Characteristics of Patients with Crimean-Congo Hemorrhagic Fever in a Recent Outbreak in Turkey and Impact of Oral Ribavirin Therapy

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We describe the epidemiological, clinical, and laboratory findings and the role of ribavirin therapy for 35 patients who received a diagnosis of Crimean-Congo hemorrhagic fever (CCHF). All patients had immunoglobulin M antibodies and/or PCR results positive for CCHF virus in blood or tissue specimens. Eighty-six percent of the patients were considered to have severe cases of CCHF. The overall case-fatality rate was 2.8%. Eight patients were given ribavirin, and all 8 survived. We suggest using ribavirin to treat patients with CCHF, particularly those with severe cases.

Crimean-Congo hemorrhagic fever (CCHF) is a potentially fatal fever due to infection with the CCHF virus that has been described in parts of Africa, Asia, eastern Europe, and the Middle East [1]. The virus belongs to the genus *Nairovirus* in the Bunyaviridae family and causes severe diseases in humans, with reported mortality rates of 15%–70% [2]. Humans become infected through the bites of ticks, by contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viremic livestock [3]. To our knowledge, CCHF has not previously been reported in Turkey, although epidemics have been reported in neighboring countries.

We present the epidemiological, clinical, and laboratory findings for 35 patients with CCHF, among whom, to our knowledge, there was the lowest case-fatality rate reported to date, and we discuss the role of ribavirin therapy in their outcomes. Furthermore, a rationale for administering ribavirin therapy to patients infected with CCHF virus is suggested, which will be helpful for future outbreaks.

Patients and methods. Ankara Numune Education and Research Hospital (Ankara, Turkey) is one of the largest referral-based tertiary care community hospitals in Turkey. Patients with acute febrile syndrome characterized by malaise, bleeding, leukopenia, and thrombocytopenia were admitted to our clinic during the spring and summer of 2002 and 2003. Patients who had IgM antibodies or PCR results positive for CCHF virus in blood or tissue specimens were included to the study. Written informed consent was obtained from patients or their family members. Serological testing was performed for detection of *Leptospira, Salmonella, Rickettsia, Brucella,* and *Toxoplasma* species; agents of Lyme disease, rubella, and herpes; and *Coxiella burnetii,* cytomegalovirus, and hepatitis A, B, and C viruses. Peripheral blood smears were studied for the presence of agents of malaria. Acute- and convalescent-phase serum specimens from all patients and a liver biopsy specimen from 1 cadaver were obtained and sent to the World Health Organization (WHO) reference laboratories in Lyon, France, and London to test for the presence of CCHF virus. The first serum samples were obtained at admission to the hospital, and the second samples were obtained 2 weeks later. The serologic studies were done using ELISA, and PCR was performed for all patients with acute cases. Laboratory parameters were measured on a daily basis after admission to the hospital.

Patients were given preparations of erythrocytes, fresh frozen plasma, and total blood, depending on their homeostatic state. At the beginning of the outbreak, antibiotics such as doxycycline and ciprofloxacin were initiated for empirical treatment of common zoonotic diseases in the region. After 1 patient died, ribavirin was added to the empirical regimen for patients with similar severe clinical findings within the first 24 h after admission. The characteristics of the patients were assessed according to the 90% fatality outcome criteria described by Swanepoel et al. [4]. According to these criteria, patients were defined as having severe disease if they had a leukocyte count $\geqslant$10,000 leukocytes/mm^3, a platelet count $\leqslant$20,000 platelets/mm^3, an aspartate transaminase (AST) level $\geqslant$200 U/L, an alanine transaminase (ALT) level $\geqslant$150 U/L, an activated partial thromboplastin time (aPTT) $\geqslant$60 seconds, and/or a fibrinogen level $\leqslant$110 mg/dL during the first 5 days after the onset of illness.

Results of diagnostic studies were not available for up to 4 weeks; therefore, all ribavirin therapy was initiated before laboratory evidence of CCHF infection was received. Oral ribavirin

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Table 1. Demographic and clinical characteristics for 35 patients with Crimean-Congo hemorrhagic fever.

Characteristic	Value
Age, years	43 ± 17
Female sex	18 (51)
History of tick bite	16 (53)
Time to hospitalization, days	5.5 ± 1.7
Duration of hospitalization, days	11 ± 4.3
Most common symptoms	
Nausea and/or vomiting	28 (80)
Fever	25 (74)
Headache	23 (66)
Myalgia	19 (54)
Diarrhea	11 (31)
Sweating	8 (23)
Physical finding	
Conjunctival injection	18 (51)
Fever, temperature >38°C	16 (46)
Hepatomegaly	13 (37)
Rash	
Maculopapular	7 (20)
Petechia	13 (37)
Bleeding	
Epistaxis	10 (29)
Hematemesis	10 (29)
Melena	6 (17)
Hematuria	5 (14)
Hemoptysis	2 (6)
Intra-abdominal	1 (3)
Vaginal	1 (3)
Stupor	12 (34)
Rales	9 (26)
Jaundice	4 (11)

NOTE. Data are no. (%) of patients or mean value ± SD.

was administered within a mean of 5.5 days after the onset of symptoms at the dosage recommended by WHO (4 g q.d. for 4 days, and 2.4 g q.d. for 6 days) [5]. The intravenous form of ribavirin was not available in Turkey.

Mean comparisons for continuous variables were done using independent groups Student's *t* tests. Proportion comparisons for categorical variables were done using χ^2 tests, although Fisher's exact test was used when data were sparse. Statistical significance was set at $P < .05$ and was determined using 2-sided comparisons. Stata software, version 8.0 (Stata), was used in the analysis.

Results. Forty-four patients were admitted from various northeastern regions of Anatolia and southern regions near the Black Sea; all were involved in animal husbandry activities. CCHF was diagnosed in 35 (80%) of 44 patients, brucellosis in 3 (6.8%), Q fever in 1 (2.3%), and Lyme disease in 1 (2.3%). No infectious etiologic agents were detected in 4 patients.

We limited our analysis to the 35 patients with CCHF infection. Thirty-two patients (91%) had CCHF virus IgM antibodies. For the 3 patients without these antibodies, CCHF virus was detected by PCR in serum specimens obtained from 2 and in a liver biopsy specimen obtained after death from 1. Nine (26%) of the 35 patients had positive PCR results. Twenty-seven patients (77%) had IgG antibodies detected in serum specimens obtained during the acute or convalescent phases.

The epidemiological and clinical characteristics of the patients are presented in table 1. Fever lasted a mean duration (±SD) of 5.5 ± 2.4 days. All patients had leukopenia, thrombocytopenia, and elevated levels of AST, ALT, lactic dehydrogenase (LDH), and creatinine phosphokinase (CPK) (table 2 and figures 1, 2, and 3). Thirty (86%) of 35 cases were defined as severe. During the first 5 days after onset of the disease, 17 patients had thrombocytopenia (≤20,000 platelets/mm^3), 30 patients had AST levels ≥200 U/L, 26 patients had ALT levels ≥150 U/L, 11 patients had an aPTT >60 s. None of the patients had leukocytosis, except for the patient who died. The leukocyte count in this patient had increased to 12,000 leukocytes/mm^3 on the day he died, 10 days after the onset of disease. Eleven (31%) of 35 patients had thrombocytopenia (≤20,000 platelets/mm^3), active bleeding despite supportive therapy (i.e., erythrocyte, fresh frozen plasma, and total blood preparations), and became stuporous. The bleeding experienced by the majority of patients developed during their hospital stay, ~5–7 days after initiation of disease. For patients with severe disease, the mean hemoglobin level at admission to the hospital was 13.7 g/dL and the mean of the nadir levels decreased to 10.7 g/dL ($P <$ .001, by paired *t* test), whereas for patients with mild-moderate disease, the mean hemoglobin level was 13.7 g/dL and the mean of the nadir levels decreased to 12.3 g/dL ($P = .149$, by paired *t* test).

The ratio of the AST/ALT levels was higher for patients with severe disease than it was for those with mild-moderate disease during each of the first 3 days after admission to the hospital ($P = .022$; $P = .003$; and $P = .047$, respectively) (figure 2). LDH and CPK levels in patients with severe disease were higher

Table 2. Pathologic laboratory findings for 35 patients with Crimean-Congo hemorrhagic fever.

Characteristic	Mean value (range)
Lowest platelet count, platelets/mm^3	26,000 (3500–108,000)
Lowest WBC count, WBCs/mm^3	1740 (150–4000)
Highest aspartate transaminase level, U/L	1050 (65–7150)
Highest alanine transaminase level, U/L	383 (79–1385)
Highest lactic dehydrogenase level, U/L	3140 (671–26,000)
Highest creatinine phosphokinase level, U/L	1495 (10–21,189)
Longest prothrombin time, s	13 (10–18)
Longest activated partial thromboplastin time, s	45 (25–74)

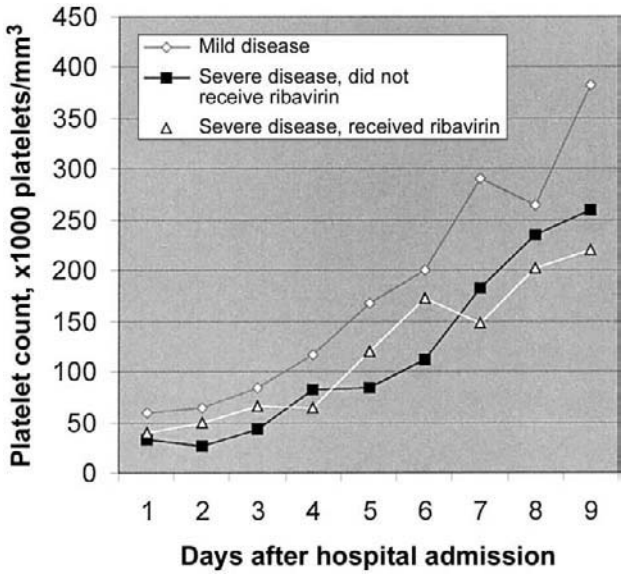

Figure 1. Platelet counts after patients were admitted to the hospital

than those in patients with mild-moderate disease, although the difference was not statistically significant ($P > .05$). Results of laboratory tests, including complete blood count and biochemical analyses, returned to normal levels within ~5–9 days after admission (figure 1).

Eight of 30 patients with severe disease were given ribavirin therapy. Among the 27 patients who did not receive ribavirin therapy, 22 were evaluated retrospectively and defined as having severe disease. The overall case-fatality rate was 2.8%. However, the case-fatality rate increased to 4.5% among patients who had severe disease and did not receive ribavirin. Therefore, the mortality rate associated with the absence of ribavirin therapy was 4.5%. No adverse events associated with ribavirin therapy were noted. There was no significant difference between the laboratory results for patients who received ribavirin and for those who did not.

Discussion. The presence of fever, malaise, and headache concomitant with laboratory findings of leukopenia and thrombocytopenia is a common clinical picture for zoonotic diseases of bacterial and viral origin. Although Turkey was shown to be an area of CCHF endemicity by various infectious diseases resources, to our knowledge, no case of CCHF has been reported until now. However, CCHF has been reported in areas of close geographic proximity, such as Russia [6], Albania [7], Kosovo [8], Greece [9], Iraq [10], Iran [11], and Pakistan [12].

The case-fatality rate has been estimated to range from 15% to 70% in various studies [2, 13, 14]. To our knowledge, we present the lowest case-fatality rate of CCHF—2.8%—in the medical literature. This could be explained by the role of vigorous supportive therapy and the administration of ribavirin within 24 h after admission to 8 patients. Another explanation could be the geographical variation of the virus. However, to reach such a conclusion, additional reports from different centers are necessary.

Although leukocytosis was reported by Swanepoel et al. [4] to be one of the criteria associated with fatal outcome, it was only observed in the patient who died on the eighth day after hospital admission. No CCHF virus IgM or IgG antibodies were detected in serum specimens obtained from this patient, but the virus was detected by PCR in a liver biopsy specimen obtained during autopsy. The absence or minimal evidence of antibody response in the patient who died was reported elsewhere [4]. Eleven patients became stuporous despite vigorous supportive therapy. However, unlike Swanepoel et al. [4], we did not observe renal failure in any of the patients.

High AST/ALT ratio could be another important prognostic factor for patients with CCHF (figure 3). AST levels that were disproportionately higher than ALT levels was described in patients with Marburg fever in 1969 [15] and in patients with Lassa fever in 1987 [16]. We suggest that the AST/ALT ratio is a prognostic factor for patients with CCHF.

In 1995, Fisher-Hoch et al. [5] reported successful treatment of 3 nosocomial cases of CCHF with oral ribavirin [5]. Ribavirin was suggested to be an effective drug in a recent study [11], and administration of this agent at any point of the illness was suggested in a study of Lassa fever [17]. Giving ribavirin to all patients with suspected CCHF might not be rational and cost-effective. However, we suggest that ribavirin should be given to patients with suspected CCHF infection who have severe thrombocytopenia, elevated ALT and AST levels, and an elevated AST/ALT ratio. In addition to these factors, LDH and

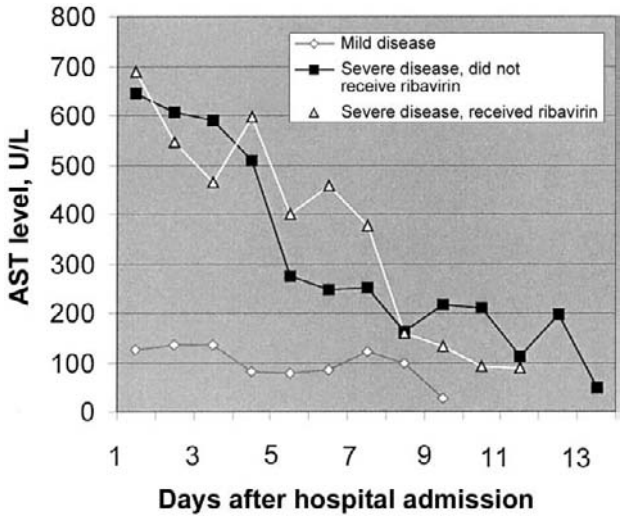

Figure 2. Aspartate transaminase (AST) levels after patients were admitted to the hospital.

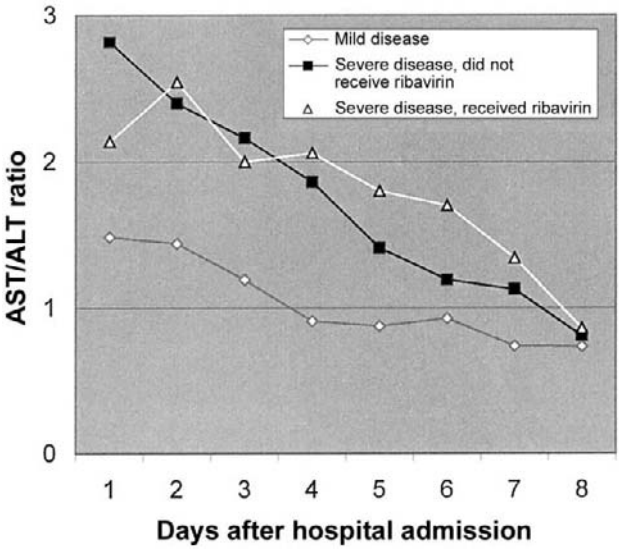

Figure 3. Aspartate transaminase (AST)/alanine transaminase (ALT) ratios after patients were admitted to the hospital.

CPK levels could be high. In conclusion, oral ribavirin should be administered to patients with severe disease with suspected CCHF virus infection.

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Conflict of interest. All authors: No conflict.

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