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## Tick Borne Crimean-Congo Haemorrhagic Fever in Fars Province, Southern Iran: Epidemiologic Characteristics and Vector Surveillance

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**Abstract:** Crimean Congo Haemorrhagic Fever (CCHF) is an acute fatal viral infection caused by a virus from Bunyaviridae family, genus *Nairovirus*. The virus has been isolated from at least 31 species of ticks: among them *Hyalomma* species are the most important vectors. Geographically, CCHF is a widespread viral infection. Its mortality rate in Iran has been estimated to be 29.6 and 11.9% in 1999 and 2000, respectively. The majority of CCHF cases could be prevented. However, in order to identify and prioritize areas for prevention, to the best of authors' knowledge to date, no systematic study has been carried out in Fars province, Iran, to assess the extent, frequency and major outcomes of this fatal infection. The current descriptive retrospective case series study was, therefore, undertaken to address some of these issues. Data on CCHF cases for a period of four years (2001-4) were collected from different official sources in Iran. Data were categorized and analyzed by SPSS software, version 13/5. Gender, age, occupation, seasonal distribution and outcome of the disease were considered in data analysis. A total of 45 cases had been registered during the study period of which 29 were suspected and 16 were confirmed cases. CCHF was more common in men (85.5%) than in women (14.5%). Similarly, the disease was more prevalent in the 20-29 years old age group (37.5%). Nineteen cases (42%) resulted in death. Seasonal distribution of the infection revealed that it was more common in spring (37.5%). Additionally, 38% of the CCHF cases occurred among butchers, slaughterhouse workers, farmers and shepherds. The case fatality rates for the suspected and confirmed cases were 55.1 and 18.75%, respectively. Data gathered from different areas of Fars province showed that out of the 18 species identified to be the potential vectors of CCHF, 13 exist in this geographical area. In conclusion, the observation that butchers, slaughterhouse workers, farmers and shepherds form the most commonly affected occupations, indicate areas where preventive interventions, in particular health education efforts, might be usefully targeted.

**Key words:** Arboviral disease, CCHF, tick, vector, Iran

### INTRODUCTION

Crimean-Congo Haemorrhagic Fever (CCHF), an acute potentially fatal arboviral human disease, is caused by a zoonotic tick-borne virus which is the type species of the *Nairovirus* genus within the family Bunyaviridae (Hoogstral, 1979). This CCHF arbovirus is an enveloped, single-stranded negative-sense RNA virus with tripartite circular genomic segments (Nuttall, 2001). It infects mammals like rodents, leporids and ungulates and/or birds to different extent. Birds, in particular, play an important role not only as a source of blood but also as phoretic hosts in disseminating ticks. Although hard (Ixodidae, mainly *Hyalomma* genus) and soft (Argasidae) ticks transmit CCHF virus to a vast variety of animals, the severe pathogenesis only affects humans (Nuttall, 2001). The human disease is, however, sporadic but a cause of concern due to high mortality and transmissibility through contact with patients. Viral control thus requires the highest level of laboratory containment, which is

maintained at biosafety level 4 conditions (Karti *et al.*, 2004). CCHF occurs sporadically in regions of Africa, Asia and Eastern Europe (Hoogstral, 1979; Fisher-Hoch *et al.*, 1995). It is characterized by Disseminated Intravascular Coagulation (DIC) with capillary fragility, frequent extensive ecchymoses, severe bleeding and hepatic dysfunction with case fatality rates ranging from 8% to 90% (Altaf *et al.*, 1998; Williams *et al.*, 2000) and an average mortality rate of about 30% (Nuttall, 2001).

CCHF virus is usually transmitted to humans by direct infected tick bites, dermal contact with viremic domestic livestock or its freshly slaughtered tissues, contaminated blood or other body fluids of human and animal, viremic blood transfusion and direct nosocomial exposure to patients. The main objective of this study was to assess the epidemiological characteristics and vector surveillance of CCHF in Fars province and to propose precautionary measures to reduce future disease outbreaks in this region.

## MATERIALS AND METHODS

This survey was conducted on CCHF cases for a period of four years (2001-04) in Fars province, southern Iran. It was a retrospective case series study and the data were gathered from the Iranian Pasteur Institute and the center for Communicable Diseases Control (CDC) in Fars. Table 1 shows a set of screening evaluations for CCHF cases involving a series of historical, physical and routine laboratory measures. All suspected, probable and confirmed (definite) cases were covered.

A probable case was defined as an acutely ill person with clinically observed signs and symptoms of sudden onset of fever, headache, myalgia and bleeding: epidemiological risk factors (e.g., history of tick bite, contact with suspected cases of CCHF, contact with domesticated animals and their products and travel to, or residence in, an endemic area for CCHF).

A suspected case was defined as one with above-named features as well as laboratory data including a platelet count of  $<150000$  cells  $\text{mm}^3$  and a leucocyte (WBC) count of  $<4000$   $\text{mm}^3$ .

Table 1: Screening evaluations for CCHF cases

History	
	Travel to, or residence in, endemic area
	Contact with livestock or their products
	Contact with tick or tick-bite
	Contact with viremic person or body fluids
	Blood transfusion
Physical	
	Marked weight loss
	Sudden onset of fever with severe headache
	Bleeding gum, nose, eyes (conjunctivitis)
	Severe dermal ecchymoses
	Flushed face, chest
	General myalgia and malaise
	Petechial rash on palate
	Bradycardia
	Hepatorenal and pulmonary failures
	Tick bite dermatofibroma
	Multi-organ hemorrhages: hematuria
Routine Lab.	
	Viremia (blood, vomitus)
	Complete blood cell count:
	Differential: Lymphopenia
	*WBC $<2000$ $\text{mm}^{-3}$
	Platelet count: Thrombocytopenia = $20 \times 10^3$ $\text{mm}^{-3}$
	Anemia: **Hb $\leq 10$ $\text{gd L}^{-1}$
Chemistries:	
	Liver function: Councilman Bodies
	Serum: raised ***AST $\geq 200$ IU $\text{L}^{-1}$
	****ALT $\geq 150$ IU $\text{L}^{-1}$
	Immunoglobulins: IgM, IgG
	Antibody titers
	ELISA, IFA
	Complement: Fixation test
	Genetics: RT-PCR (RNA S-gene)
	Biotech: Virus isolation by intracerebral inoculation of suckling mice
	Identification by HI, ELISA, IFA or neutralization

\*WBC = White Blood Cell; \*\*Hb = Hemoglobin; \*\*\*AST = Aspartate aminotransferase; \*\*\*\*ALT = Alanine amino transferase

The case definition for confirmed (definite) persons with CCHF was rescheduled as individuals who met the criteria for a probable case and positive serological test results for Enzyme-linked Immunosorbent Assay (ELISA) of IgM and/or rising titers of IgG antibodies or with a positive test for reverse transcription polymerase chain reaction (RT-PCR).

The epidemiologic data on such variables as age, gender, job, season, nationality, etc. were retrospectively collected for all cases. These were analyzed using SPSS version 13/5 software and statistical inferences were performed.

## RESULTS

In general, a total of 45 cases were reportedly registered during the four years study period. Twenty nine patients (64.5%) were suspected and 16 cases (35.5%) were confirmed to be CCHF-positive. Sixteen people (55%) from suspected cases and three patients from confirmed cases passed away, which gave a Case Fatality Rate (CFR) of 18.75% in the latter case (Table 2). Among all these cases, 71% were male and 29% were female. The most frequent suspected cases were among housekeepers (38%) and additionally the highest CFR(12.5%) were found in men.

The highest positively confirmed cases were among abattoir workers and butchers (37.5%) and farmers (31.25%) (Table 3). Moreover, the most frequent IgM positive cases (37.5%) and suspected cases (51.7%) were observed in the spring season, while in the winter, the lowest IgM-positive cases (12.5%) and suspected cases (10.3%) were reported. The most frequent suspected

Table 2: General statistics for CCHF cases

Patient	Sample					2001-4 (%)
	2001	2002	2003	2004		
Suspected	1	22	3	3	29	64.5
IgM+	4	5	4	3	16	35.5
Suspected deads	1	11	1	3	16	84.2
IgM+deads	0	1	1	1	3	15.8
*CFR (%)	0%	20%	25%	33.33%	-	-

\*CFR: Case Fatality Rate

Table 3: Occupation-related data of CCHF cases.

Occupation	Suspecteds	IgM+cases
Housewives	11	0
Slaughterhouses	4	1
Butchers	2	6
Farmers	4	5
Students	3	2
Drivers	1	0
Soldiers	0	1
Ironmongers	0	1
Shepherds	1	0
Unemployed	3	0

Table 4: Epidemiological data related to CCHF cases

Case	Season				Gender		Age group (year)							
	Spring	Summer	Autumn	Winter	Female	Male	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79
Suspecteds	15	5	6	3	11	18	0	7	12	2	7	1	1	0
IgM+Cases	6	4	4	2	2	14	0	2	6	4	2	1	1	0
IgM+Deaths	2	1	0	0	1	2	0	0	2	1	0	0	0	0

Table 5: Scientific names of tick vectors of CCHF virus found in Fars province.

Family	Tick species
Ixodidae	<i>Hyalomma anatolicum</i>
	<i>H. marginatum</i>
	<i>H. m. turanicus</i>
	<i>H. asiaticum</i>
	<i>H. impeltatum</i>
	<i>H. detritum</i>
	<i>H. rufipes</i>
	<i>Dermacentor marginatus</i>
	<i>Rhipicephalus sanguineus</i>
	<i>R. turanicus</i>
Argasidae	<i>Boophilus annulatus</i>
	<i>Argas persicus</i>
	<i>Ornithodoros lahorensis</i>

cases (41.4%) and positively confirmed cases (37.5%) were in the 20-29 years old age group. The confirmed cases of CCHF occurred in the 10-69 years old age group. Additionally, the most frequent suspected cases (62%) and positively confirmed cases (87.5%) were seen in males (Table 4).

From a total of 31 different soft and hard tick species and subspecies recognized to be the vectors of CCHF virus worldwide, 13 species were identified to be prevalent in Fars province that two of these were argasid (soft) ticks (Table 5). The two-host hard ticks, *Hyalomma* species, were the most prevalent (54%) of all species in this region.

## DISCUSSION

CCHF virus is a microparasite of engorging hard and soft ticks. It is a polythetic zoonotic arbovirus with wide spectrum host specificity. The viral agent can be transmitted trans-stadially and transovarially in ticks (Fisher-Hoch *et al.*, 1995). Direct transmission through contact with infected blood and body fluids and possibly crushed ticks is an important route of human infection. The Iranian CCHF viral clade (GenBank Accession No. AY366373-9) (Karti *et al.*, 2004) is clearly distinct from Turkish clade, but shows some phylogenetic affinity with Pakistani clade. This linkage could reinforce the idea that illegal cross-border livestock movements are presumably responsible for sporadic CCHF outbreaks in Iran. Nevertheless, epidemics of CCHF are usually focal and due to the close proximity of people to domesticated livestock and their associated viremic ticks, even in urban areas, the disease has a peridomestic nature (McCormick

and Fisher-Hoch, 2000). In fact, raised anti-CCHF viral antibody titers in humans and domesticated livestock emphasize the facility of transmission.

Of the viral haemorrhagic fevers, CCHF has the most florid haemorrhage and highest frequency of large ecchymoses. It is a disease that develops quickly following infection. Viral antigenic variation, mode and dose of inoculation may all be critical in determining the severity of disease. Man is the final accidental dead-end host for CCHF virus, and astonishingly, seems to be the only species in which CCHF virus generates severe disease.

The Case Fatality Rate (CFR) varies from one place to another reflecting to some extent the strain differences in virulence, variable access to medical and diagnostic services, variable exposure level to viremic vectors, mode of transmission, etc. In southern Russia, CFR varies thus from 5 to 10% (McCormick and Fisher-Hoch, 2000). In Turkey, Iran, Mauritania, Bulgaria, Senegal, Iraq, Dubai, and Pakistan: the CFR values were 11.0: 11.6, 19.2, 24.1: 28.6: 21.8: 30.0 and 22%, respectively (Karti *et al.*, 2004; Mardani *et al.*, 2003; Alavi-Naini *et al.*, 2006; Sharifi *et al.*, 2006; Nabeth *et al.*, 2004a; Papa *et al.*, 2004; Nabeth *et al.*, 2004b; Al-Tikriti *et al.*, 1981; Suleiman *et al.*, 1980; Burney *et al.*, 1980). In the present study, The CFR was 18.75% which is consistent with other reports.

The seasonal distribution of CCHF cases to a large extent is dependent on climatic conditions as well as the local tick host populations. In Iran, the disease is common in the spring months of April to June, as found also in this study. Any sex difference in CCHF cases is mainly due to gender disparities in agricultural and farming practices. Sheep handlers appear to be mostly at risk. As abattoir workers, butchers, shepherds and other similar occupations are mostly male-oriented: it is not unexpected to find that, as in this study, males are mainly infected with CCHF viruses.

Some two-or three-host species of hard ticks have developed the ability for each postembryonic stage to feed on a larger-sized wandering mammal. Under natural conditions, it is seldom so if ever absolutely established. Rather, each stage may feed on the larger-sized host but under other conditions immature stages parasitize smaller sized hosts. The potential for this type of host dichotomy, which is more frequent in some species of *Hyalomma* than in other genera, has numerous epidemiological

implications. Innumerable immature stages of the *Hyalomma marginatum* complex are carried intercontinentally by a large number and variety of northward and south migrating birds (Desch *et al.*, 1984).

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