Asian Journal of Research in Infectious Diseases

Volume 15, Issue 3, Page 17-25, 2024; Article no.AJRID.114632
ISSN: 2582-3221

Compendium: Management of Viral Hemorrhagic Fever (Viral Fever), Involving Its Pathogenesis

Yash Srivastav [a++*], Aniket Kumar [a], Jaya Singh [b], Aditya Srivastav [a] and Mohd. Imtiyaz Ahmad [a]

[a] Azad Institute of Pharmacy & Research, Lucknow, U.P, India.
[b] Tahira Institute of Medical Science, Gorakhpur, U.P, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJRID/2024/v15i3334

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/114632

Review Article

Received: 17/01/2024
Accepted: 21/03/2024
Published: 23/03/2024

ABSTRACT

The term "Viral Hemorrhagic Fever" (VHF) describes a severe feverish sickness characterized by aberrant vascular control, vascular damage, and hemorrhagic symptoms. Multiple viruses belonging to distinct families are the cause of this illness. The viruses that cause VHF are categorized into seven distinct families according to the International Committee on Taxonomy of Viruses' most recent classification: Hantaviridae, Nairoviridae, Filoviridae, Phenuiviridae, Paramyxoviridae, Arenavidae, and Flaviviridae are the families involved. The concept of virus hemorrhagic fevers (VHFs) originated in the 1930s when Soviet researchers were studying hantaviral hemorrhagic fever (HF) with renal dysfunction. Dengue fever/Dengue haemorrhagic fever and Kyasanur forest sickness are the two most common viral hemorrhagic fevers (VHF) in India that are transmitted by arthropod vectors. The diagnosis of community-acquired pneumonia (CCHF) in India is greatly hampered by the co-occurring symptoms of hemorrhagic fevers such as

[++] Assistant Professor (Master of Pharmacy in Pharmaceutics);
**Corresponding author: E-mail: neelashsrv76@gmail.com;*

dengue, Kyasanur forest sickness, Hantavirus hemorrhagic fever, and other illnesses such as leptospirosis, meningococcal infections, and malaria. The pathophysiology, aetiology, diagnosis, treatment, symptoms, and indicators of virus hemorrhagic fevers (VHFs) are all covered in this review article.

Keywords: Virus Hemorrhagic Fevers (VHFs); epidemiology; etiology; pathogenesis; management.

1. INTRODUCTION

Acute zoonotic diseases known as viral hemorrhagic fevers (VHFs) initially appear to be related to platelet malfunction or destruction [1]. When Soviet researchers were examining hantaviral hemorrhagic fever (HF) with renal syndrome in the 1930s, they developed the idea of virus hemorrhagic fevers (VHFs). Later on, these investigators expanded the categorization to encompass Omsk HF and Crimean-Congo HF. The four taxonomic families Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae are among the 23 enveloped RNA viruses that cause the diseases included in the VHF concept. These viruses are similar in that their genetic material is encased in single-stranded RNA, they target primary dendritic, monocyte, and macrophage cells, they replicate cytoplasmically, and they cause symptoms related to the gastrointestinal tract and nervous system. Elevated blood viremia levels and severe cases are related. Though numerous arthropods and rodents act as efficient reservoirs for viral transmission, humans are thought to be the accidental hosts. Humans can contract VHF from arthropod bites or indirectly from contaminated bodily fluids (saliva, urine, faeces, and other fluids) from patients who are experiencing the disease. Viruses that cause VHFs often have a zoonotic life cycle and are limited in their geographic range. An illness known as "viral hemorrhagic fever" in humans, which is brought on by certain viruses such as the Lassa, Dengue, Ebola, and Crimean-Congo hemorrhagic fever viruses, is frequently linked to an unclear shock syndrome. All these viruses, however, appear to be directed both directly and indirectly towards the vascular system, and specifically towards the vascular endothelium [2]. Except for the Ebola virus (EBOV), reservoirs for all four of the viral families are known to exist in zoonoses. Although fruit bats are thought to be the reservoir, only EBOV viral sequences and serological evidence have been found [3]. The bulk of the viruses linked to these illnesses are arthropod- or rodent-borne infections, meaning that they need vectors to be transmitted to humans. These illnesses are typically limited to the endemic regions where their hosts reside due to their zoonotic nature. Nevertheless, these illnesses are no longer exclusive to the regions where they originated due to rising human migration and greater globalization [4]. A collection of acute zoonotic illnesses known as viral hemorrhagic fevers (VHFs) have high fatality rates and are brought on by seven distinct virus families that can infect both people and animals. Hemorrhagic symptoms and, if left untreated, fatal platelet failure are the hallmarks of VHF. The majority of VHF is spread to people by a variety of vectors, including mosquitoes, voles, rats, bats, and ticks. Infections like Dengue, Ebola, Yellow Fever, and Hantavirus are linked to several common and fatal VHF. These illnesses can occasionally result in significant outbreaks and are endemic in a particular region of the world. Worldwide, developing and re-emerging VHFs continue to pose a serious health risk because of the dismal prognosis and dearth of treatments or vaccinations tailored to address them [5]. Just two viruses are known to regularly cause hemorrhagic fevers in India, out of the twelve that can cause the illness. Crimean Congo hemorrhagic fever (CCHF) and Chikungunya fever [6]. Management: There is currently no effective cure for VHFs. There are some people who have responded well to ribavirin treatment for Lassa fever or HFRS. Some individuals with EVD or Argentine hemorrhagic fever have responded well to treatment with convalescent-phase plasma. Patients primarily need to use supportive therapy. There is a vaccine to prevent hemorrhagic fever in Argentina. The main focus of prevention efforts is preventing contact with both the host species that harbors the disease and individuals who have an acute infection. The goal should be to stop the spread of the virus from person to person if prophylactic measures are ineffective and a case of VHFs does arise. Since rodents are among the hosts that carry the viruses that cause hemorrhagic fever, the following are some methods of disease prevention: managing the rodent population. preventing rodents from residing in or entering houses and offices [7].

2. EPIDEMIOLOGY

Diseases carried by rats are linked to viruses in the Arenaviridae family. The New World and Old World viral groups are separated out of these viruses. Every virus is associated with rodents found in America, Asia, Europe, and Africa. Contact with mouse urine or droppings can result in infection. Aerosol transmission can also happen when rodent excrement is disturbed and releases virus particles into the atmosphere. Human-to-human and nosocomial infections can also be brought on by some viruses. The arenavirus Lassa virus has been responsible for outbreaks in West Africa that have resulted in up to 50% case fatality rates. The most effective way for this virus to spread is by direct contact with multimammate rats, however infection can also happen if rodents are caught to be eaten [8]. Bunyaviruses can cause mild to severe sickness and are spread by arthropods and rodents. Rift Valley fever, hantavirus infections, and Crimean-Congo hemorrhagic fever can all be brought on by these viruses. Since Crimean-Congo hemorrhagic fever is the most common infection in humans that is transmitted by ticks, it is a condition that needs to be taken seriously. This illness is brought on by a Nairovirus, which is indigenous to Asia and Africa and is spread by Ixodid ticks. Exposure to blood or other bodily fluids can also result in transmission, which can cause a serious infection with a high risk of death [9,10]. African bats have been shown to harbor filoviruses, which are the perpetrators behind Marburg hemorrhagic sickness and the Ebola virus. Person-to-person transmission is a possibility once humans become sick, particularly in individuals who are providing care for infected patients. The Democratic Republic of the Congo has seen multiple epidemics of Ebola, with case fatality rates reaching 80% to 90%. In low-income nations, the death rate from Marburg hemorrhagic fever can reach 82%.Arthropods are a common means of transmission for flaviviruses, which can cause a wide variety of diseases. The flavivirus known as dengue is spread by the *Aedes aegypti* or *Aedes albopictus* mosquito. Clinically, this virus can cause three different types of dengue fever: severe dengue, dengue with warning signals, and dengue without warning signs. Africa, the Americas, Asia, Australia, Europe, and the Pacific Islands are among the continents where this illness is endemic, encompassing over 100 countries. With more severe morbidity and mortality linked to dengue hemorrhagic fever and dengue shock syndrome, dengue fever has a 0.8% to 2.5% death rate [11–13].

3. ETIOLOGY

The viral family that includes the viruses linked to viral hemorrhagic fevers and the illnesses they cause is as follows: Family Arenaviridae: Hemorrhagic fever caused by the Chapare virus (CHPV). Venezuelan hemorrhagic fever is caused by the Guanarito virus (GTOV). Fever caused by the Argentine hemorrhagic virus (JUNV). Fever caused by the Lassa virus (LASV). Lujo hemorrhagic fever is caused by the Lujo virus (LUJV). The cause of lymphocytic choriomeningitis is the lymphocytic choriomeningitis virus (LCMV).The Machupo virus (MACV) causes hemorrhagic fever in Bolivia. Brazilian hemorrhagic fever is caused by the Sabia virus (SABV). The Bunyaviridae family includes the Crimean-Congo hemorrhagic fever virus (CCHFV). Dobrava-Belgrade virus (DOBV) - Renal syndrome accompanied by hemorrhagic fever. Hemorrhagic fever with renal syndrome is caused by the Hantaan virus (HTNV). Hemorrhagic fever with renal syndrome is caused by the puumalavirus (PUUV). Fever caused by the Rift Valley fever virus (RVFV). Hemorrhagic fever with renal syndrome is caused by the Saaremaa virus (SAAV). Severe fever with renal syndrome is caused by the Seoul virus (SEOV). SNV stands for Sin Nombre virus-Hantavirus pulmonary syndrome. The virus that causes severe fever and thrombocytopenia syndrome (SFTSV) is responsible for severe fever and thrombocytopenia syndrome. Hemorrhagic fever with renal syndrome caused by the Tula virus (TULV). The Ebola virus, or Bundibugyo Ebolavirus (BDBV), belongs to the Filoviridae family.Hemorrhagic fever caused by the Marburg Marburgvirus (MARV). The Ebola virus disease known as Sudan ebolavirus (SUDV). The Ebola virus disease known as Tai Forest Ebolavirus (TAFV). Ebola virus disease: Zaire ebolavirus (EBOV). Family Flaviviridae: DENV-1-4, the dengue virus, causes dengue fever. Forest sickness caused by the Kyasanur Forest sickness Virus (KFDV). Omsk hemorrhagic fever is caused by the Omsk hemorrhagic fever virus (OHFV). Yellow fever virus, or YFV for short [14].

4. PATHOGENESIS

The pathophysiologic features of VHF include microvascular instability, increased vascular permeability, and poor hemostasis, albeit the

underlying processes differ depending on the virus. Death frequently comes from a process similar to septic shock, where there is insufficient effective intravascular volume circulating, which causes cellular malfunction and multiorgan system failure instead of exsanguination. The virus normally replicates in dendritic cells upon inoculation, then spreads to local lymph nodes and subsequently to a wide range of organs, including the liver, spleen, lymph node, lung, adrenal gland, and endothelium, via lymph and blood monocytes. The specific organs most impacted change depending on the VHF. Interaction of viruses with immune cells, particularly macrophages and endothelial cells, causes the cells to become activated and releases an inflammatory vasoactive process that is compatible with the state known as systemic inflammatory response syndrome. Dysfunction of endothelial cells, platelets, and/or coagulation factors may be present in impaired hemostasis. In certain VHFs, disseminated intravas coagulation (DIC) occurs frequently. The extent of tissue damage varies with VHF and may be caused by either apoptosis or necrosis. Certain VHFs may inhibit cardiotropy, which would worsen organ perfusion. Although not proven, hypothesized causes of vascular collapse include necrosis of the pituitary or adrenal glands. The virus is quickly removed from survivors' blood, but it can linger for weeks or months in a few immunologically protected areas, including the gonads, central nervous system, and ocular chambers. The last location can lead to the previously described sexual transmission during convalescence [15]. There is a dearth of comprehensive knowledge regarding the pathogenic processes of VHFs. Monocytes, macrophages, dendritic cells, and vascular endothelial cells are important viral target cells. Once infected, these cells can spread to other organs via lymphatics. Studies on experimental viral disease (EVD) have revealed that the viral protein VP35 suppresses the interferon (IFN)-regulatory factor 3, which is essential for the production of IFN α/β and antiviral immune responses. Multiorgan failure, oedema, coagulopathy, shock, tissue necrosis, and endothelial damage are caused by extensive cytokine activation and tissue factor release [16]. Most fatal cases of VHFs do not mount a strong antibody response, which may be owing to virus-induced inhibition of the host adaptive immune response. The pathophysiology of most VHFs appears to be connected to unregulated viremia. During the acute sickness, the virus can be detected in a broad range of bodily fluids, including blood, saliva, stool, and breast milk. Usually minor, inflammatory cell infiltration consists of a mixture of neutrophils and mononuclear cells. Nonetheless, the host immune response may be harmful in cases of dengue, yellow fever, and hanta virus infections, in which viremia is typically resolved prior to the most severe stage of the illness. The distinct mechanism known as antibody-mediated enhancement could potentially contribute to the onset of dengue hemorrhagic fever [15].

5. VIRAL HEMORRHAGIC FEVER SIGNS AND SYMPTOMS

The initial classification of VHFs was based on the shared signs and symptoms of the underlying disease processes. Initial symptoms of the disease may resemble those of other prevalent tropical illnesses including typhoid and malaria, such as fever and general malaise. Even after the fulminant illness process has commenced, diagnosing VHF remains challenging due to its rarity and indiscriminating symptoms. Differentiating VHF from other tropical diseases is crucial for appropriate therapy of concomitant infections and/or VHF, as well as for isolation and infection control measures that can help halt the disease's spread. Numerous teams have examined standard laboratory measures to see if certain values may be used to distinguish VHF from other illnesses. Patients with hemorrhagic fever with renal syndrome (RTS) caused by the Hantaan and Seoul viruses had elevated blood urea nitrogen and creatinine, while patients infected with the Huaiyangshan hemorrhagic fever virus showed increased ALT and creatine kinase levels [17]. Patients with EBOV, Sudan virus illness, and CCHFV have been reported to have leukopenia, thrombocytopenia, and elevated levels of ALT and aspartate aminotransferase (AST). Haematological parameters in Dengue hemorrhagic fever endemic areas showed that elevated ALT and aspartate aminotransferase, normal prothrombin time, prolonged activated partial thromboplastin time, and platelet counts of less than 100 ×109/L are useful in assessing the possibility of Dengue hemorrhagic fever. Research has indicated that a high quantity of C-reactive protein (>5 mg/L) is a better indicator of malaria than Dengue hemorrhagic fever. Research has indicated that a high quantity of C-reactive protein (>5 mg/L) is a better indicator of malaria than Dengue hemorrhagic fever [18–21]. The diagnosis of VHF cannot be made with great specificity using these test data. However, laboratory markers may

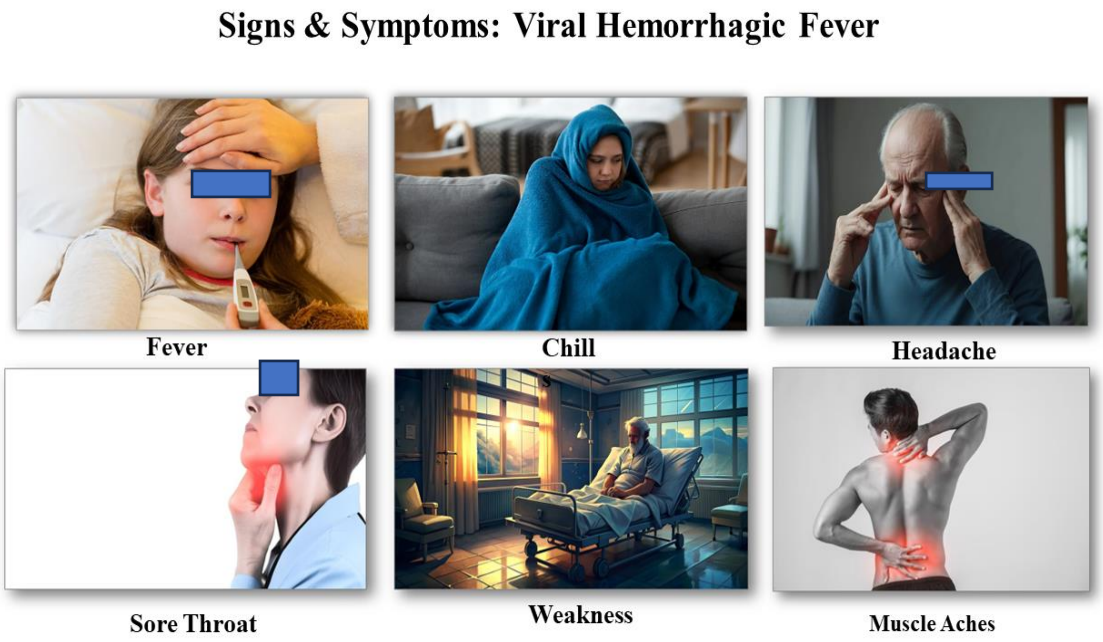

Fig. 1. Signs and Symptoms of Viral Hemorrhagic Fever

provide direction and guidance for identifying individuals with VHF in areas where direct diagnostic tools are not easily accessible. More precise and sensitive ways for identifying VHF have been shown in lab techniques that use patient specimens to directly detect viruses or the humoral immune response to them. Immunoglobulin M (IgM) and IgG specific to viruses can be measured in patient serum using serological markers, which provide a potential disease marker without the logistical and technical limitations of the gold standard of molecular detection. For Lassa and the early detection of IgM for Lassa virus (LASV) and IgG for Rift Valley fever virus (RVFV) infections, this has been successfully demonstrated [22,23].

6. INSPECTION OF RISK

In the form of an assessment algorithm, the Advisory Committee for Dangerous Pathogens (ACDP) has released guidelines for risk assessment of patients with possible VHF. A local infection expert should be consulted if there is any doubt as to whether the patient should be classified as having a "high possibility of VHF" or "low possibility of VHF." Keep in mind that "high possibility" does not equal "high probability." Rather, an alternate diagnosis is far more likely if there has been no contact with any deceased or ill individuals or any other exposure related to the locally significant VHF(s) [24].

7. DIAGNOSIS

Comprehensive metabolic panel, type and cross, coagulation studies, liver function tests, complete blood count with differential, and evaluation for bacterial infections with urinalysis, urine culture, chest x-ray, and blood cultures are all part of the clinical evaluation for viral hemorrhagic fevers. IgM and IgG specific to viruses can be detected by serological testing, which is useful but not as sensitive or precise as molecular testing. Techniques for diagnostic testing include the use of reverse transcriptase-polymerase chain reaction and virus isolation by cell culture [14]. In a patient with a compatible clinical history and within 21 days of a plausible epidemiological exposure, leucopenia, thrombocytopenia, and transaminitis (aspartate transaminase (AST) > alanine transaminase (ALT)) are suggestive of VHF, especially when the malaria film is negative. According to new ACDP guidance, similar investigations should be carried out as soon as possible in the nearby laboratory, if it is safe to do so and standard precautions (as well as extra splash measures when needed) are followed. Viralemia starts on the first day of fever and lasts the entire duration of the illness. IgM and IgG start to show up on days 3 and 7, respectively, however there is a chance that there will be a delay in antibody formation, which is linked to a worse prognosis [20,25,26]. Reverse

transcription polymerase chain reaction (PCR), which is extremely sensitive and specific and can be used on blood, urine, and saliva/throat swabs, is the method used in laboratory diagnostics. Testing is coordinated by communication between the Imported Fever Service, located at the Rare and Imported Pathogens Laboratory in Salisbury, and local infection specialists. Currently, serological testing is not done on a regular basis in the United Kingdom. Only in containment level 4 laboratories—for epidemiological or research purposes—is viral culture carried out [16]. Laboratory staff may experience anxiety when diagnosing VHF because they worry about getting sick while handling infectious specimens. Gamma irradiation and RNA extraction procedures can be used to inactivate laboratory specimens in places with the necessary resources, such as heat and detergent. Procedures for the appropriate use of protective equipment and training have helped to stop transmission during VHF epidemics and, consequently, reduce transmission to laboratory personnel, even in the absence of inactivation [27].

8. MANAGEMENT OF HEMORRHAGIC VIRAL FEVERS

Early diagnosis is crucial for the appropriate therapy of patients suspected of having viral hemorrhagic fever, as it can boost survival rates and avert nosocomial infections. All personnel who provide care for individuals under investigation should wear appropriate personal protective equipment (also known as viral hemorrhagic fever isolation precautions), and patients exhibiting symptoms or a travel history suggestive of these diseases should be isolated. Although therapy research is still under progress, supportive care is the mainstay of modern treatment. For the diseases with the greatest rates of overall mortality, see the specific management advice listed below [14]. Since more than 25 years ago, ribavirin—an antiviral medication-has been used to treat patients with Lassa fever. It is currently advised for the prevention and treatment of arenaviruses and bunyaviruses. Furthermore, ribavirin-treated patients in a randomized double-blind placebo-controlled experiment with 242 patients in the People's Republic of China who had serologically proven Hantan virus had a seven-fold lower death rate; however, these findings were not supported by further research. Although inconsistent outcomes from the treatment of CCHF patients in Iran and Turkey have been recorded, ribavirin was also proven to be effective against the CCHF virus in vitro. As potential antiviral medications for various VHFs, pyrazine carboxamide compounds like T-705 (favipiravir), T-1105, and T-1106 are being studied in vitro and in vivo. In animal models, these drugs have demonstrated good action against West Nile virus, Junin virus, arenaviruses, bunyaviruses, and Rift Valley Fever (RVF). A novel compound called FGI-106 has demonstrated broad-spectrum antiviral activity. Strong in vitro activity was demonstrated by FGI-106 against a number of deadly infections, including the Dengue, RVF, and Ebola viruses. Furthermore, it was discovered that FGI-106 shielded animals against a fatal challenge in a mouse model of Ebola virus infection. In order to identify new candidate compounds for VHF treatment, high-throughput screening (HTS) of tiny molecular libraries has lately become a viable and innovative method [28]. In order to evaluate the antiviral activity and possible cytotoxicity of chemical compounds against the Dengue virus, an automated HTS system that is integrated with optical microscopy has been put into place. This method evaluated the cytotoxicity of 5,632 compounds against the Dengue virus type 2 and its antiviral efficacy on human HEK293. Thus, 73 compounds that shown substantial antiviral activity and no cytotoxicity were recognized as promising candidates for additional in vivo studies. Filoviruses and arenaviruses are examples of BSL-4 pathogens that have been treated with HTS technology through the use of replication-incompetent virus pseudotypes. Strong entrance inhibitors against the Lassa, Junin, Sabia, Machupo, and Guaranito viruses were found during arenavirus research [29–31]. By using the HTS method, entrance inhibitors for filoviruses were also discovered. Specifically, a derivative of benzodiazepines was found to have a 50% inhibitory concentration for the Ebola and Marburg viruses, respectively, of 10 μM and 12 μM. HTS has also been used to study chemicals that could influence the interaction between a virus and its host. Specifically, PF-429242, an amino pyrrolidine molecule, has recently been found to function as a strong inhibitor of SKI-1/S1P, a cellular protease that is necessary for the processing of viral envelop protein precursors. Due to its strong stability, low toxicity, and unique pharmacokinetic characteristics, this chemical is a promising therapeutic candidate for infections caused by the CCHF and arenaviruses [32–35].

Although research has been limited, it has been demonstrated that treating Lassa virus early in the disease phase improves treatment outcomes when administered ribavirin. Currently undergoing evaluation are more recent medicines such favipiravir and monoclonal antibodies specific to LASV. As of right now, there are no viable Lassa fever vaccinations. The majority of the treatment for Crimean-Congo hemorrhagic fever is supportive. In vitro, ribavarin has shown antiviral activity against this virus. As of the now, there is no human vaccine that works. It is advised that those who work in agriculture or with animals wear bug repellent and stay away from potentially contaminated blood and other fluids from humans or other animals. Supportive care is part of the treatment for Marburg hemorrhagic fever and the Ebola virus disease. As of this now, there are no vaccinations against the Marburg virus. As of right now, only one Ebola vaccination against the Zaire ebolavirus has received FDA approval. Since there aren't any effective antiviral regimens for dengue fever at the moment, supportive care is the mainstay of management. In Southeast Asia and Latin America, there is now only one vaccine available. The World Health Organization, however, advises against giving it to anyone who hasn't previously contracted dengue [8,11,36–39]. Other than EBOV, there is currently no particular vaccine, medication, or therapeutic approach available for viral hemorrhagic fevers. Recently, two treatment medications for Ebola Zaire were approved by the Food and Drug Administration (FDA). The first medication to be approved was Inmazeb is, a mixture of three monoclonal antibodies, in October 2020. The second medication, approved in December 2020, is a monoclonal antibody called Ebanga (Research 2021). Additionally, Merck has produced the rVSVΔG-ZEBOV-GP Ebola vaccine (brand name Ervebo), which was approved by the FDA in 2019 [40].

9. CONCLUSION AND FUTURE DIRECTION

The indications and manifestations of viral hemorrhagic fevers (VHFs), in addition to their aetiology, pathophysiology, epidemiology, diagnostics, and current treatments, are all covered in great detail in our review articles. While pharmaceutical treatments offer benefits, they often come with drawbacks as well, such kidney damage. Additional randomized controlled studies are needed to find out more about the best way to treat viral hemorrhagic fevers (VHFs). We want to investigate viral hemorrhagic fevers (VHFs) further. A second study involving counseling will be conducted in our nation or state with the help of our colleagues in order to evaluate the mental and physical health of patients and to give a more thorough understanding of viral hemorrhagic fevers (VHFs) and their improved treatment.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

Authors would like to thank, Azad Institute of Pharmacy & Research, Lucknow, U.P, India, Lucknow, Uttar Pradesh, India for extending their facilities.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Zapata JC, Cox D, Salvato MS. The Role of Platelets in the Pathogenesis of Viral Hemorrhagic Fevers. PLoS Negl Trop Dis. 2014;8(6).
2. Schnittler HJ, Feldmann H. Viral hemorrhagic fever - A vascular disease? Thromb Haemost. 2003;89(6):967–72.
3. Leroy EM, Kumulungui B, Pourrut X, Rouquet P, Hassanin A, Yaba P, et al. Fruit bats as reservoirs of Ebola virus. Nature. 2005;438(7068):575–6.
4. Rodas CMR and JD. Epidemiological Surveillance of Viral Hemorrhagic Fevers With Emphasis on Clinical Virology. 2018;1604.
5. Mariappan V, Pratheesh P, Shanmugam L, Rao SR, Pillai AB. Viral hemorrhagic fever: Molecular pathogenesis and current trends of disease management-an update. Curr Res Virol Sci [Internet]. 2021;2: 100009. Available:https://www.sciencedirect.com/science/article/pii/S2666478X21000039
6. Bhalla DA. Association of Physicians of India Indian College of Physicians; 100.
7. Samaranayake L, Scully C, Nair RG, Petti S. Viral haemorrhagic fevers with emphasis on Ebola virus disease and oro-

dental healthcare. Oral Dis. 2015;21(1): 1–6.

8. Asogun DA, Günther S, Akpede GO, Ihekweazu C, Zumla A. Lassa fever: Epidemiology, clinical features, diagnosis, management and prevention. Infect Dis Clin North Am. 2019;33(4):933–51.
9. Hidalgo J, Richards GA, Jiménez JIS, Baker T, Amin P. Viral hemorrhagic fever in the tropics: Report from the task force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine. J Crit Care [Internet]. 2017;42:366–72. Available:https://doi.org/10.1016/j.jcrc.2017.11.006
10. Bente DA, Forrester NL, Watts DM, McAuley AJ, Whitehouse CA, Bray M. Crimean-Congo hemorrhagic fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Res [Internet]. 2013;100(1):159–89. Available:http://dx.doi.org/10.1016/j.antiviral.2013.07.006
11. Iannetta M, Di Caro A, Nicastri E, Vairo F, Masanja H, Kobinger G, et al. Viral Hemorrhagic Fevers Other than Ebola and Lassa. Infect Dis Clin North Am. 2019;33(4):977–1002.
12. Rougeron V, Feldmann H, Grard G, Becker S, Leroy EM. Ebola and Marburg haemorrhagic fever. J Clin Virol [Internet]. 2015;64:111–9. Available:http://dx.doi.org/10.1016/j.jcv.2015.01.014
13. Kularatne SAM. Dengue fever. BMJ. 2015;351(September):1–10.
14. Mangat R, Louie T. Viral Hemorrhagic Fevers. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available:https://www.ncbi.nlm.nih.gov/books/NBK560717/. 2024;560717.
15. Bausch DG. 194 . Viral hemorrhagic fevers. 2019;
16. Fhogartaigh CN, Aarons E. Viral haemorrhagic fever. Clin Med J R Coll Physicians London. 2015;15(1):61–6.
17. Chen ZH, Qin XC, Song R, Shen Y, Chen XP, Wang W, et al. Co-circulation of multiple hemorrhagic fever diseases with distinct clinical characteristics in Dandong, China. PLoS One. 2014;9(2).
18. Liu JW, Lee IK, Wang L, Chen RF, Yang KD. The usefulness of clinical-practice-based laboratory data in facilitating the diagnosis of dengue illness. Biomed Res Int. 2013;2013.
19. Kraft CS, Hewlett AL, Koepsell S, Winkler AM, Kratochvil CJ, Larson L, et al. The Use of TKM-100802 and Convalescent Plasma in 2 Patients with Ebola Virus Disease in the United States. Clin Infect Dis. 2015;61(4):496–502.
20. Rollin PE, Bausch DG, Sanchez A. Blood chemistry measurements and D-dimer levels associated with fatal and nonfatal outcomes in humans infected with Sudan Ebola virus. J Infect Dis. 2007;196(SUPPL. 2).
21. Epelboin L, Boullé C, Ouar-Epelboin S, Hanf M, Dussart P, Djossou F, et al. Discriminating malaria from dengue fever in endemic areas: Clinical and biological criteria, prognostic score and utility of the c-reactive protein: A retrospective matched-pair study in french Guiana. PLoS Negl Trop Dis. 2013;7(9).
22. Bukbuk DN, Fukushi S, Tani H, Yoshikawa T, Taniguchi S, Iha K, et al. Development and validation of serological assays for viral hemorrhagic fevers and determination of the prevalence of rift valley fever in Borno State, Nigeria. Trans R Soc Trop Med Hyg. 2014;108(12):768–73.
23. Ibekwe T, Nwegbu M, Okokhere P, Adomeh D, Asogun D. The sensitivity and specificity of Lassa virus IgM by ELISA as screening tool at early phase of Lassa fever infection. Niger Med J. 2012;53(4):196.
24. Centre SAC of the HPS. The Management of Viral Haemorrhagic Fevers in Ireland. 2012; Available:http://www.hpsc.ie/A-Z/Vectorborne/ViralHaemorrhagicFever/Guidance/File,12936, en.pdf
25. Mehedi M, Groseth A, Feldmann H, Ebihara H. Clinical aspects of Marburg hemorrhagic fever. Future Virol. 2011;6(9):1091–106.
26. DAB, NLF, DMW, AJM, CA. WM.B. Crimean-Congo hemorrhagic fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Res [Internet]. 2013;100(1):159–89. Available:http://0-ovidsp.ovid.com.wam.city.ac.uk/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013741328

27. Racsa LD, Kraft CS, Olinger GG, Hensley LE. Viral hemorrhagic fever diagnostics. Clin Infect Dis. 2016;62(2):214–9.
28. Ippolito G, Feldmann H, Lanini S, Vairo F, Di Caro A, Capobianchi MR, et al. Viral hemorrhagic fevers: Advancing the level of treatment. BMC Med. 2012; 10.
29. Bolken TC, Laquerre S, Zhang Y, Bailey TR, Pevear DC, Kickner SS, et al. Identification and characterization of potent small molecule inhibitor of hemorrhagic fever New World arenaviruses. Antiviral Res. 2006;69(2):86–97.
30. Lee AM, Pasquato A, Kunz S. Novel approaches in anti-arenaviral drug development. Virology [Internet]. 2011;411(2):163–9. Available:http://dx.doi.org/10.1016/j.virol.2010.11.022
31. Furuta Y, Takahashi K, Shiraki K, Sakamoto K, Smee DF, Barnard DL, et al. T-705 (favipiravir) and related compounds: Novel broad-spectrum inhibitors of RNA viral infections. Antiviral Res. 2009;82(3):95–102.
32. Pasquato A, Rochat C, Burri DJ, Pasqual G, La Torre JC de, Kunz S. Evaluation of the anti-arenaviral activity of the subtilisin kexin isozyme-1/site-1 protease inhibitor PF-429242. Virology [Internet]. 2012; 423(1):14–22. Available:http://dx.doi.org/10.1016/j.virol.2011.11.008
33. Urata S, Yun N, Pasquato A, Paessler S, Kunz S, de la Torre JC. Antiviral Activity of a Small-Molecule Inhibitor of Arenavirus Glycoprotein Processing by the Cellular Site 1 Protease. J Virol. 2011;85(2):795–803.
34. Basu A, Li B, Mills DM, Panchal RG, Cardinale SC, Butler MM, et al. Identification of a Small-Molecule Entry Inhibitor for Filoviruses. J Virol. 2011;85(7):3106–19.
35. Vincent MJ, Sanchez AJ, Erickson BR, Basak A, Chretien M, Seidah NG, et al. Crimean-Congo Hemorrhagic Fever Virus Glycoprotein Proteolytic Processing by Subtilase SKI-1. J Virol. 2003;77 (16):8640–9.
36. Ollmann Saphire E. A Vaccine against Ebola Virus. Cell [Internet]. 2020;181(1): 6. Available:http://dx.doi.org/10.1016/j.cell.2020.03.011
37. Rougeron V, Feldmann H, Grard G, Becker S, Leroy EM. Ebola and Marburg haemorrhagic fever. J Clin Virol Off Publ Pan Am Soc Clin Virol. 2015 Mar;64:111–9.
38. Kularatne SAM. Dengue fever. BMJ. 2015 Sep;351:h4661.
39. Gubler DJ, Halstead SB. Is Dengvaxia a useful vaccine for dengue endemic areas? BMJ. 2019 Oct;367:l5710.
40. Mariappan V, Pratheesh P, Shanmugam L, Rao SR, Pillai AB. Viral hemorrhagic fever: Molecular pathogenesis and current trends of disease management-an update. Curr Res Virol Sci [Internet]. 2021;2(July): 100009. Available:https://doi.org/10.1016/j.crviro.2021.100009

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/114632