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REVIEW ARTICLE

Crimean-Congo Hemorrhagic Fever

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ABSTRACT

Crimean-Congo hemorrhagic fever (CCHF), a tick-borne viral hemorrhagic fever, is a zoonotic infection that caused by CCHF virus *(CCHFV)* of the family *Bunyaviridae*, genus *Nairovirus*. Transmission occurs mainly by *Hyalomma m. marginatum* tick exposure. Blood and bloody excretions of the patients are highly infectious and contact of skin and mucous membrane may lead to CCHF transmission. CCHF was described firstly in the Crimean peninsula in 1944, in former Soviet Union and in Kelkit Valley in 2002 in Turkey. By the year 2013, it has been notified in more than 30 countries of Asia, the Middle East, Southeastern part of Europe and Africa. The disease is characterized by fever and thrombocytopenia, in severe cases, hemorrhage and shock. Although, the case fatality rate for the infection is generally ranged from 10 to 50%, it was reported as 5% for Turkey. Main targets of CCHFV are immune cells and endothelium. Both innate and adaptive immunity are important for fighting against CCHFV in the host. Headache, fever, fatigue and muscle, joint pain, conjunctival injection, facial hyperemia, thrombocytopenia, elevated liver enzymes, hepatomegaly and splenomegaly are the main symptoms and findings for CCHF. Hemorrhagic manifestations including ecchymosis, melena, hematochezia, hematemesis, and epistaxis are commonly seen in severe cases. Supportive treatment is essential and nowadays neither a special drug, nor safe vaccine for humans is available for the treatment and prevention of CCHF. In case of penetrating injury with contaminated material, the oral ribavirin prophylaxis may be offered after the area being washed with soapy water and ethanol. *J Microbiol Infect Dis 2014; Special Issue 1: S1-S9*

Key words: Crimean-Congo hemorrhagic fever (CCHF), CCHF virus, epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment, prevention

Kırım-Kongo Kanamalı Ateşi

ÖZET

Kırım-Kongo kanamalı ateşi (KKKA) Bunyaviridae ailesi, *Nairovirüs* cinsine mensup KKKA virüsü (CCHFV) tarafından oluşturulan kene kaynaklı bir viral hemorajik ateş ve zoonotik bir enfeksiyon hastalığıdır. Bulaş başlıca *Hyalomma m. marginatum* keneleri ile temas sonucu oluşur. Hastalara ait kan ve kanlı vücut çıkartıları son derece bulaştırıcı ve cilt ve mukoza temasıyla KKKA bulaşı olabilir. KKKA ilk olarak eski Sovyetler Birliği'nde 1944 yılında Kırım yarımadasında, Türkiye'de Kelkit Vadisi'nde 2002 yılında ilk olarak tarif edilmiştir. KKKA 2013 yılı itibarıyla Güneydoğu Asya, Orta Doğu, Avrupa ve Afrika'da 30'dan fazla ülkede bildirilmiştir. Hastalık ateş, trombositopeni ve ciddi vakalarda kanama ve şok ile karakterizedir. Vaka-ölüm oranı genellikle %10-%50 arasında değişmekle birlikte Türkiye için %5 olarak bildirilmiştir. CCHFV'nin konak dokuda ana hedefleri bağışıklık hücreleri ve endotel olup, CCHFV'ye karşı korunmada konakta hem doğal ve hem de özgül bağışıklık önemlidir. Baş ağrısı, ateş, halsizlik, kas ve eklem ağrısı, konjuktiva ve yüzde kızarıklık, trombositopeni, karaciğer enzimlerinde yükselme, hepatomegali ve splenomegali KKKA için önemli belirti ve bulgulardır. Ekimoz, melena, hematokezia, hematemez ve burun kanaması gibi kanama bulgular ağır vakalarda görülür. Destek tedavisi esas tedavi olup günümüzde insanlarda kullanılan KKKA'ya özgül ne bir ilaç ne de güvenli bir aşı bulunmamaktadır. Penetran yaralanma durumunda yaralanan bölgenin sabunlu su ve etanol ile yıkanmasından sonra oral ribavirin profilaksisi verilebilir.

Anahtar kelimeler: Kırım-Kongo kanamalı ateşi (KKKA), CCHFV, epidemiyoloji, patogenez, klinik belirtiler, tanı, tedavi, korunma

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INTRODUCTION

The term of viral hemorrhagic fever (VHF) designates a group of diseases, caused by enveloped RNA viruses from four different virus families (*Arenaviridae, Filoviridae, Bunyaviridae* and *Flaviviridae*), is acquired through contact with animals or the bite of an infected arthropod. At least 14 different viruses belonging to these families were defined as the cause of VHF.[1] These illnesses are characterized by fever and malaise, increased vascular permeability leading to a fall in plasma volume and the development of coagulation defects that can result in bleeding.[2,3] They can be seen in any country of the world due to increased travel and tourism although they may be frequently seen in sporadic cases in rural areas of developing countries. VHFs can sometimes cause the death of many people by making major outbreaks. Today, in spite of the modern techniques of intensive care, there is still high mortality of patients with VHF.[4] Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic disease caused by CCHF virus (CCHFV) of the family Bunyaviridae, genus Nairovirus. The case fatality rate (CFR) for the infection is generally ranged from 10 to 50%.[5] But it has been reported as 5% for Turkey.[6] Herein, CCHF, an important disease of VHF, is reviewed in the light of literature.

History, epidemiology and virus characteristics

The disease was described firstly in the Crimean peninsula in 1944 during an outbreak, which involved more than 200 cases and was called as Crimean hemorrhagic fever. Afterwards, the virus isolated in the Democratic Republic of Congo in Africa was noted to be the same pathogen, resulting in the name of CCHFV.[7] Until now, CCHF infection has been reported in more than 30 countries of Asia, the Middle East, Southeastern part of Europe and Africa.[8] By the year 2013, more than 8000 human cases were reported in Southeastern Europe (Albania, Bulgaria, Greece, and Kosovo) and Turkey. An epidemic characterized by fever and bleeding with a history of tick exposure in a wide geographical area including Tokat, Sivas, Çorum, Amasya, Yozgat, Gümüşhane, Bayburt, Erzurum, Erzincan and the surrounding area; Northern parts of the Central and Eastern Anatolia and Southern part of the Black Sea region (Kelkit Valley) in the spring and summer of 2002 in Turkey has attracted the attention. In 2003, the disease diagnosed as CCHF and it spread to other provinces of Turkey, as well.[9-11]

Other genera within the *Bunyaviridae* family include *Orthobunyavirus, Hantavirus, Phlebovirus, and Tospovirus*.[8] A common feature of this family is the genome, consisting of three segments of single stranded RNA, referred to as the S, M and L segments. The S segment encodes the viral nucleocapsid protein (NP), M the glycoproteins (G_N and G_C), and L the RNA dependent RNA polymerase.[12] A CCHFV virion is spherical, ~100 nm in diameter, and has a lipid bilayer envelope ~5-7 nm thick, through which protrude glycoprotein spikes 8-10 nm in length. The glycoproteins are involved in adhesion to their receptors in mammalian cells. Virus is then taken into the cell by endocytosis. Viral replication occurs in the cytoplasm, endoplasmic reticulum and the Golgi apparatus and then the virus is released from cells.[8] CCHFV isolates from different geographical regions in the world are genetically different. Up to date, eight phylogenetically different CCHFV clones in the world have been defined. CCHFV strains isolated in Turkey belong to the fifth clone. The Turkish CCHFV strain, isolated from the patients in Black Sea Region of Turkey in 2003 was found to be genetically linked to Drosdov and Kosovo CCHFV strains by the S genome segment and only 1% of nucleotide differences were observed among the strains.[8,10]

CCHFV previously has been isolated from more than 30 ticks including *Hyalomma anatolicum anatolicum, Hyalomma truncatum, Hyalomma marginatum rufipes, Hyalomma impeltatum, Hyalomma impressum, Amblyomma variegatum, Boophilus decolaratus* and *Rhipicephalus, Ornithodoros, Dermacentor* and *Ixodes* species. Some of those ticks have not been proven to be the biological vector yet even if the virus is isolated from the ticks.[8] It is well known that the spread of CCHFV in a region primarily coincides with the spread of *Hyalomma* ticks. Ticks are not only vectors for CCHFV but also natural reservoirs since the virus can be transmitted transstadially, transovarially or by venereal route within the tick population.[5]

It is believed that the CCHF epidemics occur in Eastern Europe and Asia because of the changes of environmental conditions by humans. The first CCHF epidemic in the Crimean peninsula, during the World War II occurred due to opening of the tick-infected regions to agriculture. CCHF epidemics in former Soviet Union and Bulgaria are related to the politics of agriculture and farming of both countries. Regions with warm climate and highly fragmentation of the landscape vegetation are suitable habitats for Hyalomma ticks and correlate with high risk

areas for CCHFV infections in Turkey.[13] Changes in ecological conditions such as an increase in bush land, as a consequence of a neglected use of agricultural land or of deforestation measures to gain farmland, contributed to an increase in proper habitats for *Hyalomma* ticks and their reservoir animals.[5] The disease has a seasonal character. In the Northern hemisphere, the highest number of CCHF cases is reached from June to July. In Turkey, the cases become evident in March and continue to the end of September month. In the Southern hemisphere the majority of cases occur in Spring and Autumn.[14] CCHF appearance varies according to geographical regions and can also be seen in January related to tick movements.[15] In addition to ticks, animals play crucial roles in the life cycle of ticks particularly in transmission and amplification of the virus. Although viraemia in animals can continue for two weeks, they do not show any clinical signs of CCHF.[16] The CCHF transmission occurs mainly by tick exposure namely by tick bite (Figure 1) and crushing infected ticks and direct contact with blood or other infected animal or human tissues.[16,17] Intrauterine or perinatal CCHF transmission from mother to baby may also occur.[18] Agricultural workers, animal raisers, veterinarians, those who are in contact with sick animals, healthcare workers in CCHF endemic areas, soldiers, and campers are at high risk for CCHF infection.[19] The epidemics of nosocomial (hospital-acquired) CCHF after contact with the infected patient have been reported in many countries with high CFRs.[20,21]

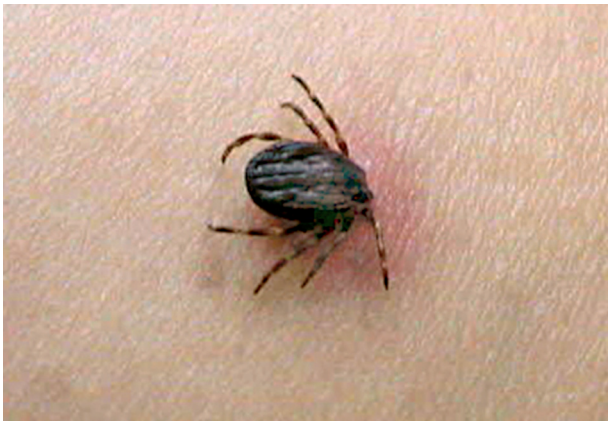

Figure 1. A tick attached to skin of a CCHF patient.

PATHOGENESIS

The main contributors for pathogenesis of CCHFV are endothelial cells and immune cells. Following the entry of CCHFV to the host, they encounter innate immune system cells including monocytes and dendritic cells. The CCHFV binds to the nucleolin on the susceptible cells through G_N and G_C glycoproteins is believed.[22] When these cells cannot successfully eliminate the viruses, they can continue replicating within them.[23] The infected cells produce various kinds of cytokines, chemokines, and inflammatory factors. One group of them is interferons (IFNs). CCHFV challenge in IFN receptor knockout mouse model causes severe infection, higher blood virus titers and fatality.[24] Toll-like receptors (TLRs) are type I transmembrane proteins that play a key role in the innate immune system and they are usually expressed in macrophages and dendritic cells, that recognize structurally conserved molecules derived from microbes. A common theme for TLRs is the induction of type I IFNs. Certain polymorphisms in the TLR8 and TLR9 gene have been linked to rapid progression of viral infections. Our previous study demonstrated that heterozygous plus homozygous mutant genotypes frequency for TLR8 Met1Val and for TLR9 -1486T/C were significantly higher in CCHF patients than that of controls. The study also demonstrated that TLR8 Met1Val, TLR8-129C/G, and TLR9-1486T/C polymorphisms were important either on the clinical severity or fatal outcome of CCHF.[25] Direct invasion of the endothelium by CCHFV is another important issue in the CCHF pathogenesis resulting in activation and upregulation of different adhesion molecules such as E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1).[26,27] Tumor necrosis factor (TNF)-α, released from innate immune system cells, is factor causing endothelium activation. Infected endothelial cells also release cytokines such as interleukin (IL)-6 and IL-8. Consequently, the increased vascular permeability causes tissue edema.[28]

In severe CCHF cases, dysregulation and excessive release of the inflammatory cytokines by endothelial activation leads to increased vascular permeability, vasodilatation, and subsequently hypotension, multiple organ failure, shock, and death.[8,29-31] The virus can also impair the innate immune system and causes a delay in adaptive immune response, which is critical for the clearance of CCHFV. The virus has many different ways to block the immune response, leading to uncontrolled viral replication followed by systemic spread of the virus throughout the body. Partial activation of dendritic cells and macrophages, delayed induction of IFNs, weak antibody response, apoptosis of

lymphocytes, and hemophagocytosis are some of these tactics.[32] The endothelial injury both leads to platelet aggregation and activation of the intrinsic coagulation pathway. The tissue factor releasing from the infected cells leads to developing of disseminated intravascular coagulation (DIC) by stimulating the extrinsic coagulation.[33] The role of DIC is clear in pathogenesis of the disease. In addition leukopenia, thrombocytopenia, anemia, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) and increased levels of fibrin degradation products, D-dimer, liver enzymes, and high CCHFV load are prominent in patients with severe CCHF.[8,10,32,34,35] Postmortem histopathology examinations of liver biopsy specimens reveal necrotic foci and massive necrosis. Cerebral hemorrhage, excessive anemia, dehydration and shock, myocardial infarction, pulmonary edema and pleural effusion were reported in fatal CCHF cases.[26]

CLINICAL MANIFESTATIONS

The incubation period of the disease depends on the mode of transmission of CCHFV. It usually takes 1-3 days after the tick bite, but may take up to 9 days.[8,36] However, some of the cases may have longer incubation period (13-53 days).[37] Patients initially exhibit nonspecific prodromal symptoms lasting less than one week.36 Clinical presentation of the disease can be in mild, moderate, and severe forms. Swanepoel et al.[36] described the cases as severe if at least one of the following laboratory values occurred in the first five days of the disease reflecting 90% of mortality: 1-blood leukocyte count ≥10^4/mm^3, 2-blood platelet count ≤2X10^4/mm^3, 3-serum aspartate aminotransferase (AST) level ≥200 IU/L, 4-Serum alanine aminotransferase (ALT) level ≥150 IU/L, and 5-aPTT ≥60 s or blood fibrinogen level ≤110 mg/dl. However, in a study from Turkey, the high serum AST and ALT levels (>700 and >900 IU/L, respectively) were found to be more sensitive in defining severe cases.[38] Additionally, our previous clinical study suggested splenomegaly and change of consciousness were the poor prognostic factors for CCHFV.[11] Furthermore a multicenter clinical study performed in 218 Turkish CCHF patients showed altered consciousness and prolonged international normalized ratio (INR) as the independent predictors for mortality by the Cox Proportional Hazards regression analysis.[9]

The initial symptoms are nonspecific, and sometimes there may be a sudden onset. The first symptom is usually headache. Then, fever, sore throat, extreme weakness, fatigue and muscle and joint pain occur commonly. The dizziness, neck pain, photophobia, jaundice, mood changes can be added to these complaints. Awareness may become blurred and the patients may be agitated in a few days. After two to four days, agitation and depression is replaced by exhaustion. Conjunctival injection and facial hyperemia may occur in up to half of the patients. In most cases, elevated liver enzymes and hepatomegaly are evident. Lymphadenopathy and splenomegaly may be detected.[4,36] In severe cases, hemorrhagic manifestations can develop in three to six days after onset of the disease. These hemorrhagic events can range from petechia to large areas of ecchymosis (Figure 2) and often appear on the mucous membranes and skin, especially on the upper body and/or extremities. Gastrointestinal bleedings in the form of melena, hematochezia and hematemesis, and epistaxis are also commonly seen by day four or five after symptoms onset. Other bleeding sites are vagina, the gums and, cerebral hemorrhage in most severe CCHF cases.[39] DIC and circulatory shock may ensue in such patients.[40] In general, death occurs 6 to 14 days after the onset of symptoms. In survivors the convalescence period begins about 10-20 days after onset of the illness. Patients usually need hospitalization for about 9-10 days.[41] Relapse of CCHF has not been reported yet.

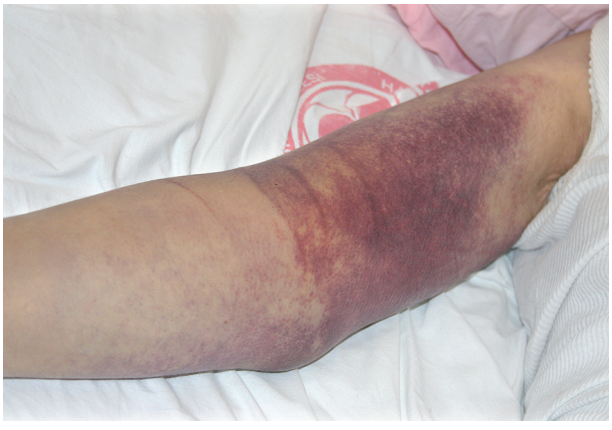

Figure 2. A large ecchymosis is seen on the arm of a CCHF patient.

LABORATORY FINDINGS

Laboratory abnormalities include usually leukopenia and thrombocytopenia, high levels of ALT and AST, prolonged bleeding time, PT and aPTT, elevated D-Dimer, and decreased fibrinogen levels.

Anemia due to bleeding and leukocytosis can also be seen in most severe and fatal CCHF patients. Atypical lymphocytes in blood smears, proteinuria and hematuria may also be observed. In the severe form of CCHF, bilirubin, urea and creatinine levels may increase.[10,11,17,42]

CCHF diagnosis

The early diagnosis is important because of the possibility of nosocomial CCHF occurrence with a high mortality. In Turkey, after the identification of CCHF infection in 2003, case definition criteria were established by the Turkish Ministry of Health for both surveillance and the treatment of CCHF cases. According to these criteria, a CCHF infection is considered if a patient has at least two of the following findings: fever, i.e. oral temperature >38°C, headache, diffuse body pain, arthralgia, weakness, diarrhea and bleeding plus epidemiological risk factor including tick exposure history and/or resident in, or travelling to a CCHF endemic region within the previous two weeks.[43] As stated above the typical laboratory findings of CCHF are thrombocytopenia, leukopenia and high levels of liver enzymes.[5] Even if the absence of a tick bite history, a CCHF suspected case should be examined carefully for the presence of a tick or tick-bite site on the body surface area. In our experience, beginning from the early phase of the disease, some of the CCHF patients may not have a thrombocytopenia on admission. Serial determinations of complete blood count (CBC) in such cases after one to two days of admittance may show thrombocytopenia. We observed that 15 out of 102 consecutive CCHF patients were not thrombocytopenic on admission (unpublished data).

Both isolation and culture procedures for CCHFV should be performed in a biosafety level (BSL)-4 laboratory conditions. The most reliable method for CCHFV isolation is intracranial or intraperitoneal inoculation of an acute phase blood sample or tick pools into newborn mice. The virus can also be isolated from blood and organ suspensions of acute phase patients by inoculating into cell lines including LLC-MK2, Vero, BHK-21, and SW-13 cells with the maximal virus yield after 4-7 days of incubation.[8,10] Serologic tests such as complement fixation, immunodiffusion, and hemagglutination inhibition, neutralizing antibody response, indirect IFA and ELISA are useful tests for CCHF diagnose.[44,45] Specific immunoglobulin (Ig)G and IgM antibodies against CCHFV may be detected in serum by ELISA method from six days after the onset of symptoms. Either the presence of IgM or a 4-fold rise in the titer of IgG antibody in serum samples between the acute and convalescence phases is diagnostic for CCHF. IgM antibody can be detectable up to four months, and IgG levels can be detectable by IFA test up to five years. Fatal CCHF patients do not usually develop a measurable antibody response, as well as in patients with early phase of infection. For this reason, the diagnosis is usually achieved by virus detection in blood or tissue samples. The reverse transcription-polymerase chain reaction (RT-PCR) and automated real-time PCR assay are molecular test methods for diagnosing of CCHF.[8,46-48]

Rickettsioses, leptospirosis, brucellosis, borreliosis, meningococcal infections, viral hepatitis, typhoid fever, sepsis, Q-fever and other VHF infections including hantavirus infections and Ebola and Marburg VHF, malaria, systemic inflammatory response syndrome (SIRS) should be considered in the differential diagnosis.[8,10] In our experience, thrombotic thrombocytopenic purpura (TTP), idiopathic thrombocytopenic purpura (ITP), and hematologic tumors must also be included in the differential diagnosis.

TREATMENT

CCHF suspected patients should be hospitalized for monitoring while patients with good condition who are able to report regularly for monitoring visits may be monitored on an outpatient basis. Patients having abnormalities in hemostatic parameters including PT, aPTT, and INR should be hospitalized. Hospitals must have a blood bank for obtaining blood products, and tertiary care hospitals must have a well-equipped intensive care unit (ICU).[43] Intramuscular injections, anti-inflammatory drugs and anticoagulant medications are contraindicated while oral or intravenous paracetamol may be administered to reduce fever.[42,43] Vital signs of patients should be closely monitored. The patient who requires respiratory support and mechanical ventilation should be followed in the ICU.[43] For the prophylaxis of gastrointestinal system bleeding, administration of oral or intravenous proton pump inhibitors is recommended.[42,43] During the hospitalization, oral cavity, lips and tongue must be treated regularly with Vaseline oil. Blood crusts in the oral cavity must be removed. Patients room must be regularly ventilated through outside. Sheets and pillowcases should have no creases in order to prevent bedsores and hemorrhages.[4]

Up to date there is no specific effective antiviral agent for CCHF approved by the US Food and

Drug Administration (FDA), but the Centers for Disease Control and Prevention (CDC) considers ribavirin 'likely' effective in the treatment of CCHF.[40,49] Although ribavirin, an antiviral drug, has been used for prophylaxis and treatment, its use is still controversial. Ribavirin, a nucleoside analogue, inhibits the replication of distinct DNA and RNA viruses including family *Bunyaviridae*.[40,50] An experimental study showed that ribavirin therapy reduced the virus titers in CCHFV infected infant mice.[51] The recommended dosage of intravenous ribavirin by the WHO is 17 mg/kg loading dose, then 17 mg/kg every 6 h for 4 days, and then 8 mg/kg every 8 h for 6 days and 30 mg/kg initial loading dose, followed by 15 mg/kg every 6 h for 4 days, followed by 7.5 mg/kg every 8 h for 6 days for oral form of ribavirin.[52,53] Even if the virus is susceptible to ribavirin in-vitro, the drug may have not therapeutic efficacy in-vivo must be reminded. In humans, the clinical efficacy of ribavirin has been investigated in several studies.[9,53-60] Fisher-Hoch et al.[53] reported three nosocomial CCHF cases were treated successfully with oral ribavirin. They also noted that the three patients to whom the drug was given on the fifth or the sixth days of the disease became afebrile 48 hours after starting ribavirin. Clinical reports from Iran suggest oral ribavirin is effective in CCHF. Firstly, Mardani et al.[54] demonstrated that the efficacy of oral ribavirin was 80% among the patients with confirmed CCHF and 34% among the patients suspected of having a CCHF. In the second report performed between 1999 and 2004, the efficacy of oral ribavirin treatment was 75% among the 255 confirmed and suspected CCHF cases.[55] The third clinical study suggested that the oral ribavirin could be effective in CCHF, if patients treated in the first five days of the disease.[59] In a report from Turkey, Ergonul et al.[56] stated all of the eight oral ribavirin treated patients survived. Another study from Turkey using a historic control showed that the mean recovery time in the ribavirin group was shorter than that of control group. However, the need for blood and blood products, mean length of stay (LOS) in hospital and CFRs were identical between the groups.[57] In the third clinical study from Turkey, no effect of intravenous form of ribavirin was found among the severe CCHF cases.[58] Our previous study on this subject showed no statistically different CFRs between ribavirin treated 126 patients and ribavirin-untreated 92 patients (7.1% vs. 11.9%).[9] Until now, there is only one prospective randomized clinical study investigating the efficacy of oral ribavirin in CCHF in Turkey. In that study, Koksal et al.[60] showed that no positive effects were observed both in clinical or laboratory parameters in CCHF patients treated with ribavirin. Due to the embryotoxic and teratogenic effects of ribavirin, it is contraindicated in pregnant women. However, the adult doses of the drug can be given if necessary. Hemolytic anemia, pruritus, rash, depression, sleep disorders, and cough are the mostly seen side effects for the drug.[36] As a result, the efficacy of both oral and intravenous ribavirin treatment in CCHF is controversial and randomized controlled studies with more samples are needed. For this reason, supportive therapy is essential for CCHF including administration of intravenous fluids, platelet suspensions, fresh frozen plasma and erythrocyte suspensions when needed. Early supportive therapy in CCHF can save life. Corticosteroid and intravenous immunoglobulin (IVIG) use and plasma exchange transfusion are other unproven supportive treatments for CCHF.[43]

The other issue is hyperimmune serum in the treatment of CCHF. Hyperimmune serum (80-200 ml), prepared from recovered CCHF patients and gammaglobulin, obtained by immunizations of horses may be effective in the treatment of the patients. In 1969, a Russian researcher Lazarev reported that the convalescent phase CCHF serum was useful only on days between 1 and 3 after disease onset. According to the author when it is used, it reduces the febrile period length and prevents or reduces the severity of hemorrhages. However, five years later, the same researcher considered that the earlier data were insufficient for its use in CCHF.[61] In 1990, Vassilenko et al.[62] suggested the use of immunotherapeutic treatment for patients with severe CCHF via the passive simultaneous transfer of two different specific immunoglobulin preparations obtained from the CCHF survivors. The author also stated that the treatment resulted in quick recovery of all patients. Administration of CCHFV hyperimmunoglobulin has been suggested as an alternative treatment approach for severe CCHF in a different clinical investigation.[63] Since the absence of randomized controlled studies, convalescent phase serum treatment in CCHF is still controversial.

PREVENTION

Since ticks play important roles in transmitting of CCHF disease, people living in endemic areas should use personal protective measures such as the avoidance of areas where tick vectors are abundant, regular examination of clothing and skin for ticks and the use of repellents containing DEET (N, N-diethyl-m-toluamide). People who are exposed to

potentially viraemic animal blood should take practical measures to protect themselves, including the use of repellents on the skin and clothing and wearing gloves or other protective clothing to prevent skin contact with infected tissue or blood. Among the viruses causing VHF, only the Lassa fever virus, Marburg and Ebola VHF viruses, Hantavirus and CCHFV can be able to person to person transmission. Transmission from person to person is particularly high during the end stage of the illness characterized by vomiting, diarrhea, shock, and often hemorrhage.[4] All patients should be isolated in a single room with an adjoining anteroom serving as only entrance. In any case, strict blood and body fluid control precautions should also be started on admission, and continued during hospitalization when transferring the patients among departments in order to limit CCHF exposure. All physicians and other healthcare workers (HCWs) should be well informed about CCHF.[8,43]

The universal precautions (gloves, gowns, goggles, masks, etc.), should be instituted during contact with the patient and their secretions, and invasive procedures should be minimized as soon as possible.[8] Our recent study showed the presence of a low CCHF seroprevalence rate (0.53%) among the HCWs in a teaching hospital. The study also showed a high compliance rate among the HCWs for personal protective equipment usage.[64] Because of transmission risks by handling infectious materials, clinical laboratory specimens should be obtained carefully, placed in plastic bags that are sealed, and then transported in clearly labeled, durable, leak-proof containers directly to the specimen handling area of the laboratory. Laboratory staff should be alerted to the nature of the specimens and they should be handled in a BSL-2 safety cabinet. Contaminated environmental surfaces or objects should be cleaned and disinfected using standard procedures.[4] The oral ribavirin prophylaxis may be offered to anyone at high risk of infection, including those who exposed directly to the blood of CCHF patients through contact or needlestick injury.[10] In case of penetrating injury, the area should be washed with soapy water and ethanol and the person should be followed up for 14 days in terms of CCHF. Other exposures should be placed under medical surveillance and individuals should be instructed to record their temperatures twice daily. If body temperature of 38.3°C or higher is measured, ribavirin should be initiated promptly as a presumptive treatment.[40]

Currently, there is no safe and effective CCHF vaccine available. A formalin inactivated CCHF vaccine after production of virus in mouse brain has been developed in Bulgaria. Despite of high antibody titers is obtained with the vaccine, the production technology is already quite old and current availability is controversial.[8,65] While a DNA vaccine has been developed against the M genome segment of CCHFV, desired immunogenic response has not been detected in an experimental study with animals.[66] The virus-specific vaccine development researches are still ongoing.

Conflict of interest: The authors report no conflict of interest.

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