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A Review on the Reappearance of Crimean-Congo Hemorrhagic Fever, a Tick-Borne Nairovirus

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ABSTRACT

Introduction and Objectives: Crimean-Congo Hemorrhagic Fever (CCHF) is the second most widely distributed arboviral disease worldwide. CCHF is transmitted to humans mainly by bites of infected ticks in the Ixodidae family, mainly those of the *Hyalomma* genus or via human contact with the blood and tissues of infected livestock. It can also be transmitted to a healthy individual through close contact with an infected person (like a nosocomial infection). Given the importance of CCHF, this review study was carried out in Iran with an emphasis on the importance of the vectors. **Materials and Methods:** In this review study, using keywords such as epidemiology, Crimean-Congo hemorrhagic fever, arbovirus, vectors, reservoirs, distribution, and control, by searching relevant websites and accredited medical journals and considering the purpose of the study, the appropriate articles were selected and the disease status in Iran from 1965 to 2019 was analyzed. **Results:** CCHF has been reported from 26 provinces of Iran. Sistan-Baluchestan province has always been among the most infected areas due to livestock smuggling from neighboring countries. The tick vectors are widespread and abundant in Iran. The main ones are the *Hyalomma marginatum* and *Hyalomma anatolicum* species. The prevalence of the disease is higher in warm seasons of the year when vectors are more active. In Iran, most cases are caused by contact with infected livestock. Direct infection through tick bites is rare and only a few such cases have been reported. Middle Eastern countries are divided into 6 groups based on the levels of healthcare systems and the numbers of CCHF cases reported annually. Iran is allocated into group one due to annual reports of the disease and has designed a healthcare system for this disease. **Conclusions:** To control CCHF, people, especially high-risk groups, must be educated about routes of transmission and prevention of CCHF. In addition, given that viremic livestock is the major source of CCHF outbreaks in Iran, livestock smuggling and non-hygienic and traditional livestock slaughter procedures must be prevented and infected livestock must be treated.

Keywords: *Epidemiology, Crimean-Congo Hemorrhagic Fever, Vectors, Reservoirs, Control, Iran*

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INTRODUCTION:

The World Health Organization (WHO) has listed the world's 10 most dangerous diseases, all of them equally important, and has urged all countries to monitor trends in illness and detect outbreaks of these diseases, whether they are observed or not. As these diseases are likely to spread further in the future, they will become of greater international importance and authorities will consider them a threat to global health security [1, 2]. Viral infections are considered as one of the principal threats to human life and health worldwide [3, 4]. Crimean-Congo Hemorrhagic Fever (CCHF) is one of these 10 diseases. There is a high correlation between the incidence of the disease and economic factors and the export and import of food and livestock in countries. Ecological changes, changes in human lifestyles and behaviors, displacement and movement of human and animal populations, genetic variations in pathogens and displacement and movement of vectors and reservoirs are the major contributors to the development and distribution of dangerous emerging and re-emerging diseases in the world. Epidemics of CCHF usually occur in areas where public health services are poor and may cause many deaths. Changes in the environment, climate, and agriculture may affect the distribution of ticks and eventually the emergence of the disease [1, 2].

Crimean-Congo hemorrhagic fever was first described in ancient medical history in 1110 by Gorgani, an Iranian physician [5]. In modern times, the first case was described in the Crimean Peninsula in 1942. Over 200 people died of CCHF in 1944. In 1956, the disease spread in the Congo, and the virus causing the disease was isolated from the infected population and named Congo virus. In 1969, the causal agent of CCHF was found to be similar to that of the disease that was detected in Congo during the 1956 epidemy. Therefore, the combination of the names of the two regions was given to the disease and it was called Crimean-Congo hemorrhagic fever [6, 7].

CCHF, one of the most important tick-borne zoonotic infectious diseases, is distributed sporadically in many geographical areas. However, it is endemic in Asia, Africa, Eastern Europe, and the Middle East. The role of ticks as vectors and reservoirs is of special importance (due to their long lifespan). CCHF is the second most widely distributed arboviral diseases in the world. It is the most important and widespread tick-borne disease in humans worldwide. The disease is common in more than thirty African, Asian, Middle Eastern, and Eastern European countries, and the spread of the disease is consistent with the global distribution map of *Hyalomma* ticks. It is estimated that over 5000 cases of the disease occur in 30 countries every year. Russia, Iran, Turkey, and Pakistan are considered important due to reliable statistics [8, 9].

The first cases of the disease in Iran were observed in the 1970s with the detection of CCHF antibodies in human and livestock serum [10]. In Iran, the antiserum specific for CCHF was reported for the first time in several sheep. In 1974, a type of typhoid with hemorrhagic symptoms was described in northwestern Iran and diagnosed with CCHF. During 1974-75, CCHFV-specific antibodies were detected in 13% of human serum, 18% of sheep serum, and 38% of cattle serum samples in the northern part of Iran. In 1978, for the first time, CCHF virus was isolated from the *Alveonasus lahorensis*, a soft tick [11, 12]. Since 1999, possible and definite cases of the disease have been reported in Iran. From 1999 to 2008, 528 human cases were reported [13-16]. The first case of nosocomial CCHF infection in Iran was reported in 1999 in Chaharmahal-Bakhtiari province [17]. The number of cases has increased since then and it is now observed in most parts of Iran [18]. So far, the CCHF has had several outbreaks in Iran [19, 20]. CCHF has been most common among butchers, stockbreeders, and farmers [21-25]. Sistan-Baluchestan province has reported the largest number of cases. Southeastern Iran is one of the most infected areas due to its borders with Afghanistan and Pakistan and because of livestock smuggling and human migration (for social and economic reasons) [26]. Studies have shown that there are more than five circulating genomic variants of CCHFV in Iran [27-29]. The strains of the CCHF virus in Iran are very similar to the Pakistani Matin strain [10]. Since 1975, surveys have shown that infection rates in livestock range from 3.8 to 100% in different parts of Iran [30-32]. Birds are generally resistant to CCHF and it is rarely reported in them. Because of the blood-feeding of ticks on birds, they play an important role in the survival of ticks, and in addition, they contribute to the distribution of these vectors, in nature. In 2007, the first case of CCHF infection in ostrich was reported in central Iran. That year, three butchers and one worker on an ostrich farm were infected with CCHF. Ostriches can reproduce the virus in their body and can distribute the disease through transmitting the infected ticks without being infected with CCHF themselves [33].

The Middle Eastern countries are divided into 6 groups based on the levels of healthcare systems and the number of CCHF cases reported annually. Iran is allocated to group one due to annual reports on the disease, and it has designed a healthcare system for this disease [16]. Every year, CCHF cases are reported in Iran and the disease has become endemic in this country. Sistan-Baluchestan province in southeastern Iran always has the highest incidence of CCHF. Therefore, given the importance of CCHF, this review study was carried out in Iran with an emphasis on the importance of the vectors.

MATERIALS AND METHODS:

In this review study, some keywords such as epidemiology, Crimean-Congo hemorrhagic fever, arbovirus, vectors, reservoirs, distribution, and control were used to search the Internet for relevant websites and authentic medical journals in scientific databases including Web of Science, Ovid, PubMed, Systematic Review, SID, Iran Medex, Scirus, Google Scholar, and Medline. We found 120 articles published in Persian and English that were submitted from 1965 to 2019. Seventy-nine of them were selected considering the objectives of the research to introduce CCHF and review and investigate the studies and their application in controlling this disease. The findings were then used in the framework of a review article and CCHF prevention methods were presented considering the hygiene and medical components. Ethical subjects including plagiarism, double submission and/or publication, redundancy, misbehavior, information fabrication, and/or falsification, etc. have been entirely considered by the researchers. All data were analyzed according to the relevant laws and guidelines of the ethical standards of the Declaration of Helsinki.

RESULTS AND DISCUSSION:

Crimean Congo hemorrhagic fever has been reported in 26 of the 31 provinces in Iran. Among them, Sistan-Baluchestan, Isfahan, Tehran, Fars, Khuzestan, Khorasan Razavi, and Yazd provinces have the highest prevalence of this disease. Gilan, Golestan, Kerman, Ardabil, and Kermanshah provinces have recently been added to those with high CCHF prevalence. The mortality rate from CCHF is approximately 30-50%. However, a mortality rate of 17.6% has been reported in Iran. The CCHF mortality rate in the last 18 years in Iran has ranged from above 60% in 1999 to below 10% in 2017 [34]. According to reports, the numbers of definite cases of the disease during 2014-2016 were 39, 53 and 62, respectively, the numbers of certain deaths were 6, 6, 6, and the mortality rates were 15, 11, and 10%, respectively. Up to the beginning of September 2017, there were 124 definite cases of the disease and seven certain deaths caused by it. The number of definite cases of the disease reported between 1999 and 2016 was 1184. During this period, the largest numbers of definite cases were reported from Sistan-Baluchestan (730 cases), Khorasan Razavi (82 cases), and Isfahan (49 cases) provinces. Most of these cases were reported in July (179 cases) and June (173 cases). Based on occupation, the largest numbers of cases were observed among butchers and farmers (226 cases), housewives (190 cases), and slaughterhouse workers (182 cases). There were 935 male victims of the disease. In a study in Qum province, 85% of the patients reported a history of contact with livestock [34-36]. A study in eastern Iran showed that contact with animals was the most common way of getting infected (23%), whereas living in rural areas, presence of ticks in the residential area, contact with fresh meat and tick bites accounted for 19, 14, 12 and 3% of the reported cases, respectively [34]. Other major risk factors include age (over 40 years), occupation (including physicians, nurses, health and hospital workers, slaughterhouse workers, veterinarians, butchers, shepherds, and housewives), hiking, camping, and other activities in rural areas, contact with blood, secretions and tissues of infected animals, contact with blood, secretions and tissue samples of infected persons, tick bites, squishing or manipulation of ticks infected with CCHF and the season of the year. In a study in Qum Province, 12 patients (35.3%) were infected in the spring, twenty-one (61.8%) in the summer and one (2.9%) in the fall, and no cases were reported in the winter [34-36]. In Iran, the disease has been observed in all seasons of the year. However, the prevalence of the disease is higher in warm seasons (spring and summer) when the ticks are active. In Iran, most cases of the disease are caused by contact with infected livestock, whereas in Turkey most infections result from tick bites or contact with infected ticks. In Iran, direct infections through tick bites are rare and only a few such cases have been reported [37-40].

CCHF is caused by arbovirus CCHFV of the *Nairovirus* genus in the Bunyaviridae family. This virus is susceptible to dryness and heat and dies in dried blood, cooked meat, and PH < 6. The thermal resistance of this virus is low and they die after 30 minutes at 56°C. In addition to ticks, the main reservoirs of CCHF are animals such as cattle, sheep, goats, camels, rabbits, rodents, hedgehogs, and ostriches. The disease does not cause any specific clinical signs in domestic animals. It is usually asymptomatic in cattle, sheep, and other mammals. One week after these animals are bitten by infected ticks, they develop a mild fever due to virus replication and circulation in the blood and recover within a short period. In fact, the virus is detected in their secretions and blood for about a week. If the livestock is slaughtered within a week, the virus can infect people [9, 37, 41].

Ways of transmitting the disease include tick bites, contact with blood, tissues, and secretions of infected animals (such as urine, feces, saliva, and vomit), ingestion of fresh, raw or half-cooked meat of infected animal, inhaling contaminated air and putting the knife contaminated with animal flesh, viscera, and blood in the mouth. Contact with animal skin or wool, close contact with patients suffering from this disease, consumption of non-pasteurized milk and dairy products and nosocomial infections are other common ways of CCHF transmission [42, 43]. The incubation period of CCHF after tick bites is usually 1 to 3 days, with a maximum of 9 days. It is usually 5 to 6 days, with a maximum of 13 days, after contact with infected tissues or blood. The pre-hemorrhagic phase lasts about 1-7 days, with a mean of 3 days, the hemorrhagic phase takes 1-10 days, with an average of 4 days, and the convalescence may take one month or more. Patients gradually recover from day 10 when the cutaneous rash becomes pale. The onset of symptoms is sudden in humans. It starts with symptoms such as fever, headache, muscle pain, weakness, irritability, anorexia, severe pain in limbs and back pain, eye pain in some cases, red eyes, abdominal pain, diarrhea, and vomiting. After 3-4 days, hemorrhage including subcutaneous hemorrhage, hematemesis, hematochezia, bleeding from gums and ears, and hematuria continue and the patient develops hepatitis [26, 40-42]. A patient with CCHF must be immediately hospitalized, treated and isolated from other patients. The foremost treatment for CCHF is supportive care that includes management of electrolyte and fluid balances and, if necessary, blood and platelet transfusions. Ribavirin capsules are the only antiviral medication that is largely effective in treating CCHF. Timely consumption of this drug will have a major influence on treatment outcome [44-46].

Ticks are blood-sucking arthropods that live on mammals, birds, reptiles, and amphibians as ectoparasites and nearly all of them are capable of feeding human blood. Ticks are classified into hard ticks (the Ixodidae family) and soft ticks (the Argasidae family) [47]. Hard ticks are ectoparasites that infest animals prompting severe transmittable infections [48]. Hard ticks (Ixiodid ticks) transmit more diseases due to being heteroxenous (multi-host). Major diseases transmitted by ticks include Lyme disease, tick-borne relapsing fever, tick-borne encephalitis, hemorrhagic fevers such as CCHF, tularemia, Q fever and babesiosis [49-52]. The saliva of ticks, especially that of hard ticks, is highly toxic and can induce tick paralysis in addition to transmitting diseases. There are various peptides such as agents present in scorpion venom and other venomous animals in the saliva of hard ticks. These peptides cause various complications including tick paralysis. Ticks inject saliva into their host to inhibit pain, prevent blood clotting and dilute it. Some of the harmful local and systemic effects of tick bites are due to the peptide compounds and various enzymes present in the saliva of ticks [53-55]. The presence of anticoagulant compounds in the saliva of ticks may cause redness and localized hematoma of the skin. Tick paralysis (an acute and progressive muscle paralysis that is potentially fatal) is caused by the presence of toxins in the saliva of ticks. Rapid detection and removal of ticks can quickly improve tick paralysis. Ticks are found in all parts of the animal's body. However, they most commonly attack the areas with low hair and thin skin such as the groin area, testicles, breasts, under the abdomen and the area under the tail and inside the ear. Notable characteristics of ticks that have caused them to be vectors of a large number of pathogens include parasitic behavior throughout their life cycle, extended periods of sucking blood from their hosts, access to a wide range of vertebrate hosts, high reproductive potential, long life span, and high levels of adaptation to harsh conditions [56-58]. To date, 899 species belonging to the Ixodidae family have been reported worldwide. Due to the abundance of ticks in Iran, numerous cases of bites and diseases transmitted by them have been reported from different regions of the country [59, 60].

Over 30 species of ticks have been identified in Iran from Ixodidae and Argasidae families [61]. The CCHF virus is naturally transmitted by hard ticks of the genus *Hyalomma* [5, 37]. Tick vectors of CCHF in Iran include *Dermacentor marginatus*, *Hyalomma anatolicum*, *Hyalomma asiaticum, Hyalomma detritum*, *Hyalomma dromedarii*, *Hyalomma marginatum*, *Hyalomma Schulze*, *Haemaphysalis inermis*, *Haemaphysalis punctata*, *Ornithodoros lahorensis*, *Rhipicephalus bursa*, and *Rhipicephalus sanguineus* [62, 63]. The geographical spread of CCHF is consistent with the geographical spread of *Hyalomma* ticks, which is up to 50 degrees north latitude. CCHF virus infection has also been detected in *Argas reflexus* in Hamadan county (western Iran). *Hyalomma marginatum* and *Hyalomma anatolicum* are invasive species actively searching for human blood and are the major vectors in epidemics. However, other species of ticks are less invasive and responsible to maintain the virus between ticks and wild and domestic animals in enzootic foci. Immature ticks become infected through sucking blood from small vertebrates, and adult ticks transmit the infection to large vertebrates such as cattle. The CCHF virus has the ability to transmit through tick eggs and during different stages of its life cycle [64-67].

Virus infection in ticks is reported to be 3.4-28% in different regions of Iran [65-67]. Increasing temperature and decreasing precipitation have increased the activity of ticks and consequently disease incidence [68]. Many studies have been conducted on ticks in Iran. In a study in Lorestan province (western Iran), Taherian et al. identified three species of *Hyalomma* as well as one species of each of the *Dermacentor*, *Haemaphysalis*, and *Rhipicephalus* genera [67]. In another study on hard ticks in Garmsar county (central Iran), three genera and nine species were reported [69, 70]. Telmadarraiy et al. studied Ixodidae fauna in West Azerbaijan province (northwestern Iran) and reported that the most and least frequently observed genera were *Rhipicephalus* (42%) and *Haemaphysalis* (3%) [71]. Razmi et al. carried out a study in Mazandaran province (northern Iran) in 2004-2005 and reported that most infected cattle were infested with hard ticks belonging to *Boophilus annulatus* and *Dermacentor* spp. (51.3 and 0.1%, respectively) [72]. In 2006-2007, a study conducted on hard ticks in goats in West Azerbaijan province showed that 2.88% of them were infested with hard ticks. The highest frequency belonged to *Rhipicephalus bursa* (58.96%) and *Hyalomma anatolicum* (35.85%) and the lowest (1.19%) to *Haemaphysalis punctata* [73]. In Iran, *Hyalomma anatolicum* is the most widely distributed tick species in the genus *Hyalomma* and it is observed in most parts of Iran [74, 75]. In a study by Asgarian et al. in Sari county (northern Iran) in 2007-2008, hard ticks belonging to six species were collected. The most commonly found species were *Rhipicephalus bursa* and *Hyalomma detritum* with 63.76 and 15.35% prevalence, respectively [76]. Iranian researchers have conducted many scattered studies on ticks that are vectors of human diseases. There are seven genera of hard ticks in Iran and most studies on their distribution were carried out in the areas bordering the Caspian Sea [77]. Ticks are considered dangerous blood-sucking parasites as they might cause tick paralysis. They cause skin complications through blood-feeding. Swelling in the skin and rash are the most common symptoms of blood-feeding by ticks in humans [78, 79]. These skin complications may be similar to those caused by bites (or stings) of other venomous animals such as snakes, scorpions and other arthropods [77, 78]. In addition to the effects resulting from tick bites (due to the entry of their mouthparts into the skin) and toxicity caused by the enzymes present in the saliva of ticks, secondary infections also occur due to the presence of opportunistic microorganisms [79]. As one of the restrictions of this study, we just applied the information gathered from the disease surveillance system to compute the burden, incidence, and fatality of CCHF. Crimean-Congo hemorrhagic fever surveillance system, like to other surveillance systems performed for other diseases, suffers from under-reporting.

CONCLUSIONS:

Management measures are required to control the disease. The most important one of them is the 'One Health' approach that requires careful and comprehensive inter-sectoral collaboration. Attention to people's role in disease control is crucial and they need to believe in health recommendations in order to change their behavior. People should purchase meat from authorized places, avoid direct contact with fresh meat and abstain from eating fresh meat and raw and half-cooked internal organs such as the liver and heart. Eating fresh and raw meat is the last way and least significant of the transmission of this disease. The more important ways of disease transmission are tick bites and contact with blood and secretions of infected livestock or humans. Education through people themselves is an effective measure launched by the Ministry of Health in Iran since several years ago. People's health behaviors should be the focus of attention and their education, notification and trust-building should be prioritized. Physicians should also be aware of their important role in community education and disease control, and the principles of disease treatment, high clinical precision and accuracy, infection control and timely treatment should be among their programs and priorities. Controlling ticks on livestock by spraying the animals' bodies and barns with insecticides such as deltamethrin and lambda cyhalothrin is the main and most important way to control the disease. Improvement of the barn environment and filling the gaps and grooves in the walls is necessary to eliminate shelters for ticks. It is necessary to pay attention to proper control measures throughout Iran, especially in the high-risk provinces, through careful and correct management.

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The authors declare that they have no competing interests.

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