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

Krutanjali Swain, Snehil Gupta, Vijay Kumar Jwalagatti, Sumitra Panigrahi, Abhilash Routray, Saraswat Sahoo and Subha Ganguly

Abstract
Crimean-Congo Hemorrhagic Fever (CCHF) is at ick 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, Baltains, 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 (Zakhlashvili 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

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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 quiet 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(Swanepeol 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 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 (Honig 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 the 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; Zakhashvili 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. kamari* 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 transovularly as well as transstadially (Sajio 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) [22]. In another study on highly CCHF endemic, Tokat province of Turkey, 7 species of ticks viz., *Haemaphysalisconcincina*, *Hyalommaanatolicum*, *Hyalommaedritum*, *Hyalomma marginatum*, *Hyalommaturanicum*, *Rhipicephalus bursa* and *Rhipicephaluslauritanius* ticks were found positive for CCHF virus using qPCR (Tekin et al., 2012) [39]. In 2013, a survey conducted in Iran provide molecular evidences of CCHFV in *Hyalommapapillosa* and *Haemaphysalis spp.* ticks via quantitative PCR and found 4.3% ticks positive for CCHF virus in Zehadan district of Iran (Mehraravan et al., 2013) [38].

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

**Human- 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 manifests a clinical condition depicting a distant evolutionary pattern of virus from human. 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 Pragya 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 Bayadtaluka and village Madhupur of Kuch district in Gujarat, three death in Jaisalmer 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) [8] 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 CCHSF 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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