Ten years after the beginning of Crimean-Congo hemorrhagic fever outbreak in Iran: A promising report

Batool Sharifi-Mood, Roya Alavi-Naini, Maliheh Metanat*
Research Center for Infectious Diseases and Tropical Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a fatal viral infection described in about 30 countries. It has the most extensive geographic distribution of the medically important tick-borne viral diseases (1-6). Human can be infected through tick bites, by crushing infected ticks, after contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viremic livestock. Health-care workers have a serious risk of infection, particularly during care of patients with hemorrhages from the nose, mouth, gums, vagina, and injection sites (4-8).

Following an incubation period of two to fourteen days, clinical features commonly show a dramatic progression characterized by hemorrhage, myalgia, and fever. Petechial rash and hemorrhagic signs such as hematemesis, melena and intracranial hemorrhage could be other presenting sings (6-10). Mortality rate of CCHF is up to 80% of clinically apparent cases, however, despite this high lethality rate, up to 80% of the infections may be subclinical (5-7). The levels of liver enzymes, creatinine phosphokinase, and lactate dehydrogenase are raised, and prolongation of bleeding markers are another laboratory findings. Infection of the endothelium has a major pathogenic role. Besides direct infection of the endothelium, indirect damage by viral factors or virus-mediated host-derived soluble factors that cause endothelial activations and dysfunction are thought to occur (4-9). Although the first human cases of CCHF in Iran were identified in the eastern and central regions of the country in spring 1999, thereafter endemic areas have substantially increased in several provinces of Iran with an increasing morbidity rate and approximately high fatalities (up to 26.5%) in the first few years of the first decade (1,3,10). About 67% of all confirmed cases in Iran have been reported from Sistan and Baluchestan province located in southeast of Iran (9). Now, according to the current experiences from this endemic region (Sistan and Baluchestan), there are a few clinical and confirmed cases which need to be highlighted about their results (11). The objective of this review is to demonstrate our experiences, especially in management and treatment of CCHF patients with oral ribavirin.

Diagnosis

CCHF infection should be suspected in any patient who have:
1- Clinical manifestations including acute onset of fever, headache, myalgia and bleeding.
2- Epidemiologic risk factors including a history of recent travel to an endemic region, living in an endemic area, history of tick bite, and
exposure to blood or tissues of an infected patient or animal.

3- Laboratory findings such as leukopenia or leukocytosis, thrombocytopenia and increased level of creatine phosphokinase, transaminases, and prolongation of prothombin time (PT).

Methods for diagnosis of CCHF virus include antibody detection by enzyme-linked immunosorbent assay (ELISA), antigen detection, virus isolation, and a molecular method for detecting the viral genome by reverse transcription-polymerase chain reaction (RT-PCR). Diagnosis of suspected CCHF is performed in specially-equipped, high biosafety level laboratories. IgG and IgM antibodies may be detected in serum by enzyme-linked immunoassay (ELISA) from about day six of illness. IgM can be detectable for four months, and IgG levels gradually decline but remain detectable for up to five years. Patients with fatal CCHF do not usually develop a measurable antibody response and in these persons, in the first few days of illness, diagnosis is made by virus detection in blood or tissue samples. The virus may be detected in blood or tissue specimens in the first five days of illness, and grown in cell culture. Viral antigens may sometimes be shown in tissue samples using immunofluorescence or ELISA.

What to do when a physician faces a CCHF patient

First Step

If clinicians feel that CCHF is a likely diagnosis, they should isolate the patient, and then report it to the local CDC and health departments. Patients with CCHF syndrome generally have significant quantities of virus in their blood and other secretions. Therefore, caution should be exercised in evaluating and treating patients with suspected CCHF. At least, these should include the following: stringent barrier nursing; wearing glove, mask, gown, needle precautions; hazard-labeling of specimens; restricted accessing to the patient; and disinfecting of contaminated materials by using hypochlorite or phenolic disinfectants or autoclaving.

Second step: Management of hemorrhagic syndrome.

Patients should be monitored carefully and closely, in a high dependency or intensive care setting. Complete blood count, liver function test, serum electrolyte levels, blood urea nitrogen, creatinin, PT and PTT should be monitored at least daily in the early phase of the illness. Optimum fluid and electrolyte balance should be targeted. Replacement with blood products such as fresh frozen plasma, erythrocyte and platelet should be considered based on patient laboratory results. Intramuscular injections and use of anti-platelet agents such as aspirin or other non-steroidal anti-inflammatory drugs should be avoided during the bleeding period. Proton pump inhibitors or H2 receptor antagonists are indicated in severe cases and those who have upper GI bleeding. Use of platelets and FFP should be considered based on platelet count and coagulation status.

Third step

There is an urgent need for a close collaboration between hospitals, academic centers, health care centers and other wards to recognize the magnitude and future of the epidemic.

Fourth Step

One of the most important steps in the management of CCHF patients is early oral ribavirin treatment especially, in the first few days of illness that showed a significant positive effect on survival. It is essential to make an early diagnosis of CCHF and start treatment and preventive measures for all suspected cases without waiting for confirmation of the diagnosis. In this regard, there are several clinical surveys in this region that revealed patients treated with oral ribavirin had clinical improvement as well as a decreased in the mortality rate from 26.5% in the first years to less than 3% during the last few years of the recent decade.
**A review of studies during last decade**

In Alavi-Naini and colleagues study in Sistan and Baluchestan, among 255 patients with CCHF, 22% died (9). Thereafter, in 2006, Metanat et al showed that of 184 CCHF patients, 89 (48.5%) have been treated by ribavirin during the first 72 hours of the disease of whom 75 (84%) survived and 14 (16%) died. Moreover, of 95 patients treated after 72 hours following the disease onset, 74% survived and 26% died. Recovery rate was higher in those who were treated during the first three days (10).

Another study in 2006 on 29 children with CCHF also demonstrated that recovery rate was higher among patients who were treated during the initial 3 days of illness (3). Indeed, of 29 children, 25 were treated by oral ribavirin within the first three days, 2 were treated after this time and 2 received nothing because of misdiagnosis. Unfortunately, both of these 2 untreated cases as well as another child who received therapy 6 days following the disease onset and 4 (16%) children who received early therapy died. Therefore, a fatality rate of 24% was calculated, however, recovery rate was still higher among those who were treated during the initial 3 days (3).

A study in the beginning of the recent outbreak showed that of 91 patients who were treated with ribavirin, 73 (80%) survived and 18 (20%) died (11). Among the survived patients, 58 (79%) were treated during the initial 72 hours and 15 were treated thereafter, however, 16 patients who received treatment after this period died. The mortality rate was lower in those who were treated during the initial three days (2% vs. 16%) (11). Between 2005 and 2007, of 32 patients who were treated within three days of the onset of the disease, only one (3%) died. There was a significant difference in the recovery rate between the two groups who were treated at the beginning of the outbreak and during the years 2005 to 2007 (p=0.001) (11). A study conducted by Izadi et al revealed that of 113 patients admitted to a hospital in Zahedan, all except 5 were treated with oral ribavirin within 2 hours of hospitalization (12). Patients who survived began oral ribavirin 24 hours earlier than those who died. This study defined that the cases who were treated during the first 4 days had a better outcome than those who were treated after this time (p=0.004). The results of the study also showed early therapy with oral ribavirin reduced bleeding tendency (12).

In another survey, a total of 34 non-adult confirmed CCHF patients were evaluated (13). The mean age of the studied subjects was 13.3±4.6 years (range, 5–18 years). Fourteen (41.2%) patients were 12 years-old or younger. The case-fatality ratio in this study was 26.5% (9 of 34). In fatal cases, the median time from onset of symptoms until death was 7 days (range, 5–11 days). In univariate analyses, impaired consciousness, petechia, hemorrhagic manifestations, and jaundice were more frequent in dead subjects than in survivors. Those who survived received earlier treatment with oral ribavirin (13).

Ribavirin is a WHO recommended anti-viral medication for CCHF (11-13). The recommended dose is an initial dose of 30mg/kg followed by 15mg/kg for four days and then 7.5mg/kg for six days for a total of 10 days (10-18). Unfortunately, ribavirin has not been included in the official list of pharmaceutical companies for use in CCHF and companies promote this drug for hepatitis C management. Intravenous form of the drug which was first recommended for ill patients, is not available for patients who can not tolerate the drug orally (18-28). Usually the affected population is from rural areas with low economical situation. It is suggested that drugs for these patients be easily available and accessible so that patients with positive clinical features and epidemiological factors could receive oral ribavirin with the onset of disease without any delay.
In conclusion, clinicians should consider oral ribavirin in the treatment of CCHF patients in the beginning of illness. Early diagnosis and treatment of CCHF are potentially associated with a lower mortality and decreased chance of secondary spread of infection.

ACKNOWLEDGEMENT

The authors wish to thank the cooperation of all laboratory and health care staff during the recent years, without their help gathering associated data was impossible.

REFERENCES


