

## Commentary Article

## A report of 12 sporadic cases of Crimean-Congo hemorrhagic fever from Pakistan

Taimur Saleem<sup>1,\*</sup>, Madiha Rabbani<sup>1</sup>, Nida Habib<sup>1</sup>, Bushra Jamil<sup>2</sup><sup>1</sup>Medical College, Aga Khan University, Stadium Road, Karachi 74800, Pakistan<sup>2</sup>Departments of Medicine and Pathology and Microbiology, Aga Khan University, Stadium Road, Karachi 74800, Pakistan

\*Corresponding author:

Dr. Taimur Saleem,

Medical College, Aga Khan University, Stadium Road, Karachi 74800, Pakistan

Telephone: +923333198838

Email: [taimur@gmail.com](mailto:taimur@gmail.com)

## Abstract

Crimean-Congo hemorrhagic fever virus was discovered in Pakistan in the 1960s while the first case of Crimean-Congo hemorrhagic fever from Pakistan was recorded in 1976. Since then, the country has witnessed at least thirteen outbreaks of this infection. We have presented the demographic, clinical, hematological and management profile of 12 sporadic cases of Crimean-Congo hemorrhagic fever that were encountered at a tertiary care teaching hospital in Karachi, Pakistan between January, 2001 and October, 2009. All of the patients were male. The mean age of the patients was  $31 \pm 13.1$  years. Six of the 12 patients (50%) were residents of Karachi while 4 patients (33.3%) were from Balochistan province of Pakistan. The diagnosis was confirmed from serum samples of patients using reverse transcriptase-polymerase chain reaction assay. The mean duration of symptoms before admission was  $5.3 \pm 2.6$  days. The most common presenting complaint was fever (100%). Mean values of the different hematological parameters at admission were: platelets ( $40.5 \pm 29.8 \times 10^9/l$ ), white blood cell count ( $6.2 \pm 3.7 \times 10^9/l$ ), hemoglobin ( $11.1 \pm 3.3$  g/dl), prothrombin time ( $16 \pm 4.1$  seconds) and international normalized ratio ( $1.4 \pm 0.35$ ). The mean duration of stay in the hospital was  $5.9 \pm 3.2$  days. Oral ribavirin was administered to 9 out of 12 patients (75%). Four of the 12 patients (33.3%) expired in this series. Crimean-Congo hemorrhagic fever still remains a fatal and endemic infection in Pakistan that requires concerted efforts from the healthcare community for its eradication. It is important to improve the health practices and health seeking behaviors of the public through educational campaigns.

**Keywords:** Crimean-Congo hemorrhagic fever, Ribavirin, Thrombocytopenia, Livestock

## Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute viral infection caused by the CCHF virus (CCHFV) that belongs to the family *Bunyaviridae* of the genus *Nairovirus*. CCHF is endemic in many parts of the world including Africa, Central Asia, Russia and Pakistan. The virus was discovered in Pakistan in the 1960s [1] while the first case of CCHF from Pakistan was recorded in 1976 [2, 3]. Since then, the country has witnessed at least thirteen outbreaks of CCHF [4].

CHF is a zoonotic virus that can be transmitted through the bite of an infected tick (*Hyalomma*) or through direct

contact with infected blood or tissues [5]. The infection culminates in a severe multisystem disease that can result in profuse, life-threatening bleeding [6]. The case-fatality rate from CCHF has been reported with great variability from 15-100% [7 – 11].

We have previously described our experience with the management of CCHF in a series of 8 patients from Pakistan who all presented during an outbreak in 2000 [4]. This current report describes features of 12 sporadic cases of CCHF that presented over a 9 year period to our institution.

**Table 1.** Characteristics of 12 patients with Crimean-Congo hemorrhagic fever

Pt.#	Age-gender (Yrs – M/F)	Occupation	Residence	Month of admission	Duration of symptoms (d)	Duration of hospitalization (d)
1	55 – M	Shopkeeper	Karachi <sup>§</sup>	November	3	10
2	20 – M	Student	Karachi <sup>§</sup>	November	3	9
3 <sup>^</sup>	29 – M	Computer Engineer	Karachi <sup>§</sup>	October	10	13
4*	18 – M	Student	Karachi <sup>§</sup>	November	4	4
5*	25 – M	Lab** Technician	Quetta <sup>£</sup>	May	6	5
6*	17 – M	Student	Kashmir	November	3	2
7*	42 – M	Animal Herder	Quetta <sup>£</sup>	July	10	3
8	22 – M	Nurse	Karachi <sup>§</sup>	November	6	6
9	30 – M	Mechanic	Qandhar <sup>†</sup>	September	6	4
10	28 – M	Travel agent	Karachi <sup>§</sup>	August	2	4
11	55 – M	Engineer	Quetta <sup>£</sup>	June	6	5
12	32 – M	Shopkeeper	Lasbella <sup>£</sup>	July	4	6

<sup>^</sup> Tested positive for both Crimean Congo Virus and Dengue Virus. This patient was also a known case of Glucose-6-Phosphate Dehydrogenase deficiency

\* Expired

<sup>§</sup> Sindh province of Pakistan

<sup>£</sup> Balochistan province of Pakistan

<sup>†</sup> Afghanistan

\*\* Positive for *Plasmodium falciparum* malaria on blood smear

## Case series

Aga Khan University Hospital (AKUH) is a tertiary care teaching hospital in the private sector of Karachi, Pakistan that receives patients from Karachi as well as other areas of Pakistan. Between January, 2001 – October, 2009, a total of 12 cases of Congo Crimean Hemorrhagic Fever were admitted at AKUH.

A preliminary diagnosis of viral hemorrhagic fever (VHF) in these patients was made on the basis of clinical presentation and laboratory parameters. The diagnosis of CCHF was confirmed from serum samples of patients using reverse transcriptase-polymerase chain reaction (RT-PCR) assay. In view of the outbreaks of dengue fever in Pakistan in the current decade, patients were also tested for dengue IgM antibody. This was positive in one patient. Blood cultures and peripheral film examination for malarial parasite (MP) were also performed in all cases. MP was negative in all but one case.

## Demographic profile

All of the patients of this case series were male. The mean age of the patients was  $31 \pm 13.1$  years. Six of the 12 patients (50%) were residents of Karachi while 4 patients (33.3%) were from Balochistan province of Pakistan (Table 1). One patient belonged to Afghanistan while one patient was from Azad Kashmir. Most of the cases were admitted in the month of November (41.7%).

## Clinical and laboratory parameters

The mean duration of symptoms before admission was  $5.3 \pm 2.6$  days. The most common presenting complaints

were fever (100%), myalgias (75%), headaches (58.3%), vomiting (41.7%), hematemesis (33.3%), epistaxis (25%) and hematuria (16.7%). Important hematological parameters are shown in

Mean values of the different hematological parameters at admission were: platelets ( $40.5 \pm 29.8 \times 10^9/l$ ), white blood cell count ( $6.2 \pm 3.7 \times 10^9/l$ ), hemoglobin ( $11.1 \pm 3.3$  g/dl), prothrombin time ( $16 \pm 4.1$  seconds), international normalized ratio ( $1.4 \pm 0.35$ ), activated partial thromboplastin time ( $34.9 \pm 11.8$  seconds). Atypical lymphocytosis was observed in 7 patients (58.3%).

## Management profile

The mean duration of stay in the hospital was  $5.9 \pm 3.2$  days. Antipyretics and intravenous fluids were administered to all patients. Broad spectrum antibiotics were given to 11 patients (91.7%). Inotropic support in the form of dopamine and/or epinephrine was given to all patients who were admitted to intensive care unit (n=5). Transfusion of blood products was done in the form of packed cells (58.3%), fresh frozen plasma (66.7%) and platelet concentrate (91.7%).

Ribavirin was administered to 9 out of 12 patients (75%). Out of these 9 patients, 5 patients were given ribavirin on the first day of admission while 4 were given ribavirin on the 2<sup>nd</sup> day of admission. Since intravenous ribavirin is not available at our institution; all of the nine patients received oral ribavirin. Four of the 12 patients (33.3%) expired in this series (Table 3).

**Table 2.** Clinical profile and laboratory parameters of 12 patients with Crimean-Congo hemorrhagic fever

Pt #	Time <sup>^</sup>	Leukocyte count <sup>§</sup>		Lymphocytes/Monocytes(%)		Platelets <sup>§</sup>		PT/INR (s) (at admission)
		Lowest(d)	Highest(d)	(d)	(d)	Lowest(d)	Highest(d)	
1	7	7.4 (1)	9 (6)	25 (1)	/ 11 (1)	26 (2)	229 (9)	14.8 / 1.24
2	8	1.5 (1)	7 (7)	43 (7)	/ 8 (1)	15 (5)	144 (9)	15 / 1.25
3	5	4.1 (3)	15 (9)	40 (9)	/ 12 (7)	13 (5)	140 (12)	22.9 / 1.76
4	1	2.3 (1)	16.8 (4)	51 (1)	/ 22 (2)	8 (1)	68 (4)	12.5 / 1.04
5	*	14 (1)	25 (5)	56 (2)	/ 14 (2)	27 (1)	100 (5)	17 / 1.54
6	1	18 (1)	28 (2)	52 (1)	/ 4 (1)	10 (1)	60 (2)	25.8 / 2.17
7	*	9 (1)	13 (3)	54 (2)	/ 15 (3)	19 (1)	90 (3)	17 / 1.54
8	3	5 (1)	7 (4)	39 (1)	/ 7 (1)	17 (2)	176 (6)	14.2 / 1.18
9	1	5 (1)	10 (3)	33 (2)	/ 19 (2)	22 (1)	165 (4)	10.6 / 0.88
10	1	6.2 (1)	8 (3)	30 (1)	/ 8 (2)	25 (1)	232 (4)	14.8 / 1.24
11	5	8 (1)	10 (5)	49 (1)	/ 17 (4)	25 (1)	41 (3)	16.1 / 1.35
12	2	3.7 (1)	8 (4)	31 (2)	/ 11 (2)	17 (3)	146 (6)	14.1 / 1.18

<sup>^</sup> Time (in days) from admission to defervescence of fever

\* Patient expired before achieving this parameter

## Discussion

We have described the demographic, clinical, laboratory and management profile of a series of 12 patients with CCHF encountered at a tertiary care hospital in Karachi, Pakistan.

### Demographic profile

Upto 75% patients in this case series were either from the city of Quetta (capital of Balochistan province) or Karachi (capital of Sindh province). This distribution almost parallels that observed in our previous experience in 2000 [4] whereby 100% patients were either from Quetta or Karachi. This reflects both the catchment area of our hospital as well as areas with high CCHF prevalence in the country. The appearance of CCHF cases in large cities of Pakistan have been attributed (although not exclusively) to the movement of sacrificial animals to the urban hubs of the country at the time of the Islamic festival of Eid-ul-Azha [4, 5]. Although efforts are now being made to set up special animal markets for the sale of sacrificial animals that are located away from residential areas, practices regarding the actual sacrificial ritual have changed little in these cities. The sacrifice of the animals is done on streets, roadside kerbs or parks whereby the residents of these areas are exposed to possibly contaminated animal blood and tissues [4]. Education of the public must be undertaken to modify these harmful practices. It also appears plausible that infected ticks from CCHF-enzootic areas were introduced into these cities along with the animals [4].

More recently, CCHF cases have been also described from other cities of Pakistan such as Rawalpindi [5, 12] and Abbatobad [13]. Cases in these areas have previously been attributed to nomadic movement [3].

In our series, most of the cases presented in the month of November (42%). This appears to coincide with the time of Eid-ul-Azha each year [4, 5]. Another study reported 83 confirmed cases of CCHF from Balochistan, Pakistan over a 5-year period. The presentation of cases in this study was largely clustered in the form of bi-annual surges in March – May and August – October [14].

Mild et al have recently analyzed the worldwide migration pattern of CCHF virus and concluded that the migration between Pakistan and its neighboring country Iran is largely unrestricted [15]. Although the present series had no patient from Iran, we encountered one patient from Afghanistan. Iran, Afghanistan and Pakistan together constitute a single geographical block and the porous borders may be linked with unrestricted bilateral movement of possibly infected livestock and people.

Although classically shepherds, farmers, butchers, and slaughterhouse workers have been described as being high-risk occupations for CCHF virus infection [16], other groups including military personnel, housewife [17], healthcare worker, laboratory physician and student [4] have also been reported to be affected. In our current series, one patient was an sheperd from Balochistan, one was a laboratory technician and one was a health care professional. Although not much is known about the baseline knowledge of the public or professionals about CCHF in Pakistan, one study from Balochistan reported

**Table 3. Ribavirin therapy administered to patients with Crimean-Congo hemorrhagic fever**

Pt #	Ribavirin given	Regimen administered	Outcome
1	Yes	1 g by mouth hourly for 4 days, then 500 mg by mouth 8 hourly for 6 days, started on 1 <sup>st</sup> day of admission	Recovered
2	Yes	400 mg by mouth 8 hourly for 8 days, started on 2 <sup>nd</sup> day of Admission	Recovered
3	Yes	400 mg by mouth, 8 hourly for 10 days, started on 2 <sup>nd</sup> day of admission	Recovered
4	No	-	Died on 4 <sup>th</sup> day of admission
5	Yes	1 g by mouth hourly for 4 days, started on 2 <sup>nd</sup> day Of admission	Died on 5 <sup>th</sup> day of admission
6	Yes	400 mg orally 8 hourly for 1 day, started on 2 <sup>nd</sup> day of Admission	Died on 2 <sup>nd</sup> day of admission
7	Yes	600 mg by mouth 8 hourly for 3 days, started on 1 <sup>st</sup> day of admission	Died on 3 <sup>rd</sup> day of admission
8	Yes	400 mg by mouth, 8 hourly for 7 days, started on 1 <sup>st</sup> day of Admission	Recovered
9	Yes	1 g by mouth, 6 hourly for 4 days followed by 600 mg By mouth 6 hourly for 7 days, started on 1 <sup>st</sup> day of admission	Recovered
10	No	-	Recovered
11	Yes	400 mg by mouth, 6 hourly for 2 days, followed by 1 g by mouth 6 hourly for 8 days, started on 1 <sup>st</sup> day of admission	Recovered
12	No	-	Recovered

poor level of knowledge regarding the clinical presentations and modes of spread of CCHF among the health care workers (doctors, nurses and laboratory technicians) [18].

### Clinical profile

We noted that patients who died were relatively young ( $\leq 25$  years) and had shorter duration of symptoms before hospitalization (except patient # 7). These patients also had higher total leukocyte counts recorded during hospitalization, greater degree of lymphocytosis and greater derangement of coagulation profiles. Deranged coagulation profile has been associated with mortality in previous studies [19].

The mean duration of symptoms before admission was  $5.3 \pm 2.6$  days. This may be attributable to the variation in the severity of the disease. The reticuloendothelial system (RES) is one of the primary targets of the CCHF virus. Subsequent release of cytokines from RES is associated with an increase in vascular permeability. The infection then evolves to cause hemorrhage, shock and circulatory collapse in the victim. Ultimately, the patient spirals into a state of multiorgan failure [5, 20]. The variability in duration of symptoms before presentation as well as the late presentation in some cases may also be linked to the health seeking behavior of the Pakistani public. Fever was the single symptom (and sign) that was uniformly present in all of our patients. Because of the pluralistic health system in Pakistan, patients with only mild fever may not visit healthcare facilities right away [21]. It is possible that these patients were only encountered after

symptomatology became prolonged or additional serious or complex signs appeared.

### Management profile

Case fatality rate in this series was 33%. In literature the case-fatality rate of CCHF has been reported with great variability from 15-100% [7 – 11]. Ribavirin was given to 75% patients; the majority received the drug on the first day of admission. The management of CCHF includes meticulous fluid and electrolyte management in patients [22]. Ribavirin is administered as well; however, clinical benefit has not been uniformly reported in association with its administration. In particular, evidence for efficacy in controlled clinical trials is lacking [22]. In our previous experience [4], a response rate of only 20% was observed in patients who received ribavirin. Anecdotal benefit from ribavirin has been reported previously for cases of CCHF, Lassa Fever, Bolivian hemorrhagic fever, Hanta virus renal syndrome [22]. However, it is clear that more effective agents are required to improve outcomes from CCHF in developing countries like Pakistan. In addition, problems with availability and cost of drugs also need to be addressed.

### Conclusion

We have reported CCHF in a series of 12 patients from Pakistan. Although management of CCHF cases has improved (as reflected by lower fatality rates compared to our previous experience) in this series, it still remains a fatal infection that requires concerted efforts from the healthcare community of Pakistan for its eradication. It is

important to improve the health practices and health seeking behaviors of the public through educational campaigns. Safer handling of live and slaughtered animals on the occasion of Eid-ul-Azha should be advocated [4]. Also, health care professionals need to be educated about relevant infection control and barrier precautions [18, 22].

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### Conflict of interest

The authors declare that they have no conflict of interest.

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