HİTİT
ÜNİVERSİTESİ
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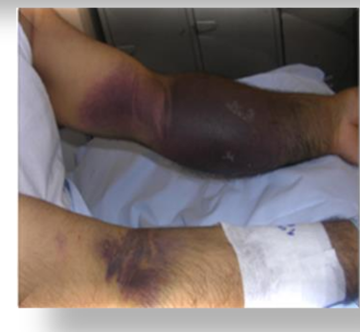


# Crimean Congo Hemorrhagic Fever

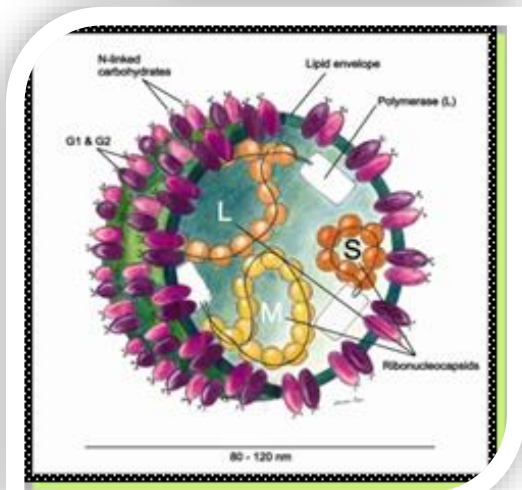
## Clinical Insights from Türkiye: Lessons learned from more than 20 years of experience

*Prof. Dr. Nurcan BAYKAM*

*Infectious Diseases and Clinical Microbiology*

*Hitit University, Faculty of Medicine*

*nurcanbaykam@hitit.edu.tr*



# An unknown hemorrhagic disease in Central-North-Eastern Anatolia!

Common epidemiologic features
Working in animal husbandry
History of tick bite

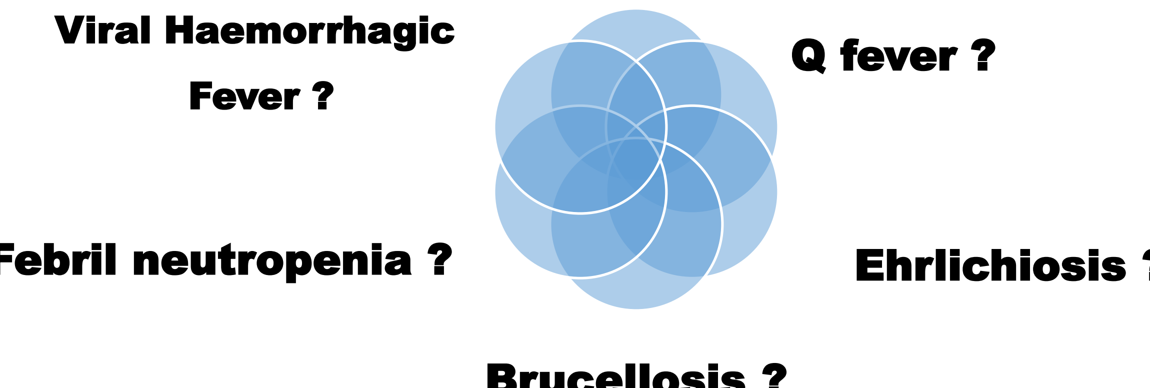
- Fever
- Headache
- Nausea
- Myalgia
- Bisitopenia
- Bleeding

2002-2003 spring and summer months

# An unknown hemorrhagic disease in Central-North-Eastern Anatolia!

In Turkey, previously, Viral Hemorrhagic Fever had not been REPORTED!

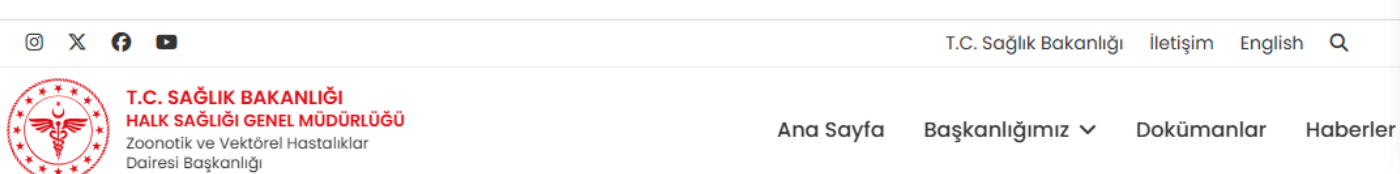
**Pre-diagnoses**

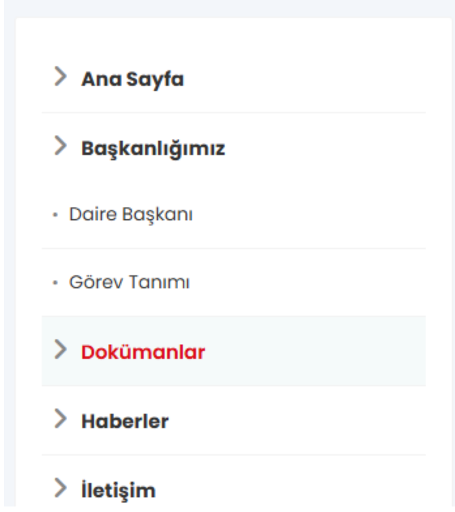


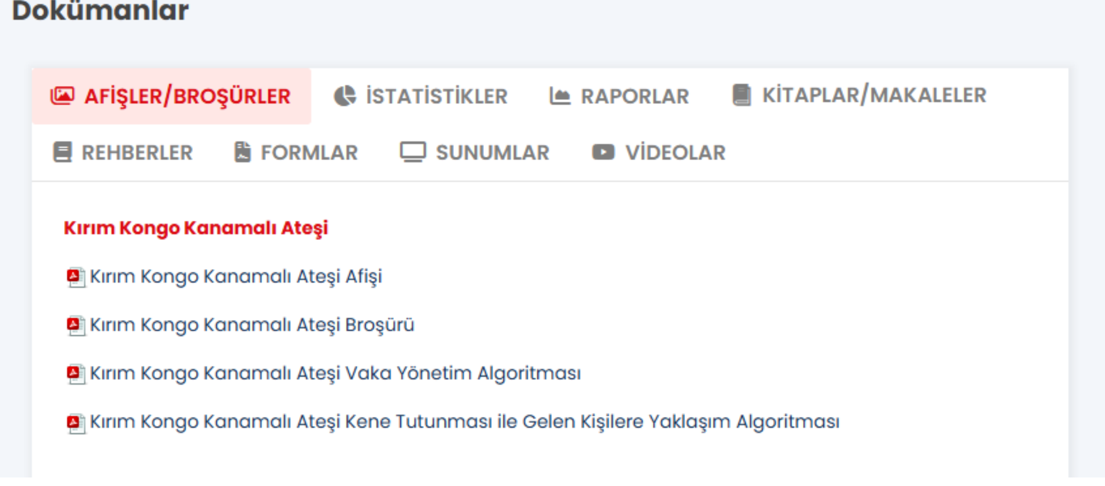

**Crimean-Congo Hemorrhagic Fever**

# National CCHF Scientific Board

- CCHF National Referral Laboratory
- National CCHF Guidelines
- CCHF Case Management Guidelines



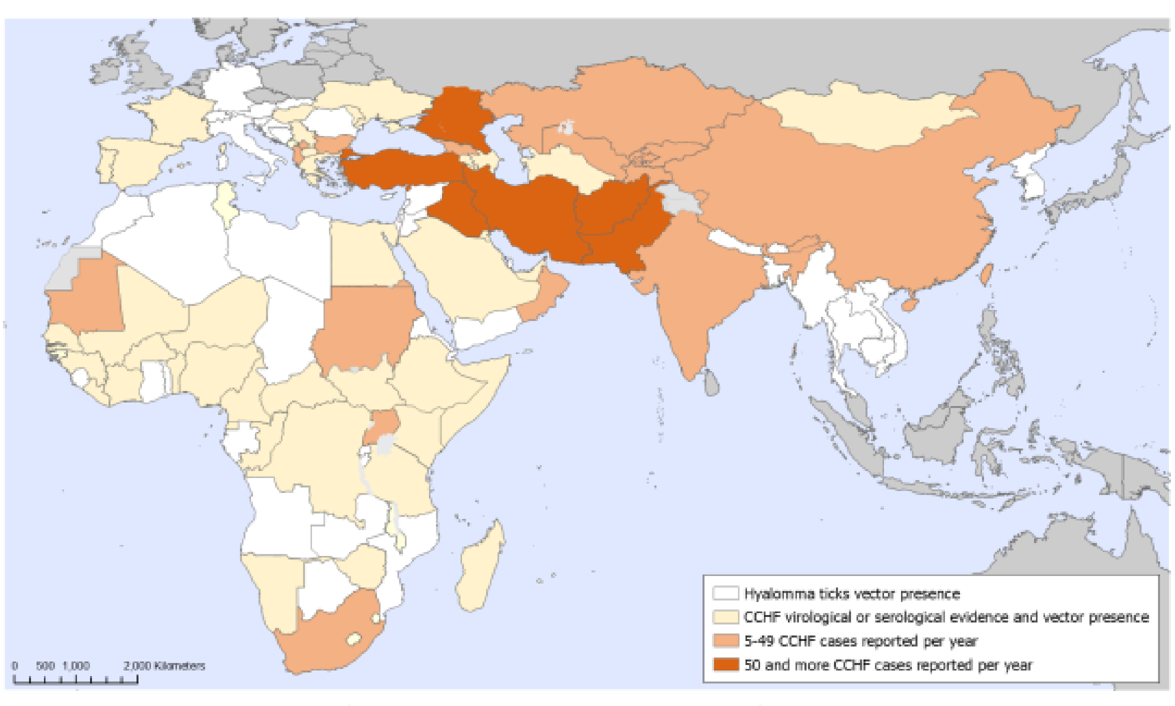



# CCHF History! 2002…. Ankara Numune Education and Research Hospital

## Infectious Diseases and Clinical Microbiology Department

# The burden of Crimean-Congo haemorrhagic fever

- CCHF is a **tickborne** viral illness that occurs in **Africa, the Balkans, the Middle East and Asia**, in countries south of the 50° parallel north.
- Most infections (~80%) will result in **subclinical disease**.
- Global burden is estimated **at 10,000 to 15,000 CCHF infections** with 1,000-2,000 deaths per year.
- Vector is widely distributed putting **3 billion people** at risk




Geographic distribution of Crimean-Congo haemorrhagic fever, updated 2024

# The Agent: Crimean-Congo Hemorrhagic Fever Virus

| Viral Profile | |
|---|---|
| **Family:** | Nairoviridae |
| **Genus:** | Orthonairovirus |
| **Genome:** | Single-stranded RNA, negative-sense. |

**Fatality rate: 5-30%**

Handling and culturing this virus requires the highest level of containment: Biosafety Level 4 (BSL-4) laboratories.

Lipid envelope

L

S

M

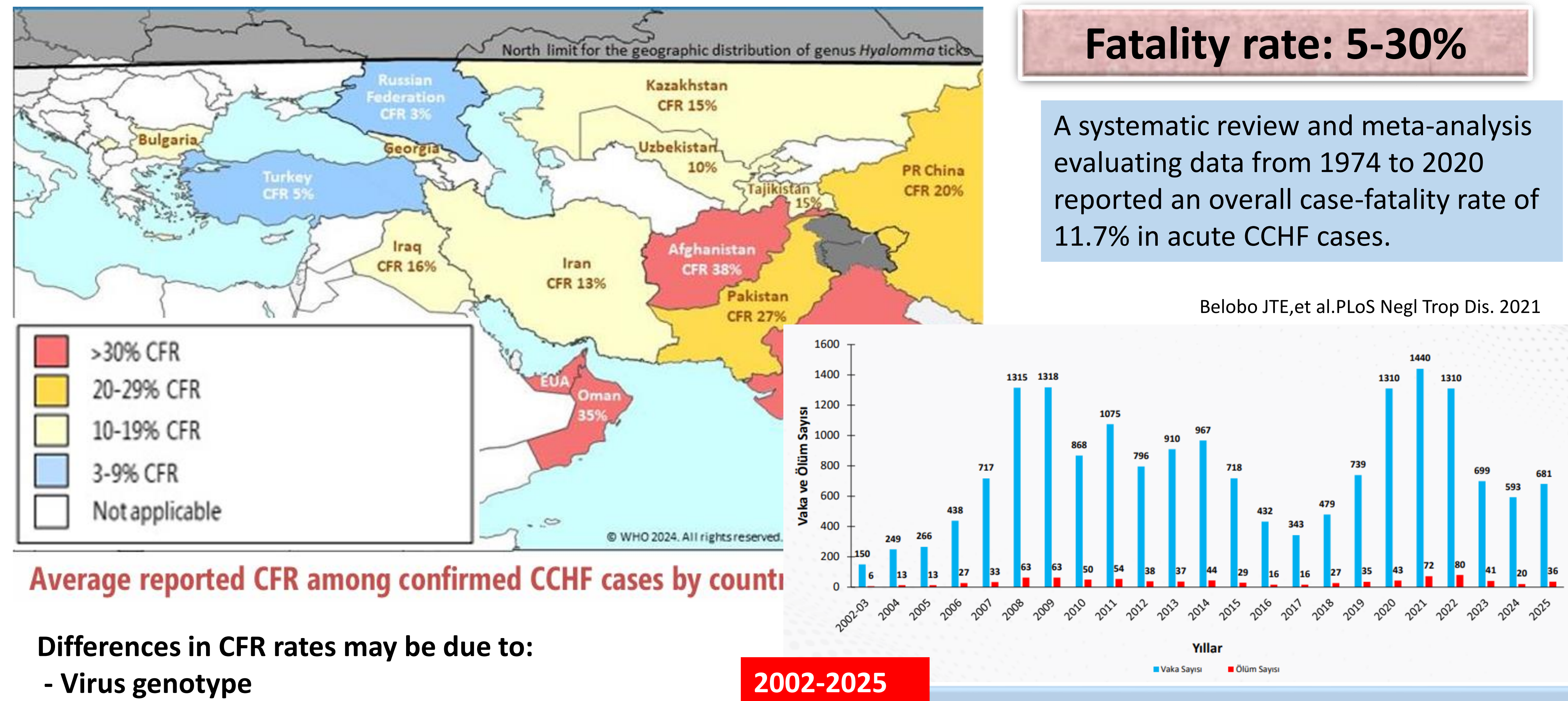
Ribonucleocapsids

Polymerase (L)

By Dr.Şebnem Eren Gök

By Dr.Şebnem Eren Gök

# Fatality rate



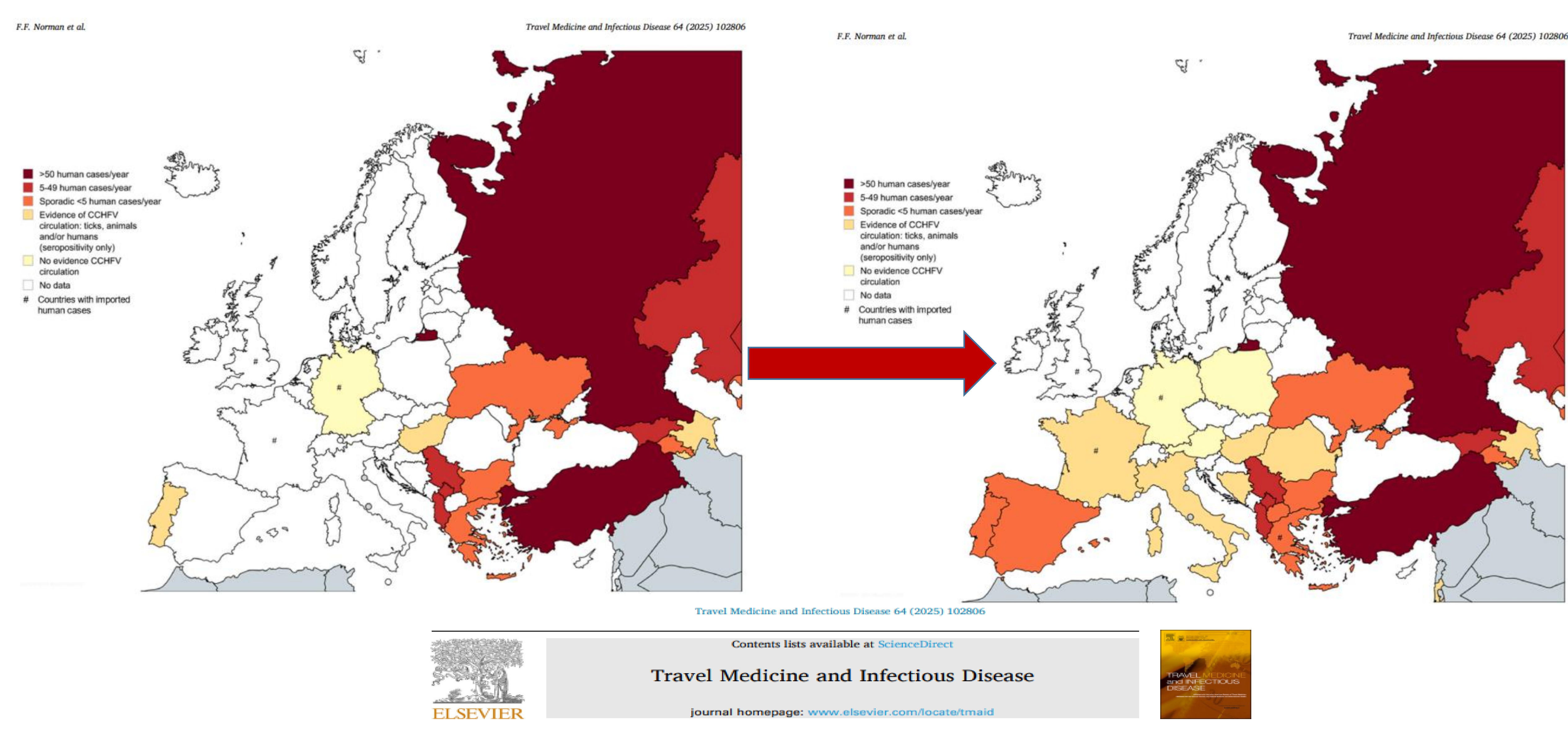

**Differences in CFR rates may be due to:**

- **Virus genotype**
- **Timely access to medical care**
- **Approaches to patient management, etc.**

**2002-2025**
**17.813 case**
**855 death**

**Turkey: Less than 5% (4.8%)**

Evidence up to 2009 included → Evidence up to 2024 included




**Map showing evidence of CCHFV presence in ticks, animals and humans, CCHF authocthonous and imported human cases in the WHO European region**

# 2016 AUGUST

Dr. Marta Mora Rillo (2017)

Dr. Octavio Arce (2021)

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

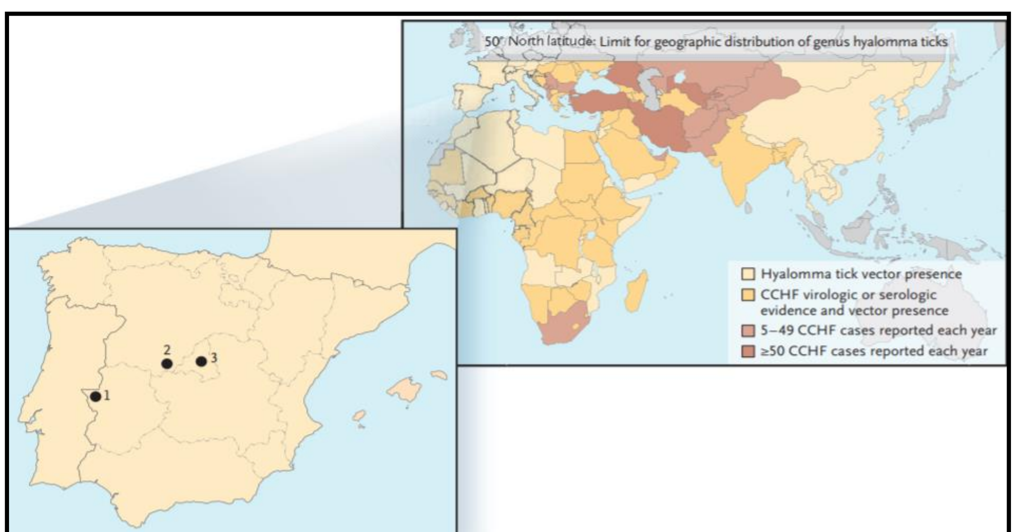
## Autochthonous Crimean–Congo Hemorrhagic Fever in Spain

A. Negredo, F. de la Calle-Prieto, E. Palencia-Herrejón, M. Mora-Rillo, J. Astray-Mochales, M. P. Sánchez-Seco, E. Bermejo Lopez, J. Menárguez, A. Fernández-Cruz, B. Sánchez-Artola, E. Keough-Delgado, E. Ramírez de Arellano, F. Lasala, J. Milla, J.L. Fraile, M. Ordobás Gavín, A. Martinez de la Gándara, L. López Perez, D. Diaz-Diaz, M.A. López-García, P. Delgado-Jimenez, A. Martín-Quirós, E. Trigo, J.C. Figueira, J. Manzanares, E. Rodriguez-Baena, L. Garcia-Comas, O. Rodríguez-Fraga, N. García-Arenzana, M.V. Fernández-Díaz, V.M. Cornejo, P. Emmerich, J. Schmidt-Chanasit, and J.R. Arribas, for the Crimean Congo Hemorrhagic Fever@Madrid Working Group*

Recent emergence of CCHFV into Spain indicates that the geographic range of this virus is expanding and the presence of its tick vector in several countries without reported disease suggest that CCHFV will continue to spread.

- **The index patient acquired the disease through a tick bite in the province of Ávila (300 km away from the province of Cáceres, where viral RNA from ticks was amplified in 2010.)**
- **The second patient was a nurse who became infected while caring for the index patient.**

**Spain should serve as a warning for Europe.**



09:32

UAAN
Control de Enfermería

m/s médecine/sciences

médecine/sciences 2021 ; 37 : 135-40

**La fièvre hémorragique de Crimée-Congo, une future problématique de santé en France ?**

Olivier Reynard, Maureen Ritter, Baptiste Martin, Viktor Volchkov

› Le virus de la fièvre hémorragique de Crimée-Congo (CCHFV) est l'agent étiologique d'une fièvre hémorragique grave affectant l'Afrique, l'Asie et le sud de l'Europe. Les modifications climatiques de ces dernières décennies induisent depuis peu une remontée de l'aire de distribution de ce virus. Encore peu de données scientifiques sont disponibles sur les interactions avec son vecteur, la tique, ou sur sa biologie propre. Cependant, la présence avérée d'infections humaines en Espagne et des sérologies positives dans le cheptel corse pourraient bien concentrer l'attention sur ce pathogène. Cette revue fait le point sur l'évolution des connaissances éco-épidémiologiques de ce virus, notamment en Europe et plus particulièrement en France. ‹

CIRI, Centre international de recherche en infectiologie, Bases moléculaires de la pathogénie virale, Univ Lyon, Inserm U1111, université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, 21 avenue Tony-Garnier, 69365, Lyon, France.
olivier.reynard@inserm.fr

International collaboration at the level of professional expertise

Hitit University and

- Pasteur Enstitute (Enf Dis Specialist and Virolog Dr. Simon Bessis)
- Marsaille University Hospital (Enf  Dis. Specialist Dr. Cyrille Gourjault )

- **Climate change contributes to the spread of CCHF.**
- **Europe, especially France, should be well prepared for this issue!**

Med Sci (Paris).2021 Feb;37(2):135-140

ENFEKSİYON
HASTALIKLARI
SERVİSİ
TC Sağlık Bakanlığı

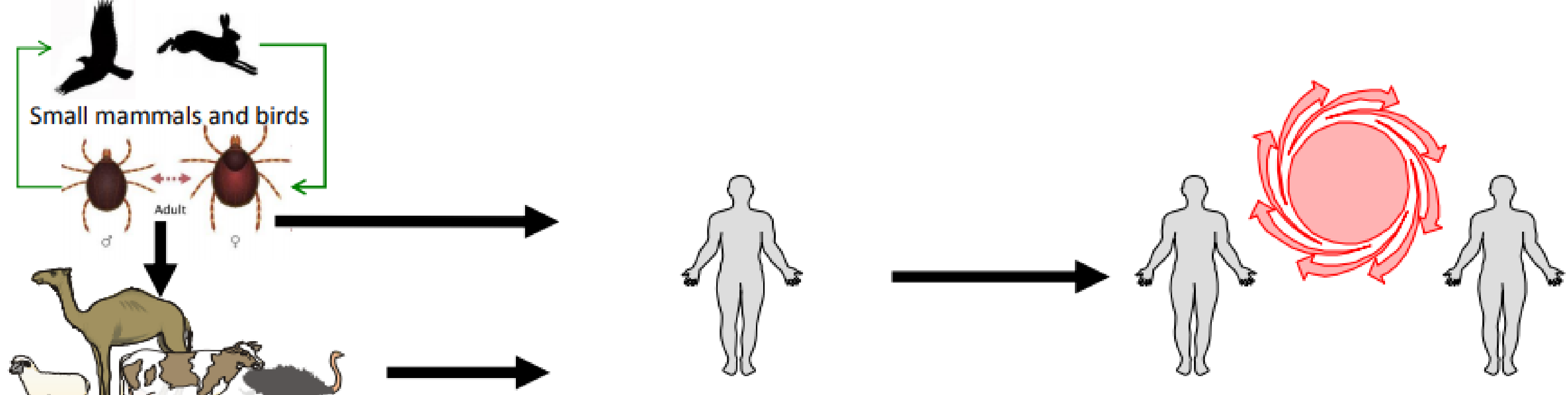
# Hitit University, Faculty of Medicine
# Erol Olçok Research and Education Hospital
# 2011-2025

| | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ölüm | 7 | 5 | 5 | 3 | 0 | 0 | 2 | 3 | 2 | 3 | 3 | 2 | 7 | 1 | 1 |
| Vaka | 92 | 52 | 54 | 63 | 44 | 22 | 22 | 33 | 52 | 74 | 109 | 81 | 43 | 38 | 37 |

**CCHF (+) : 816**
**Fatality : 5,3%**

# HUMANS are the only host of CCHFV in which DISEASE manifested

## Crimean-Congo Haemorrhagic Fever Transmission




**Reservoir *Hyalomma* ticks**

- In nature, CCHF virus maintains itself in a cycle involving ticks and vertebrate.
- Most animals don't show symptoms.

**Primary human infections**

80 to 90 % of humans are infected through:

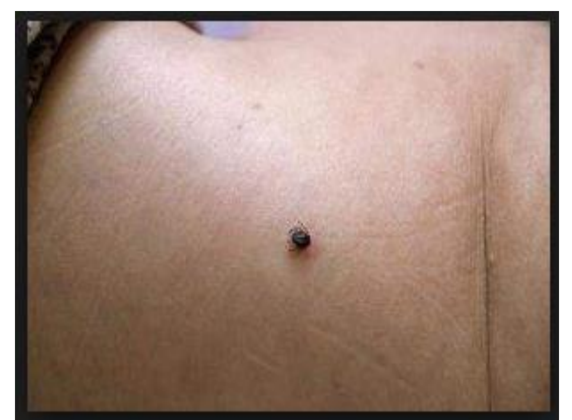
- tick bite or direct contact with blood of infected ticks;
- direct contact with blood/tissues of infected wild animals and livestock.

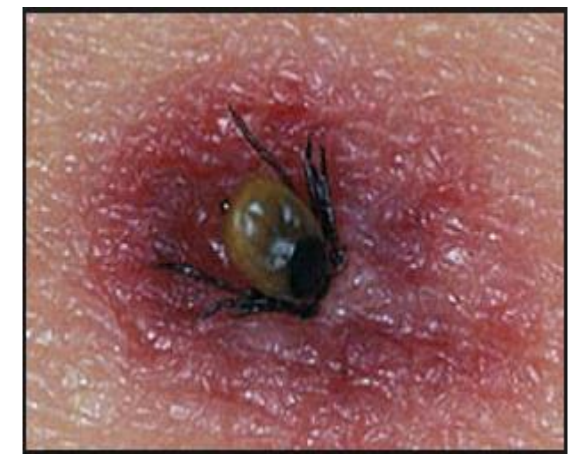
**Secondary human infections**

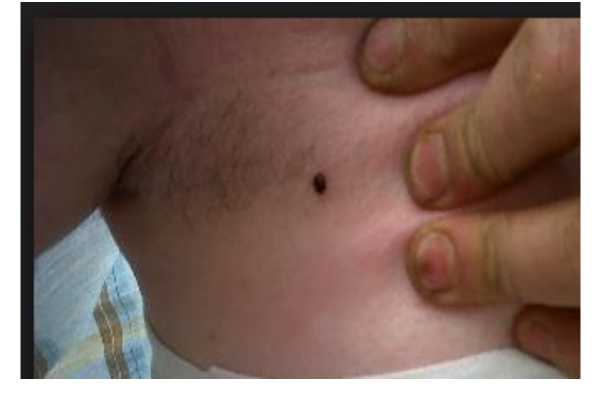
- Secondary human-to-human transmission occurs through direct contact with the blood, secretions, organs or other body fluids of infected persons.
- High transmission risk when providing direct patient care or handling dead bodies (funerals).

©WHO2018

# Transmission







Humans become infected through tick bites and through direct contact with infected animal blood or tissue.

## CCHF transmission in Healthcare Settings

**By direct contact with infected blood or body fluids of CCHF patients**

**And Vertical transmission from CCHFV positive pregnant to fetus**

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 3, March 2014

# Crimean-Congo Hemorrhagic Fever among Health Care Workers, Turkey

Aysel Kocagul Celikbas, Başak Dokuzoğuz, Nurcam Baykam, Sebnem Eren Gok, Mustafa Necati Eroğlu, Kenan Midilli, Herve Zeller, and Onder Ergonul

- **9 cases of Crimean-Congo hemorrhagic fever**
- **1 fatal, 2 asymptomatic**
- **Six of the 9 cases had histories of needlestick injuries or contact with contaminated blood without adequate barrier precautions**
- **Needlestick injuries were reported for 4 workers**
- **8 received ribavirin**

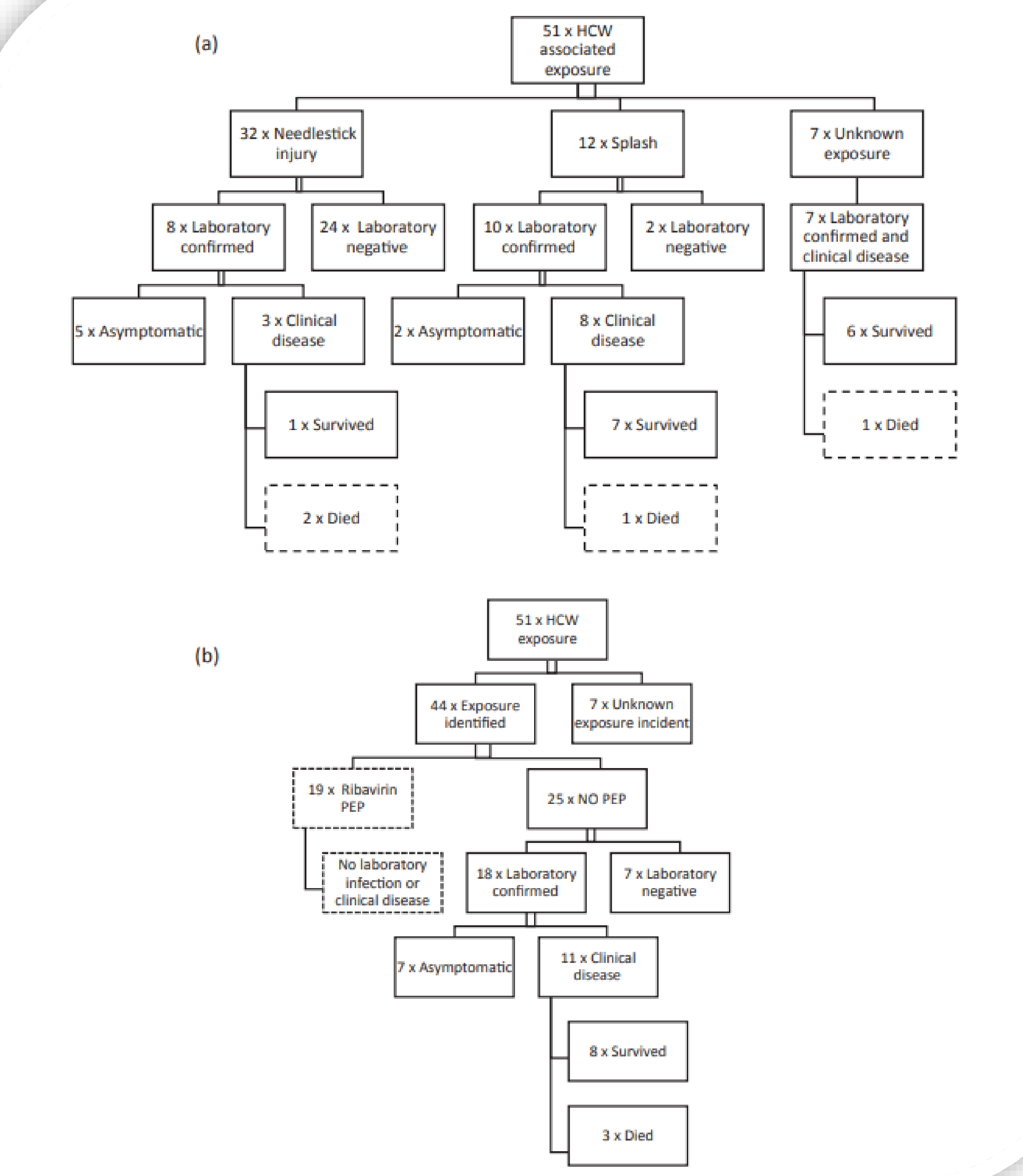
| Episode, outcome† | HCW age, y/sex/profession | Procedure | Transmission route | Ribavirin for postexposure prophylaxis | Ribavirin for therapy (d after symptom onset) | Fatal |
|---|---|---|---|---|---|---|
| Episode 1; survived, her baby died | 36/M/nurse | Wound care | Contact with surgical wound without protective equipment | No | Yes (0) | No |
| | 31/F/nurse | Intubation, aspiration | Aerosol and droplet and contact without protective equipment | No | No | No |
| Episode 2; died | 28/F/nurse | Phlebotomy | Needlestick | No | Yes (3) | Yes |
| Episode 3; died | 41/M/physician | Resuscitation | Aerosol and droplet | – | Yes (0) | No |
| | 26/M/physician | Nasal tamponade | Indirect contact | – | Yes (0) | No |
| | 29/M/physician | Nasal tamponade | Indirect contact | – | Yes (0) | No |
| Episode 4; survived | 30/M/nurse | Phlebotomy | Needlestick | No | Yes (1) | No |
| Episode 5; survived | 30/F/nurse | Phlebotomy | Needlestick | Yes | – | No |
| Episode 6; survived | 24/F/physician | Phlebotomy | Needlestick | Yes | – | No |

RESEARCH NOTE

**Healthcare-associated Crimean-Congo haemorrhagic fever in Turkey, 2002–2014: a multicentre retrospective cross-sectional study**

H. Leblebicioglu[1], M. Sunbul[1], R. Guner[2], H. Bodur[3], C. Bulut[4], F. Duygu[5], N. Elaldi[6], G. Cicek Senturk[7], Z. Ozkurt[8], G. Yilmaz[9], T. E. Fletcher[1,10] and N. J. Beeching[10,11]

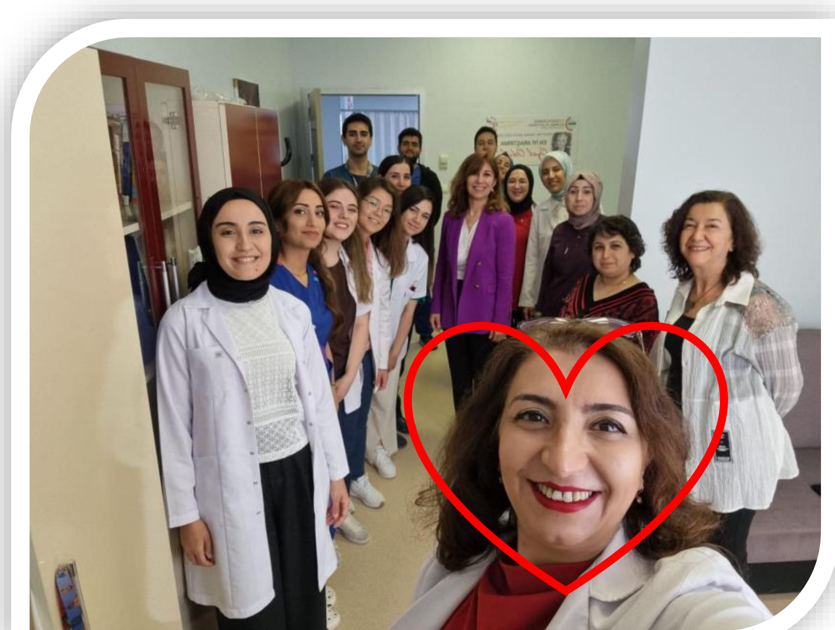
- **51 HCW associated exposure**
- **25/51 resulted in laboratory confirmed infection(49%)**
- **4/25 overall mortality (16%) .**
- **The main route of exposure was needlestick injury in 32/51 (62.7%).**
- **A potential benefit of post-exposure prophylaxis with ribavirin was identified.**




Clin Microbiol Infect 2016; 22: 387.e1–387.e4

Hitit University School of Medicine
Erol Olçok Education and Research Hospital

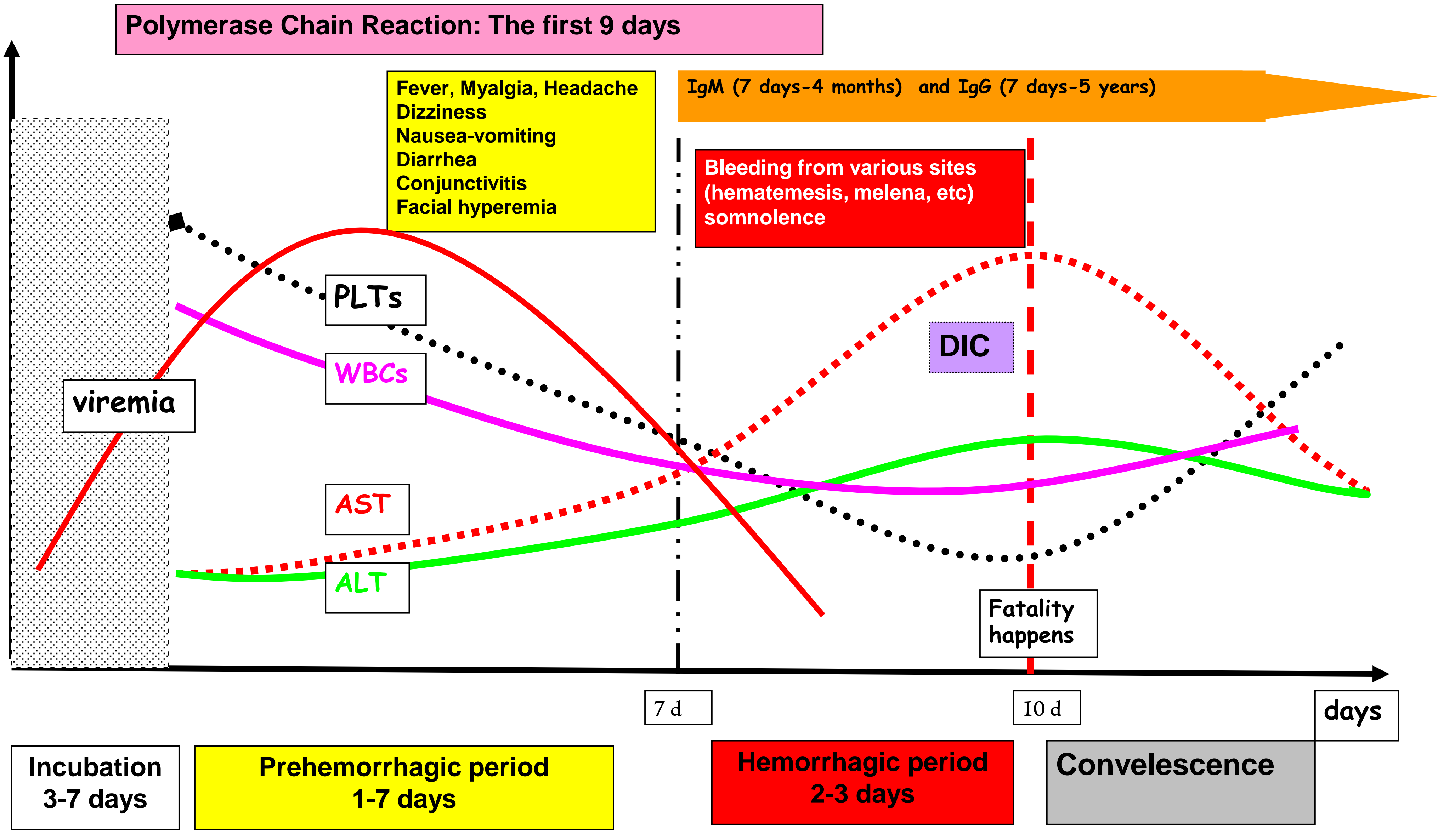
# CCHF Team on Work
# Since 2014



KENE KAYNAKLI HASTALIK
ÇALIŞMALARI UYGULAMA VE
RAŞTIRMA MERKEZI LABORATUVARI
TICK-BORNE DISEASE RESEARCH CENTER LABORATORY
ATIONAL INSTITUTES OF HEALTH (NIH/ABD) 1R01AI180125-01A1
NOLU PROJE DESTEĞİ İLE KURULMUŞTUR)

2024

# Clinical Characteristics of the Patients with CCHF
# How can we recognize these patients in the healthcare facilities?

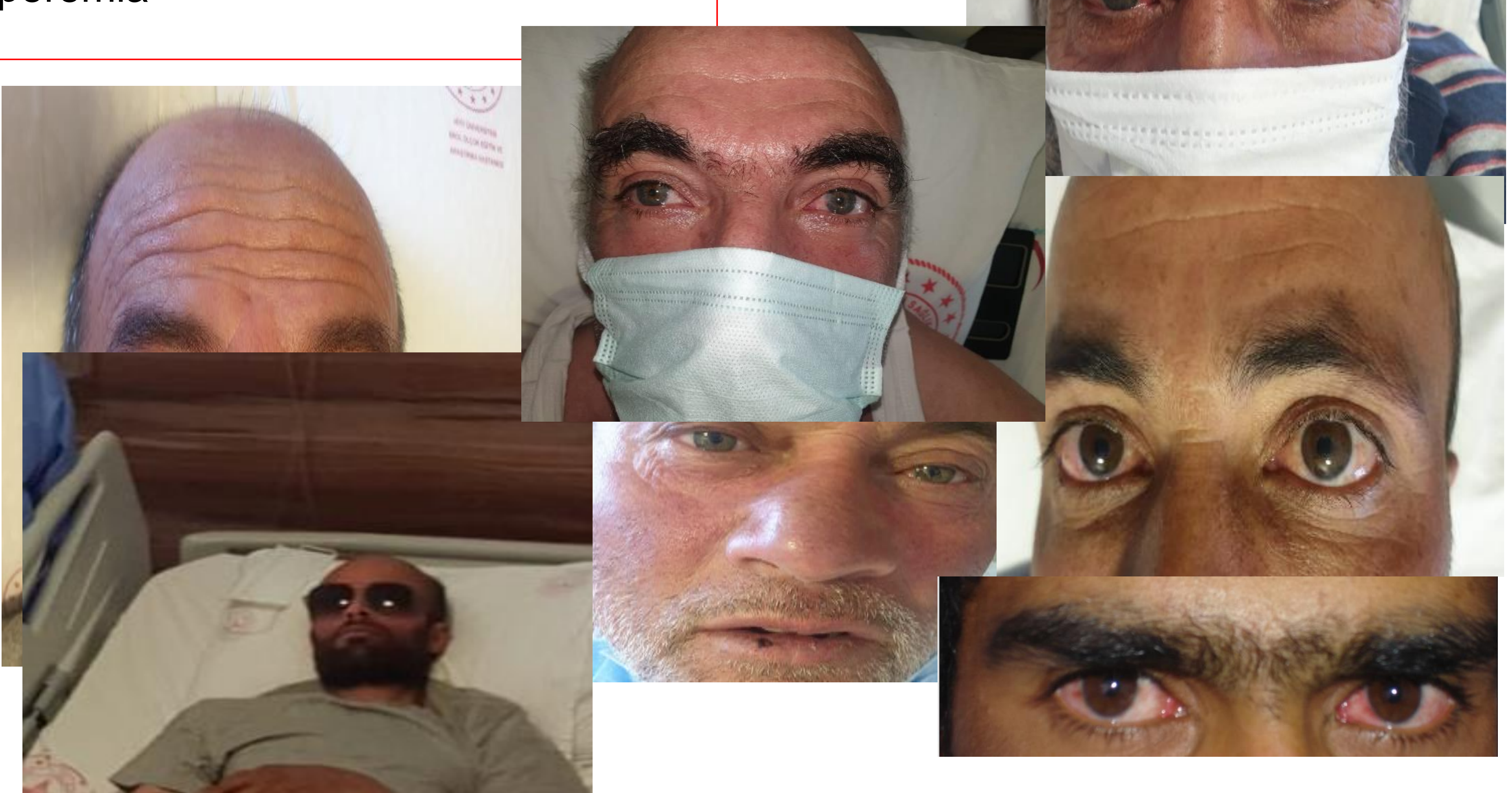



Ergonul O. Lancet ID 2006; 6: 203-214

# Pre-hemorrhagic period

Conjunctival hyperemia 10-70%

Facial hyperemia



Hitit Univ. Infectious Diseases and Clinical Microbiology Clinic Archive

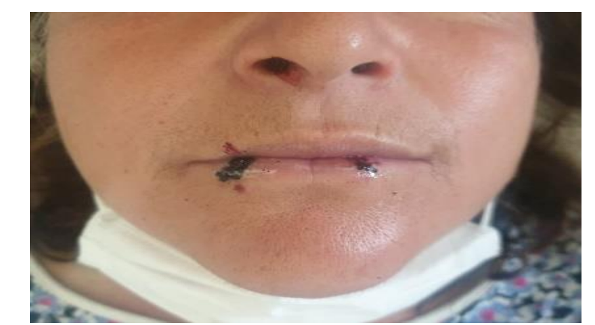
# Pre-hemorrhagic period

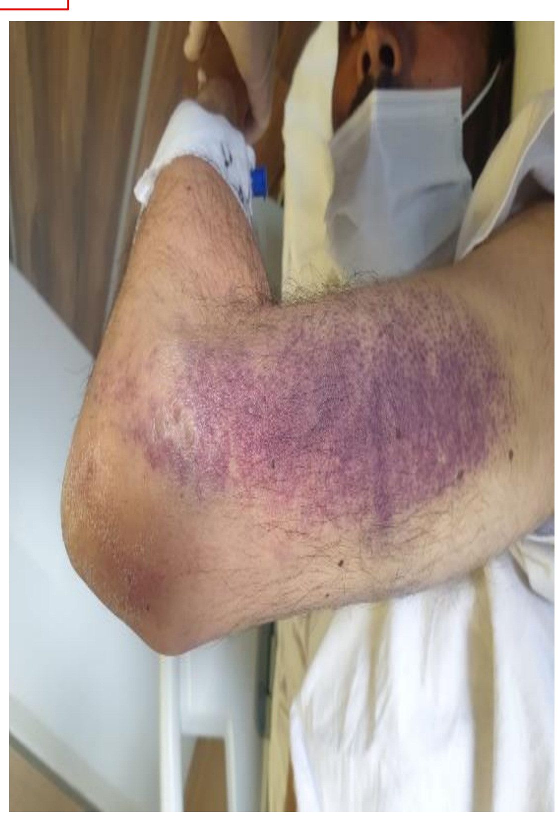
Rash

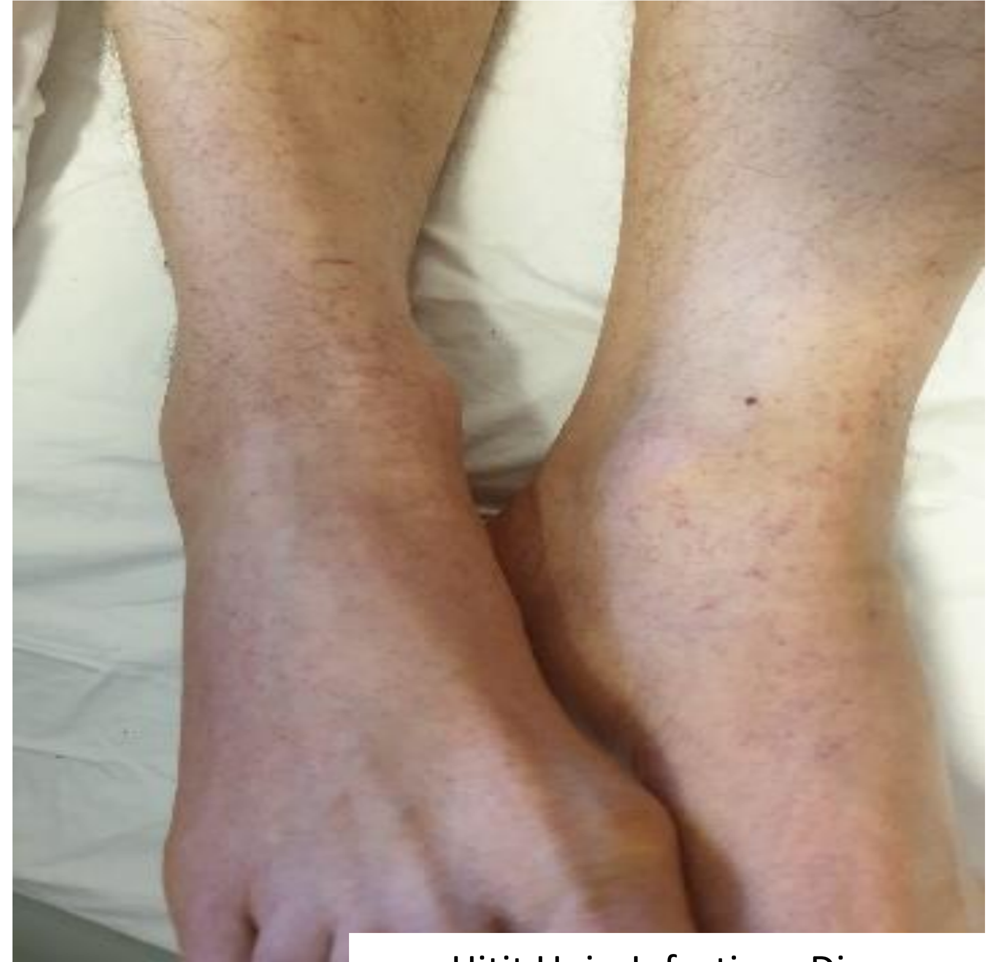
Hitit Univ. Infectious Diseases and Clinical Microbiology Clinic Archive

# Hemorrhagic period

- Petechiae
- Ecchymosis
- Nosebleed
- Hematoma







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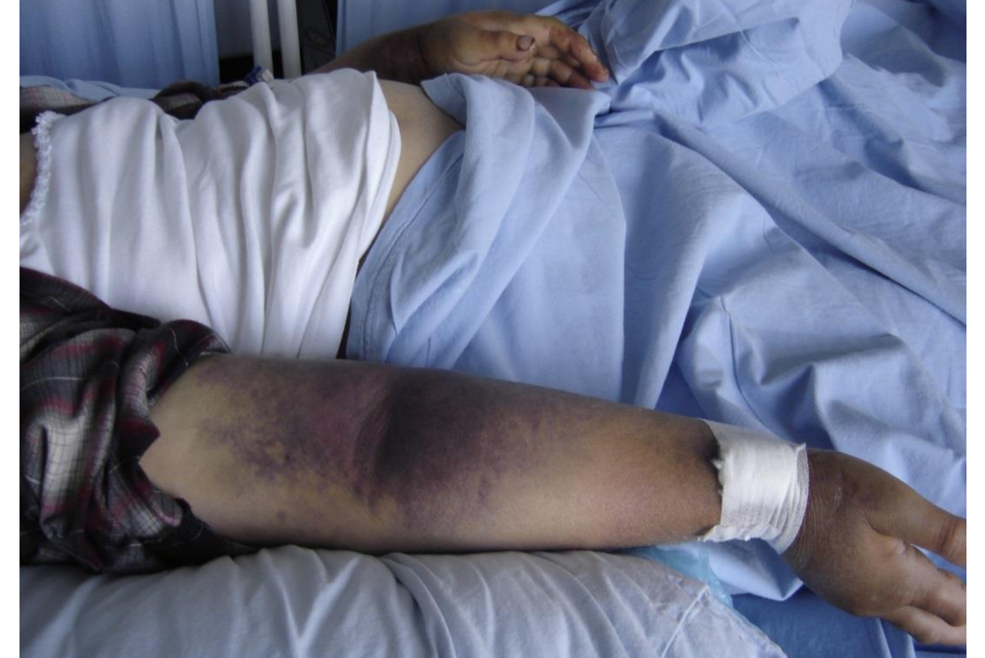
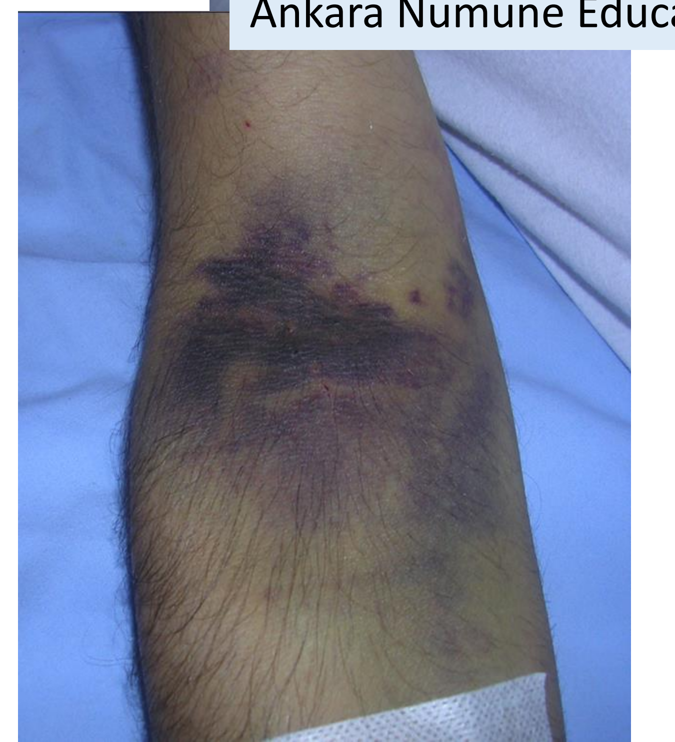
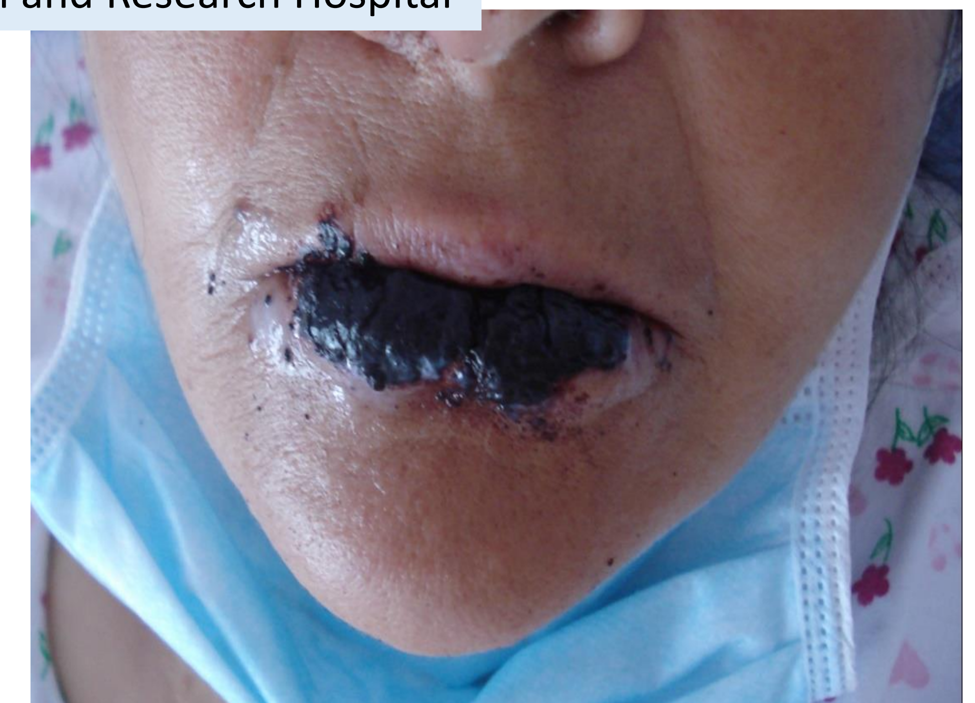


Ankara Numune Education and Research Hospital





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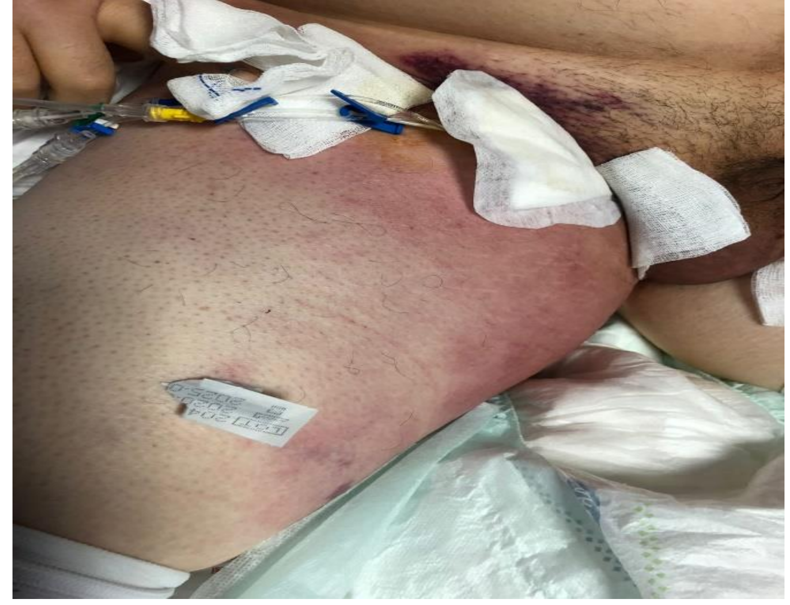
Ankara Numune Education and Research Hospital
2008 5 13

# Hemorrhagic period

- Urinary system (hematuria)
- GIS bleeding (hematemesis, melena)
- Vaginal bleeding(menometroragia)
- Respiratuar system bleeding  (hemoptizi)
- Intra cerebral bleeding
- Intralveolar bleeding



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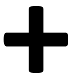
# Clinical Findings-Hemorrhagic Period

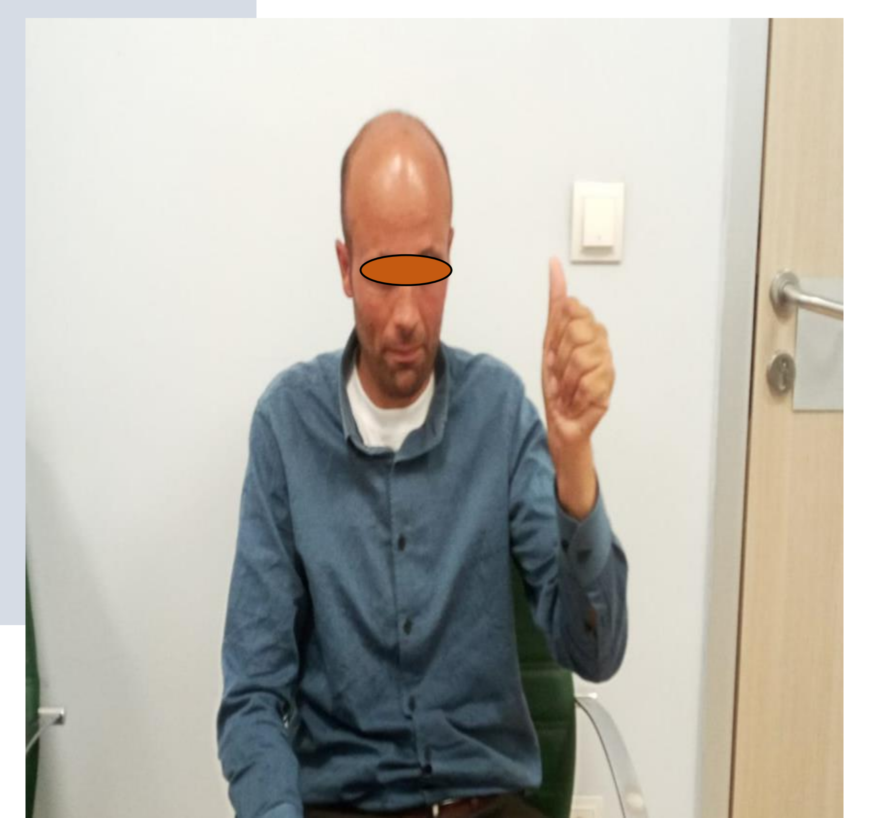
Bleeding



Somnolance
Restlessness
Coma
Shock
Multiple organ failure
Death

# Convalescence period

- Begins 10-20 days after onset of disease in survivors
    - Polyneuritis
    - Loss of memory
    - Hair loss
- No relapse



# Laboratory Findings

**Thrombocytopenia**
**Leukopenia**
**Elevated**

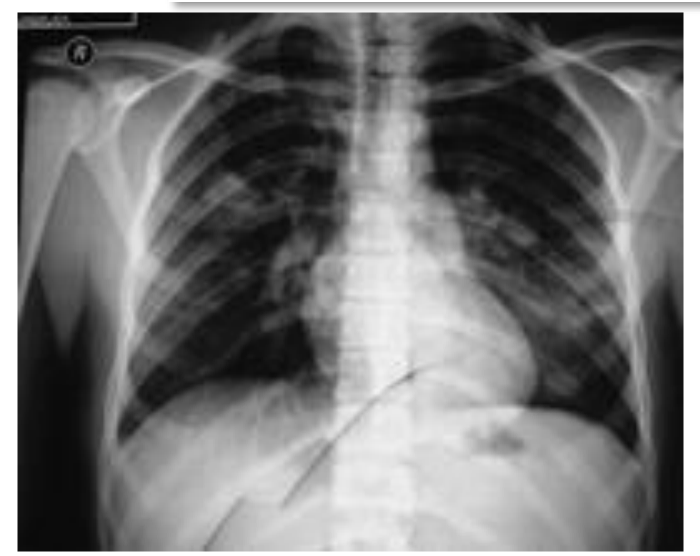
- AST (Aspartate aminotransferase)
- ALT (Alanine aminotransferase)
- LDH (Lactic dehydrogenase)
- CPK (Creatinin phosphokinase)

**Prolonged**

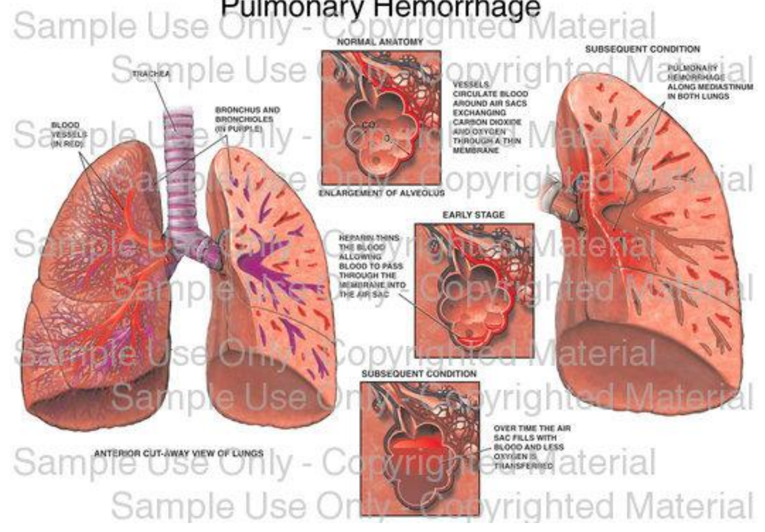
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)

**Decreased Fibrinogen level**

# CCHF and Lung Involvement



**Crimean Congo Hemorrhagic Fever and Diffuse Alveolar Haemorrhage**



Sample Use Only - Copyrighted Material

**ARDS occurs during hemorrhagic manifestations and is accompanied by a systemic inflammatory response.**

Doğanci L. Trop Doct. 2008 Oct;38(4):252-4
Sannikova IV et al. Ter Arkh.2007;79(11):20-3.

International Journal of Infectious Diseases (2009) 13, 369—373

http://intl.elsevierhealth.com/journals/ijid

Crimean-Congo hemorrhagic fever: does it involve the heart?

Aynur Engin[a,*], Mehmet Birhan Yilmaz[b], Nazif Elaldi[a], Alim Erdem[b],

# CCHF and Cardiac Involvement

- 44 confirmed CCCF cases
  - 17 (38,6%) severe,
  - 27 (61,4%) not severe

- There were impairment in cardiac functions related with death in severe cases
- The invasion of myocard by virus or endothelial damage may have a role

Vector-Borne and Zoonotic Diseases, Vol. 15, No. 9 | Short Communications

# Myocarditis in a Child with Crimean-Congo Hemorrhagic Fever

Belgin Gülhan, Saliha Kanık-Yüksek, İbrahim İlker Çetin, Aslınur Özkaya-Parlakay, and Hasan Tezer

**Published Online:** 17 Sep 2015 | https://doi.org/10.1089/vbz.2015.1769

## Cardiac findings in children with Crimean-Congo hemorrhagic fever

*Ibrahim Gul, Ali Kaya, Ahmet Sami Guven, Hekim Karapinar, Zekeriya Kucukdurmaz, Ahmet Yılmaz, Fusun Dilara Icagasioglu, Izzet Tandogan*

**Med Sci Monit 2011; 17(8): CR457-460**

DOI: 10.12659/MSM.881907

Available online:

Published: 2011-08-01

Pericardial effusion, hypokinesis

T dalgası negatifliği veya dal bloğu varlığı mortalite ile ilişkili

Yılmaz MB. Does electrocardiography at admission predict outcome in Crimean Congo hemorrhagic fever?.2011

**Transient sinus bradycardia during the course of Crimean-Congo hemorrhagic fever in children**

## Transient Sinus Bradycardia

- **Independent of the disease severity and the ribavirin treatment**

Gayretli Aydin ZG et al. Tics Tick Borne Dis. 2014

# Atypical Presentations

CASE REPORT

## Crimean Congo hemorrhagic fever infection simulating acute appendicitis

Aysel Çelikbaş[a], Önder Ergönül[a,*], Başak Dokuzoğuz[a], Şebnem Eren[a], Nurcan Baykam[a], Arife Polat-Düzgün[b]

[a] First Infectious Diseases and Clinical Microbiology Clinic, Ankara Numune Education and Research Hospital, Ankara, Turkey
[b] Third General Surgery Clinic, Ankara Numune Education and Research Hospital, Ankara, Turkey

Accepted 29 May 2004

KEYWORDS
Crimean Congo hemorrhagic fever; Acute abdomen; Transmission

**Summary** An unusual cause of acute abdominal pain simulating acute appendicitis is presented. The patient was admitted with complaints of fever, malaise, headache, nausea, vomiting, diarrhoea, and severe bleeding. Based on the clinical and epidemiological findings, a diagnosis of Crimean Congo hemorrhagic fever virus infection was suspected, and ribavirin therapy was started. While her clinical condition was improving, she experienced a sudden pain at her right lower quadrant of the abdomen. Explorative laparotomy revealed haemorrhage within the abdominal muscles. Her CCHF IgM was found to be positive.
© 2004 Published by Elsevier Ltd on behalf of The British Infection Society.

**A case of Crimean-Congo hemorrhagic fever complicated with acute pancreatitis.**

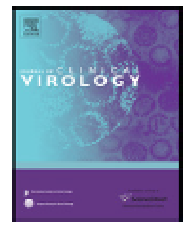
Bastug A et al. Vector Borne Zoonotic Dis. 2014 Nov;14(11):827-9

Journal of Clinical Virology 50 (2011) 162–163

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv




Case report

## A case of Crimean Congo hemorrhagic fever complicated with acalculous cholecystitis and intraabdominal abscess

R. Guner, I. Hasanoglu*, D. Yapar, M.A. Tasyaran

fect 2005

ORIGINAL ARTICLE VIROLOGY

## Pregnancy and Crimean-Congo haemorrhagic fever

O. Ergonul[1], A. Celikbas[2], U. Yildirim[3], A. Zenciroglu[4], D. Erdogan[4], I. Ziraman[5], F. Saracoglu[3], N. Demirel[4], O. Cakmak[6] and B. Dokuzoguz[1]

1) Ankara Numune Education and Research Hospital—Infectious Diseases, 2) Ankara Numune Education and Research Hospital—Infectious Diseases,

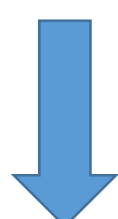
Clin Microbiol Infect 2010; 16: 647–650

| | Weeks of gestation at the time of CCHF virus infection | IgM | IgG | PCR | Outcome |
|---|---|---|---|---|---|
| First mother | 38 weeks (term) | + | + | – | Survived |
| Baby | Caesarian section | – | + | + | Fatal |
| Second mother | 19 weeks | + | NA | + | Survived |
| Baby | Vaginal delivery (term) | – | NA | – | Fatal |
| Third mother | 28 weeks | + | – | + | Fatal |
| Fetus | Died with the mother | NA | NA | NA | Fatal |

- The severity of the CCHF is not related to the pregnancy
- CCHF infection should be differentiated from HELLP syndrome
- There could be either intrauterine or perinatal transmission of the infection in pregnancy
- CCHF can be the etiology of conjenital malformations (eg NEC) even in mild clinical form

## Crimean-Congo hemorrhagic fever in pregnancy: A systematic review and case series from Russia, Kazakhstan and Turkey

N.Y. Pshenichnaya et al. / International Journal of Infectious Diseases 58 (2017) 58–64



**42 pregnant women**

**Maternal mortality: 14/41 (34%)**

**Fetal/neonatal mortality: 24/41 (58%)**

**CCHF is rare in pregnant women, but maternal and fetal mortality is high**

# Crimean-Congo Hemorrhagic Fever Case Definition

**Clinical Definition**

In patients suspected of having CCHF, at least two of the following four clinical criteria must be present.

1. Presence of at least two of the following complaints:
   1. Fever (≥38℃)
   2. Fatigue
   3. Headache
   4. Widespread body pain
   5. Joint pain
   6. Diarrhea
2. Evidence of bleeding in skin and mucous membranes
3. Thrombocytopenia and/or leukopenia unexplained by another cause
4. Elevated ALT and AST levels unexplained by another cause

**Epidemiological Criteria**

In the last 2 weeks;

1. History of tick contact or tick attachment
2. History of contact with animal blood, tissues, or secretions
3. Living in or traveling to rural areas
4. History of close contact with a confirmed case

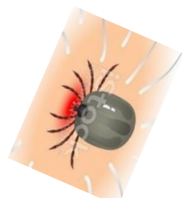
**Laboratory Criteria**

From blood, body fluids, and tissue samples;

1. Virus isolation
2. Detection of viral nucleic acid
3. Detection of virus-specific IgM antibody positivity
4. Detection of a ≥4-fold increase in virus-specific IgG titer in acute and convalescent serum samples

# Case Definition

| Suspected case | Probable case | Confirmed Case |
| --- | --- | --- |
| • Not defined | • A case that meets the clinical definition and fulfills at least one of the epidemiological criteria. | • A probable case confirmed by at least one of the laboratory criteria. |



*Epidemiol. Infect.* (2009), ■, 1–6. © Cambridge University Press 2009
doi:10.1017/S0950268809990318 Printed in the United Kingdom

# Initial high rate of misdiagnosis in Crimean Congo haemorrhagic fever patients in an endemic region of Turkey

N. TASDELEN FISGIN*, L. DOGANCI, E. TANYEL AND N. TULEK

- **Between March 2004 and August 2004,**
- **140 confirmed adult cases**
- **95 (68%) were initially misdiagnosed**
- **Antibiotics were used in 23% of cases.**

**32% CCHF**

**45% Upper respiratory system infections**

**5% GIS infections**

**5% Lower respiratory system infections**

**4% Pancyyopenia without known etiology**

**2% Urinery tract infection**

**1.5% GIS haemoraji**

**1.5% Leptospirosis**

**The initial nonspecific symptoms may resemble other common infectious diseases!**

Ticks and Tick-borne Diseases 10 (2019) 1035–1040

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdis

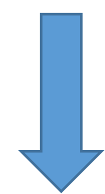
Original article

# Hitit Index to distinguish patients with and without Crimean-Congo hemorrhagic fever

Huseyin Kayadibi[a,*], Derya Yapar[b], Ozlem Akdogan[b], Nuray N Ulusu[c], Nurcan Baykam[b]

Artificial Intelligence in Rapid Diagnosis of CCHF!

We aimed to determine the diagnosis of patients by a quick, easy, inexpensive and accurate index at the first application to the health institutions



Study is expanded by adding clinical signs to laboratory parameters for to establish Hitit Index

## To Establish Hitit Index

- Hospitalization day laboratory test results of 268 CCHF suspected inpatients: to calculate the **laboratory part**
  - **149 inpatients were CCHF-positive**
  - **119 inpatients were CCHF-negative**
- 65 of these were also monitored daily during hospital stay to develop the **clinical part**
- Control group: 200 CCHF-negative outpatients

Ticks and Tick-borne Diseases 10 (2019) 1035–1040

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# Hitit Index to distinguish patients with and without Crimean-Congo hemorrhagic fever

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**Nonspesific symptoms**

KKKA

Sepsis

ÜSYE

COVID-19

**Hitit Index**

5.6 - (5.3 x lymphocyte) - (0.02 x fibrinogen) - (12 x direct bilirubin) + (0.04 x AST) + (0.32 x hematocrit) - (0.5xneutrophil) - (0.07 x CKD - EPI) - (0.001 x CK) ± conjunctival hyperemia (+1.5 in conjunctival hyperemia presence and - 1.5 in conjunctival hyperemia absence).

**<0** → Outpatient daily follow-up

**>0** → CCHF ? Hospitalization

**Hitit Index may be a useful diagnostic tool to distinguish patients with CCHF from others.**

# CCHF Differential Diagnosis

- COVID-19
- Influenza
- Viral hemorrhagic fevers
- Sepsis
- P. falciparum malaria
- Leptospirosis,
- Meningococcemia
- Trypanosomiasis
- Septicemic plague
- Hemorrhagic smallpox
- Typhoid
- Q fever
- Sandfly virus
- Tularemia
- Hemolytic uremic syndrome
- HELLP syndrome
- Vasculitis
- Toxic hepatitis
- Brucella
- Hantavirus infection
- Rickettsial diseases
- Lyme disease
- Hematologic malignancies
- Vitamin B12 deficiency
- Tick-borne encephalitis
- Babesiosis
- Idiopathic thrombocytopenic purpura

# Case 1

**Applied to Covid clinic**

- **34 years old male patient, dealing with animal husbandry.**
- **Çorum center, ….village**
- **Complaint start: 18.6.2020**
- **Application to the hospital: 21.6.2020**
- **Complaints: Fever, weakness, sore throat, cough, widespread muscle, joint pain**
- **No history of tick bite**

Initial diagnose???

- COVID-19
- Upper RSI
- Influenza
- CCHF

- Toraks CT: Normal
- SARS CoV-2 PCR: (-)

CCHF PCR: (+)

| | 1.Day (External centre) | 3. day | 6. day | 10. day |
|---|---|---|---|---|
| WBC | 6270 | 1850 | 3400 | 6420 |
| PLT | 202 | 117 | 69 | 215 |
| AST | 27 | 80 | 135 | 48 |
| ALT | 24 | 47 | 95 | 85 |
| CK | 154 | 841 | 639 | 58 |
| LDH | 210 | 508 | 555 | 255 |
| Lenfosit | 770 | 490 | 1810 | 2780 |
| Fibrinojen | 352 | 355 | 345 | 344 |
| CRP | 30 | 13,9 | 6,5 | 3.13 |
| D-dimer | 0,44 | 0,88 | Neg | Neg |
| Ferritin | 1563 | 2000 | 3879 | 705 |

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RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2021;26(3):426-432 • doi: 10.5578/flora.20219711

# Does the Hitit Index Work in the Differential Diagnosis of CCHF and COVID-19 with Non-Specific Findings?

## Hitit İndeksi, Spesifik Olmayan Bulgularla KKKA ve COVID-19 Ayırıcı Tanısında İşe Yarar Mı?

Derya YAPAR[1], Özlem AKDOĞAN[1], Hüseyin KAYADİBİ[2], Gülcan KAPLAN[1], Pınar TUNÇEL ÖZTÜRK[1], Aysel KOCAGÜL ÇELİKBAŞ[1], Nurcan BAYKAM[1]

Hitit Index Formule

5.6 - (5.3 x lymphocyte) - (0.02 x fibrinogen) - (12 x direct bilirubin) + (0.04 x AST) + (0.32 x hematocrit) - (0.5xneutrophil) - (0.07 x CKD - EPI) - (0.001 x CK) ± conjunctival hyperemia (+1.5 in conjunctival hyperemia presence and - 1.5 in conjunctival hyperemia absence).

**Can we differentiate CCHF and COVID-19 during non-specific findings using Hitit Index?**
**116 cases of COVID-19**
**110 CCHF cases (2015-2020)**

**Hitit Index Statistically significant HIGH in CCHF cases**
**Sensitivity: 88%**
**Specificity: 99%**

## Can we guess the course of the disease?

## What are the predictors of severity, fatality?

# Severity Criteria Studies in Türkiye

Consciousness disturbance and splenomegaly
*Bakir M, et al. J Med Microbiol* 2005

ORIGINAL ARTICLE 10.1111/j.1469-0691.2006.01445.x

**Analysis of risk-factors among patients with Crimean-Congo haemorrhagic fever virus infection: severity criteria revisited**

*O. Ergonul, A. Celikbas, N. Baykam, S. Eren and B. Dokuzoguz*

Viral load $\geq 1X10^9$
Predictor of prognosis
*Cevik MA, et al. CID 2007*

**Elevated serum neopterin levels, indicating strong activation of monocytes/macrophages, are a risk factor for CCHF.**
*Onguru P. J Infect. 2008*

Journal of Clinical Virology
Volume 47, Issue 4, April 2010, Pages 361–365

The effectiveness of routine laboratory findings in determining disease severity in patients with Crimean-Congo hemorrhagic fever: Severity prediction criteria

Gurdal Yilmaz[a], Iftihar Koksal[a], Murat Topbas[b], Hulya Yilmaz[c], Firdevs Aksoy[a]

ORIGINAL ARTICLE

**Evaluation of clinical and laboratory predictors of fatality in patients with Crimean-Congo haemorrhagic fever in a tertiary care hospital in Turkey**

July 2010, Vol. 42, No. 6-7 , Pages 516-521 (doi:10.3109/00365540903582418)

Cigdem Ataman Hatipoglu, Cemal Bulut, Meltem Arzu Yetkin, Gunay Tuncer Ertem, Fatma Sebnem Erdinc, Esra Kaya Kilic, Tugba Sari, Sami Kinikli, Behic Oral, and Ali Pekcan Demiroz

HTML
PDF (61 KB)

International Journal of Infectious Diseases
Volume 16, Issue 2, February 2012, Pages e89–e93

Evaluation of factors predictive of the prognosis in Crimean-Congo hemorrhagic fever: new suggestions

Baris Ozturk[a], Ediz Tutuncu[a], Ferit Kuscu[a], Yunus Gurbuz[a], Irfan Sencan[a], Hakan Tuzun[b]

*J Vector Borne Dis* 49, June 2012, pp. 105–110

A new perspective to determine the severity of cases with Crimean-Congo hemorrhagic fever

Mehmet Bakir[1], Aynur Engin[1], Mustafa Gokhan Gozel[1], Nazif Elaldi[1], Saadettin Kilickap[2] & Ziynet Cinar[3]

*[1]Department of Infectious Diseases and Clinical Microbiology; [2]Department of Medical Oncology; [3]Department of Biostatistics, Cumhuriyet University School of Medicine, Sivas, Turkey*

Ozturk et al.International Journal of Infectious Diseases 16 (2012) e89–e93

# Severity Criteria Studies in Türkiye

| | Swanepoel et al. 1989 | Bakır et al. 2005 | Ergonul et al. 2006 | Cevik et al. 2008 | Fısgın et al. 2009 | Ozturk et al.2012 |
|---|---|---|---|---|---|---|
| Sex | - | No | No | No | No | No |
| Age | - | No | No | No | Yes | No |
| Tick exposure | - | No | - | - | - | No |
| Ecchymosis | No | No | No | Yes | - | No |
| Melena | No | - | Yes | Yes | - | Yes |
| Hematemesis | No | - | Yes | Yes | - | Yes |
| Somnolence | No | - | Yes | Yes | No | - |
| Elevated AST | Yes | Yes | Yes | Yes | Yes | Yes |
| Elevated ALT | Yes | No | Yes | Yes | Yes | No |
| Elevated CPK | No | Yes | No | Yes | Yes | No |
| Elevated LDH | No | Yes | No | Yes | Yes | Yes |
| Fibrinogen | Yes | - | Yes | No | - | Yes |
| PT elongation | - | - | Yes | Yes | Yes | Yes |
| aPTT elongation | Yes | - | Yes | Yes | Yes | Yes |
| Elevated INR | - | Yes | - | - | - | Yes |
| Thrombocytopenia | Yes | Yes | Yes | Yes | Yes | Yes |
| D-dimer | - | - | - | - | - | Yes |
| CRP | - | - | - | - | - | Yes |
| hs-CRP | - | - | - | - | - | Yes |
| Leukocytosis | Yes | No | No | No | - | No |
| IgA | - | - | - | - | - | No |
| IgM | - | | | | - | Yes |
| IgG | - | | | | - | Yes |
| C3 | - | | | | - | Yes |
| C4 | - | | | | - | Yes |

- Elevation of AST,
- Low platelet counts,
- Prolongation of aPTT and PT,
- Elevated INR

PATHOGENS AND GLOBAL HEALTH
https://doi.org/10.1080/20477724.2021.2012921

Which scoring system is effective in predicting mortality in patients with Crimean Congo hemorrhagic fever? A validation study

Mehmet Bakir[a], Caner Öksüz[a], Faruk Karakeçili[b], Nurcan Baykam[c], Şener Barut[d], Seyit Ali Büyüktuna[a], Zülal Özkurt[e], Murteza Öz[a], Orçun Barkay[b], Özlem Akdoğan[c], Nazif Elaldi[a], Murşit Hasbek[f] and Aynur Engin[a]

[a]Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Sivas Cumhuriyet University, Sivas, Turkey; [b]Department of Infectious Diseases and Clinical Microbiology, Erzincan Binali Yıldırım University, Mengücek Gazi Training and Research Hospital, Erzincan, Turkey; [c]Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Çorum Hitit University, Çorum, Turkey; [d]Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Tokat Gaziosmanpaşa University, Tokat, Turkey; [e]Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ataturk University, Erzurum, Turkey; [f]Faculty of Medicine, Department of Medical Microbiology, Sivas Cumhuriyet University, Sivas, Turkey

- **5 centers**
- **388 KFD (Crimean-Congo Hemorrhagic Fever) patients**
- **Severity scoring systems were evaluated:**
  - **qSOFA (quick Sequential Organ Failure Assessment),**
  - **SOFA (Sequential Organ Failure Assessment),**
  - **APACHE II (Acute Physiology and Chronic Health Evaluation II),**
  - **SGS (Severity Grading System)**
- **The SOFA, APACHE II, and SGS systems accurately predicted mortality at admission, as well as at 72 and 120 hours, and were also correlated with each other.**

Clinical Microbiology and Infection 31 (2025) 2056–2062

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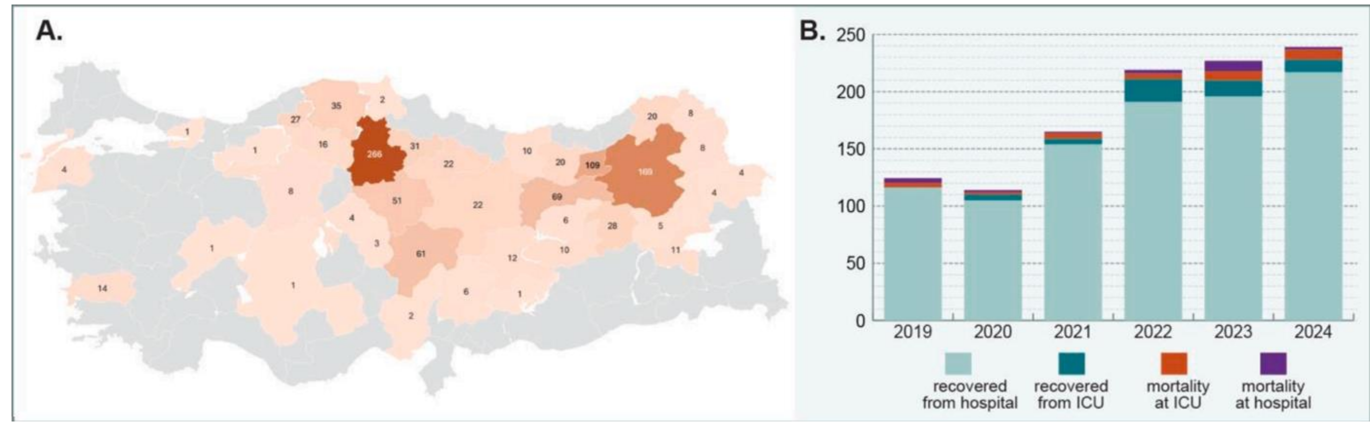
Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.org

Original article

# Key predictors of mortality in Crimean-Congo haemorrhagic fever: a retrospective multicentre cohort study

Deniz Güllü [1, 2, 3, *], Defne Yigci [1, *], Nurcan Baykam [4], Aysel Kocagül Çelikbaş [4], Derya Yapar [4], Özlem Akdoğan [4], Kemalettin Özden [5], Rukiye İnan Sarıkaya [6], İmran Hasanoğlu [7], Rahmet Güner [7], Ebru Doğan [8], Faruk Karakeçili [9], Handan Alay [5], Zeynep Türe Yüce [10], Esma Eryılmaz Eren [11], Ayşe Erbay [12], Şebnem Eren Gök [12], Çiğdem Kader [12], Gamze Ünüvar Kalın [10], Azize Yetişgen [13], Müge Özgüler [14], Arzu Şenol [14], Ömür Gündağ [14], Merve Çağlar Özer [15], Firuze Soyak [16], Büşra Tanır [14], Işıl Deniz Alıravcı [17], Güle Çınar [18], Barçın Öztürk [19], Esra Gürbüz [20], Bahadır Orkun Özbay [21], Fatihan Pınarlık [2, 3], Mert Kuşkucu [3, 22], Önder Ergönül [3, 23, *]





- A retrospective study was conducted on 1103 CCHF patients across 18 hospitals in Türkiye from 2019 to 2024
- Overall mortality rate was 5.1% (56/1103).
- Intensive care unit admission was required in 8.0% (88/1103)
- Age ≥50 years and diabetes mellitus were associated with increased mortality

Key factors such as age and comorbidities can predict mortality in CCHF patients. Timely identification of these predictors, along with early administration of ribavirin, may contribute to improved survival and better clinical outcomes.

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**Table 1**

Comparison of laboratory findings between patients who died and those who survived

| Variables | Survived ($n = 1047$) | Died ($n = 56$) | Test statistic (Z) | p value |
|---|---|---|---|---|
| Haemoglobin level (g/dL) | 14.2 (13–15.3; $n = 1045$) | 13.5 (12.5–15; $n = 54$) | −1.86 | 0.062 |
| White blood cell count ($\times 10^3$/uL) | 2.6 (1.84–3.74; $n = 1047$) | 3.3 (1.78–5.75) ($n = 54$) | −2.11 | **0.035** |
| Lymphocyte ($\times 10^3$/uL) | 0.57 (0.39–0.89; $n = 969$) | 0.68 (0.38–1.26) ($n = 50$) | −1.35 | 0.176 |
| Platelet count ($\times 10^3$/μL) | 89 (46–127; $n = 1046$) | 39 (21–121; $n = 54$) | −3.7 | **<0.001** |
| aPTT (s) | 32 (28–37; $n = 1013$) | 38 (29–54; $n = 52$) | −3.2 | **0.001** |
| INR | 1.08 (0.98–1.2; $n = 1012$) | 1.1 (0.98–1.4; $n = 49$) | −1.46 | 0.143 |
| Fibrinogen (mg/dL) | 254 (210–300; $n = 620$) | 230 (145–284; $n = 31$) | −1.94 | 0.052 |
| D-Dimer (g/L) | 1.8 (0.84–4.56; $n = 315$) | 4.76 (1.08–35.2; $n = 22$) | −2.1 | **0.036** |
| ALT (U/L) | 58 (30–124; $n = 1046$) | 135 (54–397; $n = 54$) | −4.47 | **<0.001** |
| AST (U/L) | 106 (45–251; $n = 1046$) | 222 (77–1161; $n = 54$) | −3.88 | **<0.001** |
| LDH (U/L) | 420 (275–675; $n = 996$) | 766 (383–2836; $n = 52$) | −5.43 | **<0.001** |
| CK (U/L) | 278 (136–680; $n = 990$) | 388 (202–1005; $n = 49$) | −2.04 | **0.041** |
| BUN (mg/dL) | 25 (15.5–38; $n = 951$) | 33 (17.4–47; $n = 51$) | −2.49 | **0.013** |
| Creatinine (mg/dL) | 0.88 (0.7–1.02; $n = 1034$) | 0.94 (0.7–1.53; $n = 54$) | −2.4 | **0.016** |
| CRP (mg/L) | 9.5 (3.3–27; $n = 918$) | 15 (4.3–43.7; $n = 48$) | −1.8 | 0.072 |
| PCT (ng/mL) | 0.17 (0.1–0.5; $n = 511$) | 0.53 (0.1–1; $n = 27$) | −2.37 | **0.018** |
| Ferritin (g/mL) | 1.65 (0.61–2; $n = 282$) | 1.83 (0.99–2.4; $n = 8$) | −0.76 | 0.448 |

**A scoring index was needed for case management, which could predict the fatality and could guide the clinician for therapeutic options**

MAJOR ARTICLE

# Severity Scoring Index for Crimean-Congo Hemorrhagic Fever and the Impact of Ribavirin and Corticosteroids on Fatality

Başak Dokuzoguz,[1] Aysel Kocagül Celikbas,[1] Şebnem Eren Gök,[1] Nurcan Baykam,[1] Mustafa Necati Eroglu,[1] and Önder Ergönül[2]

[1]Clinical Microbiology and Infectious Diseases Clinic, Ankara Numune Education and Research Hospital, Ankara, and [2]Infectious Diseases and Clinical Microbiology, Koç University, School of Medicine, Istanbul, Turkey

***Background.*** Patients infected with Crimean-Congo hemorrhagic fever (CCHF) virus present with a wide clini-

| | | score |
|---|---|---|
| Platelet count (x10³ /mm³) | >150 | 0 |
| | 150 -50 | 1 |
| | 49-20 | 2 |
| | <20 | 3 |
| aPTT (sec) | ≤ 34 | 0 |
| | 35 – 45 | 1 |
| | 46 - 59 | 2 |
| | > 60 | 3 |
| Fibrinogen (mg/dl) | ≥ 180 | 0 |
| | 179 – 160 | 1 |
| | 159 -120 | 2 |
| | <120 | 3 |
| Bleeding | No | 0 |
| | Petechia | 1 |
| | Echymosis | 2 |
| | Bleeding | 3 |
| Somnolence | No | 0 |
| | yes | 1 |

| | |
|---|---|
| **Score 0-2** | **Mild** |
| **Score 3-9** | **Moderate** |
| **Score 10-13** | **Severe** |

| | Ribavirin | | | Corticosteroids | | |
|---|---|---|---|---|---|---|
| | CFR/Given (%) | CFR/Not given (%) | *p* | Given (%) | not given (%) | *p* |
| Mild (0-2) | 0/77 (0) | 0/26 (0) | NA | 0 | 0/103 (0) | NA |
| Moderate (3-9) | 2/134 (1.49) | 3/17 (18) | <0.001 | 2/30 (7) | 3/121 (2) | 0.251 |
| Severe (10-13) | 16/24 (67) | 2/2 (100) | 0.326 | 9/17 (53) | 9/9 (100) | 0.013 |

# Case 2

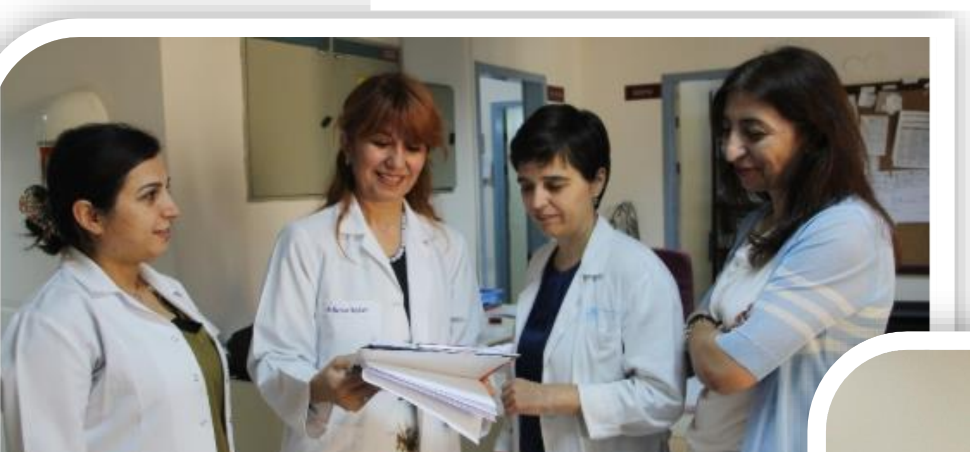
**Hospitalization date: 19/05/2021**

- **57 year old female patient**
- **She is engaged in animal husbandry, does not report tick contact**
- **2 days ago (17/05/2021) complaints start fever, malaise, muscle pain**
- **She applies to an external center and is sent home after routine tests**
- **Ecchymosis in the area where the blood was drawn**
- **Conjunctiva and face hyperemic**
- **Hematuria(+),**
- **GI bleeding(+)**
- **Epistaxis on the 2nd day of hospitalization**
- **Blurring of consciousness, general condition disorder on the 3rd day of hospitalization**
- **Hitit Index: 55**
- **SSI (Dokuzoguz): 12-13 (severe)**

| | 1.day (external center) 17/05/2021 | 3.day 19/05/2021 | 7.day 24/05/2021 | 12.day 29.05.2021 | Treatment |
|---|---|---|---|---|---|
| WBC | 7840 | 8970 | 3.900 | 4820 | • Platelet<br>• FFP<br>• Dexamethazon<br>• Criyopresipitat<br>• Ribavirin (4. day stopped)<br>• IL-1 inhibitor (5 days)<br><br>Patient survived |
| Plt | 164.000 | 9.000 | 37.000 | 130.000 | |
| Hb | 11.7 | 11.8 | 10.0 | 8.800 | |
| AST | 39 | 592 | 1238 | 99 | |
| ALT | 23 | 140 | 576 | 169 | |
| LDH | 274 | 274 | 2771 | 513 | |
| CK | 95 | 301 | 505 | 46 | |
| BUN | 32 | 60 | 58 | 38 | |
| Cr | 0.6 | 1.0 | 0.6 | 0.4 | |
| T. Bil/ D. Bil | 0.4/0.09 | 0.49/0.11 | 2.4/0.52 | 1.04/0.24 | |
| PT | | 16.6 | 9.36 | 8.69 | |
| aPTT | | 75 | 28.1 | 27 | |
| INR | | 1.8 | 1.05 | 0.9 | |
| Fibrinogen | | 110 | 184 | 255 | |
| CRP | 44 | 99 | 9 | | |
| Procalcitonin | | 0.51 | | | |

**CCHF RT-PCR (+)**

# CCHF Story! Sharing experiences in our center



CCHF Team on Work

**2014- today**

Project ID: 1R01AI180125-01A1

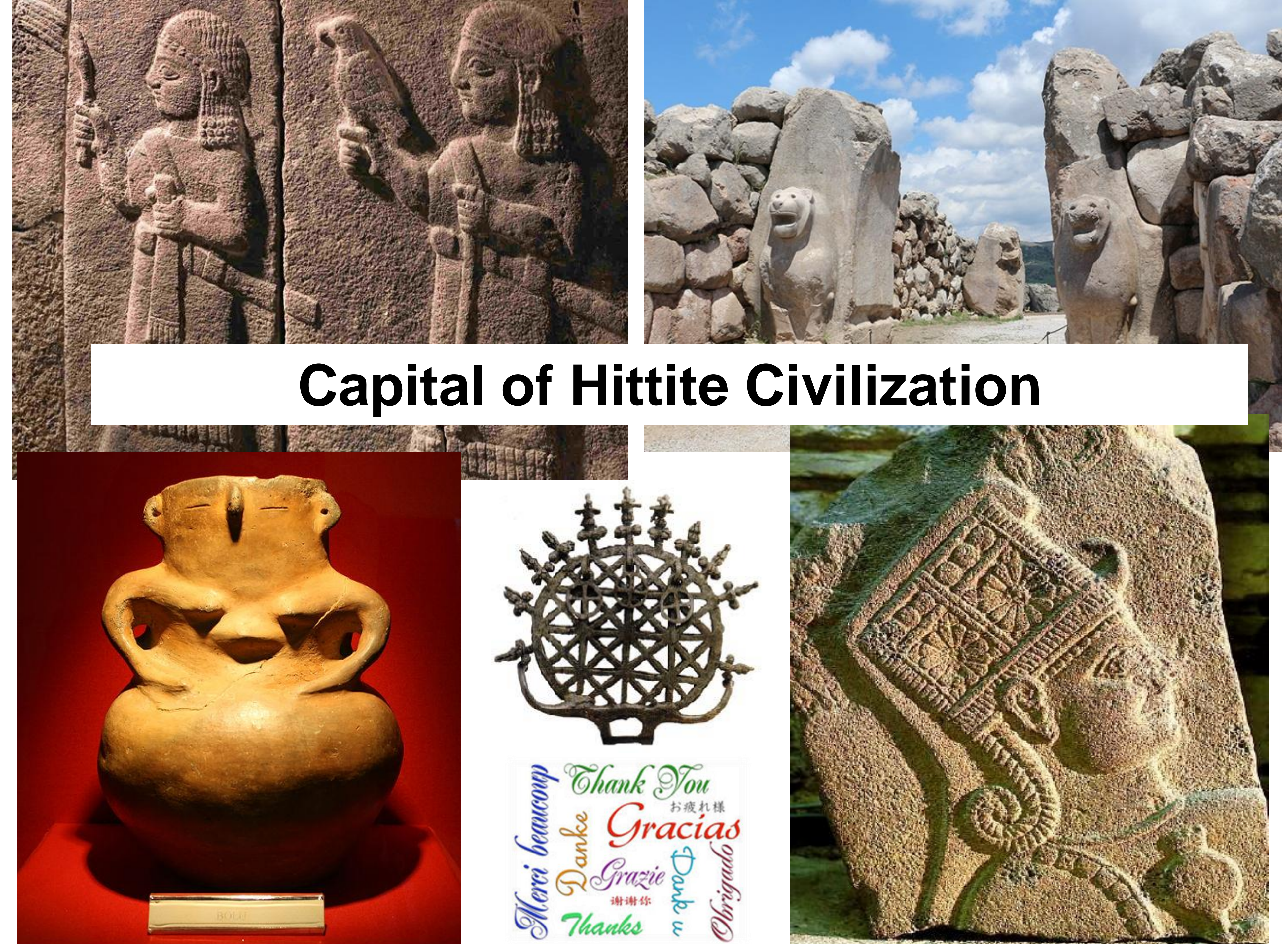
Prof. Dr. Mohammad Sajadi

Prof. Dr. Nurcan Baykam

## Isolation of broadly protective monoclonal antibodies for Crimean Congo Hemorrhagic Fever

TECNOLOGY CENTRE

# THANK YOU!


Capital of Hittite Civilization
Thank You
お疲れ様
Gracias
Merci beaucoup
Danke
Grazie
Dank u
Obrigado
谢谢你
Thanks

# Management of CCHF Cases (Hitit University)

- **HIGH INDEX OF SUSPICION. EARLY DIAGNOSIS AND TREATMENT ESSENTIAL**
  - Timely diagnosis is crucial, to put in place isolation measures and because treatment, both supportive and antiviral, should be promptly started to improve survival rates.
- **HITIT INDEX AND SEVERITY SCORING INDEX IMPORTANT FOR CLASSIFICATION AND PROPER TREATMENT.**
  - Due to unspecific symptoms and possible delay in confirmation tests (RT-PCR, serology), Hitit Index can be used to identify high-probability cases (HI >0).
  - **Severity scoring index** is used to predict mortality and to aid treatment decisions.
- **CLINICAL AND LABORATORY FOLLOW UP SHOULD BE GUIDED BY CLINICAL CONDITION (AT LEAST DAILY)**
  - This can allow early detection and treatment of complications (bleeding, consciousness impairment, thrombocytopenia, APTT prolongation, treatment side effects).
  - Universal precautions should be used when handling samples in the laboratory.
- **ABDOMINAL ULTRASOUND MAY PREDICT SEVERITY**
  - Abdominal US findings may include perivesicular fluid, thickening of gallbladder walls and intraperitoneal fluid

# Management of CCHF Cases (Hitit University)

- TREATMENT SHOULD BE GUIDED BY SEVERITY AND PHASE OF DISEASE
  - **Ribavirin**, the only currently used antiviral for CCHF, has shown benefit mainly if used in the early stage of disease, particularly for moderate cases.
  - **Steroids** are helpful in severe cases where the predominant pathological mechanism is dysregulated immune response.
- REPLACEMENT THERAPY SHOULD BE GUIDED BY CLINICAL & LABORATORY FINDINGS
  - Platelet concentrate should be given if <10.000/mm3 even in the absence of bleeding; if bleeding higher platelet count threshold can be used. Fresh frozen plasma should be given if bleeding and APTT > 35 s. If APTT >40-45 s give FFP even in the absence of bleeding.
  - Cryoprecipitate can be used if low fibrinogen levels.
- USE REPLACEMENT AND FLUID THERAPY WITH CAUTION
  - While fluids and replacement therapy are important to correct fluid loss (decreased oral intake, vomiting, diarrhea, plasma leakage) and coagulation disorders, they should be administered with caution to avoid complications such as non-cardiogenic pulmonary edema, TRALI and others.

# Management of CCHF Cases (Hitit University)

- **RIBAVIRIN (AND OTHER TREATMENTS) SHOULD BE PROMTLY STOPPED IF SIDE EFFECTS**
  - Regular evaluation for hemolytic anemia (i.e. hemoglobin, bilirubin) or other side effects should be performed;
  - Don't wait for side effects to be severe to stop treatment (consider RBV has long half-life).
- **AVOID USING ANTIBIOTICS ROUTINELY**
  - CCHF is a viral disease and bacterial coinfection/superinfection is not frequent; therefore antibiotic treatment is not generally recommended. However, two situations may require antibiotic use: if bacterial infections is a probable differential diagnosis (i.e. doxycycline for rickettsial disease) or in critical cases were bacterial translocation may occur.
- **ISOLATION BARRIERS SHOULD BE ESTABLISHED UPON SUSPICION**
  - Contact + droplet precautions should be established. If aerosol-producing procedures, FFP2/N95 masks should be used. Patients should be admitted in individual rooms. No visits should be allowed and personnel treating the patients should be limited.

# Management of CCHF Cases (Hitit University)

- **STRICT AND “COMPLEX” ISOLATION PRECAUTIONS MAY NOT BE REQUIRED**
  - Although some European countries consider CCHF cases should be cared for in HLIUs, experienced teams can manage cases with the isolation precautions mentioned before.
  - “Evidence-based” precautions, and dynamically adapted to patient’s condition, have been proven effective and are adequate for taking care of CCHF patients
- **PATIENTS CAN BE SAFELY DISCHARGED IF CLINICAL IMPROVEMENT AND PLATELETS >100.000/mm3.**
  - Relapses and late complications are extremely rare, so after patient “turns the corner”, is stable and laboratory parameters are improving, it is safe to discharge them. Polyclinic consultation can be performed ≈2 w after discharge.
- **PATIENTS SHOULD MAINTAIN PRECAUTIONS AT HOME**
  - Patients are instructed to avoid sharing the same bathroom, sharp objects and sexual contact for at least 2-3 weeks. This is consistent with evidence about CCHFV RNA presence in different fluids

RESEARCH

# Monitoring Crimean-Congo haemorrhagic fever virus RNA shedding in body secretions and serological status in hospitalised patients, Turkey, 2015

www.eurosurveillance.org

Euro Surveill. 2020;25

Dilek Yagci-Caglayik[1,2,3], Bircan Kayaaslan[4], Derya Yapar[5], Aysel Kocagul-Celikbas[5], Aslinur Ozkaya-Parlakay[6], Mestan Emek[7], Nurcan Baykam[5], Hasan Tezer[8], Gulay Korukluoglu[2], Aykut Ozkul[3,9]

1. Marmara University Pendik Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey
2. Public Health General Directorate of Turkey, Virology Laboratory, Ankara, Turkey
3. Ankara University Faculty of Veterinary Medicine, Department of Virology, Ankara, Turkey
4. Yıldırım Beyazıt University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey
5. Hitit University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Corum, Turkey
6. Health Sciences University, Ankara Children's Hematology Oncology Training and Research Hospital, Department of Pediatric Infectious Diseases, Ankara, Turkey
7. Akdeniz University Faculty of Medicine, Department of Public Health, Antalya, Turkey
8. Gazi University Faculty of Medicine, Department of Pediatric Infectious Diseases, Ankara, Turkey
9. Ankara University, Biotechnology Institute, Ankara, Turkey

We report persistence of viral RNA in urine, faeces and genital swabs despite serum clearance. This may indicate a need for extending isolation precautions, re-evaluating discharge criteria and transmission risk after discharge, and considering oral swabs as a less invasive diagnostic alternative.

## TABLE 2

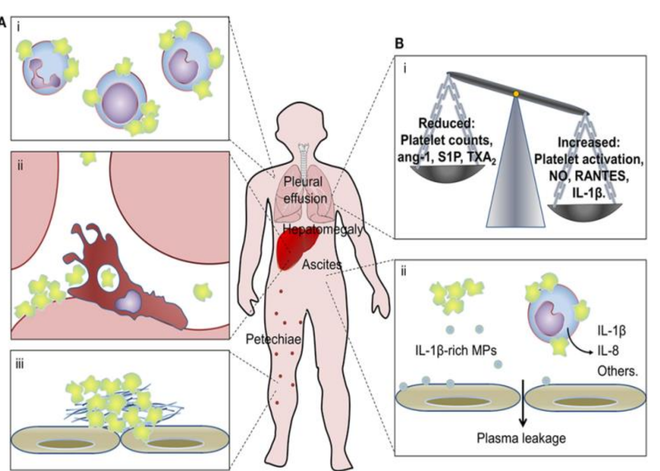
Viral RNA clearance days in ribavirin-treated patients with Crimean-Congo haemorrhagic fever, Turkey, 2015 (n =11)

| Patient code | Ribavirin start (day after symptom onset) | Viral RNA clearance (day after symptom onset) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Serum | Nasal | Oral | Urine | Vaginal | Urethral | Faecal |
| C1 | 1 | <3 | <3 | <3 | <3 | NA [a] | Not tested | <3 |
| C3 | 1 | <4 | <4 | <4 | <4 | NA [a] | Not tested | 5 |
| C2 | 1 | 6 | 5 | 4 | <3 | NA [a] | Not tested | <3 |
| H3 | 2 | 5 | 5 | 5 | <3 | NA [b] | <4 | <4 |
| Y6 | 3 | <6 | <5 | <5 | <6 | NA [b] | <7 | <5 |
| H1 | 4 | 8 | <5 | 6 | <5 | NA [b] | <5 | <5 |
| H2 | 4 | >14 | 11 | 10 | >14 | 14 | NA [c] | 14 |
| H5 | 5 | 13 | 12 | 8 | >13 | 13 | NA [c] | 12 |
| N1 | 6 | >9 | 9 | 8 | >9 | NA [b] | >9 | >9 |
| N2 | 6 | >9 | >9 | 8 | 7 | 7 | NA [c] | <6 |
| H4 | 10 | 18 | 18 | 15 | 12 | NA [b] | 11 | 19 |

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 Dokuzoguz[4]

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




- Higher proinflammatory cytokine level in mortal cases.
- Correlation between IL-6, IL-1, TNF-alpha and DIC

- **Many cytokines are released during the acute phase of CCHF**
- **Key players in disease progression (IL)-10, IL-1, IL-6 and TNF-a**
- **In fatal cases of CCHF, serum markers of pro-inflammatory mediators (such as TNF-a, IL-6) and vascular activation (sICAM-1 and sVCAM-1) are increased.**

Ergonul O, et al. J Infect Dis 2006;193: 941-4
Papa A, et al. J Clin Virol. 2015 March ; 64: 137–143.
Papa A, et al. Journal of Medical Virology.2016;88:21–27

Contents lists available at ScienceDirect

Virus Research

journal homepage: www.elsevier.com/locate/virusres

The role of $T_{reg}$ population in pathogenesis of Crimean Congo hemorrhagic fever

Umut Gazi[a], Derya Yapar[b], Djursun Karasartova[c], Ayse Semra Gureser[c], Ozlem Akdogan[b], Ozgur Unal[d], Nurcan Baykam[b,*], Aysegul Taylan Ozkan[a,c]

[a] Department of Medical and Clinical Microbiology, Faculty of Medicine, Near East University, Nicosia, Cyprus
[b] Department of Infectious Diseases and Clinical Microbiology, Hitit University, Corum, Turkey
[c] Department of Medical Microbiology, Hitit University, Corum, Turkey
[d] Infectious Diseases and Clinical Microbiology, Hitit University Erol Olcok Corum Training and Research Hospital, Corum, Turkey

- Possible association between Foxp3 dephosphorylation and CCHF pathogenesis.
- More studies are required to evaluate the effect of Foxp3 dephosphorylation on Treg function, which would not only help to enlighten the CCHF pathogenesis but also contribute to the development of effective treatment strategies.

Trop Biomed. 2022 Dec 1;39(4):587-591. doi: 10.47665/tb.39.4.016.

**Reduced phosphorylated Foxp3 levels in Crimean Congo haemorrhagic fever**

U Gazi [1], N Baykam [2], D Karasartova [3], O Tosun [4], O Akdogan [2], D Yapar [2], S Sensoz [5], A K Celikbas [2], A Semra-Gureser [3], A Taylan-Ozkan [6]

# Pathogenesis of Crimean-Congo Hemorrhagic Fever

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,[1] and Basak Dokuzoguz[1]

The role of $T_{reg}$ population in pathogenesis of Crimean Congo hemorrhagic fever

*Journal of Medical Microbiology* (2007), 56, 1126–1128

Case Report: Haemophagocytosis in a patient with Crimean–Congo haemorrhagic fever

Crimean-Congo hemorrhagic fever: Five patients

**The pathogenesis of CCHF is only poorly characterized:**

- **There is a lack of available animal models of disease.**
- **Virus handling requires biosafety level 4 containment laboratories**

J Clin Virol. 2006 Aug;36(4):272-6. Epub 2006 Jun 9.

**Cytokine levels in Crimean-Congo hemorrhagic fever.**

**It is evident that many processes contribute to the virus's entry into cells, replication, and immune response.**

Abstract

BACKGROUND: Crimean-Congo hemorrhagic fever (CCHF) virus causes severe disease in humans wi[t] took place in Albania in 2003. As in other viral hemorrhagic fevers cytokines may be involved and play disease.

*Karti SS, et al. Emerg Infect Dis 2004*

Clinical Microbiology and Infection 31 (2025) 2056–2062

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.org

Original article

# Key predictors of mortality in Crimean-Congo haemorrhagic fever: a retrospective multicentre cohort study

Deniz Güllü [1,2,3,*], Defne Yigci [1,*], Nurcan Baykam [4], Aysel Kocagül Çelikbaş [4], Derya Yapar [4], Özlem Akdoğan [4], Kemalettin Özden [5], Rukiye İnan Sarıkaya [6], İmran Hasanoğlu [7], Rahmet Güner [7], Ebru Doğan [8], Faruk Karakeçili [9], Handan Alay [5], Zeynep Türe Yüce [10], Esma Eryılmaz Eren [11], Ayşe Erbay [12], Şebnem Eren Gök [12], Çiğdem Kader [12], Gamze Ünüvar Kalın [10], Azize Yetişgen [13], Müge Özgüler [14], Arzu Şenol [14], Ömür Gündağ [14], Merve Çağlar Özer [15], Firuze Soyak [16], Büşra Tanır [14], Işıl Deniz Alıravcı [17], Güle Çınar [18], Barçın Öztürk [19], Esra Gürbüz [20], Bahadır Orkun Özbay [21], Fatihan Pınarlık [2,3], Mert Kuşkucu [3,22], Önder Ergönül [3,23,*]

- Objective: This study aimed to identify key predictors of mortality in patients with Crimean-Congo haemorrhagic fever (CCHF). Our specific goals included characterizing the demographic and clinical features of hospitalized CCHF patients in Türkiye, determining the factors associated with mortality among these patients, and evaluating the impact of early ribavirin administration.
- Methods: A retrospective study was conducted on 1103 CCHF patients across 18 hospitals in Türkiye from 1 January 2019 to 20 November 2024. All data were obtained via an online data collection system by the designated physician at each centre. Patients with laboratory-confirmed CCHF infection who were hospitalized were included in the study. Univariate analyses and time-dependent Cox regression were conducted.
- Results: Of the 1103 patients, 65.7% (725/1102) were men; 87.2% (962/1103) resided in rural areas; and the mean age was 53 years. Ticks were identified as the transmission route in 68.4% (755/1103) of the cases. Comorbidities included diabetes mellitus, chronic heart disease, and hypertension; 4.6% (51/1103) of the patients developed healthcare-related infections. Intensive care unit admission was required in 8.0% (88/1103) of the patients, and the overall mortality rate was 5.1% (56/1103). In univariate analyses, age ≥50 years (odds ratio [OR], 3.1; 95% CI, 1.58—6.08; $p < 0.001$) and diabetes mellitus (OR, 4.49; 95% CI, 2.20—9.18; $p < 0.001$) were associated with increased mortality. Both variables remained statistically significant predictors in the multivariate analysis. Although early ribavirin administration, ≤96 hours from symptom onset, did not reach statistical significance in univariate analysis (OR, 0.52; 95% CI, 0.26—1.05; $p = 0.065$), it was significantly associated with reduced mortality in time-dependent Cox regression (adjusted hazard ratios, 0.21; 95% CI, 0.07—0.69; $p = 0.010$).
- Discussion: Key factors such as age and comorbidities can predict mortality in CCHF patients. Timely identification of these redictors, along with early administration of ribavirin, may contribute to improved survival and better clinical outcomes.

# CCHF DIAGNOSİS

**Molecular diagnostic methods**

- RT-PCR (nested)
- Real-time PCR

**Detection of antibodies from serum samples**

- ELISA IgM
- ELISA IgG
- IFA
- Passive hemagglutination inhibition
- Immunofluorescence
- Neutralization
- Complement fixation
- Immunodiffusion

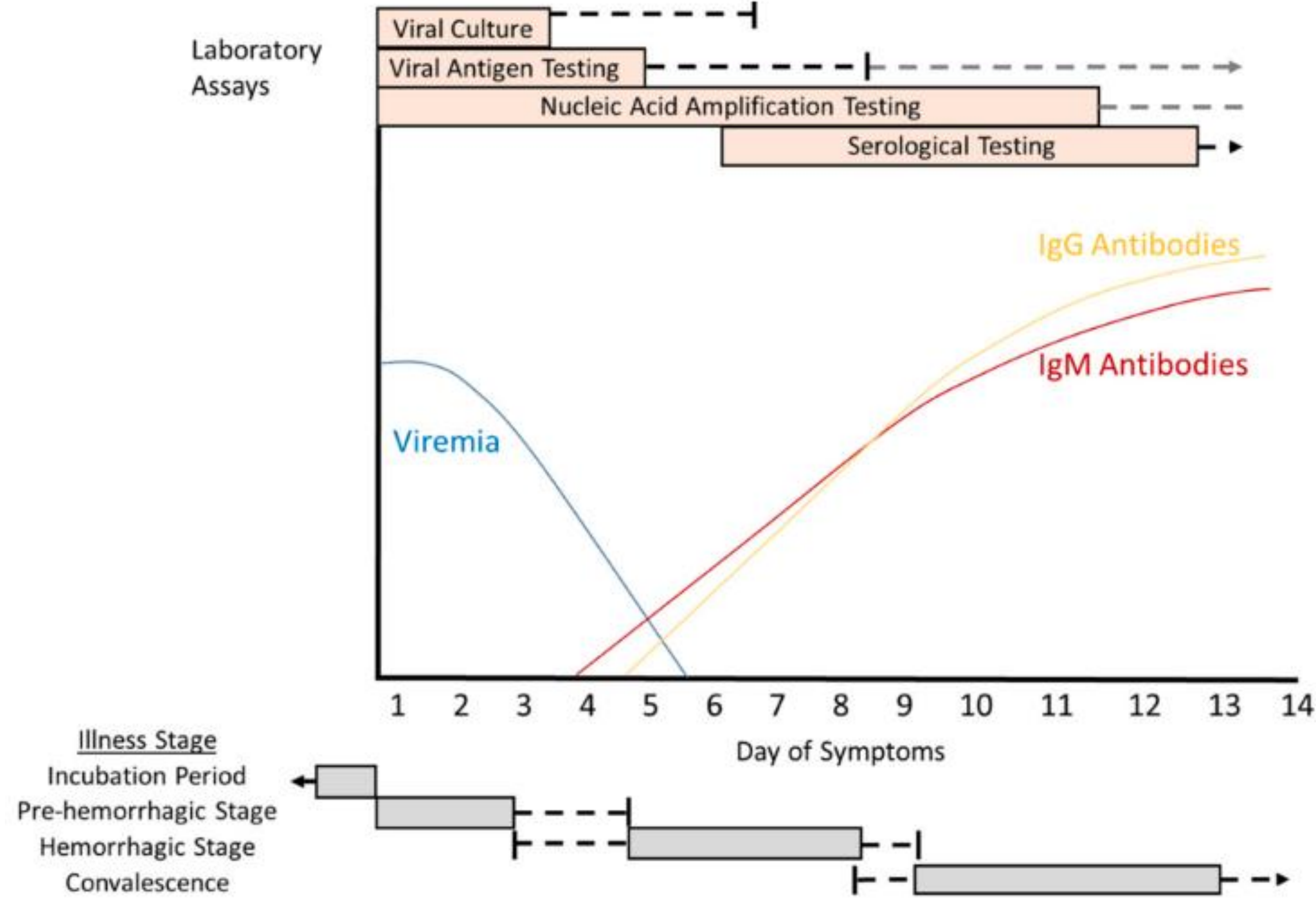
**Virus isolation from blood samples**

- Inoculation into mouse brain
- Cell culture (Vero E6, BHK 21, SW 13)

**Laboratory diagnosis during the acute phase of the disease**

**RT-PCR +/- CCHF IgM**

**(in the blood or in tissues collected from a fatal case)**




**IgM detection: 2-3 months to 6 months…**

In severe CCHF patients, antibody production is delayed or even absent.

# Detection of serum IgG in patients with CRIMEAN-CONGO HEMORRHAGONAL FEVER INFECTION

Hitit University Faculty of Medicine
Infectious Diseases and Clinical Microbiology

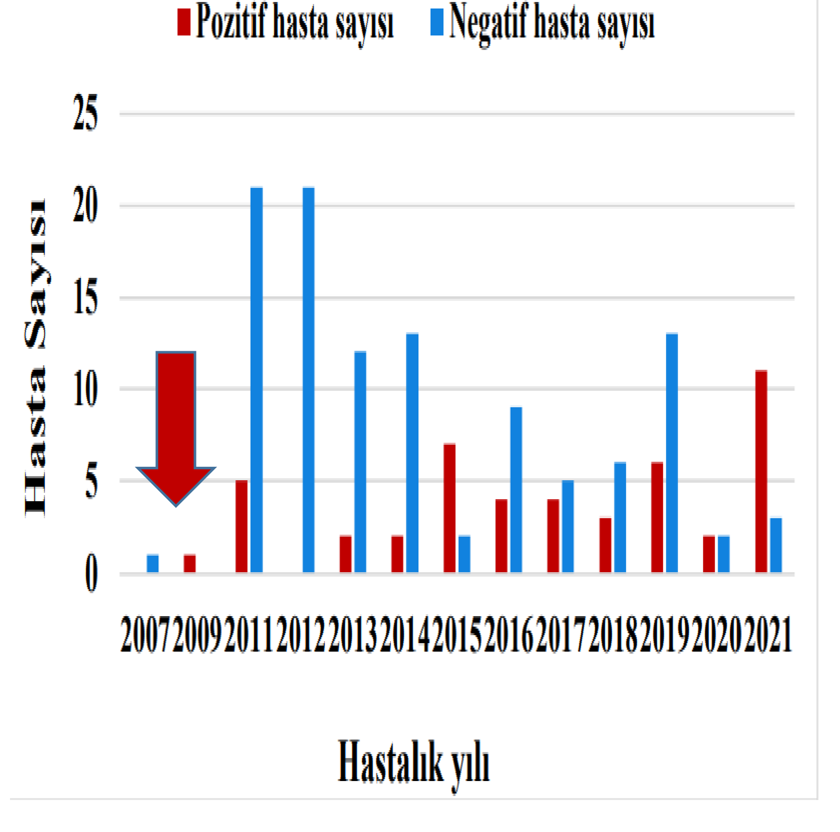
DR. GÜLCAN KAPLAN

ENFEKSİYON HASTALIKLARI ve KLİNİK MİKROBİYOLOJİ
TIPTA UZMANLIK TEZİ

- Between 2011 and 2021, 153 patients were treated and discharged with a diagnosis of CCHF (2 patients from 2009 to 2007).

RESULTS

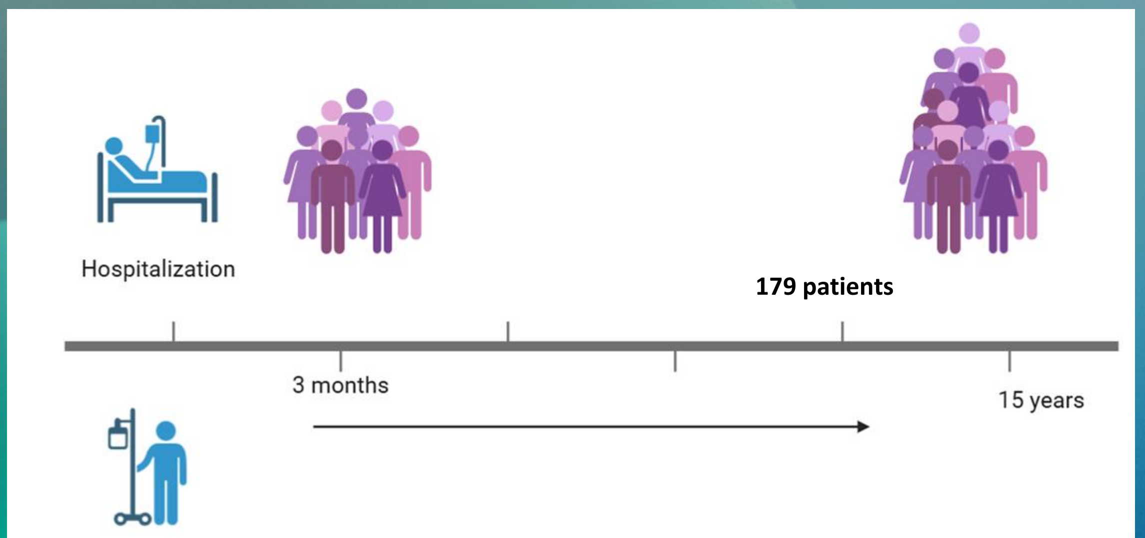
- 47 (30.3%) patients were found to have positive CCHF IgG antibodies.
- The positivity rate was found to be high if the duration of the illness was less than 7 years.
- The positivity rate was observed to decrease if the duration of the illness was longer than 8 years.
- The average duration of CCHF IgG is approximately 7 years.



# Long-Lasting Immunity Following Natural CCHFV Infection

Hanife Nur Karakoç Parlayan, Arash Aslanabadi, Derya Yapar, Quiyana Murphy , Gülcan Kaplan, Özlem Akdoğan, Aysel Çelikbaş, Ayse Koroglu, Firdevs Aksoy, Elif Karaaslan, Abdolrahim Abbasi, Maryam Karimi, Mahsa Hojabri, Gürdal Yılmaz, Stanca M. Ciupe, Scott D. Pegan, Éric Bergeron, George Lewis, Mohammad M. Sajadi, Nurcan Baykam

**Objective: To evaluate the duration of antibody response in individuals with CCHFV infection.**




| Method | Details |
|---|---|
| Antibody binding by Luminex | • CCHFV Proteins: Nucleoprotein (NP), glycoproteins (Gc, Gn, and GP38)<br>• CCHFV strains: IbAr10200, Turkey-2004, Afg09, and Kosovo/Hoti |
| Antibody neutralization by VLPs | • CCHFV strains: IbAr10200, Turkey-2004, and Kosovo/Hoti |
| We developed a mathematical model of antibody decay and computed antibody half-lives | • Antibody half-lives given by<br>• $t_{1/2} = \frac{log_{10}(2)}{k} + 3$ (Eq. 3). |

- **We detected neutralizing and non-neutralizing binding antibodies in all patients**
- **The binding half-life of the responses ranged from 19 to 304 years.**
- **GP38 had a half-life of 19 to 28 years, NP a half-life of 25 to 75 years, and Gc a half-life of 304 years.**
- **These findings have important implications for both vaccine design and seroepidemiology studies.**

Congress of the European Society of Clinical Microbiology and Infectious Diseases

P0254

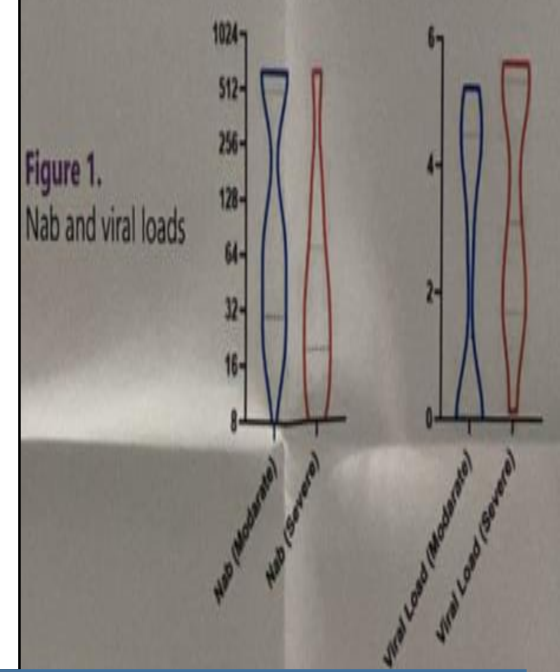
34th ECCMID Barcelona, Spain 27 – 30 April 2024

Evaluation of Viral Load and Neutralizing Antibody Levels in Crimean-Congo Hemorrhagic Fever Patients

M.A. Kuşkucu 1, A.K. Çelikbaş 2, S. Yalçın 1, T. Barlas 1, N. Baykam 2, F. Can 1, Ö. Ergönül 1.
1Koç University, School of Medicine, KUISCID - Istanbul (Turkey) - Istanbul (Turkey) - Istanbul (Turkey) - Istanbul (Turkey), 2Hitih University, School of Medicine - Çorum (Turkey) - Çorum (Turkey)

# KKKA HASTALARINDA VİRAL YÜK VE NÖTRALİZE EDİCİ ANTİKOR SEVİYELERİNİN DEĞERLENDİRİLMESİ

- İyileşen 24 KKKA vakasında viral yük, ciddiyet ve nötralizan antikor yanıtı (NAT)
- Nötralizan antikor (NAb) 1/10 ‘nun altında kalan sonuçlar negatif kabul edildi
- Hastaların 12’si ağır seyirli, 12’si ılımlı klinik seyirli idi
- Viral yük ılımlı hastalarda 24.700, ciddi seyirli vakalarda 111.500
- NAT ılımlı hastalarda 1/30, ciddi seyirli vakalarda 1/20




- Ciddi vakalar NAb yanıtının az ve viral yük fazla olması ile korele bulundu
- NAb; Ölümcül KKKA enfeksiyonların korunmasında rol oynayabileceği düşünüldü

# CCHF Case Management

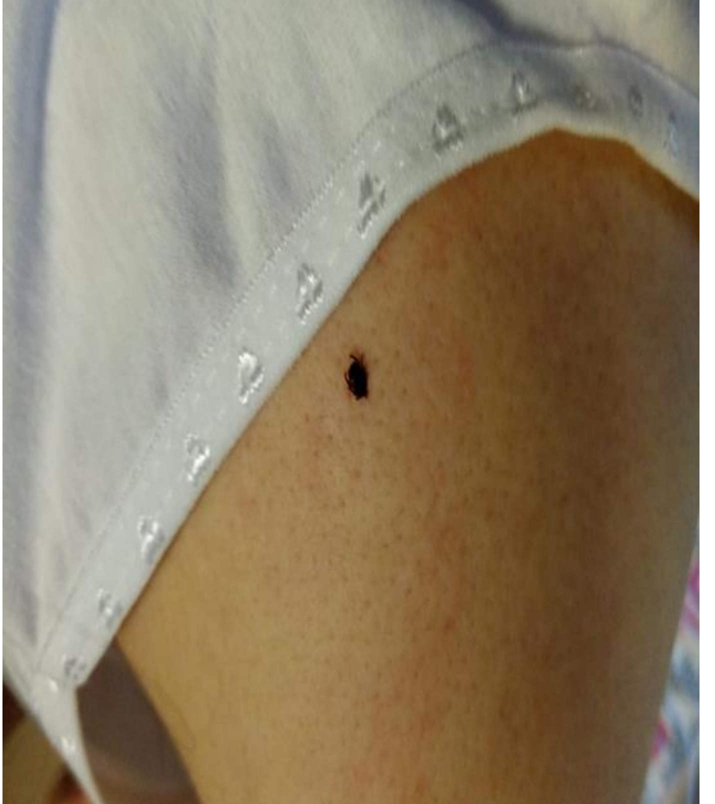
# CCHF Management

HİTİT ÜNİVERSİTESİ

- Hospitalizing patients in single-bed room
- Informing and training of healthcare workers
- Ensuring the use of PPE

# CCHF Management

**Checking the entire body for tick!!!**



# CCHF Treatment

## Supportive

- Fluid and electrolyte therapy
- FFP, Platelet replacement
- Cryoprecipitate
- Therapeutic plasma exchange (TPE)
- Respiratory support

## Antiviral

- Ribavirin
- Favipiravir
- 2’-deoxy-2’ –fluorositidin
- Overian tümör-like deubikuitinaz (OTU)
- Chlorokin
- Clorpromazin

## Anti-inflamatuar

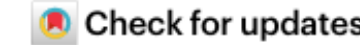
- Metilprednizolon /dexamethazone
- Interleukin inhibitors

## Immunotherapy

- Intravenous immunoglobulin (IVIG)
- Monoclonal antibodies

Gholizadeh O. Microbial Pathogenesis. 2022

nature reviews microbiology https://doi.org/10.1038/s41579-023-00871-9

Review article  Check for updates

# Crimean–Congo haemorrhagic fever virus

David W. Hawman & Heinz Feldmann

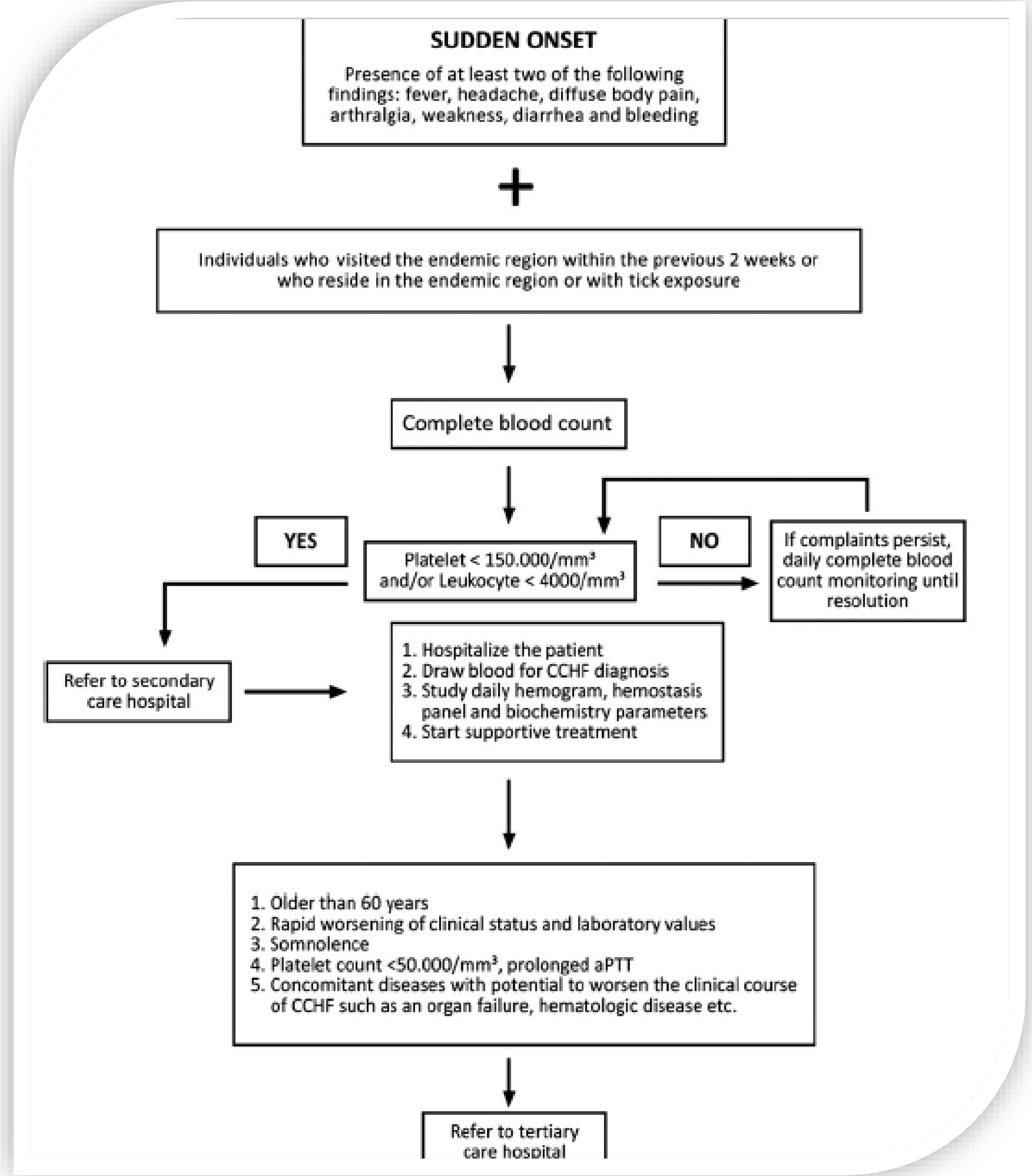
Nature Reviews Microbiology | Volume 21 | 2023 | 463–477

**Table 1 | Treatments for Crimean–Congo haemorrhagic fever**

| Compound | Class | Target | Preclinical efficacy | Clinical efficacy | Comments | Refs. |
|---|---|---|---|---|---|---|
| Ribavirin | Nucleoside analogue | RdRP | Controversial efficacy in rodent models | Controversial efficacy in patients | Poor efficacy; early treatment start needed; should be discontinued or used in combination therapy | 110,114,116,145 |
| Favipiravir | Nucleoside analogue | RdRP | Efficacy in rodent and NHP models | Limited data or benefit | Late treatment start effective in rodent models; clinical trials are needed | 114,116,147,148 |
| 2′-Deoxy-2′-fluorocytidine | Nucleoside analogue | RdRP | Not done | No clinical data | More preclinical studies are needed | 115 |
| Molnupiravir | Nucleoside analogue | RdRP | No efficacy in rodent models | No clinical data | Unlikely to proceed | 147 |
| Plasma or antibodies from survivors | Neutralizing or non-neutralizing | Viral proteins | Not done | Limited data or benefit | More preclinical and/or clinical studies are needed | 153 |
| Monoclonal antibodies | Neutralizing or non-neutralizing | Viral proteins | Limited data in rodent models | No clinical data | More preclinical and/or clinical studies are needed | 33,40,117 |
| Corticosteroids | Anti-inflammatory | Host response | Not done | Limited data or benefit | More preclinical and/or clinical studies are needed | 84,155 |

NHP, non-human primate; RdRP, RNA-dependent RNA polymerase.

# CCHF Patients are managed according to the algorithm for case management of the Ministry of Health CCHF Scientific Committee in secondary or tertiary care hospitals in Turkey



## KKKA VAKA TAKİP FORMU

**KKKA PCR:**

| AD SOYAD | | YAŞ | | Tc no: | |
|---|---|---|---|---|---|
| CİNSİYET | | MESLEK | | | |
| YATIŞ TARİHİ | | YATIŞ GÜN SAYISI | | | |
| Şikayetin başladığı tarıh | | Hastaneye başvuru tarihi | | | |
| Yaşadığı şehir | | Endemik bölgede yaşama | Evet ☐ Hayır ☐ | | |
| BULAŞ YOLU | Kene Teması ☐ | Kan Yolu ☐ | Enfekte Sıvı ☐ | Bilinmiyor☐ | |
| TANI | PCR pozitif ☐ | Seroloji pozitif ☐ | OLASI TANI | | |
| EK HASTALIK | DM ☐ | KOAH☐ | KAPAK HAST ☐ | ALKOL☐ | |
| DİĞER | KBH☐ | STEROİD☐ | KC HAST☐ | SİGARA☐ | |
| Hayvancılık ☐ | | Tarım ile Uğraş: ☐ | Kırsal bölge Seyahati: ☐ | Arazide bulunma: | |
| BRUCELLA: ( ) HbsAg: ( ) Anti-Hbs: ( ) Anti HIV: ( ) Anti HCV: ( ) | | | | | |
| COVİD PCR: | | | | | |

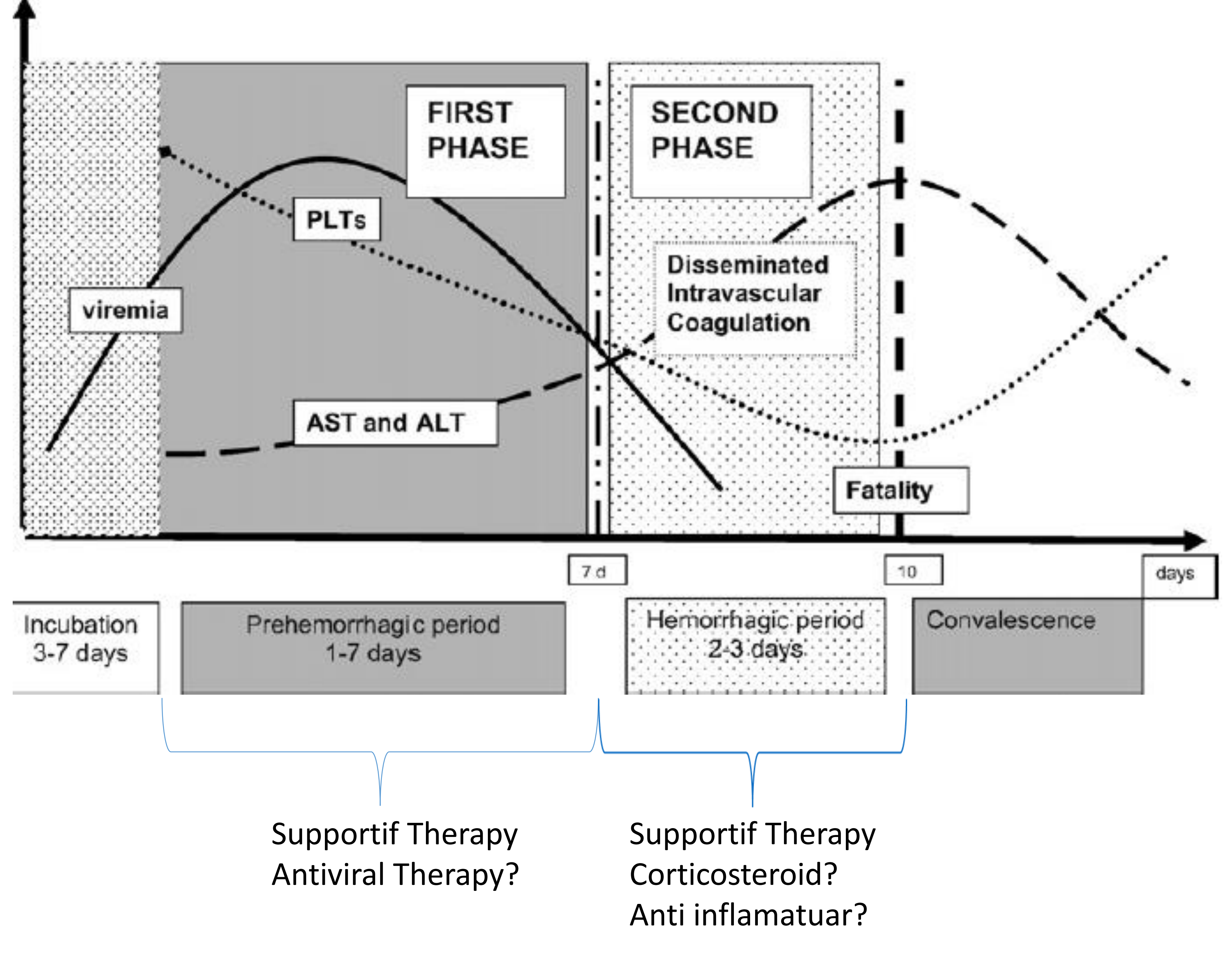
### KKKA BULGULARI

| TARİH | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| GÜN SAYISI | 1.Gün | 2.Gün | 3.Gün | 4.Gün | 5.Gün | 6.Gün | 7.Gün | 8.Gün | 9.Gün | 10.Gün |
| ATEŞ | | | | | | | | | | |
| PETEŞİ | | | | | | | | | | |
| DİŞ ETİ | | | | | | | | | | |

### LABORATUVAR BULGULARI VE TEDAVİ

| TARİH | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| GÜN SAYISI | 1.Gün | 2.Gün | 3.Gün | 4.Gün | 5.Gün | 6.Gün | 7.Gün | 8.Gün | 9.Gün | 10.Gün |
| Trombosit | | | | | | | | | | |
| Lökosit | | | | | | | | | | |
| Ly# | | | | | | | | | | |
| Ne# | | | | | | | | | | |
| RBC | | | | | | | | | | |
| Hemoglobin | | | | | | | | | | |
| Htc | | | | | | | | | | |
| GLUKOZ | | | | | | | | | | |
| AST | | | | | | | | | | |
| ALT | | | | | | | | | | |
| LDH | | | | | | | | | | |
| CK | | | | | | | | | | |
| Üre | | | | | | | | | | |
| Kreatinin | | | | | | | | | | |
| TGFH(ckd-epi) | | | | | | | | | | |
| T. Bilirübin | | | | | | | | | | |
| D. Bilirübin | | | | | | | | | | |
| PT | | | | | | | | | | |
| aPTT | | | | | | | | | | |
| INR | | | | | | | | | | |
| Kolesterol | | | | | | | | | | |
| LDL | | | | | | | | | | |
| HDL | | | | | | | | | | |
| TG | | | | | | | | | | |
| FİBRİNOJEN | | | | | | | | | | |
| D-DİMER | | | | | | | | | | |
| CRP | | | | | | | | | | |

Infectious Diseases and Clinical Microbiology Department,
Hitit University Erol Olçok Training and Research Hospital


FIRST PHASE
SECOND PHASE
PLTs
viremia
Disseminated Intravascular Coagulation
AST and ALT
Fatality
7 d
10
days
Incubation 3-7 days
Prehemorrhagic period 1-7 days
Hemorrhagic period 2-3 days
Convalescence
Supportif Therapy
Antiviral Therapy?
Supportif Therapy
Corticosteroid?
Anti inflamatuar?

# Ribavirin

- Ribavirin is a synthetic purine nucleoside analogue and is the only antiviral drug used in the treatment of CCHF cases.
- **It inhibits CCHFV replication in vivo and in vitro in a concentration-dependent manner.**
- Its effectiveness in humans is largely based on clinical observations.
- Some studies say it is helpful, while others say it doesn't.
- The clinical efficacy of ribavirin is debatable.

Soares-Weiser et al. BMC Infectious Diseases 2010, 10:207

# Some Ribavirin Efficacy Studies in CCHF

http://intl.elsevierhealth.com/journals/

The epidemiology of Crimean-Congo hemorrhagic fever in Turkey, 2002—2007☆

Gul Ruhsar Yilmaz[a,*], Turan Buzgan[a], Hasan Irmak[a], Ahmet Safran[a], Ramazan Uzun[a], Mustafa Aydin Cevik[b], Mehmet Ali Torunoglu[a]

In 2004-2007, ribavirin use in Turkey decreased from 68% to 12%, but there was no change in the CCHF mortality rate (5%).

J Antimicrob Chemother 2011; 66: 1215–1222
doi:10.1093/jac/dkr136 Advance Access publication 11 April 2011

Journal of Antimicrobial Chemotherapy

Ribavirin for patients with Crimean–Congo haemorrhagic fever: a systematic review and meta-analysis

Sibel Ascioglu[1,2*], Hakan Leblebicioglu[3], Haluk Vahaboglu[4] and K. Arnold Chan[2]

It does not support the view that ribavirin is effective in the treatment of CCHF. Because when comparing patients using and not using ribavirin, no change was observed in the recovery rate, length of hospital stay and need for blood / blood products.

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

ELSEVIER

The efficacy of ribavirin in the treatment of Crimean-Congo hemorrhagic fever in Eastern Black Sea region in Turkey

In this randomized prospective study conducted in the Black Sea region of Turkey, no positive effect was found on clinical and laboratory parameters in CCHF patients given ribavirin, and even the length of hospital stay was prolonged in patients given ribavirin. Mortality rates of patients using and not using ribavirin were similar.

DOI 10.1007/s10096-009-0728-2

ARTICLE

The role of ribavirin in the therapy of Crimean-Congo hemorrhagic fever: early use is promising

N. Tasdelen Fisgin · O. Ergonul · L. Doganci · N. Tulek

Ribavirin was effective only when given in the early stages of the disease.
Mortality rates in the ribavirin group:
*5% when given in the first 4 days of illness
*10%, >5 days
*27% in patients not given ribavirin

# Ribavirin Efficacy

BRIEF REPORT

ibavirin Had Demonstrable Effects n the Crimean-Congo Hemorrhagic ever Virus (CCHFV) Population and oad in a Patient With CCHF Infection

METHOD

Sample Collection and Processing

The epidemiologic characteristics and clinical presen CCHFV-infected secondary case presented here has be previously [3]. Five days into the course of infection received 1000 mg of ribavirin orally every 6 hours for

In a recent case in Spain, although the infected nurse was treated with ribavirin, **the treatment showed an in vivo mutagenic effect on CCHF virus, and the reduction in viral titers was the same as at disease onset.**

Original Article

Evaluation of the Efficacy of Ribavirin Therapy on Survival of Crimean-Congo Hemorrhagic Fever Patients: a Case-Control Study

Shahrokh Izadi* and Masoud Salehi

Department of Epidemiology and Biostatistics, School of Public Health, Zahedan University of

**Ribavirin appears to have a significant effect on the course of the disease, especially when given in the first 4 days.**

Severity Scoring Index for Crimean-Congo Hemorrhagic Fever and the Impact of Ribavir and Corticosteroids on Fatality

When the Severity Score (SSI) of the cases is examined, **it is seen that ribavirin reduces the case fatality rate, especially in moderately ill patients.** However, steroid therapy is beneficial, especially in severely ill patients.

Original Article

he Outcome of Patients with Crimean-Congo Hemorrhagic Fever in Zahedan, Southeast of Iran: A Comparative Study

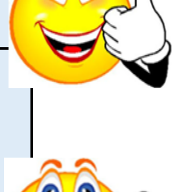
Batool Sharifi-Mood MD*, Malihe Metanat MD*, Amin Ghorbani-Vaghei MD*,

**Rapid oral ribavirin treatment increases the recovery rate of CCHF patients.**

Systematic Review and Meta-analysis of Postexposure Prophylaxis for Crimean-Congo Hemorrhagic Fever Virus among Healthcare Workers

Önder Ergönül, Siran Keske, Melis Gökçe Celdir, İlayda Arlen Kara

According to a recent meta-analysis, **ribavirin treatment should be initiated no more than 48 hours after the onset of symptoms to reduce mortality**



## TOPLINE:

Administration of ribavirin within 96 hours of symptom onset in patients with Crimean-Congo hemorrhagic fever was associated with a reduced risk for mortality, while age 50 years or more and diabetes were risk factors for mortality.

## METHODOLOGY:

- Researchers conducted a retrospective analysis to assess the predictors of mortality and effect of early ribavirin administration in patients with CCHF.
- They included data from 1103 patients with CCHF (median age, 53 years; 65.7% men) across 18 hospitals in endemic regions of Turkey between January 2019 and November 2024.
- Participants were required to have clinical suspicion of CCHF and laboratory-confirmed infection via positive reverse transcription polymerase chain reaction results.
- The primary outcome was in-hospital mortality, with particular focus on the timing of ribavirin initiation as the main exposure and other associated factors affecting mortality.

## TAKEAWAY:

- Among hospitalized patients, 8.0% were admitted to the ICU, and the overall mortality rate was 5.1%. Healthcare-related infections developed in 4.6% of patients.
- Ribavirin administration within 96 hours of symptom onset significantly reduced the risk for in-hospital mortality by 79% (adjusted hazard ratio [aHR], 0.21; *P* = .010).
- Age 50 years or more (aHR, 2.56; *P* = .011) and presence of diabetes (aHR, 2.71; *P* = .009) were associated with an increased risk for mortality.

OPEN ACCESS Freely available online

# Evaluation of Antiviral Efficacy of Ribavirin, Arbidol, and T-705 (Favipiravir) in a Mouse Model for Crimean-Congo Hemorrhagic Fever

Lisa Oestereich[1,2], Toni Rieger[1,2], Melanie Neumann[3], Christian Bernreuther[4], Maria Lehmann[1,2], Susanne Krasemann[3], Stephanie Wurr[1,2], Petra Emmerich[1,2], Xavier de Lamballerie[5], Stephan Ölschläger[1¶¤], Stephan Günther[1,2¶]*

- Licensed in Japan for the treatment of influenza
- There are studies on its effectiveness for CCHF, Hantavirus, Rift Valley fever virus (RVFV) and SARS COV-2.
- In the CCHF virus-infected IFNAR2/2 mouse experiment, co-administration of ribavirin and favipiravir had no adverse effects and was beneficial.
- In vivo efficacy of favipiravir is greater than that of ribavirin, the standard drug in CCHF treatment.
- More work is needed

Dai, S. Et al. Current Advances and Future Prospects of Antiviral Strategies. Viruses 2021
Oestereich L,et. al PLoS Negl Trop Dis 2014;8:e2804.
Mazzola LT, Kelly-Cirino C. BMJ Glob Health 2019;4

# What we are doing?

**To decide Ribavirin Therapy we should consider:**

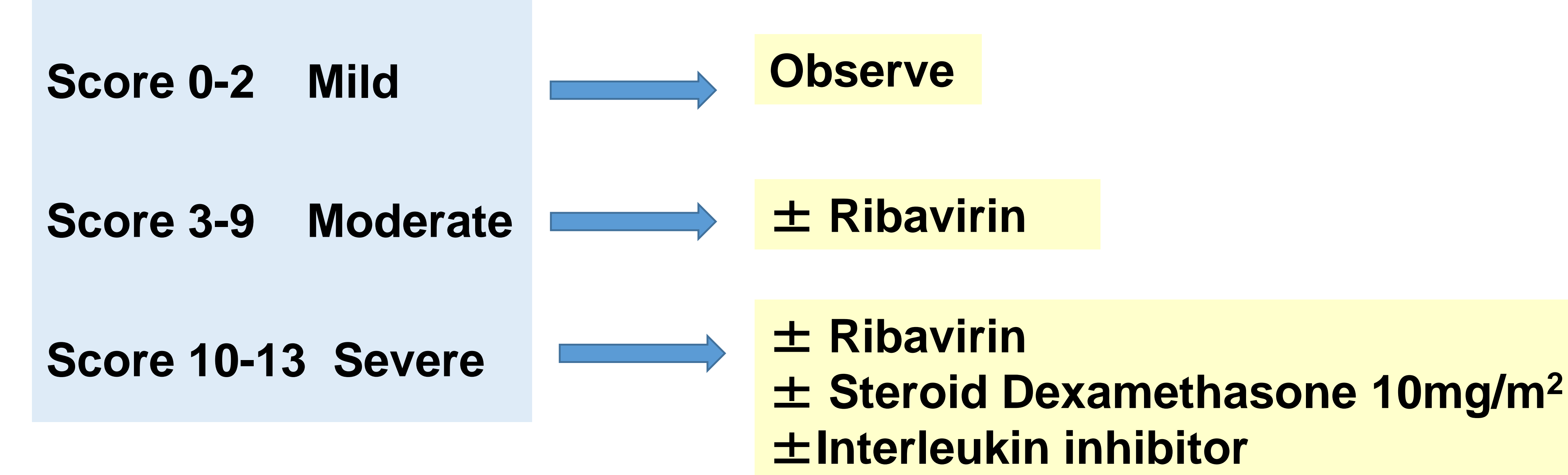
1. Day of illness
2. Severity of illness
3. Gastrointestinal bleeding for absorbtion of oral Ribavirin
4. Any contrindication for Ribavirin

- Up to 4-5 day of illness, according to the severity index of patient, we start Ribavirin.
- We stop Ribavirin when the lab parameters getting well approximately in 5-6 days.

  If they improve in 3 days, we stop Ribavirin .

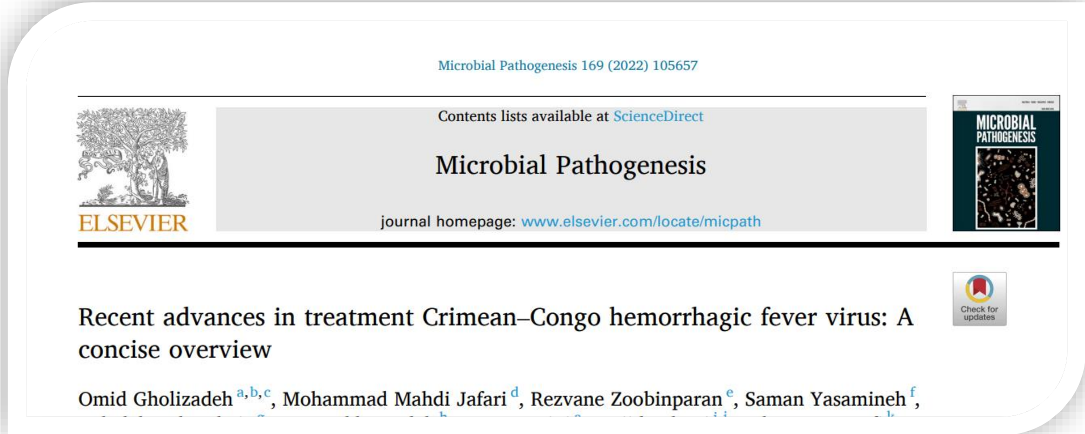
  When Plt count is increased to 100.000, we stop it

# What we are doing?




**Supportif Treatment**

- If NO bleeding and NO high fever →NO platelet replacement until <10.000/m3
- If APTT between 35-45 → 2x10 mg/kg FFP
- Fibrinogen <160 →Cryoprecipitate (Factor VIII, Factor XIII, Fib) may be given


Microbial Pathogenesis 169 (2022) 105657

Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath

Recent advances in treatment Crimean–Congo hemorrhagic fever virus: A concise overview

Omid Gholizadeh [a,b,c], Mohammad Mahdi Jafari [d], Rezvane Zoobinparan [e], Saman Yasamineh [f],

# Anti-inflamatuar treatment

## Metilprednizolon /dexamethazone

- In the treatment of critically ill patients, it inhibits the production of inflammatory cytokines such as PAF and IL, as well as PG and leukotrienes.
- It suppresses macrophage activation.
- When combined with supportive therapies and antiviral drugs, it reduces fever and inflammation, significantly decreasing the severity of the disease.

Gholizadeh O.  Microbial Pathogenesis. 2022

Anti-inflamatuar treatment

## Interleukin Inhibitors

APRIL 2025

HİTİT UNIVERSITY

# Promising Results with Anakinra in Severe Cases of Crimean-Congo Haemorrhagic Fever

**D. Yapar[1], Ö. Akdoğan[1], A. Kocagül Çelikbaş[1], N. Baykam[1]**

[1]Hitit University School of Medicine, Department of Infectious Diseases and Clinical Microbiology - Corum (Turkey)

In our clinic, **159 confirmed CCHF** patients were observed between 2017 and 2020, and **112 confirmed cases** were observed between 2021 and 2024. When evaluating severity scores in the range of 9-13, it was found that 10 out of 18 cases (55%) in the first period and 3 out of 20 cases (15%) in the second period resulted in fatalities. Anakinra was administered for three days to 20 severe patients.

| | Anakinra (-) (n=18) (%) | Anakinra (+) (n=20) (%) | *P-value* |
|---|---|---|---|
| **Age (year)** | 60.4±11.5 (37-79) | 52.4±15.5 (22-74) | 0.03 |
| **Transmission route** | | | |
| **Tick bite** | 13 (72.2%) | 13 (65%) | 0.63 |
| **Animal contact** | 2 (11.1%) | 5 (25%) | 0.27 |
| **Unknown** | 4 (22.2%) | 4 (22.2%) | 0.57 |
| **Treatment** | | | |
| **Ribavirin** | 12 (66.7%) | 7 (35%) | 0.07 |
| **Steroid** | 18 (100%) | 20 (100%) | |
| **Lab results** | | | |
| **ALT (U/L)** | 659 (95-3302) | 1115 (137-3443) | |
| **AST (U/L)** | 1718 (162-8272) | 3635 (292-14035) | |
| **Leukocyte-min /µl** | 2513 (350-7720) | 4538 (610-41000) | |
| **Leukocyte-max /µl** | 8369 (2390-14020) | 10268 (4260-33300) | |
| **Thrombocyte /µl** | 11500 (2000-21000) | 10350 (2000-22000) | |
| **Fibrinogen (mg/dl)** | 159 (61-271) | 146 (77-252) | |
| **LDH (U/L)** | 3538 (714-16670) | 5907 (792-18183) | |

| | Anakinra (-) (n=18) (%) | Anakinra (+) (n=20) (%) | *P-value* |
|---|---|---|---|
| **Fever** | 13 (72.2%) | 16 (80%) | 0.57 |
| **Myalgia** | 14 (77.8%) | 15 (75%) | 0.84 |
| **Abdominal pain** | 8 (44.4%) | 8 (40%) | 0.78 |
| **Vomiting** | 7 (38.9%) | 14 (70%) | **0.05** |
| **Diarrhea** | 3 (16.7%) | 7 (35%) | 0.2 |
| **Conjunctivitis** | 7 (38.9%) | 12 (60%) | 0.19 |
| **Acute renal failure** | 4 (22.2%) | 4 (20%) | 0.86 |
| **Somnolance** | 6 (33.3%) | 13 (65%) | **0.05** |
| **Rash** | 6 (33.3%) | 8 (40%) | 0.67 |
| **Haemorrhage** | 6 (33.3%) | 13 (65%) | **0.05** |
| **Severity Scoring Index** | **9.1** | **10.1** | **0.28** |
| **Mortality** | **10 (55.6%)** | **3 (15%)** | **0.009** |

- ✓**All the patients were SEVERE (SSI>9)**
- ✓**The mortality rate was considerably lower in patients who received anakinra compared to those who did not (*p*=0.009).**

Congress of the European Society of Clinical Microbiology and Infectious Diseases

ESCMID Global

# Hitit University, Erol Olçok Research and Education Hospital

# CCHF and Healthcare Workers

- **Contact + droplet precautions should be established.**

  - CCHF patients should be isolated
  - HCWs should use PPE, including gowns, gloves, surgical masks or face shields, and eye protection, while giving care to the patients or handling their blood and other sanguineous body fluids.

- **If aerosol-producing procedures, FFP2/N95 masks should be used.**
- **Patients should be admitted in individual rooms, but cohort isolation is acceptable if required.**
- **No visits should be allowed and personnel treating the patients should be limited.**

Kocagul CA, Dokuzoğuz B, Baykam N, et al. Emerging Infectious Diseases. 2014; 20(3):477-9.
Gozel MG, et al. International Journal of Infectious Diseases 17 (2013) e1046–e1050.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 3, March 2014

# Crimean-Congo Hemorrhagic Fever among Health Care Workers, Turkey

Aysel Kocagul Celikbas, Başak Dokuzoğuz, Nurcam Baykam, Sebnem Eren Gok, Mustafa Necati Eroğlu, Kenan Midilli, Herve Zeller, and Onder Ergonul

- **9 cases of Crimean-Congo hemorrhagic fever**
- **1 fatal, 2 asymptomatic**
- **Six of the 9 cases had histories of needlestick injuries or contact with contaminated blood without adequate barrier precautions**
- **Needlestick injuries were reported for 4 workers**
- **8 received ribavirin**

| Episode, outcome† | HCW age, y/sex/profession | Procedure | Transmission route | Ribavirin for postexposure prophylaxis | Ribavirin for therapy (d after symptom onset) | Fatal |
|---|---|---|---|---|---|---|
| Episode 1; survived, her baby died | 36/M/nurse | Wound care | Contact with surgical wound without protective equipment | No | Yes (0) | No |
| | 31/F/nurse | Intubation, aspiration | Aerosol and droplet and contact without protective equipment | No | No | No |
| Episode 2; died | 28/F/nurse | Phlebotomy | Needlestick | No | Yes (3) | Yes |
| Episode 3; died | 41/M/physician | Resuscitation | Aerosol and droplet | – | Yes (0) | No |
| | 26/M/physician | Nasal tamponade | Indirect contact | – | Yes (0) | No |
| | 29/M/physician | Nasal tamponade | Indirect contact | – | Yes (0) | No |
| Episode 4; survived | 30/M/nurse | Phlebotomy | Needlestick | No | Yes (1) | No |
| Episode 5; survived | 30/F/nurse | Phlebotomy | Needlestick | Yes | – | No |
| Episode 6; survived | 24/F/physician | Phlebotomy | Needlestick | Yes | – | No |

## Post exposure prophylaxis

# What are we doing?

**Ribavirin is useful for post-exposure prophylaxis**

**2g/day for 7 days**
**We use ribavirin**
**but there is no consensus on the dose**