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REVIEW ARTICLE

Crimean Congo Hemorrhagic Fever: Present Scenario, Prevention and Control

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Abstract

Crimean Congo hemorrhagic fever (CCHF) is a widely distributed viral hemorrhagic fever which mainly coincides with the distribution of the principal vectors of virus i.e. ticks of the genus *Hyalomma*. The virus is a member of the genus Nairovirus of the family Bunyaviridae. Humans generally end up with the infection through contact with infected blood or other tissues of the infected humans or animals or from tick bite. The infection in humans is characterized by febrile illness with headache, myalgia and petechial rash which is frequently followed by a severe hemorrhagic state with necrotic hepatitis. The case fatality rate of the disease is approximately 40%. Because of its propensity for human-to-human transmission, and the severe lethal outcome in humans, CCHF virus is placed under biohazard class-4 organisms. Confirmation of the diagnosis in the acute phase of illness consists of detection of viral nucleic acid by reverse transcriptase PCR (RT-PCR), demonstration of viral antigen by different serological tests like enzyme-linked immunoassay of serum samples, or the isolation of the virus. Similar to other hemorrhagic viruses, CCHF have a huge potential of rapid transboundary transmission. Hence, a strong surveillance team with more research efforts especially in the field of prompt diagnosis and treatment of disease is the need of the hour.

Keywords: Crimean Congo hemorrhagic fever, *Hyalomma* spp. ticks, Transboundary transmission, Nosocomial transmission, High fatality.

1. Introduction

Crimean Congo hemorrhagic fever (CCHF) is a tick borne viral zoonosis caused by Crimean Congo hemorrhagic fever virus, which belongs to genus Nairovirus of the family Bunyaviridae (Hoogstraal, 1979; Buschen-Osmound, 2007; Messina *et al.*, 2015). The genus Nairovirus have 34 viruses which are placed in seven serogroups based on the antigenic relatedness. Among these, only 3 viruses are known to cause diseases in animals and humans, namely CCHF virus, Dugbe virus and Nairobi Sheep Disease (NSD) virus. Dugbe virus causes a mild febrile illness and thrombocytopenia in humans while NSD virus mainly cause disease in sheep and goat and is considered to be identical to Ganjam virus of India (Burt *et al.*, 1996).

In electron microscopy, the CCHF virus appears spherical in shape with 90-100 nm diameter. The viral genome consist of single stranded negative sense RNA with three segments of genome: small (S), medium (M) and large (L), which encodes nucleocapsid protein (NP), the enveloped glycoprotein G1 and G2 of virus and RNA dependent RNA polymerase respectively (Marriott *et al.*, 1992; 1994).

CCHF is also known by different names in different parts of the world like Khungribta (blood taking), Khunymuny (nose bleeding), Karakhalak (Black Death) and Asian Ebola (Whitehouse, 2004). The clinical symptoms of this disease are mainly associated with humans whereas animals show no apparent disease manifestations and thereby act as asymptomatic carriers. The characteristic clinical symptoms in humans are fever, nausea, vomiting, headache, bodyache, abdominal pain, diarrhea, myalgia, petechial rash and bleeding from natural orifices (Saijo and Morikawa, 2010).

CCHF was first traced as a hemorrhagic syndrome as early as 12th century in Tadzhikistan. However, the first description of the disease was done in Crimean Peninsula in 1944-45 by a Soviet Scientist, when it infected 200 Soviet military personnel and thus was named as Crimean hemorrhagic fever (CHF) (Hoogstraal, 1979). A similar disease virus was again

isolated in 1956 from a febrile patient in Belgian, Congo which was named as Congo virus. In 1968, it was conclusively proved that both viruses were antigenically identical and the two names were combined to baptize the disease as Crimean-Congo hemorrhagic fever (Casals, 1969).

CCHF was reported from India first in Kolat village of Sanand district in Ahmedabad, Gujarat in 2011. First victim of this disease in India was a 32 year old lady, named Aminaben, who was admitted in Shalby hospital of Gujarat on 31st December 2010 with high grade fever, severe body ache, abdominal pain,nausea, vomiting and breathlessness. Next victims were Dr. Gaganjit Sharma and Nurse Asha Jhon who were treating Aminaben and fourth victim of this deadly disease was Dr. Shabbirali, working as a intern in civil hospital of Ahmadabad, Gujarat (Maurya *et al.*, 2012). Such a death pattern elucidated the high infectivity and fatality rate of this virus. The nucleocapsid gene phylogeny of positive human, livestock and ticks samples collected from this epidemiological outbreak showed that this virus was similar to Tajikistan (strain TAJ/H08966), which belonged to the Asian/middle east genetic lineage IV. This finding brought into light the transboundary distribution potential of the virus from endemic to naive countries.

2. Geographical Distribution of CCHF

CCHF is considered as one of the most widely distributed arboviral diseases in the world. The widespread prevalence is mainly associated with the ubiquitous nature of its principal vector i.e. *Hyalomma* species of ticks. Major prevalence of the disease is reported from Africa, Asia, Southeastern Europe, and the Middle East. Apart from its endemicity, the disease is considered as an "emerging zoonotic viral disease" with its rapid transmission potential and recently many sporadic outbreaks have been reported from non endemic countries including India.

3. Current Global Scenario of the Disease

The first reported outbreak occurred in 1944-45 in Crimea, Russia under the conditions of war when large numbers of soviet soldiers were exposed to tick bites due to outdoor sleeping (Hoogstraal, 1979). Subsequent epidemics in Eastern Europe and Asian countries occurred as a result of the rapid unsustainable human intervention into forest ecosystems which in turn opened multiple channels of exposure and subsequently resulted in 'spill over' of this previously confined infection.

In 1954-55, a large outbreak was reported from Bulgaria with 487 notified cases mainly in the Shumen area in North-East Bulgaria. A total of 1568 CCHF cases were notified in Bulgaria from 1953-2008 with an overall case fatality rate of 17 % (WHO, 2008). In 2003, an outbreak was reported from Mauritania (Nabeth *et al.,* 2004) and a nosocomial outbreak was reported in 2008 from Sudan (Grard, 2011; Aradaib, 2010). In 2009, CCHF cases were reported from Georgia, Kazakhstan, Tajikistan, Iran and Pakistan (OIE, 2009). In September 2010, an outbreak was reported in Pakistan's Khyber Paktunkhwa Province (ProMED, 2010).

The transboundary transmission potential of the disease is attributed to dissemination of ticks and virus through annual bird migrations in the North-South axis. Ticks are dispersed between continents by movement of livestock also. By phylogenetic analysis of CCHF strains, it was proved that the recent outbreak of CCHF in the Arabian Peninsula resulted from the trade of tick infested livestock from Africa and Asia (Hoogstraal, 1961; Hoogstraal, 1963). The high prevalence of disease in European countries may be linked to the fact that *Hyalomma* sp. ticks favor dry climates and arid type vegetation. Similarly the rise in temperature and decrease in rainfall in the Mediterranean region provides a favorable environment for the ticks (Estrada-Pena, 2007; Maltezou, 2010). The high incidence of human infection in developing and underdeveloped countries is due to the increased interaction with livestock which still continues to be the major source of livelihood and also due to the poor health care settings in these areas (Goodman, 2005).

4. Current Scenario in India

After the first outbreak in 2011, the subsequent major epidemic of this disease was reported in 2013 with 14 affected cases from village Karyana of Amreli District, Gujarat, of which 5 were fatal (CFR 35.71%) (Yadav *et al.*, 2013). The victims were associated with animal husbandry practices and had consequently contracted this fatal zoonotic viral infection (NCDC, 2013).

5. Ecology and Epidemiology of CCHF Virus

CCHF virus circulates in nature via enzootic cycle and epizootic-epidemic cycle. In enzootic cycle, Ixodid (Hard) ticks, mainly *Hyalomma* spp. acts as reservoir as well as vector for the virus (Chumakov, 1965; 1972; Pak *et al.,* 1974). The virus is maintained in nature by transovarial, transstadial and venereal transmission in ticks (Logan *et al.,* 1989; Okorie, 1997; Shepherd *et al.,* 1991; Gordan *et al.,* 1993; Dohm *et al.,* 1996; Gonzalez *et al.,* 1992). Whereas in epizootic-epidemic cycle, wild as well as domestic animals such

as cattle, goat (Wood *et al.,* 1965; Causey *el al.,* 1970), sheep (Yu-Chen *et al.,* 1985) and hare (Chumakov, 1974) acts as amplifying hosts and *Hyalomma* species of ticks acts as vector. Humans become infected either through tick bite or when they come in direct contact with blood or tissue of infected animals or/and persons. The high risk groups involve veterinarians, slaughter house personnel, butchers and hospital workers.

5.1 Hosts

The major hosts for CCHFV are animals (e.g., cattle, sheep, goats, pigs and horses), birds and humans. Clinical symptoms of the disease are exhibited by humans only; animals remain as asymptomatic carriers. (Appannanavar and Mishra, 2011).

5.2 Vectors and Reservoirs

CCHF virus is isolated from at least 31 species of ticks and one species of biting midges (*Culicoides* spp.) (Hoogstraal, 1979; Linthicum and Bailey, 1994). Among these *Hyalomma* species of ticks act as the main vector for the virus (Chumakov, 1965, 1972; Pak *et al.,* 1974). In India and Pakistan *H. anatolicum anatolicum, H. brevipunctata, H. kumari, H. hussaini* and in Europe *H. marginatum* are identified as the vectors.

Small mammals like hares, hedgehogs, rodents and ground feeding birds also act as reservoir of CCHF virus (Chumakov, 1974; Causey *et al.,* 1970). Birds generally act as mechanical carriers of CCHF virus; with no reported viremia.

5.3 Factors Related with Disease Occurrence

Following are the main factors responsible for occurrence of disease:

5.3.1 Poverty and Social Instability

In CCHF endemic areas, people are mainly involved in livestock and agricultural practices for their livelihood without following necessary precautions while handling animals as well as animal products (Maltezou *et al*., 2010).

5.3.2 Lack of Vector Control

Hyalomma species of ticks have a wide geographical distribution and it is difficult to control the transboundary migration of animals harboring infected ticks due to lack of proper control policies and robust surveillance measures (Maltezou *et al*., 2010).

5.3.3 Insufficient Medical Preparedness

Since an effective vaccine and standard treatment protocol are not available for CCHF, it is very difficult to control the infection in human population (Maltezou *et al.,* 2010).

5.3.4 Environmental Changes

Changes in climate and farming practices have made many of the previously naïve habitats favourable for *Hyalomma* spp. of ticks, consequently increasing the incidence of the disease in humans (Yapar *et al*., 2005).

5.3.5 Alteration in Natural Ecosystem

Deforestation and other human activities have prompted the divergence of tick population from wilderness to human dwellings (Maltezou *et al*., 2010).

5.3.6 Global Warming

The increase in environmental temperature proves to be favorable for tick survival (Maltezou *et al*., 2010).

5.3.7 Bird Migration

Migrating birds transmit the virus or/and ticks from one area to another and also act as mechanical carriers of the disease.

5.3.8 Animals as Reservoir

Asymptomatic nature of the disease in animals makes early measures of detection and mitigation impossible.

6. Pathogenesis and Clinical Features of CCHF

6.1 Pathogenesis

Similar to other haemorrhagic viruses, viremia develops in infected humans and the organism multiplies in the endothelial layer of blood vessels. During replication it causes pro-inflammatory response by the release of cytokines in blood like tumor necrosis factor α (TNF-α) and interlukin-6 (IL-6) (Hensley *et al.,* 2002), which further aggravates the endothelial damage resulting in endothelial toxicosis (Chumakov *et al.,* 1976). Aggregation and degranulation of platelets on the damaged endothelial surface leads to activation of intrinsic coagulation cascade resulting in disseminated intravascular coagulation (DIC) and multi organ failure, both of which can be fatal. Thrombocytopenia is one of the main clinical features of the infection (Swanepoel *et al.,* 1987, 1989; Schwarz *et al.,* 1997).

6.2 Clinical Features

Course of disease mainly occurs in four phases, incubation, pre-hemorrhagic period, hemorrhagic period and convalescent period. Incubation period ranges from 3-7 days and mainly depends on the route of infection. Infection acquired through tick bite

becomes apparent in 1-3 days (Whitehouse, 2004), while it takes 5-6 days when the entry of virus inside the body is through direct contact with infected blood or tissue (Patel *et al.,* 2011). Viremia usually occurs in this phase. The pre-hemorrhagic period of disease ranges from 1-7 days (Saijo and Morikawa, 2010). Main characteristic clinical signs of this period are fever, nausea, vomiting, diarrhea, myalgia, arthralgia, dizziness and photophobia. Subsequently, platelet and WBC count decreases and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level increases. The fatal hemorrhagic period usually ranges from 2-3 days (Saijo and Morikawa, 2010). Petechial rashes followed by ecchymoses in the internal mucous membranes like mouth and throat and on the skin surfaces are the initial symptoms of this phase. In this period, bleeding from different natural orifices like epistaxis, melena, hematemesis, hemoptysis and hematuria occurs and patients feel prolonged and pronounced sleepiness. In some patients, hepatomegaly and spleenomegaly are also seen (Ergonul, 2013). Deaths in CCHF mostly occur in this period (second week from starting of infection) mainly due to disseminated intravascular coagulation (DIC), multiorgan failure and cardiovascular arrest. The case fatality rate of disease in this stage ranges from 30-50%. If due to prompt treatment and management, patient bypasses above three phases, then the convalescent period starts which range from 10-20 days and in some cases can extend up to years. In this phase, patient feel prolonged and pronounced weakness, temporary or permanent hair loss and weak pulse. In severe cases, labored breathing, dizziness, polyneuritis, loss of vision, hearing loss and loss of memory are also reported (Hoogstraal, 1979).

7. CCHF as A Bioterrorism Agent

CCHF virus is considered as a BSL-4 pathogen according to the CDC (Centers for Disease Control and Prevention) guidelines. High fatality rate and secondary attack rate makes this virus a potential bioterrorism agent. Fortunately, there are some major impediments also, such as its slow multiplication rate in cell cultures and the requirement of a BSL-4 facility for handling the virus (Borio *et al.,* 2002).

8. Diagnosis of CCHF

Techniques like virus isolation, immunological assays and molecular diagnosis assay can be used to detect CCHF infection. All the diagnostic procedures of suspected CCHF infections should be performed in a BSL-4 facility. Virus isolation technique is a relatively less sensitive method, which needs high concentration of the virus (Shepherd *et al.,* 1986). Virus can be cultured and isolated from infected blood and tissue suspension in various cell lines such as LLC-MK2, Vero, BHK-21 and SW-13 cells with maximum virus yields (10^7-10^8 plaque forming units/ml) after the 4-7 days of inoculation (Nichol, 2001). Cytopathic effect (CPE) produced by the virus varies with cell line and strain of virus used and may even develop as a non-cytopathic persistent infection. Serological methods like immunofluorescence assay (IFA) and enzyme linked immunosorbant assay (ELISA) based on IgM and IgG detection are also developed (Donets *et al.,* 1982). IgM and IgG antibody appears in blood after 7 days of infection and remains in blood up to 4 months and 5 years respectively. Rapid detection of the virus is possible by reverse transcriptase- polymerase chain reaction (RT-PCR) and real time PCR technique. The major advantage of these molecular diagnostic techniques lies in the high specificity and sensitivity in virus detection (Schwarz *et al.,* 1996; Burt *et al.,* 1998).

9. Treatment

There is no FDA recommended drug for the treatment of CCHF. During the early stages of infection, ribavirin is found to be effective. But no randomized control trials have been performed to confirm the efficacy of ribavirin for treating CCHF cases in humans. In early stages, the use of supportive therapy leads to alleviation of clinical signs. Early remedies include use of rutin (a bioflavonoid compound obtained from buckwheat), ascorbic acid and calcium chloride, especially for the treatment of hemorrhagic cases. In severe blood loss cases, blood and plasma transfusion, infusion of plasma volume extenders like polyglutin and hemodes are practiced. Platelet transfusion is done in case of severe thrombocytopenia. Newer area of interest is use of Mx protein. Mx protein is an interferon (IFN)-inducible GTPase protein which has antiviral action. It binds with nucleoprotein of virus in the perinuclear space and inhibits the replication of the virus (Andersson *et al.,* 2004).

10. Vaccination and Immunotherapy

There is no proved effective vaccine for CCHF infection. But a formalin-inactivated suckling mouse brain-derived human vaccine is used in some parts of the world like Bulgaria, Soviet Union and Eastern Europe. Large scale vaccine development is not feasible because of the high genetic variation in the viral genome. Use of serum and plasma from convalescent cases and gamma globulin obtained from immunized horses (Hoogstraal, 1979) can cure the disease to some extent.

11. Prevention and Control of CCHF

One of the chief strategies for reduction of CCHF occurrences can be the control of disease in animals and ticks. But since animals are asymptomatic, it is almost an implausible task and the tick-animal-tick cycle goes on unabated in nature. Wide spread distribution of ticks over different geographical areas is another major impediment. A realistic option may be to educate people in the endemic areas, especially the high risk groups, about the risk factors and precautionary measures to be taken in potential situations. The basic precautions like wearing light colored long sleeve clothes, long trousers and long lashed shoes in tick endemic area can be very effective. Use of tick repellents like DEET (N-N-diethyl m-toluamide) on skin and clothes is also a viable option. Endemic areas should be avoided especially in spring and summer season when the tick activity is high.

To reduce the risk of animal-human transmission cycle, practices like wearing gloves and other protective clothing while handling animals, animal tissues or products should be followed. Since the lifespan of CCHF virus in animal body is less (7-10 days), quarantine is an effective strategy, 15 days before slaughter in endemic areas and 30 days in case of export facilities. Use of acaricide sprays on animal body during quarantine period will further increase the efficacy of the practice. Reports of nosocomial transmission warranty the use of personal protection equipments by health workers. Avoiding the consumption of unpasteurized milk and uncooked meat is also important (WHO, 2013).

12. Conclusion

The recent CCHFV episodes in humans demand an in-depth analysis of the virus-host interactions especially in animals since they are asymptomatic carriers for the virus. Prevalence studies must be conducted in endemic areas to reveal the true picture of the disease in animals and in humans and a useful animal model need to be developed for effective pathogenesis studies. Early diagnosis and treatment of CCHF will play an important role in reducing the mortality rate and secondary attack rate. The implementations of modern surveillance and alert systems in endemic areas, slaughter houses and hospital settings have been proved useful. Further research is needed to determine the efficacy of specific treatment with ribavirin and other antiviral drugs and to develop a safe and effective vaccine for human use. In addition, establishing suitable laboratory facility in endemic and potential areas is important. The scarcity of BSL-4 facilities and other sophisticated equipments is a major impediment to researchers in developing countries. Sequencing and phylogenetic analysis of the strains from different geographical area should be done to establish the epidemiological relatedness of the strains**.** Early preparedness along with suitable preventive and control measures is the foundation stone for battle against this deadly virus.

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