Crimean-congo hemorrhagic fever virus (cchfv) treatment

After an outbreak in 1944 in the Crimea region, a new disease was initially classified as Crimea Hemorrhagic fever. Afterwards, a similar disease appeared in the Congo and was later found to show similar pathogenesis as the Crimean Hemorrhagic fever. Thus, the name of the disease was modified to Crimean-Congo Hemorrhagic fever (CCHF). [i] Although this disease was recently classified, the first occurrence of this disease was noted in the 12th century. [ii] Today, it is known that the disease is caused by a small virus known as Crimean-Congo Hemorrhagic Fever Virus (CCHFV) found on ticks. For its small size, the virus is surely capable of causing a disease in a tremendous geographic region and is truly remarkable in the number of ways it employs to transfer the disease.

CCHFV belongs to the Nairovirus genus in the Bunyaviridae family. The spherical virion, with a diameter of 100 nm, is enclosed by a ‘ host cell-derived lipid bilayered envelope approximately 5-7 nm thick, through which protrude glycoprotein spikes 8-10 nm in length’. [iii] The virus’ genome consists of three negative sense RNA strands placing it in class V of the Baltimore classification system of virus. The three specific RNA strands are referred to as S, M, and L strands. These three strands are surrounded by nucleocapsid protein [iv] , making ribonucleocapsid structures. The S, M and L strand encode ‘ the virus nucleocapsid, glycoprotein, and L polymerase proteins, respectively’. [v] Furthermore, the M strand of the genome encodes a larger 75KDa G1 glycoprotein and a smaller 37KDa G2 glycoprotein [vi] which bind to the appropriate cellular receptors leading to the endocytosis of the virus. [vii] Along with the G1 and G2 proteins, Sanchez et al. also

observed an 85KDa, 140KDa, 160KDa, and N proteins present in infected CCHF virus cells. [viii]

The CCHF viruses exist in a tick-vertebrate-tick cycle with a primary reservoir in the Hyalomma tick. This tick may infect various domestic and wild vertebrates thus making them susceptible to transfer the virus to humans. However, birds, in general, seem to be immune to CCHFV infection and do not develop antibodies against CCHFV even though the ticks which feed on these birds may carry the virus. Still, occurrence of CCHFV has been noted from South Africa to Europe to Middle East to India, China, and Russia. This, according to Whitehouse, gives CCHFV the ‘ greatest geographical range of any tick-borne virus’. [ix] From this, and other evidence suggesting the presence of three genetically related isolates as well as two varying lineages of CCHFV within Turkey [x] , it is apparent that CCHFV has the ability to cause a disease throughout the world.

The most at risk populations are where the Hyalomma ticks are present; exposure may occur from a direct tick bite or from caring, or slaughtering, an infected animal. Thus, people who work outdoors, and those who work with agriculture or livestock, are most susceptible to catch the disease. Moreover, due to the ability of the virus to spread from close contact, through vertical transmission, and nosocomial transmission [xi] by exposure to the blood of infected personnel, anyone with contact to an infected individual is at risk for catching the disease. Lastly, although the virus is inactivated by the post slaughter acidification and cooking of infected meat [xii] ; countries may choose to restrict importing meat from areas where CCHFV is endemic. This may result in economic stress upon the region where CCHFV is present.

Due to the severity with which CCHFV may cause a disease in a population, it is placed in the BSL-4 category [xiii] of viruses and thus requires extreme caution when research is done. Due to this fact, there is only limited research done on the life cycle of CCHFV. Whatsoever, the steps in the life cycle are thought to be similar to those of the Bunyaviridae family of viruses. The first step in the life cycle is the entrance of the virus into the host cell [xiv] . Specifically, Simon et al. have recently shown CCHFV to bind clatherin on cellular surfaces to obtain entry into the cell via endocytosis. [xv] Once the endocytic vesicle is in the cell, the viral envelope fuses with the membrane of the endocytic vesicle and releases the ribonucleocapsids and RNA-dependant-RNA-polymerase into the cellular cytoplasm. [xvi] Within the cytoplasm, the viral RNAs steal the 5′ cap from the host mRNA in order to undergo the primary transcription. [xvii] Cellular machinery is then used to translate the product of primary transcription to make viral proteins. [xviii] Over time, accumulation of the N protein results in the virus switching to its replication phase. [xix] In this phase, the viral RNA is replicated through a cRNA intermediate. Finally, the assembly of the virion may occur at the Golgi by budding into the Golgi or by directly exiting the cell through the plasma membrane. Comparatively, if the virion is formed in the Golgi, then egress from the cell occurs when the Golgi body, containing the virion, fuses with the cellular plasma membrane. [xx]

In humans, the course of disease caused by CCHFV may be divided into four stages: incubation, prehemorrhagic, hemorrhagic, and convalescence. The incubation stage may last for 1-3 days depending of the route of viral contraction, the viral dosage, and the ability of the individual to induce

phenotypic changes in the virus. [xxi] This stage leads to the prehemorrhagic stage which is characterized by “ fever, chills, headache, dizziness, photophobia, back and abdominal pains, nausea, vomiting, diarrhea, loss of appetite, neuropsychiatric changes, and cardiovascular abnormalities”. [xxii] The third stage of the infection starts in 3-6 days after infection and has a 30-50% mortality rate in people. This hemorrhagic stage may be characterized by “ petechiae, ecchymosis, melena, hematemesis, epistasis, intestinal hemorrhage, vaginal bleeding, gingival bleeding, liver necrosis and cerebral hemorrhage”. [xxiii] Those individuals who survive the hemorrhagic stage have successfully made antibodies and fought the virus. They are said to enter the convalescence stage of the disease which generally occurs 15-20 days post infection. In this final stage of the disease, the patient usually has “ generalized weakness, weak pulse, temporary loss of hair, polyneuritis, sweating, headache, dizziness, nausea, poor appetite, labored breathing, poor vision, loss of hearing, and loss of memory”. [xxiv]

Although little is known about the mechanism of its pathogenesis, the virus causing CCHF can have fatal results on the person. The fatality of the disease occurs because of its ability to cause a wide range of symptoms including “ cerebral hemorrhage, severe anemia, severe dehydration, and shock associated with prolonged diarrhea, myocardial infarction, lung edema, and pleural effusion€¦terminal multiple organ failure, including cerebral, liver, and kidney failure and cardiac and pulmonary insufficiency”. [xxv] Furthermore, Whitehouse mentions that endothelial damage is caused by the early stages of the virus and that the inflammatory response, and antibodies, are absent in patients with this virus. This highlights the ability of

the virus to evade the immune response by shutting it off and also suggests that the CCHFV attacks the endothelial cells. Moreover, other studies suggest that the disseminated intravascular coagulopathy, which gives the virus its hallmark hemorrhagic quality, is caused by the ‘ apoptosis of lymphocytes€¦ induction of proinflammatory cytokines and the dysregulation of the coagulation cascade’. [xxvi]

For the wide range of symptoms caused by CCHFV, treatments are lacking greatly. The only drug being administered to fight the virus at the moment is Ribavirin. This drug is best administered orally as it has shown to be degraded in the GI tract and liver when administered intravenously. Moreover, it acts at the early stages of viral infection to interfere with the viral life cycle. This may be done, for example, by interfering with the cap stealing event of CCHFV. [xxvii] Additional research on suckling mice has also shown Ribavirin to be effective in the liver, to decrease viremia, and to reduce mortality. [xxviii] Similarly, a study on humans confirmed 80% efficacy rates among CCHF patients treated with Ribavirin. [xxix]

The other treatment for CCHF is only supportive and includes administration of platelets and fresh frozen plasma (FPP). Administration of platelets is thought to help by countering the effect of thrombocytopenia. Meanwhile, the theory behind administering FPP is to introduce normal clotting factors to the patient. [xxx]

Few of the drugs under consideration to fight CCHF include the antiviral Ribamidine [xxxi] and the MxA protein. [xxxii] Moreover, although more research is needed, the Interferon-stimulated genes, and the proteins ISG20,

P56, RNA-specific adenosine deaminase 1, promyelocytic leukemia protein and guanylate-binding protein 1 show antiviral activity against CCHFV. [xxxiii] Lastly, although there is no vaccine against CCHFV, hope arises due to the presence of one case in which antibodies from an individual who survived CCHF were administered to a patient suffering from CCHF; this patient recovered and survived. [xxxiv]

Due to the precautions which must be taken when working with the Crimean-Congo Hemorrhagic fever virus, and also the absence of a suitable organism for research [xxxv] , it becomes extremely difficult to determine the mechanism with which the CCHFV causes disease. In turn, all of these factors combine to account for the limited medicine we have. However, the severity of the Crimean-Conge Hemorrhagic virus and the different transmission routes among individuals demands the need for research and a better cure in both humans and animals. Perhaps, the mechanism birds use to evade the disease can be studied to give indirect insight about the virus and obtain advancements. Whatever it may be, further studies will most definitely be done to gain advancements in this field.