Crimean-Congo Hemorrhagic Fever

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14 February 2009, Vienna
Figure 1.4 Selected emerging and re-emerging infectious diseases: 1996–2004.
Crimean-Congo Haemorrhagic Fever Geographic Distribution

50° North limit for the geographic distribution of genus *Hyalomma* ticks

The First Clinical Case in 2008 in Greece

Figure
Map of Greece showing the area where a case of Crimean-Congo haemorrhagic fever was reported in June 2008

CCHF cases in Turkey
Epidemiologic characteristics

Rural area: 70% of the cases

Male/female ratio: 1.13/1

Tick bite history among patients: 69%

May, June, July: 84% of the cases

Incidence rate per 100,000: 2003, 2004, 2005 and 2006

Imported 10 cases in Istanbul in 2006

Different strains in Turkey

Fig 2: Geographical correlation of genotypes (Hewson, In: Ergonul & Whitehouse)

S Genotypes

Europe 2
Africa 2
Europe 1
Africa 3
Asia 1
Asia 2
Africa 1
H. marginatum spp. (MaxEnt algorithm)

Life cycle of Hyalomma marginatum marginatum

- **Questing adult**
- **Engorged nymph**
- **Unfed adult**
- **Off host (ground)**
- **Engorged male**
- **Eggs**
- **Larvae**
- **Engorged female**

**HOST-I**
- 14-26 days
- Engorged nymph
- Questing larvae

**HOST-II**
- 9-14 days
- Engorged female

The Course of Infection in animals

No clinical symptoms
Not known in veterinary medicine

Viremia
Lasts for 7-10 days in mammals
Seropositive and/or PCR+ Animals in Turkey

- Cattle
- Sheep
- Boars
- Hares
- Ground feeding birds
  - Partridges etc.
Climate Change

Global warming is too global. However, the climate effects!

Trends of monthly mean temperature in Sivas

Trends of monthly mean minimum temperature in Sivas
The number of days with the temperature of >5 ºC in Sivas, Tokat, Yozgat.

Ergonul O, et al. ECCMID 2005, P 1147
Clinical Features
The Suspected Case

1. Individuals, who had fever, myalgia, malaise, diarrhea, and

2. History of being in endemic area
   – Tick exposure history and/or
   – Residency or travel to CCHF endemic region
The probable case

Patients who had leukopenia, thrombocytopenia, elevated AST, ALT, and LDH levels.

Confirmed case

CCHF IgM of PCR positivity in the blood or body fluids of the patient.
The attack and the infection rates of Crimean Congo Hemorrhagic Fever Virus Infection in an endemic region

Önder Ergönül, Herve Zeller, Şirin Menekşe, Aysel Çelikbaş, Şebnem Eren, Nurcan Baykam, Başak Dokuzoğuz

ECCMID 2006, Nice

Results

The infection rate 0.27 (15/55)

The infection rate 0.42 among the individuals, who had the history of tick bite (p=0.046).

The attack rate 0.2 (11/55).

Conclusions

One of every five persons living in endemic area, and one of two persons with tick bite history in endemic area acquire the disease. The infection and attack rates are very high compared to other diseases.
The Clinical Course of Crimean-Congo Hemorrhagic Fever

Incubation: 3-7 days
Prehemorrhagic period: 1-7 days
Hemorrhagic period: 2-3 days
Convalescence

Polymerase Chain Reaction: The first 9 days
- Myalgia
- Fever
- Nausea
- Vomiting
- Diarrhea

Fatality happens

Bleeding (hematemesis, melena, etc.)
Somnolence

IgM (7 days-4 months) IgG (7 days-5 years)

Ergonul O. Lancet ID 2006; 6: 203-214
Viral Load is Higher Among Fatal Cases

Duh, et al. Emerg Infect Dis
Evaluation of Serum Levels of Interleukin (IL)-6, IL-10, and Tumor Necrosis Factor–α in Patients with Crimean-Congo Hemorrhagic Fever

Onder Ergonul,1 Semra Tuncbilek,2 Nurcan Baykam,1 Aysel Celikbas,3 and Basak Dokuzoguz4

1Infectious Diseases and Clinical Microbiology Clinic, Ankara Numune Education and Research Hospital, and 2GENOM Laboratories, Ankara, Turkey

J Infect Dis 2006; 193: 941-4
Pathogenesis

Capillary fragility
  “capillary toxicosis”, Soviet scientists
  Infection of endothelium

Coagulopathy

Multiple host induced mechanisms
  Massive apoptosis of lymphocytes
  Induction of proinflammatory cytokines
  Dysregulation of coagulation cascade
  DIC

Geisbert TW, Nature Med 2004
Crimean-Congo hemorrhagic fever: Five patients with hemophagocytic syndrome

Nuriye Tasdelen Fisgin, Tunc Fisgin, Esra Tanyel, Levent Doganci, Necla Tulek, Nil Guler, and Feride Duru

1 Department of Clinical Microbiology and Infectious Disease, Ondokuz Mayis University, Medical School, Samsun, Turkey
2 Department of Pediatric Hematology, Ondokuz Mayis University, Medical School, Samsun, Turkey
3 Department of Hematology, Ondokuz Mayis University, Medical School, Samsun, Turkey

Figure 5. Hemophagocytosis in the bone marrow aspiration smears in Patient 5.
Antibody production is weaker among fatal cases.

<table>
<thead>
<tr>
<th></th>
<th>Patients survived n=50</th>
<th>Fatal cases n=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM positives</td>
<td>37/40 (93)</td>
<td>¼ (25)</td>
</tr>
<tr>
<td>IgG positivity</td>
<td>27/40 (68)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td>PCR positivity</td>
<td>19/40 (48)</td>
<td>3/4 (50)</td>
</tr>
</tbody>
</table>

Ergonul, et al. CMI 2006

CCHFV delays activation of the innate immune response.

The Role of Different Strains in Fatality

“A higher fatality rate occurred in patients infected with isolates which had apparently acquired M segments from a group in which predominantly Asian strains are usually found.

Reassortment may affect the pathogenicity of the virus”

Fatality Among Children

33 children in Iran: 24%

42+16 children in Ankara: 0%
Under publication
Intrauterine Infection of Crimean Congo Hemorrhagic Fever


Second baby
Fetal intraabdominal fluid was visualized at the twenty two weeks of gestation, and amniocentesis was performed. In serological analysis of amniotic fluid CCHFV-PCR was found to be negative.

Intraabdominal fluid was found to increased and hydrocele was detected at the 38th weeks of gestation, and this image was compatible with bleeding or perforation (figure 3b,3c).

The risks of the delivery were explained to the family. After her vaginal delivery, baby was severely ill and was operated with the diagnosis of necrotizing enterocolitis (NEC). His laboratory findings were normal except high white blood cell count. In his blood culture, Enterobacter agglomerans was isolated.

On his 5th day, his WBC count was 4400/mm³, hemoglobin was 3 g/L, PLT count was 32 000/mm³. He died because of massive nasal, intrathecal and gastrointestinal bleedings.

First Baby
At the first day of delivery, the clinical and laboratory of findings of the baby were found to be normal. However, on his 5th day, WBC count was 8200/mm³, PLT count was 40000/mm³. The level of AST was 5372 IU, ALT 962 IU, and creatinin phosphokinase 1808 IU. He died because of massive bleeding (figure 2). His CCHF IgM was found to be negative. His CCHF IgG and CCHFV-PCR were positive.

CCHFV can transmit through placenta.

Hematoma was developed after cesarean section
Intrauterine hematoma five days after delivery.

Intraabdominal hematoma five days after delivery.
Ribavirin: Only Drug for VHF

<table>
<thead>
<tr>
<th>Virus Family</th>
<th>Disease</th>
<th>Location</th>
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<tbody>
<tr>
<td>Arenaviridae</td>
<td>Lassa Fever</td>
<td>South America HF</td>
</tr>
<tr>
<td>Bunyaviridae</td>
<td>Hanta</td>
<td>Rift Valley</td>
</tr>
<tr>
<td></td>
<td>CCHF</td>
<td></td>
</tr>
</tbody>
</table>
The Role of Ribavirin in CCHF

Ribavirin could be more effective in early phase

Ergonul O. Treatment of CCHF, Antivir Res 2008
Early Use is More Effective: Preliminary Results

Case (16 fatal) control (47 survived pts)
Among survived ribavirin had begun on average 24 h earlier (p=0.033), and about 2 days earlier in non-bleeding survivors than in bleeding survivors (p=0.013)

Izadi S, Salehi M. Jpn J Infect Dis 2009

The patients with earlier use had better laboratory improvement (p<0.05)

WHO Essential Medicines Library

ribavirin

Go back to Medicine List

MODEL LIST INFORMATION

<table>
<thead>
<tr>
<th>SECTION</th>
<th>FORMULATION</th>
<th>DISEASE/INDICATION</th>
<th>RATIONALE FOR INCLUSION</th>
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</thead>
<tbody>
<tr>
<td>06.04.03.00 Other antivirals</td>
<td>Dosage form and strength Injection for intravenous administration: 1000 mg and 800 mg in 10-mL phosphate buffer solution. Oral solid dosage forms: 200 mg; 400 mg; 600 mg.</td>
<td>Date added: 2007.</td>
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ATC Code

Type of List Core List

MODEL FORMULARY INFORMATION

GENERAL INFORMATION
Confounders in Ribavirin use

1. Severity
   1. Number of Days from onset of symptoms
      1. Prehemorrhagic
      2. Hemorrhagic
   2. Ineffective application:
      GIS symptoms in oral use (hematemesis)

4. Duration of treatment
5. Inclusion criteria
## Health Care Workers infected by CCHF

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<th>Year</th>
<th>infected</th>
<th>fatal</th>
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<td>Bulgaria</td>
<td>1950-1974</td>
<td>42</td>
<td>17</td>
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<td>South Africa</td>
<td>1967</td>
<td>5</td>
<td>?</td>
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<td></td>
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<td>7</td>
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<td>3</td>
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<tr>
<td>United Arabic</td>
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<td>Emirates</td>
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<td></td>
<td>2008</td>
<td>8</td>
<td>1</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>88</strong></td>
<td><strong>32</strong></td>
<td></td>
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Case Management

Suspected case
- Clinical symptoms
  - History
  - Biochemical tests

Preventive measures
- Isolation of the patient
- Education of the HCWs
- Use or barrier precautions

Confirmation of dx
- PCR
- ELISA

Decision for tx
- Ribavirin use
- Differential diagnosis and doxycycline
- Hematologic support
- Respiration support

Follow-up
- No recurrence
- HCWs

Ergönül O. Lancet Infect Dis 2006
Tick removal: What is the best way?

Vaccination experience is limited to Bulgaria
Efficacy: We need more clarity

Dr. Nikolai Kalvatchev
Bulgarian Experience

Passive simultaneous transfer of two different specific immunoglobulin preparations,

“CCHF-bulin” (for intramuscular use)
“CCHF-venin” (for intravenous use),

prepared from the plasma of CCHF survivor donors (Vassilenko et al., 1990).

Only 7 patients
Lessons from Turkey

1. Acceleration phase of the epidemic curve:
   Every year, more cases than a year ago.
1. Dissemination of the cases to the west.
2. More HCWs have been effected.
   1. Protection of HCWs
   2. Infection Control in Hospitals
3. Debate on ribavirin use: RCT?
4. Personal protection
   1. How to remove ticks?
   2. Repellents, permethrine