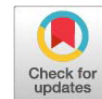


Review Article



Crimean-Congo Hemorrhagic Fever Virus: Advanced Insights into Virology, Pathogenesis, Pathology, Diagnosis, and Treatment

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Abstract | The Crimean-Congo hemorrhagic fever virus (CCHFV), which causes causative agent Crimean Congo hemorrhagic fever (CCHF), is a tick-borne illness that can cause various symptoms, from non-symptomatic infection to deadly viral hemorrhagic fever. More than 30 nations have reported cases of the disease recently. To provide a general understanding of the virology, etiology, pathophysiology, diagnostic testing, and diagnostics, and antiviral treatment of CCHF, we provide a critical reviewed of the literature. The chemical interactions and life cycle of viruses are intricate and are poorly understood. Despite our limited understanding of pathogenesis and immunobiology, multiple routes contribute to the viral entry, replication, and clinical damage. A few autopsy reports have highlighted mention hemorrhages and extravasation involving many body organs. A deeper comprehension of the pathophysiology and immunology of the CCHFV virus will enhance patient care and hasten the creation of CCHF medication countermeasures. Physicians We anticipate that physicians should familiarize themselves with the instruments available for managing and diagnosing human CCHFV infections in human.

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Introduction

As in the 12th century, similar clinical characteristics for Crimean-Congo hemorrhagic fever (CCHF) had been reported in Uzbekistan. A single-stranded RNA virus with an envelope was isolated from an afflicted patient and named the Crimean hemorrhagic fever virus in 1967 (Aslam *et al.*, 2023). Democratic Republic of the Congo in 1956 led to the discovery of another virus, known as the Congo

virus. This virus was first isolated in Congo in 1967 and the name remained Congo virus until early 1970 when it was realized that this virus was serologically related to the Crimean hemorrhagic fever virus which was isolated in the Crimea in 1944, the name therefore changed to Crimean-Congo hemorrhagic fever virus (CCHFV) (Papa *et al.*, 2022). The most common ways for humans to become infected with CCHFV are by tick bites or contact with blood from infected animals; human-to-human transmission

has also been documented, especially in hospital environments. In human beings with severe CCHFV infection, described as the presence of a live virus, a recent worldwide meta-analysis using data collected between 1975 and 2020 found a case fatality of 12 %, a prevalence of 22.5%, an overall seroprevalence of 11.6% for recent infection, and 4.3% for overall past infection. A (-ve) sense, enveloped, multisegmented, single-stranded RNA virus belonging to the genus *Orthonairovirus* and family *Nairoviridae* is called CCHFV (Fanelli and Buonavoglia, 2021). Three single-stranded, -ve sense RNA molecules make up the viral genome, which drives sophisticated replication machinery. The tri-segmented CCHFV genome is prone to errors in replication, which causes antigenic drift and seven different genotypes. Although the cell receptor that CCHFV binds to is unknown, it has recently been suggested that the low-density lipoprotein receptor (LDLR) is essential for CCHFV cell entrance. A wide spectrum of human cells is susceptible to viral infection, which can cause damage both directly through viral infection and indirectly through altered pro-inflammatory immune response and vascular permeability (Quaranta et al., 2020). Humans are the only animals that can get the disease from CCHFV infection, while other cattle and wild animals have been reported to experience asymptomatic transitory viremia that can last up to 15 days. Shock, disseminated intravascular coagulation, and vascular dysfunction that results in an overactive proinflammatory immune response, are correlated with fatal human disease (Bernard et al., 2022). Declining viremia is correlated with the detection of IgM, which is typically detectable 1 week after the illness begins, and IgG, which is typically present 1-2 weeks after sickness onset. However, there is no correlation between the antibody response to CCHFV and the outcome of the disease or vaccination-induced protection (Muzammil et al., 2024).

Virology of CCHFV

The virions of CCHFV are 85–125 nm in diameter, pleiomorphic, and mostly spherical. Ticks from the genera *Hyalomma*, *Rhipicephalus*, and *Dermacentor* serve as vectors and reservoirs for the life cycle of CCHFV, affecting both wild and domestic animals as hosts. Transovarial and transstadial tick-to-tick transmission and tick-to-vertebrate host transmission are all part of the natural cycle (Shah et al., 2023). Humans, unable to infect ticks, are considered incidental or dead-end hosts for the virus. The nonstructural protein (NS) and nucleocapsid protein (NP) are

encoded by the small (S) segment of the CCHFV virions' tri-segmented, -ve sense RNA genome. The large (L) segment encodes the RNA-dependent RNA polymerase (RdRP), while the medium (M) segment encodes several NS and membrane glycoproteins Gc and Gn (Karaaslan et al., 2021). The NP, consisting of a projecting arm, globular domain, and a tiny NS, is encoded by the S segment (NSs). The NP interacts with viral RNA to create ribonucleoprotein (RNP) complexes. Additionally, during the intracellular replication of the virus, the NP interacts with host heat shock proteins and carries out endonuclease activity that supports transcription, assembly, and viral replication. There have been theories suggesting NP and NS may also be involved in cellular apoptosis. The lipid envelope of the virion contains spikes composed of Gn and Gc. Interestingly, there is a strong correlation between the density of LDLR and CCHFV infectivity (Leventhal et al., 2021). Gc is supposed to attach to cellular receptors and has been found to attach to the LDLR present in a range of human cells. It has also been found that neutralizing antibodies generated during the course of the illness target Gc. Gn facilitates membrane fusion. MLD and GP38 may be involved in glycoprotein processing and inclusion into virions. The L segment encodes a single, large protein with the RdRp enzyme and cap-snatching mechanisms that are required for genome replication. Additionally, in the interferon-signaling pathway, the ovarian tumor protease (OTU) contained in the RdRp protein may inhibit various host-cell antiviral systems. Genetically heterogeneous, CCHFV exhibits sequence diversity of 20% in the S segment, 31% in the M segment, and 22% in the L segment among viral isolates (Hawman and Feldmann, 2023). Seven CCHFV genotypes correlate with the geographic region of parent virus identification based on S segment sequencing data; consequently, Atkinson named the diverse genotypes: Asia 1 and 2, Europe 1 and 2, and Africa 1-3. Carroll classified these lineages into six clades: I (Africa 3), II (Africa 2), III (Africa 1), IV (Asia 1 and 2), V (Europe 1), and VI (Europe 2) (Ergünay et al., 2020). A study has demonstrated that multiple methods enable CCHFV to evolve and acquire genetic diversity (Rose, 2021). Antigenic drift from a shared ancestor can cause the virus to accumulate mutations. Additionally, when coinfection with two distinct strains takes place, the multisegmented genome permits reassortment events, producing a sharp antigenic change. Because it can rise due to increased long-distance transfer of infected ticks, re-

assortment is particularly problematic. It is believed that AP92 is either avirulent or has extremely low virulence in people based on indirect epidemiologic data (Granja, 2022).

Pathogenesis of CCHF

Numerous pathways appear to be involved in viral entry, replication, and immune response, even though CCHF pathophysiology and immunobiology are not well characterized. Following infection by a tick, CCHFV enters the skin's basolateral compartment through the epithelium and infects macrophages, dendritic cells, and endothelial cells in nearby capillaries and tiny blood vessels (Jannath and Islam, 2024). The Gc part of the envelope protein assists the virus in entry into a host cell, probably through interaction with LDLR. The decline in the incubation period of CCHF within paritas to tick-associated exposure has been explained as a result of tick-saliva assisted transmission (SAT) to viruses to facilitate their penetration and replication as opposed to exposure to blood and tissue of infected animals (Neogi *et al.*, 2022). In addition to water, ions, host proteins, and exosomes, tick saliva contains a variety of peptide and non-peptide compounds. By opposing host-derived vasoconstrictors, blocking various host cell responses such as platelet aggregation, complement pathways, wound healing, and local coagulation pathways, and fostering local analgesia through bradykinin inhibition, several tick saliva components may be involved in SAT. Depending on the particular tick species, different components of tick saliva may mediate different aspects of SAT (Ambikan *et al.*, 2023). Human cell lines from the kidney, muscle, vascular endothelium, brain, lymphocytes, liver, lung, and bone marrow reproduce CCHFV in vitro. After first entering the body and replicating, CCHFV spreads hematogenously in vivo, potentially infecting the kidneys, liver, lungs, spleen, and adrenal glands. In humanized mouse models, glial cell and astrocyte infection has been reported, but not in human patients as of yet. Apoptosis is one of the primary cellular damages caused by CCHFV infection. Indirect harm caused by the virus includes increased vascular permeability due to the overexpression of soluble adhesion molecules. Damage to the vascular endothelium stimulates platelet aggregation and degranulation, which in turn triggers the intrinsic coagulation cascade and, in extreme situations, results in disseminated intravascular coagulation (Frank *et al.*, 2024). Proinflammatory cytokines are released as a result of CCHFV infection, and this can result in

immune-mediated harm. Severe cases and lethal outcomes have been linked to a robust proinflammatory response. It is yet unknown what immune correlates defend against and resolve CCHF. The development of an antibody response is linked to improved illness outcomes, and IgM and IgG responses are linked to decreasing viremia. Antibodies' function in preventing infection is still unknown, though. Severe instances of CCHF are known to have a low humoral immune response. On the other hand, survivors develop humoral and cellular immunity specific to CCHFV, and there have been no reports of human reinfection to date. Research conducted on nonhuman primates infected with CCHFV indicates that neutralizing activity and antibody titers are not highly correlated with illness severity or outcomes (Ergünay *et al.*, 2020)(Figure 1).

Pathology

Few reports of autopsies or necropsies involving CCHF patients have been released to date. Histopathologic studies on two skin biopsies revealed diffuse erythrocyte extravasation into the epithelial interstitium, which was linked to skin hemorrhages (Portillo *et al.*, 2021). Anecdotally, a liver biopsy taken during a nosocomial outbreak in South Africa in 1984 revealed diffuse extravasation and inter hepatocyte erythrocyte infiltration. The hepatic sinusoids and portal arteries' epithelial cells showed intracytoplasmic virions, while electron microscopy revealed indications of hepatocyte autolysis and pericapillary edema. There were several necrotic foci and widespread necrosis as evidence of liver abnormalities (Kuehnert *et al.*, 2021). Remarkably, immunofluorescence revealed viral antigen foci that were out of proportion to the degree of necrosis, pointing to potential damage mechanisms aside from the direct cytopathic effect of the virus. Patients with more significant liver involvement had greater thrombus development in their portal and central veins. More recent immunohistochemical assessments of liver pathology showed hemorrhagic necrosis and infection of hepatocytes, and Kupffer cells, along with mononuclear portal inflammation. There were also reports of significant lymphocyte depletion and splenic lymphoid apoptosis along with dilated sinusoids (Pittman *et al.*, 2023). A macroscopic examination reveals intestinal hyperemia, liver and spleen capsule bleeding, and petechial hemorrhage of the serosa. In addition to hepatocyte necrosis, necropsy from an autochthonous case in Spain showed bone marrow hemorrhages, full colonic epithelial denudation,

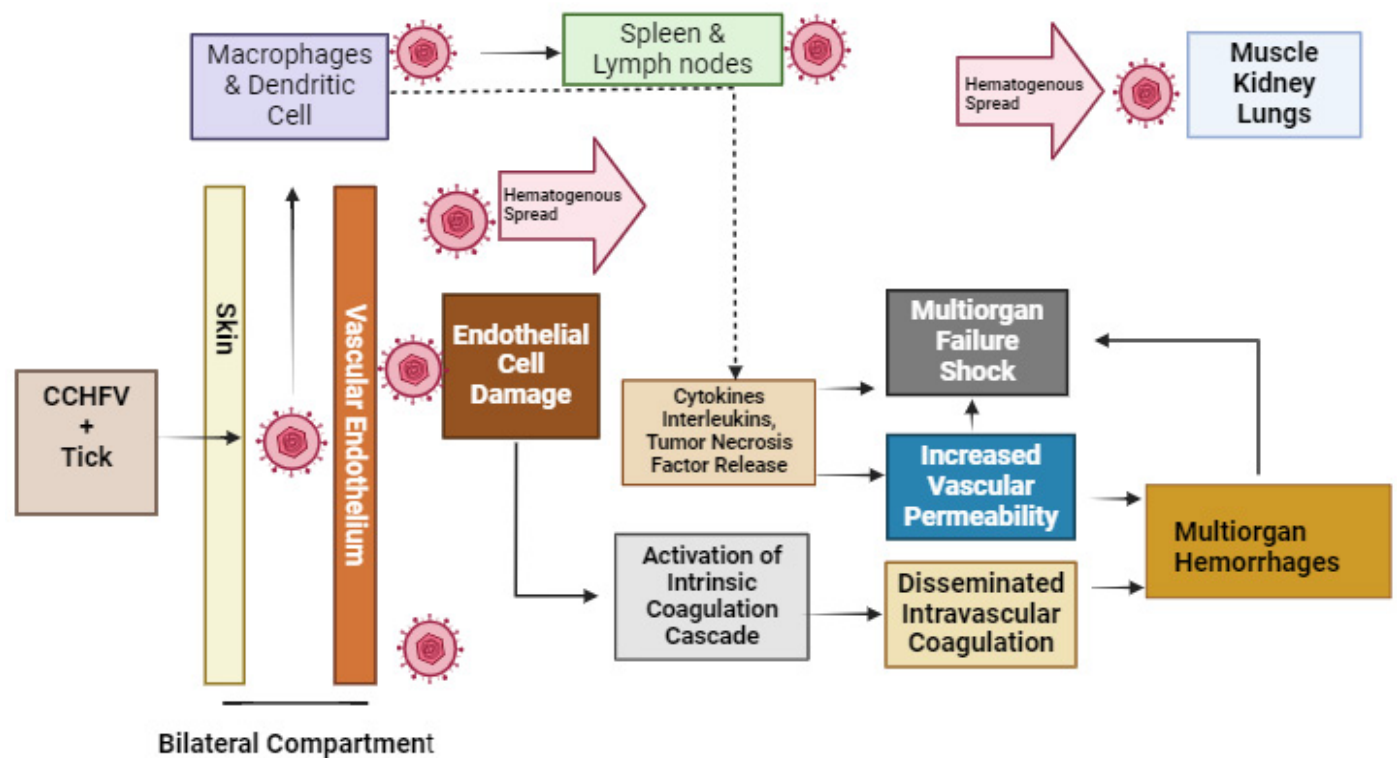


Figure 1: Pathogenesis of crimean congo hemorrhagic fever.

sporadic microthrombi, and cytoplasmic macro- and micro-vesiculation (Gholizadeh *et al.*, 2022).

Diagnosis

The nonspecific characteristics of CCHF are critical for quick diagnosis and the start of violent therapy because they raise a high index of suspicion based on clinical signs and symptoms, epidemiologic history, and preliminary laboratory results (Büyüktuna and Doğan, 2021). In contrast to patients whose infections are detected early, patients in Turkey who experience delays in diagnosis have higher death rates. These delays have been observed in as much as 68% of cases. The Selection of the test is influenced by the clinical phase, and the diagnosis can be made by either the identification of an immune response to CCHFV or viral detection as shown in Table 1. Serologic testing is saved for delayed diagnoses or use after day 5 of symptom onset, even though the majority of viral detection tests will be more sensitive than immunoassays for diagnosis during the hemorrhagic phases (Raabe, 2020). To clarify the diagnosis in a patient suspected of having CCHF, a direct viral assay may be necessary if a negative antibody test is obtained during the second week of illness. Tests for direct viral identification are helpful when CCHF is in its

viremic stages. A broad variety of CCHFV strains can be found using viral cultures employing cell lines or intracerebral injection of nursing mice; yet, these procedures are laborious and can take several days to yield results. RT-PCR can be helpful for diagnosis up to 2 weeks after onset of illness (Hamidinejad *et al.*, 2021). However, due to the great genetic diversity of CCHFV, the accuracy of those tests varies and depends on how well the primers used match the different virus strains. Early in the course of the disease, viral antigen detection procedures can also be employed, such as immunohistochemistry for tissue from autopsy or biopsies or ELISA for blood (Büyüktuna and Doğan, 2021). Assay sensitivity declines as antibodies become detectable, although those assays can be performed on inactivated materials, need less sophisticated laboratory equipment, and provide results quickly. IgM can be detected as early as 3 to 4 days and is often detected 1 week after the development of infection. It peaks in 1 to 4 weeks and practically disappears by the fourth month after the onset of symptoms (Tipih and Burt, 2020). In addition to the direct viral identification techniques mentioned, evidence of an acute infection-consistent serologic response can also be used to confirm the diagnosis of CCHF (Leventhal *et al.*, 2022). ELISA and immunofluorescence tests

Table 1: Laboratory tests for diagnosis of Crimean Congo hemorrhagic fever virus.

Test Selection	Timing	Advantages	Disadvantages	References
RT-PCR, NAAT	Less than 10-12 days after onset of symptoms	In BSL-2 or 3 facilities, NAAT can be performed on inactivated material. There are numerous multiplex tests available, some of which can measure viral load.	varying sensitivity based on how well the primers and the infecting strain match. Depending on the location, sensitivity and specificity can change.	(Serretiello <i>et al.</i> , 2020)
Viral Culture	shortly after the onset of symptoms	Detect a broad variety of CCHFV strains.	BSL-3 or 4 laboratories are needed, and they are hard to come by in endemic areas. takes several days to produce an outcome.	(Cross <i>et al.</i> , 2020) (Serretiello <i>et al.</i> , 2020)
Immunohisto-chemistry	1-2 weeks after onset of symptoms	can support the diagnosis of fatal cases in retrospect.	Requires Biopsy.	(Pongombo, 2022)
Viral IgG detection ELISA	4-5 days after onset of symptoms	Timely provide results. less specialization is needed in Laboratory equipment	sensitivity declines with the detection of CCHFV antibodies.	(Shrivastava <i>et al.</i> , 2021)

are the most popular methods for CCHFV serologic testing, which is normally advised 4-6 days following the onset of symptoms, the ELISA results are reliable with severe infections. Certain CCHFV antibody assays have been shown to cross-react with the Hazara virus, and the Nairobi sheep disease serogroup, which also causes disease in some CCHF endemic locations (Matthews, 2022).

Antiviral Treatment

Ribavirin has also been used to treat CCHF in addition to post-exposure prophylaxis. In mouse models, ribavirin lowers CCHFV levels (Fabara *et al.*, 2021). However, infected humans treated with ribavirin did not show comparable reductions in viremia compared to untreated control patients. Nevertheless, the majority of evidence from human studies of ribavirin for CCHF treatment comes from retrospective analyses and case-control studies (Dai *et al.*, 2021). Apart from diverse study designs, other heterogeneous factors that could impact study results are differences in ribavirin administration routes and dosages, when to start ribavirin, co-administration of other possible medications that modify the course of the disease, patient severity, and variances in the predominant strains of CCHFV in different regions (Nasirian, 2020). These elements make it more difficult to compare the efficacy of ribavirin between studies. Favipiravir inhibits RNA polymerase activity in a broad range of viruses. Studies conducted in vitro indicate that favipiravir-induced premature chain termination for CCHFV surpasses that of ribavirin and that combining ribavirin and favipiravir has synergistic antiviral effects (Łagocka *et al.*, 2021).

Conclusions and Recommendations

CCHFV is a tick-borne, encapsulated, RNA virus. The chemical interactions and natural cycle of the virus are intricate and are poorly understood. We have revealed that several biochemical events are involved in the viral entry, replication, and development of pathological manifestations. There are very scanty reports of scarcity of information on autopsy of multi-organ involvement with extravasation and hemorrhages, and hence the pathogenesis and immunobiology need further studies in the future. Increasing our understanding of the pathophysiology and immunology of CCHFV will improve patient treatment and expedite the creation of CCHFV-specific medications. Given its extensive geographic distribution, capacity to spread to new areas, genetic diversity tendency, and potential for severe and deadly illness, CCHFV continues to pose a hazard to public health. While infection control strategies can help lower the risk of CCHFV transmission in community and clinical settings, they must be applied correctly and consistently. New prophylactics, therapies, and diagnostic tests for CCHF are desperately needed. The current lack of approved therapeutic and preventive medications, knowledge gaps regarding the pathophysiology and immunology of CCHFV, and the sluggish development of medical countermeasures against CCHFV are partly caused by the scarcity of animal models and the stringent biosafety measures required to work with CCHFV safely.

Author's Contributions

Muhammad Sajid: Conceptualized and wrote the manuscript.

Muhammad Azam, Muhammad Hamid and Usama Ayyub: Contribute to Investigation and Data Collection.

Conflict of interest

The authors have declared no conflict of interest.

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