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Crimean Congo Hemorrhagic Fever (CCHF): A chronicle of human, tick and animal

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Abstract

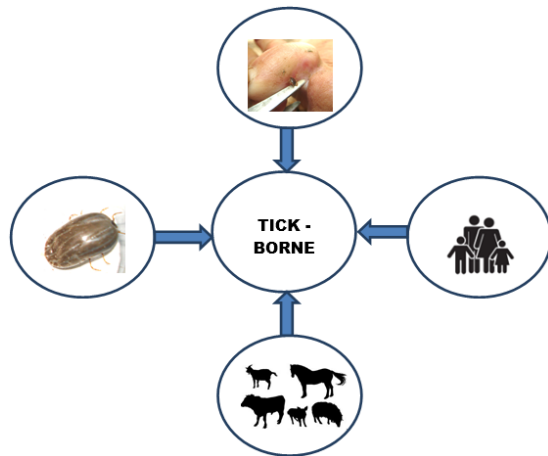
Crimean-Congo Hemorrhagic Fever (CCHF) is a tick borne zoonotic viral disease with case fatality ranging from 9-50% and endemic in Africa, Asia, Eastern Europe, and the Middle East. The virus propagates in a silent enzootic tick-vertebrate-tick cycle, which on external interventions leads to outbreak like situation. The regular mode of infection in humans are tick bites, nosocomial infection, crushing of infected ticks, direct contact with CCHF virus infected blood or tissue as during slaughtering infected animals. In a short span of 6 years, India witnessed several outbreaks, which begins from Gujarat to the recent Uttar Pradesh incidence. India being a tropical country and niche for more than 106 species of ticks, CCHFV poses significant threat to health of livestock owners, farmers as well as veterinarians. In India, *Hyalomma anatolicum* is mainly accredited for transmission of CCHF virus, however, in the recent studies, all the major tick genera are found to be infected with CCHF virus. The present review on CCHF will focus on discussing the update information on the disease pattern which is quiet necessary after CCHF outbreaks reported from India. The information provided might be helpful in designing future control strategy and may help to answer the questions raised in the minds about this disease.

Keywords: Crimean-Congo Hemorrhagic Fever, *Hyalomma anatolicum*, Tick and tick borne disease, Human infection

Introduction

Ticks are one of the most successful arthropod creatures accredited next to the mosquito as vector of human diseases (Jongejan and Uilenberg, 2004; Guerrero *et al.*, 2012) [30, 22]. Out of 914 globally known ticks (Berger *et al.*, 2014) [3], 106 are reported from India (Geeverghese *et al.*, 1997) [23]. Ticks serve as vector of several human diseases such as KFD, CCHF, Indian tick typhus, Lyme disease, human babesiosis and so on (Nagar and Ghosh, 2014) [24]. Among the various tick borne diseases, outbreaks of CCHF in last 6 years generates alarming situation in India and strict measures should be carried out to keep a check on the re-emergence of the disease. CCHF disease in human was noticed for the first time in Crimea in 1944 (Chumakov, 1945) [8], the virus was isolated for the first time from a febrile patient in Belgian Congo in the year 1956 and thus named as CCHF virus in 1973 by International Committee on Taxonomy on Viruses (Chumakov *et al.*, 1968) [9]. The virus was first time isolated from *Hyalomma* ticks and peak mortality also recorded collaborating with *Hyalomma* spp. dominant season, thus biologist initially accredited *Hyalomma* spp. as sole transmitting agent of CCHFV. Ergonul in 2006 [13] reported that CCHFV has been found in more than 31 countries across Africa, Balkans, Asia, southeast Europe, and the Middle East, closely approximating the known global distribution of *Hyalomma* spp. Ticks. In the last decade CCHF virus has been recognized as a growing problem in Europe and Asia with an upsurge of cases in Kosovo (Jameson *et al.*, 2012) [29] and the emergence of human clinical cases in Greece (Papa *et al.*, 2008) [48], Turkey (Karti *et al.*, 2004) [33], Georgia (Zakhashvili *et al.*, 2010) [76], and India (Mishra *et al.*, 2011; Patel *et al.*, 2011; Lahariya *et al.*, 2012; Mourya *et al.*, 2012; Yadav *et al.*, 2013; Yadav *et al.*, 2014) [41, 49, 38, 43, 72, 74]. Biologists have laid down several hypotheses for the sudden emergence of CCHF in human cycle, including global warming, habitat fragmentation, changes in land use patterns, livestock trade and movements and migratory birds (Ergunay *et al.*, 2011; Estrada-Pena *et al.*, 2010; Uyar *et al.*, 2011) [16, 18, 64]. Being a vector borne disease, the occurrence of CCHF is region specific and seasonal, typically subtropical climate, with mountains and rivers and a widely distributed rich

diversity of wild animal and tick species favors the amplification of virus. Moreover, 75-80% humidity and temperature around 28 °C (subtropical climate) favored tick activity and multiplication.



CCHF virus propagates via enzootic tick-vertebrate-tick cycle in latent form of infection. Wild life animal serve as tick reservoir for livestock animals and often results in failure of any tick control strategy (Camicas *et al.*, 1990) [7]. In midst of tick-animal interface, human get accidental infestation with ticks. Amongst ticks, their bionomics plays an important role in disease transmission and for transmission of any disease through saliva, an attachment of 48-72 hrs is required. Humans are quite often reported to be suffered from tick bites in CCHF clinical cases and the case fatality lies in the range 10-50% in case of tick-human interface (Swanepoel *et al.*, 1987) [57]. Due to its bionomics, biting nature, quick movements and localization of cases in *Hyalomma* prone area and *Hyalomma* predominant seasons (Hoogstraal, 1979) [28], and moreover initial successful attempts in isolation of CCHFV from *Hyalomma* sp ticks, *Hyalomma* is predominantly accused for transmitting the infection to human. In addition, another most common way of infection in human is by contact with infected blood or other tissues of livestock. Human to human transmission can be encountered in case of close contact with infected blood, secretions, organs or other body fluids of infected persons. Nosocomial infection can occur due to due to improper autoclave of instruments, reuse of needles and contamination of medical supplies and in such cases mortality rate may hike upto 80% (Shepherd *et al.*, 1985) [55]. The regular monitoring and recording of the tick fauna and the associated pathogens are important for the control of tick and tick-borne diseases. In India, Geeverghese *et al.* (1997) [23] attempted the enlisting of Indian ticks followed by Ghosh *et al.* (2007) [21] which presented the tick distribution in various states of India. There is no commercially available vaccine against CCHFV for humans and animals. The information of population dynamics of ticks and tick borne disease are important for successfully laid down of strategies related to CCHF virus control, and this requires further inter-sectoral collaboration under the supervision of health authorities.

Epidemiology and Phylogenetic diversity of CCHF Virus

Crimean-Congo hemorrhagic fever (CCHF) which is characterised by a sudden onset of high fever, chills, severe headache, dizziness, back, and abdominal pains is a tick-borne disease caused by arbovirus Crimean-Congo hemorrhagic fever virus (CCHFV), which is a member of the

Bunyaviridae family of viruses, of the genus Nairovirus (Whitehouse, 2004; Whitehouse 2008) [69, 70]. It is considered as biosafety level IV pathogen due to its pathogenicity and high (upto 50%) case fatality (Honiget *et al.*, 2004) [26]. CCHFV is an enveloped virus having negative polarity single stranded RNA genome constituting tripartite viz. S (nucleocapsid), M (membrane glycoprotein), and L (polymerase) genome segments, respectively (Bishop, 1996; Hewson *et al.*, 2004; Kinsella *et al.*, 2004; Deyde *et al.*, 2006) [4, 27, 35, 11]. The structure and replication strategy of CCHF virus is indistinguishable from any other member of Bunyaviridae (Schmaljohn and Hooper, 2001) [52]. The advances in molecular and biochemical analyses showed CCHFV encodes larger protein with different post translational modifications as compared to other members of Bunyaviridae. Phylogenetic analyses of S-RNA and L-RNA segment of CCHFV revealed significant divergence based on geographical ground and grouped diverse isolates into seven different clades. However, the phylogenetic grouping based on M-RNA segment sequences significantly differ from S-RNA and L-RNA segments indicating high frequency of genetic reassortment in M-RNA segment (Morikawa *et al.*, 2007) [42]. On sequencing of CCHF virus genome from India, livestock and tick virus was found similar to Tajikistan strain (TAJ/H08966), which belongs in the Asian/Middle East lineage IV (Mourya *et al.*, 2011) [41]. Even being an arbovirus, CCHFV showed significantly high genomic plasticity allowing it to adapt diversified environments resulting in its widespread (30 countries) geographical distribution (Flick *et al.*, 2003) [20]. The virus is distributed over much of Asia, extending from China to the Middle East and Southern Russia and focal endemic areas in Africa and southern Europe, including Kosovo and Turkey (Ergonul, 2006) [13]. Yearly epidemics, as well as sporadic cases of CCHF are seen in some of these areas, often with high case fatality (5 to 60%). The fatality rate differences may be due to phylogenetic variation of the virus, transmission route, and/or different treatment facilities (Whitehouse, 2008) [70]. The virus replication is inhibited by ribavirin resulting in significantly low titer in experimentally infected vero cells post treatment (Watts *et al.*, 1989) [68]. *In vivo* experimentation showed the loss of hepatotropism and neurotropism of virus after treatment with ribavirin, however, persistence of viremia was noticed by the researchers (Tignor *et al.*, 1993) [61].

Role of animals in CCHF outbreaks

CCHF virus, similar to other zoonotic agents, appears to produce little or no disease in its natural hosts but causes severe disease in humans. CCHF virus infection has been detected in numerous domestic and wild vertebrates through virus isolation and majority by sero-epidemiological survey to detect antibodies to CCHF virus. Hares, hedgehogs, cattle, sheep, goats, horses, yaks and swine were reported as the main natural hosts of the CCHF virus (Camicas *et al.*, 1990) [7]. Birds were considered resistant to CCHFV infection until the mankind witnessed death of a worker slaughtering ostriches on a farm in Cape Province of South Africa. Later on low titer of virus was recorded from guinea fowl also but it was concluded that birds are asymptomatic carrier of infection (Shepherd *et al.*, 1987) [54]. Migratory birds are often transport the ticks and their associated pathogens across the barriers such as rivers, deserts and mountains, oceans and continents. In domestic animals, the infection is usually sub-clinical and lasts from a few days to a few weeks. So, shepherds, campers, agricultural workers, veterinarians, abattoir workers, and

other persons in close contact with livestock and ticks are at risk of infection (Ergonul, 2006; Gonzalez *et al.*, 1998; Zakhshvili *et al.*, 2010) [13, 25, 76].

Role of ticks in transmission of CCHF

Invariably most of the literature accredited *Hyalomma* species for the transmission of CCHF in Pakistan since its first isolation in 1960s from adult ticks (Begum *et al.*, 1970; Aslam *et al.*, 2016) [2, 1]. In India, CCHF virus has been isolated from the *Hyalomma anatolicum* for the first time (Mourya *et al.*, 2011) [41]. In India, 8 species of *Hyalomma* viz., *H. anatolicum*, *H. detritum*, *H. dromedarii*, *H. brevipunctata*, *H. issaci*, *H. hussaini*, *H. kumari* and *H. turanicum* were found to be distributed in 24 states of India (Ghosh *et al.*, 2007) [21]. There is no such report of any attempt of isolation of CCHFV from other species of ticks in India. However, with the advent of molecular detection in ticks, biologists have reported involvement of more than 31 species of ticks, which includes both hard tick and soft tick in transmission of CCHF virus (Tahmasebia *et al.*, 2010) [58, 60].

The fatal viral infection had reported from about 30 countries, including India. Although the outbreaks have been recorded in peak *Hyalomma* seasons, the virus was also isolated from ticks of other genera such as *Rhipicephalus* spp., *Dermacentor* spp., *Haemaphysalis* spp., *Ixodes* spp. and *Argas* spp. both transovarially as well as transstadially (Saijo *et al.*, 2002; Turell, 2007; Tahmasebiet *et al.*, 2010) [51, 63, 58, 60]. In a study at Turkey, 165 ticks were examined by RT-PCR for the presence of the CCHFV, of which 27% were found positive for CCHF virus (Karan *et al.*, 2012) [32]. In an another study on highly CCHF endemic, Tokat province of Turkey, 7 species of ticks viz., *Haemaphysalis concinna*, *Hyalomma anatolicum*, *Hyalomma detritum*, *Hyalomma marginatum*, *Hyalomma turanicum*, *Rhipicephalus bursa* and *Rhipicephalus turanicus* ticks were found positive for CCHF virus using qPCR (Tekin *et al.*, 2012) [59]. In 2013, a survey conducted in Iran provide molecular evidences of CCHFV in *Hyalomma* sp. and *Haemaphysalis* sp. ticks via quantitative PCR and found 4.3% ticks positive for CCHF virus in Zehadan district of Iran (Mehravaran *et al.*, 2013) [39].

Table 1: Global distribution of tick vector responsible for transmission of CCHFV

S. No.	Country	Tick Species	References
1	India	<i>Hyalomma anatolicum</i>	Mourya <i>et al.</i> , 2011
2	West and Southern Africa	<i>H. marginatum rufipes</i> and <i>H. Turanicum</i>	Morikawa <i>et al.</i> , 2007
3	Madagascar	<i>Rhipicephalus</i> (= <i>Boophilus</i>) <i>microplus</i>	Fontenille D., 1989.
4	China	<i>H. asiaticum</i>	Xia <i>et al.</i> , 2011
5	Uzbekistan	<i>H. asiaticum asiaticum</i>	Ahmed <i>et al.</i> , 2007
6	Tajikistan	<i>Dermacentor niveus</i>	Tumanova <i>et al.</i> , 2005
7	Pakistan	<i>H. anatolicum</i>	Begum <i>et al.</i> , 1970
8	Iran	<i>H. anatolicum</i> , <i>H. detritum</i> , <i>R. sanguineus</i> , <i>Argas reflexus</i>	Tahmasebiet <i>et al.</i> , 2010
9	Russia	<i>H. marginatum marginatum</i>	Yashina <i>et al.</i> , 2003
10	Turkey	<i>H. marginatum marginatum</i>	Yilmaz <i>et al.</i> , 2009
11	Greece	<i>Rhipicephalus bursa</i>	Papadopoulos <i>et al.</i> , 1980
12	Bulgaria	<i>Hyalomma plumbeum</i> (<i>H. marginatum</i>), <i>Rhipicephalus sanguineus</i> , and <i>Boophilus calcaratus</i>	Vasilenko <i>et al.</i> , 1970

Humans- the ultimate victim of the chronicle

Humans are the only known hosts of CCHFV where it manifests a clinical condition depicting a distant evolutionary pattern of virus from human. Disease in vernacular languages are also known as Khungribta (blood taking), Khum Ymuny (Nose bleeding) and Karakhalak (Black death) in different parts of the world (Hoogstraal, 1979; [28]). In humans, CCHF is characterized by acute febrile illness leading to a fatal hemorrhagic syndrome. Humans can become infected by tick bites, contact with tick fluids such as saliva and haemolymph as while crushing infected ticks, direct or indirect contact with a CCHF patient, or by contact with blood or tissues of infected animal (Ergonul, 2006) [13]. Nosocomial transmission is reported as major culprit for CCHF outbreaks in world (Vorou *et al.*, 2007) [66]. CCHF in humans passes through the 4 phases, viz., incubation, pre-hemorrhagic, hemorrhagic, and convalescence periods (Ergonul, 2006) [13]. Incubation period on an average lies for 3-7 days followed by pre-hemorrhagic phase having flu like symptoms with temperature in the range of 39-41 °C. In hemorrhagic phase, individual may manifest hematemesis, melena, gingival and vaginal bleeding, hematuria and menometrorrhagia or dark coffee coloured urine and tar like faeces leading to DIC and failure of liver, kidney and lung (Swanpoel *et al.*, 1987) [57]. In certain unusual cases, incubation period upto 53 days is also reported (Kaya *et al.*, 2011) [36]. Mortality in clinical outbreak may ranges upto 30-50% (Nichol, 2001; Hoogstraal 1979; Bishop,

1996; Whitehouse, 2004) [45, 28, 4, 69]. In convalescent phase, xerostomia, polyneuritis and loss of memory may be noticed. Laboratory examination reveals elevated level of ALT, AST, CPK, LDH and prolonged PT and activated Partial Thromboplastin Time (aPTT), leucopenia and thrombocytopenia (Ergun and Ciftci, 2007; Kara, 2008) [15, 31]. Diagnosis of CCHFV can be made using blood, serum, tissue or urine samples but requires BSL-4 facility for processing of samples. Cell lines such as Vero and BHK-21 provides high yields and easily accessible to the researchers. Serological diagnosis can be made upto 4 months targeting IgM and up to 5 years on targeting IgG (Donets *et al.*, 1982) [12]. Other diagnostic techniques such as IgM captured ELISA, Immunofluorescence assay (IFAT), CFTb and HAI are also developed but found to have very low sensitivity and reproducibility (Hoogstraal, 1974). In contrary, qPCR provides high sensitivity and specificity and provides result within 8 hours (Burt *et al.*, 1998) [5].

Indian scenario of CCHF

India being a developing country, poor in resources and laboratory facilities required to handle CCHF virus. Though the cases were reported from neighbouring countries but not clinically evident until January, 2011 outbreak in Ahmadabad (Gujarat), there were no immediate preparation for dealing with the situation (Mourya *et al.*, 2012) [43]. The outbreak was followed by report of resurgence of CCHF in Amreli and

Ahmedabad district of Gujarat (Yadav Pragma *et al.*, 2012, 2013) [43, 72]. The NIV, Pune reported the seroprevalence of CCHFV in domestic animals from Sirohi district of Rajasthan (Mourya *et al.*, 2011) [41]. In 2013, a cluster of human cases were reported from Karyana, Surendra Nagar, Patan, Kutch and Amreli district of Gujarat (Yadav *et al.*, 2013) [72]. In 2014, three death were recorded in Bayadataluka and village Madhapur of Kuch district in Gujarat, three death in Jaiselmer and Jodhpur district of Rajasthan and one case reported from Himachal Pradesh. Seroprevalence study of domestic animals of Gujarat showed that at least 15 districts are having prevalence of CCHF virus (Mourya *et al.*, 2014) [44]. Bhanot *et al.* (2015) [6] reported a clinical case of CCHF from Moradabad, Uttar Pradesh. In Jodhpur (Rajasthan), 2 male nurse died due to CCHF in 2015. In 2015, Gujarat again witnessed death due to CCHF in Ratadiya village of Mundra taluka of district Kutch.

Conclusion

Pocket studies had been conducted on identification of virus in tick system either by molecular or cell culture technique in India. A 106 tick species are reported from India (Geeverghese *et al.*, 1997) [23], thus a systematic planned study is emphasized here to identify the tick vector responsible for CCHF in India, thereby a control strategy can be laid down to check the re-emergence of disease in India. Although ticks are major vector of CCSF but nosocomial infection cannot be left aside while designing any control strategy. Seroprevalence studies shows animals are key reservoir, majority ticks are the potential vectors and humans are the most susceptible victims for CCHF virus. Thus shepherds, campers, agricultural and abattoir workers, veterinarians, and other high-risk persons should protect themselves from direct contact with virus-contaminated tissues or blood and against tick bites. To control the CCHF in endemic region, organize a suitable public awareness programme about its spread, symptoms, and prevention.

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