Review Article

Optional Modalities for Treatment of Patients with Severe Crimean-Congo Hemorrhagic Fever

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Abstract

Crimean-Congo hemorrhagic fever (CCHF) is an acute viral hemorrhagic fever caused by the Nairovirus in the family of Bunyaviridae, transmitted to humans by the bite of the Hyalomma tick or by direct contact with blood or tissue of an infected animal or human. CCHF is a severe disease with a high mortality rate ranging from 2% to 70%. Early diagnosis and treatment of CCHF infection is critical to rescue the patients and control the disease. The important approach to treatment of CCHF is based on general supportive measures, monitoring of the patient's hematologic and coagulation status, with replacement of cells and other factors as needed, and the prompt use of ribavirin.

In this article, we underline current therapeutic approaches to CCHF infection.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) has the most expansive geographic range of tick-borne viruses, occurring in some parts of Africa, Eastern Europe, Asia, and in the Middle East (1-3). After infection, the disease progresses through four different phases: incubation, pre-hemorrhagic, hemorrhagic and convalescence. The duration and severity of all these phases vary depending on the routes of transmission, viral load and genotypic variations of the virus (4-8). Hemorrhagic manifestations may develop from various sites in severe cases and may rapidly progress to disseminated intravascular coagulation (DIC) and then shock. It was shown that bleeding tendencies and coagulopathy disorders in patients with CCHF are primarily related to host-induced immune mechanisms rather than direct damage of endothelial cells by the virus (9). The host-induced immune mechanisms, as a consequence of virus-associated T-cell stimulation, cause a cytokine storm leads to increase in interleukin (IL)-1, IL-6, IL-12, IL-18, tumor necrosis factor–α, and interferon-γ in patients with CCHF, especially those with fatal outcome (9-11). Additionally, there is an immune-mediated liver dysfunction during the acute infection phase that may increase the bleeding and coagulopathy (9). According to above mechanisms, immunosuppressive agents such as high-dose methylprednisolone (HDMP), anti TNF-α and IVIG may be used to block or reduce the macrophage/monocyte activation or cell-mediated immune response (9). Risk factors for mortality have been defined in many recent studies as severe thrombocytopenia (less than 50.000), prolonged activated partial thromboplastin time (aPTT), melena, increased level of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactate dehydrogenase (LDH), and somnolence (1,2,8-12).

Treatment options for CCHF, especially in patients with high risk factors, are still limited and are based on general supportive managements: monitoring the patient's hematological and coagulation parameters and platelets, fresh frozen plasma (FFP), and packed red blood cell transfusion (13-17). During recent years, ribavirin was shown to be effective in the treatment of patients with CCHF. Interferon, specific immunoglobulin preparations have been used in limited case series and studies on these agents are continuing. Thrombocytopenia is the major risk factor in patients with CCHF and mortality is high when platelet count is less than 50.000 (15-18). Herein, we emphasize current therapeutic approaches to CCHF infection.

Therapy

1-Supportive therapy

Supportive therapy is an essential part of case management in CCHF (4, 9). Preventive measures should be taken when potential bleeding foci of the patient is considered. Using histamine receptor blockers for peptic ulcer patients, the avoidance of intramuscular injections, aspirin or other drugs with actions on the coagulation system, and non-steroidal anti-inflammatory drugs should be considered. Fluid and electrolyte balance should also

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be monitored carefully (4,9,18,19). Supportive treatment also includes administration of platelet, FFP, and sometimes erythrocyte preparations (9).
The replacement therapy with these blood products should be performed by checking complete blood count (CBC), which should be done daily or sometimes two times/day (9,19). Blood products such as thrombocyte solutions or FFP are to be used according to each individual patient's need. Sometimes, it is hard to decide where to start or stop the blood product replacement.

2-Ribavirin

Ribavirin is the only antiviral drug that has been used to treat viral hemorrhagic fever syndromes, including CCHF and Lassa fever (4-16). Ribavirin is a purine nucleoside analog which inhibits the *in vitro* replication of a wide range of RNA and DNA viruses, including adenoviruses, arenaviruses, bunyaviruses, herpesviruses, myxoviruses, paramyxoviruses, poxviruses, and retroviruses (16). WHO recommended intravenous ribavirin for treatment of patients with CCHF, but numerous reports have indicated that oral ribavirin is also an effective drug against CCHF (13-22). Treatment is more effective if ribavirin is started within the three initial days of the onset of fever (15). Ribavirin is well-absorbed from gastrointestinal tract and the oral formulation would be expected to achieve blood levels in comparison to those attained by the intravenous formulation. A current recommended regimen, adjusted for body weight, is 30 mg/kg as an initial loading dose, then 15 mg/kg every 6 h (4×1 g) for 4 days, and 7.5 mg/kg every 8 h (4×0.5 g) for 6 days (4,14-16). In 2003, Mardani et al compared the fatality rate among CCHF patients in Iran who received treatment with oral ribavirin and those who did not. The efficacy of oral ribavirin was reported to be 80% among patients with confirmed CCHF (13). In 2004, Ergonul examined the effect of oral ribavirin therapy in 35 confirmed cases of CCHF in Turkey. For analysis, they grouped the patients according to severity of their illness. Of their 35 patients, 30 (86%) were classified as severe by the Swanepoel criteria. Eight were given ribavirin, and all survived, while the overall mortality among the untreated cases was 4.5% (4). Dr Metanat et al in 2006 studied the role of ribavirin in treatment of patients with CCHF. They concluded that 84% of patients who were treated during the initial 72 hours survived and 14% died. Out of 95 cases that were treated after this period, 75% survived and 25% expired (14). We studied the effect of ribavirin in 2009 and found among 91 patients who were treated with ribavirin between 1999 and 2003, 73 (80%) survived and 18 (20%) died of the disease (15). Among the survived patients, 58 (79%) were treated during the initial 72 hours and 15 were treated thereafter. Sixteen patients, who were treated after this period, expired. The mortality rate was lower in those who were treated during the initial three days (two vs. 16). During 2005 – 2007, of 32 patients who were treated within three days of the onset of the disease, only one (3%) died (15). We conclude prompt treatment with oral ribavirin can increase the recovery rate in patients with Crimean-Congo hemorrhagic fever.

3- Interferon

Type I interferon has important antiviral activity against many hemorrhagic fever viruses *in vitro* and in animal models; but up to now, no clinical studies have reported the effect of interferons against CCHF (23,24). Although there is not any clinical trial on this issue yet, a number of *in vitro* studies showed that treatment with interferon may have a beneficial effect. For example, MxA protein, which belongs to the dynamin superfamily of large GTPases, has antiviral activity against many viruses, including CCHF virus. MxA colocalizes and interacts with CCHF virus nucleocapsid protein in the perinuclear region of infected cells; therefore it is suggested that this interaction inhibits the virus replication process (4,19,23-25).

4- Corticosteroid

Bleeding tendencies and coagulopathy disorders in patients with CCHF are primarily related to host-induced immune mechanisms rather than direct damage of endothelium (9-11). Cytokine storm leads to increase in interleukins, interferon-γ, and TNF-α, especially those with fatal outcome such as severe thrombocytopenia (9). Massive and uncontrolled expression of cytokines from the surface of virus-infected monocytes and macrophages may activate hemophagocytosis. Pancytopenia, bicytopenia, and thrombocytopenia can be related to virus-associated hemophagocytic syndrome (VAHPS). Hence, the inhibition of macrophage/monocyte activation or a cell-mediated immune response can improve the outcome (10-11). Thrombocytopenia is the major risk factor of CCHF and high case fatality rate. There are only two clinical trials on the effect of HDMP in patients with CCHF. The first report is done by Dilber in 2010 (9). This study included only five patients with CCHF who were given HDMP if there were findings compatible with VAHPS and the effects of HDMP were evaluated. Fever subsided and platelet count increased within 24 hours. Leukocyte count increased and visceral bleedings improved. HDMP treatment was discontinued within approximately five days. After HDMP, only one patient required blood products. Although, the sample of patients was very small, they concluded HDMP was effective in CCHF, especially on fever and platelet count.
In 2011, we also studied the effect of HDMP in patients with severe CCHF (platelet count less than 50000/mm^3) (unpublished data). The purpose of this study was to compare treated patients with severe thrombocytopenia using HDMP, in addition to ribavirin and supportive therapy, to cases with the same conditions not using HDMP. We studied 35 patients with confirmed CCHF diagnosis and severe thrombocytopenia who were admitted to Boo-Ali Hospital in Zahedan, between Jan 2010 and Oct 2011. In case group, patients were given oral ribavirin, supportive managements and HDMP (10mg/kg as single dose for three days in the morning and then 5mg/kg for two more days). Platelet count was

checked in the days 1, 2, 3 and 5 after beginning of the treatment and was compared with control patients who were treated with ribavirin and supportive management only. Following HDMP therapy in hospitalized patients with severe thrombocytopenia, platelet count was increased within 36 hours and leukocyte count within 24 hours from beginning of the treatment. Cutaneous and visceral bleedings were also improved faster after beginning of HDMP therapy. A few patients required transfusion of blood products in case group comparing to control group ($p<0.05$). No patients died in case group but two patients with platelet count lower than $10.000/mm^3$ on admission died in control group. We found HDMP is effective in treatment of patients with CCHF and severe thrombocytopenia. Further investigations are necessary to determine the efficacy of corticosteroid and its effect on outcome.

Conclusion

Although ribavirin and supportive therapy are important for treatment of CCHF, we need other drugs such as corticosteroid, anti TNF-α and also IVIG in some patients to inhibit cytokine storm. We need more investigations on efficacy of corticosteroid and other immunosuppressive agents in order to analyze the timing and duration of treatment and their effect on outcome.

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