



An Overview of Complications and Mortality of Crimean-Congo Hemorrhagic Fever

Hamidreza Kouhpayeh^{1,*}

¹Tropical and Infectious Diseases Department, Zahedan University of Medical Sciences, Zahedan, Iran

*Corresponding author: Medical Sciences Research Center, Emam Ali Hospital, Zahedan University of Medical Sciences, Khalije Fars Highway, Dr. Hessabi Sq., Zahedan, Iran. Email: hkouhpayeh@yahoo.com

Received 2019 March 18; Revised 2019 May 19; Accepted 2019 June 10.

Abstract

Context: Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne acute viral hemorrhagic fever with variable complications and mortality. Its mortality rate could be as high as 60% - 80% or as low as 0% - 5%. The most common complications are hemorrhage, shock, DIC, and multi-organ failure that might result in death.

Evidence Acquisition: This review was conducted based on 18 articles, two text books, and the experience gained by the author on CCHF cases since 1999. The articles were taken from different sources, specially Google Scholar. Three of the articles were published by the author and his colleagues. Different sections of the reviewed articles including results, conclusion, and discussion were used for this overview.

Results: The most common complication of CCHF in different studies has been hematologic disorders of which, thrombocytopenia and increased PTT and PT time are the most common disorders seen in up to 100% of CCHF patients. Bleeding in different organs, especially the oral cavity, is the next common complication. The average mortality rate is 10% to 40%, but it might vary from as low as 0-5% in Iran to as high as 60% - 80% in different regions. The usual causes of death are shock, DIC, and multi-organ failure including hepatic, renal, and respiratory failure. Moreover, rare complications such as intracerebral hemorrhage, compartment syndrome, intra-abdominal, pleural and pericardial effusions, acute pancreatitis, myocarditis, and cholecystitis are reported.

Conclusions: CCHF has many common and rare complications some of which may lead to death. The most important causes of mortality are hemorrhage, shock, and multi-organ failure, but the mortality rate is very different and is related to the experience of the treatment center in early diagnosis and treatment of the disease and its fatal complications. Moreover, there are other less common or rare complications of CCHF that may be difficult to be diagnosed and managed by inexperienced physicians.

Keywords: CCHF, Complications, Mortality

1. Context

Crimean-Congo hemorrhagic fever (CCHF) is an acute febrile hemorrhagic disease that is fatal in some cases. It is transmitted by the tick bite, contact with blood or secretions of CCHF patients, or contact with livestock (1-3).

This disease was reported in 1945 from the Crimea region of the former Soviet Union for the first time and thereafter, it was reported in middle east countries, The Balkan region, Eastern Europe, the Southwest of the former Soviet Union, Africa, Iran, Turkey, and other neighboring countries of Iran (1, 2).

In Iran, CCHF was reported in Sarab city in East Azarbaijan in 1966 by Dr. Aminalashrafi for the first time. However, many years before, CCHF was an endemic disease of the region and was recognized with the name of Ghareh Mikh typhoid (2). Sixty cases of CCHF were hospitalized in

the cities of Sarab, Ardabil, and Khalkhal between 1971 and 1975 with manifestations of fever, myalgia headache, purpura, nasal and gingival bleeding, hypotension, bradycardia, thrombocytopenia, and leukopenia (2). New cases of CCHF were also reported in 1999 to 2004. The majority of the cases (24 cases) were reported in Sistan and Baluchistan (SB) province that were due to the import of CCHF-infected livestock from Afghanistan to Zabol city in the province (4).

CCHF is more prevalent in ranchers, shepherds, butchers, farmers, and abattoir workers, but some cases of CCHF have been reported in medical and nursing personnel due to nosocomial transmission. Even some fatal cases were seen in physicians (1, 3).

Without treatment, the CCHF mortality rate is about 26% to 80% usually due to severe hemorrhage, disseminated intravascular coagulation (DIC), circulatory shock, and multi-organ failure (1, 2). The most common compli-

cations of CCHF are hemorrhage in different organs, DIC, shock, and multi-organ failure (1, 2).

Based on the endemicity of CCHF in our country and neighboring countries, it is necessary for general practitioners and specialists to be familiar with variable manifestations and complications of the disease concerning the fact that there are unusual complications making the disease difficult to diagnose by physicians.

The mortality rate of CCHF differs in various regions and medical centers and it is dependent on virus virulence, immunologic condition of the patient, the possibility of early diagnosis and treatment, and the quality of supportive treatment. Thus, the mortality rate of CCHF is very variable from as low as 0% - 5% to more than 80% (1, 2, 5, 6). Therefore, it is important for physicians to recognize the complications of CCHF in due time. An early diagnosis and treatment of complications might reduce the fatality rate of the disease very significantly.

2. Evidence Acquisition

This is a review article on the complications and mortality of CCHF based on 18 published articles from 2002 to 2018, two text books, and the experimental knowledge of CCHF that the author has acquired as an infectious disease clinician since 1999. Three of the 18 reviewed articles have been published by the author and colleagues in the Infectious Disease Department at Zahedan University of Medical Sciences. The selection of other articles was based on topics, abstracts, results, and the year of publication of the articles. The search for the articles in the Google search engine was through Google Scholar, PubMed, BMC, Medscape, Science Direct, and WHO resources by keywords including CCHF, complications, and mortality. Finally, the abstracts and results of the articles were used and summarized for the reporting of this review article.

3. Results

The results of the selected studies on the disease's complications and mortalities were described as the incidence rate and the type of CCHF complications and the rate and causes of CCHF mortality.

In a study by Kouhpayeh et al. in 2002, the first 18 CCHF cases in SB province in the Southeast of Iran were reported (7). In this study, the incidence rates of complications were as follows: hematologic disorders 100%, clinical hemorrhages 93.7%, DIC 88%, and shock 27.7%. Among hematologic disorders, thrombocytopenia was the most common (100%), followed by the prolongation of PT and PTT (88%), leukopenia (72%), and anemia (72%). Different

forms of hemorrhage including oral and gingival bleeding, epistaxis, melena or rectal hemorrhage, hematemesis, hematuria, hemoptysis, vaginal bleeding, petechia, purpura, and echimosi were seen, among of which was oral and gingival bleeding as the most common one (88%). Five patients died due to shock and DIC (27.7%). The measurement of liver enzymes was done in 13 cases showing the elevation of ALT and AST levels in all the cases. Thrombocytopenia in the range of less than 20,000 was the most common finding. Other less common complications included hair loss and peripheral mononeuritis with paresis of the upper limb that occurred in the convalescent phase, all of which improved after few months (4).

A study by Alavi-Naini et al. in the Southeast of Iran in 2005 reviewed 255 CCHF cases. It was shown that 89% of the cases had bleeding, most commonly in the oral and/or nasal mucosa; the disease was fatal for 37 of 236 patients (15.7%) who were treated with oral ribavirin and 12 of 19 patients (63.2%) who were not treated (5).

The epidemiologic and clinical aspects of CCHF were examined in a review article by Agravat et al. in India in 2014. They expressed that the mortality rate in hospitalized patients ranged from 9% to as high as 50%. Hepatitis, rapid kidney disorder, sudden liver failure, pulmonary failure, and loss of memory and hair during the convalescent period were described as the important complications of CCHF (8).

In a case report by Sharifi-Mood et al. the rare complication "compartment syndrome" was reported in two cases. This syndrome was created by hemorrhage in the arm and forearm of the upper limbs (7).

In a study of pediatric patients with CCHF by Kara et al. in Turkey in 2015, nine children with a mean age of 116 months were evaluated. Only had two cases epistaxis and petechia, but all of them had low leukocyte and platelet count of more than $1905/\text{mm}^3$ and $66000/\text{mm}^3$, respectively. Without ribavirin therapy, all of the patients survived without complications (9).

In a research article by Kazancioglu et al. in Turkey in 2014 on 92 CCHF cases, a high level of aPTT on the third day of hospitalization, diarrhea, somnolence, and delay in hospital admission were independently associated with fatality (15 of 92 cases) (10). Ultrasonographic abnormalities including pericholecystic fluid and increased thickness of gallbladder wall were seen in 38% of all cases and 85.7% of fetal cases. Chest X-ray abnormality was seen in 20% of all cases and 53.8% of fetal cases. All complications were seen in 36.9% of all cases and 93.3% of fetal cases (10). The mentioned complications included bleeding in 21.7% of all cases and 73.3% of fatal cases, secondary infections in 21.7% of all cases and 60% of fetal cases, renal failure in 15.2% of all cases and 66.7% of fetal cases, and respiratory failure lead-

ing to mechanical ventilation in 8.7% of all cases and 53.3% of fetal cases (10).

In a case report by Ahmeti and Raka in Kosova in 2006, a fetal case of CCHF in an eight-year-old boy was reported who died of hemorrhagic shock and pulmonary edema (11).

A study by Onguru et al. in Turkey in 2007 showed in 83 CCHF patients that the platelet count of less than 20×10^9 cells/L and aPPT of more than 60 seconds were associated with mortality. The overall fatality rate in 83 CCHF patients was 10.1% and the overall bleeding rate was 30.1% (12).

A systematic review by Pshenichnaya et al. in 2017 on 42 pregnant CCHF cases in Russia, Turkey, Iran, and five other countries indicated a maternal mortality of 34% and fetal/neonatal mortality of 58.5% due to hemorrhage. Nosocomial transmission was occurred from 6 of 37 pregnant women to 38 other cases. There was no statistically significant difference in maternal death between the first 20 weeks of pregnancy and weeks 20 - 40 (13).

In the study by Metanat et al. in 2013 on 53 CCHF cases in Zahedan, Iran, they showed that hepatitis was prevalent in 45% of the cases and 21% of the patients died, all of whom had liver enzyme levels of more than 10 times the upper normal limit (UNL). Nine of 19 patients with hepatitis (48%) died. Thus, they expressed that a serum transaminase level of ≥ 5 UNL is a risk factor for severe disease and high mortality in CCHF patients (14).

In a case report of nine CCHF cases by Ayatollahi et al. from Yazd, Iran, in 2015, all the nine cases were improved with ribavirin treatment without any mortality and with only one case of hematuria (6).

Sari et al. in Turkey in 2015 reported a case of CCHF who was complicated with pararenal abscess. With antibiotic therapy and percutaneous drainage, the patient regressed (15).

An update on CCHF was done by Appannanavar and Mishra et al. in India in 2011 that described the disease was fatal in 40% - 60% of cases and the death occurred as a result of multi-organ failure, DIC, and circulatory shock. The hemorrhage phase was common and lasted 4 - 5 days in different organs, which may be associated with acute respiratory distress syndrome (ARDS) and diffuse alveolar hemorrhage (16).

Alavi-Naini et al. in Zahedan, Iran, in 2004 reported an unusual intracerebral hemorrhage in a CCHF patient. They expressed that this rare complication of CCHF may induce CNS manifestations of convulsion, coma, confusion, behavioral disorders, and lateralized neurologic signs such as hemiplegia (17).

Gulhan et al. in Turkey in 2015 reported a rare case of myocarditis in a child with CCHF. The patient was a 13-year-old boy with myocarditis who completely resolved after

the convalescent period of the disease (18).

Gul et al. in Turkey in 2011 evaluated 23 hospitalized CCHF patients with a mean age of 12 years for cardiac involvement by electrocardiography and echocardiography. All electrocardiographic parameters were within the normal range. Seven patients (30%) had minimal pericardial effusion with a diameter of < 1 cm. Fifteen (65%) patients had segmental wall motion abnormalities as hypokinesia. During a follow-up with echocardiography, all cases of wall motion abnormality resolved, but pericardial effusion remained in 2 of 7 patients (28%). They concluded that cardiac involvement is more frequent in children with CCHF than in adults, but its course is milder in children than in adults (19).

Bastug et al. in Turkey in 2014 reported one case of CCHF complicated with acute pancreatitis and pleural and abdominal effusions (20).

The WHO website in 2013 ascribed the key facts of CCHF and stated that the evidence of hepatitis is usually seen in CCHF and that severely ill patients may experience rapid kidney deterioration, sudden liver failure, or pulmonary failure after the fifth day of illness. Moreover, WHO has described that the mortality rate of CCHF is about 30% that may raise up to 40% (21).

Oztoprak et al. in Turkey in 2018 investigated the central nervous system involvement in CCHF with magnetic resonance imaging (MRI) in conjunction with clinical and laboratory findings. None of 36 patients showed an MRI finding of acute intracranial event during the course of the disease (22).

In a literature review by Tarvenir and Ozkurt et al. in 2014, overall 15 cases were reported from Turkey. Maternal and fetal mortality rates were found to be 6.6% (1/15) and 40% (6/15), respectively. Fetal lost was found to be 3/4 in the first trimester, 4/8 in the second trimester, and 2/7 in the third trimester. There was hemorrhage in 8 of 15 pregnant women (53.3%). Maternal mortality recorded 1/8 (12.5%) in the cases with bleeding, and fetal/neonatal mortality was 6/6 in the fetus of mothers with bleeding (23).

Yilmaz et al. in Turkey in 2018 studied 22 pediatric CCHF cases who were admitted to a PICU. Bleeding was seen in 17 of 22 cases (77.3%) that was treated by the transfusion of thrombocyte and FFP. Only had 14 patients ribavirin use. There was morbidity and mortality in cases for whom ribavirin was not administered because of side effects and allergies. The mortality rate was determined as zero (24).

The average mortality rate has been reported about 30%, but its overall rate ranges from as low as 0-5% to as high as more than 80% (1, 2, 5, 6, 25). According to the Zoonosis Department of the Health Ministry of Iran, the annual incidence rate of CCHF between 2000 and 2018 varied from 22 to 155 cases across the country and from 4 to 79

cases in SB province (25). The total mortality rate of CCHF in Iran between 2000 and 2005 was variable from 7% to 42% annually, but in SB province with the highest incidence of CCHF, it was higher and more variable from 32% to 50% annually. From 2006 to 2018, the mortality rate of the disease in the country and SB province had a significant reduction with variable annual case fatality rate (CFR) from 2% to 18% across the country and 0% to 28% in SB province. This reduction in the annual CFR has been also more prominent in recent years from 2015 to 2018 both in country (5% - 9%) and in SB province (0% - 5%), which was relatively lower in SB province. Thus, there has been a significant descending trend in the CFR of CCHF after 2015 relative to 2000 from as high as 50% to as low as 0 to 5% in Iran, especially SB province (25).

4. Conclusions

In brief, the complications and mortality causes of CCHF include mild-to-severe hemorrhage in very different sites of patients, especially the oral cavity, due to hematologic disorders including thrombocytopenia and prolonged PT and PTT. Multi-organ failure including hepatic, kidney, and respiratory failure, circulatory shock, DIC and hepatitis are the most common causes of death in CCHF. Less common complications include the loss of memory and hair, mononeuritis, alveolar hemorrhage, secondary infection, intracerebral hemorrhage, compartment syndrome, etc. In pregnant CCHF cases, maternal mortality and fetal/neonatal mortality due to hemorrhage are common.

The mortality rate of CCHF according to WHO has been expressed from 30% to 40%. In different studies in various regions, it ranges from 0% to 50% in hospitalized patients and even up to 80% in patients who are not treated. In our country, Iran, the fatality rate has reduced very significantly in recent years, which is the result of increased experience of physicians in the early diagnosis and treatment and improved management of CCHF patients and also due to more progress in early reporting system and surveillance programs for CCHF in the health system of the country, especially SB province.

Footnotes

Authors' Contribution: The main and corespondent authors are the same and only author.

Conflict of Interests: It is not to declared by the authors.

Ethical Considerations: It is a systematic review article and does not need ethical considerations.

Funding/Support: No funding or support.

References

- Bente DA. *Bunyavirus hemorrhagic fevers, mandell, douglas and bennetts, principles and practice of infectious diseases*. 2015.
- Saebi E. *Crimean hemorrhagic fever, text book of infectious diseases in Iran, viral diseases*. 1993. p. 607-16.
- Rodriguez LL, Maupin GO, Ksiazek TG, Rollin PE, Khan AS, Schwarz TF, et al. Molecular investigation of a multisource outbreak of Crimean-Congo hemorrhagic fever in the United Arab Emirates. *Am J Trop Med Hyg*. 1997;57(5):512-8. doi: [10.4269/ajtmh.1997.57.512](https://doi.org/10.4269/ajtmh.1997.57.512). [PubMed: [9392588](https://pubmed.ncbi.nlm.nih.gov/9392588/)].
- Kouhpayeh HR, Naderi M. Epidemiologic and clinical and laboratory evaluation of 18 hospitalized cases of Crimean-Congo hemorrhagic fever in Bu-Ali hospital of Zahedan. *Iran J Infect Dis Infect Med*. 2002;7:19-22.
- Alavi-Naini R, Moghtaderi A, Koohpayeh HR, Sharifi-Mood B, Naderi M, Metanat M, et al. Crimean-Congo hemorrhagic fever in Southeast of Iran. *J Infect*. 2006;52(5):378-82. doi: [10.1016/j.jinf.2005.07.015](https://doi.org/10.1016/j.jinf.2005.07.015). [PubMed: [16182370](https://pubmed.ncbi.nlm.nih.gov/16182370/)].
- Ayatollahi J, Shahcheraghi SH, Mirjalili M. Report of nine cases of Crimean-Congo haemorrhagic fever from Iran. *Niger Med J*. 2015;56(2):156-9. doi: [10.4103/0300-1652.153409](https://doi.org/10.4103/0300-1652.153409). [PubMed: [25838635](https://pubmed.ncbi.nlm.nih.gov/25838635/)]. [PubMed Central: [PMC4382609](https://pubmed.ncbi.nlm.nih.gov/PMC4382609/)].
- Sharifi-Mood B, Mardani M, Kouhpayeh HR. Compartment syndrome: A very rare complication of Crimean-Congo hemorrhagic fever. *Iran J Clin Infect Dis*. 2006;1(4):205-8.
- Agravat V, Agarwal S, Piparva K. Crimean-Congo haemorrhagic fever: An overview. *Int J Res Med Sci*. 2014;2(2):392-7. doi: [10.5455/2320-6012.ijrms20140504](https://doi.org/10.5455/2320-6012.ijrms20140504).
- Kara SS, Kara D, Fettah A. Various clinical conditions can mimic Crimean-Congo hemorrhagic fever in pediatric patients in endemic regions. *J Infect Public Health*. 2016;9(5):626-32. doi: [10.1016/j.jiph.2016.01.007](https://doi.org/10.1016/j.jiph.2016.01.007). [PubMed: [26868277](https://pubmed.ncbi.nlm.nih.gov/26868277/)].
- Kazancıoğlu S, Akinci E, Bastug A, Kayaaslan B, But A, Aslaner H, et al. Does the course of laboratory parameters help us to predict the outcome of CCHF? *Turk J Med Sci*. 2016;46(2):328-34. doi: [10.3906/sag-1408-89](https://doi.org/10.3906/sag-1408-89). [PubMed: [27511493](https://pubmed.ncbi.nlm.nih.gov/27511493/)].
- Ahmeti S, Raka L. Crimean-Congo haemorrhagic fever in Kosova : A fatal case report. *Virology*. 2006;3:85. doi: [10.1186/1743-422X-3-85](https://doi.org/10.1186/1743-422X-3-85). [PubMed: [17034648](https://pubmed.ncbi.nlm.nih.gov/17034648/)]. [PubMed Central: [PMC1624825](https://pubmed.ncbi.nlm.nih.gov/PMC1624825/)].
- Onguru P, Dagdas S, Bodur H, Yilmaz M, Akinci E, Eren S, et al. Coagulopathy parameters in patients with Crimean-Congo hemorrhagic fever and its relation with mortality. *J Clin Lab Anal*. 2010;24(3):163-6. doi: [10.1002/jcla.20383](https://doi.org/10.1002/jcla.20383). [PubMed: [20486197](https://pubmed.ncbi.nlm.nih.gov/20486197/)].
- Pshenichnaya NY, Leblebicioglu H, Bozkurt I, Sannikova IV, Abuova GN, Zhuravlev AS, et al. Crimean-Congo hemorrhagic fever in pregnancy: A systematic review and case series from Russia, Kazakhstan and Turkey. *Int J Infect Dis*. 2017;58:58-64. doi: [10.1016/j.ijid.2017.02.019](https://doi.org/10.1016/j.ijid.2017.02.019). [PubMed: [28249811](https://pubmed.ncbi.nlm.nih.gov/28249811/)]. [PubMed Central: [PMC5421160](https://pubmed.ncbi.nlm.nih.gov/PMC5421160/)].
- Metanat M, Sharifi-Mood B, Alavi-Naini R, Amjadi A. Hepatitis in patients with Crimean-Congo Hemorrhagic fever. *Zahedan J Res Med Sci*. 2014;16(4):32-4.
- Sari T, Temocin F, Demirelli M, Oral B, Tulek N. A case of Crimean Congo hemorrhagic fever complicated with pararenal abscess. *Arch Clin Infect Dis*. 2015;10(4). e28484. doi: [10.5812/archcid.28484](https://doi.org/10.5812/archcid.28484).
- Appannanavar SB, Mishra B. An update on crimean congo hemorrhagic fever. *J Glob Infect Dis*. 2011;3(3):285-92. doi: [10.4103/0974-777X.83537](https://doi.org/10.4103/0974-777X.83537). [PubMed: [21887063](https://pubmed.ncbi.nlm.nih.gov/21887063/)]. [PubMed Central: [PMC3162818](https://pubmed.ncbi.nlm.nih.gov/PMC3162818/)].
- Alavi-Naini R, Moghtaderi A, Metanat M. An unusual intracerebral hemorrhage. *Can J Infect Dis Med Microbiol*. 2004;15(3):175-7. doi: [10.1155/2004/769260](https://doi.org/10.1155/2004/769260). [PubMed: [18159490](https://pubmed.ncbi.nlm.nih.gov/18159490/)]. [PubMed Central: [PMC2094967](https://pubmed.ncbi.nlm.nih.gov/PMC2094967/)].

18. Gulhan B, Kanik-Yukse S, Cetin J, Ozkaya-Parlakay A, Tezer H. Myocarditis in a child with Crimean-Congo hemorrhagic fever. *Vector Borne Zoonotic Dis.* 2015;**15**(9):565-7. doi: [10.1089/vbz.2015.1769](https://doi.org/10.1089/vbz.2015.1769). [PubMed: [26347941](https://pubmed.ncbi.nlm.nih.gov/26347941/)].
19. Gul I, Kaya A, Guven AS, Karapinar H, Kucukdurmaz Z, Yilmaz A, et al. Cardiac findings in children with Crimean-Congo hemorrhagic fever. *Med Sci Monit.* 2011;**17**(8):CR457-60. doi: [10.12659/MSM.881907](https://doi.org/10.12659/MSM.881907). [PubMed: [21804465](https://pubmed.ncbi.nlm.nih.gov/21804465/)].
20. Bastug A, Kayaaslan B, But A, Aslaner H, Sertcelik A, Akinci E, et al. A case of Crimean-Congo hemorrhagic fever complicated with acute pancreatitis. *Vector Borne Zoonotic Dis.* 2014;**14**(11):827-9. doi: [10.1089/vbz.2014.1623](https://doi.org/10.1089/vbz.2014.1623). [PubMed: [25409276](https://pubmed.ncbi.nlm.nih.gov/25409276/)].
21. World Health Organization. *Crimean-Congo hemorrhagic fever, key facts.* 31 Jan 2013.
22. Oztoprak B, Oztoprak I, Engin A. Is the brain spared in Crimean-Congo haemorrhagic fever? An MR-SWI study to reveal CNS involvement. *Eur Radiol.* 2018;**28**(9):3893-901. doi: [10.1007/s00330-018-5310-9](https://doi.org/10.1007/s00330-018-5310-9). [PubMed: [29532238](https://pubmed.ncbi.nlm.nih.gov/29532238/)].
23. Tarvenir C, Ozkurt Z. *Turkish German Gynecology Congress at April 30th -May 4th., Antalya, Turkey.* 2014.
24. Yilmaz R, Karaaslan E, Gül A, Albayrak SE, Kasap T. The analysis of pediatric intensive care unit admissions of crimean congo hemorrhagic fever patients in the most endemic region in Turkey. *Erciyes Med J.* 2018;**40**(1). S16.
25. Iranian Health Ministry. *Iranian Health Ministry, Health Deputy, Zoonosis Department.* April 2019. Available from: <http://www.behdasht.gov.ir/page/EN>.