

Treatment and Prophylaxis with Ribavirin for Crimean-Congo Hemorrhagic Fever - Is it effective?

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Introduction

Viral Hemorrhagic Fever (VHF) refers to an illness associated with a number of geographically restricted viruses. These include Lassa, Marburg, Ebola and Crimean-Congo Hemorrhagic Fever (CCHF) viruses. While no cases of VHF due to Ebola, Lassa or Marburg viruses has been reported in Pakistan CCHF outbreaks have occurred. Mortality is high and treatment is mainly supportive. We report a fatal case of CCHF. Multiple healthcare workers who were in contact with the index case were given ribavirin as prophylaxis in this outbreak. A brief review of CCHF is given with benefits of the drug.

Case Report

A thirty year old male was brought to the emergency room from Peshawar in December 2000. He had sudden onset of high-grade fever associated with rigors, chills and sore throat seven days before admission. After five days he had bleeding from gums, hematemesis and black colored stools (malena). Later he became confused and disoriented. His father who slaughtered some sheep two weeks ago died of similar symptoms few days ago at a local hospital.

On examination the patient was confused and disoriented. His pulse was 110/min, blood pressure 110/75 mmHg, respiratory rate 20/min and temperature 100°F. He was icteric with petechial rash all over the body, especially on lower extremities. He had neck stiffness. Rest of the examination was unremarkable with no respiratory distress, heart murmur, lymphadenopathy or hepatosplenomegaly. On admission his laboratory investigations showed a hemoglobin 13.4 g/dl, hematocrit 39%, white blood cell count 2100/ μ l, platelet 1100/ μ l, sodium 124 meq/L, potassium 3.4 meq/L, blood urea nitrogen 49 mg/dl, creatinine 2.3 mg/dl, glucose 171 mg/dl, ALT 852 U/L, AST 3281 U/L, total bilirubin 4 mg/dl, direct bilirubin 3 mg/dl, alkaline phosphatase 777 U/L, prothrombin time 20 seconds, partial prothrombin time >2 minutes, FDP >10 μ g/ml and fibrinogen 300 mg/dl. A chest roentgenogram showed basilar atelectasis. C SF analysis was normal.

A presumptive diagnosis of CCHF was made and the patient was isolated. Packed red blood cells, platelets and fresh frozen plasma was given. Ceftriaxone and piperacillin-tazobactam were also administered. Serum was sent to Center for Disease Control and Prevention (CDC) regional laboratory in Johannesburg, South Africa for serologic testing. The patient died after approximately 36 hours of hospitalization from respiratory failure and massive hemorrhage. Serum samples were drawn from eight healthcare workers including doctors and nurses who were involved in care of this patient and also sent to CDC's regional laboratory. Prophylaxis with oral ribavirin was immediately started for all contacts. The regimen used was a loading dose of 2 gram followed by 4

gram/day in 4 divided doses for 4 days then 2 gram/day in 4 divided doses for 6 days (total 30 grams over 10 days). All tolerated the drug well and none developed any clinical symptoms.

Four attendants who had contact with the patient were also given ribavirin prophylaxis. One of these attendants, aged 30 years, developed similar symptoms (fever, bleeding from gums, thrombocytopenia and prolonged prothrombin time) after 24 hours. He was switched to intravenous ribavirin with 2 gram loading dose followed by 1 gram every 6 hours for 4 days and 500 mg every 6 hours for 6 days. He showed improvement after 4 days. His fever and bleeding subsided and he was discharged in stable condition.

Serum samples of the index patient, his attendant and the eight HCW were sent to CDC for CCHF IgM antibodies (ELISA). Samples from the index patient and his attendant were positive while the rest of the samples were negative. None of the other exposed healthcare workers or the patient's attendants developed symptoms. The other three attendants were not tested.

Discussion

CCHF virus is an enveloped, single stranded RNA bunyavirus. It has long been recognized in Asia, but came to international attention after an outbreak in Crimean peninsula in 1944 and 1945. It was later recognized that the causative agent was identical to Congo virus, isolated in Zaire, hence the name CCHF. Many animals like cattle, sheep, goats and hare act as reservoirs for the virus. At least 27 species of ticks including Ixodid (hard) ticks, particularly those of the genus hyalomma, act both as a reservoir and vector for CCHF virus. Humans become infected by tick bites or by crushing ticks. Contact with blood, secretions or excretions of infected animals or humans may also transmit infection. The incubation period of CCHF is 2-9 days. Initial symptoms are non-specific and include fever, headache, myalgia, arthralgia, abdominal pain and vomiting. Sore throat, conjunctivitis, jaundice, photophobia and various sensory and mood alterations may develop. A petechial rash is common. It is usually followed by large ecchymoses and finally hemorrhage from different parts of the body.

CCHF had been documented from many countries including Pakistan.^{1,2} It has been reported in Oman³, Saudi Arabia⁴, Kuwait⁵, Dubai⁶, United Arab Emirates⁷, Mauritania⁸, South Africa⁹, Jammu and Kashmir⁴⁰ and China.¹¹ In Pakistan Burney et al reported the first cases CCHF after a nosocomial outbreak spread from a shepherd.⁷ Altaf et al reported another nosocomial outbreak in Quetta in 1994.⁸ A more recent outbreak was reported from Aga Khan University, Karachi.¹⁷ There were two confirmed deaths due to CCHF. Seven suspected deaths were also attributed to CCHF. All these cases were related to an outbreak in Balochistan province where additional twelve deaths were reported.¹⁷

Diagnosis requires isolating the virus from blood or detecting rising antibody titers by IFA, complement fixation or one of several other methods. However the enzyme-linked immunosorbent assay developed to detect Crimean-Congo Hemorrhagic Fever (CCHF) virus - specific immunoglobulin M (IgM) is more sensitive than indirect fluorescence tests. A reverse transcription-polymerase chain reaction (RT-PCR) has also been developed providing diagnosis within 24 hours in almost 50% patients upto 2 weeks after an illness.¹³ Laboratory abnormalities include progressive neutropenia, lymphopeni

a, thrombocytopenia, anemia, hyperbilirubinemia and raised liver enzymes. Since CCHF is highly infectious isolation is of paramount importance. Multiple outbreaks have been reported because of delay in recognizing the disease and failure in proper isolation. The CDC guidelines recommend standard precautions and strict barrier precautions to limit the spread of CCHF virus.¹⁸ High mortality in at least 2/3 patients has been reported.^{7,15} Treatment is supportive. Specific therapy is not available or proven. A study from South Africa evaluated treatment in nine cases with hyperimmune serum, ribavirin and interferon. While hyperimmune serum showed response in some patients, ribavirin and interferon use was inconclusive.¹⁴ Antiviral agents such as ribavirin is recommended by the CDC guidelines. Ribavirin inhibits CCHF in vitro but its efficacy in clinical practice remains unconfirmed. There has been no clinical trials to document its efficacy. The first reported oral use of ribavirin for three infected patients showed this agent to be of value for this potentially fatal hemorrhagic fever.¹⁵ These patients showed improvement in fever, hematological and biochemical profile. We used ribavirin in a secondary case and eleven other exposed persons. None of these eleven persons developed clinical CCHF. The secondary case recovered after ribavirin was used. It is difficult to conclude the efficacy of ribavirin in severe and advanced CCHF. However strict and immediate isolation with ribavirin prophylaxis may have prevented the spread of CCHF among the exposed persons. In early and mild CCHF and those who are exposed, it may be of value in prevention of severe CCHF.

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