A Crimean - Congo haemorrhagic fever outbreak in Northern Balochistan

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ORIGINAL ARTICLE

A CRIMEAN - CONGO HAEMORRHAGIC FEVER OUTBREAK IN NORTHERN BALOCHISTAN

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ABSTRACT

Objective: To describe the clinical characteristics, epidemiology, predictors of fatal outcome (PFO), and management effects of Crimean-Congo haemorrhagic fever (CCHF) patients during an outbreak in Northern Balochistan.

Design: Descriptive study.

Place and Duration of Study: Fatima Jinnah Hospital and Combined Military Hospital, Quetta, from June to October, 2001.

Patients and Methods: Patients presenting with a fever of less than 2 weeks duration and bleeding manifestations were included. Clinical history was recorded and patients were placed on oral ribavirin, and hematological support. Diagnosis was established by PCR for CCHF or detection of CCHF specific IgM and IgG.

Results: Eighty-four patients were received, 34 (40.5%) were suspected of suffering from classical CCHF. All 34 (100%) patients presented with a history of fever and bleeding (epistaxis, gum bleeding, melena or haematuria). Mean platelet count was 30 x 10^9/L and mean ALT (alanine transferase) was 288 U/L. Among fatal cases, the mean platelet count was 18.4 x 10^9/L and ALT was 781 units/L. PCR for CCHF viral RNA performed on 10 patients was positive in 3 (30%) patients. CCHF specific IgM and IgG was positive in 17.6% (6/34). Four patients were brought in moribund condition and expired before treatment could be started, 4 patients expired during treatment and 76.5% (26/34) were cured. The overall mortality was 23.5% (8/34). Main predictors of fatal outcome were ALT ≥ 150 units/L, activated partial thromboplastin time(aPT) ≥ 60 seconds, prothrombin time (PT) ≥ 34 seconds, aspartate transferase (AST) ≥ 200 units/L, platelets ≤ 20 x 10^9/L, and fibrinogen ≤ 110 mg/dL.

Conclusion: In this series of CCHF occurring in Northern parts of Balochistan, gastrointestinal tract bleeding was the worst prognostic factor associated with fatal outcome. Providing education to healthcare workers and at risk populations, hematological support, anti-viral drugs, and barrier nursing may help reduce mortality.

KEY WORDS: *Crimean-Congo hemorrhagic fever (CCHF). Endemic. Anti-viral. Oral Ribavirin. Clinical management. Gastrointestinal hemorrhage.*

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) virus is an enveloped, single-stranded Bunyaviridae. An outbreak in Crimea in 1944, with a virus identical to the Congo virus, led the name to CCHF.[1,2] Many wild and domestic animals act as reservoirs for the virus. Ixodid ticks, particularly those of the genus Hyalomma, act both as a reservoir and vector. The disease is endemic in Eastern Europe, North West China[3], Central Asia, Indian subcontinent, Middle East and throughout much of Africa. Humans become infected being bitten by ticks or by crushing ticks, often while working with domestic animals or livestock. Contact with blood, secretions, or excretions of infected animals or humans may also transmit infection. In areas with endemic CCHF, the disease may occur most often in the spring or summer. Nosocomial transmission is well described in recent reports from Pakistan , Iraq , Dubai, South Africa.[4-10] Available evidence suggests that simple precautions, such as barrier nursing, effectively prevent secondary transmission.[11]

The incubation period for CCHF is about 2-9 days. Initial symptoms are non-specific and include sudden fever, headache, myalgia, arthralgia, abdominal pain, and vomiting. A petechial rash is common and may precede a gross and obvious hemorrhagic diathesis, manifested by ecchymoses, bleeding from needle-puncture sites, and hemorrhage from multiple sites.[12] The case-fatality rate has been estimated to range from 15% to 70% but mild infections also occur.

The diagnosis requires isolating the virus from blood during the first week of illness or detecting CCHF specific IgM.[13] Nonspecific laboratory abnormalities include progressive neutropenia, lymphopenia, thrombocytopenia, anemia, and elevated liver enzymes are common. The treatment is supportive and may require intensive care. While ribavirin has been used and proved effective to some extent, immune plasma effectiveness has not been evaluated.[14,15]

In May 2001, after receiving the initial reports regarding the occurrence of fever with bleeding among cases in Balochistan,

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a CCHF treatment center was established at the Fatima Jinnah Hospital (FJH), Quetta, Pakistan, to clinically manage the CCHF patients. The aim of this study was to describe the clinical characteristics, epidemiology, predictors of fatal outcome (PFO), and management effects of CCHF patients managed in FJH.

Patients and Methods

After the initial reports regarding the occurrence of fever with bleeding among cases in the region, a CCHF treatment center was established at the Fatima Jinnah Hospital (FJH), Quetta in accordance with the World Health Organization (WHO) guidelines on infection control for viral hemorrhagic fevers. Information was disseminated throughout the province via media. All Basic Health Units (BHU) and District Health Departments (DHD) of the province collaborated in this program.

All patients presenting with a fever of < 2 weeks duration and bleeding manifestations were referred to the above CCHF treatment center. Detailed clinical history and examination was carried out and recorded. Patients were divided into three groups on the basis of history and clinical examination: probable cases (those clinically suggestive of suffering from CCHF); ruled-out cases (those unlikely to be suffering from CCHF); and suspect cases (those requiring further evaluation and observation). Suspect cases were kept in a separate section of the FJH-CCHF treatment center. Patients with Plasmodium Falciparum on blood film examination, platelet count >100x109 /L, and patients with obvious features of other disease like typhoid and hereditary bleeding diathesis were excluded from the study.

Patients labeled as probable cases were kept in isolation, and barrier nursing was enforced. Blood samples were obtained for complete blood counts, serum alanine aminotransferase (ALT), serum aspartate transferase (AST), bilirubin, urea/creatinine, Prothrombin time (PT), activated partial thromboplastin time (aPTT), viral RNA detection by polymerase chain reaction (PCR), CCHF specific Immunoglobulin detection (IgG, IgM) and for blood grouping/cross-match. All probable cases were transfused with platelet concentrates and fresh frozen plasma irrespective of their haemostatic status till bleeding stopped. Red cell concentrates were transfused in only those patients who were having hematocrit below 30%. All probable cases were given oral ribavirin 2 grams initially, followed by 1 gram 6 hourly for 4 days and 500 milligram 8 hourly for 6 days. In case of children 15 mg kg body weight, ribavirin 4 times daily for 10 days was given. Patients were discharged after 7 days of convalescence.

Data was collected on SPSS 10.0 programmer; descriptive statistics were applied to analyze the data. Chi-square test was applied to find out the statistically significant difference of values. The Odds ratio for risk assessment of fatality was calculated by 2 x 2 table using ALT, AST, aPTT, fibrinogen, and TLC and platelet counts of fatal cases with same analytes of non fatal cases.

Results

Eighty-four patients were seen between the study period. Forty-five, out of 84 (53.6%) patients were clinically suggestive of suffering from CCHF. On blood film examination, 10.7% (9/84) patients were detected suffering from *Falciparum malaria* and 2.4% (2/84) from acute leukemia and were excluded.

Thirty-four (40.5%), out of the 84 patients were treated as definite clinical cases of CCHF. Thirty (88.2%) patients belonged to Northern Balochistan. Districtwise distribution is shown in Figure 1. Four patients (11.8%) came from adjoining regions of Afghanistan. The largest number of cases was observed in the month of June, followed by a small peak in September. Twenty-six patients (76.5%) were male and 8 (23.5%) were female. Age of patients varied from 4 years to 75 years with a median of 30 years. All 34 patients (100%) presented with fever, followed by epistaxis (82%) and ecchymosis (68%). Only 52% presented with a gum bleed. Eleven patients presented with melena of whom 4 (36.6%) expired, followed by 18 cases of gum bleeding out of whom 5 expired (27.8%), of the 6 cases with haematuria, one (16.7%) expired. The presenting symptoms and their distributions are described in Table I.

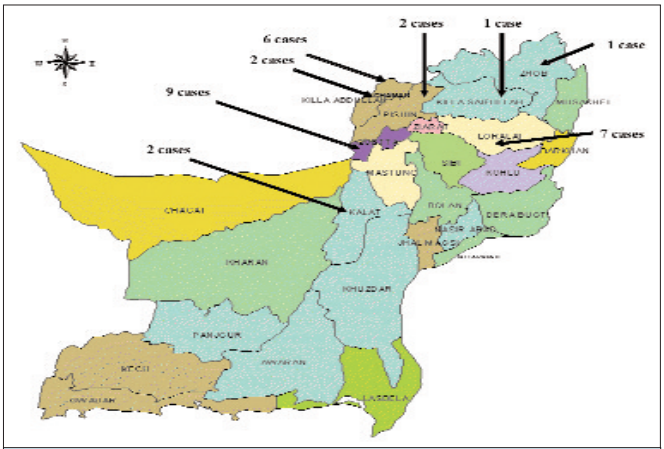

Figure 1: Topological distribution of the CCHF cases from Balochistan 2001 outbreak

Table I: Common symptoms of CCHF from Balochistan 2001 outbreak.

Symptom	% of	Range patients	Mean (days)	Presenting symptoms as (days) a percent of mortality
Fever	100%	2-14	6	23.5% (8 died out of 34)
Epistaxis	82%	1-15	4	14.28% (4 died out of 28)
Body aches	73%	2-15	6	24% (6 died out of 25)
Purpuric spots	71%	1-15	4.5	20.83% (5 died out of 24)
Ecchymosis	68%	1-15	4	21.7% (5 died out of 23)
Gum bleeds	52%	1-5	2.5	27.77% (5 died out of 18)
Melena	32%	1-5	2	36.36% (4 died out of 11)
Haematuria	17.5%	1-4	2	16.66% (1 died out of 6)

Serum bilirubin ranged between 0.4-5.3 mg/dl (mean 1.3 mg/dl). ALT ranged between 60-4224 U/L (mean 288 U/L), serum urea 3-30 mmol/L (mean 8.4 mmol/L), creatinine 75-450 m mol/L mean 125 m mol/L, haemoglobin 3.8-14.4 g/dl mean 9.71, platelet count 3.0-100 x 10^9/L (mean 30.0 x 10^9/L) and total leukocyte count (TLC) 0.7-15.7 x 10^9/L (mean 4.4 x10^9/L). Antibody titers (IgG and IgM) were tested in all patients and were found positive in 17.6% (6/34). PCR was performed on 10 patients; it was positive in 30% (3/10).

Two of these PCR positive patients were found negative for IgG and IgM, whereas one patient tested positive both with PCR as well as IgG and IgM. Four patients were received in a moribund state and expired before treatment could be initiated. Four patients died during treatment. All non-morbid (30) cases were transfused with a mean of 5.2 units of 50 ml platelets and a mean of 5.0 units of 200 ml fresh frozen plasma. Nineteen patients were given 2.2 units of 200 ml of red cells who had a hematocrit concentration below 30%.

Among fatal cases, the mean ALT was 780 U/L [variation 28-4224], aPTT was 76.9 seconds [variation from 40-100]; PT was 28 seconds [ranging from 20 -50 sec], AST was 225.6 seconds [ranging from 35-400] ; and platelets were 18 x 10^9/L [range 10-31]. TLC was 4.97 x 10^9/L [ranging from 1.1-10.4]. Fibrinogen was 80 mg/dL [Range 20-200].

When comparing means of fatal outcome predictors (Table II), the mean ALT was 5-fold, the aPTT was 1.5-fold, AST was 1.7-fold and TLC was 1.2-fold higher in fatal cases than in cured cases. Platelets were 1.3-fold and fibrinogen was 1.6-fold higher in cured as against fatal cases. Table III compares the 90% or more fatal outcome predictors. All analyte predictors had an odds ratio above 1 but only aPTT with a fatal outcome predictor of ≥ 60 seconds and AST with a fatal outcome predictor of ≥ 200 U/L were statistically significant.

The overall mortality was 23.5% (8/34). The mortality was 13.3% (4/30) in patients that were treated. In 86.7% (26/30) patients, who survived, bleeding stopped on the average in 3 days, whereas other symptoms were resolved in 4 days. The average stay in hospital was of 10 days.

Discussion

Sporadic cases of CCHF have been reported in Balochistan since 1976 and epidemics in various parts of Pakistan since 1987.[17-18] There is evidence that the disease is present in neighboring Afghanistan but due to lack of epidemiological surveys it remains largely unreported. In autumn 2001, a CCHF outbreak was reported along the western border of Afghanistan with Iran. In our population, the largest number of cases appeared in the month of June and then tapered off in October. Most common areas effected were of Northern Balochistan and associated areas that includes Pashin, Chamman, Zohb , Ziarat, Sibi, Loralai and Kohlu. The study of Pirkani GS 2006 concludes that most of the cases occur in Northern Balochistan that agrees to our study.[19-20]

Virus causing CCHF in this region is of high virulence with mortality ranging from 30-75%. It is notorious for nosocomial outbreaks, typically following admission of an index case to a health care facility where it was not suspected; the mortality rate in such cases has been reported to be up to 40%.[21] Most of the outbreaks in Pakistan have resulted in deaths of health care workers (HCW) with a recent history of case of a bleeding patient with exposure to bodily fluids or with a history of operating a patient with an acute abdomen. Basic knowledge of CCHF in HCW is poor.[22] In a knowledge assessing survey, only 66% of HCW had some knowledge of CCHF.[23] In this study, once the HCW in the province were educated with regard to the presence of disease and precautions were taken, no new case of death in HCW was found.

Table II: Predictors of fatal outcome (PFO) derived from fatal cases, and cured cases

Analyte	Fatal cases (n=8) Mean	± SD	95% Confidence Interval of the Difference	Cured cases (n=26) Mean	± SD	95% Confidence Interval of the Difference	Ref Range
ALT	780.8	142	400-1981	147.5 U/L	125	97-198	(> 40 units/L)
AST	225.6	127.5	119 -332	132.1 U/L	76	101-163	(> 36 units/L)
aPTT	76.9	23	57-97	52.4 Sec	15	46-58	(Control 32 sec)
PT	37	12.7	27-48	20 Sec	8	18-25	(Control14 sec)
Fibrinogen	80.0	65	26-134	125.8 mg/dl	62	100-150	(>100mg/dL)
Platelets	18.4	8.2	11-25	23 x 0^9/L	13	18-28	(150-400 x 10^9/L)
TLC	5.0	5.0	4.9-0.76	4.2 x 10^9/L	3	4.1-2.9	(4-11x 10^9/L)

ALT: Alanine Aminotransferase. AST: Aspartate Aminotransferase. PT: Prothrombin time. aPTT: activated partial thromboplastin time. TLC: Total leukocyte count.

Table III: ODD Ratio of 90% or more fatal outcome predictors

Analyte	Ref range units	FOP*	Fatal Cases	Cured Cases	OR	95% CI	p-value
ALT	<40	≥ 150 U/L	6	11	4.09	0.56 - 36.66	0.11
	U/L	< 150 U/L	2	15			
aPTT	32 Sec	≥ 60 sec	6	9	5.67	0.76 - 51.93	0.047 ‡
	Control	< 60 sec	2	17			
AST	< 36	≥ 200	6	6	10.00	1.26 - 99.56	0.008 ‡
	U/L	< 200	2	20			
Platelets	150-400	≤ 20 x 10^9	5	12	1.94	0.30 - 13.34	0.42
	x 109/L	> 20 x 10^9	3	14			
TLC	4-11	≥ 10 x 10^9/L	1	1	3.57	0.0 - 154.92	0.37
	x 109/L	< 10 x 10^9/L	7	25			
Fibrinogen	>100	≤ 110 mg/dL	6	15	2.20	0.30 - 19.57	0.38
	mg/dL	> 110 mg/dL	2	11			

A confirmed diagnosis of CCHF is based upon viral RNA detection in blood and secretions of patient. IgM develops in about 5-6 days and is critical for early diagnosis.

The mainstay of diagnosis is clinical assessment. A history of fever of < 2 week duration, bleeding manifestations in resident of endemic area, and recent contact with CCHF patients are sufficient for suspicion of CCHF and warrant proper workup. In a study by Sheikh *et al.,* 41% of suspected cases proved CCHF on serology and molecular studies while in this study 30% cases were proved on serology and molecular studies that partially agrees to the findings of *Sheikh AS*. However, most of the studies performed in Pakistan conclude that a platelet count < $100X10^9$/L, raised ALT, leucopenia and absence of Plasmodium falciparum (on slide) are reliable supportive investigations.[24-25]

The manifestations of disease vary widely. In this study population, fever, epistaxis, body aches and purpuric spots were the main presenting signs and symptoms (Table I). It is feasible to isolate and observe every case with bleeding manifestations and fever of short duration during an epidemic even if supportive investigations are not initially suggestive of disease. In our population, the finding of gastrointestinal bleeding was a grave prognostic feature as all the patients brought in moribund had melena. The second grave prognostic finding was gum bleeding. Only 6 patients had haematuria out of whom one died and 28 of the patients reported with epistaxis out of whom 4 died. It is also possible that patients with melena may also have gum bleeding, epistaxis or haematuria but these were missed as the patients with melena were in moribund condition and required intensive care that committed to stabilizing the patient.

The predictors of fatal outcome (Table II) had mean ranges of analyte were very similar to those identified by Swanepoel *et al.* except TCL which was ≥ 5.0 x 10^9/L. Further analysis showed that in our population, all of the 90% or more fatal outcome predictor (FOP) odds ratios, as suggested by Swanepoel *et al.*, were higher, but were only statistically significant for aPTT, and AST and the confidence interval for AST was very large (Table III). This finding should not undermine the importance of the FOP documented by Swanepoel *et al.* but suggests that further studies be conducted in varied populations to exactly determine the value of the FOP.[27]

In this study, response to the treatment with oral ribavirin, fresh frozen plasma and platelets was encouraging that agrees to other studies.[15,26] Mortality among the treated patients of this outbreak was 13%. In most cases, bleeding stopped after the first dose of fresh frozen plasma (FFP) and platelets. Only 6/30 patients required repeated dose of FFP and platelets. Feeling of well-being usually occurred on the third and fourth day. Three of the patients did not show improvement to initial therapy and died on the second and third day of admission. The fourth patient, a young female, expired due to severe gastrointestinal hemorrhages on tenth day of treatment, a day before her planned discharge from hospital.

The main limitation of this study was that due to unavailability of diagnostic facility in the centre clinical management was employed without laboratory confirmation of cases. It is possible that data inferred from laboratory unconfirmed cases may be misleading, thus most of the conclusions drawn are based on laboratory confirmed cases only.

Conclusion

The patients presenting with fever, epistaxis, body aches, purpuric spots, ecchymosis, gum bleeding, melena and haematuria should be suspected and evaluated for CCHF. Gastrointestinal tract bleeding was the worst prognostic factor associated with fatal outcome. Timely diagnosis of CCHF in properly equipped laboratory is of paramount importance for the treatment and better management of cases as well as HCW. Providing education to healthcare workers and at risk populations, hematological support, anti-viral therapy and barrier nursing precautions may help reduce mortality.

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