Kırım-Kongo Kanamalı Ateşi

KLİMİK Aylık Toplantısı

Doç. Dr. Aziz A. Hamidi

SBÜ. Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği

28 Mayıs 2024

Sunum Planı

- Tanım
- Epidemiyoloji
- Etken
- Patogenez
- Klinik
- Tedavi
- Koruma (aşı)

Tanım

- Ateş
- Kanama } ile karakterize
- Zonooz
- Kene tutunması ile bulaşan

Etken

- Bunyavirales
- Orthonairovirus genusu
- Nairoviridae ailesi

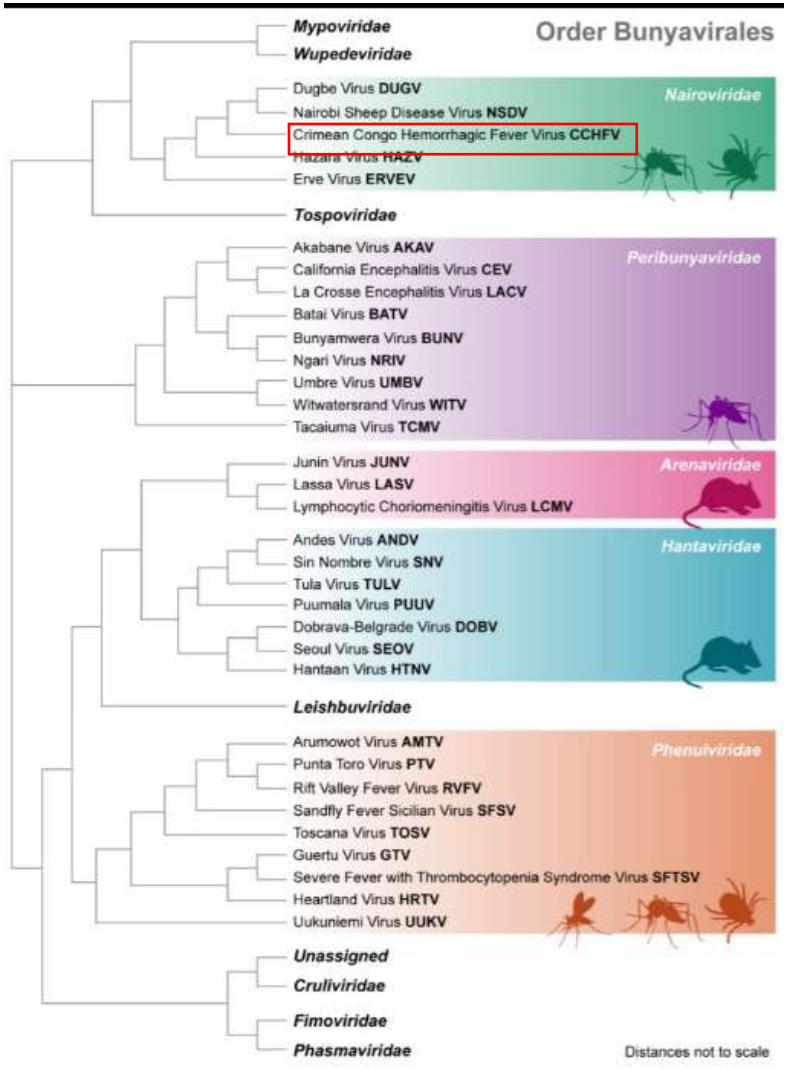
viruses

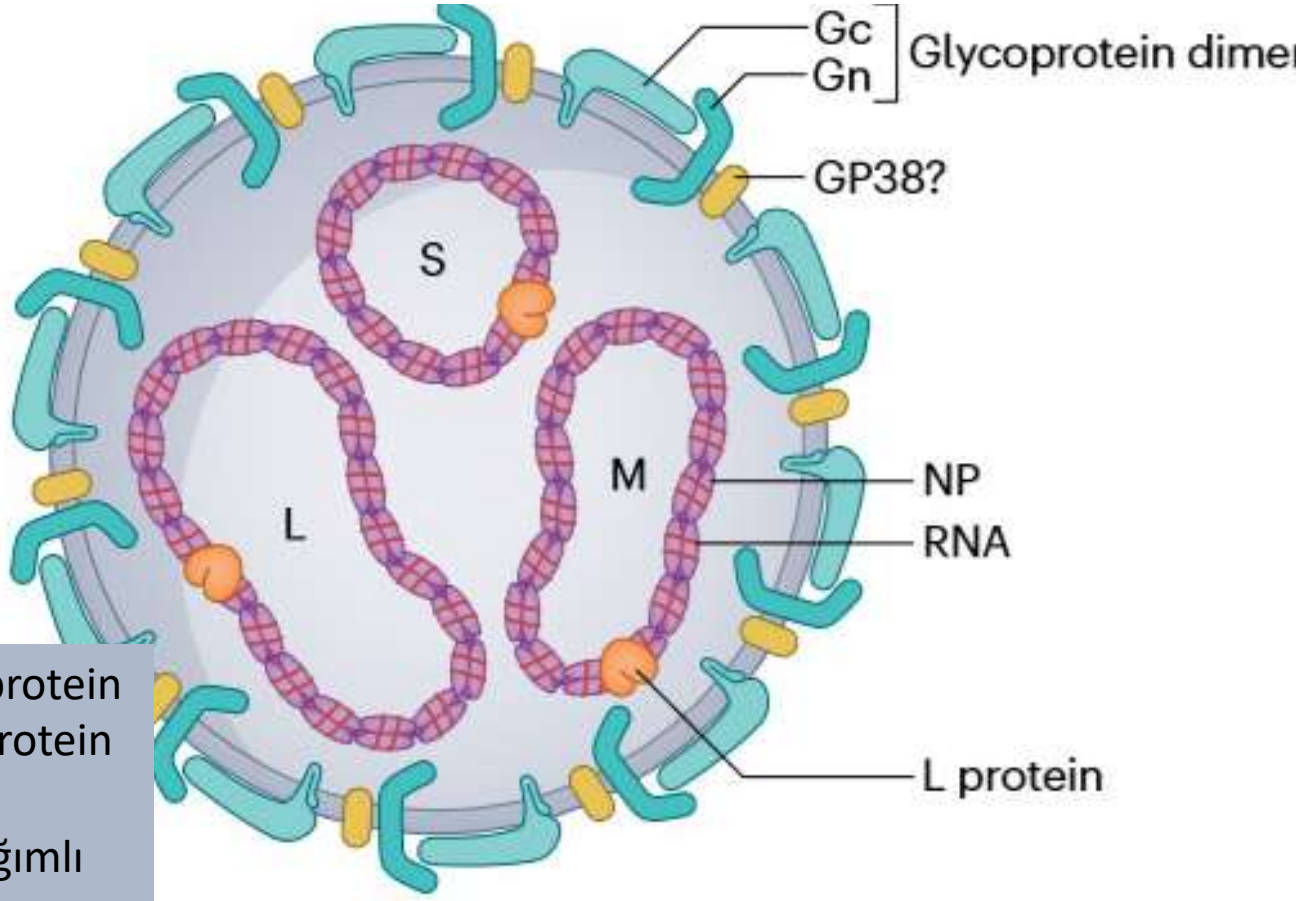
MDPI

Review

A Look into *Bunyavirales* Genomes: Functions of Non-Structural (NS) Proteins

Shanna S. Leventhal, Drew Wilson, Heinz Feldmann and David W. Hawman *





❖S segmenti: Viral nukleoprotein
❖M segmenti: Viral glukoprotein öncülleri
❖L segmenti: Viral RNA bağımlı RNA polimeraz

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

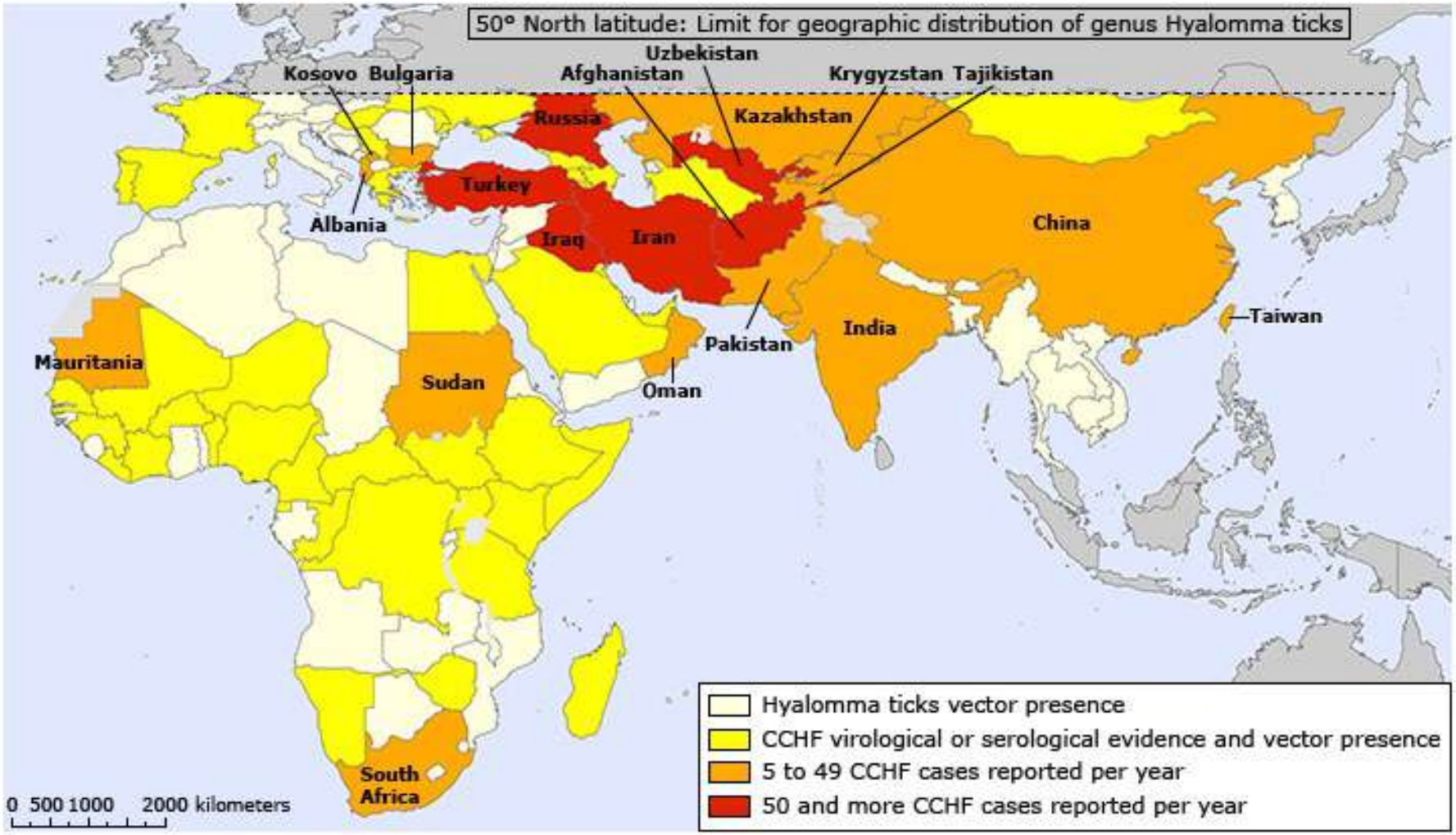
Etken

- ✓Dış ortama dayanıksız
- ✓Ultraviole ile hızla inaktive olur
- ✓Konak dışında uzun süre aktif kalamaz
- ✓56 ^{0}C'de 30 dakikada inaktive olur
- ✓%1 Sodyum hipoklorid ve %2 gulteraldehite duyarlı
- ✓Ortam PH'sına duyarlı

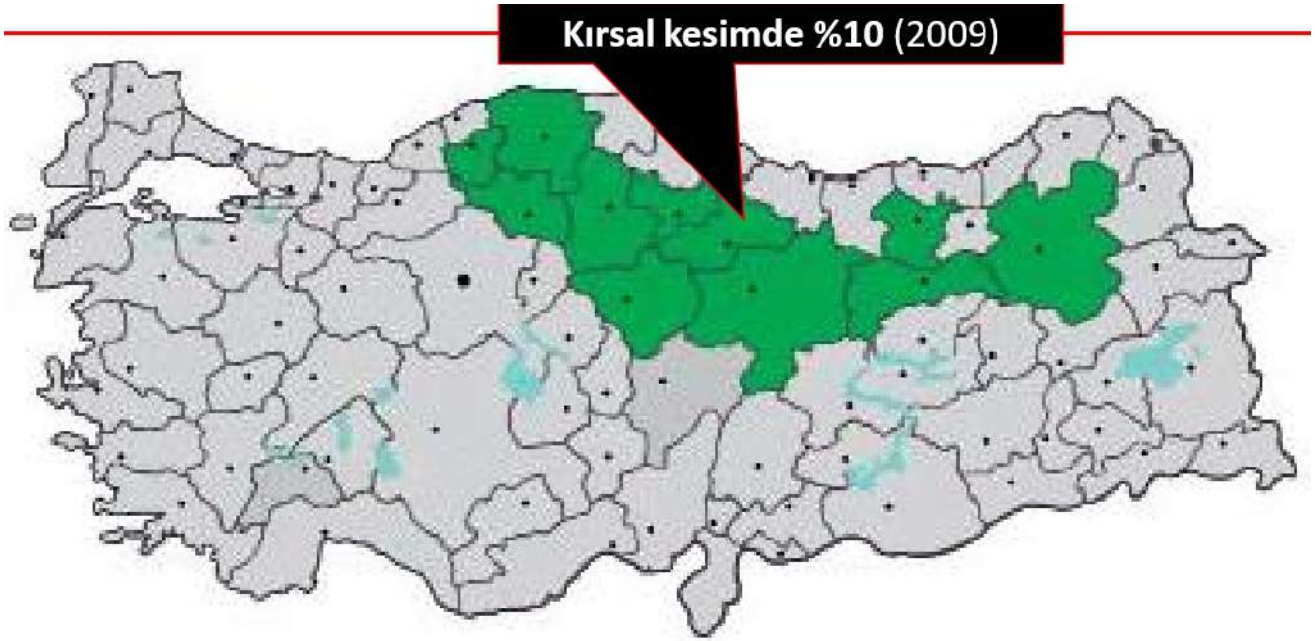
Epidemiyoloji

- Her yıl >1000 vaka
- Güneydoğu Avrupa ve Batı Asya
- Mevsimsel özellik
- İlkbahar-Yaz
- Pakistan'da biannual (Mart-Mayıs ve Ağostos-Ekim)
- Türkiye'de yazın ilk ayları

Geographic distribution of Crimean-Congo Haemorrhagic Fever

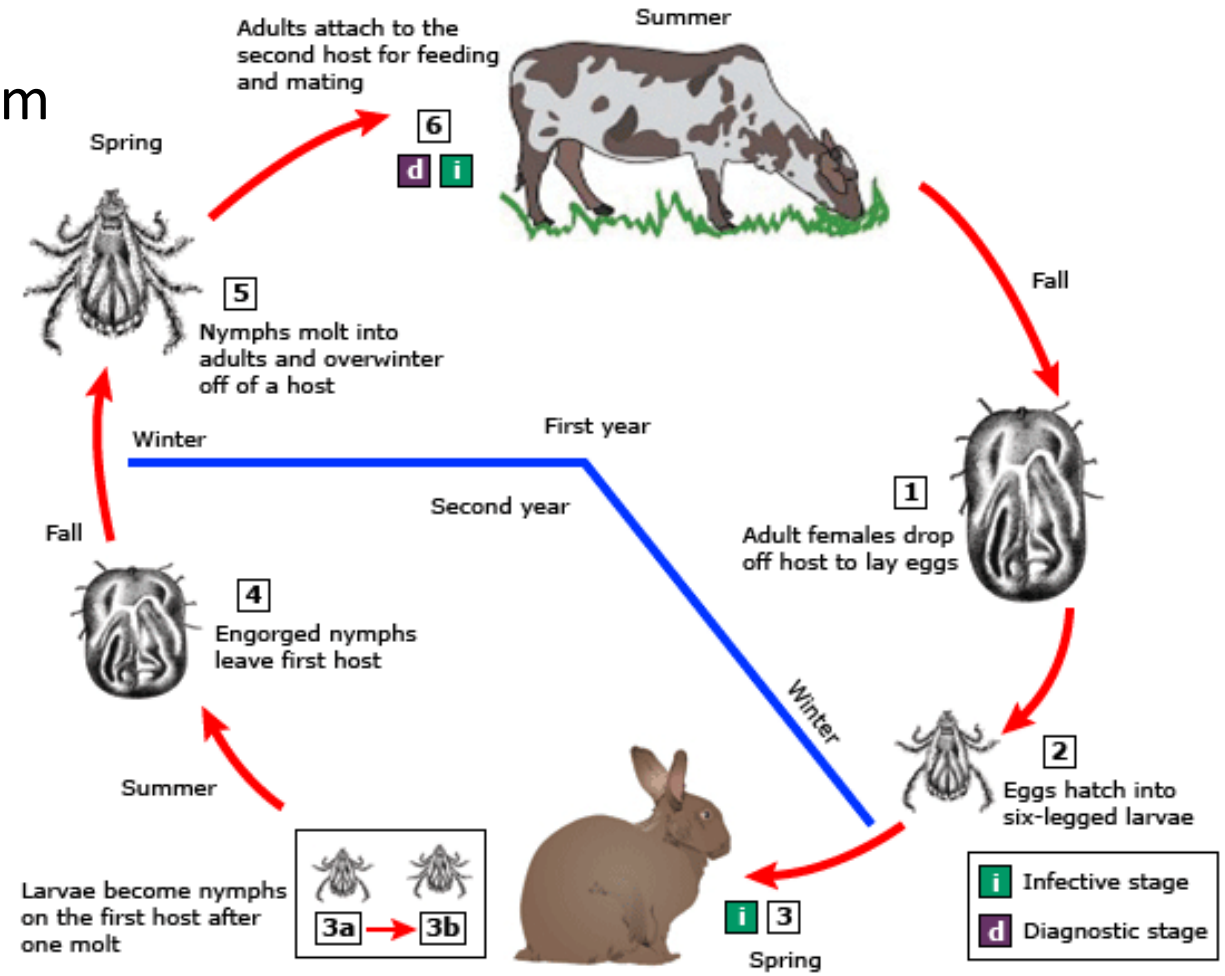


Reproduced from: Crimean-Congo haemorrhagic fever. World Health Organization. Copyright © 2022. Available at: https://www.who.int/health-topics/crimean-congo-haemorrhagic-fever/ (Accessed on June 29, 2022).


Kırsal kesimde %10 (2009)


Kirklareli
Edirne
Tekirdag
Istanbul
Canakkale
Balikesir
Bursa
Bilecik
Kocaeli
Sakarya
Yalova
Duzce
Bolu
Zonguldak
Bartin
Karabuk
Kastamonu
Cankiri
Sinop
Samsun
Amasya
Corum
Tokat
Ordu
Giresun
Trabzon
Gumushane
Bayburt
Rize
Artvin
Ardahan
Kars
Erzurum
Igdir
Agri
Erzincan
Tunceli
Bingol
Mus
Bitlis
Van
Elazig
Malatya
Sivas
Yozgat
Kirsehir
Ankara
Kirikkale
Eskisehir
Kutahya
Manisa
Izmir
Usak
Afyon
Aksaray
Nevsehir
Kayseri
Konya
Isparta
Aydin
Denizli
Burdur
Mugla
Antalya
Nigde
Karaman
Mersin
Adana
Osmaniye
Hatay
Kahramanmaras
Gaziantep
Kilis
Adiyaman
Sanliurfa
Diyarbakir
Batman
Siirt
Mardin
Sirnak
Hakkari

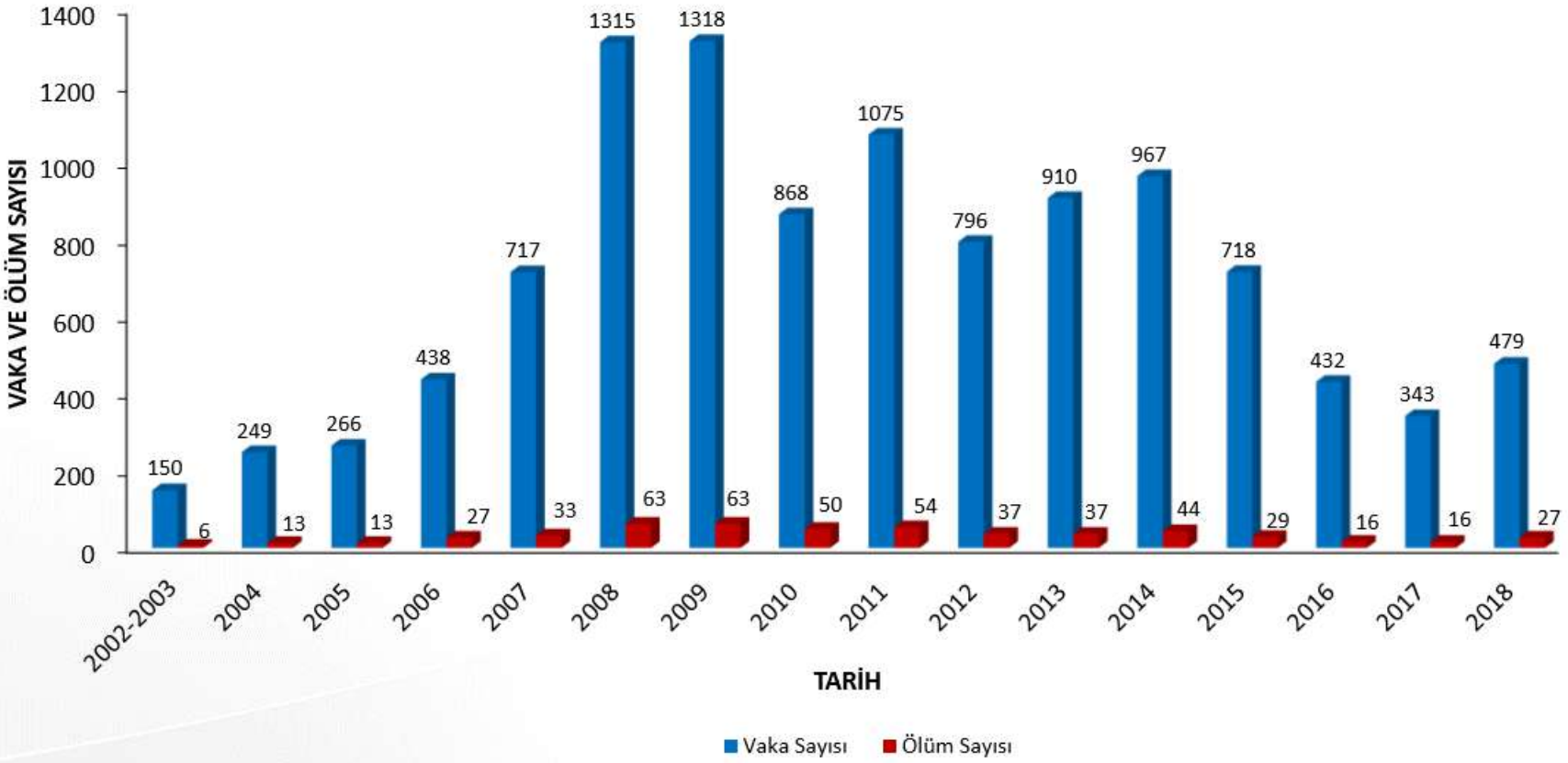
Hyalomma Marginatum



Epidemiyoloji

- Ülkemizde 2002 yılında dikkati çekti
- 2003 yılında virus tanımlandı
- 2002-2018 yılları arasında 11.041 olgu tanımlandı
- 528 ölüm
- Vaka-ölüm oranı %4,78

Kırım Kongo Kanamalı Ateşi Vaka ve Ölüm Sayıları, Türkiye, 2002-2018



Heliyon 9 (2023) e19593

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Temporal tendency, seasonality and relationship with climatic factors of Crimean-Congo Hemorrhagic Fever cases (East of Turkey: 2012–2021)

Sinan Yılmaz [a,*,1], Sibel İba Yilmaz [b,1], Handan Alay [c], Zahide Koşan [a], Zeynep Eren [d]

[a] Atatürk University Faculty of Medicine, Department of Public Health, Erzurum, Turkey
[b] Health Sciences University, Erzurum Faculty of Medicine, Clinic of Infectious Diseases, Erzurum, Turkey
[c] Atatürk University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Erzurum, Turkey
[d] Atatürk University, Faculty of Engineering, Department of Environmental Technologies, Erzurum, Turkey

Table 2
Distribution of Crimean-Congo Hemorrhagic Fever cases by years and annual averages of meteorological data.

Years	Mid-Year Population	Number of Cases	Incidence (per 100.000)	Temperature (°C)	Cumulative Precipitation (mm)	Relative Humudity (%)	Wind Speed (m/sec)
		Sum ± SE	Sum ± SE	Mean ± SE	Sum ± SE	Mean ± SE	Mean ± SE
2012	778.195	43 ± 3.0	5,5 ± 0.4	5.6 ± 0.6	276.2 ± 34.5	68.4 ± 0.8	2.8 ± 0.1
2013	766.729	68 ± 4.7	8,9 ± 0.6	5.3 ± 0.6	272.8 ± 34.5	66.2 ± 0.9	2.9 ± 0.1
2014	763.320	72 ± 7.0	9,4 ± 0.9	7.0 ± 0.6	382.9 ± 50.1	66.5 ± 0.9	2.9 ± 0.1
2015	762.321	88 ± 10.2	11,5 ± 1.3	6.2 ± 0.6	436.8 ± 53.4	66.7 ± 0.9	2.7 ± 0.1
2016	762.021	109 ± 6.8	14,3 ± 0.9	5.5 ± 0.6	475.4 ± 53.6	66.4 ± 0.8	3.4 ± 0.1
2017	760.476	59 ± 4.8	7,8 ± 0.6	5.7 ± 0.6	281.0 ± 39.4	63.3 ± 0.9	3.0 ± 0.1
2018	767.848	98 ± 7.0	12,8 ± 0.9	7.7 ± 0.5	493.3 ± 57.1	69.2 ± 0.8	3.1 ± 0.1
2019	762.062	94 ± 6.2	12,3 ± 0.8	6.3 ± 0.6	355.2 ± 48.2	65.7 ± 0.9	2.8 ± 0.1
2020	758.279	168 ± 11.7	22,2 ± 1.5	6.8 ± 0.5	333.4 ± 49.2	63.9 ± 0.9	3.3 ± 0.1
2021	756.893	175 ± 10.2	23,1 ± 1.3	7.1 ± 0.6	345.4 ± 43.8	62.8 ± 0.9	3.4 ± 0.1

Table 1
Distribution of Crimean-Congo Hemorrhagic Fever cases by age groups.

Age Groups (years)	Sex		Total n (%)**
	Male n (%)*	Female n (%)*	
0–9	9 (81.8)	2 (18.2)	11 (1.1)
10–19	65 (77.4)	19 (22.6)	84 (8.6)
20–44	185 (57.6)	136 (42.4)	321 (33.0)
45 ≤	292 (52.3)	266 (47.7)	558 (57.3)
Total	551 (56.6)	423 (43.4)	974 (100.0)

- Başlangıç Mart, zirve Temmuz ve bitiş Ekim → net bir mevsimlilik
- İklim değişikliği dolaylı bir etki yapar (hava sıcaklığı ve kümülatif yağışa bağlı nem oranı)
- İklim koşulları vektör keneler için giderek daha elverişli hale geliyor

Clinical Microbiology and Infection 26 (2020) 123.e1–123.e7

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

A prospective prediction tool for understanding Crimean–Congo haemorrhagic fever dynamics in Turkey

Ç. Ak [1], Ö. Ergönül [2], M. Gönen [3, 4, *]

[1] Graduate School of Sciences and Engineering, Koç University, İstanbul, Turkey
[2] Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Koç University, İstanbul, Turkey
[3] Department of Industrial Engineering, College of Engineering, Koç University, İstanbul, Turkey
[4] School of Medicine, Koç University, İstanbul, Turkey

Faktörler

- ✓ Kırsaldaki risk altında olan papülasyon
- ✓ Coğrafya
- ✓ İklim
- ✓ Kene

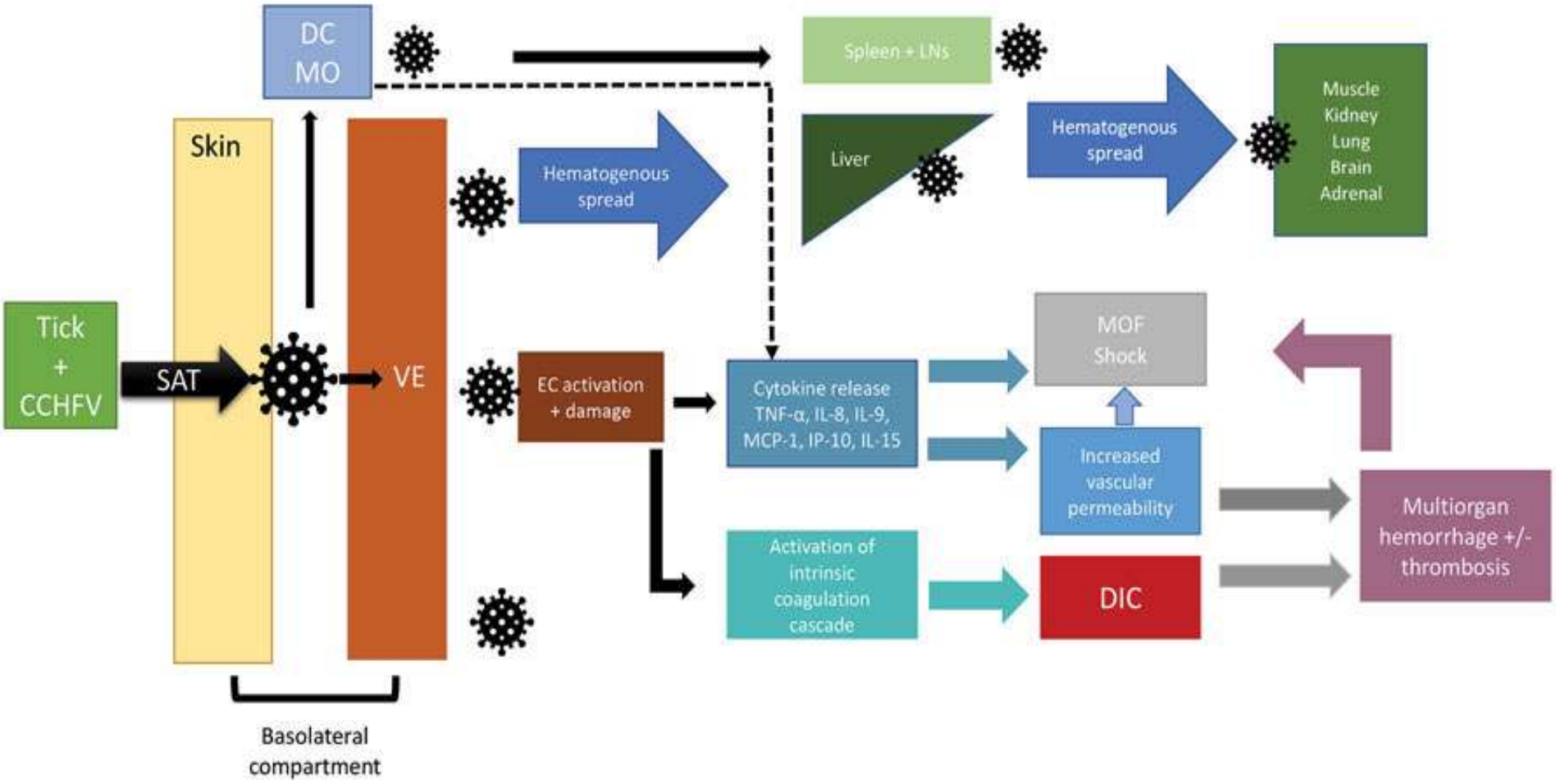
Sonuç: 2016 ve 2017 yılı vaka sayısını doğru tahmin eden model

Gaussian processes
Machine learning
Spatiotemporal epidemiology
Vector-borne disease

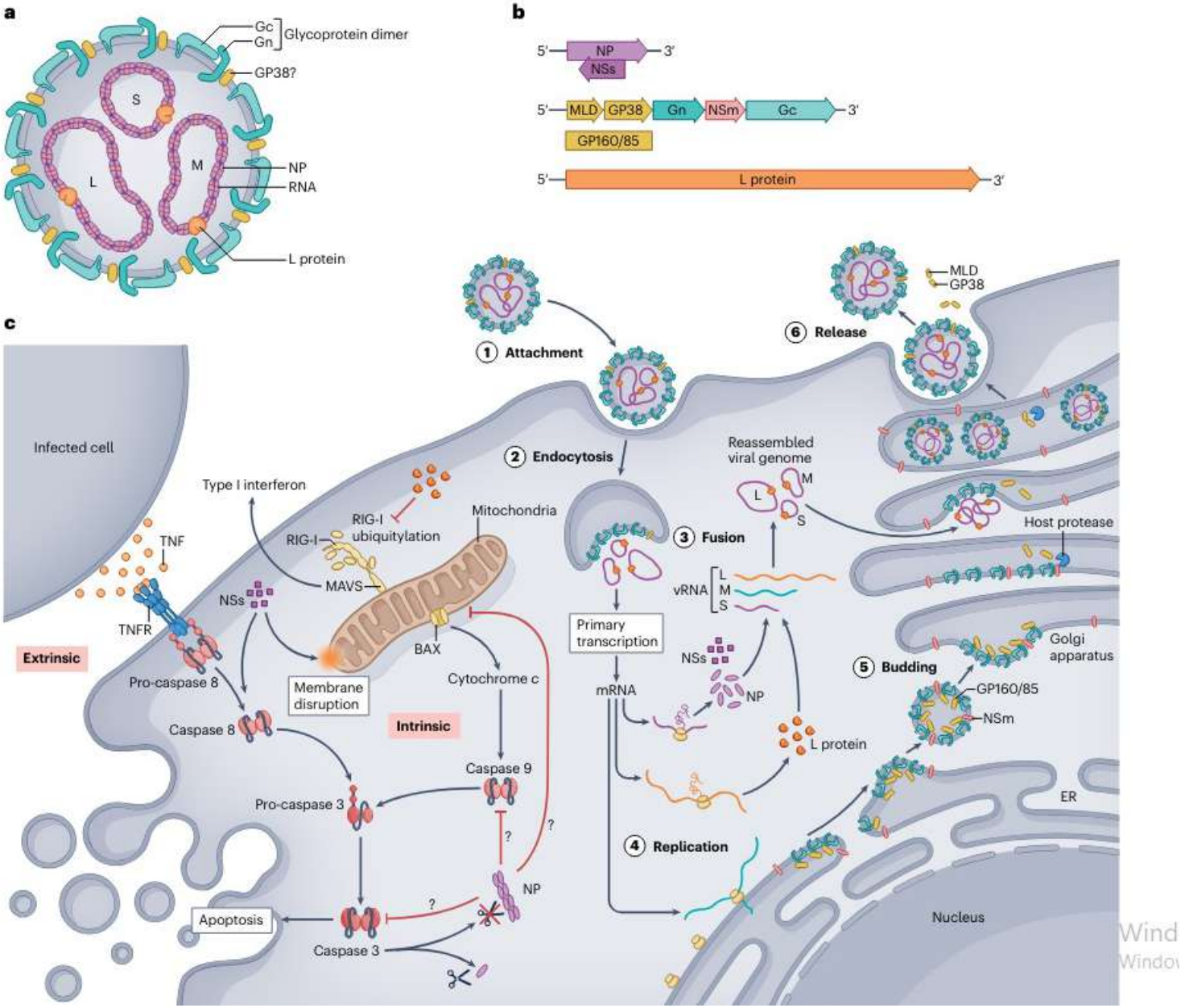
were 432 and 343, respectively. Pearson's correlation coefficient and normalized root mean squared error values for 2016 and 2017 predictions were (0.83; 0.58) and (0.87; 0.52), respectively. The most important covariates were found to be the number of settlements with fewer than 25 000 inhabitants, latitude, longitude and potential evapotranspiration (evaporation and transpiration).

Conclusions: Main driving factors of CCHF dynamics were human population at risk in rural areas, geographical dependency and climate effect on ticks. Our model was able to prospectively predict the

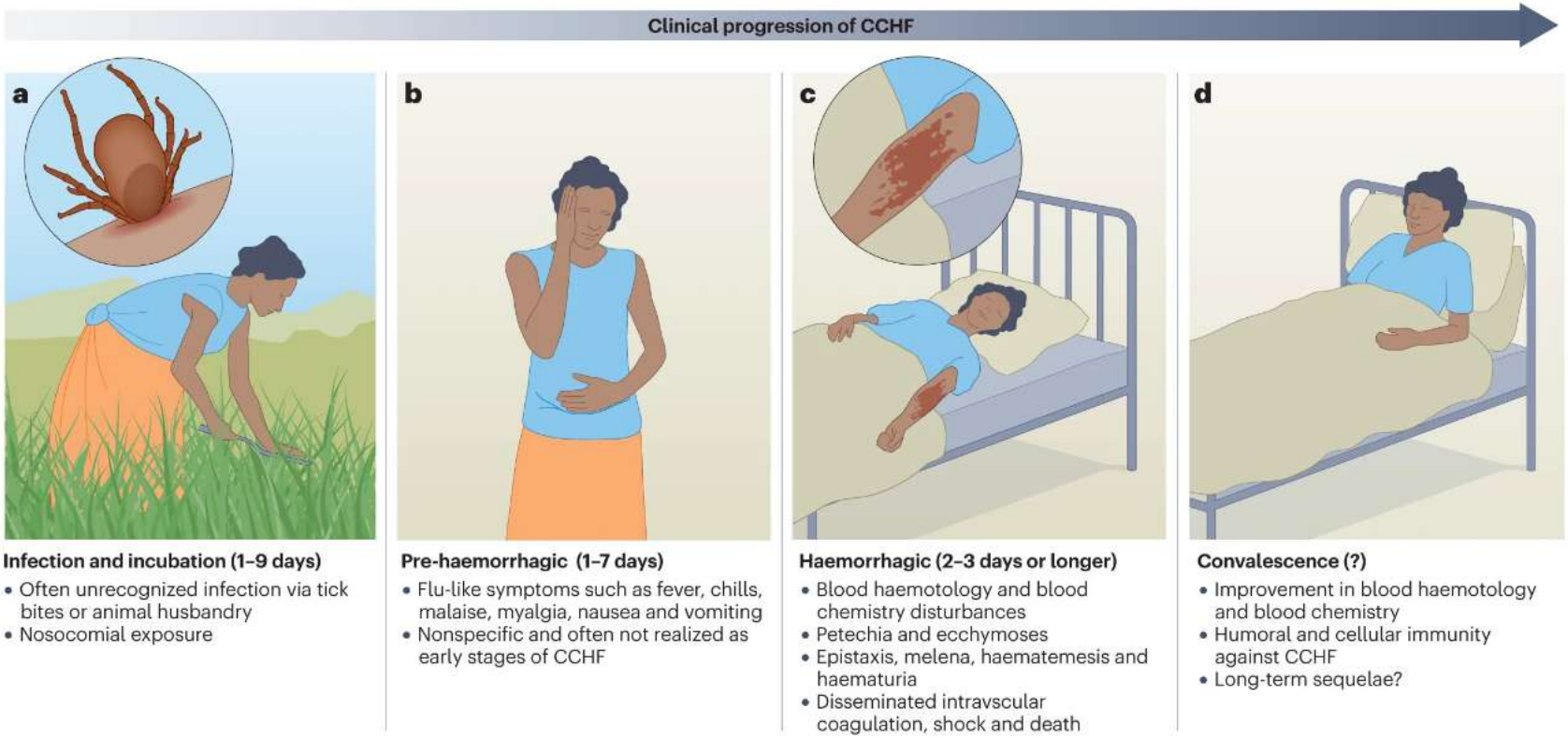
Patogenez



Frank MG, Weaver G, Raabe V. Crimean Congo Hemorrhagic Fever Virus for Clinicians—Virology, Pathogenesis, and Pathology. Emerg Infect Dis. 2024;30(5):847-853.


a
Gc
Gn
Glycoprotein dimer
GP38?
S
M
L
NP
RNA
L protein
b
5′
NP
NSs
3′
MLD
GP38
Gn
NSm
Gc
GP160/85
L protein
c
Infected cell
1 Attachment
2 Endocytosis
3 Fusion
4 Replication
5 Budding
6 Release
MLD
GP38
Reassembled viral genome
Host protease
Golgi apparatus
GP160/85
NSm
ER
Nucleus
Type I interferon
RIG-I
RIG-I ubiquitylation
MAVS
Mitochondria
TNF
TNFR
NSs
Extrinsic
Intrinsic
Pro-caspase 8
Caspase 8
Membrane disruption
BAX
Cytochrome c
Caspase 9
Pro-caspase 3
Caspase 3
Apoptosis
NP
Primary transcription
mRNA
vRNA
L
M
S
L protein

Klinik



İnkübasyon dönemi:
1-3

- Kene tutunması
- Bilinmeyen
- Nozokomyal

Prehemorajik dönem

- Ateş
- Halsizlik
- Miyalji
- Bulantı-Kusma

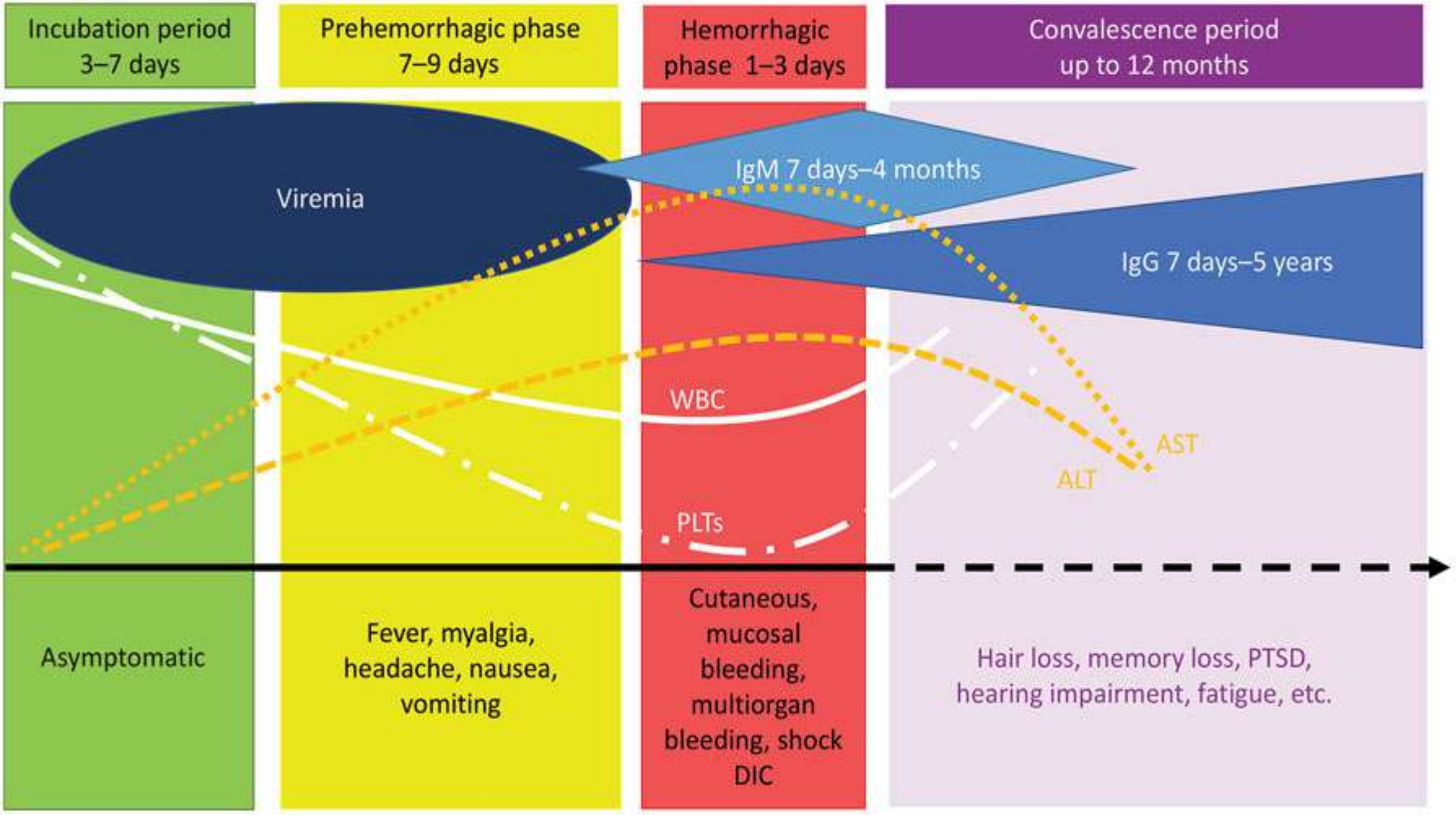
Hemorajik dönem

- Kanama
- Karaciğer hasarı
- İmmun inflamatuvar yanıt
- DIC
- Şok
- Ölüm

Konvalesans dönemi:
10-14 gün

- Laboratuvar sonuçların düzelmesi

Klinik



Frank MG, Weaver G, Raabe V. Crimean-Congo Hemorrhagic Fever Virus for Clinicians—Diagnosis, Clinical Management, and Therapeutics. Emerg Infect Dis. 2024;30(5):864-873.

Tanı

- Nasıl erken tanı koyarım? (Tanıda gecikme)
  - Non spesifik semptomlar
  - Diğer infeksiyonlara benzerliği
    - %68 (n=95) yanlış tanı (misdiagnosis)
    - 4,8 gün gecikme
  - Antiviral tedavi

- Kimde ağır seyreder?

Tasdelen Fisgin N, Et al. (2010). Initial high rate of misdiagnosis in Crimean Congo haemorrhagic fever patients in an endemic region of Turkey. *Epidemiology and infection*, *138*(1), 139–144.

KKKA Vaka Tanımı - 1

Klinik tanımlama

Aşağıdaki 4 klinik kriterden **en az ikisinin** olması

1. Aşağıda belirtilen şikayetlerden en az ikisinin bulunması

- Ateş (≥38°C)
- Halsizlik
- Baş Ağrısı
- Yaygın Vücut Ağrısı
- Eklem Ağrısı
- İshal

2. Cilt ve mukozaya ait kanama bulguları

3. Başka bir nedenle açıklanamayan trombositopeni ve |veya lökopeni

4. Başka bir nedenle açıklanamayan ALT ve AST yüksekliği

KKKA Vaka Tanımı - 1

Epidemiyolojik Kriterler

Hastalığın başlamasından önceki **iki hafta** içinde:

1. Keneyle temas veya kene tutunma öyküsü
2. Hayvan kanı, dokusu ve sekresyonlarıyla temas öyküsü
3. Kırsal kesimde yaşama veya kırsal alana seyahat öyküsü
4. Kesin tanı almış vaka ile yakın temas öyküsü

- Endemik bölge  Endemik olmayan bölge yaklaşımı

KKKA Vaka Tanımı - 1

Laboratuvar Kriterleri

1. Virüs izolasyonu
2. Virüse özgül IgM antikoru pozitifliğinin saptanması
3. Akut ve konvelesan dönem serumlarında virüse özgül IgG titresinde >4 kat artış saptanması
4. Viral nükleik asidin saptanması

Olası vaka: Klinik tanımlama + En az 1 epidemiyolojik kriter
Kesin vaka: Laboratuvar kriterlerden en az biri

❖ Erken Tanı

Acil Serviste Kırım Kongo Kanamalı Ateşi Ayırıcı Tanısında Hitit İndeksinin Değerlendirilmesi

# of Crimean-Congo Hemorrhagic Fever in the Emergency Department

Hitit Index Formula: 5.6 − (5.3 × lymphocyte) − (0.02 × fibrinogen) − (12 × direct bilirubin) + (0.04 × AST) + (0.32 × hematocrit) − (0.5 × neutrophil) − (0.07 × CKD − EPI) − (0.001 × CK) ± conjunctival hyperemia (+1.5 in conjunctival hyperemia presence and −1.5 in conjunctival hyperemia absence) [5].

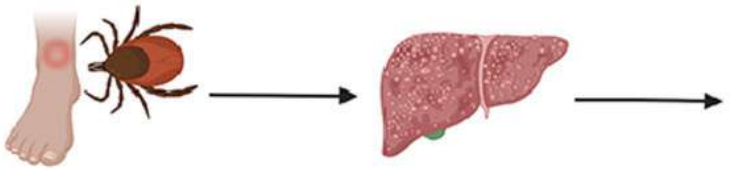
[2] Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Hitit University, 19040 Çorum, Turkey; gulcankaplan@hitit.edu.tr (G.K.); nurcanbaykam@hitit.edu.tr (N.B.)
* Correspondence: sevalkomut@hitit.edu.tr (S.K.)

Abstract: *Background and Objectives*: Crimean-Congo Hemorrhagic Fever (CCHF) is a viral zoonotic infection, which is seen over a wide geographic area. The mortality rate is in inverse proportion to the ability of patients to access healthcare services. Therefore, early identification of patients is extremely important. The aim of this study was to test the sensitivity and specificity of the Hitit Index in the differentiation of CCHF cases at the time of presentation at the Emergency Department and to h molecular (CCHFV RNA) and/or serological diagnostic *Methods:* The patients included were those who presented the complaint of a tick bite or those identified as potential nd/or laboratory findings. For cases that met the study s calculated automatically from the parameters included in the index formula uploaded to the automation system in the ED at the time of presentation. Through comparisons of the agreement of the Hitit Index with the CCHFV-RNA and/or IgM results the power of the Hitit Index for differentiation of CCHF cases in ED was evaluated. *Results:* The data of

Sonuç:
-Yüksek duyarlılık ve özgüllük düzeyleri
- Gereksiz hastaneye yatışı önler
- Erken tanı ile mortalite oranlarının azaltır

❖ Erken Tanı

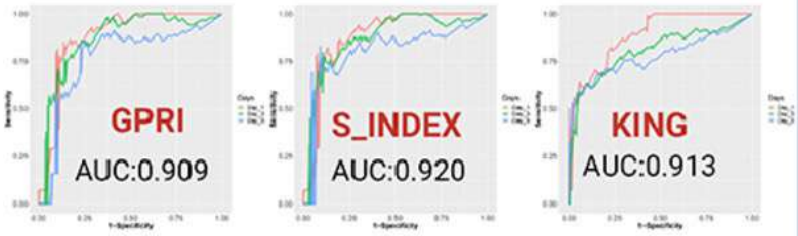
Analysis of liver fibrosis equations as a potential role of predictive models in Crimea… Hemorrhagic Fever



14 hepatic fibrosis indices for distinguishing fatal cases and intensive care unit requirement (ICU) in CCHF

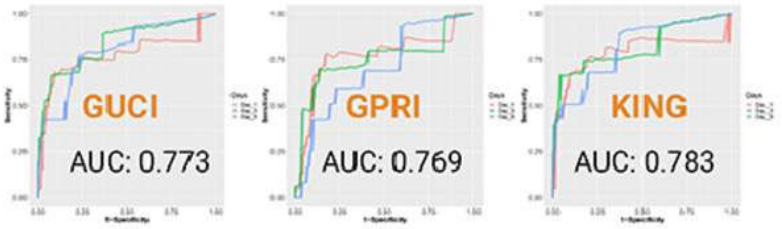
1. Aspartate aminotransferase (AST)-alanine aminotransferase ratio (AAR)
2. Age-platelet index (API)
3. Cirrhosis discriminant score (CDS)
4. AST-platelet ratio index (APRI)
5. F-index
6. FIB
7. S-index

Time-dependent receiver operating characteristic to predict mortality



194 hasta
10 hasta ex
S indeksi ve King skoru 10 günlük sağkalım için tahmin edici

Time-dependent receiver operating characteristic to predict intensive care unit requirement



CONCLUSIONS

1. S-index and KING index emerged as early predictors of 10-day survival, while KING, GUCI, and GPRI indices demonstrated predictive capabilities for ICU admission on the first day.
2. The identified indices have the potential to assist healthcare providers in making timely and informed decisions regarding patient management and treatment strategies.

Bolat, S. et al. (2024). Analysis of liver fibrosis equations as a potential role of predictive models in Crimean-Congo hemorrhagic fever. *Acta tropica*, *251*, 107121.

❖ Erken Tanı

Biomark Med. 2023 Jun;17(11):533-540. doi: 10.2217/bmm-2023-0330. Epub 2023 Oct 4.

Kırım-Kongo kanamalı ateşi tanısında prediktif epidemiyolojik, klinik ve laboratuvar parametreleri

hemorrhagic fever

Türkkan Ö Kaygusuz [1], Ayşe S Tartar [1], Şafak Ö Balin [1], Ayhan Akbulut [1], Kutbeddin Demirdağ [1]

Affiliations + expand

PMID: 37791843 DOI: 10.2217/bmm-2023-0330

aPTT'nin KKKA için bağımsız tahmin edici faktör

Abstract

Background: The aim of this study is to determine predictive parameters that can be used in the differential diagnosis of Crimean-Congo Hemorrhagic Fever (CCHF) and other diseases with similar clinical and laboratory findings. **Materials & methods:** In this study, epidemiological, clinical and laboratory parameters of 107 CCHF-positive and 71 CCHF-negative patients were compared. **Results:** Alanine amino transferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase, red blood cell, hemoglobin and hematocrit were significantly higher in CCHF-positive patients, whereas total and direct bilirubin, alkaline phosphatase, prothrombin time, international normalization ratio, white blood cell, C-reactive protein and procalcitonin were higher in CCHF-negative patients. In binary logistic regression analysis, an increase in activated partial thromboplastin time level was identified as an independent predictor of having CCHF, while alanine amino transferase, white blood cell and C-reactive protein elevations were identified as independent predictors of not having CCHF.
Conclusion: In endemic areas where PCR and serological tests are delayed, knowing the predictive parameters may be of vital importance in the early diagnosis of CCHF.

Keywords: Crimean–Congo hemorrhagic fever; clinic; epidemiological; laboratory; parameters; predictive.

❖Kimde ağır seyreder?

Kaya *et al. BMC Infectious Diseases* 2014, **14**:416
http://www.biomedcentral.com/1471-2334/14/416

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Sequential determination of serum viral titers, virus-specific IgG antibodies, and TNF-α, IL-6, IL-10, and IFN-γ levels in patients with Crimean-Congo hemorrhagic fever

Safak Kaya[1*], Nazif Elaldi[2], Ayhan Kubar[3], Nevcihan Gursoy[4], Meral Yilmaz[5], Gulderen Karakus[5], Turabi Gunes[5], Zubeyde Polat[6], Mustafa Gokhan Gozel[2], Aynur Engin[2], Ilyas Dokmetas[2], Mehmet Bakir[2], Neziha Yilmaz[7] and Mehmet Sencan[8]

✓21 sağ kalan hasta
✓11 ölen hasta
✓Hastaneye kabulde ölen grupta viral yük 5.5E+09 kopya/ml, sağ kalan grupta 5.7+07 kopya/ml

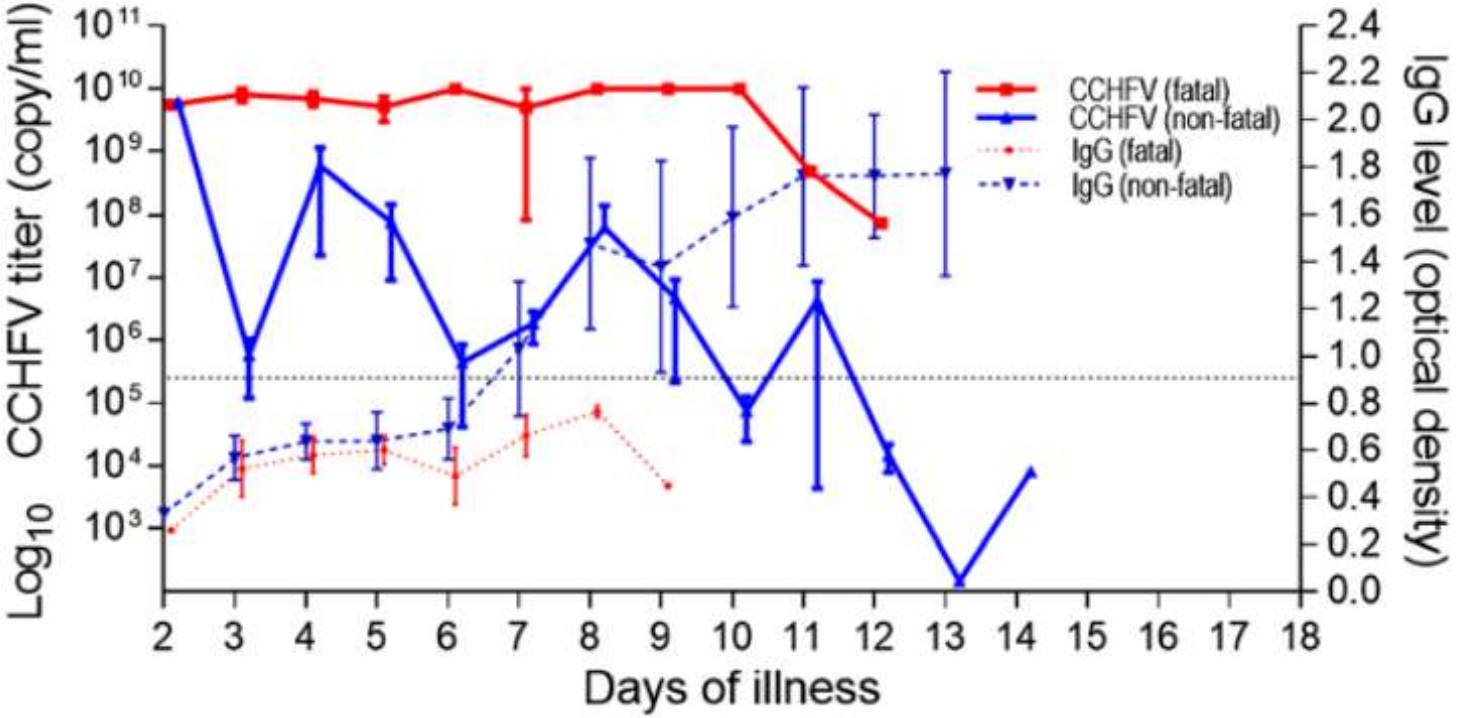


Figure 1 Kinetics of serum virus titers (left y-axis) in logarithmic scale and CCHFV specific IgG antibodies (right y-axis) by days of illness in fatal and non-fatal CCHF groups. Data are expressed as mean ± SE. The threshold optic density value for anti-CCHFV IgG

Sonuç: Yüksek viral yük, yüksek konsantrasyonda TNF alfa ve IL-6 varlığı, DIC gelişmesi ve özgün antikor yokluğu ölümle kuvvetli bir biçimde ilişkili bulunmuştur.

PLOS NEGLECTED TROPICAL DISEASES

❖Kimde ağır seyreder?

Gujarat, Hindistan'dan fatal ve fatal olmayan Kırım-Kongo kanamalı ateşi hastalarında viral yükün, humoral yanıtın ve filogenetik analizin sıralı olarak belirlenmesi, 2019

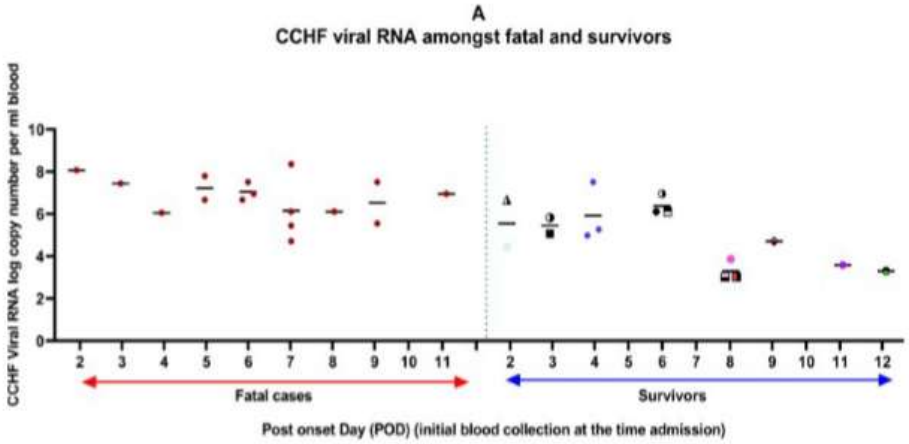
in fatal and non-fatal cases of Crimean-Congo hemorrhagic fever patients from Gujarat, India, 2019

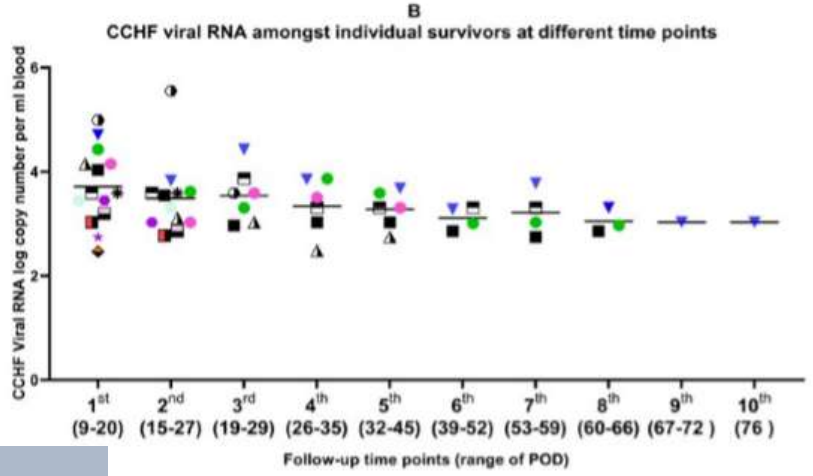
Rima R. Sahay[1☯], Anita M. Shete[1☯], Pragya D. Yadav[1*], Savita Patil[1], Triparna Majumdar[1], Rajlaxmi Jain[1], Dimpal A. Nyayanit[1], Himanshu Kaushal[1], Sunil J. Panjwani[2], Kamlesh J. Upadhyay[3], Chetan L. Varevadiya[4], Alpesh Vora[2], Amit Kanani[5], Raman R. Gangakhedkar[6]

1 Indian Council of Medical Research-National Institute of Virology, Maximum Containment Facility, Pune, Maharashtra, India, **2** Government Medical College and Sir-T Hospital Bhavnagar, Gujarat, India, **3** BJ Medical College and Civil Hospital, Ahmedabad, Gujarat, India, **4** Health Department, District Panchayat, Morbi, Gujarat, India, **5** Animal Husbandry Department, Foot and Mouth Disease Scheme, Ahmedabad, Gujarat, India, **6** Epidemiology and Communicable Diseases (ECD) Division, Indian Council of Medical Research, New Delhi, India

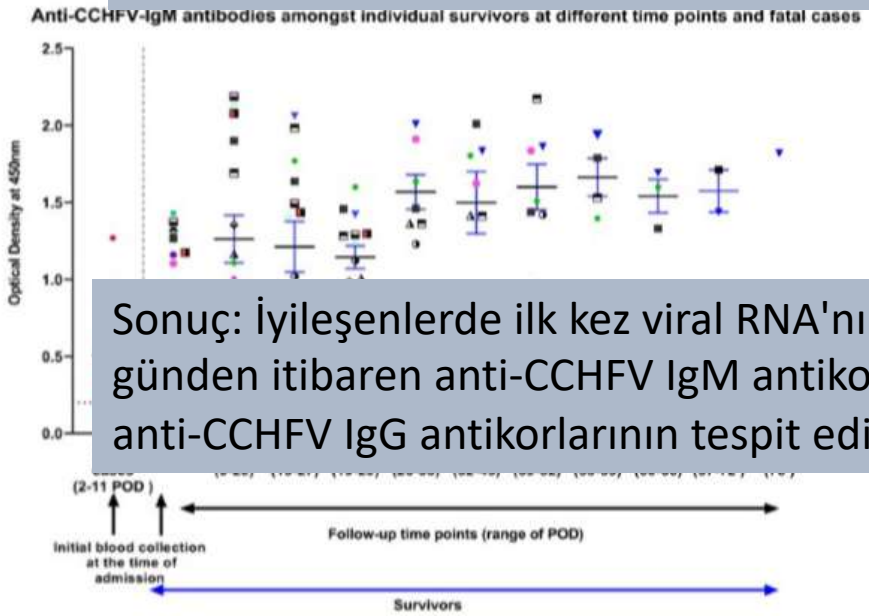
Check for updates

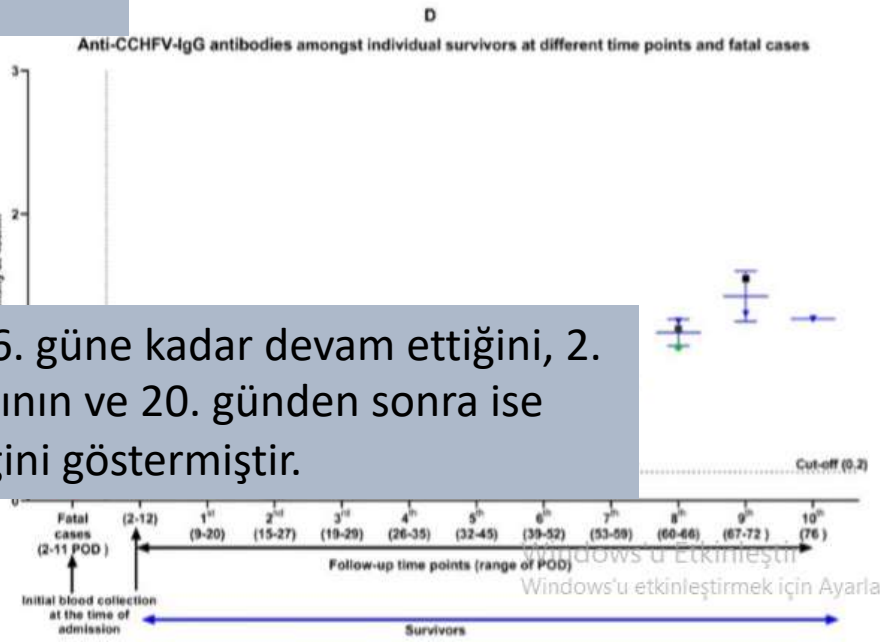
34 hasta (17 ölen, 17 yaşayan)
Viral yük, IgG ve IgM





Ortalama viral yük: Ölenlerde 7,2x10^6, yaşayanlarda 1.0x10^5





Sonuç: İyileşenlerde ilk kez viral RNA'nın 76. güne kadar devam ettiğini, 2. günden itibaren anti-CCHFV IgM antikorlarının ve 20. günden sonra ise anti-CCHFV IgG antikorlarının tespit edildiğini göstermiştir.

Ayırıcı Tanı

- Sıtma
- Riketsiyoz
- Bruselloz
- Leptospiroz
- Viral hepatit
- Meningokoksemi
- ITP
- Akut lösem
- Diğer viral kanamalı ateşler
  - Ebola
  - Marbug
  - Lassa
  - Sarı humma

Tedavi

- Destek tedavi
- Antiviral tedavi
- Diğer tedaviler

Tedavi

- Destek Tedavisi
  - ✓Sıvı-elektrolit
  - ✓Taze donmuş plazma, trombosit süspansiyonu
  - ✓Tam kan, eritrosit süspansiyonu
  - ✓Yoğun bakım birimi

Tedavi

- Antiviral Tedavi
  - ✓Ribavirin
  - ✓Favipravir
  - ✓Molnupravir

❖Antiviral Tedavi

› Eur J Clin Microbiol Infect Dis. 2009 Aug;28(8):929-33. doi: 10.1007/s10096-009-0728-2. Epub 2009 Mar 20.

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

N Tasdelen Fisgin [1], O Ergonul, L Doganci, N Tulek

Affiliations + expand

PMID: 19301047 DOI: 10.1007/s10096-009-0728-2

Abstract

✓21 hasta erken ribavirin (<4 gün)
✓20 hasta geç ribavirin (>5 gün)
✓11 hasta ribavirin almadı
✓Erken başlanan grupta PLT daha yüksek, AST ve ALT daha düşük
Sonuç: Ribavirin yararlı ve erken başlanması önerilir

significantly lower than of the NUR group on days 8 and 9, and the mean alanine transferase level was significantly lower on day 8 after the onset of the symptoms. There is a beneficial effect of ribavirin if given at an early phase of the CCHF. We suggest ribavirin use especially in the early phase of the disease.

❖Antiviral Tedavi

World Health Organization

Health Topics | Countries | Newsroom | Emergencies

Home / Newsroom / Fact sheets / Detail / Crimean-Congo haemorrhagic fever

Crimean-Congo haemorrhagic fever

Treatment

General supportive care with treatment of symptoms is the main approach to managing CCHF in people.

The antiviral drug ribavirin has been used to treat CCHF infection with apparent benefit. Both oral and intravenous formulations seem to be effective.

- **CCHF outbreaks have a case fatality rate of up to 40%.**

❖KKKA'nın yönetiminde temel yaklaşım semptomların tedavisiyle birlikte genel destek tedavisidir.

❖Antiviral ilaç ribavirin, KKKA tedavisinde belirgin bir yararla kullanılmıştır. Hem oral hem de intravenöz formülasyonlar etkili görünmektedir.

Overview

Tropical Diseases (2020)

- Symptoms include nausea, vomiting, fever, headache, myalgias, and stupor (1/3).
- Signs: conjunctival injection, hepatomegaly, petechiae (1/3).
- Lab: Decreased platelets, decreased WBC, increased ALT, AST, LDH, CPK (100%).

ETIOLOGIES

- Crimean-Congo hemorrhagic fever virus

PRIMARY REGIMENS

- Ribavirin, 30 mg/kg po initial dose, then 15 mg/kg po q6h x 4 days, then 7.5 mg/kg q8h po x 6 days (WHO recommendation)
- See Comments

ALTERNATIVE REGIMENS

- IVIG associated with decreased inflammation
- High Dose Corticosteroids have been effective

COMMENTS

- In case series of 281 patients, Ribavirin reduced case-fatality rate; dexamethasone

❖Antiviral Tedavi

Published in final edited form as:
Antiviral Res. 2020 September ; 181: 104858. doi:10.1016/j.antiviral.2020.104858

Sinomolgus makaklarında Kırım-Kongo kanamalı ateşi virusuna karşı favipiravirin (T-705) etkinliği

Efficacy of favipiravir (T-705) against Crimean-Congo hemorrhagic fever virus infection in cynomolgus macaques

David W. Hawman[a,*], Elaine Haddock[a], Kimberly Meade-White[a], Glenn Nardone[b], Friederike Feldmann[a], Patrick W. Hanley[a], Jamie Lovaglio[a], Dana Scott[a], Takashi Komeno[c], Nozomi Nakajima[c], Yousuke Furuta[c], Brian B. Gowen[d], Heinz Feldmann[a,]**

[a]Rocky Mountain Laboratories, NIAID/NIH, Hamilton, MT, USA

[b]Research Technologies Branch, NIAID/NIH, Rockville, MD, USA

[c]FUJIFILM Toyama Chemical Co., Ltd., Toyama, Japan

[d]Utah State University, Logan, UT, United States

✓ Kümülatif olarak, verilerimiz favipiravirin KKKA'nın sinomolgus makak modelinde in vivo olarak KKKA'ya karşı etkili olduğunu göstermektedir.
✓Verilerimiz favipiravirin KKKA hastaları için klinik faydası olabileceğini düşündürmektedir..

during care of infected patients. In humans, CCHFV can cause a sudden onset of a non-specific febrile illness that can rapidly progress to severe hemorrhagic manifestations. Currently, there

Tedavi

- Diğer tedaviler
  - ✓Plazma tedavisi
  - ✓Monoklonal antikor
  - ✓IL reseptör antagonistleri
  - ✓Antiinflmatuvar (kortikosteroidler)

❖Diğer tedaviler

J Med Virol. 2024 Jan;96(1):e29347. doi: 10.1002/jmv.29347.

IL-36 signaling pathway dysregulation in Crimean-Congo hemorrhagic fever virus patients: A potential therapeutic avenue

Kübra Doğan [1], Seyit A Büyüktuna [2]

Affiliations + expand

PMID: 38152020 DOI: 10.1002/jmv.29347

Abstract

Crimean-Congo hemorrhagic fever (CCHF) is a severe viral disease. The scientific literature is growing, emphasizing the significance of the interleukin (IL)-36 family in the proinflammatory signaling pathway. However, to date, no research has explored the potential of IL-36 family members as

- 60 hasta, 29 kontrol
- IL-36 alfa, beta ve gama
- Hastalarda IL-36 alfa ve beta belirgin olarak yüksek bulundu
- PLT sayısı ve IL-36 alfa ve gama arasında negatif korelasyon

between the two groups. Among the CCHF patients, those who did not survive exhibited significantly elevated IL-36α and IL-36γ levels compared to survivors ($p < 0.01$). Positive correlations were identified between IL-36α and IL-36γ levels with activated partial thromboplastin time, and D-dimer ($p < 0.01$). Conversely, platelet levels showed a negative correlation with IL-36α and IL-36γ levels ($p < 0.01$). The increased levels of IL-36α, IL-36β, and IL-36γ in patients indicate their participation in proinflammatory reactions in CCHF patients. Understanding the role of IL-36 family members in CCHF pathogenesis could offer valuable insights into disease progression and facilitate the development of targeted therapeutic strategies.

European Review for Medical and Pharmacological Sciences 2023; 27: 8934-8942

Cytokine release syndrome in Crimean-Congo hemorrhagic fever: can IL-1 receptor antagonist levels be a guide in its treatment?

N. ÇELIK[1], E. LALOĞLU[2]

Table II. Comparison of IL-1 and IL-1RA levels in patients with Crimean-Congo hemorrhagic fever between severe and non-severe disease and patients who survived and died.

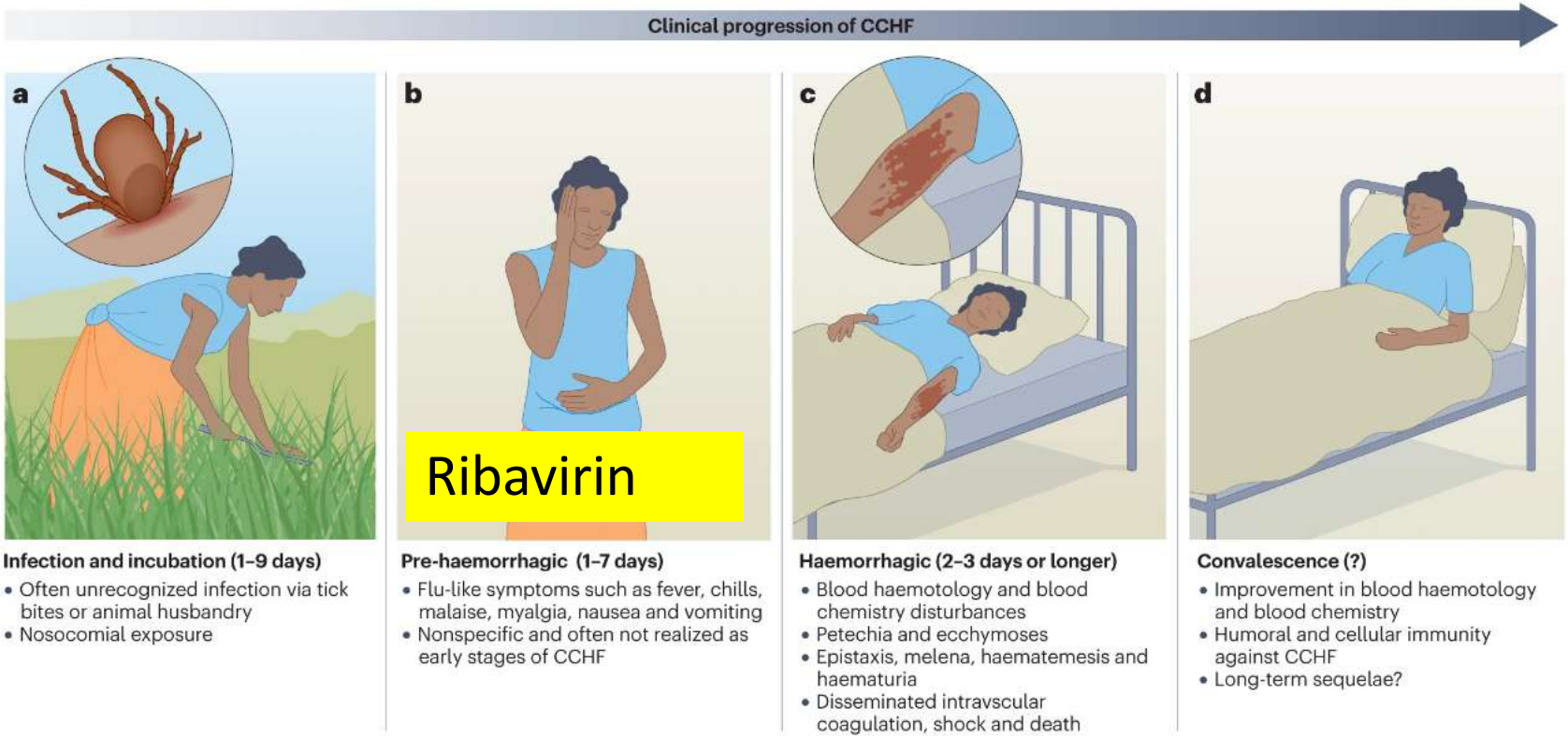
Parameter	Moderate (n=35) mean±SD	Severe (n=26) mean±SD	Survivor (n=51) mean±SD	Non-survivor (n=10) mean±SD	Control (n=40) mean±SD	*p*
IL-1 (ng/L)	139.02±29.89	277.78±49.72	172.93±57.78	326.82±40.198	53.02±38.73	<0.001[a,b,c]
IL-1RA (ng/L)	473.59±143.68	874.73±226.66	568.97±196.21	1,030.08±275.66	104.59±54.75	<0.001[a,b,c]

[a]=Comparison of moderate and severe patients, [b]=Comparison of survivor and non-survivor patients, [c]=Comparison of patients

- IL-1RA seviyelerindeki artışın inflamatuvar savaşın şiddetini belirlemede yararlı bir rehber
- inflamasyonun etkilerini azaltmak için dışarıdan IL-1RA desteğinin faydalı olabilir

Tedavi	Sınıf	Hedef	Preklinik etkinliği	Klinik etkinlik	Yorumlar
Ribavirin	NA	RdRP	Kemirgen modellerinde tartışmalı	Hastalarda tartışmalı etkinlik	Zayıf etkinlik; erken tedavi başlangıcı gereklidir; kesilmeli veya kombinasyon tedavisinde kullanılmalıdır
Favipravir	NA	RdRP	Hayvan modellerinde etkin	Sınırlı veri	Geç tedavi başlangıcı kemirgen modellerinde etkili; klinik deneylere ihtiyaç var
2-deoksiflurositidin	NA	RdRP	Yapılmadı	Klinik veri yok	Daha fazla preklinik çalışmaya ihtiyaç var
Molnupravir	NA	RdRP	Kemirgen modellerinde etkisiz	Klinik veri yok	İlerleme olasılığı düşük
Yaşayan hastalardan plazma/antikor	Nötrolizan/non nötrolizan	Viral proteinler	Yapılmadı	Sınırlı veri	Daha fazla klinik/preklinik çalışmaya ihtiyaç var
Monoklonal antikorlar	Nötrolizan/non nötrolizan	Viral proteinler	Kemirgen modellerinde sınırlı veri	Klinik veri yok	Daha fazla klinik/preklinik çalışmaya ihtiyaç var
Kortikosteroidler	Antiinflmatuvar	Konak yanıtı	Yapılmadı	Sınırlı veri	Daha fazla klinik/preklinik çalışmaya ihtiyaç var

Tedavi



İnkübasyon dönemi:
1-3

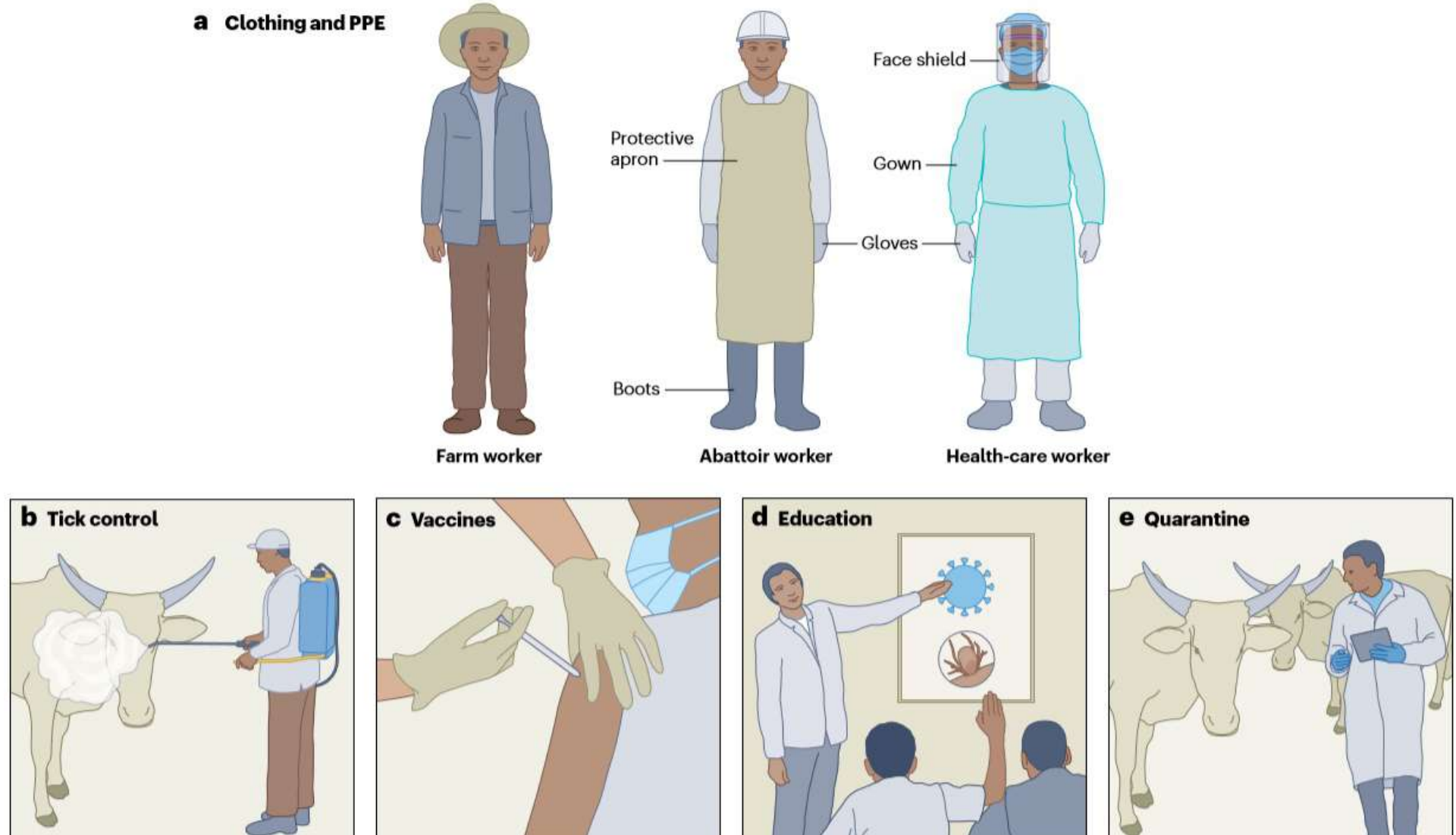
- Kene tutunması
- Bilinmeyen
- Nozokomyal

Prehemorajik dönem
- Ateş
- Halsizlik
- Miyalji
- Bulantı-Kusma

Hemorajik dönem
- Kanama
- Karaciğer hasarı
- İmmun inflamatuvar yanıt
- DIC
- Şok
- Ölüm

Konvalesans dönemi:
10-14 gün
- Laboratuvar sonuçların düzelmesi

Koruma


a Clothing and PPE
Protective apron
Boots
Face shield
Gown
Gloves
Farm worker
Abattoir worker
Health-care worker
b Tick control
c Vaccines
d Education
e Quarantine

World Health Organization

Infection prevention and control and water, sanitation and hygiene measures for Crimean-Congo haemorrhagic fever in health-care settings

Operational guide

May 2024

- Standart önlemler + Temas izolasyonu
- Aerosol oluşturan tıbbi işlem yapılırsa +havayolu izolasyonu

Key messages

- **Immediately isolate patients with suspected or confirmed Crimean-Congo haemorrhagic fever (CCHF) in single-bed patient rooms. If single-bed rooms are limited, do not cohort patients with suspected CCHF.**
- Use contact precautions, including appropriate personal protective equipment (PPE) (fluid resistant gown and examination gloves) when caring for patients with suspected or confirmed CCHF.
- Use airborne and contact precautions, including appropriate PPE (fit-tested respirator, fluid-resistant gown and examination gloves) and eye protection (face shield or goggles) when aerosol-generating medical procedures are performed on patients with CCHF.
- Visitors and caregivers must wear PPE for contact precautions in isolation rooms and in all areas where at least 1 metre of physical distance from a patient with CCHF cannot be maintained. Visitors should be instructed on procedures for hand hygiene and putting on and taking off PPE.
- Closely monitor adherence to standard precautions, particularly: injection and sharps

- N95 maske için yeterli kanıt yok ancak aerosol üreten işlemler sırasında kullanılması önerilir.

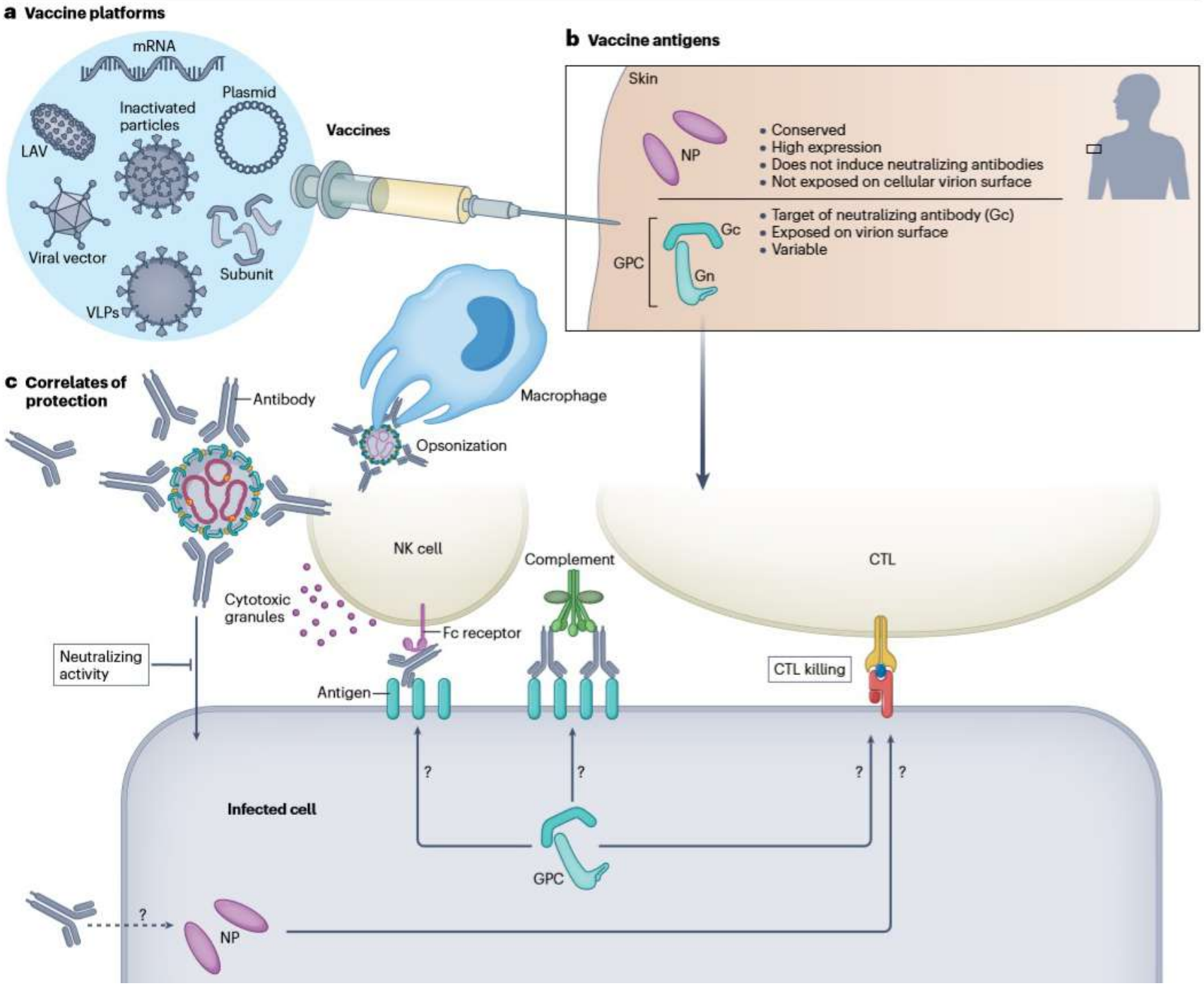
Emerging Infectious Diseases •www.cdc.gov/eid • Vol. 30, No. 5, May 2024

Koruma

- Temas sonrası profilaksi
  - İğne batması, kan ve sıvı teması, göze kan sıçraması
  - Bölgenin su ve alkol ile temizlenmesi
  - Ribavirin profilaksisi

Guven G, et al. An Unexpected Fatal CCHF Case and Management of Exposed Health Care Workers. *Int J Infect Dis*. 2017;55:118-121.

Ergönül, Ö., et al. (2018). Systematic Review and Meta-analysis of Postexposure Prophylaxis for Crimean-Congo Hemorrhagic Fever Virus among Healthcare Workers. *Emerging infectious diseases*, *24*(9), 1642–1648.


a Vaccine platforms
mRNA
Plasmid
Inactivated particles
LAV
Viral vector
Subunit
VLPs
Vaccines
b Vaccine antigens
Skin
NP
• Conserved
• High expression
• Does not induce neutralizing antibodies
• Not exposed on cellular virion surface
GPC
Gc
Gn
• Target of neutralizing antibody (Gc)
• Exposed on virion surface
• Variable
c Correlates of protection
Antibody
Macrophage
Opsonization
NK cell
Complement
CTL
Cytotoxic granules
Fc receptor
Neutralizing activity
Antigen
CTL killing
Infected cell
?
GPC
NP

Vaccine 30 (2012) 6225–6229

Contents lists available at SciVerse ScienceDirect

Vaccine

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

Short communication

Healthy individuals' immune response to the Bulgarian Crimean-Congo hemorrhagic fever virus vaccine

Mehrdad Mousavi-Jazi[a,*], Helen Karlberg[a,b], Anna Papa[c], Iva Christova[d], Ali Mirazimi[a,b,e,*]

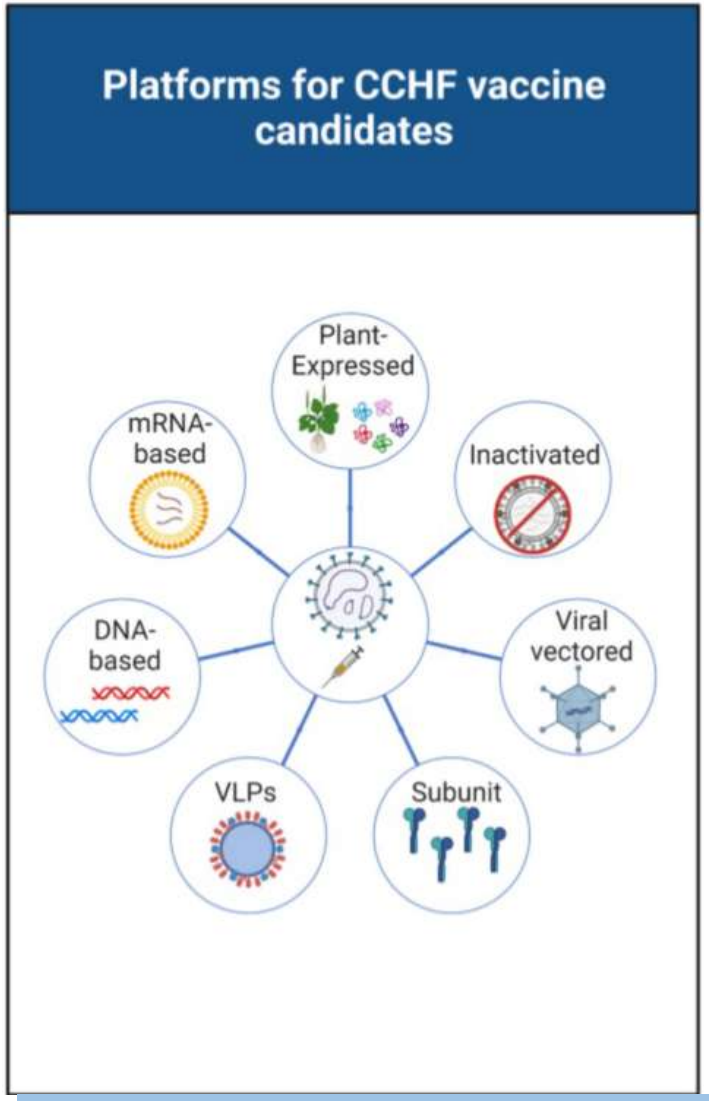
[a] Swedish Institute for Communicable Disease Control, Stockholm, Sweden
[b] Karolinska Institute, Stockholm, Sweden
[c] Aristotle University of Thessaloniki, Medical School, Thessaloniki, Greece
[d] National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria
[e] Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

ARTICLE INFO

ABSTRACT

✓8 sağlıklı gönüllü
✓Tek doz ve 4 doz
✓Yüksek IgG antikoru
✓Ancak düşük nötrolize edici özellik
Sonuç: Eldeki tek aşı olan Bulgaristan aşısının (inaktif aşı) klinik ekinliği yoktur. Farklı aşıların üretimine gereksinim var.

Aşılar

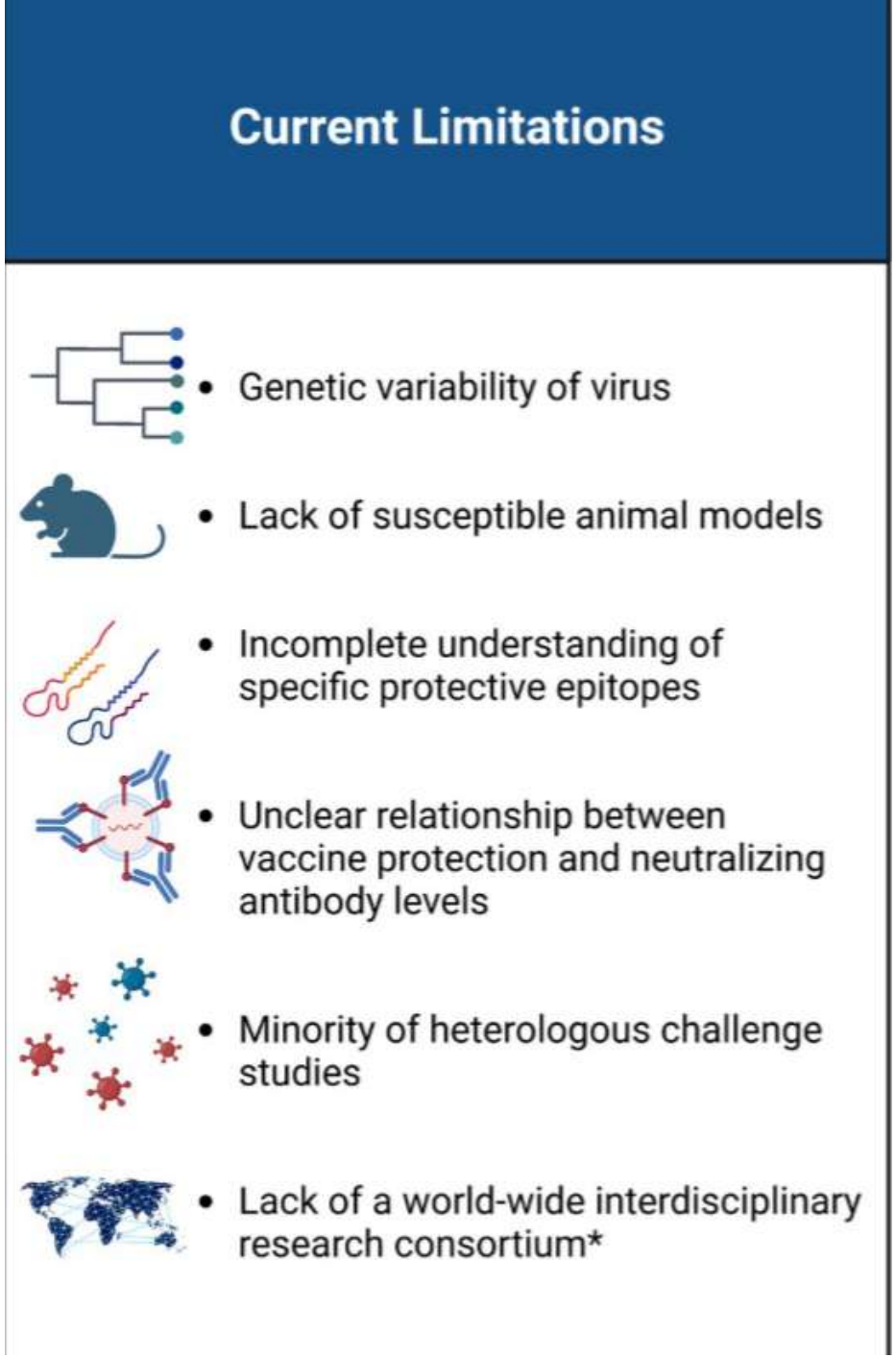


Ahata B and Akc ¸apınar GB (2023) CCHFV vaccine development, current challenges, limitations, and future directions. Front. Immunol.

Aşılar

Aşı tipi	IgG	Nötrolizan antikor	T hücre yanıtı	Koruma
Bitkice eksprese edilen	Evet	Belirsiz	Belirsiz	Belirsiz
İnaktif aşılar (tüm virus adjuvanlı)	Evet	Evet	Evet	%80
Vektör aşıları (adenovirus)	Evet	Evet	Evet	%100
Alt birim aşıları (Gc)	Evet	Evet	Belirsiz	Belirsiz
Virus benzeri partikül (VLPs)	Evet	Evet	Evet	%40
DNA temelli aşılar	Evet	Evet	Belirsiz	Belirsiz
mRNA aşıları	Evet	Evet	Evet	%100

Ahata B and Akc ¸apınar GB (2023) CCHFV vaccine development, current challenges, limitations, and future directions. Front. Immunol.



- Virusun genetik çeşitliliği
- Duyarlı hayvan modelinin olmayışı
- Spesifik koruyucu epitopların tam olarak anlaşılamaması
- Nötrolizan antikorlar ve aşının koruyuculuğu arasındaki ilişkinin net olmaması
- Heterolog çalışmaların azlığı
- Dünya çapında disiplinlerarası araştırma birliğinin yokluğu

npj | vaccines

Article | Open access | Published: 20 May 2024

A replicating RNA vaccine confers protection in a rhesus macaque model of Crimean-Congo hemorrhagic fever

David W. Hawman ✉, Shanna S. Leventhal, Kimberly Meade-White, Amit Khandhar, Justin Murray, Jamie Lovaglio, Carl Shaia, Greg Saturday, Troy Hinkley, Jesse Erasmus & Heinz Feldmann ✉

npj Vaccines **9**, Article number: 86 (2024) | Cite this article

İnsan olmayan primatlarda immunojenik ve koruyucu

Dinlediğiniz İçin Teşekkürler