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Crimean–Congo Haemorrhagic Fever (CCHF): A Zoonoses

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A B S T R A C T

Crimean-Congo haemorrhagic fever (CCHF), a serious human disease with short incubation period, is the most wide spread tick-borne viral infection of man. It is caused by a negative-sense RNA virus (Nairovirus genus) in the *Nairoviridae* family within the Bunyavirales order. The CCHF virus (CCHFV) is transmitted mainly by ticks of *Hyalomma* spp. The disease is zoonotic and was first described in humans in 1940s in former Soviet Union. The disease was reported in India in 2011 with involvement of *Hyalomma anatolicum* ticks. Antibodies to CCHFV have been demonstrated in livestock including bovines, sheep and goat. A detailed review is being presented on CCHF including its epidemiology, pathogenesis, diagnosis, prevention and control measures. Humans are infected by tick bites, contact with animal blood, and also during handling of infected/ sick animals. The infection can also be nosocomial. Biosafety and Biosecurity measures including sanitation and control of ticks would be of much help in bringing CCHF under control.

Introduction

Crimean-Congo haemorrhagic fever (CCHF), is a serious tick-borne viral infection of man. It occurs over larger parts of XinJiang region of China, Middle East region, Southern Russia, Africa, Asia, Southern and Eastern Europe including the Iberian region (Leblebicioglu, 2010; Dowall *et al.,* 2017; Hawman and Feldman, 2018). The first outbreak of a disease as a Crimean haemorrhagic fever was described in 1944–1945, when military personnel in former Soviet Union were infected in Crimea region. The Crimean haemorrhagic fever virus and Congo virus (isolated in Congo in 1956) shared antigenic similarity. Therefore, the disease was subsequently renamed as Crimean-Congo haemorrhagic fever (CCHF) and the virus as Crimean-Congo

haemorrhagic fever virus (CCHFV) (Ergonul, 2006; Peyrefitte *et al.,* 2015). CCHF is a severe haemorrhagic fever caused by CCHF virus of the genus *Nairovirus (*family *Nairoviridae within* Order *Bunyavirales).* Several genera of *Ixodid* ticks act as vector and reservoir for CCHFV. However, *Hyalomma spp* ticks play an important role in the transmission of this virus (Whitehouse, 2008). The natural reservoir and vector for CCHFV are mostly *Hyalomma* ticks; Role of other ticks such as *Rhipicephalus, Boophilus, Ixodes* and *Dermacentor* species acting as vectors cannot be ruled out (Bente *et al.,* 2013; Leblebicioglu *et al.,* 2016). CCHFV usually circulates in an enzootic tick-vertebrate-tick cycle. The virus amplifies in various mammalian species that remain asymptomatic. Ticks get infected at any stage of life-cycle during feeding on viraemic animals. Humans are infected by tick bites and other contact means.

The infection can also be nosocomial. The incubation period is short; 3-7 days. This infection was considered as a threatening emergence in humans (Fillâtre *et al.,* 2019). The CCHFV exhibits wide genetic diversity.5% difference at the amino acid level at nucleoprotein and L protein and up to 25% in the glycoprotein precursor is noticed (Bente *et al.,* 2013). The evaluation of therapeutic candidates for CCHF has been hindered due to the lack of an animal model for CCHF in humans. Many animal models that have been evaluated so far develop viraemia upon infection, but do not develop any clinical features of the disease. The mammals lacking a fully functional immune system, including neonatal mice, signal transducer and activator of transcription 1 (STAT-1) knockout mice and interferon α/β receptor (IFNAR−/−) knockout mice upon CCHFV infection develop the disease (Mendoza *et al.,* 2018). The new born mouse model of CCHFV has been used to study disease pathogenesis, efficacy of treatments and transmission dynamics of the virus via ticks (Logan *et al.,* 1989; Tignor and Hanham, 1993). STAT-1 and IFNAR−/− knockout mice have both recently been used as lethal models of CCHF disease (Zivcec *et al.,* 2013).

The Virus

The CCHF virus is widely distributed in Africa, Southern and Eastern Europe, the Middle East and Asia' (Hawman and Feldmann, 2018). The virus was first isolated in 1968 and is a lethal one (Dowall *et al.,* 2017). The CCHFV is a negative-sense RNA virus in the Nairoviridae family within the Bunyavirales order (ICTV taxonomy, 2018 release),the name is derived from Nairobi sheep disease which causes Nairobi sheep disease orthonairovirus (ICTV, 9th Report, 2011).In 2017, the ICTV reclassified the family Bunyaviridae as order Bunyavirales. All five genera of the former family Bunyaviridae (Hantavirus, Nairovirus, Orthobunyavirus, Phlebovirus, Tospovirus) are now novel viral families, viz., Hantaviridae, Feraviridae, Fimoviridae, Jonviridae, Nairoviridae, Peribunyaviridae, Phasmaviridae, Phenuiviridae, and Tospoviridae. The virus contains three genomic segments *viz.,* small, medium, and large that encode for the nucleoprotein, glycoprotein, and RNA-dependent RNA-polymerase, respectively (Whitehouse, 2008). The genus *Nairovirus* contains the Crimean-Congo hemorrhagic fever group (CCHFV and Hazara virus) and the Nairobi sheep disease group (Nairobi sheep disease virus -NSDV and Dugbe virus (García-Sastre and Endy, 2009). Both CCHF and NSD group viruses are transmitted primarily by ticks sometimes virus has also been isolated from culicoides, flies and mosquitoes. For most Nairoviruses, it is still to be explored whether they are pathogenic for humans (Whitehouse, 2008).

Dugbe virus (DUGV) which is genetically close to CCHFV and mildly pathogenic virus.

The genome of Nairoviruses is much larger compared to other genera members because of double the size of L segment (Strauss and Strauss, 2008). There are seven species in this group with distinct names having multiple strains. The Nairobi sheep disease virus, first identified as the causative agent of the disease in 1917, transmitted by the tick *Rhipicephalus appendiculatus*, having symptoms of acute gastro enteritis and hemorrhagic symptoms in sheep and goats, with mortality over 90%. Humans can be infected by the virus with mild illness. The Ganjam virus present in India is closely related to this virus that causes disease in sheep and goats which is transmitted by the tick *Haemaphysalis intermedia*. Members of *Nairoviridae family* are enveloped and spherical with diameter of 80 to 120nm, and have three segments of Negative-stranded RNA linear genome; L segment is between 6.8 and 12 kb, M segment between 3.2 and 4.9 kb and S segment between 1 and 3 kb. The gene segments code for four to six proteins. The gene fragments are covered by the copies of the nucleoprotein. The nairovirus genome consists of three segments of single-stranded, negative-sense RNA, designated large (L), medium (M) and small (S). These genome segments encode four structural proteins; the L segment codes for RNA-dependent RNA polymerase, the M segment encodes two structural membrane glycoproteins Gn and Gc, and the S segment encodes the nucleocapsid protein N. Non-structural proteins encoded by the M segment are synthesized as products of the processing of the glycoprotein precursor. Like Bunyaviruses, the 3′ and 5′ terminal sequences of each genome segment are conserved and complementary to each other, forming a pan-handle structure with conserved polymerase binding sites. Virus replication occurs in the cytoplasm of infected cells, and viral particles bud principally through the Golgi apparatus (Peyrefitte *et al.,* 2015). The viral glycoproteins contain receptor-recognition sites and influence viral cell tropism and the ability of the viruses to infect vertebrate and tick hosts.

The viral RNA dependent RNA polymerase (L protein) binds to a promoter on each encapsidated segment, and transcribes the mRNA. The virus attaches to host receptors though Gn-Gc glycoprotein dimer, and is endocytosed into vesicles in the host cell. Transcription is terminated by a strong hairpin sequence at the end of each gene, and the transcripts are capped by L protein during synthesis using cap snatching process in the cytoplasm.

Transmission and Epidemiology

CCHFV circulates in tick-vertebrate-tick cycle which is the most widespread tick-borne virus on earth, and it is a matter of concern that the geographic distribution of *Hyalomma* ticks is expanding. Migratory birds play an important role in disseminating Hyalomma ticks into northern parts of Europe and exposing naïve human populations to CCHFV (Dowall *et al.,* 2017). The virus is maintained by tick-mediated transmission between several species of vertebrate including wild and domestic mammals, viz., ungulate livestock, rabbits, mice, birds and hedgehogs etc. These animals develop transient viraemia and remain asymptomatic. Direct transmission to humans occurs during slaughter and butchering of CCHFV positive animals. Infection of human beings also occurs through tick bite, and exposure to the blood or other body fluids of an infected CCHF patient (Whitehouse, 2004; Dowall *et al.,* 2017). The eradication of the tick vector has been inefficient to control CCHF (Keshtkar- Jahromi *et al.,* 2011). It is difficult

to control CCHFV by culling domestic animal host reservoirs like cattle, goats and sheep, as they remain asymptomatic even when highly viraemic (Whitehouse, 2004).

Geographic distribution of CCHF coincides with that of *Ixodid* ticks. *Hyalomma marginatum* and *Hyalomma asiaticum* are the main CCHFV vector in Europe and Asia, respectively (Al-Abria *et al.,* 2017). CCHF is the most widely distributed tick-borne viral infection in different parts of Asia, Africa, the Middle East, Eastern Europe and the Balkans (Ergonul, 2006). The disease was reported in Gujarat, India in 2011 with involvement of *Hyalomma anatolicum* ticks (Mourya *et al.,* 2012) and subsequently in Sirohi, Rajasthan in 2014 in India (Makwana *et al.,* 2015), Shanmugam *et al* (1973) tested 655 serum samples collected from sheep, horse, goat and other domestic animals from all over India, of which 34 showed evidence of CCHFV antibodies. In another study, 5,636 (4,781 bovine and 855 sheep and goat) animal serum samples from 22 states and 1 union territory were tested for CCHFV IgG; Overall, 260 (5.43%) of 4,781 bovine samples and 94 (10.99%) of 855 sheep/ goat samples tested positive for CCHFV IgG (Mourya *et al.,* 2015). The first case of CCHF in Pakistan was reported in 1976 and an additional 14 cases were reported during 1976–2010, and since then, an increase in the incidence of CCHF has been reported (Haider *et al.,* 2016). Human-to-human transmission of CCHFV has been reported in nosocomial settings with high mortality among health care workers (Conger *et al.,* 2015; Al-Abria *et al.,* 2017). Serological studies among livestock have indicated the presence of the disease in Iran, Egypt, Somalia, and Tunisia. The disease is endemic in Afghanistan, Iran, Pakistan, Sudan, Saudi Arabia and United Arab Emirates (UAE). Role of migratory birds, mice, cats, and dogs in CCHF transmission remains to be elucidated (Al-Abria *et al.,* 2017). A CCHFV strain, AP92, was isolated from *Rhipicephalus* bursa ticks collected in 1975 from goats in Vergina village in northern Greece (Ergonul, 2006). Seropositivity in humans in Greece was linked to the Rodopi strain of the virus that differs genetically from the AP92 strain, which is considered as non-pathogenic or of low pathogenicity for humans (Papa *et al.,* 2010; Sidira *et al.,* 2011).

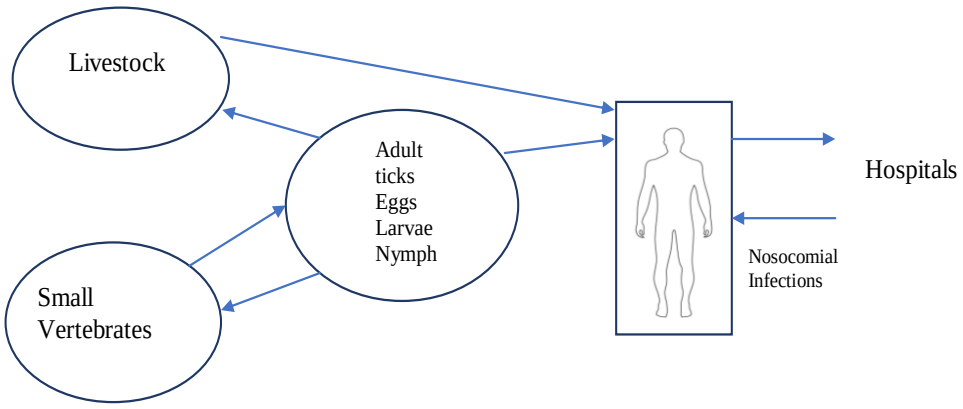
The disease and pathogenesis

Crimean–Congo haemorrhagic fever (CCHF) is a widespread tick- borne viral zoonosis with a case fatality rate of 9- 50% in humans (Mendoza *et al.,* 2018). CCHF virus remains a risk group- 4 pathogen for its ability to cause severe to fatal disease in humans and the absence of effective options for pre- or post- exposure prophylaxis. Therefore, CCHF virus is still deemed a possible weapon for bioterrorism (Bronze *et al.,* 2002). The highly haemorrhagic and pathogenic nature of CCHF virus makes it to terror that in the hands of terrorists, it may be utilized as bioweapon and bioterrorism which is classified as category C infectious agent (Munibullah *et al.,* 2018).

CCHF is an emerging disease with increasing incidence and geographic range since its identification (Dowall *et al.,* 2017). 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 haemorrhagic disease (Hoogstraal, 1979). In the late 1960s, it was later known that the causative agent of this disease in the Crimea was similar to the causative agent of haemorrhagic disease in the Belgian Congo (Democratic Republic of the Congo) (Casals, 1969), and the virus was named as “Crimean–Congo haemorrhagic fever virus”. Vertebrate hosts such as domestic livestock and wild animals such as hares serve as amplifying hosts of CCHFV, and ticks get infected

during feeding on viraemic animals (Gargili *et al.*, 2017). The *Hyalomma* vector is found throughout Africa, Southern and Eastern Europe, Asia including the Middle East and India. Cases of CCHF are reported throughout these regions, and an estimated 10,000 to 15,000 human infections with CCHF virus occur each year, although most of these are subclinical and unrecognized (Hawman and Feldmann, 2018). The disease occurs sporadically throughout much of Africa, Asia and Europe and results in an approximately 30% case–fatality rate (Whitehouse, 2008). Upon infection, CCHF progresses through four stages of disease, namely incubation, pre- haemorrhagic, haemorrhagic and convalescence (Mendoza *et al.*, 2018). The incubation period is usually 1–3 days when CCHFV is transmitted via tick bite and 5–13 days when transmitted via contact with infected blood or tissues (Mendoza *et al.*, 2018). The role of the adaptive immune response in the control of primary CCHFV infection has been limited by the lack of suitable animal models. Data suggest that CCHFV is directly capable of causing liver damage independent of the adaptive immune response of host to control viral replication (Bente *et al.*, 2010; Lindquist *et al.*, 2018). Type I interferon-deficient and STAT1 (Signal transducer and activator of transcription 1)-deficient mice succumbed prior to detectable antibody response (Bente *et al.*, 2010). The human cell surface nucleolin was identified as virus receptor, and CCHFV was shown to enter cells via a clathrin-, pH- and cholesterol-dependent mechanism (Simon *et al.*, 2009) (Fig. 1).

Fig.1 Transmission cycle of CCHFV



In humans, the disease is characterized by sudden onset of fever, muscular pain and headache etc, and then progresses to the haemorrhagic phase with petechiae, hematomas/ ecchymosis, and haemorrhages from various sites around the body. The pre-haemorrhagic stage comprises of non-specific symptoms like fever, muscle soreness, chills, photophobia, headache and nausea. In non- severe cases, individuals clear the infection and the pre- haemorrhagic stage symptoms resolve. In severe cases, the disease progresses to the haemorrhagic stage that occurs 3–6 days after infection, with symptoms such as petechiae and haemorrhages in internal organs, gastrointestinal system, gums and nose (Shayan *et al.*, 2015; Mendoza *et al.*, 2018). Fatal cases result from multiple organ failure. The fatality rate of CCHF has ranged from

9% to 50% in past outbreaks (Dilber *et al.*, 2010). Risk factors for death include elevated inflammatory cytokines and liver enzymes, high viral loads, decreased platelets, and absence of antibody responses (Hawman and Feldmann, 2018). Vascular dysfunction, resulting in haemorrhage and loss of fluid from the plasma into the interstitial space are the usual symptoms of CCHF, and patients suffer from disseminated intravascular coagulation (Burt *et al.,* 1997). Ebola haemorrhagic fever shares many features with CCHF (Bray, 2007). In general, Bunyaviruses infect many types of cell. However, dendritic cells and macrophages of human beings are supposed to be the primary target cells of human arboviruses. Monocyte derived dendritic cells and macrophages are the primary target cells of the CCHFV, and upon infection these cells induce efficient alpha interferon response (Peyrefitte *et al.,* 2010). There was upregulation of CD-83 and CD-86 indicating CCHFV induced partial maturation of dendritic cells associated with activation of secretion of interleukin-6 and 8. In macrophages, CCHFV infection elicited a high IL-6 and TNF-α response and a moderate chemokine response. Whereas, infection with Dugbe virus (DUGV), a mildly pathogenic virus genetically close to CCHFV, induced a higher cytokine/chemokine response in macrophages. These results suggested that CCHFV is able to inhibit the activation of inflammatory mediators selectively in *in vitro* infection and that these differences could be relevant in pathogenesis (Peyrefitte *et al.,* 2010). Convalescence from the haemorrhagic phase of the disease is characterized by memory loss, headache, dizziness, weak pulse, hair loss, anorexia and vision abnormalities (Shayan *et al.,* 2015). Long term sequelae, such as neurological problems and impaired vision, have been documented; but are rarely permanent (Hoogstraal, 1979). It is not clear whether survivors develop immunity to subsequent CCHFV infections, but IgG responses which are lacking in fatal cases are induced in non-fatal cases in humans (Ergonul *et al.,* 2006). As CCHF cases often have nonspecific flu like symptoms, late diagnosis of CCHF cases may hinder in controlling nosocomial infections (Fletcher *et al.,* 2017). High viral loads, absence of early antibody responses, and high levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), high levels of inflammatory cytokines, thrombocytopenia and prolonged clotting times are seen in severe cases (Hawman and Feldmann,2018). Polymorphisms in TLR 7, 8, 9, and 10 have been found to be correlated with disease severity (Arslan *et al.,* 2015; Engin *et al.,* 2010; Kızıldağ *et al.,* 2018). The Non-structural Protein of the virus induces apoptosis (Barnwal *et al.,* 2016). CCHFV also antagonizes innate immune signalling (Scholte *et al.,* 2017).

The role for adaptive immune responses against CCHFV in human pathogenesis is less clear; low/ absence of anti-CCHFV antibody responses have been found to correlate with severe disease and death (Ergonul*et al.,* 2006). The role of T cells in controlling primary CCHFV infection is unclear; levels of circulating CD3+CD8+ T cells in peripheral blood were found positively correlated with fatal outcome of the disease, and human CCHF survivors have been shown to exhibit long-lived CD8+ T-cell responses to CCHFV (Akinci *et al.,* 2009; Goedhals *et al.,* 2017). Immunohistochemistry and in situ hybridisation studies showed that mononuclear phagocytes, endothelial cells and hepatocytes are the main targets of CCHFV infection, and haemophagocytosis can play a role in the pathogenesis of the disease (Burt *et al.,* 1997). Studies indicate that CCHF resembles Ebola haemorrhagic fever in terms of high mortality, sharing the same target cells viz., macrophages, dendritic cells, endothelial cells and hepatocytes; short

incubation period, common clinical symptoms and blood cell picture (neutropenia, thrombocytopenia, lymphocytopenia, immature neutrophils), and elevated levels of IL-6 and TNF-α (Peyrefitte *et al.*, 2015).

Laboratory diagnosis

Virus isolation: This is a confirmatory method wherein suspected samples are inoculated in to cell lines such as LLC-MK2, Vero, BHK-21, and SW-13.4 that may show no or little cytopathic effect which can be traced by specific monoclonal antibodies in immunofluorescence method. BSL 4 laboratory is the pre requisite for isolation of virus (Appannavar and Mishra, 2011)

Molecular Methods: Detection of the CCHFV nucleic acid is the most sensitive one and is done either by reverse transcriptase PCR or by real time RT PCR which can give the results rapidly. Mostly blood from the patient is the sample of choice.

Serological assays: Enzyme-linked immunosorbent assay for the detection of human IgM and IgG antibodies specific to CCHFV are available. IgM antibodies persists for 4 months post infection while IgG antibodies for 5 years (Appannavar and Mishra, 2011) Presently, ELISA is also used for detection of antibodies against CCHFV in bovines, sheep and goat.

Prevention and Control

Exposure to infected ticks should be avoided or minimized. Insect repellents containing N, N-Diethylmeta-toluamide (DEET) are effective in protecting against ticks. Early and manual removal of ticks from infested animals are recommended. Acaricides are being used for domestic animals and in their sheds to control CCHF virus-infected ticks in enzootic regions. A vaccine derived from the inactivated mouse brain is used in Bulgaria, but it is not widely available. A DNA vaccine containing the CCHF genome M segment has shown to produce neutralizing antibodies in mice (Badalov, 1969); however, the protective efficacy of the vaccine has not been evaluated (Yadav *et al.*, 2014).

In conclusion the CCHF is considered as an emerging zoonotic disease of humans. Ticks carrying CCHFV have also been proven to carry other Nairovirus related viral agents of both human and animals. Therefore, a systematic surveillance of CCHF virus in ticks and livestock need to be carried out employing precise diagnostic tools. Biosecurity along with good sanitation in and around animal shed and human habitats is of prime importance to control the zoonoses.

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