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Crimean-Congo Hemorrhagic Fever: A Reemerging Disease

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Context: Crimean-Congo hemorrhagic fever (CCHF) is a fatal viral disease which has 30% to 80% mortality rate. In endemic areas, livestock handlers, skin processors, veterinary staff, livestock market employees, farmers, and health care staff are at risk. Diagnosis is made based on clinical manifestations, epidemiologic factors, and laboratory tests. Here, we reviewed the epidemiology, clinical manifestation, diagnosis, treatment, and the prophylaxis of CCHF.

Evidence Acquisition: We searched electronic databases (PubMed and Scopus) from January 1980 to May 2014. Key words including CCHF, epidemiology, clinical manifestation, treatment, and prevention routes were searched.

Results: CCHF is widely distributed in different countries worldwide and is also endemic in our country, Iran. Treatment is mainly supportive; however, if the patient is suspected to have CCHF, ribavirin therapy is needed immediately. High dose methylprednisolone, interferon, and intraveonus immunoglobulin (IVIG) are other treatment protocols. Postexposure prophylaxis should be considered potentially in people who were exposed to CCHF virus, such as those who have mucous membrane contact or percutaneous injuries in contact with body secretions or blood of infected animal or patients with CCHF.

Conclusions: CCHF is a fatal viral disease. Therefore, preexposure and postexposure prophylaxis should be potentially considered to decrease the rate of infection.

*Keywords:*Prevention; Transmission; Communicable Diseases, Emerging; Hemorrhagic Fevers, Viral; Crimean-Congo hemorrhagic fever

1. Context

Crimean-Congo hemorrhagic fever is an acute febrile hemorrhagic disease caused by a tick-borne virus belonging to the genus *Nairovirus* of the Bunyaviridae family. The primary routes of disease transmission to humans include tick bites (*Hyalomma marginatum*) or direct contact with blood or body discharges of the infected human or viremic livestock (1). CCHF is one of the most widely distributed viral hemorrhagic fevers in Africa, Middle East, Asia, and in many parts of Eastern Europe. Changes in climate can expand the range of tick vector, and increase the incidence of disease. CCHF causes a severe lethal disease with 30% to 80% mortality rate (2, 3). The CCHF virus is also a potential bio-terrorist agent, it has been listed as C priority pathogen of CDC/NIAID Category (4). Early treatment within the first three days of disease can significantly decrease the mortality rate (4-6). Mortality is typically due to hypovolemic shock resulted from severe bleeding, disseminated infection, and disseminated intravascular coagulation (DIC) (1, 4). Since 1999, the Iranian Ministry of Health reported from the high incidence of disease in Sistan-Balouchestan, Isfahan, and Golestan provinces (2-4). Now, CCHF is an endemic disease in Iran, especially in the southeast region of Iran, in the Afghanistan and Pakistan border. About 67% of cases in Iran have been reported from Sistan-Baluchestan, a southeastern province of Iran (1, 2, 4). Neighboring countries of Iran including Afghanistan, Pakistan, and Turkey have reported an increased prevalence of CCHF during recent decade.

2. Evidence Acquisition

We searched the electronic databases (PubMed and Scopus) from January 1980 to May 2014. Key words including CCHF, epidemiology, clinical manifestation, treatment and prevention routes were searched.

3. Results

3.1. Geographic Distribution

CCHF is widespread in Africa, Middle East and Asia. It has also been reported in many parts of Europe including southern parts of the former Union of Soviet Social-

Implication for health policy/practice/research/medical education:
CCHF is one of the most widely distributed viral hemorrhagic fevers in Africa, in the Middle East, Asia, and in the many parts of Eastern Europe. It is now an endemic disease in Iran. The virus can lead to a severe lethal disease with 30 to 80% mortality rate. Prompt diagnosis and proper treatment lead to a good outcome. Pre –exposure and post-exposure prophylaxis should be considered potentially to decrease the rate of infection.

ist Republics (USSR) (Tajikistan, Kazakhstan, Uzbekistan, Crimea, Rostov, Astrakhan), Iran, Pakistan, United Arab Emirates, Turkey, Bulgaria, Greece, Albania and Kosovo province of the former Yugoslavia (1-4). Serological findings showed that CCHF may also be found in some parts of Portugal, Hungary, and France (4). CCHF was described in the Crimea in 1944 during an outbreak, which involved more than 200 cases, and later the same virus was isolated from patients in Congo, where the name of Crimean-Congo hemorrhagic fever virus (CCHFV) has come from. First cases with CCHF in Iran have been reported in 1970 when blood samples of sheep were sent to Russia for investigation. But, it was reported as a reemerging disease in 1999 from western portions of Iran (1-3, 7). The incidence of this virus infection is correlated with the distribution of *Hyalomma* spp. Seasonal variations have been described. In Iran, its high incidence has been reported in August and September, while in Pakistan, the disease incidence was higher between March and May, and again, between August and October (7, 8). Changes in climate have been suggested to be one of the factors facilitated the reproduction of the tick population, and consequently the increased incidence of tick-borne infectious diseases such as CCHF (8).

3.2. Transmission

CCHF virus usually transmitted between asymptomatic animals (many species of mammals) and ticks in an enzootic cycle. This virus infects many species of ticks, including Ixodidae family (hard ticks) (1-3). Members of the genus *Hyalomma* are the main vectors. *Hyalomma marginatumis* is an important vector. Transovarial and venereal transmission have been observed in this genus (4, 7). Many species of mammals can transmit CCHF to ticks when they are infected with viral agent. Small vertebrates such as rats, hares, and hedgehogs, which are infected by immature ticks, may be particularly important as amplifying hosts. With a few exceptions (ostriches), birds seem to be refractory to this infection (1, 2, 4, 7, 8). However, they may act as mechanical vectors by transporting the infected ticks. Migratory birds might spread the virus to distant geographic areas. Humans can be infected incidentally by the bite of infected arthropods, direct contact with blood or body discharges of the infected human or viremic livestock, or via aerosol generated from infected human or rodents. Horizontal transmission of CCHFV from a mother to her offspring has also been reported (9). Nosocomial transmission has been reported in Pakistan, Iran, South Africa, UAE, and Iraq (7). Risk of nosocomial transmission can be diminished by the appropriate infection-control measures, careful management of infected patients, and sometimes, providing prophylactic treatments for health-care workers after exposure to infection (7, 9). History of tick bite is one of the most important risk factors for CCHF. Livestock handlers, skin processors, veterinary staff, livestock market employees, farmers and other personnel employed in jobs requiring some contact with animals and animal products are also at high risk for CCHF (2, 3, 10).

3.3. Clinical Signs

The incubation period ranges from 2 to 9 days with the mean incubation time of 5 days (1, 2, 4). Incubation period can be shorter (a few hours) and sometimes longer (three weeks) and this is time related to inoculated viral size and the route of infection (4). There is a variety of clinical manifestations following viral CCHF infection and not all patients developed the classic form of CCHF syndrome. Patients had nonspecific prodrome, which typically lasts less than one week (2, 3, 11). Symptoms typically begin with sudden high fever, headache, backache, malaise, arthralgia, severe myalgia, nausea, vomiting, abdominal pain, and diarrhea (1, 11). Early signs typically include fever, tachypnea, hypotension, relative bradycardia, pharyngitis and sometimes conjunctivitis (4, 7). This early stage of disease is called the prehemorrhagic phase. It is followed, after several days, by the hemorrhagic phase, which is developed suddenly, is usually short, lasting for an average of 2 to 5 days (7, 11). A petechial rash is the first symptom. The rash is followed by petechiae, ecchymoses on the skin and mucous membranes. Epistaxis, hematemesis, hematuria, melena, hemoptysis, and bleeding from venipuncture sites are also common. Bleeding can occur in other organs, including the brain (1, 4, 7, 11). Hepatitis occurs in some patients, and may result in jaundice and hepatomegaly. Some patients die from hemorrhages (brain hemorrhage, hemorrhagic pneumonia or cardio-vascular disturbances). In patients who survived, 10 to 20-day recovery after the onset of illness was reported. The convalescent phase is characterized by generalized weakness, weak pulse and tachycardia (11). Other symptoms including sweating, nausea, mouth dryness, headache, dizziness, low appetite, polyneuritis, and memory loss have also been observed (4). Some patients temporarily lose all of their hair. Recovery is usually complete but is slow, and may take up to one year (4). Subclinical infections can occur which are more prevalent than clinical picture 5:1. Mild febrile cases without hemorrhages are also reported.

3.4. Diagnosis

Diagnosis is made based on the clinical manifestations, epidemiologic factors, and laboratory tests. Laboratory abnormalities were anemia, leukopenia, thrombocytopenia, increased AST/ALT levels, increased LDH level, prolonged prothrombin time (PT), elevated fibrin degradation products (FDPs), increased serum ferritin level and decreased plasma fibrinogen level (1, 2, 4, 11). The most prevalent laboratory abnormalities in hemorrhagic forms are pancytopenia, prolonged PT & PTT and increased serum transaminase especially AST (3, 4, 7, 10). CCHF virus is identified by indirect immune-fluorescence (IFA), enzyme-linked immunesorbent assay (ELISA), or reverse transcription-polymerase chain reaction (RT-PCR) assays. Serologic tests are less sensitive than PCR (10, 11). IgG and IgM can usually be found with indirect immune-fluorescence or ELISA af-

ter 7-9 days of infection. In fatal cases, patients died without developing antibodies (1, 4, 10, 11). Virus isolation must be performed in biocontainment laboratories (1, 4, 7, 10). Crimean-Congo hemorrhagic fever is often diagnosed by RT-PCR of blood samples, which is a highly sensitive technique. However, due to the genetic variability of CCHFV strains, a single set of primers cannot discover all the virus variants. A real-time RT-PCR assay that can detect numerous variants has recently been used (4).

3.5. Treatment

Treatment is mainly supportive. Most of patients with CCHF have passed a self-limited course. Therefore, direct observation and supportive treatment is recommended (1, 3, 4). However, if the patient meets the criteria for probable CCHF, ribavirin therapy should be started immediately (3, 4, 6, 10-22). Intensive monitoring, to guide volume and blood component replacement, is also recommended. Preventive measures such as administration of histamine receptor blockers to prevent peptic ulcers, to avoid intramuscular injections, and administration of aspirin and other anti-inflammatory drugs are recommended (1, 4, 7, 15, 20). Fluid and electrolyte balance should also be monitored carefully. Replacement therapy with necessary blood products should be performed by checking complete blood count, which must be done daily or twice a day (7, 9, 10). Despite the effect of ribavirin on the outcome of the disease, sometimes clinicians are faced with high mortality rate during supportive therapy and treatment with ribavirin. Passive immunotherapy with hyper immune serum has been tested in a few cases, but the effect of this treatment is controversial (7). Also, the interferon-induced MxA protein has been shown to have an inhibitory effect on several members of Bunyaviridae family, but the effect of MxA against CCHFV has not been previously studied (4, 7, 15). It seems high-dose of methyl prednisolone and IVIG are effective in the treatment of patients with CCHF (4, 7, 12, 19-24). In a case control study in Iran, Zahedan, we compared the effect of high dose methyl prednisolone (HDMP) in the patients with CCHF. Following HDMP therapy in hospitalized patients with severe thrombocytopenia, platelet count increased within 36 hours and leukocyte count within 48 hours of the treatment. A few patients required transfusion of blood products in intervention group compared to controls. None of the patients died in intervention group (20). These optional treatments need more investigations.

3.6. Prevention

Measures to avoid tick bites like tick repellents, avoidance of tick habitation, and systematic examination of clothing and skin for ticks are the most important routes of prevention. Cloths should be worn to prevent tick attachment, including long pants in the boots and long-sleeved shirts (4, 7, 10, 11). Acaricides should be used on livestock and other domestic animals to control ticks, particularly before slaughtering or exporting to another region. In meat, virus is usually inactivated by post-slaughter acidification. It is also killed by cooking (56°C for 30 minutes). Unpasteurized milk should not be drunk (4, 7). Laboratory workers must follow strict biosafety precautions and negative-pressure respiratory isolation should be measured, particularly if coughing, vomiting, or other activities generating large-droplet aerosols occurred. Strict universal precautions are necessary to prevent nosocomial infections (4, 10, 11). People entering to the patient's room should wear gloves and gowns, and those approaching within one meter should wear face shields or surgical masks and eye protection to prevent contact with blood or other body fluids (1, 11). Studies on vaccines against CCHF virus are limited and the vaccine is not available in many countries because of its method of preparation. An inactivated vaccine from mouse brains has been used in the former Soviet Union and Bulgaria (4). Postexposure prophylaxis should be considered potentially for people exposed to CCHF virus; in a bio terrorist attack and all known high-risk individuals such as those who have mucous membrane contact like kissing or sexual contact with a patient or those with percutaneous injury in contact with the infectious body secretions, or blood of patients with CCHF (7, 9, 11, 25-29), also those with close contacts such as living or shaking hands with the patients, process laboratory specimens, or health care workers who care such patients before initiation of standard precautions. They should be placed under medical surveillance and should be instructed to record their temperatures twice a day. If a temperature of 38.3°C or higher develops, treatment with ribavirin should be initiated promptly as presumptive treatment of CCHF (7, 9-11). Oral ribavirin, 200 mg twice daily, for 5 days is the recommended dose for post-exposure prophylaxis (7).

4. Conclusions

Crimean-Congo hemorrhagic fever is one of the most widely distributed viral hemorrhagic fevers in Africa, Middle East, Asia, and in many parts of Eastern Europe. The virus can lead to a severe lethal disease with 30 to 80% mortality rate. Prompt diagnosis and proper treatment lead to a good outcome. Preexposure and postexposure prophylaxis should be considered potentially to decrease the rate of infection.

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Authors' Contributions

All authors contributed equally to this work.

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