



REVIEW

Current situation of Crimean-Congo hemorrhagic fever in Southeastern Europe and neighboring countries: a public health risk for the European Union?



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Summary Crimean-Congo hemorrhagic fever (CCHF) is the most widespread tick-borne viral infection of humans, occurring across western China through southern Asia, Middle East, and Southeastern Europe (SEE) and in the most of African countries. CCHF virus is maintained through vertical and horizontal transmission in several genera of ticks, mainly in *Hyalomma*, which spreads the virus to a variety of wild and domestic mammals, which develop a transient viremia without signs of illness. Human infections occur through tick bite or exposure to the blood or other body fluids of an infected animal or of a CCHF patient.

In SEE the number of clinical cases of CCHF as well as the areal of the infected ticks continuously rapidly increased after 2000.

The aim of this study was to present actual situation of CCHF in SEE. Sources of information include published literature and personal unpublished data.

Conclusions: Based on: 1. *Hyaloma's* presence in Western EU countries, 2. Changes in climatic conditions and 3. Absence of an active vaccination against CCHF, it can be expected that this disease will continue to present real threat for human health in SEE and Southwestern Europe (SWE).

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1. Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute viral disease (*Nairovirus*, family *Bunyaviridae*) and a very contagious zoonosis transmitted to humans by many types of ticks, mainly *Hyalomma* genus, and by direct contact with blood or excretions and secretions of viremic patients and hosts. A number of domestic animals like hares, cattle, sheep, and goats are the main animal hosts. CCHF are endemic in Turkey, Asia, parts of Africa, Middle East and some countries in Eastern Europe. Because the CCHF is very contagious disease, the virus can be spread by excretions and secretions between health workers and close contact persons. This can be evidenced as community or nosocomial infection causing community or intra hospital outbreaks. Human to human transmission is typical for healthcare workers, close relatives contacts and exposure to blood or other body fluids of CCHF patients [1,2,3].

This disease was classified as Biosafety level 4 by Centre for Disease Control (CDC) and World Health Organization (WHO) therefore, high bio-contaminant facilities are required for working with excretions, secretions and CCHFV. WHO is acting with health workers in endemic areas promoting preventive measures and recommending the necessary steps in order to reduce the incidence of infected inhabitants and health care workers in endemic foci [4]. European Centre for Disease Control (ECDC) is more focused on developing protocols for CCHF, promoting interdisciplinary approach, building laboratory diagnostic capacities and networks links between WHO, World Organization for Animal Health (OIE), European Network for Diagnostics of "Imported" Viral Diseases (ENVID-CLRN) and International Network for Capacity Building for the Control of Emerging Viral Vector Borne Zoonotic Diseases (Arbo-Zoo Net) [5].

Well informed and trained health workers are a good prerequisite for preventing, detecting and taking adequate measures for specific infectious diseases that present threat to general population. If we take a look on first registered cases with CCHF, we can see that in some countries, the required time to make the correct diagnosis and starting adequate measures for prevention and treatment was much longer in the beginning than after some experience with this. In this regard, we analyzed last CCHF publications based on diagnosis, prevention, treatment and threats to EU bordering countries from endemic SEE countries.

2. Methods and objectives

The objective of this study was to present the actual situation with CCHF in SEE and the threat to neighboring and distant countries. The review aims to analyze and summarize findings available in the literature and present the personal experiences, related to animal reservoirs, transmitting vectors, local environmental conditions, clinical presentation of the diseases preventive measures and treatment.

For this purpose, we searched in PubMed database for related articles. In addition, we used conference presentations and personal communications. PubMed search

was performed in January 2016. It was done using following word combination:

- CCHF epidemiology,
- CCHFV genetic diversity
- CCHFV animal reservoirs,
- CCHFV transmitted vectors,
- CCHFV environmental conditions,
- CCHF clinical presentation,
- CCHF treatment,
- CCHF preventive measures.

3. Results

From PubMed search we found 572 publications, from them 298 were published during the last 5 years. As for detailed analysis we took publications filtered based on SEE and other European countries, Middle East and Turkey.

3.1. Genetic diversity of Congo-Crimean hemorrhagic fever virus (CCHFV)

In the last 10 years the CCHF virus characteristics are presented within 515 publications. CCHFV displays the greatest degree of sequence diversity of any *arbovirus*, with divergence of 20, 22 and 31% among the S-, L- and M-segments of virus isolates. Based on the analysis S-, M- and L-segments researchers have generated phylogenetic trees of the viral genome and labeled these as lineage I–VI [6].

Within Europe, there are present lineages V and VI (Kosovo, Albania, Turkey, and Bulgaria) and lineage VI in Greece [7–9]. The list of CCHFV lineages/clades according to viral S-segment and regional distribution are presented in Table 1.

3.2. Pathogenesis of CCHF

When CCHF was first identified in 1944, it was clear that its major pathologic abnormality was the vascular dysfunction, resulting in hemorrhage and loss of fluid from the plasma into the interstitial space. Soviet clinicians referred to the disease as "infectious capillary toxicosis", based on autopsy findings that "the main pathologic process in the organs is caused by blood circulatory disturbances, chiefly in capillaries and small vessels..." [10]. Since then, there are analyzed mostly known cytokines that are involved in pathogenesis and outcome of this disease. These observations are published in 38 publications in PubMed. It was found that CCHF patients display abnormal coagulation parameters from an early stage of illness, and that severe disease is characterized by disseminated intravascular coagulation (DIC) [11]. However, it is not known whether vascular dysfunction is brought about directly (through viral infection of the endothelium), or indirectly (through the effects of circulating proinflammatory mediators). The only current evidence that CCHFV can directly infect the human vasculature is a 1997 report on necropsies of 12 cases, which described the detection of viral RNA and antigens in mononuclear phagocytes, hepatocytes and endothelial

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