



Anti-inflammatory consensus from Türkiye

Dr. Handan Alay

Ataturk University Faculty of Medicine, Infectious Diseases and Clinical
Microbiology, Erzurum, Türkiye



(Presentation Outline)

1. Background

Crimean-Congo Hemorrhagic Fever and systemic inflammation
Role of host immune response in disease severity

2. Pathophysiological Rationale

Cytokine-driven inflammation
Role of IL-1, IL-6 and endothelial injury

3. Corticosteroid Therapy in CCHF

4. IL-1 and IL-6 Targeted Therapies

5. Evidence from Other Viral Hemorrhagic Fevers

6. Turkish Delphi Consensus

Expert recommendations on immunomodulation

Crimean-Congo Hemorrhagic Fever (CCHF)

- Crimean-Congo hemorrhagic fever (CCHF) is characterized by:
 - Severe **systemic inflammation**
 - **Endothelial dysfunction**
 - **Coagulopathy** and hemorrhage
- Disease severity is not driven solely by viral replication
- **Host inflammatory response** plays a central role in:
 - Disease progression
 - Multiorgan failure
 - Mortality

Pathophysiological Rationale

Elevated levels of:

- **Pro-inflammatory cytokines** (IL-1 β , IL-6, TNF- α)
- Acute phase reactants

This hyperinflammatory state resembles **cytokine-driven inflammatory syndromes**

Observed associations:

- Higher cytokine levels → higher mortality

> J Med Virol. 2017 Oct;89(10):1707-1713. doi: 10.1002/jmv.24864. Epub 2017 Jul 6.

Cytokine response in Crimean–Congo hemorrhagic fever virus infection

Önder Ergönül ¹, Ceren Şeref ², Şebnem Eren ³, Aysel Çelikbaş ³, Nurcan Baykam ⁴, Başak Dokuzoğuz ³, Mehmet Gönen ² ⁵, Füsun Can ⁶

In CCHF patients, median levels of IL-6, IL-8, IL-10, IL-10/12, IFN- γ , MCP-1, and MIP-1 β were significantly higher compared to healthy controls. IL-6 and IL-8 can predict the poor outcome, within the first 5 days of disease course.

> J Med Virol. 2016 Jan;88(1):21-7. doi: 10.1002/jmv.24312. Epub 2015 Jul 7.

Cytokines as biomarkers of Crimean–Congo hemorrhagic fever

Anna Papa ¹, Katerina Tsergouli ¹, Dilek Yağcı Çağlayık ², Silvia Bino ³, Najada Como ⁴, Yavuz Uyar ⁵, Gulay Korukluoglu ²

IL-1b, IL-5, IL-6, IL-8, IL-9, IL-10, IL-15, IP10, MCP1, TNF α , and RANTES levels showed significant differences between fatal and non-fatal cases ($P < 0.05$).

Evaluation of serum levels of interleukin (IL)-6, IL-10, and tumor necrosis factor-alpha in patients with Crimean-Congo hemorrhagic fever

Onder Ergonul ¹, Semra Tuncbilek, Nurcan Baykam, Aysel Celikbas, Basak Dokuzoguz

We investigated the role played by cytokines in the mortality of patients with Crimean-Congo hemorrhagic fever (CCHF). Serum levels of several cytokines were measured in 3 patients with fatal CCHF and in 27 patients with nonfatal CCHF.

Levels of interleukin (IL)-6 ($P < \text{ or } = .001$) and tumor necrosis factor (TNF)-alpha ($P = 0.004$) were significantly higher in patients with fatal CCHF than in patients with nonfatal CCHF, whereas levels of IL-10 were not significantly different between the 2 groups ($P = .937$). Disseminated intravascular coagulation (DIC) scores were also higher in the patients with fatal CCHF ($P = .023$). Levels of IL-6 and TNF-alpha were positively correlated with DIC scores, whereas levels of IL-10 were negatively correlated with DIC scores. In conclusion, these findings demonstrate that **proinflammatory cytokines play a major role in the mortality of patients with CCHF.**

Anti-inflammatory Therapies in the Literature

Corticosteroids:

- Corticosteroids have been used empirically in severe CCHF
- Proposed mechanisms:
 - Reduction of cytokine storm
 - Stabilization of endothelial injury
 - Modulation of immune-mediated thrombocytopenia

> Clin Infect Dis. 2013 Nov;57(9):1270-4. doi: 10.1093/cid/cit527. Epub 2013 Aug 14.

Severity scoring index for Crimean–Congo hemorrhagic fever and the impact of ribavirin and corticosteroids on fatality

Basak Dokuzoguz ¹, Aysel Kocagül Celikbas, Şebnem Eren Gök, Nurcan Baykam, Mustafa Necati Eroglu, Önder Ergönül

- Developed **CCHF Severity Scoring Index (SSI)**
- Retrospective cohort study
- Findings:
- Corticosteroid use associated with:
 - Improved laboratory parameters
 - Possible reduction in fatality in severe cases

The SSI is an accurate predictor of death and will therefore be a useful tool for case management and for drug-assessment studies. After stratification of cases by SSI, ribavirin was found to be effective in reducing the case-fatality rate, especially among moderately ill patients, whereas **steroids were found to be beneficial particularly among patients with severe disease.**

Efficacy of high-dose methylprednisolone in patients with Crimean-Congo haemorrhagic fever and severe thrombocytopenia

Batool Sharifi-Mood ¹, Roya Alavi-Naini, Maliheh Metanat, Mehdi Mohammadi, Asad Shakeri, Ali Amjadi

Patients with:

- Severe thrombocytopenia
- Advanced disease

Results:

- Rapid platelet recovery
- Improvement in clinical status
- Decrease in the need for blood products.

Table 2. Laboratory findings and blood products required during treatment of patients with Crimean-Congo haemorrhagic fever in the intervention and control groups.

Characteristics	Intervention group (ribavirin + HDMP) n = 13	Control group (ribavirin) n = 22	P
Lowest platelet count (/mL; mean ± SD)	19600 ± 6800	15000 ± 5400	NS
Lowest Hb (g/dL; mean ± SD)	11.1 ± 1.3	11.6 ± 1.7	NS
Lowest WBC count (/mL; mean ± SD)	3100 ± 1280	3700 ± 1650	NS
Increased platelet count 36 h after treatment	13	7	<0.001
Increased leukocyte count 48 h after treatment	13	8	<0.001
Total platelet suspension transfused	8 (60 Units)	21 (370 Units)	<0.001
Total erythrocyte suspension transfused	0	3 (20 units)	<0.001
Total FFP needed during treatment	3 (12 units)	12 (85 units)	<0.001

HDMP, high-dose methyl-prednisolone; Hb, haemoglobin; WBC, white blood cell; FFP, fresh frozen plasma; SD, standard deviation; NS, not significant

Corticosteroid Use in CCHF

Study	Country	Design	Patients	Steroid Regimen	Main Findings
Dokuzoguz et al., CID 2013	Türkiye	Retrospective cohort	281	Non-standardized corticosteroids	↓ Fatality in severe cases
Sharifi-Mood et al., Trop Doct 2013	Iran	Comparative study	33	High-dose methylprednisolone	Rapid platelet recovery
Hashemi-Shahri et al., Int J Infect 2017	Iran	Randomized trial	30	Dexamethasone 10 mg/m ²	↓ Blood product use
Erduran et al., J Pediatr Hematol Oncol 2013	Türkiye	Case series (CCHF+HLH)	12	Methylprednisolone 5–30 mg/kg/day	Clinical improvement
Cetin et al., J Vector Borne Dis 2025	Türkiye	Retrospective analysis	55	Dexamethasone	No significant clinical benefit of dexamethasone

- Mostly retrospective
- Case reports
- No standardized:
 - Dose
 - Timing
 - Duration

IL-1 and IL-6 Pathway Inhibition

- Severe CCHF shows features of:
 - Hyperinflammatory syndromes
 - Cytokine-mediated endothelial injury
- IL-1 and IL-6:
 - Central mediators of systemic inflammation
 - Successfully targeted in:
 - COVID-19 cytokine storm
 - HLH / MAS

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

N. ÇELİK¹, E. LALOĞLU²

A study conducted in our country reported that interleukin-1 (IL-1) levels were elevated in all patients with Crimean-Congo hemorrhagic fever, with particularly high levels observed in fatal cases, indicating an intense inflammatory process and suggesting that IL-1 receptor antagonists may be required as a therapeutic option.”

Utility of anakinra in Crimean Congo haemorrhagic fever with haemophagocytic lymphohistiocytosis: a case report

[Get access >](#)

Ümit Çelik, Ayşe Hitay Telefon ✉, Tuğba Kandemir Gülmez, Elif Afat Turgut, Rabia Miray Kisla Ekinci, Merve Kılıç Çil, Mehmet Deniz Erhan

Crimean Congo haemorrhagic fever (CCHF) is an emerging, life-threatening tick-borne infection that can be fatal. As yet, there is no definitive treatment. In this case report we present a severe paediatric CCHF case that was successfully treated with anakinra. A previously healthy **13-year-old female** presented with high fever, fatigue, rash and loss of appetite. Bone marrow aspiration showed rare **haemophagocytosis** and the patient's clinical condition continued to deteriorate. Anakinra was given on the day 5 of admission, as she was in the midst of cytokine storm syndrome. By the third day of anakinra, the patient's symptoms and laboratory tests improved. After 14 d of anakinra, she was discharged in full recovery. Anakinra may be a new therapeutic agent in CCHF, in which inflammation plays important role.

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

D. Yapar¹, Ö. Akdoğan¹, A. Kocagül Çelikbaş¹, N. Baykam¹

¹Hitit 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 ($p=0.009$).

Use of Corticosteroids and IL-1 / IL-6 Blockade in Other Viral Hemorrhagic Fevers

Disease	Target / Agent	Study Type	Regimen	Main Outcomes
Ebola Virus Disease (acute) (1)	Corticosteroids	WHO Living Guideline	Not routinely recommended	No evidence supporting routine corticosteroid use in acute EVD.
Ebola (relapsing meningoencephalitis) (2)	High-dose corticosteroids + Remdesivir	Case report	High-dose steroids with antiviral therapy	Clinical improvement reported in CNS relapse.
Lassa Fever (3, 4)	Dexamethasone (+ Ribavirin)	Case reports / Phase II trial	Adjunct dexamethasone with ribavirin	Safety described; efficacy not established.
Severe Fever with Thrombocytopenia Syndrome (SFTS) (5)	Tocilizumab ± Corticosteroids	Randomized Clinical Trial	IL-6 receptor blockade ± steroids	Reduced fatality reported in severe hospitalized cases.
Rift Valley Fever (6)	Corticosteroids	National Guideline	Adjunct steroids not recommended	Guidelines advise against routine steroid use.

There is no strong clinical evidence supporting the use of corticosteroids or IL-1/IL-6–targeted therapies in Ebola and Lassa fever;

The available data are largely limited to case reports, while the most meaningful clinical evidence for cytokine blockade comes from certain VHF-like conditions such as SFTS

1. World Health Organization. *Clinical management of Ebola virus disease: living guidance*. Geneva: WHO; 2022. Available from: <https://www.who.int/publications/i/item/9789240055742>
2. Jacobs M, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A, et al. Late Ebola virus relapse causing meningoencephalitis: a case report. *N Engl J Med*. 2016;374(24):2423–2424. doi:10.1056/NEJMc1600616
3. Okogbenin S, et al. Adjunctive dexamethasone use in Lassa fever: case reports. *Case Rep Infect Dis*. 2022. (DOI available via journal site).
4. *ClinicalTrials.gov*. Adjunct dexamethasone for Lassa fever (NCT06222723). Bethesda (MD): National Library of Medicine; 2024.
5. Randomized clinical trial of tocilizumab in severe fever with thrombocytopenia syndrome. *J Infect*. 2024. (DOI available via journal site).
6. Rwanda Biomedical Centre. *Rift Valley Fever Clinical Guideline*. Kigali: RBC; 2018.

(Turkish Delphi Consensus)

This uncertainty highlights the need for structured expert consensus.

Diagnosis, management, and prevention of Crimean-Congo haemorrhagic fever: a Delphi-based consensus from two decades of experience in Türkiye

Önder Ergönül^{1,2}, Deniz Güllü^{2,3,4}, Defne Yigci³, Aysel Kocagül Çelikbaş⁵, Handan Alay⁶, Şebnem Eren Gök⁷, Derya Yapar⁵, Fatma Kesmez Can⁶, Çiğdem Kader⁷, Özlem Akdoğan⁵, Ömer Kardeşahin⁸, Nuriye Yalçın Çolak⁷, Ayten Yanık⁸, İmran Hasanoğlu⁹, Tülay Ünver Ulusoy¹⁰, Tuğba Yanık Yalçın¹¹, Rukiye İnan Sarıkaya¹², Feyza İzci Çetinkaya¹³, Büşra Tanır¹⁴, Ömür Gündoğdu¹⁴, Gamze Kalın Ünüvar¹⁵, Faruk Karakeçili¹⁶, Zeynep Türe Yüce¹⁷, İlknur Şenel¹⁸, Merve Çağlar Özer¹⁹, Riveyda Korkmazer¹⁹, Firdevs Aksoy²⁰, Firuze Soyak²¹, Üner Kayabaş²², Azize Yetişgen²³, Elif Çiftçi²⁴, Sarp Singil²⁴, Esmâ Eryılmaz Eren²², Barçın Öztürk²⁵, Bahadır Orkun Özbay²⁶, Fatihan Pınarlık^{2,4}, Bahar Madran²⁷, Şiran Keske^{1,2}, Mert Kuşkuçcu^{2,28}, Rahmet Güner⁹, Ayşe Erbay⁷, Kemalettin Özden⁶, Nurcan Baykam⁵

Consensus on Corticosteroid Use

- Within the Delphi process, experts reported pragmatic use of corticosteroids in severe cases or in patients with rapidly worsening severity scores, largely driven by the absence of alternative therapeutic options. (SSI > 8?)
- Consensus supported this selective use but did not favour any specific corticosteroid agent or pulse-dose therapy.
 - Methylprednisolone, prednisone, or dexamethasone do not have superiority
 - Strictly NO PULSE STEROID therapy

Consensus on IL-1 / IL-6 Antagonists

Experts emphasised the need for biologically informed approaches, including prospective evaluation of inflammatory pathways such as interleukin-1 and interleukin-6.

Despite pragmatic use in selected scenarios, immunomodulatory therapies were not considered suitable for routine recommendation without prospective evidence.

- Anakinra, tocilizumab might be beneficial, but access to these drugs are problematic.

Thank You

