

# Crimean-Congo Hemorrhagic Fever: Epidemiology, Pathogenic Mechanism, Treatment Approaches, Prevention and Control Strategies

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## ABSTRACT

Crimean-Congo hemorrhagic fever is a tick-borne viral zoonotic disease. Various domestic and wild animals serve as reservoir host. It infects humans by tick bites or handling of infected live infected stock. CCHF is found in many countries in Africa, Asia, Eastern Europe and Central Asia with case fertility rate of more than 30% in many regions. It was initially identified in the Crimean region of Russia in 1944 later in the Congo basin in 1967, and its first case in Pakistan was reported in 1976 in Rawalpindi. It is highly infective virus and have no specific treatment usually affecting host immune system making it susceptible to many other diseases. Many supportive treatments are used for its treatment like ribavirin, monoclonal antibodies and some corticosteroids. The main ways to prevent CCHF are to maintain hygiene practices. The main purpose of this review is to develop better understanding of the epidemiology, pathogenesis and prevention of CCHF virus as it is a serious zoonotic disease from past two decades and there is no appropriate animal model to study the disease.

### Introduction:

Crimean-Congo hemorrhagic fever is a tick-borne viral disease. CCHF virus belongs to the genus *Nairovirus* of the family *Bunyaviridae*. An important vector ixodid tick belongs to the *Hyalomma* genus infect more than 40 countries (1).

CCHF is found in many countries in Africa, Asia, Europe and Central Asia. Various domestic and wild animals, such as sheep, cattle, goats, small mammals, rodents and birds serve as reservoir hosts. These animals can carry the virus without showing significant symptoms (2).

CCHFV mostly infected humans through tick bites or handling and butchering live infected stock. Early symptoms are often nonspecific and can resemble those of other febrile illnesses. Case fertility rate can be higher than 30% in many regions. There are currently no specific treatment and vaccines are available (3).

### Epidemiology

CCHFV was first discovered in the Russian Crimean area in 1944, and then again in the Congo valley in 1967. Over fifty nations in Asia, Europe, Africa, and Central Asia have recorded cases of CCHFV (4). Pakistan saw its first incidence recorded in 1976 from a hospital in Rawalpindi. There were then eleven more cases, three of which resulted in deaths. In Pakistan, there were 356 instances between 2014 and 2020, with a 25% fertility rate. There were 38% of incidents from Balochistan, 23% from Punjab, 14% from Sindh, and 6% from Islamabad (1). In another research, the frequency was found to be 16.2% in Sindh, 52.4% in KPK, 59.3% in Balochistan, and 24.7% in Punjab. Due to animal contact, people who reside in rural regions are more likely to become sick. Within Pakistan, stains that are frequently observed in nearby nations like India and Iran frequently spread and disseminate. The chance of CCHF spreading is increased by several factors. It spreads more quickly because of the twice-yearly weather shifts that occur from March to May and from August to October. Those that move animals through cities, have nomadic lifestyles, have unclean slaughterhouses, lack of qualified personnel for animal care, and poor sanitation all contribute to the ease with which CCHF spreads (5).

### Pathogenesis

There is no appropriate animal model to study the disease, it primarily affects areas without access to modern medical care, and because of its high virulence, work on the disease must be done under containment at BSL-4. These factors contribute to the lack of understanding regarding the pathogenesis of CCHF. The majority of current knowledge is based on in vitro research and human case studies, with a large portion being extrapolated from knowledge of other viral hemorrhagic fevers (6).

The host's immune system is weakened by the hemorrhagic fever virus, making it more vulnerable to illness. Targeting antiviral cells causes the virus to replicate quickly and damage the vascular and lymphatic systems in order to do this. The main mechanism underlying the pathophysiology of CCHF is epithelial infection, whereby the epithelium is continuously harmed by viral replication. Indirectly, the virus activates endothelial cells and impairs normal cellular functioning by releasing tissue-toxic substances or producing host-

derived soluble factors. The intrinsic coagulation pathway is activated when platelets are drawn to the injured endothelium. Early signs and symptoms include clear endothelial dysfunction that leads to hemostatic failure (5).

### Treatment

There are not many treatment choices for CCHF. At present, the FDA has not licensed any particular antiviral treatment for use in humans with CCHF. Over time, ribavirin, an antiviral medication, has demonstrated the most potential. Furthermore, several reports of cases have been released, indicating that ribavirin administered orally or intravenously is a successful treatment for CCHFV infection (7).

Sidwell and colleagues developed ribavirin. Ribavirin is typically effective against viruses belonging to the *Bunyaviridae* family. Ribavirin significantly reduced mortality in patients with hemorrhagic fever and renal syndrome in a single prospective, randomized, double-blind, placebo-controlled trial conducted against a hemorrhagic fever virus (8).

For the treatment, of CCHF use Monoclonal antibodies These antibodies are neutralizing and non-neutralizing, and they are all generated by a single cell. Neutralizing antibodies bind to the virus and stop it from entering the cell. They target the Gc and Gn antigens of viruses. Non-neutralizing antibodies function via phagocytosis, NK-mediated killing, ADCC, and CDC. Antibodies that do not neutralize, like 13G8 mAb, target the p38 protein, which is produced when the CCHF glycoprotein is broken down by proteases (9).

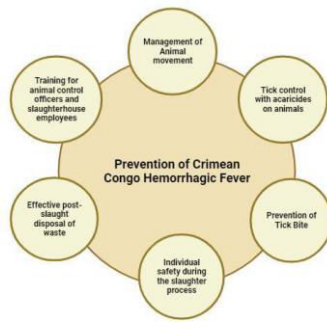
In Anti-inflammatory treatment, according to observations, high-dose corticosteroid medications like dexamethasone and methylprednisolone may minimize the negative effects of cytokine storms, including apoptosis, decreased immune and endothelial cell function, vascular leakage, DIC, organ failure, and increased permeability. By interacting with immunological and inflammatory cells like macrophages, corticosteroids also prevent the release of cytokines and other chemicals like lipid mediators, respiratory burst mediators, and nitric oxide. Patients with severe diseases are treated with corticosteroids. The severity of the disease is significantly decreased when corticosteroids are used together with other medicines, such as supportive therapies and antiviral medications. When combined with IVIG and FFP, methylprednisolone reduces macrophage activation and appears to suppress CCHF linked to Hemophagocytic lymphohistiocytosis (10).

### Prevention and control

Preventing or reducing viral exposure is the key to CCHF prevention and control. People who live in endemic areas and are susceptible to insect bites especially from *Hyalomma* ticks are thought to be at risk of developing CCHF. These would include people who labour outside, particularly those who manage animals (such as shepherds of sheep or goats). Tick reduction in endemic areas has been partially achieved through environmental cleanliness of underbrush habitats (11).

The main ways to prevent CCHF are to stay away from tick bites, wear personal protective equipment (PPE), and use insecticides in livestock production facilities to control the disease in animals. It is challenging to prevent and control CCHF in tick vectors and animal hosts. This is due to the

fact that ticks are common and numerous in endemic areas, however the illness in animals is asymptomatic. Before killing an animal, insecticides can be used to control ticks; moreover, a 14-day quarantine period before killing has also been employed. As of right now, there are no vaccinations available to protect animals (12).



**Conclusion**

CCHFV is a serious infective disease which can affect our immune system to make us susceptible to many other diseases. Its prevalence increases in different countries including Pakistan during past two decades. Currently there is no vaccination or medication is available to control this disease, but some supportive drugs are being used for treatment of infection i.e., ribavirin. The only way to prevent this infection is to maintain hygiene practices and handle animals with care especially at slaughter houses.

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