

## Review Article

# Crimean-congo haemorrhagic fever: a global perspective

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### ABSTRACT

Crimean-Congo Haemorrhagic Fever (CCHF) is caused by infection with a tick-borne virus (Nairovirus) in the family Bunyaviridae, causing severe and often fatal haemorrhagic fever in humans. CCHF is pervasive, now found in Europe, Asia, Africa, the Middle East and the Indian subcontinent. CCHF spreads to humans either by tick bites or by contact with blood and tissues from infected animals or humans. CCHF outbreaks constitute a threat to public health services because of its epidemic potential, its high case fatality ratio (10-40%), and its potential for nosocomial outbreaks and its quandaries in treatment and prevention. It is characterized by sudden onset with initial sign symptoms including fever, chills, agitations, myalgia, headaches, vomiting, abdominal pain, arthralgia, ecchymosis, melena, haematuria, nose bleeding, vaginal bleeding, bradycardia, thrombocytopenia. It is diagnosed by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) assay, ELISA test, antigen detection tests. Overall supportive therapy is the mainstay of patient management in CCHF. Seriously ill patients require intensive care. Ribavirin for the treatment of CCHF cases it is most effective, if administered very soon after the onset of clinical signs (e.g., during the first 48 hours). Prevention should be taken which reduce risk of tick to human transmission and human to human transmission.

**Keywords:** Clinical manifestations, Crimean-congo haemorrhagic fever, Crimean-congo haemorrhagic fever virus, Diagnosis, Epidemiology, Pathogenesis, Prevention, Treatment

### INTRODUCTION

Crimean-Congo Haemorrhagic Fever (CCHF) is one of the high-priority pathogens recognized on the WHO R and D Blueprint because of its high case fatality rate, possible for nosocomial outbreaks and difficulties in treatment and prevention.<sup>1-3</sup>

Crimean-Congo Haemorrhagic Fever (CCHF) is caused by infection with a tick-borne virus (Nairovirus) in the family Bunyaviridae, causing severe and often fatal haemorrhagic fever in humans.

The disease was first characterized in the Crimea in 1944 and given the name Crimean hemorrhagic fever, but the

virus was first isolated in Congo in 1956 and was named.<sup>4,1</sup>

The normal cycle of CCHFV includes transovarial and transstadial transmission among tick and a tick-vertebrate - tick cycle include a variety of wild and domestic animal. Infection can also be transferred between infected and uninfected tick during co-feeding on a host so named "Non viraemic transmission" phenomenon.<sup>5</sup>

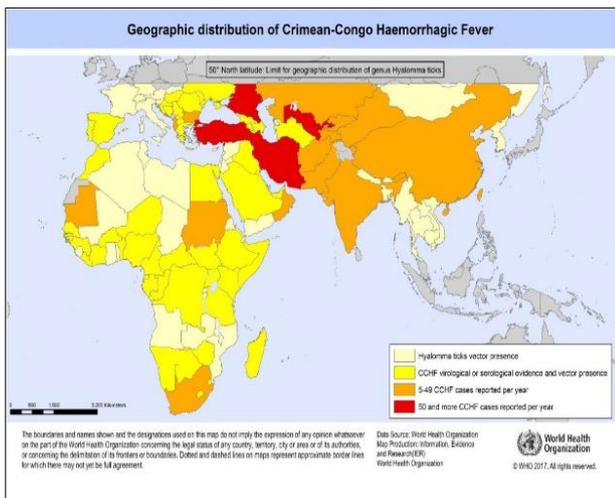
CCHF is considered an 'emerging' disease across the globe, with many countries, reporting new infections in current decades.<sup>6,7</sup> CCHF is pervasive, now found in Europe, Asia, Africa, the Middle East and the Indian

subcontinent, with currently no vaccine available for widespread human or animal use.<sup>8,9</sup>

### Geographic distribution

CCHF appears to be prevalent in Africa, the Middle East and Asia, and also occurs in parts of southern and eastern Europe. Different clades and strains circulate in different regions (Figure 1). This virus appears to be preserved only where ticks of the genus *Hyalomma* are recognized. Within Europe and Asia, evidence for its presence has been reported as far north as Spain, Portugal, Hungary, Romania, Bulgaria, Ukraine, Kosovo, Albania, Macedonia, southern Russia, Mongolia, Kazakhstan and Uzbekistan, although human clinical cases have not been prominent in all of these countries. While *Hyalomma* ticks are found infrequently in northern Europe and Asia, perhaps after transport on migrating birds, these regions are considered inhospitable for the perpetual establishment of *Hyalomma* species.<sup>10</sup> In SEAR, the first laboratory confirmed case was reported on 19 January, 2011 in Gujarat state of India bordering with Pakistan.<sup>11,12</sup>

The National institute of Virology (NIV) has confirmed cases of CCHF in Rajasthan and Gujarat in August. CCHF kills up to 30% of those infected. “Of the 80 samples that author received for confirmatory testing, 78 samples were from Gujarat and two from Rajasthan. Most of the positive cases are from Gujarat, and only one case tested positive from Rajasthan,” said a source in the NIV. The NIV is country’s apex laboratory running under the Indian Council of Medical Research. It receives samples from states for confirmatory tests during any outbreaks.<sup>11</sup>



**Figure 1: Geographic distribution of Crimean-Congo Haemorrhagic Fever.**

### RISK FACTORS

- History of tick bite

- Having contact with livestock
- High risk occupations. (Livestock handlers, veterinary staff, livestock market workers, and people engaged in jobs requiring some contact with animals and/or animal products are significant risk factors in CCHF.<sup>13</sup>

The majority of cases have arisen in people intricate in the livestock industry, such as agricultural workers, slaughterhouse workers and veterinarians. Even rare contact with livestock could be effective in transmission of virus.

Increasing number of cases have occurred among the medical and nursing staff caring for patients infected with CCHF in hospital and in laboratory personnel carrying out investigations of these patients. In these cases the infection has apparently been developed by contagion, particularly by contact with the patient's blood or contaminated blood specimens. It is stated that utmost dangerous conditions for acquiring CCHF in nosocomial setting are interventions for controlling gastrointestinal bleedings and emergency operations in patients who have not been diagnosed with CCHF virus before operation. CCHF has also occurred in hospitals due to improper sterilization of medical equipment, reuse of injection needles, and contagion of medical supplies. There is also possibility of horizontal transmission of CCHF virus from mother to child. As for all vector-borne diseases, environmental factors, human behavior and climate are life-threatening determinants for the establishment and preservation of CCHF endemicity in an area. The fluctuations in climatic conditions is one of the factors that has aided in survival of a large number of *Hyalomma* ticks and of the hosts of both immature and adult stages and consequently increase incidence of CCHF. The global warming will make the world as a better place for parasites, biting flies or ticks which serve as vectors of diseases persist alive throughout the year and that increases the risk of occurrence of CCHF. It is specified that high mortality rates of CCHF may indicate its usage as bioterrorism agent. CCHF virus has been listed in US as CDC/NIAID category C priority pathogen.<sup>14</sup>

### CAUSES AND MODE OF TRANSMISSION

Crimean-Congo hemorrhagic fever (CCHF) spreads to humans either by tick bites, or by contact with blood and tissues from infected animals or humans. CCHF outbreaks constitute a threat to public health services because of its epidemic potential, its high case fatality ratio (10-40%), and its potential for nosocomial outbreaks and its quandaries in treatment and prevention.<sup>15</sup>

#### Mode of transmission

##### Animal to human transmission

Human beings may acquire the CCHF virus by direct contact with blood or other tissues of infected livestock

or they may become infected through a tick bite or crushing of infected tick.

*Human to human transmission*

Person to person transmission can occur, especially during close contact. Humans can become infected if blood, body fluids and wastes from patients with the disease comes into contact with broken skin or mucous membranes, as occurs when medical care personnel sustain accidental needle stick injury. Hemorrhages from severely ill patients are a significant source of exposure for relatives and healthcare workers.

Viral RNA has also been detected in saliva and urine, and occasionally and in low amounts in conjunctival, nasal and rectal swabs. Sexual transmission was proposed to be the source of the illness in a few cases. In advanced stages of the disease, aerosol contact of blood of the patient can also lead to transmission of the virus.<sup>15,16</sup>

*Population at risk*

In endemic countries, majority of cases have occurred in those involved with the livestock industry, such as agricultural workers, slaughterhouse workers and veterinarians. Health care workers attending on suspect / probable/ confirmed CCHF cases and not following contact precautions are at high risk of getting infection. Hospital acquired infection outbreaks (Nosocomial infections) have been stated in many countries.

*Transmission cycle*

CCHF virus circulates in an enzootic tick vertebrate tick cycle, and there is no evidence that the virus causes disease in animals.

*Incubation period*

The incubation period for the illness depends upon the mode of acquirement of the virus. Following infection via tick bite, the incubation period is usually one to three days, with a maximum of nine days. The incubation period following contact with infected blood or tissues is usually five to six days, with a documented maximum of 13 days.<sup>10</sup>

*Communicability*

Highly infectious in the hospital settings. Nosocomial infections are common after exposure to blood and secretions.

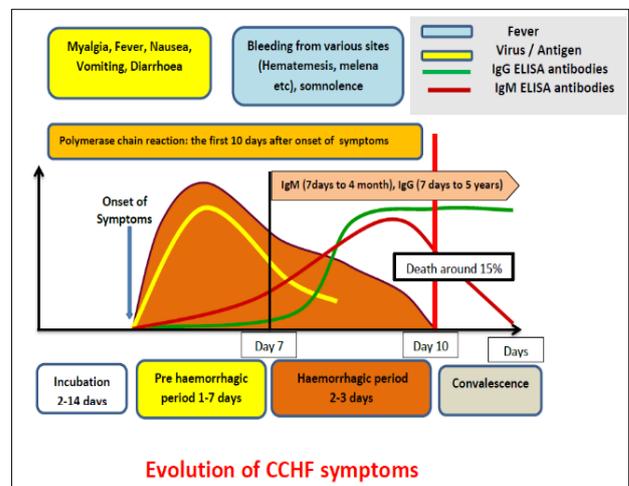
*Susceptibility*

Immunity after infection is probably lifelong.<sup>16</sup>

**SIGN AND SYMPTOMS**

Sudden onset with initial sign symptoms including fever, chills, agitations, myalgia, headaches, vomiting, abdominal pain, arthralgia, red eyes, flushed face, sore throat, petechiae on the palate, jaundice is common and changes in mood and sensory perception in severe cases. As the illness progresses (after a few days) bleeding from mucous membranes, hematomas, ecchymosis, melena, hematuria, nose bleeding, vaginal bleeding, bradycardia, thrombocytopenia, leukopenia uncontrolled bleeding at injection sites can be seen. In documented outbreaks of CCHF, fatality rates in hospitalized patients have ranged from 9% to as high as 50%.<sup>15,17</sup>

*Evolution of CCHF*



**Figure 2: Evolution of CCHF.**

**DIAGNOSIS**

Early diagnosis is an essential requirement, not only for patient management but also for prevention of further transmission of disease, as it is a highly contagious disease.<sup>18</sup>

*Definitive diagnosis requires testing,*

- Reverse transcriptase polymerase chain reaction (RT-PCR) assay.<sup>4</sup>
- The ELISA test is considered the most sensitive and specific. IgG and IgM antibodies may be detected in serum by ELISA from about six days of illness. CCHF is confirmed either by detection of specific IgM antibodies or a four-fold increase of IgG titers.<sup>4, 14,16,19</sup>
- Antigen detection tests.
- Virus isolation by cell culture.<sup>15</sup>
- Other laboratory investigations showed cytopenia, raised prothrombin time (PT) and activated partial thromboplastin time (aPTT), raised creatinine phosphokinase (CPK) and lactic dehydrogenase (LDH) as well as altered

liver and renal functions. Patients with above symptoms can rapidly progress to bleeding from multiple sites and death.<sup>16</sup>

- High serum ferritin levels have also been reported as indicator of severity of disease.<sup>20</sup>

## TREATMENT

Overall supportive therapy is the mainstay of patient management in CCHF. Seriously ill patients require intensive care. Early aggressive intensive monitoring is required i.e. monitor fluid, electrolyte balance, renal function, blood pressure, and oxygenation, and careful rehydration. Support of coagulation system with blood component therapy.

The WHO recommends Ribavirin for the treatment of CCHF cases. This drug Ribavirin is believed to improve the prognosis and most effective, if administered very soon after the onset of clinical signs (e.g., during the first 48 hours). Both oral and intravenous formulations seem to be effective.<sup>10,21</sup> Passive immunotherapy with hyperimmune serum has been tested in a few cases, but the value of this treatment is controversial.<sup>21</sup> Favipiravir, alone or in combination with ribavirin, appears to be promising in animal models but had not been tested in humans.<sup>10</sup>

Supportive drug therapy including: Analgesics, Antiemetic for vomiting, anxiolytic for agitation, antibiotics and/or antimalarial drugs.<sup>15</sup>

## PREVENTION

### *Reducing risk of ticks to human transmission*

- Protect yourself from tick bites
- Avoid tick infested/ habitat areas.
- Wear light colored clothing for easy finding of ticks on clothes.
- Wear clothing that minimizes skin exposure or protective clothing (e.g., long-sleeved shirts, long pants tucked into boots).
- Use chemical repellent with DEET and acaricides on boots and clothing.<sup>21</sup>
- Clothing and skin should be examined regularly for ticks, which should be removed. Whenever possible, this should be done without touching the tick with bare hands.
- Environmental modification around dwellings (e.g., removal of brush and long grass, insecticides) might be appropriate in some circumstances.<sup>10,15</sup>

### *Safely remove the ticks*

- Use fine-tipped tweezers.
- Grasp the tick as close as possible to the skin.
- Do not twist or jerk the tick.

- Gently pull straight up until all parts of the ticks are removed.
- Wash hands with soap and water.
- Apply antiseptic on tick bite or clean with soap and water.
- Never press a tick with fingers.<sup>10,15</sup>

### *Reducing human to human transmission*

- Avoid contact with infected CCHF patients and deceased.
- Wash hands regularly with soap and water.
- Encourage early treatment in CCHF Treatment Center.
- Use gloves and mask and practice hand-hygiene when caring for suspected CCHF patient at home.
- Seek health advice.<sup>15</sup>

### *Prevention in animal setting*

- Protective clothing and gloves should be worn during exposure to viremic animals, particularly when blood and tissues are handled, and the hands should be washed instantly afterward.
- Reduce ticks in the environment by using acaricide (tick killer) in farms and livestock production facilities to decline tick infestations on animals or in sheds.
- Tick control with acaricides is only an accurate option for well-managed livestock production facilities.
- Quarantine for animals before they enter slaughterhouses or routinely treat ruminants with acaricides 4 weeks prior to slaughter. This activity will reduce the risk of the animal being viraemic during slaughter.
- Wear mask, gloves and gowns when slaughtering and butchering animals in slaughterhouses or at home to prevent skin contact with infected animal tissue or blood.
- Unpasteurized milk should not be drunk.
- CCHFV is thought to be inactivated in meat by post-slaughter acidification; however, some conditions such as chronic stress may reduce acidification, and two recent cases were associated with eating freshly slaughtered raw meat acquired from a butcher. Holding meat at 4-8°C for 24 hours after slaughter has been recommended. It is safest to always cook meat and other animal tissues thoroughly, and to use good hygiene (e.g., hand washing, avoidance of mucous membrane contact) when preparing them for cooking.<sup>10,15</sup>

### *Standard barrier nursing precautions*

The standard barrier nursing precautions should be employed at a minimum, when caring for human patients.

Some countries may recommend higher standards. The use of a N95 or equivalent respirator, eye protection, and single airborne precaution room or well-ventilated setting has been advised during any medical procedure that may produce aerosols or droplets. Safe burial practices have been published for fatal cases.

Laboratory workers must follow stringent biosafety precautions. People who have had high-risk exposures are often treated prophylactically with ribavirin, and a recent retrospective analysis suggests it has been effective in preventing illnesses. Post exposure prophylaxis with hyper immune serum is reportedly used in some countries.<sup>10,19,22</sup>

#### **Community engagement and awareness**

- Engage with communities to promote desired health practices and behaviors, including reduction of ticks exposure and safe meat preparation.
- Provide accurate and timely health advice and information on the disease.<sup>15</sup>

#### **DISCUSSION**

CCHF is a disease of public health significance with a high mortality rate that had risen in incidence and exposed geographical spread over the past decade. The present scenario in India proposes the prerequisite to look seriously into numerous important aspects of this zoonotic disease, which includes recognizing areas at risk, diagnosis, intervention, patient management, vaccine development, control of laboratory acquired and nosocomial infection, tick control, livestock survey and this, should be done in primacy before it further spreads to other states.

According to ecological models, the rise in temperature and drop in rainfall in the WHO EMR could result in a sharp rise in the distribution of suitable habitats for Hyalomma ticks and subsequently drive CCHF infection northwards. Thus, the development and implementation of a strategic framework for the prevention and control of CCHF is important to curtail the on-going and new threats posed by CCHF.<sup>6</sup>

The case fatality rate is thought to be approximately 5-30% in most instances, although rates as high as 80% have been reported occasionally in limited outbreaks. Factors such as the availability and quality of healthcare, virus dose, route of exposure, coinfections, and possibly the viral strain, are thought to influence mortality.

In the past, nearly all cases of Crimean-Congo hemorrhagic fever were thought to be severe. However, serological surveys have revealed the existence of milder illnesses or subclinical infections in <2% to 30% of the population in some endemic regions.<sup>10</sup>

A comprehensive national strategy on CCHF cutting across all pertinent sectors with highlighting on strengthened surveillance, rapid response to protect valuable human lives, partnership building and research to guide public policy is needed.<sup>14</sup>

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