



An Overview of Crimean Congo Hemorrhagic Fever

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ABSTRACT

Crimean Congo hemorrhagic fever (CCHF) is a zoonotic disease. It is caused by an RNA virus in wild and domestic mammals, birds and ticks. It is the family of Bunyaviridae from Arbovirus group. The main vector and reservoir of CCHF virus are hard-body ticks principally of the *Hyalomma* genus. The *Hyalomma* tick bite infection has the highest rate of nosocomial transmission especially due to direct human to human contact. India reported its first CCHF case in the year 2011 from Ahmadabad, Gujarat. Since then, several sporadic cases and outbreaks of CCHF have been reported the most from Gujarat and few from Rajasthan and Uttar Pradesh States of India. Animals do not show clinical signs but may act as a source of infection for humans. The virus is transmitted from animals to humans either by direct contact with blood or tissue of infected animal. Laboratory tests used to diagnose CCHF include reverse transcriptase (RT)-PCR, immunofluorescence assay (IFA), antibody (IgG, IgM) and antigen-capture ELISA, and isolation of virus. Ribavirin acts as effective anti-viral agent against CCHFV by inhibiting its replication. Supportive therapy including the administration of erythrocytes, thrombocytes, and fresh frozen plasma acts as an important strategy to control CCHF at an early stage.

Key words:

Crimean Congo hemorrhagic fever,
Hyalommaticks,
Arbovirus, Bunyaviridae.

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INTRODUCTION

About the disease

Crimean Congo hemorrhagic fever (CCHF) is a widely distributed lethal zoonotic disease. It is caused by an RNA virus in wild and domestic mammals, birds and ticks. This virus has been classified as a Nairovirus genus in the family of Bunyaviridae from Arbovirus group. Sheep, goats and cattle develop high titers of virus in blood, but tend not to fall ill. Humans are usually infected with CCHF virus through a tick bite or close contact with viral contaminated tissues or with the blood of domestic animals or infected patients¹. Patient data and animal studies show that after an initial local replication, the virus spreads systemically and targets the liver and endothelium where it causes a massive dysregulation of the immune response sometimes culminating in hemorrhagic fever. Recently, CCHFV was designated as one of ten high priority emerging infectious diseases by the World Health Organization (WHO) due to its epidemic emergence potential and lack of approved medical countermeasures².

CAUSES

CCHFV is a member of Nairovirus genus of the Bunyaviridae family. It is enveloped spherical virus approximately 100 nm in diameter. The lipid envelope is host derived 5-7 nm thick, through which glycoprotein spikes, 8-10 nm in length protrude out. The genome, around 19.2 kb, consists of three segments of negative sense single stranded RNA segments designated as Large (L), Medium (M) and Small (S) and encode for viral polymerase.⁴ CCHF as a disease was first described in humans

in the 1940s when soldiers re-occupying abandoned farmland in the Crimea became ill with a hemorrhagic disease. In the late 1960s, it was discovered that the causative agent of this hemorrhagic disease in the Crimea was similar to the causative agent of hemorrhagic disease in the Belgian Congo (current Democratic Republic of the Congo), and the name "Crimean-Congo hemorrhagic fever virus" was ascribed to the pathogen. The main vector and reservoir of CCHFV are hard-body ticks principally of the *Hyalomma* genus, although there is limited evidence that other species of ticks such as *Rhipicephalus* and *Dermacentor* species may be vectors. Vertebrate hosts such as domestic livestock and wild animals such as hares likely serve as amplifying hosts of CCHFV, with uninfected ticks becoming infected during feeding on viremic animals or during co-feeding with infected ticks³.

EPIDEMIOLOGY

Crimean Congo Hemorrhagic Fever (CCHF), a zoonotic viral hemorrhagic fever is a cause of significant morbidity and mortality; especially in underdeveloped countries. Some species of Argasid Ornithodoros in Argasidae family have been reported to be infected. The highly lethal virus is known for producing devastating outbreaks in humans which are very common in areas with developing healthcare systems such as in Africa, Middle East Asia, and Balkans. CCHF outbreaks constitute a threat to public health services because of its prolonged and intense course of infection. It has epidemic potential, high case fatality ratio (10-40%), and difficulties in

treatment and prevention. The Hyalomma tick bite infection has a high rate of nosocomial transmission especially due to direct human to human contact. In Pakistan, sporadic outbreaks have been reported frequently, mostly due to contact with viremic livestock blood and nosocomial transmission. The hospital-borne spread has been associated with a lack of, or improper use of personal protective equipment when dealing with infected patients. It mostly occurs during early contact with an undiagnosed patient before taking appropriate protective measures. The first case of CCHF in Pakistan was reported in 1976 and since then continuous cases of CCHF have been emerging throughout the country. In Pakistan 2010, outbreak in Khyber Pakhtunkhwa (KPK) province precipitated and 100 cases were reported and had a 10% fatality rate. Similarly on 11 July 2014, in Hayatabad Medical Complex (HMC) ,Kpk, 8 patients died, out of which 6 were Afghan nationals and a nurse⁵.

India reported its first CCHF case in the year 2011 from Ahmedabad, Gujarat. Since then, several sporadic cases and outbreaks of CCHF have been reported mostly from Gujarat and few from Rajasthan and Uttar Pradesh States of India . Over some time, the majority of CCHF cases have been published from various districts of Gujarat thus making Gujarat an endemic state for CCHF disease in India. Though serological evidence against CCHF in humans has been reported in India , a systematic data on CCHF seroprevalence is lacking. CCHF IgG seropositivity of 5.4% in cattle and 10.99% in sheep and goats from most of the states of India has been recorded earlier without any remarkable difference between Gujarat and the other states thus indicating the prevalence of this virus throughout the country⁶.

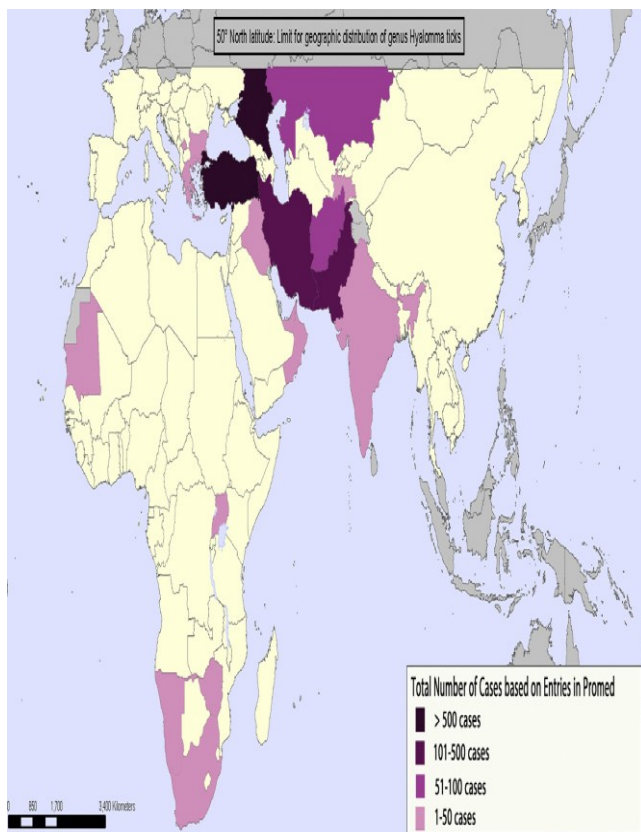


Figure 1. Total number of reported cases of CCHF by country, based on entries in Pro MED between the years 1998 and 2013 ⁷.

CLINICAL MANIFESTATIONS

Following a short developmental phase, the characteristics of the disease is; abrupt start of elevated fever, harsh head pain, chills, dizziness, abdominal and back trouble. Other signs include vomiting, nausea, and diarrhea, neuropsychiatric and cardiovascular alterations. Clinical symptoms of infection commonly include fever, hemorrhages and myalgia. Levels of liver (hepatic) enzymes are raised, and bleeding markers are frequently increased .The incubation time of disease starts from days to week; the duration mostly depends of on the transmission route of the disease as well as the quantity of inoculum. The pre-hemorrhagic period typically starts with headache, dizziness, vomiting fever, and myalgia and end after three days. The disease is shorter hemorrhagic fever stage and characteristics GIT-system blood loss, respiratory plus urinary tract furthermore blood loss from skin ranging from petechiae to ecchymosis. Additional signs comprise distended liver as well as spleen which round about 30% of patient's knowledge. The mortality rate can be reached up to seventy percent, but average is 30%⁸.

RISK FACTORS

The virus can be transmitted from person to person through contact with animal blood or products, contact with infectious body fluids of an infected person and by handling the infected ticks. The areas outside the range of tick distribution are at little or no risk of exposure to ticks. Crushing and rubbing the infected tick on skin or slaughtering the infected animal is also one of the main risk factors towards the exposure of CCHFV. Another well documented risk factor is nosocomial infection. This is most common among health care workers, particularly during the hemorrhagic period of the disease⁹.

TRANSMISSION

Transmission from tick or animal-to-human: Animals do not show clinical signs but may act as a source of infection for humans. The virus is transmitted from animals to humans either by direct contact with blood or tissue of infected animal. The tick biting or crushing of tick on skin or mucous membrane may be potential routes for transmission of CCHFV from tick to human.

Human-to-human transmission: Human- to- human transmission occurs by direct contact of virus contaminated blood or tissues from infected patient. This may occur primarily in hospital setting causing nosocomial infection. Aerosol or airborne infection is also reported in Russia. There may be horizontal transmission from a mother to her child which indicates the need of preventive measures for in-house outbreaks of CCHF⁴.

Vertical transmission: Tick vectors of CCHFV show the transfer of virus from adult females to males during fertilisation and from adult females to their eggs. CCHFV replicates in the mid-gut lining if ticks and spread to different body tissues such as salivary glands and reproductive organs. A large population of infected ticks is maintained because of transovarian transmission via thousands of eggs produced by females.

Horizontal transmission: Virus gains entry into human body through tick's bite or via direct contact with infected animal blood (veterinarians, slaughter house workers, And farmers etc.). Person-to-person transmission through different body fluids specifically blood, semen, and saliva has been observed. Three cases of sexual transmission among spouses have been

documented recently¹⁰.

PATHOPHYSIOLOGY

CCHF pathogenesis is likely derived from a complex interaction between the virus and host cells. Kupffer cells, hepatic endothelial cells, and hepatocytes are supposedly major targets in CCHF. The necrosis of hepatocytes leads to an increase in liver enzymes. A recent study on CCHF76 reports that the AST/ALT ratio is higher for patients with severe disease than for those with mild disease. Also, increased myeloperoxidase expression in leukocytes leads to increased leukocyte lysis. Therefore, leucopenia in patients with CCHF may be attributed to lysis. Endothelial damage can activate the coagulation cascade, which ultimately leads to diminished platelet numbers or function. Also, activation of coagulation may contribute to the development of disseminated intravascular coagulation (DIC) and multi organ failure. The leakage of the vasculature observed in CCHF occurs due to its direct infection by the virus or damage by secreted cytokines. Recent reports suggest higher levels of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α in patients with CCHF. Further, IL-6 and TNF- α level are higher in fatal cases, compared with nonfatal cases. Thus, endothelial damage may lead to hemostatic failure and characteristic skin rash¹¹.

Fig 2: Life cycle of *hyalomma ticks spp.* and horizontal and vertical transmission of CCHFV.⁸

DIAGNOSIS

Laboratory tests used to diagnose CCHF include reverse transcriptase (RT)-PCR, immunofluorescence assay (IFA), antibody (IgG, IgM) and antigen-capture ELISA, and virus isolation. Patients suspected of CCHF are primarily diagnosed by RT-PCR as these assays provide the highest detection sensitivity to active infection at the earliest time point. Lineage detection may be challenged by the high diversity and in situ evolution of CCHFV, particularly for RT-PCR assays which rely on a conserved genomic sequence for detection. Serological detection is less impacted by minor genomic variations. Given CCHFV strain variations, it is recommended that nucleic acid amplification tests (NAAT, eg, RT-PCR) be used in combination with immunological assays for highest detection sensitivity; however many low-resource settings may not have the capacity for PCR testing, especially at the early stages of an outbreak. Virus isolation is rarely used as a diagnostic tool because of the stringent biosafety containment level (BSL-4) required. NAAT typically requires the highest laboratory infrastructure, including bio safety hoods and a clean room or PCR workstation, while most serological tests (ELISA, IFA) can be run on the benchtop in a more modest laboratory environment. Ideally, point-of-care (POC) NAAT tests are fully automated, with samples delivered to an integrated cartridge that contains all the reagents necessary for sample processing and analysis; this process can be performed without a bio safety hood, depending on the sample preparation requirements (here defined as BSL-2 for human disease). Once the cartridge is inserted into the instrument, no further manual steps are required. Rapid diagnostic tests (RDTs) are typically designed for field or home use. Turnaround time for each test is specified by the manufacturer; turnaround time per result can include additional time (days to weeks) for sample transport and processing at the reference lab. Several commercial assays for PCR and serology are available (online supplementary table

S1 and S2), although the majority of international laboratories use inhouse assays, likely due to an investment in tests developed from regional CCHFV strains. It has also been suggested that commercial tests may be too expensive, difficult to order or not available to international customers. The majority of the inhouse assays have a publication history, several with published data on diagnostic performance or external quality assessment¹².

COMPLICATIONS

The main complications of CCHF are hematological complications. Most of the deaths are results of massive hemorrhagia, disseminated intravascular coagulation, and shock. Some other complications like hemophagocytosis and infections may be seen during the course of the diseases. The convalescence period begins 10 days after the onset of symptoms and may be longer. Although recovery is complete in CCHF, the long-term effect of the disease is not very well known. As the cases have increased around the world, some miscellaneous complications of CCHF are being reported. Compartment syndrome and orchitis are among some of the complications of CCHF. It can be complicated in many different ways such as acalculous cholecystitis and intraabdominal abscess¹³.

TREATMENT

Supportive therapy including the administration of erythrocytes, thrombocytes, and fresh frozen plasma acts as an important strategy to control CCHF at an early stage. Ribavirin acts as an effective anti-viral agent against CCHFV by inhibiting its replication.¹⁴ A recent study has demonstrated the synergistic effect of combination of two FDA approved molecules i.e., chloroquine or chlorpromazine and ribavirin against CCHFV.¹⁵ Another novel molecule MxA belonging to interferon induced GTPases family and dynamin superfamily inhibited CCHFV production and replication.¹⁶ DNA vaccination expressing Gc genes and Gn elicited neutralizing antibodies in mice; however, the efficacy in humans is still to be determined^{17,18}.

Vaccines

Currently, the only vaccine for CCHFV is an inactivated preparation of virus grown in neonatal mouse brains; however, this vaccine is used only in Bulgaria and is not approved for use in other countries with at-risk populations. The scalability and safety concerns of this type of vaccine will likely prevent widespread deployment of this vaccine, and new vaccine platforms for CCHFV are needed³.

PREVENTION AND CONTROL MEASURES

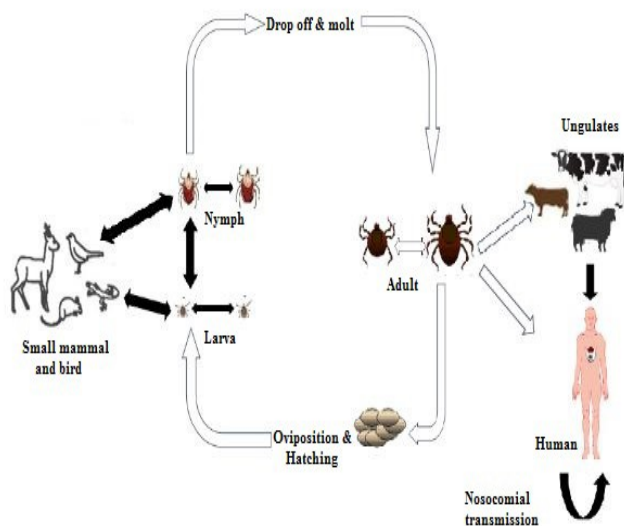
The mainstay of prevention and control of CCHF viral infection should target both at the community level and in the nosocomial set up. At the community level, care should be taken to prevent human contact with livestock and minimize the tick burden in these vertebrate hosts. Measures such as avoidance of tick habitat, regular examination of clothing and skin for ticks, and use of tick repellents should be taken to prevent tick bites. Fully covered clothing is recommended to prevent tick attachment to body parts. While handling livestock or domesticated animals, appropriate acaricidal agents should be used to control tick population. Protective clothing and gloves should be used whenever there is chance of contact with skin or mucous membranes of viremic animals, particularly when blood and tissues are handled. Consumption of

unpasteurized milk and uncooked meat should be avoided. Human-to-human transmission of CCHF virus is seen when direct contact with blood and body fluids occurs, especially in a healthcare setup when appropriate infection control measures are not taken. Strict universal precautions are necessary when caring for patients and this can be achieved by barrier nursing, isolation, and use of protective gears such as gloves, gowns, face-shields, and goggles with side shields. Safe burial practices, including the use of liquid bleach solution as a disinfectant, and covering the body in polythene bags have been published. Laboratory workers must follow stringent bio safety precautions and viral isolation techniques should be carried out in laboratories where bio safety level 4 is available. CCHFV can be inactivated by disinfectants including 1% hypochlorite and 2% glutaraldehyde; these can be destroyed by heating at 56°C (133°F) for 30 min. Prophylactic treatment with ribavirin has occasionally been used after high-risk exposures but its role is controversial¹⁹.

ROLE OF PHARMACIST

Improving the public awareness and helping them to avoid exposures to that causative organism.

Pharmacists are accessible and often make up the front line of health care professionals who patients afflicted with these infections contact for advice on treatment remedies. Although, not all zoonoses are fatal, they can cause significant morbidity and mortality if left untreated. Therefore, pharmacists must have an understanding of the epidemiology and common manifestations associated with zoonoses, particularly those that are common in their locality. Having this understanding enables pharmacists to effectively counsel the patient and



recommend appropriate preventive measures²⁰.

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