



## RESEARCH PAPER

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## Outcome of patients with crimean-congo hemorrhagic fever in Peshawar, Pakistan

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### Abstract

Crimean-Congo Hemorrhagic Fever (CCHF) is an arthropod born zoonotic viral infection that is transmitted to humans by tick bite and contact with secretions, blood and tissues infected with the virus. CCHF is a fatal disease with mortality rate of 10-40%. This study was aimed to demonstrate the effect of Ribavirin on the outcome of patients with CCHF in a tertiary care hospital, Peshawar, Pakistan. Thirty confirmed cases of CCHF were enrolled in this cross-sectional study over a period of one year. Patients were divided into two groups based on their time of arrival to hospital. Group 1: Those who presented within 07 days of onset of disease (presented early). Group 2: Those who presented after 07 days of onset disease (presented late). Oral Ribavirin was given to all patients according to dose recommended by world health organization (WHO). Outcome in these two groups was compared. Out of 30 patients, 20 patients presented early and received concomitant Ribavirin. Among them, 18 patients recovered and 02 expired. Ten patients presented late and received concomitant Ribavirin. Among them, 02 patients recovered and 08 expired. CCHF is a deadly disease. The disease rapidly progresses to death if not treated timely. Early Ribavirin therapy significantly improves the recovery outcomes of CCHF.

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## Introduction

Crimean Congo Hemorrhagic Fever (CCHF) has been reported as early as 110A.D (Hoogstraal, 1979). The disease was first discovered in the west Crimean territory of the former USSR in 1944 (Chumako, 1979). Congo prototypes were first isolated in Zaire in 1956 (Simpson, 1979; Williams *et al.*, 1996). In 1969, Casals showed biologic and antigenic similarities between the Crimean and the Congo prototypes (Casals, 1969). Thereafter, the name Crimean-Congo Hemorrhagic Fever Virus gradually took fame. Since then CCHF has been described in many areas of Africa, the Middle east, Europe, Southern parts of the former USSR (Ukraine, Moldova and Transcaucasus) and in central Asian countries (Turkmenistan, Tajikistan, Kazakhstan and Uzbekistan). Turkey, Bulgaria, Greece and Albania (Gear, 1979).

CCHF is a wide spread zoonotic disease caused by a tick-borne virus (Nairovirus) of the family Bunyaviridae with a case fatality rate of 10-40% (Williams *et al.*, 1996). It is a small enveloped virus and holds a tripartite negative-sense single stranded RNA genome. Ticks, especially of the *Hyalomma* genus are both reservoir and vector for the CCHF virus (Begum *et al.*, 1970). Numerous wild and domestic animals, such as cattle, buffaloes, goats, and sheep are silent carriers of this virus and the adult ticks feed on these animals (Engin *et al.*, 2010). In animals, transient fever is the only sign which often goes undiagnosed and unnoticed. In humans the onset of CCHF is sudden and initial symptoms are fever, headache, back pain, joint pain and vomiting. As the illness progresses, large areas of severe bruising, severe bleeding from nose and gums, and uncontrolled bleeding at injection sites can be seen, beginning on about the fourth day of illness and lasting for about two weeks (Ergonul *et al.*, 2006). General supportive care with treatment of symptoms is the main approach to managing CCHF in people. The antiviral drug Ribavirin has been used to treat CCHF infection with apparent benefit. Both oral and intravenous formulations seem to be effective (Fisher-Hoch *et al.*, 1995).

In Pakistan, CCHF was first reported in 1976 (Athar *et al.*, 2003). Though Baluchistan remains the most affected province, yet 14 outbreaks have been reported from almost all geographical regions of the country (Altaf *et al.*, 1998; Jamil *et al.*, 2005; Durrani *et al.*, 2007). This study was aimed to determine the clinical outcome of patients suffering from CCHF presented to Lady Reading Hospital, Medical Teaching Institute, Peshawar, Pakistan.

## Materials and methods

This cross-sectional study was conducted at department of Medicine Lady Reading Hospital (LRH), Medical teaching institute. Lady Reading Hospital (LRH) is an 1800- bed, public sector, tertiary care teaching hospital that serves almost 1.97 million residents of Peshawar, the sixth most populous city in Pakistan.

### Study population

Study population included 30 patients suffering from CCHF, enrolled between 1<sup>st</sup> June 2017 and 31<sup>st</sup> May 2018. Diagnosis of CCHF was confirmed by rising level of IgM and IgG antibodies to Crimean Congo Hemorrhagic Fever Virus (CCHFV) by Enzyme Linked Immunosorbent Assay (ELISA) and Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) for CCHFV RNA.

### Ribavirin dosage

Oral Ribavirin was given to all patients included in the study according to dose recommended by World Health Organization (WHO) i.e. initial loading dose 30mg/kg followed by 15mg/kg every 6 hours for 4 days, the 7.5 mg/kg every 8 hours for 6 days (Sheikh *et al.*, 2004). All cases were kept in separate section of the ward with strict barrier care.

### Grouping of study population

Patients were divided into two groups based on their arrival to hospital. Those patients who presented within 07 days of onset of disease and concomitant early initiation of Ribavirin therapy (early presentation to hospital and concomitant early initiation of Ribavirin therapy) were included in

group one. On the other hand, group two consisted of those patients who presented after 07 days of onset of disease (late presentation to hospital and concomitant late initiation of Ribavirin therapy).

Outcome between these two groups was compared using Pearson chi-square test. Data was analyzed through SPSS version 22 and statistical significance was considered at P value 0.05. Our study was according to declaration of Helsinki. The study was approved by the hospital ethical committee.

## Results

A total of 30 patients were included in the study. Among these patients, 26 (86.66%) were male and 4 (13.34%) were female. Male to female ratio was 6.5:1. Age of the patients ranged from 17 to 70 years with mean age was  $38 \pm 13$  years. The mean duration of presentation was 7 days (range 4-11 days) to hospital. Among the enrolled subjects, 20 (66.66%) patients presented within 07 days after the onset of illness to hospital (presented early) while 10 (33.34%) were those who presented late (after 07 days after the onset of symptoms) Table 1.

**Table 1.** Gender-wise population and treatment presentation of subjects.

Gender		Presentation of Patients					
Male		Female		Presented early		Presented late	
no	%ge	no	%ge	no	%ge	no	%ge
26	86.66	4	13.34	20	66.66	10	33.34

Among the early presented twenty patients with concomitant early Ribavirin therapy, 18 (90.0%) patients recovered and 02 (10.0%) expired. Recovery to expiry ratio was 9:1. At the other end, in those 10 patients who presented late with concomitant late Ribavirin therapy, 08 (80.0%) expired and 02 (20.0%) recovered as shown in Table 2. Recovery to

expiry ratio was 1:4. Comparing the two groups mortality was much lower in the group who presented early and received early Ribavirin therapy. We found a significant association between outcome and early presentation to hospital and early Ribavirin therapy ( $p$  value=0.001).

**Table 2.** Clinical Outcome of patients with Crimean –Congo hemorrhagic fever. Peshawar, Pakistan.

Outcome	Presentation to Hospital(days)		Total
	Early Presentation	Late Presentation	
Patient Recovered	18	2	20
Patient Expired	2	8	10
Total	20	10	30

## Discussion

Though treatment is mainly symptomatic and conservative, the only antiviral that has contributed in recovery is Ribavirin. Ribavirin has anti-CCHFV activity *in vitro* and in animal models (Warts *et al.*, 1989). Recent reports suggest promising efficacy provided it is given in the early phase of the disease (Soares-Weiser *et al.*, 2010). Pakistan is at a high risk of contracting CCHFV. The reasons for this are; inadequate healthcare infrastructure, livestock

population, Eid –ul-Azha festival, the rural community and nomadic lifestyle (Muhammad *et al.*, 2017). The prevalence of CCHF is highest in Baluchistan and Khyber Pakhtunkhwa (KPK) province (Alam *et al.*, 2006). KPK is situated in the north-west region of the country. The first case of CCHF was reported from Abbottabad district in 2005 (Waqar *et al.*, 2006). But now cases have been described from other districts of the province including Peshawar, Karak, Lakimarwat, Hangu,

Mardan and Federally Administered Tribal Areas (a semi-autonomous tribal region in north-western Pakistan) (Bosan *et al.*, 2002; Durrani *et al.*, 2007). Majority of these cases are referred to tertiary care hospitals in Peshawar (the capital of Khyber Pakhtunkhwa).

Mortality rate in our study was 33.3% compared to the 5-30% (Casals, 1978) and 10-40% (Fajs *et al.*, 2014), reported in the literature. Out of 10 expired patients, 8 patients (80%) were those who arrived late to the hospital and received late Ribavirin therapy. Similar results were showed by Iavi-Naini and his colleagues from Iran (Iavi-Naini *et al.*, 2006).

They reported that 72% of their patients who died of the disease were referred to hospital late and received late Ribavirin after seven days of the onset of the illness. In one report from south-eastern Iran in 2006, 21% of CCHF affected patients died because of late arrival to tertiary level hospital (Metanat *et al.*, 2006). In our study, several factors are responsible for the late presentation to hospital including delay in disease recognition and lack of awareness among the public about this condition. Majority of our patients belonged to remote areas where diagnostic and health facilities are limited. Also transport facilities are lacking in these hilly and far long areas. This fact also contributes in late arrival to the tertiary care unit.

Out of 20 patients who arrived early at the hospital and received early Ribavirin therapy, 18 patients survived (90.0%). Survival was much better compared to survival in the other group. Fischer-Hoch and his colleagues started early Ribavirin to 03 patients with CCHF and all of them recovered as mentioned in their study (Fisher-Hoch *et al.*, 1995). Swanepoel and his colleagues from South Africa conducted a trial on CCHF treatment with Ribavirin and compared the outcome in two groups. They found that the outcome was better in those who presented early to the hospital (within 4 days of onset of disease) and received early Ribavirin (zero mortality out of seven patients) as compared to those who presented late (after 4 days), 3 out of 5 patients died

(Swanepoel *et al.*, 1987). This is in coherence with the results of our study in which early hospital presentation and early Ribavirin therapy lead to 90% recovery rate and late presentation lead to 80% mortality. Early Ribavirin therapy is associated with decrease mortality in patients with CCHF as demonstrated by Izadi and his colleagues in their trails (Izadi *et al.*, 2009). Our study is limited to a single tertiary care hospital, which may not be a true representative of the mortality rate of CCHF in the general population. It is essential for better policy making to observe the data from multiple centers for a longer period.

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#### Conflicts of interest

The authors have no conflict of interest concerning the cases in this paper.

#### Conclusion

It was found that the survival percentage of patients arrived early at the hospital and received Ribavirin was much better than late presented patients. The findings show that the CCHF is a deadly disease and rapidly progresses to death if left untreated. Early recognition of the disease and prompt treatment is the rule for better outcome. Oral Ribavirin is an effective treatment if given in early phase of the disease.

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