*Original Article*

# RIBAVIRIN: AN EFFECTIVE TREATMENT OF CRIMEAN-CONGO HAEMORRHAGIC FEVER

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**ABSTRACT**

***Objective:*** To determine the efficacy of Ribavirin, an anti-viral drug, in patients diagnosed to have CCHF.

***Design:*** A hospital-based prospective study.

***Place and Duration:*** The Department of pathology in collaboration with the Department of Medicine, Sandeman Provincial Teaching Hospital, Quetta, Balochistan, conducted this study from March 1st, 1998 to December 31st, 1999.

***Patients and Methods:*** A total of 94 cases were included in the study on high index of suspicion of CCHF. The major criteria of admission were a short history of high-grade fever associated with bleeding from more than one site, i.e., haematemesis, epistaxis etc. the mean age was 34.71±12.81 years. All the suspected cases were kept in isolation unit of the hospital and barrier nursing was advised.

***Results:*** All the 94 cases were sent to CDC, Atlanta, USA for confirmation and 39 (41.4 %) were confirmed to have CCHF. Symptomatic treatment like platelet concentrate transfusions, fresh-blood transfusions and antipyretics were given to all cases. Oral Ribavirin was given only to the confirmed cases. It was started in a dose of 2 gm initially, followed by 1 gm 6 hourly for 4 days and then 500 mg 8 hourly for 6 days. After a mean period of 2.30±0.69 days of treatment with Ribarivin, the clinical as well as the laboratory parameters started improving and returned to normal levels after 10 -day course of treatment. Mild anaemia and thrombocytosis were seen as adverse effects in some of the patients.

***Conclusions:*** For treatment of this fatal disease, we recommend use of oral Ribavirin in all patients diagnosed to have CCHF in the above-mentioned doses, on the basis of our study results.

**KEY WORDS:** CCHF, Ribavirin, Anti-viral drug, Balochistan, Outbreak

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## INTRODUCTION

Crimean-Congo Haemorrhagic Fever (CCHF) virus of the family Bunyaviridae, genus Nairovirus, is the cause of significant human morbidity and mortality in Asia, Europe and Africa.[1-8]

A Russian scientist first observed the disease in Crimea in 1944.[9] An identical virus named Congo virus was isolated from the blood of a febrile child in Kisangam city of Congo in 1956. Casals showed that the virus isolated in cases of Crimean Haemorrhagic Fever and the Congo virus were serologically indistinguishable, hence the common name Crimean–Congo Haemorrhagic Fever (CCHF) was used for the disease.[10]

Ticks from small vertebrate host, acquire the virus. Human beings get infection on acquiring the virus by direct contact with blood or other infected live stock tissues of the infected animal or they may become infected from directly tick bite.[11] Majority of cases are reported in those who are involved with live stock

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industry such as agricultural workers, slaughter-house workers and veterinarians.[7] The virus enters the blood and its target organs are liver, lungs and lymphoid tissue.[12] The disease is characterized by a febrile illness with headache, myalgia, petechial rash & epistexis which is usually followed by necrotic hepatitis. In severe cases complications frequently reported are hepatorenal & pulmonary failure; coagulation is impaired leading to haemorrhage.[13.] The bleeding manifestations are the result of severe thrombocytopenia.

The risk of person-to-person transmission is highest during the later stages of illness; infection has not been reported in persons whose contact with an infected patient occurred only during the incubation period i.e. before the patient became febrile.[14] Epidemiological studies in humans indicate that infection is not transmitted from person-to-person through the air-bourne route.[15,16]

In Pakistan the disease was first recognized in 1976 when a laparotomy was performed on a patient with abdominal pain, haematemesis and melaena. Three persons died including a surgeon operating on a patient and an operation theatre attendant while 11 other persons were found infected.[2]

Ribavirin has been shown to have activity invitro against CCHF virus in concentrations as low as 5µg/ml.[17] The intravenous preparation is recommended for treatment of Viral Haemorrhagic Fevers and the oral form for post-exposure prophylaxis.[15] Intravenous Ribavirin has also been established as effective antiviral therapy for Lassa virus infections in Sierra Leon[18], where more than 1500 patients have been treated. Oral Ribavirin has also shown to be effective in patients with less severe disease.[18] The drug has been given to over 1000 patients in various clinical trials, including 800 patients with AIDS[19], several hundred with influenza[20] and 150 with Haemorrhagic Fever with renal syndrome.[21] With the exception of a dose-related reduction in circulating red - blood cell numbers, no significant adverse effects have been reported. The injectable form of Ribavirin is not available in Pakistan.

This study was conducted in order to determine the efficacy of oral Ribavirin in patients with confirmed diagnosis of CCHF.

## PATIENTS AND METHODS

The study was conducted at Department of Pathology in collaboration of Department of Medicine, Sandeman Provincial Teaching Hospital, Quetta, the largest tertiary care hospital in the province of Balochistan, Pakistan. The study expanded over a time period of 22 months between March 1st, 1998 and December 31st 1999. The criteria of admission were a short history of high-grade fever associated with bleeding from more than one site. For example, haematemesis, epistaxis, melaena, haematuria, etc. A total of 94 cases were inducted in the study. The mean age was 34.71 $\pm$12.81 years, irrespective of the gender. All the suspected cases were carefully examined according to the standard protocol. The Doctor and the assistant staff wear disposable gowns, caps, masks and double surgical gloves and the Unit was isolated. All the consumable used on the patients were incernated. On high index of suspicion of CCHF, all the cases were initially kept in isolation unit of the hospital and barrier nursing was advised. Those proved otherwise later on, were shifted out of the isolation unit and were excluded from the study. A 24-hour referral laboratory was affiliated with the isolation unit, which could provide any urgent investigation at hand.

Two sets of blood samples were drawn on the first day of admission under precautionary measures and sent to the laboratory; one set for testing and the other for preservation. The laboratory staff was warned of precautionary steps. Every case included in the study was passed through a set of tests including Hemoglobin (Hb), Total Leucocytes Count (TLC), Differential Leucocytes Count (DLC) and Platelets count (PLT). Those having severe thrombocytopenia with normal or mildly low Hb, reduced TLC and normal DLC were additionally passed through the another set of tests which included Prothombin Time (PT), Activated Partial Thromboplastin Time (APTT),

Aspartate aminotransferase (AST), Alanine Transaminase (ALT) and Total Bilirubin. The preserved blood samples of all cases were packed in double packing and transported to Centers for Disease Control and Prevention (CDC), Atlanta according to their laid down protocol. The samples passed through a battery of tests i.e PCR, IgG & IgM for CCHF. The results were received via email within 72 hours after the dispatch of samples. Sampling was done instantly & the time from sampling to confirmation was less than 96 hours. Any case giving a positive result to one or more of the above tests for CCHF was taken as confirmed case of CCHF. Before the results reached from CDC the cases were managed symptomatically, upon confirmation of CCHF the specific treatment i.e. oral Ribarivin was started.

## RESULTS

Blood samples of ninetyfour cases were sent to CDC, Atlanta, USA, 39 (41.4%) were diagnosed as having CCHF. Remaining 55 (58.6%) cases were later diagnosed as Aplastic Anaemia and idiopathic thrombocytopenic purpura (ITP). All the 94 cases had high-grade fever of short history, associated with bleeding from more than one site i.e. heamatemesis, epistaxis etc.

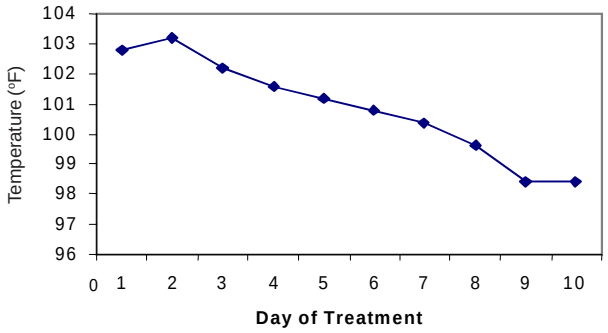


*Figure 1:* Pattern of fever in CCHF patients on Ribavirin

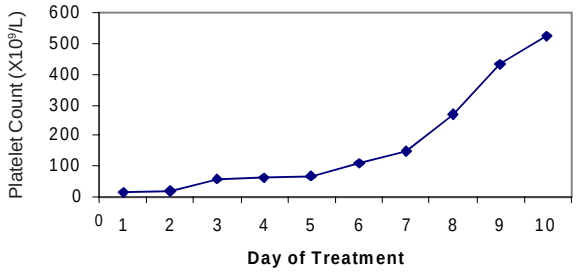


*Figure 2:* Serial platelets count in patients of CCHF on Ribavirin

The mean period for first clinical manifestation in CCHF cases before hospitalization was 3.82±0.64 days. The 39 (41.4%) diagnosed cases of CCHF were kept in isolation unit for 10-21 days and all the precautionary measures including the barrier nursing were strictly under-taken. The patients with diagnosis other than CCHF were shifted out of the isolation unit and were treated accordingly. All patients with CCHF were managed with supportive measures including platelet concentrate transfusions, fresh blood transfusions and antipyretics. Oral Ribavirin was started with a mean period of 6.20 ±0.76 days from the first clinical manifestation and before the results were obtained from CDC, ATLANTA, USA the supportive and symptomatic treatment continued.

After starting treatment with Ribavirin, all the patients continued to deteriorate for the next two days. The fever did not settle and the platelet counts kept on falling even with platelet concentrate transfusions, as shown in figure 1 & 2. The hemorrhage from different sites continued along with the markedly

*TABLE-I*
Laboratory investigations of CCHF patients on admission

| *Laboratory Test* | *Values Mean ± SD* |
|---|---|
| Hb (g/dL) | 11.43 ± 2.49 |
| TLC (cells/µL) | 3497.43 ± 1391.22 |
| PLT (x $10^9$/L) | 29.435 ± 17.509 |
| PT (sec) | 12.41 ± 2.20 |
| APTT (sec) | 112.05 ± 29.12 |
| AST (U/L) | 353.84 ± 189.71 |
| ALT (U/L) | 50.00 ± 22.12 |
| T. Bil. (mg/dL) | 1.38 ± 0.49 |

**KEY:** Hb: Haemoglobin, TLC: Total leucocyte count, PLT: Platelet count, PT: Prothrombin time, APTT: Activated partial thromboplastin time, AST: Aspartate aminotransferase, ALT: Alanine transaminase, T.Bil: Total bilirubin

deranged activated partial thromboplastin time. The aspartate aminotranferase (AST) levels were markedly elevated while alanine transaminase (ALT) levels were moderately elevated. Interestingly the total bilirubin concentration remained within normal limits. The clinical as well as the laboratory scenario changed after a mean period of 2.30 ±0.69 days of treatment with Ribavirin. The high grade fever started to settle down and clinically the patients started improving. The serial platelet counts showed a trend towards normality (fig.2). The coagulation profile started improving and AST and ALT levels declined gradually. After 10-day course of Ribavirin, all the patients regained their normal state of health with normal laboratory parameters. However, mild anaemia and thrombocytosis were seen in some of the patients as adverse effects of the drug. Anaemia was due to extravascular haemolysis and possibly due to erytheroid suppression in the bone marrow while thrombocytosis was of reactive nature. The laboratory investigations on admission are shown in Table-I. The day-to-day serial investigations after starting Ribavirin are shown in Table-II, reflecting a 10-days follow up, as per study design. The pattern of fever after starting the drug is shown in Figure 1, while the serial platelet counts after starting Ribavirin are shown in Figure 2. Two (5.12%) of the patients expired during the course. The main causes of death

*TABLE-II*

Serial laboratory investigations after starting Ribavirin

| *Test* | *Day 1* | *Day 2* | *Day 3* | *Day 5* | *Day 7* | *Day 10* |
|---|---|---|---|---|---|---|
| Hb (g / dL) | 11.89 ± 2.59 | 10.82 ± 1.99 | 10.33 ± 2.18 | 10.30 ± 1.65 | 10.38 ± 1.81 | 10.74 ± 1.80 |
| TLC (cells / µL) | 3082.05 ± 1100.68 | 2843.58 ± 1059.49 | 3061.53 ± 989.31 | 4141.02 ± 769.04 | 4714.28 ± 698.05 | 6180.95 ± 1059.53 |
| PLT ($x 10^9$ / L) | 16.102 ± 8.837 | 21.128 ± 11.098 | 57.435 ± 14.346 | 69.487 ± 12.125 | 201.025 ± 82.805 | 521.794 ± 105.876 |
| PT (sec) | 13.74 ± 0.96 | 14.10 ± 1.16 | 13.64 ± 1.00 | 13.46 ± 0.99 | 13.56 ± 0.91 | 13.66 ± 2.24 |
| APTT (sec) | 110.69 ± 20.48 | 97.17 ± 15.71 | 94.07 ± 15.53 | 82.61 ± 15.26 | 67.69 ± 12.86 | 44.33 ± 8.92 |
| AST (U / L) | 507.69 ± 137.90 | 420.51 ± 115.11 | 269.23 ± 82.80 | 207.94 ± 112.08 | 139.74 ± 73.94 | 70.97 ± 58.33 |
| ALT (U / L ) | 241.02 ± 96.56 | 217.94 ± 91.39 | 185.71 ± 83.04 | 128.97 ± 69.99 | 82.30 ± 32.40 | 59.48 ± 16.05 |
| T. Bil. (mg / dL ) | 1.22 ± 0.21 | 1.16 ± 0.21 | 1.12 ± 0.23 | 1.03 ± 0.18 | 1.04 ± 0.14 | 0.93 ± 0.16 |

All values are Mean ± S.D.

**KEY:** Hb: Haemoglobin, TLC: Total leucocyte count, PLT: Platelet count, PT: Prothrombin time, APTT: Activated partial thromboplastin time, AST: Aspartate aminotransferase, ALT: Alanine transaminase, T.Bil: Total bilirubin

in these patients were delay in the start of treatment due to late arrival to the hospital resulting in complications like disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS).

Three members of the working team lost their lives to CCHF. One was a staff nurse who had a needle stick injury. Two others were sweepers who were exposed to the blood of CCHF cases. All these three cases died before the results of their tests for CCHF reached from CDC, Atlanta, USA. None of these cases received Ribavirin. It appears that in these cases the disease proved very fulminent. All these cases were admitted on high-grade pyrexia and were kept in the isolation unit on the very protocol. The samples were sent within 24 hours of admission and the results reached within the due time. All these three cases expired between day 5&6 of the initial symptoms. These were not a part of this study.

## DISCUSSION

Ribavirin is a purine nucleoside analog that inhibits the replication in-vitro of a wide range of RNA and DNA viruses, including myxoviruses, paramyxoviruses, arenaviruses, bunyaviruses, retroviruses, herpesviruses, adenoviruses and poxviruses.[23] Ribavirin is phosphorylated but its mode of action is still unclear; it may act at several sites including cellular enzymes, to interfere with viral nucleic acid synthesis. The mono- and triphosphate derivatives are believed to be responsible for the antiviral activity of the compound.[24] Susceptible DNA viruses include herpesviruses, adenoviruses, and poxviruses. Susceptible RNA viruses include Lassa Virus, members of bunyaviridae group, influenza, parainfluenza, measles, mumps and respiratory syncytial viruses and human immunodeficiency virus.[24-26]

The treatment of Haemorrhagic Fevers is primarily symptomatic. However, Ribavirin has been reported to reduce mortality in patients with Lassa fever,[18] Haemorrhagic Fever with renal syndrome[21] and possibly Crimean-Congo Haemorrhagic Fever.[27]

For treatment of Lassa fever, Ribavirin has been given intravenously in a suggested dose of 2 gm initially, then one gm every 6 hours for 4 days, then 500 mg every 8 hours for 6 days.[18] Treatment is most effective if started within six days of the onset of fever. For prophylaxis, a dose of Ribavirin 600 mg by mouth 4 times daily for 10 days has been suggested for adults.[28]

In our study, due to the non-availability of intravenous form, oral Ribavirin was given to the patients, although oral Ribavirin has been used for post-exposure prophylaxis for CCHF infection.[29] When administered orally or intravenously, Ribavirin causes anaemia due to extravascular haemolysis and suppression of the bone marrow.[30] Long-term oral therapy is associated with both gastrointestinal and CNS symptoms.[30] Ribavirin is well absorbed from the gastrointestinal tract[31] and would be expected to attain levels in the blood comparable with in-vitro sensitivity of CCHF to Ribavirin.[17]

In our study, Ribavirin was started with a mean period of 6.20±0.76 days of onset of fever after confirmation of the diagnosis of CCHF by CDC, Atlanta, USA. Before administration of Ribavirin, the haematological changes were fairly uniform and despite severe bleeding the haemoglobin concentration remained fairly high in most cases, probably because of haemoconcentration. In those patients who survived, mild iron deficiency anaemia was noted in convalescence. Mild leucopenia and pronounced thrombocytopaenia characterized the blood picture in all cases. These changes became more pronounced about 7 days after the onset of illness and lasted for approximately three days after starting treatment with Ribavirin. After that there was rapid improvement in levels of both platelets and leucocytes and a trend towards normalization of APTT and AST. The patients were cured of the disease after a 10-day course of Ribavirin. Mild anaemia and thrombocytosis were seen in some of the patients. The two deaths that occurred were the result of delayed hospital transfer resulting in development of complica-

tions of CCHF like massive bleeding, ARDS and DIC.

## CONCLUSIONS

It would be reasonable on a priority ground to manage patients with CCHF with barrier nursing, platelet concentrate transfusions and fresh - blood transfusions, together with control of fluid and electrolyte balance. We would also recommend use of oral Ribavirin within the first week of onset of illness in a dose of 2 gm as a loading dose, then 4 gm / day in four divided doses, for four days; dropping to 2 gm / day for six days, completing 10-day course. The oral treatment is cheaper and easier to administer, is of remarkable efficacy and is usually well tolerated with mild gastrointestinal symptoms. This would certainly shorten the protracted convalescence and would result in a much better outcome of this fatal disease.

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