Crimean-Congo Haemorrhagic Fever:

What do we know (or don’t know) about clinical manifestations and complications of CCHF and considerations for planning clinical trials (10 min)
CCHF in Turkey
CCHF in Turkey
CCHF R&D Roadmap: Vision

Prioritises the development of countermeasures – diagnostics, therapeutics and vaccines for human or animal use - that are most needed by CCHF-affected countries and sets the direction and timelines for future CCHF product research and development activities.

Vision
To be able to reduce death and morbidity from CCHF through safe and affordable effective treatments informed by rapid, reliable, simple-to-use and easily accessible diagnostics by 2023
and
To be able to prevent or mitigate CCHF disease through deployment of safe, affordable and effective vaccines or other preventive measures by 2030
TRANSLATION 721 (T721)
MEDICAL ZOOLOGY DEPARTMENT
UNITED STATES NAVAL MEDICAL RESEARCH UNIT No. 3
CAIRO, EGYPT

TRANSLATION FROM RUSSIAN. BEREZIN, V. V., CHUMAKOV, M. P.,
RESHEKNOV, I. A., & ZGURSKAYA, G. N. (1971)* Study of the role
of birds in the ecology of Crimean hemorrhagic fever virus. Mater. 6.

Birds are the chief hosts of immature *Hyalomma plumbeum plumbeum*—
tick vectors of Crimean hemorrhagic fever (CHF) in Astrakhan Oblast. In
1968, CHF virus was isolated from nymphs collected from roots. Thus, we
aimed to clarify the role of birds in CHF virus ecology.

More than 500 bird blood sera, chiefly of Corvidae which are the
main infection donors to immature *H. plumbeum*, were examined by sero-
logical tests (DFA and CF). All were negative. No CHF virus was isolated
from blood and organs of 366 birds belonging to 35 species.

TRANSLATION 876 (T876)
MEDICAL ZOOLOGY DEPARTMENT
UNITED STATES NAVAL MEDICAL RESEARCH UNIT NUMBER THREE
CAIRO, EGYPT

TRANSLATION FROM RUSSIAN. CHUMAKOV, M.P. (1972)*. Investigations
of arboviruses in the USSR and the question of possible association through
migratory birds between natural arbovirus infection foci in the USSR and warm-
climate countries. In Transcontinental connections of migratory
birds and their role in distribution of arboviruses edited by Cherepanov, A. L.
Mater. 5. Smp. Izuch. Roll Pereletn. Pitts. Rasp. Arbovirus. (Novosibirsk,

When Hammon et al (1942) first suggested the term "arthropod-borne
viruses" (abbreviated to arboviruses), it was considered that these agents (for
example those of seasonal encephalitis) always reproduce in certain arthropod
tissue (mosquitoes, ticks, and other bloodsucking species) and are transmitted
to other susceptible organisms only by bloodsucking arthropods.
CCHF Clinical features – clinical trial case definitions

• The clinical spectrum of illness and disease severity in patients with CCHF is broad, and it is estimated that up to 88% of infections may be sub-clinical (Bodur 2012).

• In highly endemic areas such as Tokat and Sivas provinces in Turkey, the CCHF IgG seroprevalence has been shown to be as high as 12.8% in rural populations (Gunes 2009).

• The majority of the patients with CCHF in Turkey report a history of tick bite (70%) (Yilmaz 2009).

• The incubation period ranges from 1-13 days (typically 1-3 days after tick bite), and has been shown to be shorter in fatal cases (Nabeth 2004 & Vorou 2007).
CCHF Clinical features

- Data from a large cohort in Turkey (n=1670) showed that the most common complaints at presentation were fever (90%), fatigue (90%), headache (70%), myalgia (70%) and nausea (65%).
- Haemorrhagic manifestations were reported in 23% of patients at admission (Haematomas, ecchymosis, epistaxis, vaginal bleeding)
- Leucopenia (88.9%), thrombocytopenia (93.2%) and elevated transaminases (85.9%), LDH (75.8%) and CK (65.9) were the most common laboratory abnormalities at presentation (Yilmaz 2009)
CCHF clinical features

- Median time to presentation/hospital admission 3-4 days
- Median duration of hospitalisation 8 days
- Median age 50 years

- Alanine transaminase and aspartate transaminase (ALT/AST) reach peak levels at day 7/8 of illness.
- The lowest median white blood count was at day 4 with the median lowest platelet count occurring at day 6 of illness.
- The highest median/peak of creatine kinase and APTT observed was at Day 4.
- Acute renal impairment occurred by RIFLE criteria uncommon (4%) - at the time of the AKI stage 3 creatinine kinase levels were elevated at 688/685 U/L.
- Critical care admission 5-10%.
Varying CCHF Case fatality rates......

KAZAKHSTAN
704 cases
CFR: 14.8%
[1948-2013]

RUSSIA
1745 cases
CFR: 4.3%
[1999-2014]

PAKISTAN
252 cases
CFR: 13.9%
[2011-2014]

TURKEY
9787 cases
CFR: 4.8%
[2012-2015]

IRAN
871 cases
CFR: 17.6%
[1999-2012]

Nurmakhnov T, et al. IJID 2015;38:19-23
Volynkina AS et al. Plague, 2015: no. 1
Leblebicioglu H et al. Antiviral Research 2016;126:21-34
CCHF Prognostic indicators

- The first study evaluating prognostic indicators in CCHF was by Swanepoel et al in South Africa in 1989. They reported that the occurrence of any of the following factors during the first 5 days of illness was >90% predictive of a fatal outcome:

  Leucocyte counts $>10 \times 10^9/L$; platelet counts $<20 \times 10^9/L$; AST $>200$ IU/L; ALT $>150$ IU/L; APTT $>60$ seconds; and fibrinogen $<110$ mg/dL.


**Clinical features** associated with mortality by multivariate analysis: Impaired consciousness; diarrhoea; and haemorrhagic manifestations

The most consistently abnormal **laboratory parameters** in multivariate analysis: Elevated APTT; Elevated ALT; with raised LDH an independent predictor of death in 2 studies; and platelet count $<20 \times 10^9/L$ a predictor in one study.
CCHF standard laboratory measurements by severity

**Aspartate transaminase (AST)**

- **Mild**
  - 0
  - 1000
  - 2000
  - 3000

- **Moderate/severe**
  - 0
  - 1000
  - 2000
  - 3000

*Statistical significance:* \( p < 0.001 \)

**Creatine kinase (CK)**

- **Mild**
  - 0
  - 2000
  - 4000
  - 6000

- **Moderate/severe**
  - 0
  - 2000
  - 4000
  - 6000

*Statistical significance:* \( p < 0.006 \)

**Platelet count by severity**

- **Mild**
  - 0
  - 50
  - 100
  - 150
  - 200
  - 250

- **Moderate/severe**
  - 0
  - 50
  - 100
  - 150
  - 200
  - 250

*Statistical significance:* \( p < 0.001 \)
There are a number of CCHF severity scoring systems

Swanepoel criteria

- Platelet count ≤20 X 10^9/L
- aPTT ≥ 60 seconds
- Aspartate transaminase ≥200 U/L
- Alanine transaminase ≥150 U/L
- White blood cells ≥10,000 cells/μL
- Fibrinogen <110 mg/dL

<table>
<thead>
<tr>
<th>Item</th>
<th>Classification</th>
<th>SGS points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartate transaminase</td>
<td>≤5 x ULN</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;5 x ULN</td>
<td>1</td>
</tr>
<tr>
<td>Alanine transaminase</td>
<td>≤ULN</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;ULN</td>
<td>1</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>&lt;3 x ULN</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;3 x ULN</td>
<td>1</td>
</tr>
<tr>
<td>White blood cells</td>
<td>&lt;10,000 cells/μL</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥10,000 cells/μL</td>
<td>1</td>
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<tr>
<td>Hepatomegaly</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
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</tr>
<tr>
<td>Organ failure</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
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<tr>
<td>Bleeding</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;60 years</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥60 years</td>
<td>1</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100,000 cells/μL</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥50,000, &lt;100,000 cells/μL</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt;50,000 cells/μL</td>
<td>2</td>
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<tr>
<td>Prolongation of PT</td>
<td>≤3 s</td>
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<tr>
<td></td>
<td>3 s, &lt;6 s</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>≥6 s</td>
<td>2</td>
</tr>
<tr>
<td>aPTT</td>
<td>≤70</td>
<td>0</td>
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<tr>
<td></td>
<td>&gt;70</td>
<td>1</td>
</tr>
<tr>
<td>INR</td>
<td>≤1.6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥1.6</td>
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Table 1. Characteristics of SSI Parameters for Crimean-Congo Hemorrhagic Fever

<table>
<thead>
<tr>
<th>SSI Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count, ×10^3 platelets/mm^3</td>
<td></td>
</tr>
<tr>
<td>&gt;150</td>
<td>0</td>
</tr>
<tr>
<td>150–50</td>
<td>1</td>
</tr>
<tr>
<td>49–20</td>
<td>2</td>
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<tr>
<td>&lt;40</td>
<td>3</td>
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<tr>
<td>aPTT, sec</td>
<td></td>
</tr>
<tr>
<td>&lt;34</td>
<td>0</td>
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<tr>
<td>35–45</td>
<td>1</td>
</tr>
<tr>
<td>46–59</td>
<td>2</td>
</tr>
<tr>
<td>&gt;60</td>
<td>3</td>
</tr>
<tr>
<td>Fibrinogen level, mg/dL</td>
<td></td>
</tr>
<tr>
<td>≥180</td>
<td>0</td>
</tr>
<tr>
<td>179–160</td>
<td>1</td>
</tr>
<tr>
<td>159–120</td>
<td>2</td>
</tr>
<tr>
<td>&lt;120</td>
<td>3</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Petechiae</td>
<td>1</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3</td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>
CCHF Viral dynamics in plasma

Mean viral load by severity

Mild

Moderate/severe

Mean viral load by lowest platelets

Plts > 50

Plts < 50
CCHF Viral dynamics – urine

- Prolonged urine CCHFv PCR positivity had been demonstrated in one previous study from Kosovo 2009 – 36 days!
- 679 urines screened from 103 plasma CCHFV PCR positive patients
- ……
• Ribavirin was administered a median of 4 days after onset of symptoms.
• 25% of participants were CCHF PCR negative when ribavirin was commenced and for 72% of the days it was administered.
• Higher CCHF viral load is associated with increased disease severity (mild vs moderate/severe), lower platelet counts and fatal outcome.
• APTT, PT, LDH, CK and creatinine correlated with CCHF viral load, as did the duration of fever; myalgia and vomiting.
CCHF antibody responses

- Antibody production in CCHF has been suggested as an important early survival factor, with reduced antibody response demonstrated in fatal cases.
- No correlation with IgM titre and death or severity has been demonstrated. Previous studies have not undertaken serial daily ELISA but mainly focussed on analysis of diagnostic samples.
- At admission:
  - 42% of patients are IgM positive, with all patients IgM positive by day 8 of illness, continuing to 30 days.
  - 50% of patients are IgG positive, with >95% positive by day 8 of illness.
CCHF - Loss of haemostasis and bleeding
• ROTEM® provides global information on the dynamics of clot development, stabilisation and dissolution that reflect in vivo haemostasis.
• It has been utilised in detecting and managing coagulopathy in trauma care, cardiac surgery and liver transplantation
• It has not previously been undertaken in VHF but pilot use of a similar technique (TEM) was utilised in an exported EVD case in the UK.

ROTEM in CCHF

- 212 ROTEM analyses were performed on 65 participants admitted with confirmed CCHF
- Predominantly platelet dysfunction and thrombocytopenia
- Resulting in abnormal clot development/stabilisation
- ROTEM may improve this situation through early detection and rationalised use of blood products.

Fletcher T et al. Lancet Infect Dis (in press)
**Treatment**

- **Standard treatment is supportive therapy +/- Antiviral**
- Early aggressive intensive care support
- Support of coagulation system with blood component therapy
- Careful monitoring
  - Oxygenation
  - Fluid & electrolyte balance
  - Blood pressure
- Early use of inotropic/vasopressor agents
- Ventilatory and renal replacement support for severe cases
- Pain management
- Parenteral nutrition

Infection prevention and control practice for Crimean-Congo hemorrhagic fever—A multicenter cross-sectional survey in Eurasia


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Table 2. CCHF infection prevention and control responses (23 centers).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Yes, number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCWs specifically allocated to CCHF patients</td>
<td>10/23 (43.5)</td>
</tr>
<tr>
<td>Adequate staffing to provide care to CCHF patients</td>
<td>14/23 (60.9)</td>
</tr>
<tr>
<td>Reduction in nursing staff levels for CCHF in-patients overnight</td>
<td>19/23 (82.6)</td>
</tr>
<tr>
<td>Isolation rooms for CCHF patients in the Emergency Department</td>
<td>17/23 (74)</td>
</tr>
<tr>
<td>Isolation rooms for CCHF patients in the Intensive Care Unit</td>
<td>17/23 (74)</td>
</tr>
<tr>
<td>Isolation rooms in the Infectious diseases have:</td>
<td></td>
</tr>
<tr>
<td>- Anterooms</td>
<td>10/23 (43.5)</td>
</tr>
<tr>
<td>- Dedicated ventilation systems</td>
<td>8/23 (34.8)</td>
</tr>
<tr>
<td>- Negative pressure ventilation</td>
<td>5/23 (21.7)</td>
</tr>
<tr>
<td>- HEPA filtration</td>
<td>4/23 (17.4)</td>
</tr>
<tr>
<td>Cohorting of confirmed CCHF cases</td>
<td>16/23 (69.6)</td>
</tr>
<tr>
<td>Cohorting of suspect and confirmed CCHF cases together</td>
<td>9/23 (39.1)</td>
</tr>
<tr>
<td>Relatives allowed to enter CCHF patient rooms</td>
<td>7/23 (30.4)</td>
</tr>
<tr>
<td>Adequate personal protective equipment (PPE) in the facility</td>
<td>22/23 (95.7)</td>
</tr>
<tr>
<td>Routine use of PPE when entering CCHF patient’s rooms</td>
<td>21/23 (61.3)</td>
</tr>
<tr>
<td>Adequate training in donning &amp; doffing of PPE</td>
<td>20/23 (87)</td>
</tr>
<tr>
<td>Supervised donning &amp; doffing of PPE</td>
<td>14/23 (60.9)</td>
</tr>
<tr>
<td>PPE donning &amp; doffing posters available</td>
<td>18/23 (78.3)</td>
</tr>
<tr>
<td>Number of healthcare worker CCHF exposures in the last 5 years?</td>
<td></td>
</tr>
<tr>
<td>- 1-5</td>
<td>18/23 (78.3)</td>
</tr>
<tr>
<td>- &gt;5</td>
<td>5/23 (21.7)</td>
</tr>
<tr>
<td>Special burial protocol for fatal CCHF cases</td>
<td>18/23 (78.3)</td>
</tr>
<tr>
<td>Terminal cleaning of CCHF patient’s rooms</td>
<td>20/23 (87)</td>
</tr>
<tr>
<td>Needle safe devices used in CCHF patients</td>
<td>16/23 (69.6)</td>
</tr>
<tr>
<td>Frequency of Healthcare worker CCHF education:</td>
<td></td>
</tr>
<tr>
<td>- Annually</td>
<td>13/21 (61.9)</td>
</tr>
<tr>
<td>- Monthly</td>
<td>1/21 (4.8)</td>
</tr>
<tr>
<td>- Once</td>
<td>7/21 (33.3)</td>
</tr>
</tbody>
</table>
Understand and mitigate the nosocomial risk


Key Messages for Social Mobilization and Community Engagement in Intense Transmission Areas

September 2014
Thank you
Near patient PCR platforms

- Portable real-time PCR
- Simplified sample preparation
- Commercial and new platforms
- Currently being evaluated with PHE Porton, BNITM
- 2019 NCDC and MoH Turkey
• Early testing at PHE
• RT-qPCR identified 10/10 CCHF strains
• Ct values lower (0.3-4 Ct)
The ‘UMIT’ CCHF trial

Suspected or confirmed CCHF enrolled to Umit trial (200)

**Year 1**

**Ribavirin**
(Day 0 33mg/kg, Day 0-4 16mg/kg QDS, Day 5-10 8mg/kg TDS)  
*n=20*

**Favipiravir low dose**
(Day 0 1800mg BD, Day 1-10 800mg BD)  
*n=20*

**Favipiravir high dose**
(Day 0 2600mg BD, Day 1-10 1200mg BD)  
*n=20*

**Placebo**
(Day 0 9 tablets BD, Day 1-10 4 tablets BD)  
*n=20*

**CCHF PCR Negative**  
*n=30*

Day 1-10: Blood sampling (8mls) for PK/PD analysis at baseline, 6 hours then every 12 hours (pre-dose) until day 2, then daily until discharge.  
Day 1-10: Daily clinical review. Timing of hospital discharge as clinically indicated.

Day 30 (+/-3 days): Outpatient visit

Interim PK-PD analysis to inform favipiravir dose for combination therapy

**Year 2**

**Ribavirin**
(Day 0 33mg/kg, Day 0-4 16mg/kg QDS, Day 5-10 8mg/kg TDS)  
*n=20*

**Favipiravir low dose**
(Day 0 1800mg BD, Day 1-10 800mg BD)  
*n=20*

**Favipiravir high dose**
(Day 0 2600mg BD, Day 1-10 1200mg BD)  
*n=20*

**Placebo**
(Day 0 9 tablets BD, Day 1-10 4 tablets BD)  
*n=20*

**Combination therapy** ribavirin and favipiravir (dose to be based on the results of interim analysis)  
*n=40*

**CCHF PCR Negative**  
*n=20*

Day 1-10: Blood sampling (8mls) for PK/PD analysis at baseline, 6 hours then every 12 hours (pre-dose) until day 2, then daily until discharge.  
Day 1-10: Daily clinical review. Timing of hospital discharge as clinically indicated.

Day 30 (+/-3 days): Outpatient visit

The ‘UMIT’ CCHF trial
CCHF R&D ROADMAP TASKFORCE

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Liverpool School of Tropical Medicine, UK

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Ministry of Health, Islamic Republic of Iran

Dr Gary Kobinger
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