

CRIMEAN CONGO HEMORRHAGIC FEVER - AN ARTICLE REVIEW

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ABSTRACT

Crimean–Congo hemorrhagic fever (CCHF) caused by negative-sense, single-stranded RNA virus in the genus *Nairovirus*, family Bunyaviridae. (CCHF) is a tick-borne infectious disease characterized by fever, malaise, headache, nausea, vomiting, diarrhoea, sore throat, muscle aches, hemorrhage and thrombocytopenia. CCHF has the most extensive geographic range of the medically significant tick-borne viruses occurring in Africa, Europe and Asia & found recently in India (Ahmadabad) in 2011, become a serious threat to public health. CCHF was first diagnosed and conformed by IgM serology or RT-PCR in Turkey in 2002. Intravenous or oral ribavirin has been used in several countries to treat the disease for more than 20 years. Virus-associated hemophagocytic syndrome has been found to contribute to the exacerbation of CCHF in some patients, and the administration of methylprednisolone at high doses was observationally undertaken in patients with CCHF and virus-associated hemophagocytic syndrome, with promising results. The intention of this review is to summarize the current status of CCHF with effective therapeutics and preventive measures.

KEYWORDS: Crimean Congohemorrhagic fever, Hemagglutinability, ribavirin, serodiagnosis.

INTRODUCTION

Infectious diseases remain the single greatest contributor to morbidity and mortality in the world. However, only some 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, a few of (Lassa, Marburg, Ebola, agents of South American VHF, Hanta, and Crimean-Congo) share a distinctive characteristic that has important clinical and public health consequences, namely the potential for person-to-person transmission.¹ The disease is endemic in many countries in Africa, Europe and Asia, and during 2001, cases or outbreaks have been recorded in Kosovo, Albania, Iran, Pakistan, and South Africa.

Crimean–Congo hemorrhagic fever (CCHF), also known as Asian Ebola, is a fatal viral disease that is rapidly increasing worldwide.^{2, 3} Crimean–Congo hemorrhagic fever (CCHF) is a tick-borne zoonosis caused by a virus of the *Nairovirus* group in the family Bunyaviridae. CCHF viruses are transmitted by *Hyalomma* genus ticks, particularly by *Hyalomma marginatum marginatum*.⁴ **Table 1**

Soviet scientists first recognized the disease they called Crimean hemorrhagic fever in 1944 and well-known its

viral etiology by course of the virus through human "volunteers" (fatality rate unreported), but were not capable to isolate the agent at that time.

In June 1967, Soviet virologist Mikhail Chumakov registered an isolate from a fatal case that occurred in Samarkand (on the ancient Silk Road in Central Asia, not the Crimea) in the Catalogue of Arthropod-borne Viruses.⁵ Four months earlier, virologists Jack Woodall, D Simpson and others had published initial reports^{6,7} on a virus they called the Congo virus, first, isolated in 1956 by physician Ghislaine Courtois, head of the Provincial Medical Laboratory, Stanleyville, Belgian Congo. Strain V3010, isolated by Courtois, was sent to the Rockefeller Foundation Virus Laboratory (RFVL) in New York City and found to be alike to another strain from Uganda, but to no other named virus at that time. Chumakov later sent his strain to the RFVL, where it was found to be identical to the Congo virus.⁸ A disease given the name Crimean hemorrhagic fever was described in the people bitten by ticks while harvesting corps and sleeping outdoors on the Crimean Peninsula 1944. It was demonstrated by the inoculation of human subject that the disease was caused by filterable agent present in the blood of patients during the acute age of illness.

The causative virus was finally isolated in the laboratory host, suckling mice, in 1967.⁹ In 1968 it was found that

the agent of Crimean Hemorrhagic Fever was identical to a virus named Congo which had been isolated in 1956 from the blood of a Febrile child in Stanleyville (now Kisangani) and the Belgian Congo (now Democratic Republic of Congo) and since that time the two names have been used in combination.⁹ The International Committee on Taxonomy of Viruses proposed the name Congo-Crimean hemorrhagic fever virus, but the Soviets insisted on Crimean-Congo hemorrhagic fever virus. Against all principles of scientific nomenclature based on priority of publication, it was adopted as the official name in 1973 in possibly the first instance of a virus losing its name to politics and the Cold War.

GEOGRAPHICAL DISTRIBUTION (Fig 1)

The disease is endemic in Africa, Europe (Balkans) and Asia and continues to emerge. There have been outbreaks and an increasing number of case reports in CCHF have been recorded in Afghanistan (2001 to 2008), Armenia (2006), Iran (2001-2009), Kazakhstan (2005, 2009), Kosovo (2001 to 2008), Bulgaria (1955 to 2008), Mauritania (2002 to 2003), Pakistan (2001 to 2009), Russia (1999 to 2009) Senegal (2004 with a human imported case in France) South Africa (1989 to 2009), Sudan (2004, 2008), Tajikistan (2002, 2004, 2009), Georgia (2009), Serbia (2001, 2004, 2009), Greece (2008), and Turkey (2003 to 2009) have drawn the international community attention to this emerging problem in India.

India

It is found in Gujarat in Ahmedabad mainly. The viral Congo Hemorrhagic Fever that has already claimed three lives in Kolat village in Sanand, 20 km from Ahmedabad- the main city of Gujarat state in India. 30-year old Amina Momin has been the first casualty of this virus. Even the doctor and nurse treating Amina, Dr. Gagan Sharma and Asha John .The first victim - 40-year-old Amina - died on the 3rd January 2011.Dr.Shabbir Ali, 25, working as an intern at Civil Hospital, became the latest victim of CCHFvirus and died on Monday on 31stJanuary.He is the second doctor after Gaganjeet Sharma, and the fourth victim overall, to die of the deadly disease in Ahmedabad. All deaths have occurred in less than a month. Dr.Shabbir was admitted to Sterling Hospital on Saturday evening with high-grade fever, vomiting and internal bleeding, symptomatic of CCHF infection.

ETIOLOGY

The virus has been classified as Nairovirus in the genus Bunyavirus in the family of Bunyaviridae. Nairovirus contains 32 viruses arranged in 7 serogroups on basis of antigenic affinities. CCHF virus, Hazara virus from Pakistan and Khasan virus from former Soviet Union

form one sero-group 3'4'5.¹⁰ The classification of the nairoviruses was originally based on the antigenic relatedness the grouping have subsequently been sustained through demonstration of morphological and molecular affinities between the viruses. Nairovirus are spherical, 90-120 nm in diameter and have host cell derived bilipid layer envelope incorporated virus-coded glycoprotein spikes .Single stranded , negative sense RNA genome consist of three segments: L (large) , 4.1×10^6 to 4.9×10^6 Da ;M (medium) , 1.5×10^6 to 1.9×10^6 Da; and S (small) , 0.6×10^6 to 0.7×10^6 Da in virions .¹¹ The virions contains three major structural protein : to envelope glycoprotein's (G 1 and G 2) and nucleocapsid protein (N) plus minor quantities of viral transcriptase or L(large) protein. Hazara virus is reported to have three glycoprotein .Each of the three genome segments contains one open reading frame, flanked by noncoding regions. The S segment of CCHF and Hazara viruses encode the viral N protein .CCHF S RNA comprises 1,672 nucleotides and has a single open reading frame, which encodes the N protein the major structural protein of the virus.¹⁰

Four structural proteins are encoded: the RNA-dependent RNA polymerase (L protein), expressed by the large (L)-genome segment; the mature glycoprotein G_N and G_C, encoded by the medium (M)-genome segment, and the nucleoprotein (N), encoded by the small (S)-genome segment.These three segments are encapsulated by nucleoprotein N, and associated with L protein, resulting in the formation of ribonucleoprotein particles. The polyprotein encoded by the M-genome segment is cotranslationally cleaved into precursor molecules, PreG_N and PreG_C, which are, subsequently post-translationally processed into the mature glycoprotein, G_N and G_C, respectively.¹²The viral glycoprotein are believed to be responsible for recognition of receptor site on susceptible cells and manifestation of viral hemagglutinability and for protective immune response in the host.¹⁰

STABILITY

Being enveloped, the virus is sensitive to lipid solvents.¹⁰Its infectivity is destroyed by low concentrations of formalin and β-propiolactone. It is labile in infected tissues after deathpresumably due to a fall in pH, but infectivity retained for few days at ambient temperature in suspected serum for 3 weeks at 4° C. Infectivity is stable at temperature below -60° C but is destroyed by boiling or autoclave.¹⁰ CCHF virus is highly dangerous pathogen and it is investigated in high biosafety laboratories.

MODE OF TRANSMISSION

From Human to Human

Mechanism The virus is transmitted to humans by the bite of Ixodid tick (mostly of the *Hyalomma* genus), crushing engorged infected ticks or by contact with blood or tissues from human patients or infected livestock.¹² Direct contact with virus-contaminated blood or tissues from infected animals or humans is another source of virus transmission and is generally characterized by more severe clinical symptoms and high mortality.¹³

The virus may also be transmitted from human to human which occurs primarily in the hospital setting.¹⁴ Hospital health-care workers are at serious risk of transmission of CCHF infection when caring for patients with hemorrhages from the nose, mouth, gums, vagina, and injection sites. The transmission of the CCHF infections and deaths among health-care workers has been reported. Airborne acquisitions of the infection was suspected in several cases in Russia, but were not documented. Horizontal transmission from a mother to her child has also been reported.¹⁵

From Tick to Human

Mechanism CCHF virus is transmitted to humans by bites from Ixodid ticks, especially the genus of *Hyalomma*. The virus is also transmitted to humans either by direct contact with blood or tissues from infected animals, mainly sheep, or by patient's blood, vomit containing blood, or respiratory secretions.

The latter human-to-human infection sometimes causes nosocomial outbreaks of CCHF.¹⁶ The virus is transmitted to humans by the bite of infected ticks, direct contact with blood or infected tissues from viremic animals, and direct contact with the blood or secretions of an infected person.¹⁷ Transmission also may occur from aerosol contact of blood from patients with advanced stages of the disease.¹⁸

From Animal to Human

Mechanism The virus is also transmitted to humans either by direct contact with blood or tissues from infected animals, mainly sheep.¹⁶ Cattle, sheep and goats do not become ill after infection but are viremic for about 1 week. During this period of time the virus may be transmitted to humans who have close contact to these animals such as agricultural workers, slaughterhouse workers, and veterinarians¹⁴ and crushing infected ticks may also be hazardous.

From Animal to Tick

Mechanism Immature ticks acquire the virus by feeding on infected small vertebrates. They remain infected throughout their development and on maturation they

transmit the infection to large animals, such as livestock.¹⁷

From Tick To Tick

Mechanism Among invertebrates, CCHF viral infection has been demonstrated only in ticks, including viral isolations from numerous species/subspecies of seven genera of the family Ixodidae, and two species of the family Argasidae. An especially important biological feature of ticks in general as potential vector/reservoirs of arboviruses is their ability to transmit arboviruses transovarially. Evidence of this phenomenon for CCHF virus in nature is based mainly on limited isolations from eggs of *H. marginatum* and *Dermacentor marginatus*.¹⁹

INCUBATION PERIOD

If the virus is transmitted via tick bite, the incubation period appears to be shorter (1-9 days) than after transmission via infected animals (5-13 days).¹⁴

The incubation period is usually 5-6 days after contact with blood¹⁷ In general, the incubation period after a tick bite can be as short as 1-3 days, but can much longer, depending on several factors including route of exposure. For example, in South Africa, among 21 patients for which reliable data were obtained, the time to onset of disease after exposure by tick bite was 3.2 days, to blood or tissue of livestock was 5.0 days, and to blood of human cases was 5.6 days.

CLINICAL SYMPTOMS AND PATHOPHYSIOLOGY

Patients with CCHF present with symptoms ranging in severity from fever only, or fever with flu-like symptoms, to hemorrhage with multiple organ failure, resulting in death. The time course of the typical infection consists of four phases: incubation (3-7 days), prehemorrhagic (1-7 days), hemorrhagic (2-3 days) and convalescent.²⁰

There are two phases first hypothetical phase and second hypothetical phase. The first starts from exposure to the virus, and is characterized by its replication and spread in the bloodstream, which usually lasts up to 15 days. In clinical terms, this period starts from the onset of prehemorrhagic symptoms (fever, myalgia, nausea and vomiting), and ends with bleeding from various sites.²⁰ Average incubation time was 3.2 days when infected through a tick bite, while it was 5 and 5.6 days when infected through exposure to blood or tissue of livestock, and through exposure to blood from human cases.²⁰

Fig 2 Severe headache and muscle aches, nausea, diarrhea and other nonspecific symptoms. Severe cases progress rapidly to disseminated intravascular coagulation (DIC), bleeding and shock.¹⁰ Also include petechiae, large ecchymoses, melena and hematemesis tend to be more

prominent in CCHF than in other types of viral hemorrhagic fever.

The second hypothetical phase of CCHF includes hemorrhagic and convalescence is characterized by the decline of viremia, but bleeding from various sites. In this phase, proinflammatory cytokines are released and the coagulation cascade is disrupted in some patients, leading to disseminated intravascular coagulation.¹⁵ A hemorrhagic state develops from 3rd to the 5th day and manifestations like petechial hemorrhage or purpura in the skin and bleeding from mucous membranes manifest asepistaxis, hemoptysis, hematemesis, melena and hematuria.²⁰ Oliguria is a common symptom, which is presumably associated with renal failure caused by the direct influence of CCHFV infections and/or by indirect influence through hypovolemic shock. Virus-associated hemophagocytic syndrome (VAHPS) is an important factor, which has been reported to contribute to the clinical manifestations and severity of CCHF recently and is characterized by fever, hepatosplenomegaly, cytopenia, elevated ferritin, lactatedehydrogenase and triglyceride levels and, most importantly, hemophagocytosis in the bone marrow, liver and lymph nodes. It was reported that VAHPS is possibly one of the major factors responsible for the high CFR rate in patients with CCHF and all the cytokines tested, TNF- α , soluble TNF receptor, IL-6 and IL-10 were significantly elevated in a fatal case of CCHF, but not in a nonfatal case. CCHF was more common in males, and approximately 70% of cases had a history of a tick bite.²⁰ Onset of symptoms is sudden, with fever, myalgia (aching muscles), dizziness, neck pain and stiffness, backache, headache, sore eyes and photophobia (sensitivity to light), nausea, vomiting and sore throat accompanied by diarrhoea and generalized abdominal pain. In next few days, the patient may experience sharp mood swings, and may become confused and aggressive. After two to four days, the disturbance may be replaced by sleepiness, depression and lassitude, and the abdominal pain may localize to the right upper quadrant, with detectable hepatomegaly (liver enlargement). Other clinical signs which emerge include tachycardia (fast heart rate), lymphadenopathy (enlarged lymph nodes), and a petechial rash (a rash caused by bleeding into the skin), both on internal mucosal surfaces, such as in the mouth and throat, and on the skin. The petechiae may give way to ecchymoses (like a petechial rash, but covering larger areas) and other hemorrhagic phenomena such as melaena (bleeding from the upper bowel, passed as altered blood in the faeces), haematuria (blood in the urine), epistaxis (nosebleeds) and bleeding from the gums. There is usually evidence of hepatitis. The

severely ill may develop hepatorenal (i.e., liver and kidney) and pulmonary failure after the fifth day of illness.

The mortality rate from CCHF is approximately 30%, with death occurring in the second week of illness. In those patients who recover, improvement generally begins on the ninth or tenth day after onset of illness. Clinical stages of CCHF Treatment could be considered in two phases. The first begins with exposure to the virus and is characterized by viremia, which usually ends within 15 days. Ribavirin is most likely to be beneficial during this phase, through its directantiviral activity. The second is characterized by the decline of viremia and the onset of bleeding from various sites. In some patients, immunologic mechanismssuch as cytokine storm disrupt the coagulation cascade and disseminated intravascular coagulation occurs. Because ribavirin is unlikely to be effective in the absence of viremia, other treatment alternatives should be considered for thispatients.¹⁰

PATHOGENESIS

The mechanism of pathogenesis by CCHF is not known but due to analogy to other arthropod born viruses it is suggested that liver is target organ for this virus.¹⁰ CCHF include the need for specialized laboratories (i.e., biosafetylevel-4 (BSL-4) containment) and lack of available animal models of disease. Limited knowledge of pathogenesis is often obtained from blood changes and liver biopsies of CCHF patients. CCHF virus undergoes some replication at there is hematogenous and lymph-borne spread of infection to organs such as the liver, which are major sites of replication.⁹

The mononuclear phagocyte kinase levels, whilebiliburin, creatinine, and urea level increase and serum protein levels decline during the second week.⁹ Capillary fragility is a feature of the disease. Formation of circulating immune complexes with activation of complement and this would contribute to damage of the capillary bed and hence to the genesis of skin rash and renal and pulmonary failure. The characteristic endothelial damage seen in CCHF is not necessarily the result of direct infection of the endothelial cells by CCHFV. At least in the case of Ebola hemorrhagic fever, evidence is mounting that much of the cellular damage and resulting coagulopathy actually results from multiple host-induced mechanisms.

These include massive apoptosis of lymphocytes both intravascular and in lymphoid organs; induction of proinflammatory cytokines, including tumor necrosis factor (TNF)-alpha; and the deregulation of the coagulation cascade. Tissue damage in organs result in release of procoagulants into the blood stream and the impairment of the circulation by the occurrence of

disseminated intra vascular coagulopathy result to contribute further tissue damage.¹⁰

PREVENTION

Prevention and Control

The prevention and control in public need the following steps:^{21, 22}

- 1) Educate public about the mode of transmission through tick bites, handling ticks, and handling and butchering animals, and the means for personal protection.
- 2) Tick control with acaricide (chemicals intended to kill ticks) is a realistic option for well managed livestock production facilities. Animal dipping in an insecticide solution is recommended.
- 3) Public should avoid tick-infested areas when feasible especially when ticks are active(spring to fall). To minimize exposure, wear light clothing that covers legs and arms, tuck pants into socks, regularly examine clothing and skin for ticks, and apply tick repellent such as diethyltoluamide to the skin or permethrin (a repellent and contact acaricide) to pant legs and sleeves.
- 4) Persons who work with livestock or other animals in the endemic areas should take practical measures to protect themselves. They include the use of repellents on the skin (e.g. DEET) and clothing (e.g. permethrin).
- 5) Butchers should wear gloves and other protective clothing to prevent skin contact with infected tissues or blood.
- 6) In case of death of CCHF patient, family should be informed to follow safe burial practices.

Safe Burial Practices

1. Thick and long rubber gloves or double pair of surgical gloves should be used for washing the body for burial.²²
2. The dead body should be sprayed with 1:10 liquid bleach solution and then placed in a plastic bag which should be sealed with adhesive tape.²²
3. It should then be wrapped in the winding sheet for burial.²²
4. Disinfect the transport vehicle by spraying 1:10 liquid bleach solution on any surfaces touching the body and burn all clothing of the deceased.²²

Hospitals and Health Facilities

1. Hospitals should maintain stock of Ribavirin; in Pakistan it is available in the market as Ribazole.
2. Bio-safety is the key to avoiding nosocomial infection. Patients with suspected or confirmed CCHF should be isolated and cared for using barrier-nursing techniques to prevent nosocomial spread of infection..

Bio-safety measures

The biosafety measures are:²²

- a. The patient should be treated in a separate room under strict barrier nursing.
- b. Only designated medical / Para-medical staff and attendants should attend the patient. Non-essential staff and attendants should not be allowed to enter the room.
- c. All secretions of the patient and hospital clothing in use of the patient should be treated as infectious and should be autoclaved before incinerating.
- d. All medical and Para-medical staff and attendants should wear disposable gloves, disposable masks and gowns (gowns should be autoclaved before sending to the laundry or incineration). Use of disposable items should be ensured by supervisor.
- e. Every effort should be made to avoid spills, pricks, injury and accidents during the management of patients. Needles should not be re-capped but discarded in proper safety disposal box.
- f. All used material e.g. syringes, gloves, canulla, tubing etc, should be collected in autoclave-able bag and autoclaved before incinerating.
- g. All instruments should be de-contaminated and autoclaved before re-use.
- h. All surfaces should be decontaminated with liquid bleach.

DIAGNOSIS

The traditional method for CCHF isolation has been by intracranial (i.c.) or intraperitoneal (i.p.) inoculation of a sample (e.g., blood from an acute-phase patient or ground tick pools) into newborn mice. Isolation in cell culture is simpler and provides a more rapid result, but is generally considered less sensitive and can generally only detect high concentrations of virus. Virus can be isolated from blood and organ suspensions in a wide variety of susceptible cell lines including LLC-MK2, Vero, BHK-21, and SW-13 cells with maximal virus yields (10⁷-10⁸ plaque-forming units/ml) after 4-7 days of incubation. Depending on the cell line and strain, the virus may produce little or no cytopathic effect (CPE) and develop into a noncytopathic persistent infection of the cells. Virus can be identified by performing immunofluorescence assay (IFA) with specific monoclonal antibodies. IgM and IgG antibodies are detect by ELISA and immuno fluorescence assays within 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. 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 ELISA methods are quite specific and much more sensitive than immunofluorescence assays and neutralization tests. Recently, a recombinant nucleoprotein-based IgG ELISA for serological diagnosis of CCHF virus infections was developed.¹⁷ Molecular-based diagnostic assays, such as the reverse transcription-polymerase chain reaction (RT-PCR), provide a useful complement to serodiagnosis and now often serve as the front-line tool in the diagnosis of CCHF. RT-PCR detects the genetic material of the virus, and can be designed to be highly specific; it is possible to make a presumptive diagnosis of CCHF. Due to the high sensitivity of RT-PCR, positive results can often be obtained from samples which are culture negative. One-step real-time RT-PCR assay for detecting CCHFV using primers to the nucleoprotein gene; however, they used the DNA-intercalating dye, SybrGreen I, for detecting the PCR.

MANAGEMENT

CCHF should be managed by diagnosing and treating for other likely causes of fever. If there is no response to anti-malarial and antibiotic treatment, the patient's platelet count should be checked and examined in view of the criteria mentioned above for "probable CCHF". All specimens of blood or tissues taken for diagnostic purposes should be collected and handled using universal safety precautions.²²

TREATMENT

The current approach to treatment of CCHF is based on general supportive measures, monitoring of the patient's hematologic and coagulation status, with replacement of cells and factors as needed, and the use of ribavirin.

1. Ribavirin

Ribavirin is a synthetic purine nucleoside analogue with a modified base and d-ribose sugar which inhibits the replication of a wide range of RNA and DNA viruses in vitro it is used in combination with interferon- α for the treatment of hepatitis C virus infections, and in aerosol form is used to treat pediatric infection by respiratory syncytial virus.²³ Ribavirin is the only antiviral drug which has been used to treat viral hemorrhagic fever syndromes, like CCHF and Lassa fever. Viruses in the Bunyaviridae family are generally sensitive to ribavirin. Ribavirin is most likely to be effective during first phase.

Ribavirin-Intravenous treatment

The intravenous preparation of ribavirin is recommended for treatment of viral hemorrhagic fevers, and the oral form for post exposure prophylaxis.²⁴ Intravenous Ribavirin should be administered within 6 days of illness onset as follows: 30 mg/kg loading dose,

followed by 16 mg/kg 4 times a day for 4 days, then 8 mg/kg 3 times a day for 6 days.²⁵

Applicable There is currently no specific antiviral therapy for CCHF approved for use in humans by the FDA. However, the antiviral drug, ribavirin, has shown the most promise over the year.²⁶ Ribavirin, a broad-spectrum antiviral agent, is supposed to be a potential therapeutic for CCHF.

Contraindication It should be noted that men and women who take ribavirin for prophylaxis should avoid conception for six months after taking it because of ribavirin's teratogenic effects.²⁵ and it is contraindicated in pregnant women. It should not be used when renal impairment is present.

Complication With IV administration, reversible suppression of erythropoietin, mild hemolysis, and mild direct hyperbilirubinemia occur.

Success Rate E.g.: Pakistan, three nosocomial cases of CCHF was treated with oral ribavirin for 10 days, and they made a complete recovery. More recently, in a large cohort study in Iran, the efficacy of oral ribavirin was 80% among patients with confirmed CCHF and in turkey 86% success.²⁶

Ribavirin - Oral treatment

Ribavirin therapy was started early (within 4 days after the onset of the disease) for 7 patients, and none died. Ribavirin therapy was initiated late (at least 5 days after the onset of the disease) for 5 patients, and 3 died. In another report, oral ribavirin was used in the treatment of 3 patients in Pakistan with nosocomial CCHF, administered at a dosage of 4 g daily for 4 days and then 2.4 g daily for the following 6 days. The 3 patients were not expected to respond to therapy, but this treatment saved their lives.²⁴

Applicable Oral Ribavirin has been used for post exposure prophylaxis for patients with CCHF, but its efficacy has not been formally assessed²⁴ Ribavirin has been used orally or IV with some success in a limited number of patients for the treatment of Crimean-Congo hemorrhagic fever (CCHF). Ribavirin prophylaxis is generally well tolerated, potentially useful and should therefore be recommended for health care workers who are at risk of exposures such as percutaneous injuries.

Contraindication Oral ribavirin is contraindicated in women who are or may become pregnant and also is contraindicated in male partners of such women, in patients with hemoglobinopathies, and in patients with creatinine clearances less than 50 mL/min.²⁷

Complication Anemia (most commonly), insomnia, depression, irritability, and suicidal behavior have been reported with PO administration; with IV administration,

reversible suppression of erythropoiesis, mild hemolysis, and mild direct hyperbilirubinemia.

2. Supportive therapy

Non-steroidal anti-inflammatory drugs should be avoided. Fluid and electrolyte balance should also be monitored.

It also includes the administration of thrombocytes, fresh frozen plasma (FFP), and sometimes erythrocyte preparations. The replacement therapy with these blood products should be performed by checking complete blood count, which should be done daily.

3. Immunotherapy

A new specific immunoglobulin CCHF-Venin has been prepared the plasma pool of boosted donors, by a combined ethanolpolyethyleneglycol fractionation method with an ion-exchange purification step. The final product is free from immunoglobulin aggregates, vasoactive substances, and polyethylene glycol, and meets national and international requirements for intravenous immunoglobulin. It contains antibodies to CCHF virus of a titre of 8.²⁸

Applicable There was an early recognition of the possible benefits of treatments using serum prepared from the blood of recovered CCHF patients or gamma globulin obtained from immunization of horses. In more recent times, immunotherapy was attempted via passive transfer of CCHF survivor convalescent plasma.²⁶ CCHF immune serum is beneficial when administered intravenously in a dose of 250 ml over 1 to 2 hours on successive days, and when given early in infection.

Success Rate In the summer of 1989 seven patients with severe CCHF received, besides conventional treatment, immune plasma. The patients recovered quickly, their leucocytes and platelet counts returned to normal, and coagulation abnormalities were corrected. Their bleeding tendency ceased. No side-effects were observed and the patients were discharged in good health.²⁸

4. Vaccination A vaccine for CCHF derived from inactivated mouse brain is used in Bulgaria, but is not available outside of that country.

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Table 1: VIRUS CLASSIFICATION

HEMORRHAGIC CRIMEAN CONGO FEVER VIRUS
GROUP: Group V ((-)ssRNA)
FAMILY: Bunyaviridae
GENUS: Nairovirus
SPECIES: Crimean Congo hemorrhagic fever virus

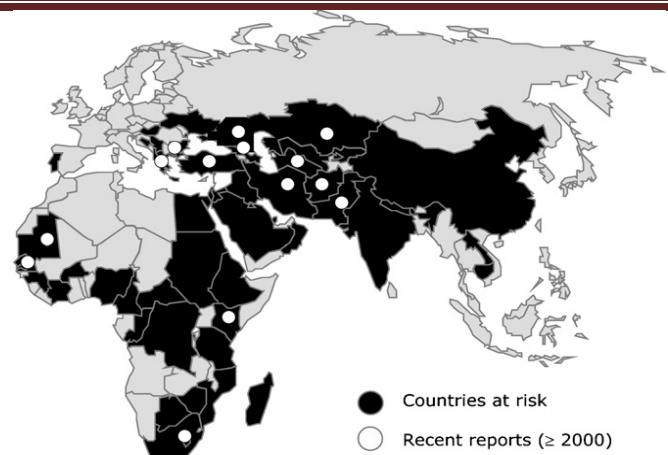


Fig. 1. Geographical distribution of CCHF

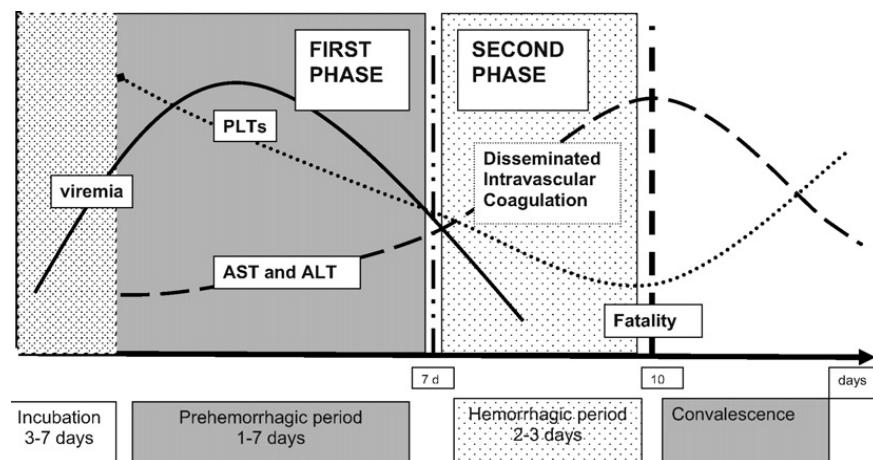


Fig.2. Clinical stages of CCHF Treatment