second most affected group. Hospital health-care workers are at serious risk of transmission of CCHF infection when caring for patients with haemorrhages from the nose, mouth, gums, vagina, and injection sites. The transmission of the CCHF infections and deaths among health-care workers has been reported in parallel with outbreaks in the general population (table 2).

In one hospital outbreak, it was reported that 8·7% of health-care workers who were exposed to infected blood and 33% of those who had a needlestick injury developed the disease.[41] CCHF virus has repeatedly caused nosocomial outbreaks with high mortality, and percutaneous exposure presents the highest risk of transmission.[11,37,38,41] The most dangerous settings for acquiring CCHF virus are interventions to gastrointestinal bleedings, and emergency operations on patients that have yet to be diagnosed with CCHF.[42] In general, these patients were diagnosed after the operation, and injuries to the operating team during the operation are usually under-reported. Airborne acquisition of the infection was suspected in several cases in Russia,[1,2] but were not documented. Horizontal transmission from a mother to her child has also been reported.[83]

Course of infection and clinical features

Human beings are the only known host of CCHF virus in which disease is manifested.[2,4] In one Russian study[84] the probability of developing CCHF for people who had been infected was found to be 0·215—ie, one of every five infected people develops CCHF.

The typical course of CCHF infection has four distinct phases: incubation, prehaemorrhagic, haemorrhagic, and convalescence periods (figure 3).[1] The incubation period that follows a tick bite is usually short—3–7 days—but it is difficult to obtain precise data.[1,44] The incubation period could differ depending on several factors including viral dose and route of exposure—eg, it could be shorter with bloodborne transmissions. In South Africa, the time to onset of disease after exposure to tick bite was 3·2 days, 5 days following exposure to blood or tissue of livestock, and 5·6 days after exposure to blood of infected human beings.[43] The mean duration of the disease course before presenting at a hospital was reported to be 5·5 days in Turkey[3] and 3·5 days in the UAE.[24]

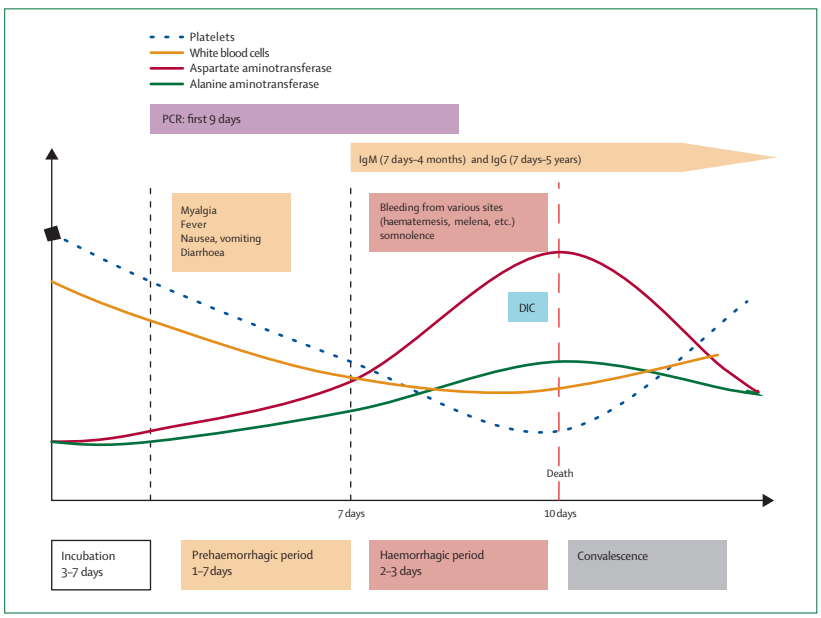

Figure 3: **Clinical and laboratory course of CCHF**
DIC=disseminated intravascular coagulation.

The prehaemorrhagic period is characterised by the sudden onset of fever (39–41°C), headache, myalgia, and dizziness.[1–4,6,7,24,44] On average, fever persists for 4–5 days.[1] Additional symptoms of diarrhoea, nausea, and vomiting are also seen in some cases.[2,24,44] Hyperaemia of the face, neck, and chest, congested sclera, and conjunctivitis are commonly noted. The prehaemorrhagic period lasts an average of 3 days (range: 1–7 days).[1]

The haemorrhagic period is short (usually 2–3 days), develops rapidly, and usually begins between the third to fifth day of disease. There is no relation between the temperature of the feverish patient and onset of haemorrhage.[1] Haemorrhagic manifestations range from petechiae to large haematomas appearing on the mucous membranes and skin (figure 4). Bleeding from other sites, including the vagina, gingival bleeding, and cerebral haemorrhage have been reported.[43] The most common bleeding sites are the nose, gastrointestinal system (haematemesis, melena, and intra-abdominal), uterus (menometrorrhagia) and urinary tract (haematuria), and

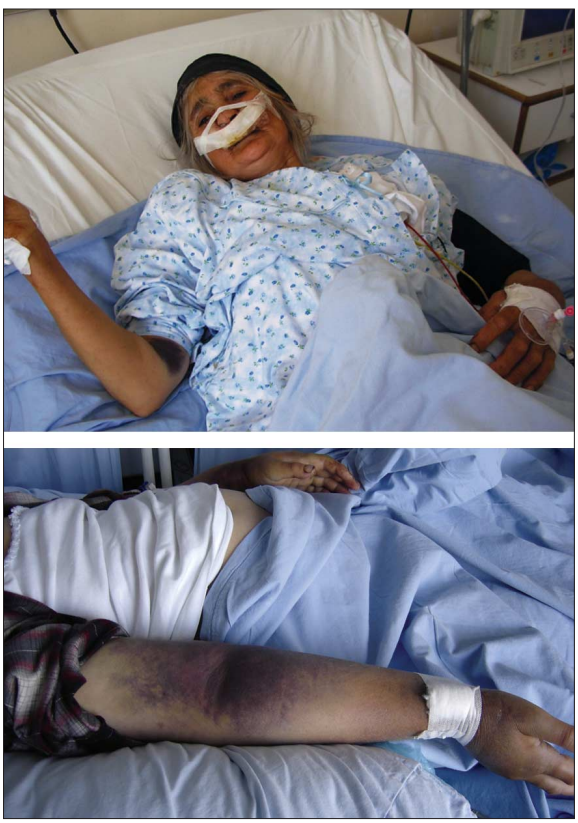

Figure 4: **CCHF patients from the Ankara Numune Education and Research Hospital**

the respiratory tract (haemoptysis).[2,85] Atypical presentations of bleeding are also seen. For example, in one patient with stubborn abdominal pain, acute appendicitis was suspected, but haemorrhage and bleeding in the internal and external oblique muscles and caecum were detected, with no pathology of the appendix.[86] Hepatomegaly and splenomegaly have been reported to be occur in one-third of patients.[1] In Turkey, hepatomegaly was detected in 20–40% of cases,[3,6–8] and two studies reported splenomegaly, with frequencies of 14% and 23%.[7,8]

The convalescence period begins in survivors about 10–20 days after the onset of illness. Patients remain in hospital for around 9–10 days.[3,24] In the convalescent period, labile pulse, tachycardia, temporary complete loss of hair, polyneuritis, difficulty in breathing, xerostomia, poor vision, loss of hearing, and loss of memory have been reported,[1] although none of these findings were noted in the recent outbreak in Turkey. Although cardiovascular changes—eg, bradycardia and low blood pressure—were reported in an earlier review,[1] these have not been emphasised recently.[3,6,7,24] Hepatorenal insufficiency was reported in South Africa[6] but not in Turkey. There is no known relapse of the infection, and a biphasic course of the disease—as noted in published work from the former Soviet Union[1]—was not observed in Turkey.

Biochemical tests

Thrombocytopenia appears to be a consistent feature of CCHF infection.[2,24,44] Patients had leucopenia and raised levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and creatinine phosphokinase. Coagulation tests such as prothrombin time and activated partial thromboplastin time are prolonged. The level of fibrinogen might be decreased, and fibrin degradation products could be increased. Laboratory tests, including complete blood count, and biochemical tests returned to normal levels within approximately 5–9 days among surviving patients (figure 5).[85]

Predictors of mortality

Swanepoel and colleagues[30] described clinical laboratory criteria that could be measured early in the course of disease (during the first 5 days) and that predicted a fatal outcome in 90% of patients with any of these findings: white blood cell count of 10×10^9 cells per L or above, platelet count of 20×10^9 per L or below, aspartate aminotransferase level of 200 U/L or over, alanine aminotransferase of 150 U/L or over, activated partial thromboplastin time of 60 seconds or more, or fibrinogen levels of 110 mg/dL or under. Other case series have confirmed that levels of aspartate aminotransferase and alanine aminotransferase are significantly higher among severe cases ($p<0\cdot05$).[3,85] In a study from Turkey, higher aspartate aminotransferase and alanine aminotransferase levels (>700 and >900 IU/L, respectively) were found to have higher sensitivity for severe cases.[85] Leucocytosis was observed in only one out of four fatal patients.[85]

In keeping with the prognostic importance of abnormalities of activated partial thromboplastin time and fibrinogen noted by Swanepoel and coworkers,[44] patients with fatal outcomes in other series have had overt disseminated intravascular coagulation, according to criteria defined by the International Society of Thrombosis and Haemostasis.[85,87] Haematemesis, melena, and somnolence are significantly more common among patients with a fatal outcome ($p=0\cdot009$, $p=0\cdot001$, and $p=0\cdot022$, respectively).[7,85] Of particular importance is the fact that in fatal cases there is little evidence of an antibody response.[39,85]

Pathogenesis

The pathogenesis of CCHF is not well described. A common pathogenic feature of haemorrhagic fever viruses is their ability to disable the host immune response by attacking and manipulating the cells that initiate the antiviral response.[88] This damage is characterised by marked replication of the virus together with dysregulation of the vascular system and lymphoid organs.[89]

Infection of the endothelium has an important role in CCHF pathogenesis.[90,91] The endothelium can be targeted in two ways—indirectly by viral factors or virus-mediated

host-derived soluble factors that cause endothelial activations and dysfunction, and/or directly by virus infection and replication in endothelial cells.[90] Endothelial damage contributes to haemostatic failure by stimulating platelet aggregation and degranulation, with consequent activation of the intrinsic coagulation cascade. Indeed, fatal CCHF cases had grossly abnormal indicators of coagulation system function from an early stage of illness, and disseminated intravascular coagulation is noted as an early and promiment feature of the disease process.

In one study from Turkey, reactive haemophagocytosis was detected in seven (50%) of 14 patients, which suggested that haemophagocytosis could have a role in the cytopenia observed during CCHF infection.[6] Because haemophagocytic lymphohistiocytosis[92] has been attributed to excessive activation of monocytes by high levels of Th1 cytokines—eg, interferon gamma, tumour necrosis factor alpha, interleukin 1, or interleukin 6—this finding provides indirect evidence for the participation of cytokines in other aspects of CCHF pathogenesis. In one study of CCHF patients, the levels of interleukin 1, interleukin 6, and tumour necrosis factor alpha were higher among those patients that subsequently died compared with those that survived.[93] The disseminated intravascular coagulation score was higher among fatal cases, correlating positively with interleukin 6 and tumour necrosis factor alpha levels, and negatively with interleukin 10 levels.[93]

Diagnosis

Early diagnosis is critical both for patient survival and for the prevention of potential nosocomial infections and transmission in the community. Suspected cases should be evaluated and their management carefully planned, including supportive care, particularly haematological support (panel). The differential diagnosis list differs according to geographic location, and includes bacterial, viral, and non-infectious causes (table 3).

Virus isolation

Virus isolation studies should be done in high-containment laboratories, generally recommended to be biosafety level four. Isolation in cell culture is simpler and more rapid, but less sensitive, than traditional methods such as intracranial inoculation of a sample into newborn mice.[94] Virus can be isolated using cell lines including LLC-MK2, Vero, BHK-21, and SW-13.[4] Virus isolation can be achieved in 2–5 days, but cell cultures lack sensitivity, and usually only allow detection of the relatively high viraemia encountered during the first 5 days of illness. The virus may produce little or no cytopathic effect, but can be identified by doing immunofluorescence assay tests with specific monoclonal antibodies.[4] Although reverse transcriptase PCR is extremely useful for rapid diagnosis, only virus isolation yields a virus that can be subjected to further biological and sequencing studies.

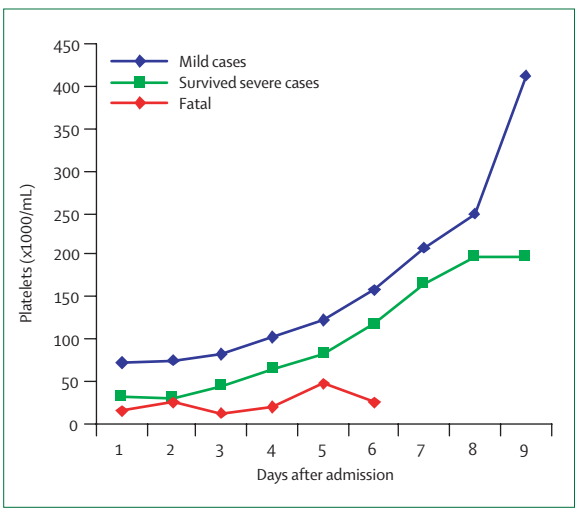

Figure 5: **The course of the disease in accordance with the thrombocyte level[2]**

Antigen capture ELISA has also been shown to be useful. In spite of its relative lack of sensitivity, this process can detect the most severe cases that would require antiviral therapy or could be candidates for a trial of an antiviral drug.[94,95]

Panel: An algorithm for case management

Evaluation of a suspected case

- Clinical symptoms (fever, myalgia, bleeding from various sites)
- Patient history: referral from endemic area; outdoor activities (picnic, tracking, etc) in endemic area; history of tick exposure; exposure to potentially viraemic domestic animal blood
- Laboratory tests (low platelet and high white blood cell count, raised levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and creatinine phosphokinase)

Preventive measures

- Isolate the patient
- Inform and educate colleagues and staff
- Use barrier precautions

Investigations for confirmation

- Serum for PCR (early in disease) and ELISA (late in disease or convalescence): IgM positivity or PCR positive confirms diagnosis, IgG positivity cannot; sera for differential diagnosis

Decision making for therapy

- Define the severity criteria and decide on ribavirin use or not.
- Do not neglect other causes of clinical picture. Starting doxycycline or equivalent should be considered
- Haematological support: fresh frozen plasma to improve haemostasis; thrombocyte solutions
- Respiratory support

Follow up

- No relapse occurs after the disease. Therefore there is no need for follow up of cases
- Health-care workers exposed to the virus should be followed up with complete blood counts and biochemical tests for 14 days

Disease	Geographic location	Transmission	Differentials with CCHF (clinical or laboratory findings)
Infections			
Brucellosis	Worldwide, particularly Mediterranean basin, the Arabian peninsula, the Indian subcontinent, and in parts of Mexico, Central America, and South America		Pancytopenia, Wright agglutination
Q fever	Worldwide	Tick	Serology (ELISA or IFAT)
Rickettsia	Worldwide	Tick	Weil-Felix test
Ehrlichiosis	America, Europe, middle east, southeast Asia	Tick	Serology (ELISA)
Lyme	Worldwide, mainly northern hemisphere	Tick	Serology (ELISA), western blot
Leptospira	Worldwide	Rodents	Agglutination test
Salmonella	Worldwide	NA	Widal test
Tick-borne encephalitis	Northern hemisphere	Tick	ELISA
Malaria	Worldwide	Mosquito	Peripheral smear
Other viral haemorrhagic infections			
Arenaviridae			
South America haemorrhagic fever	Argentina, Bolivia, Brasil, and Venezuela	Interhuman	Neurological symptoms
Lassa fever	West Africa	Interhuman	Pharyngitis, retrosternal pain, proteinuria, central nervous system involvement
Other Bunyaviridae			
Rift Valley fever	Sub-Saharan Africa	Mosquito	Hepatitis, retinal vasculitis, encephalitis
Hanta fever with renal syndrome	Worldwide	Rodents	Renal findings, serology, PCR
Hantavirus pulmonary syndrome	America	Interhuman	Pulmonary findings, serology, PCR
Filoviridae			
Marburg and Ebola	Africa, Philippines	Interhuman	Marked weight loss and prostration. Hepatitis, uveitis, orchitis, arthralgia in convalescence
Filaviviridae			
Yellow fever	Africa, South America	Mosquito	Jaundice
Dengue	Tropics and subtropics, worldwide	Mosquito	Generalised macular rash
Kyasanur forest disease	India	Tick	Haemorrhagic pulmonary oedema, renal failure, neurological symptoms
Omsk haemorrhagic fever	Western Siberia	Tick	Neuropsychiatric sequelae
Al Khumrah	Middle east, Africa	Tick (?), mosquito (?)	Not known
Non-infectious			
Vitamin B12 deficiency	Worldwide		Pancytopenia, and B12 level in serum
Febrile neutropenia	Worldwide		Underlying disease

NA=not applicable

Table 3: **Differential diagnosis of CCHF**

Molecular methods

Reverse transcriptase PCR is the method of choice for rapid laboratory diagnosis of CCHF virus infection.[96] The method is highly specific, sensitive, and rapid.[97] A further improvement has been the development of automated real-time assays, which have a lower contamination rate, higher sensitivity and specificity, and are more rapid than conventional reverse transcriptase PCR.[4,98]

Serology

IgM and IgG antibodies are detectable by ELISA and immunofluorescence assays from about 7 days after the onset of disease.[99] Specific IgM declines to undetectable levels by 4 months post-infection, but IgG remains detectable for at least 5 years. Recent or current infection is confirmed by demonstrating seroconversion, or a fourfold or greater increase in antibody titre in paired serum samples, or IgM antibodies with IgM antibody capture (MAC)-ELISA in a single sample.[100] ELISA methods are quite specific and much more sensitive than immunofluorescence assays and neutralisation tests.[95] Recently, a recombinant nucleoprotein-based IgG ELISA for serological diagnosis of CCHF virus infections was developed.[101]

Treatment

Supportive therapy is the most essential part of case management, and includes the administration of thrombocytes, fresh frozen plasma, and erythrocyte preparations. Replacement therapy with these blood products should be done after checking the patient's complete blood count, which should be done once or

twice a day. Potential bleeding foci should be considered and conservative measures taken—eg, the use of histamine receptor blockers for peptic ulcer patients, avoidance of intramuscular injections, and not using aspirin or other drugs with actions on the coagulation system. Fluid and electrolyte balance should also be monitored meticulously.

Ribavirin is the recommended antiviral agent for infected patients, although its mechanism of action is not clear. In one in-vitro study,[102] ribavirin was shown to inhibit viral activity, and some CCHF viral strains appeared more sensitive than others. In an experimental study done in mice,[103] ribavirin treatment substantially reduced infant mouse mortality and extended the mean time to death. It should be noted that 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.[3,22,104]

Mild cases do not need to be treated with ribavirin.[3] In case management, severe cases should be defined and treated. Severe cases in Turkey are defined according to a revised form of the Swanepoel criteria.[85] Oral and intravenous forms of ribavirin are available in many countries. 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).[105] Haemolytic anaemia, hypocalcaemia, and hypomagnesaemia were reported in patients that received ribavirin to treat severe acute respiratory syndrome.[106,107] However, no adverse events related to ribavirin therapy were noted among CCHF patients in Turkey. The use of ribavirin is contraindicated in pregnant women.

One study suggested treatment using passive immunotherapy, transferring the plasma of convalescing survivors to infected patients.[108] However, the study had no control groups and was limited to seven patients.

Paragas and colleagues[109] screened drugs for potential activity against CCHF virus and found that ribavirin inhibited the replication of CCHF virus, ribamidine had antiviral activity that was 4·5-fold to eightfold less than that of ribavirin, and three other drugs (6-azauridine, selenazofurin, and tiazofurin) had no significant antiviral activity. A newly identified molecule known as MxA, which is a member of the interferon-induced GTPases that belong to the dynamin superfamily, prevented the replication of CCHF viral RNA when present intracellularly,[110] and inhibited the production of new infectious virus particles by interacting with a component of the nucleocapsid.

Prevention

People living in endemic areas should use personal protective measures that include the avoidance of areas where tick vectors are abundant, particularly when they are active; regular examination of clothing and skin for ticks, and their removal; and the use of repellents.[105] People who are exposed to potentially viraemic animal blood should take practical measures to protect themselves, including the use of repellents on the skin and clothing and wearing gloves or other protective clothing to prevent skin contact with infected tissue or blood.[105]

The recommended safety measures for health-care workers include barrier nursing and isolation, and the use of gloves, gowns, face-shields, and goggles with side shields when in contact with patients or soiled environmental surfaces. Simple barrier precautions have been reported to be effective.[111] Strict adherence to universal barrier precautions in hospitals in Turkey during the recent outbreak meant that no antibodies against CCHF virus were found in at-risk health-care workers when serologically screened after the outbreak.[112] In a recent study, prophylactic ribavirin was administered to a health-care worker who had a needlestick injury. The health-care worker did not subsequently develop CCHF.[22] The administration of oral ribavirin prophylaxis was offered to anyone at high risk of infection, such as those who were directly exposed to the blood of CCHF patients through contact or needlestick injury. However, rigorous daily follow-up of any such individual by checking white blood cell counts and biochemical tests for at least 14 days after the exposure should be sufficient; ribavirin should only be administered if fever develops.

In 1974, an immunisation programme was introduced for medical workers and military personnel in CCHF-endemic areas.[18] The vaccine consisted of a mouse brain preparation inactivated by chloroform, heated at 58°C, and adsorbed on aluminium hydroxide. It was proposed that the vaccine was helpful in reducing the number of cases and the case fatality rate in this area.[18] Vaccine was also given to 583 human volunteers in Bulgaria, and was reported to elicit antibody production in 96·6% of these individuals.[2] However, experiences with vaccines against CCHF virus are limited of limited duration and confined to a few locations. The vaccine would not be suitable for use in many countries because of its method of preparation.

Future research areas

The dynamics of the enzootic environment and transmission cycle of the CCHF virus need to be further detailed. The role of climatic factors, reservoir hosts, and vectors should be described. These studies need multidisciplinary team work, including entomologists, microbiologists, epidemiologists, veterinarians, and

Search strategy and selection criteria

Data for this review were identified by searches of PubMed, Google, and references from relevant articles, using the search terms "Crimean Congo haemorrhagic fever", "viral haemorrhagic fever", and "ribavirin". No date limits were set; only the abstracts of non-English language papers were included.

clinicians. New data on viral replication offers substantial potential for the development of new drugs. Further studies on the pathogenesis of viral haemorrhagic fevers will shed light on the mechanisms of disseminated intravascular coagulation and probably bacterial sepsis. Understanding new mechanisms of CCHF viral infection or other viral haemorrhagic fevers will assist in the development of new therapeutic molecules. Agents used to treat disseminated intravascular coagulation—eg, heparin or other coagulation blockers—could be tried in the control of clinical course of CCHF.

Conflicts of interest

I declare that I have no conflicts of interest.

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