Crimean-Congo Hemorrhagic Fever (CCHF): Our Experience at a Tertiary Hospital

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ABSTRACT

Objective: To share our experience of managing Crimean-Congo Hemorrhagic Fever cases at tertiary care hospital.
Study Design: Hospital based case series.
Place and Duration of study: Medicine department Combined Military Hospital Peshawar, from 2017 to 2019.
Methodology: A total of 10RT-PCR positive cases of Crimean-Congo Hemorrhagic Fever were included in the study. Data were collected retrospectively from Stat office of the hospital. All cases which were PCR negative, having multiple co-morbid conditions and having alternative diagnoses were excluded from the study. Demographic, epidemiological, clinical and laboratory parameters were noted on a specially designed Proforma.
Results: All patients were males armed forces personnel employed in the tribal areas of KPK. All patients initially developed fever and generalized body pains. Among them 2 (20%) patients developed petechial rash and 1(10%) suffered from epistaxis, melena and hematuria. All (100%) of the patients' lab data revealed leukopenia, thrombocytopenia, elevated ALT and LDH. Complete recovery was noted in all patients. 8 (80%) of the patients received ribavirin and platelet transfusion. All patients under study also received oral Vitamin C supplement. Average hospital stay was 14 days.
Conclusion: Crimean-Congo Hemorrhagic Fever is a fatal disease. People visiting to endemic areas are at particular risk such as soldiers. It is manifested by fever, petechial rash and thrombocytopenia. Treatment is supportive. The role of oral vitamin C supplements and ribavirin to hasten recovery needs further high-powerstudies andshould be given to all suspected and confirmed cases.

Keywords: Crimean-congo hemorrhagic fever (CCHF), Ribavirin. Reverse transcriptase polymerase chain reaction (RT-PCR).

How to Cite This Article: *Khan W Z, Ali G, Ahmed A, Tariq M, Gardezi A, Khan S N. Crimean-Congo Hemorrhagic Fever (CCHF): Our Experience at a Tertiary Hospital. Pak Armed Forces Med J 2022; 72(Suppl-2): S160-163. DOI: https://10.51253/pafmj.v72iSUPPL-2.3339*

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a viral hemorrhagic fever which is caused by CCHF virus, a member of the Nairo virus genus within the family Bunyaviridae. CCHF is zoonotic disease transmitted by ticks of the genus Hyalomma and manifested as fever, petechial rash, epistaxis and hemorrhage in humans.[1,2] CCHF was first observed in Soviet soldiers in Crimea in 1944 and was named Crimean fever. In 1956 a similar virus was detected in a child from Congo andnamed Congo virus. Later on, it was found that the virus was found to be same and thus the name Crimean-Congo hemorrhagic fever (CCHF) emerged.[3]

CCHF is endemic in areas of African continent such as Congo, South Africa, Nigeria, Senegal, Uganda, Kenya and in Asian countries including Pakistan, India, Afghanistan, Iran, Central Asian countries, Turkey.[4,5] The most common source of CCHF virus is the domestic live stock (sheep, goat, cattle and pig) which are infected by adult ticks. The disease is transmitted from animal reservoir to humans by the bite of hyalomma ticks or direct contact with the blood and body fluids of infected animals.[6] The populations at risk are those handling domestic livestock, veterinarians, hunters, hikers, soldiers, healthcare workers and travelers to endemic areas. Clinical manife-stations of CCHF include headache, fever, sore throat, myalgia, nausea and vomiting followed by subconjunctival hemorrhages, epistaxis, pulmonary hemorrhages, melena, hematuria and vaginal bleeding in female patients. Laboratory findings include thrombocytopenia, leukopenia, hyperbilirubinemia, elevated liver enzymes, prolongation of prothrombin time, activated partial thromboplastin time and anemia.[7] Severe disease is due to exaggerated inflammatory response leading to vascular permeability, hypotension, shock and multiorgan failure and death. Diagnosis is confirmed by compatible clinical history, examination findings and RT-PCR for CCHF virus RNA and specific immunoglobulin (IgM) by enzyme linked immunosorbent assay.[11] CCHF should be differentiated from other viral hemorrhagic fevers like Dengue hemorrhagic fever, Ebola, Lassa and yellow fever. Among the other common differentials are severe Malaria, Leptospirosis, Fulminant viral hepatitis, meningococcemia and acute leukemia.

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Received: 24 Sep 2019; revision received: 10 Feb 2020; accepted: 19 Feb 2020

There is no proven antiviral treatment for CCHF. Ribavirin has been reported to reduce viral replication and mortality in animal models but efficacy in humans is yet to be established.[8] Treatment is supportive with management of fluid and electrolyte balance. Platelet count should be kept above 50,000/mm,[3] in case of active bleeding and more than 20,000/mm,[3] in the absence of bleeding. Drugs like aspirin and other NSAIDs should be avoided.

To avoid spread of infection to health care workers strict barrier nursing including standard contact and droplet precautions are to be ensured.

The mortality rate varies in various countries but ranges from 4-20%.[9,10] Emergence of CCHF has been reported from various parts of Pakistan (Baluchistan, Tribal districts of Khyber Pakhtunkhwa) due to unhygienic practices in slaughter houses and handling of infected animals especially on the occasion of Eid ul Azha (religious festival).[7] We conducted this study to share our experience of handling CCHF cases, their presentation, response to treatment and outcome so that it may provide help or guidance to other researchers with in the country and abroad for more larger studies in future.

METHODOLOGY

The study was conducted at the department of General Medicine Combined Military Hospital (CMH) Peshawar, from September 2017 to September 2019. Data were collected retros-pectively from state office CMH Peshawar of CCHF cases over the study period.

Inclusion Criteria: RT-PCR positive cases of CCHF viral RNA were included in this study.

Excluison Criteria: RT-PCR negative cases, cases with multiple co-morbid conditions and cases with diagnosis of Malaria, Leptospirosis, acute fulminant hepatic failure and other viral hemorrhagic fever (Dengue) were excluded.

A total of ten cases were included in the study who reported with history of fever, myalgia, petechial rash, epistaxis, melena and hematuria. After approval from the ethical council of the hospital (Certificate No-0021) informed written consent was taken. Data were noted on especially designed proforma, including demographic data, contact with animals or their body fluids, clinical history at presentation, laboratory parameters, treatmentprovided, complications, number of days of hospitalization and outcome.

Data analysis was performed on SPSS-22. The qualitative variables were presented by calculating frequency and percentages. The quantitative variables were presented by calculating mean and standard deviation. Effect modifiers like age, gender, marital status, and weight were stratified. After stratification chi square test was applied and $p \leq 0.05$ was counted statistically significant.

RESULTS

The study included ten patients over the span of two years from September 2017 to September 2019 to combined military hospital Peshawar. All patients were male adults serving in various field units of army (Table-I).

Table-I: Demographics and epidemiological characteristics of patients (n=10).

Characteristics		No. of Patients
Gender	Male	10 (100%)
	Female	-
Age Group (Years)	10-19	1 (10%)
	20-29	1 (10%)
	30-39	5 (50%)
	40-49	2 (20%)
	50-59	1 (10%)
Marital Status	Single	3 (30%)
	Married	7 (70%)
Occupation	Government Servants	10 (100%)
Contact/Exposure to CCHF Virus	All Employed in Endemic Areas	10 (100%)

Majority were married, 7(70%). All patients 10 (100%) gave positive history of performing duties in the tribal districts of Khyber Pakhtunkhwa (KPK), Pakistan near the PAK-Afghan border where CCHF is endemic (Figure).

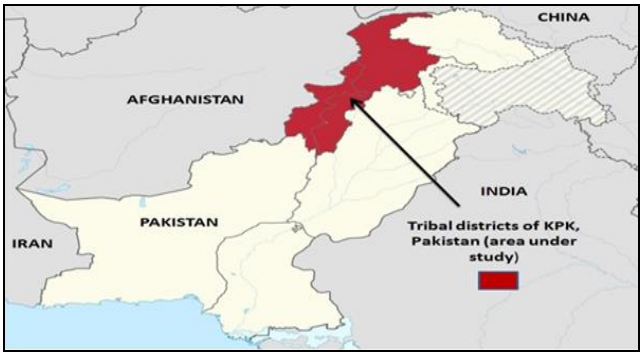

Figure : Area from where cases of CCHF were referred.

Upon presentation the initial symptoms were (Table-II) feverin 10 (100%), body achein 10 (100%), headache in 2 (20%) and petechial rash in 2 Patients (20%). 1 (10%) patient however had epistaxis, melena and hematuria right from the beginning. Physical examination revealed tachycardia in all patients, low blood pressure (less than 90mm Hg systolic) in two patients (20%) and drowsiness in 2 patients (20%). Dia-

gnosis of all cases (100%) was confirmed on RT- PCR for CCHF virus RNA. Other hematological/lab parameters found were leukopenia (100%), Thrombocytopenia (100%), anemia (80%), Elevated ALT and LDH in 100% patients (Table-II).

Table-II: Symptoms, Physical examination findings and laboratory data of patients (n=10).

Characteristics		No of Patients
Symptoms	Fever	10 (100%)
	Headache	2 (20%)
	Body Ache	10 (100%)
	Rash	2 (20%)
	Epistaxis	1 (10%)
	Melena	1 (100%)
	Hematuria	1 (100%)
	Subconjunctival Hemorrhages	8 (80%)
Physical Examination Findings	Tachycardia	10 (100%)
	Hypotension	2 (20%)
	Rash	2 (20%)
	Drowsiness	2 (20%)
Laboratory Parameters	Leukopenia (TLC< 4000/microliter	10 (100%)
	Thrombocytopenia (Platelets < 15000/microliter)	10 (100%)
	Anemia (Hb<13.5 g/dl in men)	8 (80%)
	Raised ALT (>40 U/L)	10 (100%)
	Elevated LDH (>450 U/L)	10 (100%)
	CCHF virus RT-PCR	10 (100%)

Eight patients (80%) were prescribed ribavirin 400mg thrice daily however two patients (20%) recovered before the PCR report retrieval and did not take ribavirin. 80% of the patients were transfused platelets. Average hospital stay was 14 days. Hospital stay was 2 days lesser in those treated with ribavirin. All 10 (100%) patient recovered completely (Table-III).

Table-III: Treatment modality, Hospital stays and outcome (n=10).

Characteristics			No. of Patients
Treatment modality	Ribavirin	Yes	8 (80%)
		No	2 (20%)
	Vitamin C	Yes	10 (100%)
		No	-
	Platelet Transfusions	Yes	8 (80%)
		No	2 (20%)
Hospital Stays (Days)	1-10		2 (20%)
	11-20		6 (60%)
	21-30		2 (20%)
Outcome	Recovery		10 (100%)
	Death		-

Oral Vitamin C Supplementation was provided to all cases as a supportive measure for vascular endothelial protection.

DISCUSSION

CCHF is a viral hemorrhagic disease caused by CCHF virus and is endemic in areas of Pakistan such is Baluchistan, tribal districts of KPK and Punjab provinces.[11,12] Most of the cases are reported from bordering areas with Afghanistan and Iran around the Eidul Azha (Religious festival during which sacrifice of animals is done).[13-15] Risk groups are those dealing with the livestock, cattle particularly those working in slaughterhouses. The virus gets entry into human via tick bite or direct contact with the body fluids of infected animal to broken skin. People living in endemic areas or visiting to endemic zones are at particular risk.[16-18]

In our study we found that all the cases were armed forces personnel who performed duties in endemic tribal districts of KPK province Pakistan. Fever and body pains are the initial hallmark symptoms of the disease followed by sub-conjunctival hemorrhages, epistaxis and bleeding tendencies from body orifices which were observed in our study as well. Studies performed in Turkey found similar symptoms, fatigue (100%), fever (89.8%), headache (90.3%)and body ache (92.2%).[14] Fall in platelet count and leukopenia was observed in majority (80%) of our patients which was comparable to the results found by Kilinc *et al*,[10] in Turkey, Mourya *et al*,[19] in India and Sharififard *et al*,[20] in Iran.

All patients recovered after treatment. Majority (80%) of the patients in our study required platelet transfusion during the hospital stay in addition to other supportive measures such as Intravenous fluids and ionotropic support. Majority (80%) of patients received ribavirin treatment which resulted in hastening recovery, lesser number of days in the hospital and fewer life-threatening complications such as multiorgan failure syndrome as also observed by Arab-Bafranzi *et al*,[21] in a recent study in Iran. However, 2 patients (20%) recovered without ribavirin treatment till the availability of their RT- PCR for CCHF virus RNA came to be positive. This proved that role of ribavirin in the treatment of CCHF is not clear and based upon anecdotal evidence as observed by Johnson *et al*,[13]

Clinical picture and laboratory findings of CCHF mimic other diseases like dengue fever, malaria, enteric fever etc. While empirical treatment is given for other diseases, ribavirin treatment is given after confirmation of CCHF by PCR testing. Testing for CCHF is available at AFIP (reference lab) and requires 2-3 days for the results to become available. Furthermore, many

patients have only mild symptoms of CCHF and are already in recovery phase when they arrive at CMH Peshawar and thus do not require ribavirin treatment. Patients not given ribavirin in our study had mild symptoms and had improved before availability of PCR result. Patients not receiving ribavirin treatment had milder symptoms and had shorter time to recover. In Ribavirin group, time to recovery was not influenced by the treatment and seems to be depen-dent on severity of disease at presentation. No alternative antiviral treatment was used for treatment of CCHF.

Validation of efficacy of ribavirin for its use in treatment of CCHF would require case control cohorts. However, ethical issues related to availability of CCHF positive controls are the reason this model of study cannot be applied in CCHF cases. Despite knowing that the evidence for use of ribavirin is anecdotal, treatment cannot be denied to patients of CCHF due to high mortality of the disease.[22] In our study, patients who did not receive ribavirin had almost complete recovery by the time of availability of PCR result.

In our study each patient was provided with oral vitamin C tablet as a supportive measure as vitamin C has protective role in vascular endothelial injury.[23] All patients recovered completely.

CONCLUSION

CCHF is a fatal disease caused by CCHF virus and transmitted by tick bite in endemic areas. People visiting to endemic areas are at particular risk such as soldiers. Fever, petechial rash and thrombocytopenia are the presenting features. Treatment is supportive, oral vitamin C supplements and ribavirin should be given to all suspected and confirmed cases.

Conflict Of Interest: None

Author's Contribution

ZWK: Abstract writing, GA: Clinicial data collection, AA: Data analysis, MT: Literature review, AG: Lab data collection, NSK: Proof reading.

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