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CCHF: A current threat and its diagnosis

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Abstract
Crimean Congo hemorrhagic fever (CCHF) is one of the deadly hemorrhagic fevers that are endemic in Africa, Asia, Eastern Europe, and the Middle East. It is a tick-borne zoonotic viral disease caused by CCHF virus. CCHF not only forms an important public health threat but has a significant effect on the healthcare personnel, especially in resource-poor countries. India has always been a potentially endemic area until an outbreak hit parts of Gujarat, taking many lives. The current review is an attempt to summarize the updated knowledge on the disease particularly in modern era, with special emphasis on diagnosis of disease. The knowledge about the disease may help take precautions regarding entry of virus in India and future threat to community.

Keywords: Crimean Congo hemorrhagic fever, Diagnosis, Update

Introduction
Crimean Congo hemorrhagic fever (CCHF) has recently been in the news with first ever reports of its outbreak in India from the village of Kolat which is 30 Kms southwest of Ahmedabad in Gujarat. A 30year old woman and a doctor and nurse treating her in Ahmedabad succumbed to this illness creating panic in the local population and the country as well. General public including the medical fraternity was not fully aware of this disease, thus a fear of unknown was spread initially.

History
CCHF is not new disease as Crimean Congo hemorrhagic fever (CCHF) was first described in the 12th century as a hemorrhagic syndrome in present day Tajikistan (Ergönül, 2006) [7]. During that era, it was speculated that the disease‘s transmission was associated to louse or ticks that normally parasite black birds. However, in the modern era, the first outbreak of the CCHF was reported in 1944-1945 in the Crimea region when more than 200 cases occurred and at that time the disease was called Crimean Hemorrhagic Fever. Ten years later and specifically in 1956, the virus was isolated from a febrile patient in Belgian Congo and this isolate was noted to have the same antigenic structure with the Crimean strains. For this reason, the virus was called Crimean Congo Hemorrhagic Fever (Simpson *et al*., 1967; Ergönül, 2006) [18, 7]. Nowadays, outbreaks of CCHF have been documented in Africa, the Middle East, Eastern Europe, and Western Asia (Hoogstraal, 1979) [9].

Etiology
CCHF is a severe hemorrhagic fever with a case fatality rate of up to 50%. The virus that causes the disease is a tick-borne virus belonging to the family Bunyaviridae, genus Nairovirus (Martin *et al*., 1985) [12]. Like other nairoviruses, CCHF virus is an enveloped single stranded negative-sense RNA virus.

Transmission
The virus is transmitted to humans through the bite of infected ticks or by direct contact with viremic animals or humans (Ergönül, 2006) [7]. Infected humans can spread the disease via close contacts which may result in community outbreaks and nosocomial infections (Jamil *et al*., 2005) [10]. The potential human to human transmission along with the high mortality rates, the fears that the virus could be used as a bioterrorism agent and the increase of the incidence and geographic range of the Crimean Congo hemorrhagic fever make the virus an important human pathogen.

Epidemiology

Like other tick borne zoonotic agents, CCHF virus circulates in nature in an enzootic tick-vertebrate-tick cycle. Humans are being infected mainly through direct contact with blood or tissues from infected livestock or through tick bites. CCHF virus is transmitted by *Hyalomma* genus ticks and in particular by *Hyalomma marginatum marginatum.* Ticks of the genus *Hyalomma* serve indeed as vectors and reservoir of the CCHF virus and the geographic distribution of the disease coincide with the global distribution of *Hyalomma* ticks (Vorou *et al*., 2007) [20].

The virus is reported in over than 30 countries in Africa (Democratic Republic of Congo, Uganda, Mauritania, Nigeria, S. Africa, Senegal, etc.), Southeast Europe (Russia, Bulgaria, Kosovo, Turkey, Greece, etc.), the Middle East (Iraq, Iran, Saudi Arabia, Oman) and Asia (China, Kazakhstan, Tajikistan, Uzbekistan, Pakistan) (Morikawa *et al*., 2007; Koutis, 2007) [13, 11]. In this regard, the geographical distribution of CCHF virus is the greatest among all tick-borne viruses. CCHF virus has been isolated from adult *Hyalomma* genus ticks in the_60s and transovarial and transstadial transmissions have been already suggested since viral isolates have been also found in field collected eggs and unfed immature stages of *H. marginatum*, respectively (Watts *et al*., 1988) [21]. CCHF virus has been also isolated in laboratory from other tick genera eg. *Rhipicephalus*, *Ornithoros*, *Boophilus*, *Dermacentor* and *Ixodes spp.*

Although, the virus persists in ticks, vertebrates are needed to provide blood meals for the ticks and a variety of livestock can become infected with the CCHF virus. In fact, numerous domestic and wild vertebrates have been reported to present antibody response and/or viremia (Vorou *et al*., 2007) [20]. This livestock includes cattle, goats, sheep, horses, pigs hares, ostriches, camels, donkeys, mice and domestic dogs. In contrast to human infections the livestock‘s infections generally result in unapparent or subclinical disease (Whitehouse, 2004). However, the infected livestock during the viremic phase is dangerous for the disease transmission in humans. In this regard, domestic ruminant animals such as cattle, sheep and goats will present viremia for one week after becoming infected (Athar *et al*., 2003) [2]. Although it has been shown that the majority of birds is resistant to infection (Whitehouse, 2004) the potential role of migratory birds in the disease dissemination could not be ignored.

Clinical features and pathogenesis

CCHFV infections are asymptomatic in animals and birds are thought to be resistant. Humans are the main victims to this disease. The course of the disease can be divided into four phases- incubation, prehemorrhagic, hemorrhagic and convalescence (Hoogstraal, 1979) [9]. The incubation period depends on the mode of infection. Infections acquired via tick bites usually become Infections acquired via tick bites usually become apparent after 1-3 days (Whitehouse, 2004). Exposure to blood or tissues results in longer incubation period. In Indian cases, the incubation period ranged from 7-12 days through the later mode (Patel *et al.*, 2011) [15].

Pre-hemorrhagic symptoms are non specific and include fever, chills, severe headache, dizziness, photophobia, myalgia and arthralagia. This phase may last for 1-7 days (Saijo and Morikawa, 2010) [17]. The hemorrhagic phase develops suddenly lasting for 2-3 days. A petechial rash may be the first symptom both on the internal mucosal surfaces such as mouth and throat and on the skin. They are followed by ecchymoses and other hemorrhagic phenomenon such as hematemesis, melena, epistaxis, hematuria, and hemoptysis. Hepatomegaly and spleenomegaly can be seen in some patients (Appannanavar and Mishra, 2011). There may be rapid kidney deterioration. Death may occur in many cases. The mortality rate is 30% and the case fatality rate is up to 40% (WHO, 2013). In Indian cases death occurred due to cardio respiratory arrest, multiorgan failure and disseminated intravascular coagulation (DIC) and gastrointestinal bleeding in one case. In patients who survive recovery begins 10-20 days after onset of illness. Recovery may take up to a year (Patel *et al.*, 2011) [15].

No clear pathogenesis is described for CCHF. Endothelial damage is a common feature leading to capillary fragility and accounts for the characteristic rash and contributes to hemostatic failure by stimulating platelet aggregation and degranulation (Whitehouse, 2004). Thrombocytopenia occurs and dysregulation of the coagulation cascade leads to DIC. Proinflammatory cytokines are important in pathogenesis and the IL-6and TNF-α level are significantly higher in fatal CCHF (Ergönül, 2006) [7]. A study shows that viral genome can be detected from saliva and urine of infected patient. In CCHF there is increased serum ferritin level which can be used as a marker for disease activity and prognosis (Barut *et al*., 2010) [4].

Public health importance

Humans readily succumb to CCHFV infection. However domestic animals are either refractory or undergo mild infection with transient viremia sometimes, but they act as a main source of infection for humans (Prajapati, 2011) [16]. Persons living in close contact with animals are at the high risk of getting CCHF. Veterinarians and farmers may castrate, dehorn, attach ear tags and immunize young animals and thus expose themselves to the virus infected blood. They may have broken skin or scratch on the skin through which they may get infected. Consumption of unboiled or uncooked meat and milk of infected animal may be a potential source of infection. There is lack of evidence of disease in urban consumers of meat but the infected animal may reach to abattoir to pose a potential threat for workers and meat consumers. Exposure to aerosols while working with infected animals and in the hospital setting are the potential hazards. The population in the infected or infection prone area should be aware of the potential routes of infection and the safety measures to be taken to avoid the infection. CCHFV may be used for bioterrorism or as a biowarfare agent. Due to this it is included in CDC/NIAID Category C Pathogen (CFSPH, 2007).

Diagnosis

To save the patient and to prevent the further transmission of disease, early diagnosis is essential. The key indicators to suspect CCHF infection includes compatible clinical manifestations like fever and bleeding, history of tick bite, travel to endemic area and contact with infected cases and tick infested animals. The disease should be differentiated from the other VHFs, malaria, dengue, yellow fever, Kyasanur forest disease, rickettsiosis and leptospirosis (Ergonul, (2013) [8]. The knowledge of ecology and endemicity of CCHFV should be kept in mind to proceed with further diagnosis. The methods of diagnosis include virus isolation, immunological assays like ELISA and molecular diagnostic methods like reverse transcription- polymerase chain reaction (RT-PCR) (CFSPH, 2007). CCHFV can be isolated from the blood, plasma and tissue of infected patient for the diagnosis. Virus isolation should be performed in a high bio-containment laboratory

(CFSPH, 2007). A variety of cell lines including vero, BHK-21, LLC-MK2 and SW-13 can be used for virus culture. Cell culture can detect only high virus concentration and only useful during first five days of disease. Generally the virus produces no or little cytopathic effects so it can be identified by immunofluorescence assay using specific monoclonal antibodies (Whitehouse, 2004). The traditional method of animal inoculation of newborn mice is more sensitive than cell culture and also detects the virus for longer period. The virus isolation by cell culture is of limited value because it needs a biosafety level-4 laboratory (BSL-4) which is unavailable in most of the endemic areas (Ergonul, 2013) [8]. In the first few days of illness usually the patients do not develop a measurable antibody response so the serological tests are useful in the second week of illness. There are various serological tests available for detection of CCHFV but these tests are of limited use in fatal cases as patients generally die without developing antibodies. The conventional serological test for CCHFV like Complement fixation, heamagglutination inhibition and immunodiffusion suffered lack of sensitivity and reproducibility (Hoogstraal, 1979) [9]. This problem was solved by Indirect Immunofluorescence assay (IFA) and Enzyme-linked immunosorbent assay (ELISA) for the detection of IgM and IgG antibodies. Both IgM and IgG can be detected up to 7-9 days of illness by indirect FIA (Donets,1982). ELISA has replaced the conventional methods for antibody detection. IgM can be detected up to 4 months and IgG persist for 5 years post - infection but its level decrease (Hoogstraal, 1979) [9].

Molecular diagnostic assays such as reverse transcriptase polymerase chain reaction now serve as the front-line tool in the diagnosis of CCHF. PCR based methods are sensitive, specific, rapid and can be done without the need to culture the virus which requires BSL-4 facility (Hoogstraal, 1979) [9]. Molecular epidemiology can also be performed by this technique. A further improvement on the conventional RT-PCR assay has been the advent of automated real-time PCR based assays. The real-time PCR is more advantageousover conventional RT- PCR methods with respect to sensitivity, specificity and time taken for detection. Real- time PCR also offers less contamination rate. There are various detection chemistries available for the real time PCR like SYBR green, TaqMan and molecular beacon etc. There are several real-time RT-PCR assays reported till now for CCHFV detection. Some important assays developed for CCHFV detection are SYBR green, TaqMan and TaqMan-Minor Groove Binding (MGB) probe based assays (Wölfel et al., 2007).

Treatment

In case of CCHF, treatment is mainly supportive. It includes careful management of fluid and electrolyte balance depending upon the severity of illness. Currently there is no specific antiviral therapy for CCHF approved by United States Food and Drug Administration (FDA) for human use. Ribavarin, a guanosine analogue is found effective against CCHFV (Bajpai and Nadkar, 2011) [3]. CCHFV is susceptible to ribavirin *in vitro* (Watts *et al.*, 1989). According to some reports oral and intravenous ribavirin is effective for treating CCHFV infections (Christova *et al.*, 2009) [5]. In India one case recovered by the oral administration of ribavirin and discharged after ten days. Passive immunotherapy using specific immunoglobulin CCHF-Venin is also found beneficial in CCHFV treatment (Khan *et al.*, 2011) [1].

Prevention and control

The prevention and control should be both at community level as well as in nosocomial set up. Minimizing human contact with suspected livestock and reducing the tick burden in the animals are the primary and most important preventive measures (WHO, 2013). Animals should be carefully monitored for tick infestation and treated by appropriate acaricidal agents particularly before slaughter or export. Wearing fully covered clothes and use of tick repellent is recommended to prevent tick attachment on the body surface. The unpasteurized milk and uncooked meat should not be taken. Human- to- human infection mainly occurs in the nosocomial setup by the contact of infected blood or tissue. So use of protective clothing, gloves, goggles and face-masks reduces the chances of exposure. Safe burial practices with proper use of disinfectants should be followed. Veterinarians, research workers, slaughter house workers and medical professionals should take utmost care to reduce the contact with suspected material. They should take the prophylactic treatment after high risk exposure. Laboratory and research workers are advised to follow stringent biosafety precautions during handling the pathogen and the work should be carried out under BSL-4 facilities. Virus can be inactivated by using 1% hypochlorite and 2% glutaraldehyde. Heating at 56°C for 30 minutes also destroy the virus (CFSPH, 2007).

Vaccination

Vaccine against CCHF is not available in most of the countries. However a formalin inactivated vaccine derived from suckling mouse brain has been used in Bulgaria and former Soviet Union (Papa *et al.*, 2011) [14]. There is no vaccine available for animal use (WHO, 2013).

Conclusion

CCHF is an emerging disease in India. Its zoonotic potential and fatality have created a great havoc in the general population as well as in health care community. Since animals play an important role in the transmission of virus to human, the persons associated with animals are at the great risk of CCHFV infection. This disease is new to India so people should be aware of the various aspects of this fatal disease mainly its modes of transmission, clinical manifestations, public health importance and preventive measures.

Contribution

Dr S. Solnaki wrote the first draft of the paper. Dr Durga Devi contributed to the writing of this article.

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