

DRUG THERAPY FOR CRIMEAN-CONGO HEMORRHAGIC FEVER

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ABSTRACT

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne disease affected by virus reported from more than 35 countries in Africa, Asia, south-east Europe, and the Middle East. The majority of human cases are workers in livestock industry, agriculture, slaughterhouses, veterinary practice and 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. Laboratory abnormalities may include anemia, leukopenia, thrombocytopenia 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 control of crimean-congo hemorrhagic fever with a special focus on oral ribavirin as a choice of medical treatment.

Keywords: *Crimean-Congo*, hemorrhagic fever, tick-borne virus, treatment.

INTRODUCTION

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 is 13 – 36% in animals^{3,4}. A 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*^{3,4}. The most important source of virus transmission is immature tick, which feeds small vertebrates' blood. Once infected India from the village of Kolat which is 30 Kms southwest of Ahmedabad in Gujarat. A 30 year old woman and a doctor and nurse treating her in Ahmedabad succumbed to this illness creating panic in the local population and the country as well. General public including the medical fraternity was not fully aware of this disease, thus a fear of unknown was spread initially.¹

HISTORICAL BACKGROUND

CCHF like symptoms affecting people were described initially by physicians in 12th century from the region currently known as Tazhikistan. It was described as a clinical entity in 1944-1945 when 200 Soviet military personnel were infected in war affected Crimea. Similar disease affected the population in Congo and Uganda in 1967, thus the name Crimean Congo hemorrhagic fever.³ In 1967, a breakthrough in CCHF research came when Chumakov and his colleagues at the Institute of Poliomyelitis and Viral Encephalitides in Moscow first used newborn white mice for the isolation of CCHF virus. This resulted in a Drosdov strain which became the prototype strain for experimental work.^[4]

ETIOLOGICAL AGENT

CCHF as mentioned before is caused by a virus. This virus is a member of the *Nairovirus* genus of the family *Bunyaviridae*, *Hantavirus* also belongs to the same family. *Nairovirus* genus contains 7 species of virus with 34 strains reported till date. All of these viruses are transmitted by either ixodid or argasid ticks (i.e., hard or soft ticks, respectively). Structurally the CCHF virus is an RNA virus, it is spherical, approximately 100 nm indiameter, and has a host cell-derived lipid bilayered envelope.

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) 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

SYMPTOMS AND EFFECTS

- After an incubation period of 2-7 days there is a sudden onset of flu-like symptoms including a severe headache
- Chills
- Fever
- Muscular pain
- Lumbar and abdominal pain
- Nausea and vomiting.
- After 3-5 days, hemorrhage begins and is seen as a red or purple discoloration of the skin and the development of nosebleeds.
- In about half of all cases the liver is enlarged (hepatomegaly).
- Blood is found in saliva, urine, black skin patches and vomit.
- This will lead to shock, vascular collapse and death about 10 days after the onset of symptoms. If the patient survives and the fever begins to subside, then a long slow recovery is possible.

VIROLOGY

The virus is a member of the genus *Nairovirus*, family *Bunyaviridae*. The genome is circular, ambisense RNA in three parts - Small (S), Middle (M) and Large (L). The L segment is 11-14.4 kilobases in length while the M and S segments are 4.4-6.3 and 1.7-2.1 kilobases long respectively. The L segment encodes the RNA polymerase; the M segment encodes the envelope proteins (Gc and Gn); and the S segment encodes the nucleocapsid protein. The envelope protein is initially translated as a glycoprotein precursor which is then cleaved into two smaller proteins.

The virions are 80-120 nanometers (nm) in diameter and are pleomorphic. There are no host ribosomes within the viron. Each viron contains three copies of the genome. The envelope is single layered and is formed from a lipid bilayer 5nm thick. It has no protrusions. The envelope proteins form small projections ~5-10nm long. The nucleocapsids are filamentous and circular with a length of 200-3000 nm.

Based on the sequence data seven genotypes have been recognised: Africa 1 (Senegal), Africa 2 (Democratic Republic of

the Congo and South Africa), Africa 3 (southern and western Africa), Europe 1 (Albania, Bulgaria, Kosovo, Russia and Turkey), Europe 2 (Greece), Asia 1 (the Middle East, Iran and Pakistan) and Asia 2 (China, Kazakhstan, Tajikistan and Uzbekistan). This virus appears to have evolved 3100-3500 years ago.^[1] The mutation rates for the three parts of the genome were estimated to be: 1.09×10^{-4} , 1.52×10^{-4} and 0.58×10^{-4} substitutions/site/year for the S, M, and L segments respectively.

VECTORS

Sporadic infection of people is usually caused by *Hyalomma* tick bite. Clusters of illness typically appear after people treat, butcher or eat infected livestock, particularly ruminants and ostriches. Outbreaks have occurred in clinical facilities where health workers have been exposed to infected blood and fomites. The causative organism is found in Asia, Eastern Europe, the Middle East, a belt across central Africa and South Africa and Madagascar.

The main environmental reservoir for the virus is small mammals (particularly European hare, Middle-African hedgehogs and multimammate rats). Ticks carry the virus to domestic animal stock. Sheep, goats and cattle develop high titers of virus in blood, but tend not to fall ill. Birds are generally resistant with the exception of ostriches. *Hyalomma detritum*, *Hyalomma marginatum marginatum* species that have been identified as infected with this virus include *Argas reflexus*, *Hyalomma anatolicum*, and *Rhipicephalus sanguineus*²⁹

CLINICAL FEATURES

Humans get this infection after a bite of an infected tick or contact with infected blood of animals. CCHF can be transmitted from one infected human to another by contact with infectious blood or body fluids. Most of the human cases are workers in livestock and agriculture industry, slaughterhouses, and viruses is their ability to disable the host immune response by attacking and manipulating the cells that initiate the antiviral response. Capillary fragility is a common feature of CCHF, suggesting infection of the endothelium. Endothelial damage accounts for the characteristic rash and contribute to haemostatic failure by stimulating platelet aggregation and degranulation, with consequent activation of the intrinsic coagulation cascade. Reactive hemophagocytosis have been reported from studies in Turkey which suggested that

cytopenias observed during CCHF infection could be attributed to it. Proinflammatory cytokines like IL-1, IL-6, and TNF-alpha also contribute in pathogenesis and mortality.

TRANSMISSION

CCHFV usually circulates between asymptomatic animals and ticks in an enzootic cycle. This virus has been found in at least 31 species of ticks, including seven genera of the family Ixodidae (hard ticks). Members of the genus *Hyalomma* seem to be the principal vectors. Transovarial, transstadial and venereal transmission occur in this genus. *Hyalomma marginatum marginatum* is particularly important as a vector in Europe, but CCHFV is also found in *Hyalomma anatolicum anatolicum* and other *Hyalomma* spp. Other ixodid ticks including members of the genera *Rhipicephalus*, *Boophilus*, *Dermacentor* and *Ixodes* may also transmit the virus locally. Although CCHFV has been reported in other families of invertebrates, these species may not be biological vectors; the virus may have been ingested in a recent blood meal. In one study, CCHFV was reported from a biting midge (*Culicoides* spp.). It has also been found in two species of Argasidae (soft ticks); however, experimental infections suggest that CCHFV does not replicate in this family of ticks.

LABORATORY DIAGNOSIS

Methods of diagnosis include detection of antibodies to viral antigen 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 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.

Thus ELISA test may not be helpful in initial days of infection when the antibody levels are low. In the initial stages virus may be isolated from blood or tissue specimens and grown in cell culture, but virus isolation is of limited value because it requires a biosafety level 4 (BSL-4) laboratories, which is not available in most endemic areas. More recently, PCR, a molecular method for detecting the viral genome, has been successfully applied in the diagnosis of viral hemorrhagic fevers. Chinikar et al¹² found few cases with positive RT-PCR among those whose illness had been confirmed by serology. Viral antigen detection by ELISA and RT-PCR is the most useful diagnostic technique in the acute clinical

setting. Diagnosis should be based initially on clinical findings, and laboratory tests be used to confirm or exclude it.

- Detection of antigens or antibody to the agent in the blood (serology);
- Leukopenia;
- Thrombocytopenia;
- ELISA is available;
- RT-PCR;
- IgM capture assays help to differentiate bunyavirus infections;
- Check for tick bites and possible exposure.²⁸

TREATMENT

Treatment is mainly supportive. Ribavirin is used in some cases. Observational studies in humans and studies in experimentally infected mice support the use of this drug; however, no randomized human clinical trials have been published. Passive immunotherapy with hyperimmune serum has been tested in a few cases, but the value of this treatment is controversial. The mainstay of treatment in CCHF is supportive in nature with careful maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure. Management of DIC, sepsis, shock and MODS based on the established guidelines should be undertaken. Treatment options specific to the disease are limited.

There have been reports of possible benefits with treatment of patients using serum prepared from the blood of recovered CCHF patients or gammaglobulin obtained from immunization of horses.¹³ recently immunotherapy has also been attempted via passive transfer of CCHF survivor convalescent plasma.¹⁴ but these results are based on uncontrolled experiments and definitive evidence regarding their effectiveness is lacking.

The antiviral drug Ribavirin has shown benefits in in-vitro studies although it has not been approved by US FDA for Laboratory workers handling viral material are also at high risk of contracting the disease. CCHF thus has been classified as biosafety level 4, category A or B pathogen which could potentially be a bioterrorism tool. Thus universal precautions should be observed in the patient-care areas and the laboratory.

The suspected patient should be placed in isolation, 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.

DRUG THERAPY

Ribavirin (figure-6) is a guano sine 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. Aerosolized ribavirin is absorbed systemically, as indicated by the presence of measurable concentrations in the plasma. Clinical efficacy has been demonstrated for the treatment of infections caused by hemorrhagic fever viruses (with oral and intravenous formulations of ribavirin).

A major problem in using ribavirin is its side effects. Anemia is one. But the above-mentioned studies did not show any significant adverse effects that limiting the recommended dose for hemorrhagic fevers. Ribavirin is well absorbed from gastrointestinal tract and concentration of its major metabolite is higher in urine after oral administration than after intravenous route.

PREVENTION AND CONTROL

Groups of individuals who are considered to be at risk of contracting CCHF virus like animal handlers, abattoir workers, and veterinarians should use effective personal protective measures against tick bites. However, acaricide treatment of livestock in CCHFV endemic areas is effective in reducing the population of infected ticks. Permethrin-impregnated clothing should be used, trousers should be tucked into boots or socks, light-colored clothing should be worn to facilitate tick identification with use of insect repellants on exposed skin, and daily skin inspection for ticks are essential for prevention.¹⁰ Other groups who are at risk include those caring for CCHF patients.

In fact, the risk of nosocomial infection in health-care workers is well documented and can be extremely high, especially during the hemorrhagic period of disease.²³⁻²⁵ Protective clothing and gloves should be worn whenever skin or mucous membranes could be exposed to vermic animals, particularly when blood and tissues are handled. Unpasteurized milk should not be drunk. In meat, CCHFV is usually inactivated by post-slaughter acidification. It is also killed by cooking.

PREVENTION OF TRANSMISSION

In the absence of a vaccine, the only way to reduce infection in people is by raising awareness of the risk factors and educating

people about the measures they can take to reduce their exposure to the virus.

How to safely remove ticks

- Public health educational messages should focus on the following:
- Reduce the risk of animal-to-human transmission eliminating or at least controlling tick infestations on animals or in stables/barns;
- Quarantine for animals before they enter slaughterhouses or routine treatment of ruminants with pesticides 2 weeks prior to slaughter;
- Using masks, gloves and gowns when slaughtering and butchering animals.
- Reduce the risk of tick-to-human transmission
- Avoid tick bites (use of approved acaricide and repellent, appropriate clothing, frequent body inspection searching for ticks);
- Remove ticks safely from the skin.
- Reduce the risk of tick-to-human transmission in the community arising from direct or close contact with infected patients, particularly with their body fluid.

Close physical contact with CCHF patients should be avoided.

- Gloves and appropriate personal protective equipment should be worn when taking care of ill patients at home. Regular hand-washing after visiting sick relatives in hospital, as well as while taking care of ill patients at home should be carried out^[28]

CONCLUSION

From this report, the most important lesson to be derived is that late diagnosis decreases the efficacy of treatment and aggravates the outcome of the disease. Diagnosis of CCHF is important to prevent the spread of CCHF virus among the health-care workers and relatives of patients. Treatment with ribavirin may be useful if given within the early stage of disease²⁶. The presence of visceral bleeding is a predictor of poor prognosis. The other lesson to be learned from this case is that every febrile haemorrhagic syndrome encountered in endemic areas, such as parts of Kosova, should probably be considered to be viral haemorrhagic fever, until proven otherwise.



Fig. 1: viral effecting countrys (in Africa, Asia, South-East Europe and the Middle East)

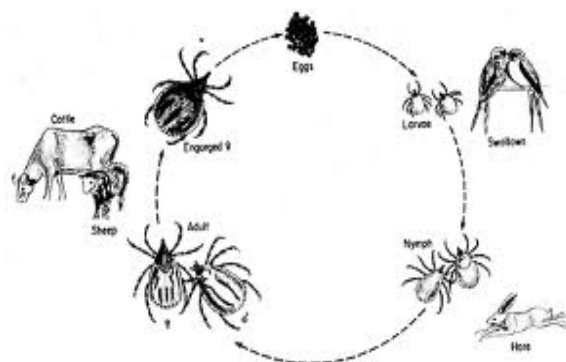


Fig. 2: Ticks spreading Cycle in animals



Fig. 3: After 3-5 days, hemorrhage begins and is Seen as a red or purple discoloration of the skin

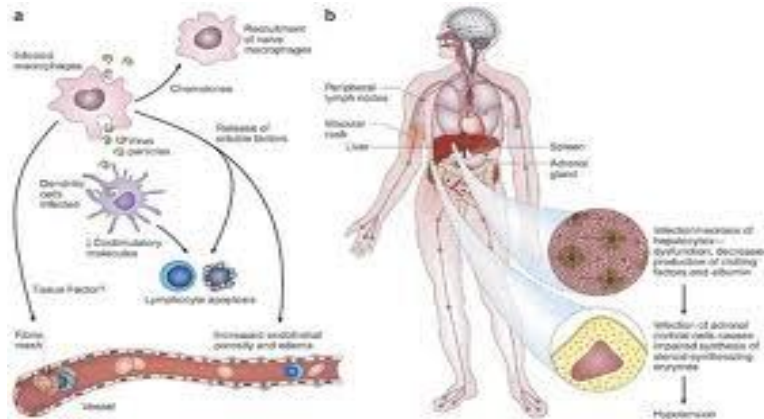


Fig. 4: Mechanism of Action of Viral Cycle in human

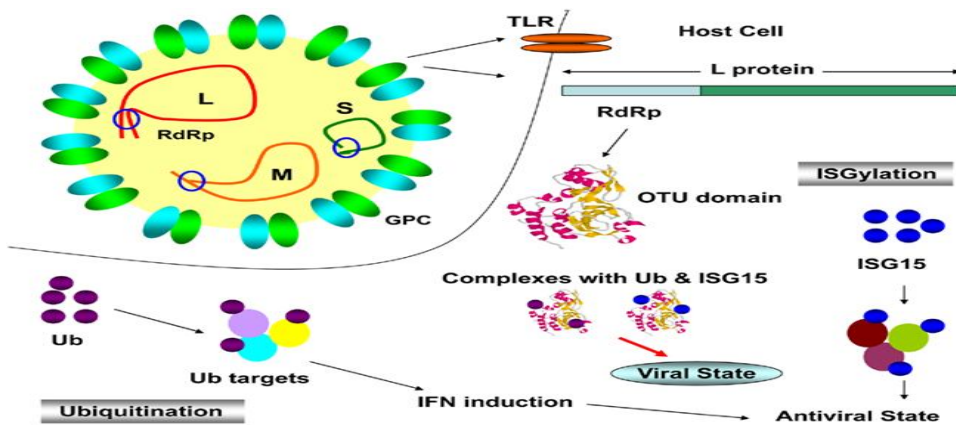


Fig. 5: Ribavirin action on the host cell of viral effected

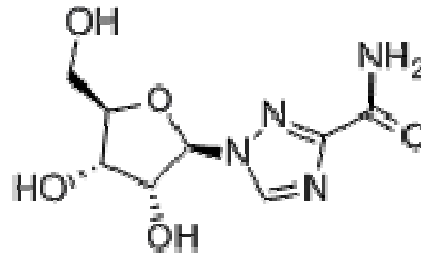


Fig. 6: Ribavirin structure

Removal of a Tick

Using a pair of tweezers, find where the tick's mouthparts have entered the skin. Place the ends of the tweezers around the base of the mouthparts and while applying gentle pressure pull the tick up slowly and steadily until it releases its hold. Dispose of the tick in a sealable plastic bag in the trash *outside* your home.

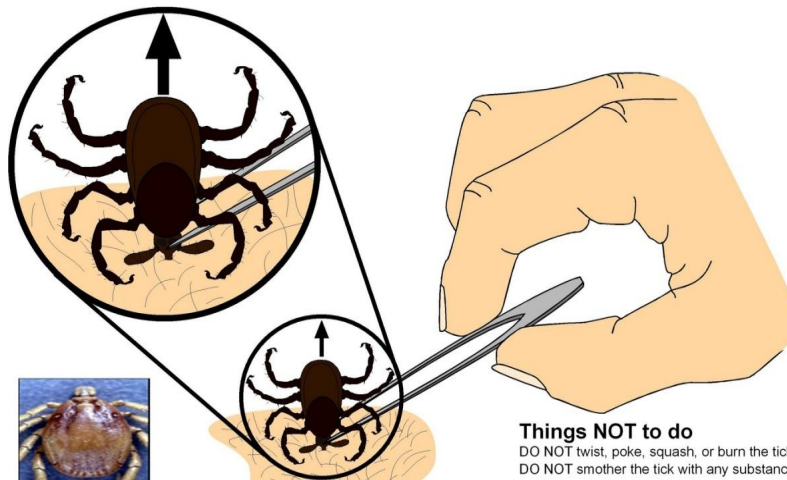


Fig. 7: removal of tick

Abbreviations

VHFs (viral hemorrhagic fevers)
 ELISA (enzyme-linked immunosorbent assay)
 RT-PCR (polymerase chain reaction)

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