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Review Article

Crimean-Congo Hemorrhagic Fever

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Crimean-Congo hemorrhagic fever is a tick-borne viral disease reported from more than 30 countries in Africa, Asia, South-East Europe, and the Middle East. The majority of human cases are workers in livestock industry, agriculture, slaughterhouses, and veterinary practice. Nosocomial transmission is also well described. Clinical manifestations are nonspecific and symptoms typically include high fever, headache, malaise, arthralgia, myalgia, nausea, abdominal pain, and nonbloody diarrhea. Patients may show signs of progressive hemorrhagic diathesis. Laboratory abnormalities may include anemia, leukopenia, thrombocytopenia, increased AST/ALT levels, and prolonged prothrombin, bleeding, and activated partial thromboplastin times. Diagnostic methods include antibody detection by enzyme-linked immunosorbent assay, virus isolation, antigen detection, and polymerase chain reaction. The mainstay of treatment of Crimean-Congo hemorrhagic fever is supportive, with careful maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure. The Crimean-Congo hemorrhagic fever virus is susceptible to ribavirin *in vitro*. There is no controlled study evaluating oral versus intravenous ribavirin in treating Crimean-Congo hemorrhagic fever patients, but few studies have evaluated oral ribavirin. This article reviews the epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment, prevention, and prognosis of Crimean-Congo hemorrhagic fever with a special focus on oral ribavirin as a choice of medical treatment.

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Introduction

Infectious diseases remain the single greatest contributor to morbidity and mortality in the world. However, few diseases have the capacity to stimulate the interest and instill concern both in the general population and the health-care community as do viral hemorrhagic fevers (VHFs). Some of the major hemorrhagic fever viruses, some (Lassa, Marburg, Ebola, agents of South American VHF, Hanta, and Crimean-Congo) share a distinct characteristic that has important clinical and public health consequences, namely the potential for person-to-person transmission.[1] Crimean-Congo hemorrhagic fever (CCHF) was described in the Crimea in 1944 during an outbreak, which involved more than 200 cases and was called Crimean hemorrhagic fever. A later virus isolate from Congo was noted to be the same pathogen, resulting in the name Crimean-Congo hemorrhagic fever virus (CCHFV).[2]

In nature, HFVs reside in animal hosts or arthropod vectors. CCHFV can infect a wide range of domestic and wild animals, including sheep and cattle. Animals are infected with CCHFV by the bite of infected ticks. Seroprevalence is 13 – 36% in animals.[3, 4] A seroepidemiological study of CCHF in local and imported sheep in Isfahan Province of Iran revealed the endemic spreading of the virus in sheep and the need for special attention to prevent the infection in the community and during occupational exposures.[5]

A number of tick genera can be infected with CCHFV, but the most efficient and common vectors for CCHFV are the members of the genus *Hyalomma*.[6] The most important source of virus transmission is immature *Hyalomma* tick, which feeds small vertebrates' blood. Once infected, the

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tick remains infected throughout its life, and the mature tick may transmit the infection to large vertebrates, such as livestock. Domestic ruminant animals, such as cattle, sheep, and goats will have viremia for one week after becoming infected.[7]

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.[6, 8, 9] Birds migrated from the Balkans were suggested to be the cause of the 2002 outbreak in Turkey.[10] However, there is no precise data on CCHFV in birds and in ticks that live as parasite on birds.

Here, we review the published studies on CCHF (epidemiology, routes of transmission, risk factors, clinical manifestations, laboratory findings, diagnosis, treatment, and prevention) with an emphasis on new treatment modalities.

Epidemiology

Like other tick-borne zoonotic agents, CCHFV generally circulates in nature in an enzootic tick-vertebrate-tick cycle. Although many domestic and wild vertebrates are infected with CCHFV, as evidenced by development of viremia and/or antibody response, birds, in general, appear to be resistant to this infection.[11]

The known geographical distribution of CCHFV is the greatest among all tick-borne viruses. There are reports of viral isolation and/or disease from more than 30 countries in Africa, Asia, South-East Europe, and the Middle East (Figure 1).[6, 12] Evidence for the presence of the virus in France, Portugal, Egypt, and India is based on limited serological observations.

Interestingly, after several decades of only serological evidence for the existence of CCHFV in Turkey, an outbreak of the disease in the eastern Black Sea region of the country was recently reported.[10] Additionally, viral particles were isolated from two of the patients, and phylogenetic analysis of the isolates suggested that two different genetic lineages of CCHFV were circulating in Turkey. These closely resemble virus lineages found in Kosovo and southwestern part of Russia and were clearly distinct from those found in a recent CCHF outbreak in neighboring Iran in 2002,[13] consistent with CCHFV being enzootic in Turkey.

Figure 1. The worldwide geographic distribution of CCHF viral isolates and human disease.[11]

Seasonal variations have been described. In Iran, the high incidence was in August and September.[14] In Pakistan, CCHF was more common between March and May and again, between August and October, depicting a biannual surge.[15] Changes in climatic conditions have been suggested to be one of the factors that have facilitated reproduction of the tick population, and consequently the increased incidence of tick-borne infectious diseases.[16, 17]

Molecular epidemiology of African and Asian CCHF isolates has been investigated by Burt and Swanepoel in 2005.[18] Phylogenetic relationships were examined for 70 CCHFV isolates from southern, central, and western parts of Africa, the Middle East, and Greece using sequence data determined for a region of the S segment of the genome. Analysis revealed up to 18% genetic differences. Tree topology supports previous evidence for the existence of three groups of genetically related isolates; A, B, and C. Within group A, there are two clades: an African clade and a predominantly Asian clade comprising isolates from Pakistan, China, Iran, Russia, and Madagascar. Group B includes isolates from South and West Africa, and Iran, and group C includes a single isolate from Greece. Despite the potential of dispersal of the virus between Africa and Eurasia, it appears that circulation of the virus is largely compartmentalized within the two land masses, and the inference is that the geographic distribution of phylogenetic groups is related to the distribution and dispersal of tick vectors of the virus.[18]

Transmission

Community-acquired CCHF happens through transmission of the virus by direct contact with blood or other infected tissues of livestock or from an infected tick bite. Most of the human cases are workers in livestock and agriculture industry,

slaughterhouses, and veterinary practice.[7] Humans can be infected incidentally by the bite of an infected arthropod or via aerosol generated from infected rodents' excreta. Infected humans can spread the disease via close contacts which may result in community outbreaks and nosocomial infections. Possible horizontal transmission of CCHFV from a mother to her child indicates the importance of preventive measures for in-house outbreaks of CCHF. [19]

Nosocomial transmission is well described in reports from Pakistan, Iraq, United Arab Emirates, South Africa, and Iran.[20 – 22] CCHFV has repeatedly caused nosocomial outbreaks with high mortality, and percutaneous exposure presents the highest risk of transmission.[22 – 25] The most dangerous settings for acquiring CCHFV are interventions for controlling gastrointestinal bleedings, and emergency operations on patients who have yet to be diagnosed as having CCHF.[26] In general, these patients will be diagnosed after the operation, and injuries to the operating team during the operation are usually under-reported. Risk of nosocomial transmission can be minimized by proper and timely infection-control measures, careful management of infected patients, and, in some cases, providing prophylactic treatment to health-care workers after exposure.[27, 28]

However, community-based control measures are necessary to decrease disease transmission and prevent further spread in the community.[29]

Risk factors

A case-control study on epidemiological characteristics of patients diagnosed as having CCHF in Iran[30] showed that history of tick bite is one of the most important risk factors for CCHF acquisition. Other important risk factors included high-risk occupations (butchers, physicians, veterinarians), having contact with livestock, and age over 40 years.[30]

Abattoir workers who work with large domestic animals are also at risk. Acquisition of the virus usually takes place while slaughtering animals.[9, 24, 31] In a multivariate analysis in Turkey, farming, living in a rural area, and being bitten by tick were determined as risk factors for CCHF.[32] Hiking, camping, and other rural activities are also risk factors for tick exposure.[33]

Consuming meat is not a risk factor by itself because the virus is inactivated by postslaughter acidification of the tissues and would not survive cooking in any case.[33]

Hospital health-care workers are at serious risk of transmission of CCHF infection when caring for patients with hemorrhagic manifestations. Transmission of the CCHF infections and death among health-care workers have been reported in parallel with outbreaks in the general population.[26] Seroprevalence study of anti-CCHF IgG among 223 health-care workers in Iran showed that 3.87% of the exposed health-care workers were positive while none of the unexposed workers were positive. Seropositivity was more frequent among those whose intact skin had come in contact with nonsanguineous body fluids and those who had had percutaneous contacts.[34] So, it is proposed that health-care workers take all the protective measures when handling CCHF patients, particularly blood and other body fluids.

Clinical manifestations

Humans appear to be the only host of CCHFV in which the disease is manifested (except for newborn mice). In contrast to the inapparent infection in most other vertebrate hosts, human infection with CCHFV often results in severe hemorrhagic disease.[11] The typical course of CCHF infection has four distinct phases: incubation, prehemorrhagic, hemorrhagic, and convalescence periods.

The incubation period for CCHF ranges from 2 to 9 days.[35] The mean incubation period in Iranian patients was 4.2 days. The disease was more prevalent in middle-aged men (reflecting the culture and lifestyle of Iranian families).[14] Several factors including route of exposure may influence incubation period. In South Africa, among 21 patients for whom reliable data were obtained, the time to onset of disease was 3.2 days after tick-bite, 5 days after live stock blood or tissue exposure and 5.6 days after human blood exposure.[36]

There is a variety of potential clinical manifestations following infection with this virus, and not all patients develop the classic form of CCHF syndrome. Patients initially exhibit a nonspecific prodrome, which typically lasts less than one week.[6] Clinical manifestations are non-specific and may include fever, myalgia, rash, and encephalitis. Symptoms typically include high fever, headache, malaise, arthralgia, myalgia, nausea, abdominal pain, and nonbloody diarrhea. Early signs typically include fever, hypotension, relative bradycardia,

tachypnea, conjunctivitis, and pharyngitis. Most cases are associated with cutaneous flushing or rash.[6]

The hemorrhagic period is short (usually 2 – 3 days), develops rapidly, and usually begins between the third to fifth days of disease.[6] There is no relation between the temperature of the feverish patient and the onset of hemorrhage.[6] Patients may show signs of progressive hemorrhagic diathesis, such as petechiae, mucous membrane and conjunctival hemorrhage, hematuria, hematemesis, and melena. Disseminated intravascular coagulation (DIC) and circulatory shock may ensue.[29]

Central nervous system dysfunction may be present and manifest by delirium, convulsion, cerebellar signs, or coma and imparts a poor prognosis.[29]

Distinguishing features of Turkish patients included: high fever (73%), malaise (86%), headache (80%), nausea (75%), vomiting (68%), diarrhea (33%), conjunctival injection (42%), heart murmur (4.9%), cough (29%), and rales (16%).[37] Clinical features of hemorrhagic forms of CCHF were described in Iran.[14] In this study, clinical manifestations included fever, severe headache, myalgia, loss of appetite, and nausea. Epistaxis, bleeding from the gums and venipuncture sites, petechia and large ecchymotic areas on trunk or extremities (Figure 2) were common. Menometrorrhagia was seen in female patients. Less prevalent signs were relative bradycardia, hypotension, tachypnea, abdominal tenderness, watery diarrhea, icterus, and lethargy.[14] Hemorrhage within the abdominal muscles can simulate acute appendicitis in CCHF patients.[38] Hemorrhagic manifestations were detected in 48.0% of Turkish patients. These manifestations included epistaxis (17.4%), hematemesis (7.6%), melena (1.0%), and hemorrhage from various sites (21.7%).[37]

Hepatomegaly and splenomegaly have been reported to occur in one-third of patients.[6] In Turkey, hepatomegaly was detected in 20 – 40% of cases.[10, 32, 37, 39]

The convalescence period begins in survivors about 10 – 20 days after the onset of illness. Patients usually need hospitalization for about 9 – 10 days.[39, 40] In the convalescence period, tachycardia, temporary complete hair loss, polyneuritis, difficulty in breathing, xerostomia, poor vision, loss of hearing, and loss of memory have been reported,[6] although none of these findings were noted in the recent outbreaks in Turkey and Iran.[13, 37] Hepatorenal insufficiency was reported in South Africa,[14] but not in Turkey and Iran. There is no known relapse of the infection.[33]

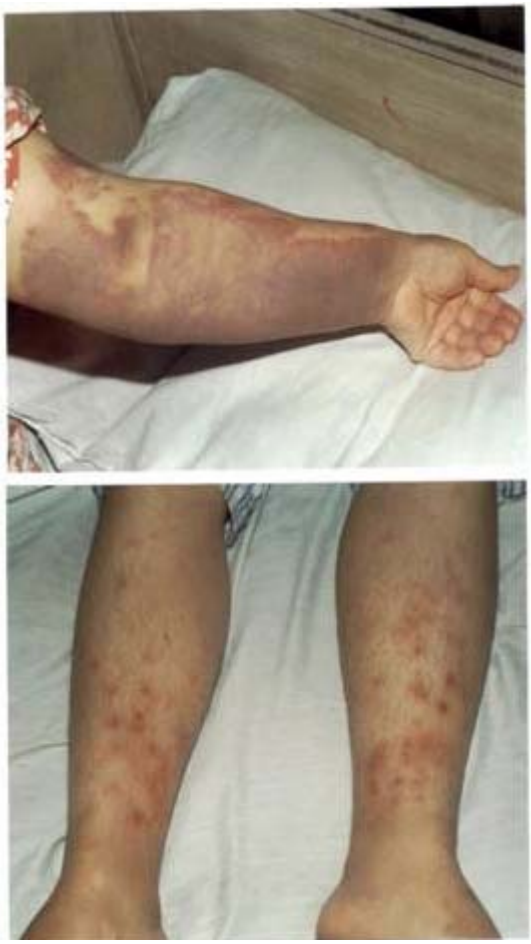

Figure 2. Skin manifestations in an Iranian patient diagnosed as having CCHF presented with severe hemorrhagic form.

Laboratory findings

Laboratory abnormalities may include anemia, leukopenia, thrombocytopenia, increased AST/ALT levels, prolonged bleeding time, prothrombin time (PT), and activated partial thromboplastin time (PTT), elevated fibrin degradation products (FDPs), and decreased fibrinogen. Urinalysis may reveal proteinuria and hematuria, and patients may develop oliguria and azotemia.[41, 42]

The most prevalent laboratory abnormalities in hemorrhagic forms are hematuria, proteinuria, prolonged PTT, and AST >100 IU/dL. Less prevalent findings include anemia, leukopenia, ALT >100 IU/dL, and prolonged PT.[16] Characteristics of 35 patients with CCHF in a recent

outbreak in Turkey showed that all patients had leukopenia, low platelet (PLT) count, and elevated levels of AST, ALT, lactic dehydrogenase (LDH), and creatine phosphokinase (CPK). None of their patients had leukocytosis, except one who died. Thirty-one percent of the patients had thrombocytopenia and active bleeding despite supportive treatment. Bleeding developed during hospital stay in most patients, about 5 – 7 days after the onset of disease. In patients with severe disease, mean hemoglobin level decreased from 13.7 g/dL to 10.7 g/dL, whereas in patients with mild to moderate disease, mean hemoglobin level decreased from 13.7 g/dL to 12.3 g/dL.[39]

Pathogenesis

The pathogenesis of CCHF is not well described. A common pathogenic feature of hemorrhagic fever viruses is their ability to disable the host immune response by attacking and manipulating the cells that initiate the antiviral response.[43] This damage is characterized by marked replication of the virus together with dysregulation of the vascular system and lymphoid organs.[44] Infection of the endothelium has an important role in CCHF pathogenesis.[45, 46] Endothelial damage contributes to hemostatic 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 DIC is noted as an early and prominent feature of the disease process.[47]

In a study from Turkey, reactive hemophagocytosis was detected in seven (50%) of 14 patients, which suggested that hemophagocytosis could have a role in the cytopenia observed during CCHF infection.[10]

In another study, the levels of interleukin (IL)-1, IL-6, and TNF-alpha were higher among patients who subsequently died as compared to survivors. The DIC score was higher among fatal cases, correlating positively with IL-6 and TNF-alpha levels, and negatively with IL-10 levels.[48] In conclusion, these findings demonstrate that proinflammatory cytokines play a major role in pathogenesis and mortality of patients with CCHF.

Diagnosis

CCHF should be considered in those having:

- compatible clinical manifestations (e.g., fever, muscle pain, and bleeding),
- epidemiological risk factors (tick bite, exposure to tick splashing, for example crushing a tick between two exposed body parts),
- travel to or staying in endemic area for CCHF (we consider travel to or residence in the Iranian provinces of Sistan and Balouchestan, Isfahan, and Golestan to be an epidemiological risk factor because in 1999, when the first cases were reported, we noticed most of them were from these three provinces),
- contact with suspected cases of CCHF, or contact with animals, and
- compatible laboratory findings like a PLT count of $<150{,}000/mm^3$ and a WBC count of <3000 or >9000 $/mm^3$.[13]

Laboratory diagnosis of suspected CCHF should be performed in specially-equipped, high biosafety level laboratories. Methods of diagnosis include antibody detection by enzyme-linked immunosorbent assay (ELISA), virus isolation, antigen detection, and polymerase chain reaction (PCR).

IgG and IgM antibodies may be detected in serum by enzyme-linked immunoassay (EIA) or ELISA from about the sixth day of the illness. Either the presence of IgM or a 4-fold rise in the titer of IgG antibody in serum samples between the acute and convalescence phases is diagnostic of the disease. IgM remains detectable for up to four months, and IgG levels decline but remain detectable for up to five years. Patients with fatal disease do not usually develop a measurable antibody response and in these individuals, as well as in patients in the first few days of illness, diagnosis is achieved by virus detection in blood or tissue samples.[49]

The virus may be isolated from blood or tissue specimens in the first five days of illness, and grown in cell culture.[49] Virus isolation is of limited value because it requires a biosafety level 4 (BSL-4) laboratory, which is not available in most endemic areas.

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.[50] Virus can be isolated using cell lines including LLC-MK2, Vero, BHK-21, and SW-13.[11] Virus isolation can be achieved in 2 – 5 days, but cell cultures lack sensitivity, and usually only allow detection of the relatively high viremia 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.[11]

Viral antigens may sometimes be shown in tissue samples using immunofluorescence or EIA.[49]

In 1989, antibody response to CCHF was evaluated by Shepherd et al in South Africa.[51] IgG and IgM antibodies became demonstrable by indirect immunofluorescence on days 7 to 9 of illness in 35 survivors of CCHF. Maximum titers of antibody were usually attained in the second to third week of illness. IgM titers declined gradually thereafter and were low or negative by the forth month. In some patients, IgG titers increased markedly between 2 and 4 months after the onset of illness and remained readily demonstrable by indirect immunofluorescence 3 years after infection. Endogenous antibody response was demonstrated in only two of 15 patients who died of infection. Most patients developed relatively low levels of neutralizing antibodies (range: 1:8 to 1:32 by fluorescent-focus reduction tests), but some developed titers of 1:256 to 1:512.[51]

More recently, PCR, a molecular method for detecting the viral genome, has been successfully applied in the diagnosis of viral hemorrhagic fevers. Chinikar et al[52] found few cases with positive RT-PCR among those whose illness had been confirmed by serology. They concluded that because the viremia period is very short in CCHF patients, antibody detection is preferred for diagnosis. Viral antigen detection by ELISA and RT-PCR is the most useful diagnostic technique in the acute clinical setting.

We suggest that diagnosis should be based initially on clinical findings, and laboratory tests be used to confirm or exclude it. Laboratory tests are time consuming and in the event of a large outbreak, may be delayed or perhaps not possible in the acute phase given the available laboratory facilities.

Treatment

The mainstay of treatment of CCHF is supportive, with careful maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure. In addition, treatment of other suspected possible causes, such as bacterial sepsis, should not be withheld while awaiting confirmation or exclusion of the diagnosis of CCHF.

In an outbreak in the former USSR, soviet physicians found little clinical benefit from administration of immune plasma in convalescence phase, although plasma with high neutralizing antibody titers has been reported as potentially useful.[28]

Drug therapy

There are no antiviral drugs approved by the United States Food and Drug Administration (FDA) for the treatment of CCHF.[29] Ribavirin is a guanosine analogue that has an incomplete purine ring rather than an acyclic ribose moiety. After intracellular phosphorylation, ribavirin triphosphate interferes with early events in viral transcription, such as capping and elongation of messenger RNA, and inhibits ribonucleoprotein synthesis.[53, 54] It has a broad spectrum of activity *in vitro* against RNA viruses. The concentration of its major metabolite — 1, 2, 4-triazole-3-carboxamide — is higher in urine after oral administration than after intravenous administration, implying that the drug is degraded in the gastrointestinal tract and liver.[54] Aerosolized ribavirin is absorbed systemically, as indicated by the presence of measurable concentrations in the plasma.[55] Clinical efficacy has been demonstrated for the treatment of infections caused by hemorrhagic fever viruses (with oral and intravenous formulations of ribavirin).[56, 57]

The CCHFV is susceptible *in vitro* to ribavirin. In some uncontrolled studies on both sporadic and outbreak cases of CCHF, Lassa fever, Bolivian hemorrhagic fever, and hemorrhagic fever with renal syndrome caused by Hanta virus, ribavirin has been reported to have some anecdotal benefit when administered either parenterally or orally.[20, 57, 58]

Paragas and colleagues[59] screened drugs for potential activity against CCHFV and found that ribavirin inhibited the replication of CCHFV, ribamidine had antiviral activity that was 4.5- to 8-fold less than that of ribavirin. 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 replication of CCHF viral RNA when presented intracellularly and inhibited production of new infectious virus particles by interacting with a component of the nucleocapsid.[60]

Recommendation for drug therapy has not been

approved by the FDA and it should always be administered under an investigational new drug protocol. In an epidemic situation, these requirements may need to be modified to permit timely administration of the drug.[29]

In a situation which a modest number of patients require treatment, it is recommended that an intravenous regimen of ribavirin be given in accordance with the recommendations of Center for Disease Control (CDC) for treating patients with suspected VHF of unknown cause, pending identification of the agent.[61] A similar dose has been used in the treatment of Lassa fever.[56]

In an outbreak situation in which the number of persons requiring treatment is too high to deliver intravenous treatment for everybody, an oral regimen of ribavirin is recommended. But there are no available studies on tolerability or efficacy of higher doses of oral ribavirin.[29]

Ribavirin is contraindicated in pregnancy and because most of patients with CCHF have self limited diseases, direct observation and supportive treatment is recommended (unpublished data).

However, in the context of VHF of unknown cause, it is believed that the benefits of treatment with ribavirin outweigh the fatal risks, and ribavirin is therefore recommended.[62]

The use of oral or intravenous ribavirin has not been approved by the FDA for children. Only aerosolized ribavirin has been approved by the FDA for children, to treat respiratory syncytial virus infection.[29] Ribavirin is available as 200-mg capsules. However, Schering-Plough Corp. (Kenilworth, NJ) has produced a pediatric syrup formulation, which is not commercially available yet.[29]

What evidence supports oral ribavirin?

In 1994, in Pakistan, Fisher-Hoch et al reported three health workers — two surgeons and a hospital worker — infected with CCHFV who were treated with oral ribavirin. Intravenous ribavirin was unavailable. All patients were severely ill. Based on published reports, all had an estimated probability of death of 90% or more. The patients became afebrile within 48 hours of treatment with ribavirin. All patients made a complete recovery and developed IgG and IgM antibody to CCHFV.[20]

In 1999, in Pakistan, Sheikh et al evaluated the efficacy of oral ribavirin in CCHF cases. A total of 94 cases, highly suspicious as having CCHF, were included in the study. CCHF was confirmed in 39 of the 94 cases by the CDC. Oral ribavirin was given to confirmed cases only. After a mean period of 2.3 ± 0.7 days of starting a ribavirin, the patients improved and the laboratory parameters returned to normal levels.[63] Ribavirin was continued for 10 days.

In a historical cohort study in Iran, we compared the mortality rate among patients suspected of having CCHF who received oral ribavirin and those who did not. Ninety-seven (69.8%) of 139 treated patients suspected of having CCHF and 61 (88.9%) of 69 treated patients with confirmed CCHF survived.[13]

In another study, ribavirin was administered by nasogastric tube. Only one of them died. So it is recommended that in severe and comatose cases of CCHF, ribavirin be administered via this route.[14]

In 2003, in Turkey, Ergonul et al described the role of ribavirin in treating 35 patients who were diagnosed as having CCHF. All of the eight patients who were given oral ribavirin survived.[39]

In 2006, in Turkey, Ozkurt et al demonstrated that the mean recovery time in the cases treated with ribavirin was shorter than those of controls. But the need for blood and blood product, mean length of hospital stay, fatality rates, and hospital expenditure values were not significantly different between the group treated with ribavirin and controls.[32]

The doses of oral ribavirin used in the above studies were in accordance with the CDC recommendations[33] for suspected VHF of unknown cause, pending identification of the agent.

In summary there is no controlled study evaluating oral versus intravenous ribavirin in treating CCHF patients, but limited studies have evaluated oral ribavirin. Until controlled studies are available on this topic, current evidence supports administration of ribavirin for treatment of CCHFV.

A major problem in using ribavirin is its side effects. Anemia is one.[63] But the above-mentioned studies did not show any significant adverse effects that limiting the recommended dose for hemorrhagic fevers. So, ribavirin seems safe in treating CCHF cases.

Ribavirin is well absorbed from gastrointestinal tract and concentration of its major metabolite is higher in urine after oral administration than after intravenous route. Another advantage of oral formulation is its cost. CCHF is an endemic

disease mostly in developing countries (Middle East and Africa) and using a cheaper drug with the same efficacy is a great advantage.

These data show that oral ribavirin is an acceptable treatment for CCHF cases and considering availability, adverse effects, cost, and effectiveness, it can be considered as an effective treatment in areas of endemicity that intravenous formulation is not available.

Follow-up

Recovering is complete and no relapse has been reported up to now.[33] 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.[34]

Prognosis

The case-fatality rate has been estimated to range from 15% to 70% in various studies.[22, 64,65] The lowest case-fatality rate of CCHF (2.8%) in the medical literature is reported from Turkey. This could be due to vigorous supportive treatment and administration of ribavirin within 24 hours after admission to their patients. Another explanation could be the geographical variation of the virus. However, to reach such a conclusion, additional reports from different centers are necessary.[40] Swanepoel's evaluation[36] of 15 fatal and 35 nonfatal CCHF patients in South Africa showed that the patients with fatal infections had thrombocytopenia, and markedly elevated levels of AST, ALT, gamma-glutamyltransferase, LDH, creatine kinase (CK), bilirubin, creatinine, and urea. Total protein, albumin, fibrinogen, and hemoglobin levels were depressed. Values for prothrombin, activated PTT, thrombin time, and FDPs were grossly elevated, which indicated the occurrence of DIC. Many of the clinical pathological changes were evident at an early stage of the disease and had a highly predictive value for fatal outcome of infection. Changes were present but less marked in nonfatal infections.

The data obtained from 60 cases in Turkey[32] also showed that the rates of fever during hospitalization, confusion, neck stiffness, bleeding from multiple sites, and presence of petechia/ ecchymoses were higher in CCHF patients who died compared to those who survived. Mean values of ALT, AST, LDH, CK, PTT, INR, and urea were higher, and mean PLT count was lower in patients who died. Another study in Turkey indicated impaired consciousness and splenomegaly as independent predictors of adverse outcome.[39] Of particular importance is the fact that in fatal cases there is little evidence of an antibody response.[66]

These data show that hemorrhagic manifestations, confusion, and laboratory evidence of DIC are predictors of fatal outcome.

Prevention

For the individual, use of effective personal protective measures against tick bites and limiting animal exposure are the best ways to avoid the infection. Use of permethrin-impregnated clothing and gear, tucking trousers into boots or socks, wearing light-colored clothing to facilitate tick identification, insect repellants on exposed skin, and daily skin inspection for ticks are mainstays of prevention.[61]

Nosocomial spread within the health-care setting is possible, and appropriate universal precautions should be observed in the patient-care areas and the laboratory.[21]

A suspected patient should be placed in a private room, and negative-pressure respiratory isolation should be considered, particularly if coughing, vomiting, or other activities generating large-droplet aerosols occur. Those entering the patient's room should wear gloves and gowns, and those approaching within one meter should wear face shields or surgical masks and eye protection to prevent contact with blood or other body fluids.[61]

The risk of nosocomial spread is greater with severely ill patients. For large groups of people at risk (such as within a refugee camp), local application of acaricide can be considered during seasonal risk (spring to fall).[2]

Experience with vaccines against CCHFV is limited and the vaccine would not be suitable for use in many countries because of its method of preparation.[33]

Postexposure prophylaxis

Postexposure prophylaxis should be considered potentially for those exposed to HFVs (including CCHFV) in a bioterroristic attack and all known high-risk individuals such as those who have mucous membrane contact (kissing or sexual contact with a patient) or have percutaneous injury in contact with the patients' secretions, excretions, or blood. Prophylaxis should also be considered for those with close contacts such as living or shaking

hands with the patients, process laboratory specimens, or care such a patient before initiation of standard precautions. They should be placed under medical surveillance and should be instructed to record their temperatures twice daily. If a temperature of 38.3°C or higher develops, treatment with ribavirin should be initiated promptly as presumptive treatment of CCHF.[29] Oral ribavirin, 200 mg twice daily, for 5 days is the recommended dosage for postexposure prophylaxis.[67]

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Conflicts of interest

All authors declare no conflicts of interest.

References

1 Lacy MA, Smego RA Jr. Viral hemorrhagic fevers. In: Aranoff SA, ed. *Advances in Pediatric Infectious Diseases*. St. Louis: Mosby Year Book; 1997: 21 – 53.

2 Wallace MR, Hale BR, Utz GC, Olson PE, Earhart KC, Thornton SA, et al. Endemic infectious diseases of Afghanistan. *Clin Infect Dis*. 2002; **34(suppl 5):** S171 – S207.

3 Gonzalez JP, LeGuenno B, Guillaud M, Wilson ML. A fatal case of Crimean-Congo hemorrhagic fever in Mauritania: virological and serological evidence suggesting epidemic transmission. *Trans R Soc Trop Med Hyg*. 1990; **84:** 573 – 576.

4 Morrill JC, Soliman AK, Imam IZ, Botros BA, Moussa MI, Watts DM. Serological evidence of Crimean-Congo hemorrhagic fever viral infection among camels imported into Egypt. *J Trop Med Hyg*. 1990; **93:** 201 – 204.

5 Darvishi M, Ataee B, Chinikar S, Jalali N, Mardani M, Mirkhani M. Seroepidemiology of Crimean-Congo hemorrhagic fever in local and imported sheep in Isfahan Province of Iran. *Clin Microbiol Infect*. 2005; **11 (suppl 2):** 649.

6 Hoogstraal H. The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. *J Med Entomol*. 1979; **15:** 307 – 317.

7 Athar MN, Baqai HZ, Ahmad M, Khalid MA, Bashir N, Ahmad AM, et al. Short report: Crimean-Congo hemorrhagic fever outbreak in Rawalpindi, Pakistan. *Am J Trop Med Hyg*. 2003; **69:** 284 – 287.

8 Khan AS, Maupin GO, Rollin PE, Noor AM, Shurie HH, Shalabi AG, et al. An outbreak of Crimean-Congo hemorrhagic fever in the United Arab Emirates, 1994 – 1995. *Am J Trop Med Hyg*. 1997; **57:** 519 – 525.

9 Rodriguez LL, Maupin GO, Ksiazek TG, Rollin PE, Khan AS, Schwarz TF, et al. Molecular investigation of a multisource outbreak of Crimean-Congo hemorrhagic fever in the United Arab Emirates. *Am J Trop Med Hyg*. 1997; **57:** 512 – 518.

10 Karti S, Odabasi Z, Korten V, Yilmaz M, Sonmez M, Caylan R, et al. Crimean-Congo hemorrhagic fever in Turkey. *Emerg Infect Dis*. 2004; **19:** 1379 – 1384.

11 Whitehouse CA. Crimean-Congo hemorrhagic fever. *Antiviral Res*. 2004; **64:** 145 – 160.

12 Swanepoel R. Nairovirus infections. In: Porterfield JS, ed. *Exotic Viral Infections*. London: Chapman and Hall; 1995: 285 – 293.

13 Mardani M, Jahromi MK, Naieni KH, Zeinali M. The efficacy of oral ribavirin in the treatment of Crimean-Congo hemorrhagic fever in Iran. *Clin Infect Dis*. 2003; **36:**1613 – 1618.

14 Mardani M, Bijani B. Clinico-epidemiologic features and outcome analysis of hemorrhagic forms of Crimean-Congo hemorrhagic fever (CCHF) in Iran. 41st Annual Meeting of IDSA, October 9 – 12, 2003; San-Diego, United States: 763.

15 Sheikh AS, Sheikh AA, Sheikh NS, Rafi US, Asif M, Afridi F, et al. Bi-annual surge of Crimean-Congo hemorrhagic fever (CCHF): a five-year experience. *Int J Infect Dis*. 2005; **9:** 37 – 42.

16 Gubler DJ, Reiter P, Ebi KL, Yap W, Nasci R, Patz JA. Climate variability and change in the United States: potential impacts on vector- and rodent-borne diseases. *Environ Health Perspect*. 2001; **109:** 223 – 233.

17 Estrada-Pena A. Forecasting habitat suitability for ticks and prevention of tick-borne diseases. *Vet Parasitol*. 2001; **98:** 111 – 132.

18 Burt FJ, Swanepoel R. Molecular epidemiology of African and Asian Crimean-Congo hemorrhagic fever isolates. *Epidemiol Infect*. 2005; **133:** 659 – 666.

19 Masayuki S, Qing T, Bawudong S, Lei H, Yuzhen Z. Possible horizontal transmission of Crimean-Congo hemorrhagic fever virus from a mother to her child. *Jpn J Infec Dis*. 2004; **57:** 55 – 57.

20 Fisher-Hoch SP, Khan AJ, Rehman S, Mirza S, Khurshid M, McCormick JB. Crimean-Congo hemorrhagic fever treated with oral ribavirin. *Lancet*. 1995; **346:** 472 – 475.

21 Mardani M. Nosocomial Crimean-Congo hemorrhagic fever in Iran, 1999 – 2000. *Clin Microbiol Infec*. 2001; **7(suppl 1):** 213.

22 van Eeden PJ, van Eeden SF, Joubert JR, King JB, van de Wal BW, Michell WL, et al. A nosocomial outbreak of Crimean-Congo hemorrhagic fever at Tygerberg Hospital. Part I. Clinical features. *S Afr Med J*. 1985; **68:** 711 – 715.

23 Casals J. Antigenic similarity between the virus causing Crimean hemorrhagic fever and Congo virus. *Proc Soc Exp Biol Med*. 1969; **131:** 233 – 236.

24 Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, Miller GB. A common-source outbreak of Crimean-Congo hemorrhagic fever on a dairy farm. *S Afr Med J*. 1985; **68:** 635 – 637.

25 van de Wal BW, Joubert JR, van Eeden PJ, King JB. A nosocomial outbreak of Crimean-Congo hemorrhagic fever at Tygerberg Hospital. Part IV. Preventive and prophylactic measures. *S Afr Med J*. 1985; **68:** 729 – 732.

26 Shepherd AJ, Swanepoel R, Shepherd SP, Leman PA, Blackburn NK, Hallet AF. A nosocomial outbreak of Crimean-Congo hemorrhagic fever at Tygerberg Hospital. Part V. Virological and serological

observations. *S Afr Med J*. 1985; **68:** 733 – 736.
27 Weber DJ, Rutala WA. Risks and prevention of nosocomial transmission of rare zoonotic diseases. *Clin Infect Dis*. 2001; **32:** 446 – 456.
28 Centers for Disease Control (CDC). Management of patients with suspected viral hemorrhagic fever. *MMWR Morb Mortal Wkly Rep*. 1988; **37(suppl 3):** 1 – 16.
29 Borio L, Inglesby T, Peters CJ, Schmaljohn AL, Hughes JM, Jahrling PB, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA*. 2002; **287:** 2391 – 2405.
30 Izadi S, Holakouie-Naieni K, Madjdzadeh SR, Nadim A. Crimean-Congo hemorrhagic fever in Sistan and Balouchestan Province of Iran, a case-control study on epidemiological characteristics. *Inter J Infect Dis*. 2004; **8:** 299 – 306.
31 El-Azazy OM, Scrimgeour EM. Crimean-Congo hemorrhagic fever virus infection in the western province of Saudi Arabia. *Trans R Soc Trop Med Hyg*. 1997; **91:** 275 – 278.
32 Ozkurt Z, Kiki I, Erol S, Erdem F, Yilmaz N, Parlak M, et al. Crimean-Congo hemorrhagic fever in eastern Turkey: clinical features, risk factors, and efficacy of ribavirin therapy. *J Infect.* 2006; **52:** 207 – 215.
33 Ergonul O. Crimean-Congo hemorrhagic fever. *Lancet Infect Dis*. 2006; **6:** 203 – 214.
34 Mardani M, Rahnavardi M, Rajaeinejad M, Holakoui-Naini K, Pourmalek F, Rostami M, et al. Crimean Congo hemorrhagic fever among health care workers in Iran. A seroprevalence study in two endemic regions. *Am J Trop Med Hyg*. 2007. In press.
35 Swanepoel R, Gill DE, Shepherd AJ, Leman PA, Mynhardt JH, Harvey S. The clinical pathology of Crimean-Congo hemorrhagic fever. *Rev Infect Dis*. 1989; **11(suppl 4):** 794 – 800.
36 Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, McGillivray GM, Erasmus MJ, et al. Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. *Am J Trop Med Hyg*. 1987; **36:** 120 – 132.
37 Bakir M, Ugurlu M, Dokuzoguz B, Bodur H, Tasyaran MA, Vahaboglu H, et al. Crimean-Congo hemorrhagic fever outbreak in Middle Anatolia: a multicenter study of clinical features and outcome measures. *J Med Microbiol*. 2005; **54:** 385 – 389.
38 Celikbas A, Ergonul O, Dokuzoguz B, Eren S, Baykam N, Polat-Duzgun A. Crimean-Congo hemorrhagic fever infection simulating acute appendicitis. *J Infect*. 2005; **50:** 363 – 365.
39 Ergonul O, Celikbas A, Dokuzoguz B, Eren S, Baykam N, Esener H. The characteristics of Crimean-Congo hemorrhagic fever in a recent outbreak in Turkey and the impact of oral ribavirin therapy. *Clin Infect Dis*. 2004; **39:** 285 – 289.
40 Schwarz TF, Nsanze H, Ameen AM. Clinical features of Crimean-Congo hemorrhagic fever in the United Arab Emirates. *Infection*. 1997; **25:** 364 – 367.
41 Swanapoel R, Coetzer JA. Rift Valley fever. In: Royal Society (Great Britain), ed. *Infectious Diseases of Livestock with Special Reference to Southern Africa*. Vol 1. New York: Oxford University Press; 1994.
42 Peters CJ, Kuehne RW, Mercado RR, Le Bow RH, Spertzel RO, Webb PA. Hemorrhagic fever in Cochabamba, Bolivia, 1971. *Am J Epidemiol*. 1974; **99:** 425 – 433.
43 Geisbert TW, Jahrling PB. Exotic emerging viral diseases: progress and challenges. *Nat Med*. 2004; **10:** 110 – 121.
44 Feldman H, Jones S, Klenk HD, Schnittler HJ. Ebola virus: from discovery to vaccine. *Nat Immunol*. 2003; **3:** 677 – 685.
45 Schnittler HJ, Feldman H. Viral haemorrhagic fever — a vascular disease? *Thromb Haemost*. 2003; **89:** 967 – 972.
46 Burt FJ, Swanepoel R, Shieh WJ, Smith JF, Leman PA, Greer PW, et al. Immunohistochemical and *in situ* localization of Crimean-Congo hemorrhagic fever virus in human tissues and implications for CCHF pathogenesis. *Arch Pathol Lab Med*. 1997; **121:** 839 – 846.
47 Swanepoel R, Leman PA, Burt FJ, Jardine J, Verwoerd DJ, Capua I, et al. Experimental infection of ostriches with Crimean-Congo hemorrhagic fever virus. *Epidemiol Infect*. 1998; **121:** 427 – 432.
48 Ergonul O, Tuncbilek S, Baykam N, Celikbas A, Dokuzoguz B. Evaluation of serum levels of IL-6, IL-10, and TNF-alpha in patients with Crimean-Congo hemorrhagic fever. *J Infect Dis*. 2006; **193:** 941 – 944.
49 Crimean-Congo hemorrhagic fever. WHO fact sheets 2001 November: 208.
50 Shepherd AJ, Swanepoel R, Leman PA, Shepherd SP. Comparison of methods for isolation and titration of Crimean-Congo hemorrhagic fever virus. *J Clin Microbiol*. 1986; **24:** 654 – 656.
51 Shepherd AJ, Swanepoel R, Leman PA. Antibody response in Crimean-Congo hemorrhagic fever. *Rev Infect Dis*. 1989; **11 (suppl 4):** 801 – 806.
52 Chinikar S, Mirahmadi R, Mazaheri V, Nabeth P, Saron MF. A survey of Crimean-Congo hemorrhagic fever in Iran. *Clin Microbiol Infect.* 2003; **9 (suppl 1):** 81.
53 Wray SK, Gilbert BE, Knight V. Effect of ribavirin triphosphate on primer generation and elongation during influenza virus transcription *in vitro*. *Antiviral Res.* 1985; **5:** 39 – 48.
54 Wray SK, Gilbert BE, Noall MW, Knight V. Mode of action of ribavirin: effect of nucleotide pool alterations on influenza virus ribonucleoprotein synthesis. *Antiviral Res*. 1985; **5:** 29 – 37.
55 Paroni R, Del Puppo M, Borghi C, Sirtori CR, Galli-Kienle M. Pharmacokinetics of ribavirin and urinary excretion of the major metabolite 1,2,4-triazole-3-carboxamide in normal volunteers. *Int J Clin Pharmacol Ther*. 1989; **27:** 302 – 307.
56 Connor JD. Ribavirin pharmacokinetics. *Pediatr Infect Dis J*. 1990; **9 (suppl):** S91 – S92.
57 McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever: effective therapy with ribavirin. *N Engl J Med*. 1986; **314:** 20 – 26.
58 Huggins JW, Hsiang CM, Cosgriff TM, Guang MY, Smith JI, Wu ZO, et al. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. *J Infect Dis*. 1991; **164:** 1119 – 1127.
59 Paragas J, Whitehouse CA, Bray M, Endy TP. A simple assay for determining antiviral activity against Crimean-Congo hemorrhagic fever virus. *Antiviral Res.* 2004; **62:** 21 – 25.

60 Andersson I, Bladh L, Mousavi-Jazi M, Magnusson KE, Lundkvist A, Haller O, et al. Human MxA protein inhibits the replication of Crimean-Congo hemorrhagic fever virus. *J Virol*. 2004; **78:** 4323 – 4329.
61 Centers for Disease Control (CDC). Management of patients with suspected Viral Hemorrhagic Fever — United States. *MMWR*. 1995; **44:** 475 – 479.
62 Frame JD. Clinical features of Lassa fever in Liberia. *Rev Infect Dis*. 1989; **11(suppl 4):** 783 – 789.
63 Sheikh AS, Sheikh AA, Sheikh NS, Tariq M. Ribavirin: an effective treatment of Crimean-Congo hemorrhagic fever. *Pak J Med Sci*. 2004; **20:** 201 – 206.
64 Centers for Disease Control and Prevention. Viral hemorrhagic fever: initial management of suspected and confirmed cases. *MMWR Morb Mortal Wkly Rep*. 1983; **32 (suppl 2):** 27 – 38.
65 Shuman M. Abnormalities of platelet and vascular function. In: Goldman L, Bennett JC, eds. *Cecil Textbook of Medicine*. 21st ed. Philadelphia: WB Saunders Company; 2000: 996 – 1012.
66 van Eeden PJ, van Eeden SF, Joubert JR, King JB, van de Wal BW, Groenwald JH. A nosocomial outbreak of Crimean-Congo hemorrhagic fever at Tygerberg Hospital. Part II. Management of patients. *S Afr Med J*. 1985; **68:** 718 – 721.
67 Mardani M. Crimean-Congo hemorrhagic fever. In: Mortazavi-Tabatabaei SA, ed. *Important Zoonoses in Iran*. Tehran: Ministry of Health and Education; 2005: 219 – 220.