Review Article

Crimean-Congo Hemorrhagic Fever

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Abstract

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne viral disease reported from more than 30 countries in Africa, Asia, South-East Europe, and the Middle East. Laboratory findings include prolonged prothrombin, bleeding, and activated partial thromboplastin times. Diagnostic methods include antibody detection by enzyme-linked immunosorbent assay (ELISA), virus isolation, antigen detection, and polymerase chain reaction (PCR). The mainstay of treatment is supportive, with careful maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure. There is no controlled study evaluating oral versus intravenous ribavirin in treating CCHF patients, but few studies have evaluated oral ribavirin. This article reviews the epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment, prevention, and prognosis of CCHF with especial focus on oral ribavirin as the only choice of medical treatment.

Keywords: Crimean-Congo hemorrhagic fever; tick-borne virus; treatment; ribavirin; prophylaxis

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne viral disease. The virus is a member of the *Bunyaviridae* family (1). The primary modes of transmission to human are tick bites, handling of ticks, exposure to blood or tissues of viremic livestock, and direct contact with blood and body fluids of infected persons. After 3-7days of incubation period, sudden onset of fever, myalgia, headache, and gastrointestinal symptoms develop. Hemorrhagic signs can include petechiae, cutaneous ecchymosis, or epistaxis, gastrointestinal tract, or urogenital tract bleeding (2). Among hospitalized patients, case fatality rates range from 5% to 30% (3, 4). Ticks of genus *Hyalomma* are the primary vectors for CCHF, and the primary vectors for Crimean-Congo hemorrhagic fever virus (CCHFV). The virus is endemic throughout Africa, the Middle East, Eastern Europe, and Central Asia. CCHF was described in the Crimea in 1944 during an outbreak, which involved more than 200 cases and was called Crimean hemorrhagic fever. A later virus isolate from Congo was noted to be the same pathogen, resulting in the name Crimean-Congo hemorrhagic fever virus (CCHFV) (5).

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In nature, HFVs reside in animal hosts or arthropod vectors. CCHFV can infect a wide range of domestic and wild animals, including sheep and cattle. Animals are infected with CCHFV by the bite of infected ticks. Seroprevalence is 13-36% in animals (6, 7). A seroepidemiological study of CCHF in local and imported sheep in Isfahan Province of Iran revealed the endemic spreading of the virus in sheep and the need for special attention to prevent the infection in the community and during occupational exposures (8).

A number of tick genera can be infected with CCHFV, but the most efficient and common vectors for CCHFV are the members of the genus *Hyalomma* (9). The most important source of virus transmission is immature *Hyalomma* tick, which feeds small vertebrates blood. Once infected, the tick remains infected throughout its life, and the mature tick may transmit the infection to large vertebrates, such as livestock. Domestic ruminant animals, such as cattle, sheep, and goats will have viremia for one week after becoming infected (10).

Epidemiology

Like other tick-borne zoonotic agents, CCHFV generally circulates in nature in an enzootic tick- vertebrate-tick cycle. Although many domestic and wild vertebrates are infected with CCHFV, as evidenced by development of viremia and/or antibody response, birds except ostrich, in general, appear to be resistant to this infection (11).

The known geographical distribution of CCHFV is the greatest among all tick-borne viruses. There are reports of viral isolation and/or disease from more than 30 countries

in Africa, Asia, South-East Europe, and the Middle East (9, 12).

Interestingly, after several decades of only serological evidence for the existence of CCHFV in Turkey, an outbreak of the disease in the eastern Black Sea region of the country was recently reported (13). Additionally, viral particles were isolated from two of the patients, and phylogenetic analysis of the isolates suggested that two different genetic lineages of CCHFV were circulating in Turkey. These closely resemble virus lineages found in Kosovo and southwestern part of Russia and were clearly distinct from those found in a recent CCHF outbreak in neighboring Iran in 2002 (14) consistent with CCHFV being enzootic in Turkey.

Seasonal variations have been described. In Iran, the high incidence was reported to occur in August and September (15) while in Pakistan, CCHF was more common between March and May and again, between August and October, depicting a biannual surge (16). Changes in climatic conditions have been suggested to be one of the factors that have facilitated reproduction of the tick population, and consequently the increased incidence of tick-borne infectious diseases (17, 18).

Recently it has been mentioned that global warming will make the world as a better place for parasites, and tropical parasitic disease previously unseen in the areas of the continental climatic zones will be widespread around here. Increase in temperature help to reduce the development periods of parasites which use intermediate hosts. Global warming provides biting flies or ticks which serve as vectors disease to remain alive throughout the year, and this increases the risk of occurrence of animal diseases or human diseases such as CCHF (19).

Transmission

Community-acquired CCHF happens through transmission of the virus by direct contact with blood or other infected tissues of livestock or from an infected tick bite. Most of the human cases are workers in livestock and agriculture industry, slaughterhouses, and veterinary practice (10). Humans can be infected incidentally by the bite of an infected arthropod or via aerosol generated from infected rodents' excreta. Infected humans can spread the disease via close contacts which may result in community outbreaks and nosocomial infections. Possible horizontal transmission of CCHFV from a mother to her child indicates the importance of preventive measures for in-house outbreaks of CCHF (20).

Nosocomial transmission is well described in reports from Pakistan, Iraq, United Arab Emirates, South Africa, and Iran (21-23). CCHFV has repeatedly caused nosocomial outbreaks with high mortality, and percutaneous exposure presents the highest risk of transmission (23-26).

The most dangerous settings for acquiring CCHFV are interventions for controlling gastrointestinal bleedings, and emergency operations on patients who have yet to be diagnosed as having CCHF (27). In general, these patients will be diagnosed after the operation, and injuries to the operating team during the operation are usually under-reported. Risk of nosocomial transmission can be minimized by proper and timely infection-control measures, careful management of infected patients, and, in some cases, providing prophylactic treatment to health-care workers after exposure (28, 29). However, community-based control measures are necessary to decrease disease transmission and prevent further spread in the community (30).

Risk factors

A case-control study on epidemiological characteristics of patients diagnosed as having CCHF in Iran (31) showed that history of tick bite is one of the most important risk factors for CCHF acquisition. Other important risk factors included high-risk occupations (butchers, physicians, veterinarians), having contact with livestock, and age over 40 years (31). Abattoir workers who work with large domestic animals are also at risk. Acquisition of the virus usually takes place while slaughtering animals (25, 32, 33). In a multivariate analysis in Turkey, farming, living in a rural area, and being bitten by tick were determined as risk factors for CCHF (34). Hiking, camping, and other rural activities are also risk factors for tick exposure (35).

Consuming meat is not a risk factor by itself because the virus is inactivated by post-slaughter acidification of the tissues and would not survive cooking in any case (35).

Hospital health-care workers are at serious risk of transmission of CCHF infection when caring for patients with hemorrhagic manifestations. Transmission of the CCHF infections and death among health-care workers have been reported in parallel with outbreaks in the general population (27). Seroprevalence study of anti-CCHF IgG among 223 health-care workers in Iran showed that 3.87% of the exposed healthcare workers were positive while none of the unexposed workers were positive. Seropositivity was more frequent among those whose intact skin had come in contact with non-sanguineous body fluids and those who had had percutaneous contacts (36). So, it is proposed that health-care workers take all the protective measures when handling CCHF patients, particularly blood and other body fluids.

Clinical manifestations

The incubation period for CCHF ranges from 2 to 9 days (37). The mean incubation period in Iranian patients was 4.2 days. The disease was more prevalent in middle-aged men (reflecting the culture and lifestyle of Iranian families) (15). Several factors including route of exposure may influence incubation period. In South Africa, among 21 patients for whom reliable data were obtained, the time to onset of disease was 3.2 days after tick bite, 5 days after

livestock blood or tissue exposure and 5.6 days after human blood exposure (38).

There is a variety of potential clinical manifestations following infection with this virus, and not all patients develop the classic form of CCHF syndrome. Patients initially exhibit a nonspecific prodrome, which typically lasts less than one week (9). Clinical manifestations are non-specific and include fever, myalgia, rash, and signs of encephalitis. Symptoms typically include high fever, headache, malaise, arthralgia, myalgia, nausea, abdominal pain, and nonbloody diarrhea. Early signs typically include fever, hypotension, relative bradycardia, tachypnea, conjunctivitis, and pharyngitis. Most cases are associated with cutaneous flushing or rash (9).

The hemorrhagic period is short (usually 2-3 days), develops rapidly, and usually begins between the third to fifth days of disease (9). There is no relation between the temperature of the feverish patient and the onset of hemorrhage (9). Patients may show signs of progressive hemorrhagic diathesis, such as petechiae, mucous membrane and conjunctival hemorrhage, hematuria, hematemesis, and melena. Disseminated intravascular coagulation (DIC) and circulatory shock may ensue (30). Central nervous system dysfunction may be present and manifests itself by delirium, convulsion, cerebellar signs, or coma and imparts a poor prognosis (30).

Distinguishing features of Turkish patients included high fever (73%), malaise (86%), headache (80%), nausea (75%), vomiting (68%), diarrhea (33%), conjunctival injection (42%), heart murmur (4.9%), cough (29%), and rales (16%) (39). Clinical features of hemorrhagic forms of CCHF were described in Iran (15). In this study, clinical manifestations included fever, severe headache, myalgia, loss of appetite, and nausea. Epistaxis, bleeding from the gums and venipuncture sites, petechia and large ecchymotic areas on trunk or extremities were common. Menometrorrhagia was seen in female patients. Less prevalent signs were relative bradycardia, hypotension, tachypnea, abdominal tenderness, watery diarrhea, icterus, and lethargy (15). Hemorrhage within the abdominal muscles can simulate acute appendicitis in CCHF patients (40). Hemorrhagic manifestations were detected in 48.0% of Turkish patients. These manifestations included epistaxis (17.4%), hematemesis (7.6%), melena (1.0%), and hemorrhage from various sites (21.7%) (39).

Hepatomegaly and splenomegaly have been reported to occur in one-third of patients (6). In Turkey, hepatomegaly was detected in 20-40% of cases (13, 34, 39, 41).

The convalescence period begins in survivors about 10-20 days after the onset of illness.

And most patients usually need hospitalization for about 9-10 days (41, 42).

Figure 1: An Iranian case of CCHF presented with fever and massive GI bleeding and large echymoses on both hands.

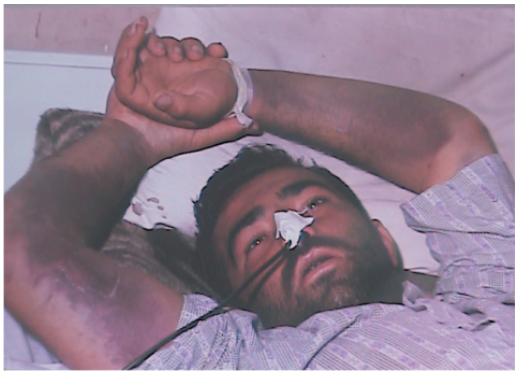
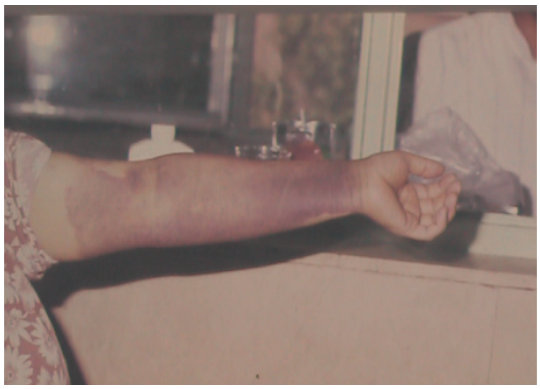


Figure 2: Large echymosis of left hand of an Iranian patient with confirmed Crimean-Congo hemorrhagic fever from Golestan Province, Iran.



Laboratory findings

Laboratory abnormalities may include anemia, leukopenia, thrombocytopenia, increased AST/ALT levels, prolonged bleeding time, prothrombin time (PT), and activated partial thromboplastin time (aPTT), elevated fibrin degradation products (FDPs), and decreased plasma fibrinogen level. Urinalysis may reveal proteinuria and hematuria, and patients may develop oliguria and azotemia (43, 44). The most prevalent laboratory abnormalities in hemorrhagic forms are hematuria, proteinuria, prolonged PTT, and AST> 100 IU/dL (41).

Pathogenesis

The pathogenesis of CCHF is not well described. A common pathogenic feature of

hemorrhagic fever viruses is their ability to disable he host immune response by attacking and manipulating the cells that initiate the antiviral response (45). This damage is characterized by marked replication of the virus together with dysregulation of the vascular system and lymphoid organs (46). Infection of the endothelium has an important role in CCHF pathogenesis (47, 48). Endothelial damage contributes to hemostatic failure by stimulating platelet aggregation and degranulation, with consequent activation

of the intrinsic coagulation cascade. Indeed, fatal CCHF cases had grossly abnormal indicators of coagulation system function from an early stage of illness, and DIC is noted as an early and prominent feature of the disease process (49).

Diagnosis

CCHF should be considered in those having compatible clinical manifestations (e.g., fever, muscle pain, and bleeding), with epidemiological risk factors (tick bite, exposure to tick splashing, for example crushing a tick between two exposed body parts), or travel to or staying in endemic areas for CCHF (we consider travel to or residence in the Iranian provinces of Sistan and Balouchestan, Isfahan, and Golestan to be an epidemiological risk factor because in 1999, when the first cases were reported, we noticed most of them were from these three provinces), or contact with suspected cases of CCHF, or contact with animals, and another important compatible laboratory findings is low platelet count of < 150,000/mm^3 and a WBC count of < 3000 or > 9000/mm^3 (14).

Laboratory diagnosis of suspected CCHF should be performed in specially-equipped, high biosafety level laboratories. Methods of diagnosis include antibody detection by enzyme-linked immunosorbent assay (ELISA), virus isolation, antigen detection, and polymerase chain reaction (PCR).

IgG and IgM antibodies may be detected in serum by enzyme-linked immunoassay (EIA) or ELISA from about the sixth day of the illness. Either the presence of IgM or a 4-fold rise in the titer of IgG antibody in serum samples between the acute and convalescence phases is diagnostic of the disease. IgM remains detectable for up to four months, and IgG levels decline but remain detectable for up to five years. Patients with fatal disease may not usually develop a measurable antibody response and in these individuals, as well as in patients in the first few days of illness, diagnosis is achieved by virus detection in blood or tissue samples (50).

The virus may be isolated from blood or tissue specimens in the first five days of illness, and grown in cell culture (50). Virus isolation is of limited value because it requires a biosafety level 4 (BSL-4) laboratory, which is not available in most endemic areas. More recently, PCR, a molecular method for detecting the viral genome, has been successfully applied in the diagnosis of viral hemorrhagic fevers.

We suggest that diagnosis should be based initially on clinical findings, and laboratory tests be used to confirm or exclude it. Laboratory tests are time consuming and in the event of a large outbreak, may be delayed.

Treatment

The mainstay of treatment of CCHF is supportive, with careful maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure. In addition, treatment of other suspected differential diagnosis, such as bacterial sepsis, should not be withheld while awaiting confirmation or exclusion of the diagnosis of CCHF.

Drug therapy

The CCHFV is susceptible *in vitro* to ribavirin. In some uncontrolled studies on both sporadic and outbreak cases of CCHF, Lassa fever, Bolivian hemorrhagic fever, and hemorrhagic fever with renal syndrome caused by Hanta virus, ribavirin has been reported to have some anecdotal benefit when administered either parenterally or orally (21, 51, 52). In an outbreak situation in which the number of persons requiring treatment is too high to deliver intravenous treatment for everybody, an oral regimen of ribavirin is recommended. In another study, in Pakistan, the authors reported three healthcare workers (two surgeons and a hospital worker) infected with CCHFV who were treated with oral ribavirin. Intravenous ribavirin was unavailable. All patients were severely ill. Based on published reports, all had an estimated probability of death of 90% or more. The patients became febrile within 48 hours of treatment with ribavirin. All patients made a complete recovery and developed IgG and IgM antibody to CCHFV (21).

Ribavirin is contraindicated in pregnancy and because most of patients with CCHF have a self- limited course, direct observation and supportive treatment is recommended. However, in the context of VHF of unknown cause, it is believed that the benefits of treatment with ribavirin outweigh the fatal risks, and ribavirin is therefore recommended (53).

Also, the interferon-induced MxA protein has been shown to have an inhibitory effect on several number of the *Bunyaviridae* family, but the effect of MxA against CCHFV has not previously been studied (54).

In a historical cohort study in Iran, we compared the mortality rate among patients suspected of having CCHF who received oral ribavirin and those who did not. In another study, ribavirin was administered by nasogastric tube. Only one of them died. So it is recommended that in severe and comatose cases of CCHF, ribavirin be administered via this route (15).

In 2003, in Turkey, Ergonul et al. described the role of ribavirin in treating 35 patients who were diagnosed as having CCHF. All of the eight patients who were given oral ribavirin survived (41).

Once more in 2006, in Turkey, Ozkurt et al. demonstrated that the mean recovery time in the cases treated with ribavirin was shorter than those of controls. But the need for blood and blood products, mean length of hospital stay, fatality rates, and hospital expenditure values were not significantly different between the group treated with ribavirin and controls (34).

The doses of oral ribavirin used in the above studies were in accordance with the CDC recommendations for suspected VHF of unknown cause, pending identification of the agent.A major problem in using ribavirin is its side effects. Anemia is one (55). But the above-mentioned studies did not show any significant adverse effects which would limit the recommended dose for hemorrhagic fevers. So, ribavirin seems safe in treating CCHF cases.

In summary there is no controlled study evaluating oral versus intravenous ribavirin in treating CCHF patients, but limited studies have evaluated oral ribavirin. Until controlled studies are available on this topic, current evidence supports administration of ribavirin for treatment of CCHFV.

Prognosis

The case-fatality rate has been estimated to range from 15% to 70% in various studies (23, 56, 57). The lowest case-fatality rate of CCHF in the medical literature (2.8%) has been reported from Turkey.

Swanepoel's evaluation (38) of 15 fatal and 35 nonfatal CCHF patients in South Africa showed that the patients with fatal infections had thrombocytopenia, and markedly elevated levels of AST, ALT, gamma-glutamyl transferase, LDH, creatine kinase (CK), bilirubin, creatinine, and hemoglobin levels were depressed Values for prothrombin, aPTT, thrombin time, and FDPs were grossly elevated, which indicated the occurrence of DIC. Many of the clinical pathological changes were evident at an early stage of the disease and had a highly predictive value for fatal outcome of infection. Changes were present but less marked in nonfatal infections. These data show that hemorrhagic manifestations, confusion, and laboratory evidence of DIC are predictors of fatal outcome.

Prevention

For the individual, use of effective personal protective measures against tick bites and limiting animal exposure are the best ways to avoid the infection. Use of permethrin-impregnated clothing and gear, tucking trousers into boots or socks, wearing light-colored clothing to facilitate tick identification, insect repellants on exposed skin, and daily skin inspection for ticks are mainstays of prevention (56).

Nosocomial spread within the healthcare setting is possible, and appropriate universal precautions should be observed in patient-care areas as well as laboratory environments (22).

A suspected patient should be placed in an isolating room, and negative-pressure respiratory isolation should be considered, particularly if coughing, vomiting, or other activities generating large-droplet aerosols occur. Those entering the patient's room should wear gloves and gowns, and those approaching within one meter should wear face shields or surgical masks and eye protection to prevent contact with blood or other body fluids (56).

The risk of nosocomial spread is greater with severely ill patients. For large groups of people at risk (such as within a refugee camp), local application of acaricide can be considered during seasonal risk (spring to fall) (5). Experience with vaccines against CCHFV is limited and the vaccine is not available for routine use in many countries because of its method of preparation (35).

Post-exposure prophylaxis

Post-exposure prophylaxis should be considered potentially for those exposed to HFVs (including CCHFV) in a bioterroristic attack and all known high-risk individuals such as those who have mucous membrane contact (kissing or sexual contact with a patient) or have percutaneous injury in contact with the patients' secretions, excretions, or blood. This also involves those with close contacts such as living or shaking hands with the patients, process laboratory specimens, or healthcare workers who care such patients before initiation of standard precautions. They should be placed under medical surveillance and should be instructed to record their temperatures twice daily. If a temperature of 38.3°C or higher develops treatment with ribavirin should be initiated promptly as presumptive treatment of CCHF (30). Oral ribavirin, 200 mg twice daily, for 5 days is the recommended dosage for post-exposure prophylaxis (59).

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References

1. Schmaljohn CS, Nichol ST. *Bunyaviridae*. In: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, editors. Fields virology, 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2007. p. 1741–89.
2. Ergönül O. Crimean-Congo haemorrhagic fever. Lancet Infect Dis 2006; 6: 203-14.
3. Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, McGillivray GM, Erasmus MJ. Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. Am J Trop Med Hyg 1987; 36: 120-32.
4. Yilmaz GR, Buzgan T, Irmak H, Safran A, Uzun R, Cevik MA. The epidemiology of Crimean Congo hemorrhagic fever in Turkey, 2002–2007. Int J Infect Dis 2009; 13: 380-6.
5. Wallace MR, Hale BR, Utz GC, Olson PE, Earhart KC, Thornton SA, et al. Endemic infectious disease of Afghanistan. Clin Infec Dis 2002; 34 (suppl 5): S171-207.
6. Gonzalez JP, LeGuenno B, Guillaud M, Wilson ML. A fatal case of Crimean-Congo hemorrhagic fever in Mauritania: virological and serological evidence suggesting epidemic transmission. Trans R Soc Trop Med Hyg 1990; 84**:** 573-76.
7. Morrill JC, Soliman AK, Imam IZ, Botros BA, Moussa MI, Watts DM. Serological evidence of Crimean-Congo

hemorrhagic fever viral infection among camels imported into Egypt. J Trop Med Hyg 1990; 93**:** 201-4.
8. Darvishi M, Ataee B, Chinikar S, Jalali N, Mardani M, Mirkhani M. Seroepidemiology of Crimean-Congo hemorrhagic fever in local and imported sheep in Isfahan Province of Iran. Clin Microbiol Infect 2005; 11 (suppl 2): 649.
9. Hoogstraal H. The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J Med Entomol 1979; 15**:** 307-17.
10. Athar MN, Baqai HZ, Ahmad M, Khalid MA, Bashir N, Ahmad AM, et al. Short report: Crimean-Congo hemorrhagic fever outbreak in Rawalpindi, Pakistan. Am J Trop Med Hyg 2003; 69**:** 284-87.
11. Whitehouse CA. Crimean-Congo hemorrhagic fever. Antiviral Res 2004; 64: 145-60.
12. Swanepoel R. Nairovirus infections. In: Porterfield JS, ed. *Exotic Viral Infections*. London: Chapman and Hall; 1995: 285-93.
13. Karti S, Odabasi Z, Korten V, Yilmaz M, Sonmez M, Caylan R, et al. Crimean-Congo hemorrhagic fever in Turkey. Emerg Infect Dis 2004; 19**:** 1379-84.
14. Mardani M, Jahromi MK, Naieni KH, Zeinali M. The efficacy of oral ribavirin in the treatment of Crimean-Congo hemorrhagic fever in Iran. Clin Infect Dis 2003; 36**:** 1613-18.
15. Mardani M, Bijani B. Clinico-epidemiologic features and outcome analysis of hemorrhagic forms of Crimean-Congo hemorrhagic fever (CCHF) in Iran. 41st Annual Meeting of IDSA, October 9-12, 2003; San-Diego, United States: 763.
16. Sheikh AS, Sheikh AA, Sheikh NS, Rafi US, Asif M, Afridi F, et al. Bi-annual surge of Crimean-Congo hemorrhagic fever (CCHF): a five-year experience. Int J Infect Dis 2005; 9**:** 37-42.
17. Gubler DJ, Reiter P, Ebi KL, Yap W, Nasci R, Patz JA. Climate variability and change in the United States: potential impacts on vector- and rodent-borne diseases. Environ Health Perspect 2001; 109**:** 223-33.
18. Estrada-Pena A. Forecasting habitat suitability for ticks and prevention of tick-borne diseases. Vet Parasitol 2001; 98**:** 111-32.
19. Kara M. Global warming and parasites. Masayuki S, Qing T, Bawudong S, Lei H, Yuzhen Z. Possible horizontal transmission of Crimean-Congo hemorrhagic fever virus from a mother to her child. Jpn J Infec Dis 2004; 57**:** 55-57.
20. Fisher-Hoch SP, Khan AJ, Rehman S, Mirza S, Khurshid M, McCormick JB. Crimean-Congo hemorrhagic fever treated with oral ribavirin. Lancet 1995; 346**:** 472-75.
21. Mardani M. Nosocomial Crimean-Congo hemorrhagic fever in Iran, 1999-2000. Clin Microbiol Infec 2001; **7** (suppl 1): 213.
22. van Eeden PJ, van Eeden SF, Joubert JR, King JB, van de Wal BW, Michell WL, et al. A nosocomial outbreak of Crimean-Congo hemorrhagic fever at Tygerberg Hospital. Part I. Clinical features. S Afr Med J 1985; 68: 711-15.
23. Casals J. Antigenic similarity between the virus causing Crimean hemorrhagic fever and Congo virus. Proc Soc Exp Biol Med 1969; 131: 233-36.
24. Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, Miller GB. A common-source outbreak of Crimean- Congo hemorrhagic fever on a dairy farm. S Afr Med J 1985; 68: 635-37.
25. van de Wal BW, Joubert JR, van Eeden PJ, King JB. A nosocomial outbreak of Crimean-Congo hemorrhagic fever at Tygerberg Hospital. Part IV. Preventive and prophylactic measures. S Afr Med J 1985; 68: 729-32.
26. Shepherd AJ, Swanepoel R, Shepherd SP, Leman PA, Blackburn NK, Hallet AF. A nosocomial outbreak of Crimean-Congo hemorrhagic fever at Tygerberg Hospital. Part V. Virological and serological observations. S Afr Med J 1985; 68: 733-36.
27. Weber DJ, Rutala WA. Risks and prevention of nosocomial transmission of rare zoonotic diseases. Clin Infect Dis 2001; **32:** 446-56.
28. Centers for Disease Control (CDC). Management of patients with suspected viral hemorrhagic fever. MMWR Morb Mortal Wkly Rep 1988; 37 (suppl 3): 1-16.
29. Borio L, Inglesby T, Peters CJ, Schmaljohn AL, Hughes JM, Jahrling PB, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. JAMA 2002; 287: 2391-2405.
30. Izadi S, Holakouie-Naieni K, Madjdzadeh SR, Nadim A. Crimean-Congo hemorrhagic fever in Sistan and Balouchestan Province of Iran, a case-control study on epidemiological characteristics. Inter J Infect Dis 2004; 8: 299-306.
31. 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: 512-18.
32. El-Azazy OM, Scrimgeour EM. Crimean-Congo hemorrhagic fever virus infection in the western province of Saudi Arabia. Trans R Soc Trop Med Hyg 1997; 91: 275-78.
33. Ozkurt Z, Kiki I, Erol S, Erdem F, Yilmaz N, Parlak M, et al. Crimean-Congo hemorrhagic fever in eastern Turkey: clinical features, risk factors, and efficacy of ribavirin therapy. J Infect 2006; 52: 207-15.
34. Ergonul O. Crimean-Congo hemorrhagic fever. Lancet Infect Dis 2006; 6: 203-214.
35. Mardani M, Rahnavardi M, Rajaeinejad M, HolakouiNaini K, Pourmalek F, Rostami M, et al. Crimean Congohemorrhagic fever among health care workers in Iran. Aseroprevalence study in two endemic regions. *76:443-445*
36. Swanepoel R, Gill DE, Shepherd AJ, Leman PA, Mynhardt JH, Harvey S. The clinical pathology of Crimean-Congo hemorrhagic fever. Rev Infect Dis 1989; 11(suppl 4): 794-800.
37. Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, McGillivray GM, Erasmus MJ, et al. Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. Am J Trop Med Hyg 1987; 36**:** 120-32.
38. Bakir M, Ugurlu M, Dokuzoguz B, Bodur H, TasyaranMA, Vahaboglu H, et al. Crimean-Congo hemorrhagic fever outbreak in Middle Anatolia: a multicenter study of clinical features and outcome measures. J Med Microbiol 2005; 54: 385-89.
39. Celikbas A, Ergonul O, Dokuzoguz B, Eren S, BaykamN, Polat-Duzgun A. Crimean-Congo hemorrhagic feverinfection simulating acute appendicitis. J Infect 2005; 50: 363-65.
40. Ergonul O, Celikbas A, Dokuzoguz B, Eren S, BaykamN, Esener H. The characteristics of Crimean-Congo hemorrhagic fever in a recent outbreak in Turkey and the

impact of oral ribavirin therapy. Clin Infect Dis 2004; 39: 285-89.
41. Schwarz TF, Nsanze H, Ameen AM. Clinical features of Crimean-Congo hemorrhagic fever in the United ArabEmirates. Infection 1997; 25: 364-67.
42. Swanapoel R, Coetzer JA. Rift Valley fever. In: Royal Society (Great Britain), ed. *Infectious Diseases of Livestock with Special Reference to Southern Africa*. Vol 1. New York: Oxford University Press; 1994.
43. Peters CJ, Kuehne RW, Mercado RR, Le Bow RH, Spertzel RO, Webb PA. Hemorrhagic fever in Cochabamba, Bolivia, 1971. *Am J Epidemiol* 1974; **99:** 425-33.
44. Geisbert TW, Jahrling PB. Exotic emerging viral diseases: progress and challenges. Nat Med 2004; 10: 110-21.
45. Feldman H, Jones S, Klenk HD, Schnittler HJ. Ebola virus: from discovery to vaccine. Nat Immunol 2003; 3: 677-85.
46. Schnittler HJ, Feldman H. Viral haemorrhagic fever- a vascular disease? Thromb Haemost 2003; 89: 967-72.
47. Burt FJ, Swanepoel R, Shieh WJ, Smith JF, Leman PA, Greer PW, et al. Immunohistochemical and *in situ*localization of Crimean-Congo hemorrhagic fever virusin human tissues and implications for CCHF pathogenesis. Arch Pathol Lab Med 1997; 121: 839-46.
48. Swanepoel R, Leman PA, Burt FJ, Jardine J, VerwoerdDJ, Capua I, et al. Experimental infection of ostricheswith Crimean-Congo hemorrhagic fever virus. Epidemiol Infect 1998; 121: 427-32.
49. Crimean-Congo hemorrhagic fever. McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever: effective therapy with ribavirin. N Engl J Med 1986; 314: 20-26.
50. Huggins JW, Hsiang CM, Cosgriff TM, Guang MY, Smith JI, Wu ZO, et al. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. J Infect Dis 1991; 164: 1119-27.
51. Frame JD. Clinical features of Lassa fever in Liberia. Rev Infect Dis 1989; 11 (suppl 4): 783-89.
52. MxA protein inhibits the replication of Crimean-Congo hemorrhagic fever virus. J Virol 2004; 78: 4323-29.
53. Sheikh AS, Sheikh AA, Sheikh NS, Tariq M. Ribavirin: an effective treatment of Crimean-Congo hemorrhagic fever. Pak J Med Sci 2004; 20: 201-206.
54. Centers for Disease Control and Prevention. Viral hemorrhagic fever: initial management of suspected and confirmed cases. MMWR Morb Mortal Wkly Rep 1983; 32 (suppl 2): 27-38.
55. Shuman M. Abnormalities of platelet and vascular function. In: Goldman L, Bennett JC, eds. *Cecil Textbook of Medicine*. 21st ed. Philadelphia: WB Saunders Company; 2000: 996-1012.
56. Centers for Disease Control (CDC). Management of patients with suspected Viral Hemorrhagic Fever United States. Mardani M. Crimean-Congo hemorrhagic fever. In: Mortazavi-Tabatabaei SA, ed. *Important Zoonoses in Iran*. Tehran: Ministry of Health and Medical Education; 2005: 219-20.