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Emerging Threat: The Rising Significance of Crimean-Congo Hemorrhagic Fever as a Zoonotic Virus

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Introduction

This viral disease was first found in the 1960s in the Congo and later in Crimea regions of the African continent. This virus causes severe febrile illnesses and is widespread across Africa, the Middle East, Southeast Asia, and parts of Europe, following the range of its Hyalomma tick host (1). The virus can infect various animals like hares, rodents, ostriches, and livestock without showing symptoms, aiding in its spread. CCHFV is transmitted to humans through tick bites or contact with infected animals, leading to fever and, in severe cases, dangerous bleeding with an average mortality rate of 30-50% (2). Till today there are no approved vaccines or treatment protocols for CCHF. Recent research has provided more insights into how the virus works, leading to advancements in potential vaccines and therapies for this deadly disease (3).

Molecular biology of CCHF virus:

Within the order Bunyavirales, the virus falls under the family Nairoviridae, renowned for its capacity to induce severe hemorrhagic illness in humans. It is an enveloped negative-sense RNA virus. The viral surface glycoproteins Gn and Gc are responsible for receptor binding and entry into host cells. Unlike other viruses in the same family that cause little to no disease in humans, CCHFV has a more complex genomic organization (4).

Reports of CCHF in India:

The initial confirmation of CCHF in India was recorded in Gujarat State in 2011 during a nosocomial outbreak. Since then, many Gujarat State areas have reported multiple outbreaks and

occasional instances of this disease. Research carried out at the National Institute of Virology (NIV), Pune, has revealed that domestic animals from Rajasthan State's Sirohi district have anti-CCHF IgG antibodies (11).

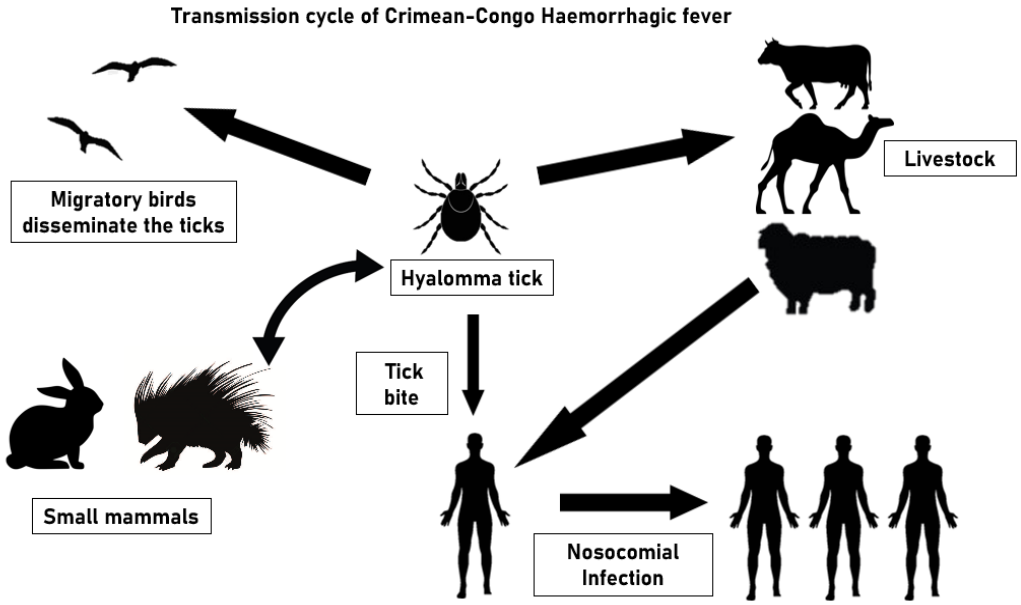

Fig 1. Transmission cycle of CCHF virus

Clinical manifestation:

There are four separate phases. The initial infection is frequently misdiagnosed after exposure by tick bites or animal husbandry, but nosocomial or intrafamily transmission can also happen while sick patients are being cared for. Depending on the source of exposure, the incubation period following infection might be as little as 1-3 days (5). Human infections may advance to a pre-hemorrhagic stage following the incubation phase, which is marked by a variety of nonspecific symptoms such fever, malaise, myalgia, and nausea. Within the first week following infection, the disease can quickly advance from this pre-hemorrhagic phase to hemorrhagic disease. Uncontrolled bleeding, liver damage, inflammatory immunological responses, and, in extreme situations, disseminated intravascular coagulation, shock, and death are the hallmarks of this stage of the illness. Recovery starts 10–14 days after infection in those who make it, and it's linked to the establishment of anti-CCHFV immunity as well as a return to normal blood chemistry and hematology (6).

Diagnosis:

To manage patients and stop the spread of Crimean-Congo hemorrhagic fever (CCHF), it is critically important to detect the illness rapidly. Initially, CCHF may resemble other febrile illnesses.

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Although some factors such as occupation, outdoor activities, tick bites, residing in or visiting afflicted regions, or contact with sick people may provide hints, a definitive diagnosis can only be made by laboratory testing. Blood samples are recommended for direct viral detection or indirect immune response monitoring. Sample handling must be done properly for safety. Quantitative reverse transcription polymerase chain reaction (qRT–PCR) is an effective and quick detection tool; some tests may identify different forms of CCHFV (7). Tests tailored to a given location may be necessary due to genetic variations in the virus. Simpler testing tools, such as loop-mediated isothermal amplification, could be helpful in isolated locations. Targeting a particular protein provides an additional viral detection method, but potentially less sensitive than PCR (8).

Virus isolation is a slower process done in specialized labs. Testing for antibodies with enzyme-linked immunosorbent assays or immunofluorescent assays can confirm infections. Kits can be used to check for antibody production, which can be delayed in severe cases. Confirmatory tests using pseudotype viruses or virus-like particles expressing CCHFV proteins can be more widely used and easier to handle. While labs often conduct CCHF diagnostics, onsite testing can help speed up the response. Regular quality checks are vital to ensure accurate results, as past issues with test sensitivity and specificity underline the need for improved protocols.

Treatment:

Antivirals:

Ribavirin, a commonly used treatment, has sparked debate regarding its efficacy due to conflicting data. Favipiravir, another drug, has demonstrated promising outcomes in animal studies, even post-infection. However, its long-term effectiveness and ability to fully control the virus remain uncertain (9). Other potential treatments like 2′-deoxy-2′-fluorocytidine and molnupiravir are under exploration, working through various mechanisms such as disrupting the viral replicase or inhibiting specific viral proteins. While showing success in laboratory settings, further research is necessary to validate their effectiveness in treating CCHF in humans (10).

***Antibody-based therapy*:**

Have shown promising results in treating the illness and several studies have revealed that using plasma or antibodies from CCHF survivors can benefit severely ill patients. While convalescent plasma treatments have limitations, research has demonstrated the effectiveness of mouse and human monoclonal antibodies in protecting against CCHFV in infected mice. Some antibodies have shown the ability to protect neonatal mice but failed in adult mice lacking a specific type of immune response.

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Interestingly, certain antibodies targeting non-neutralizing epitopes in the CCHFV GP38 protein have also shown protective effects in animal models. Overall, further studies are needed to determine the best timing and dosages for antibody treatments against CCHFV, as well as to explore different mechanisms of action for these antibodies (9).

Anti-inflammatory drugs:

Anti-inflammatory drugs have shown promise by the dysregulated inflammatory and cytokine storms that contribute to the disease's severity. Research conducted on interferon-blockaded mice highlighted the potential protective effects of TN receptor blockade and antibodies that block TNF signaling against lethal CHF infection. The availability of clinically approved TNF therapeutics and other cytokine-targeting treatments may offer new avenues for the management of CCHF in the future. Further investigation is needed to assess the effectiveness of anti-inflammatory drugs in combating this serious illness (10).

Preventive measures:

To prevent infections, it is crucial to address the various risk factors associated with the exposure groups of CCHF.

For farmers,

- wearing long sleeves and pants, limiting time spent in areas infested with ticks, and using pest management strategies to control tick populations on the farm can reduce the risk of transmission.

Healthcare settings

- wearing personal protective equipment (PPE) is necessary when caring for patients with CCHFV to prevent transmission.
- Educating people in endemic areas about the risks of CCHF, such as tick bites and workplace hazards, can help individuals reduce their exposure risk and recognize early symptoms.
- Quarantining livestock that may be carrying the virus or infected ticks before transportation or slaughter can also help prevent the further spread of CCHFV to new areas.

Conclusion:

Despite the global prevalence of the Crimean-Congo Hemorrhagic Fever Virus (CCHFV) and the substantial population at risk, numerous uncertainties persist regarding the virus's disease-causing mechanisms. There is a critical need for further investigation to unveil novel functions of viral proteins and to advance the development of enhanced tools and animal models for studying CCHFV

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pathogenesis. In regions where the disease is endemic, preventive measures such as education, tick exposure reduction, livestock treatment to manage tick infestations, and the implementation of quarantine and protective measures during high-risk activities are imperative. Rapid diagnostic methods, effective vaccines, and antiviral treatments are pivotal in mitigating the impact of CCHF on individuals and healthcare systems. Understanding the protective mechanisms of vaccines against CCHFV can offer valuable insights into immune system responses against the infection, informing the development of treatment strategies that bolster immune defenses while minimizing adverse effects. Collaborative efforts across diverse fields including virology, immunology, vaccinology, entomology, veterinary science, and public health are essential to effectively address the significant threat posed by CCHFV infection in endemic areas.

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