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A review on Crimean-Congo hemorrhagic fever in India

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Abstract
Crimean-Congo hemorrhagic fever (CCHF) is an emerging tick-borne viral zoonotic disease caused by Nairovirus of Bunyaviridae family. It causes fatal hemorrhagic fever in humans with a case fatality rate of as high as 10-40%. Clinically the disease is characterized by hemorrhages, chilling, sudden onset of high fever, headache, dizziness, gastrointestinal symptoms, and myalgia. Some patients may also experience liver dysfunction, and changes in sensory and motor functions. The disease is mostly asymptomatic in animals but plays a vital role in the transmission of disease to humans. Therefore, the persons associated with animals like veterinarians, farmers and slaughter house workers are at the high risk of getting the infection. CCHF is transmitted to humans by bite of an infected tick, crushing infected ticks with bare hands, or coming into contact with infected animal blood or tissues either before or after the animal is slaughtered. Human-to-human transmission occurs through contact with infectious blood or body fluids. CCHF has been reported from nearly 52 countries worldwide. CCHF is responsible for outbreaks in many areas of the Middle East, Europe, Asia, and Africa. In India, the first confirmed case of CCHF was reported from Gujarat. Subsequently cases have been reported from Rajasthan, Gujarat, Uttar Pradesh and Kerala. The disease has a great public health importance. Early diagnosis using enzyme-linked immunoassay (ELISA) and reverse transcription-polymerase chain reaction (RT-PCR) is helpful for prevention. Currently there is no antiviral drug available for CCHF, although ribavirin is administered in severe cases. This review summarises the current status of disease in India, its global distribution, aetiology, epidemiology, clinicals features, pathology, treatment and diagnosis.

Keywords: Crimean-Congo hemorrhagic fever (CCHF), RT-PCR, human-to-human transmission

Introduction
In the past few years, the world has witnessed a growing number of global public health crisis arising from the emergence of infectious diseases with zoonotic origins, many of which are transmitted by ticks and mosquitoes. According to the World Health Organization (WHO), vectors account for over 17% of all infectious diseases, leading to more than 700,000 deaths each year [1]. Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne zoonotic viral disease caused by the Crimean-Congo hemorrhagic fever virus (CCHFV). The virus belongs to the Nairovirus genus within the Bunyaviridae family [2]. The primary vector and reservoir for CCHFV are hard ticks, particularly those of the Hyalomma genus, which are widespread in Asian countries [3]. However, other tick species may also contribute to the maintenance of the virus in endemic regions. CCHFV is transmitted through a cycle involving ticks, animal hosts (such as cattle, sheep, goats, and hares), and humans. In animals, the infection is usually asymptomatic, making seroprevalence studies crucial for identifying areas of risk for the human population. The infection can be transmitted to humans by being bitten by an infected tick, crushing infected ticks with bare hands, or coming into contact with infected animal blood or tissues either before or after the animal is slaughtered [4]. Human-to-human transmission occurs through contact with infectious blood or body fluids. The majority of CCHF cases have been reported among high-risk groups such as animal herders, farmers, slaughterhouse workers, butchers, veterinarians, and healthcare professionals [5]. Nosocomial spread has also occurred due to the use of improperly sterilized medical equipment, reuse of injection needles, and contamination of medical supplies [6]. CCHF is a transboundary disease that spreads across borders through multiple pathways, including infected ticks carried by migratory birds, global trade, and the expanding host range of Hyalomma ticks driven by climate change [7].
The initial clinical presentation and early laboratory findings of the disease can resemble those of other viral hemorrhagic diseases.

Therefore, early diagnosis of the viral illness involves detecting viral nucleic acid using reverse transcription-polymerase chain reaction (RT-PCR) [8]. In later stages, the diagnosis can be confirmed by detecting specific antibodies to the virus. The case fatality rate of CCHF ranges from 10% to 40% [9]. The primary focus of treatment is to provide supportive care, although ribavirin is administered in severe cases. Currently, two vaccines have been developed but are not recommended for public administration [10].

History and Geographic Distribution

CCHF was first identified on the Crimea Peninsula in 1944 and initially named Crimean hemorrhagic fever. It was later discovered in 1969 that the pathogen responsible for Crimean hemorrhagic fever was the same as the one causing an illness previously identified in the Congo Basin in 1956 [11]. Consequently, the disease came to be known as Crimean-Congo hemorrhagic fever. Currently, CCHF is endemic in nearly 52 countries across Africa, Eastern and Southern Europe, and Central Asia [12, 13]. In recent years, there has been an expansion of the geographical distribution of the virus, with an increasing number of human cases reported worldwide. The emergence and re-emergence of CCHF have also been observed in various parts of the world, including the Balkan countries, Southwest Russia, the Middle East, India, and Spain. The reasons behind these incidents can be attributed to human activities, specifically changes in agricultural practices, habitat fragmentation, and the importation of infected animals and ticks. The five countries with the strongest evidence for the presence of CCHF are Turkey, Iran, Afghanistan, Tajikistan, and Pakistan [14]. In Pakistan, the first confirmed case of Congo fever was reported in 1976 in Rawalpindi, and since then, many outbreaks have been reported throughout the country. Southeast Asian countries are particularly vulnerable due to their increasing population and the developing state of healthcare infrastructure and communities [15].

Status of CCHF in India

CCHFV often remains undetected in livestock, leading to difficulties in effectively addressing the risk of zoonotic transmission to humans. Previously, seropositivity in animals has been documented in various regions of India, including Maharashtra, Kerala, Tamil Nadu, Mysore, Pondicherry, and Jammu and Kashmir [16]. In 2013, a serosurvey conducted in 15 districts of Gujarat revealed that out of 1226 animal samples tested, 278 (22.67%) animals exhibited IgG antibodies against CCHFV. Sheep showed the highest antibody positivity (41.21%), followed by goats (33.62%) and bovine (12.09%) [17]. Based on these data, the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV) Pune, conducted a cross-sectional study from 2013 to 2014. This study involved the collection of 5636 serum samples from cattle, sheep, and goats across 22 states and one Union Territory in India. Among these samples, 354 tested positive for anti-CCHF antibodies, indicating the widespread presence of the virus throughout the country [18].

On the contrary, CCHF infection in humans was initially confined to countries located in north and west of India. However, in 2011, India recorded its first confirmed case of CCHF in Ahmedabad, Gujarat, resulting from transmission within a healthcare facility [19]. From 2011 to 2019, Gujarat reported several CCHF cases, establishing itself as an endemic region for the disease in India. Similarly, Rajasthan, a neighbouring state of Gujarat, reported its initial case in 2014 from the Sirohi district, followed by a few cases in Jaisalmer and Jodhpur districts in 2015 [20, 21]. Furthermore, in 2019, Rajasthan again reported five cases of CCHF, with three from Jaisalmer and one each from Jodhpur and Sirohi district [22]. In response to these findings, health authorities issued a high alert in Gujarat and Rajasthan, emphasizing the need for accurate diagnosis and preventive measures. In 2015, an outbreak was reported in Moradabad, Uttar Pradesh [23]. Kerala also reported a case in 2018 from Thrissur district, involving an expatriate from the UAE [24].

Etiology

CCHF belongs to the Nairovirus genus within the Bunyaviridae family [25]. It is a spherical, enveloped virus with a diameter of about 100 nm [26]. The genome, approximately 19.2 kb in size, comprises three segments of negative-sense single-stranded RNA denoted as Large (L), Medium (M), and Small (S). These segments encode for viral polymerase (L), Glycoprotein precursor (GPC), and Nucleocapsid (N) respectively [27]. The virus is accountable for causing fatal viral hemorrhagic fever (VHF) in humans, exhibiting notably high mortality rate [28]. The Nairovirus genus comprises 34 identified viruses, which are further categorized into seven serogroups based on antigenic similarities. The maintenance of these groupings is achieved through the observation of both morphological and phylogenetic resemblances. Within this genus, only three viruses - CCHFV, Dugbe, and Nairobi sheep disease virus have been identified as causing diseases in humans.

Epidemiology

CCHF virus usually circulates naturally through a cycle involving ticks and various vertebrate hosts. This virus has been found in both domestic and wild animals, including cattle, goats, sheep, hares, hedgehogs. It's worth noting that birds seem to be resistant to CCHF virus infection [29]. Vertebrate animals play a crucial role as a blood source for ticks, particularly those of the Hyalomma genus, which act as the primary vector for the CCHF virus. The CCHF virus exhibits a widespread geographic distribution among all tickborne viruses [25]. Prior to 1970, most of the cases were reported from the Soviet Union, Bulgaria, and some regions of Africa such as the Democratic Republic of the Congo and Uganda [30]. In 1965, an outbreak with an alarming 80% case fatality rate occurred in China [31]. Few isolated cases were also reported from middle eastern countries such as Iraq, the United Arab Emirates, Saudi Arabia, Oman, Pakistan and China [32]. Serological evidence of CCHF virus presence has been reported from Greece, India, Egypt, Portugal, Hungary, France, and Benin [33]. Notably, CCHF virus is endemic in the Balkans, including Bulgaria, the former Yugoslavia, and Albania [34, 35, 36]. The increased transmission of the virus is influenced by various environmental factors. CCHFV emergence is tied to ecological changes, poverty, social instability, inadequate healthcare services, and the absence of standardized infection control practices.

Clinical features and Pathogenesis

The incubation period varies depending on how the virus is acquired. When the virus is transmitted through a tick bite, the incubation period typically lasts between one and three days, with a maximum of nine days. However, if the infection occurs through contact with infected blood or tissues, the incubation period is generally five to six days but can extend up to 10-14 days [37]. Initially, the infection manifests as a non-specific

febrile illness that can progress to a severe hemorrhagic condition. Common symptoms include a headache, muscle pain, high fever, abdominal discomfort, vomiting, red eyes, bruising, and small bleeding under the skin. Some patients may also experience liver dysfunction, gastrointestinal issues, and changes in sensory and motor functions [10]. The pathogenesis of CCHF lacks a clear description. However, it commonly involves endothelial damage, resulting in capillary fragility. This damage is responsible for the distinct rash seen in patients and contributes to hemostatic failure by promoting platelet aggregation and degranulation [26]. Thrombocytopenia and disruptions in the coagulation cascade is also seen. The pathogenesis of the disease also involves the significant presence of proinflammatory cytokines, with elevated levels of IL-6 and TNF-α [28].

Diagnosis

Crimean Congo Haemorrhagic fever requires swift and precise diagnosis to prevent case fatality. Early diagnosis is important to save patients life and prevent spread of disease. Diagnosis involves detailed medical history of the patient, molecular identification with in a week or later serological testing. Combing both the methods for diagnosis is most effective approach [38]. The primary signs of CCHF infection consist of consistent clinical symptoms such as fever and bleeding, a record of being bitten by ticks, traveling to regions where the disease is prevalent, and coming in touch with sick individuals and animals infested with ticks. Therefore it becomes very difficult to distinguish it from other viral hemorrhagic fevers (VHFs) such as dengue, yellow fever, and Kyasanur forest disease.

Virus isolation should be conducted within a laboratory equipped with a high level of biocontainment. The diagnosis of CCHFV can be made by isolating the virus from the blood, plasma, and tissue of an infected patient. Various cell lines such as vero, BHK-21, LLC-MK2, and SW-13 are suitable for virus culture. Cell culture is capable of detecting only high levels of viral concentration and is only effective for the initial five days of the sickness. The virus often does not cause significant damage to cells, making it possible to detect it with an immunofluorescence technique that utilizes particular monoclonal antibodies [26]. ELISA has replaced traditional techniques for antibody detection. IgM antibodies can be detectable for a period of up to 4 months following infection, whereas IgG antibodies survive for a duration of 5 years. However, the amount of IgG antibodies gradually decreases over time. Reverse transcriptase polymerase chain reaction (RT-PCR) is now the primary method used to diagnose CCHF. PCR-based techniques are very sensitive, specific, and quick, and can be performed without the necessity of culturing the virus, hence eliminating the need for a BSL-4 facility [25].

Treatment

Supportive treatment is the primary approach for managing CCHF. It involves meticulous regulation of fluid and electrolyte equilibrium, which is tailored to the severity of the sickness. At present, the United States Food and Drug Administration (FDA) has not approved any particular antiviral medication for human use against CCHF. Oral and intravenous use of ribavirin has been reported to be effective in treating infections caused severe CCHF cases [40].

Vaccination

Vaccine development efforts first began in the 1960s, with Soviet scientists proposing the immunization of local populations due to the endemic nature of CCHFV. By 1970, the Soviet Ministry of Health granted approval for the use of an inactivated vaccine for the prophylaxis of CCHF. In 1974, Bulgaria authorized the use of the Soviet vaccine in areas of the country endemic to CCHFV. This vaccine was administered to military personnel, as well as medical and agricultural workers aged 16 and above. According to newly released information from the Bulgarian Ministry of Health, there has been a significant four-fold decrease in reported CCHF cases over a span of 22 years. Progress in vaccine development necessitates the creation of DNA vaccines, vaccines based on recombinant viral proteins, and virus-like particle vaccines. However, the scarcity of suitable animal models for CCHF has significantly impeded research progress [41].

Prevention and Control

Preventive and control measures should be implemented both at the community and healthcare facility levels. Vigilant monitoring of animals for tick infestations is crucial, and appropriate acaricidal medications should be used, particularly before slaughter or export. To minimize the risk of tick attachment, it is recommended to wear protective clothing covering the entire body and use tick repellents. Consuming raw milk and undercooked meat should be avoided. The transmission of the virus between individuals primarily occurs in healthcare settings through direct contact with infected blood or tissue. Utilizing protective gear such as clothes, gloves, goggles, and face masks significantly reduces the risk of exposure. Professionals such as veterinarians, researchers, slaughterhouse workers, and medical staff should exercise extreme caution to minimize their exposure to potentially hazardous substances. Strict adherence to biosafety measures is strongly recommended for laboratory and research personnel handling the pathogen, and work should be conducted in facilities meeting BSL-4 standards. The virus can be rendered inactive by using a solution containing 1% hypochlorite and 2% glutaraldehyde. Additionally, exposing the virus to a temperature of 56 °C for 30 minutes also leads to its destruction [42].

Public Health Significance

CCHF poses a considerable threat to human health due to its high infectivity [38]. While domestic animals typically experience mild infections, they play a crucial role as the primary source of transmission to humans. Livestock that is affected during the viremic phase poses a significant risk for transmitting the disease to humans. Domestic ruminant animals, including cattle, sheep, and goats, exhibit viremia for a duration of one week following infection. Individuals in close contact with animals, such as veterinarians and farmers, face an elevated risk of CCHFV infection. Activities like castration, dehorning, and animal immunization expose them to potentially virus-infected blood. Moreover, the consumption of raw milk or undercooked meat from infected animals presents a potential source of infection [43]. Exposure to aerosols during interactions with infected animals or within a hospital setting further amplifies the risk. It is crucial for the population in areas prone to infection to be knowledgeable about potential routes of infection and to implement safety measures to prevent the spread of CCHF. Hence, it is crucial for populations in infected or high-risk areas to be vigilant about infection routes and implement safety measures to prevent the spread of CCHF.

Conclusion

CCHF is an emerging viral zoonotic disease posing a significant public health threat. Its ongoing geographic expansion is a cause for concern. Epidemiological studies are the primary sources of information, crucial for monitoring and understanding areas with natural CCHF transmission and reservoirs. The causative virus circulates among various animal reservoirs and tick populations worldwide, which necessitates continuous surveillance and a comprehensive understanding of disease transmission.The disease particularly demands one health approaches to combat its spread. Given the extremely high mortality of CCHF and the ever-present threat of outbreaks, coupled with the absence of effective treatment or preventive strategies, it is imperative to raise awareness and foster preparedness in high-risk areas.

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