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Viral Hemorrhagic Fevers – A Recurrent Public Health Threat (A Literature Review)

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Abstract: Viral Hemorrhagic Fever (VHFs) encompasses a wide array of systemic diseases The viral pathogens associated with VHF reveal considerable taxonomic diversity; but they are similar by their genomic makeup, where all being enveloped, and have a single-strand RNA. Routes of transmission to humans include handling infected animals reservoirs or via arthropod vectors. Despite their limited geographic distributions, these viruses considered continual natural infectious impendences. As revealed in most recent classifications by International Committee on Taxonomy of Virus, main VHF-occasion agents are classified to seven distinct families including: Hantaviridae, Nairoviridae, Phenuiviridae, Filoviridae, Paramyxoviridae, Arenaviridae, and Flaviviridae. These viruses have common core biological features, such as containing an enveloped single-strand RNA genome, target primarydendritic / monocyte/ macrophage cells, undergo cytoplasmic replication, and produce gastrointestinal and neurological symptoms. Severe cases are interlinked with high viremia levels in

the blood. These viral entities pose significant threats to public health with their alarmingly high rates of morbidity and mortality This overview seeks to illuminate the intricacies of viral hemorrhagic fevers: examining their causes, symptoms, modes of transmission, prevention strategies, and the treatments that exist. It's a call to action—raising awareness about the grave dangers posed by VHFs and fortifying efforts to halt their spread. The reality is stark: hemorrhagic fever is a formidable foe for humanity, boasting a high mortality rate thanks to its virulent nature.

1. Viral hemorrhagic fever (VHF)

The construct of VHF syndrome serves as a useful framework in clinical medicine to categorize a series of acute febrile illnesses. Clinically, VHF is characterized by the sudden onset of fever accompanied by extreme malaise, severe fatigue (prostration), and systemic signs indicated of augmented vascular permeability along with dysregulation of circulation homeostasis. Hemorrhagic phenomena are usually observed, especially among those with severe ill; but these signs do not lead to a life-threatening depletion of blood volume. Rather, they reflect endothelial injury and being as indicators for disease severity in particular organ systems. The viral pathogens associated with VHF reveal considerable taxonomic diversity; but they are similar by their genomic makeup, where all being enveloped, and have a single-strand RNA. Routes of transmission to humans include handling infected animals reservoirs or via arthropod vectors. Despite their limited geographic distributions, these viruses considered continual natural infectious impendences.

As revealed in most recent classifications by International Committee on Taxonomy of Virus, main VHF-occasion agents are classified to seven distinct families including: *Hantaviridae*, *Nairoviridae*, *Phenuiviridae*, *Filoviridae*, *Paramyxoviridae*, *Arenaviridae*, and *Flaviviridae*. These viruses have common core biological features, such as containing an enveloped single-strand RNA genome, target primary dendritic/monocyte/macrophage cells, undergo cytoplasmic replication, and produce gastrointestinal and neurological symptoms. Severe cases are interlinked with high viremia levels in the blood (Cobo, 2016). Whilst human are deeming to be occasional host, many arthropoda and rodents act as main reservoir hosts; where the human's infections usually caused by arthropod bites or indirect exposing to infectious body fluids like stool, urine, saliva, or other secretion of infected subjects. VHF viruses peculiarly maintain zoonotic transmissions pathways and evince geographical confinement. However, globalization and multiply international travel expedite the distribution of these pathogens beyond endemic area.

Generally, the clinical features and severity of are modified by different variables, such as specified viral etiology and host-certain epidemiological and physiological aspects (Ippolito *et al.*, 2012). Consequently, grasping mechanism that controlled infection's pathogenesis of VHF might provide better curative options.

2. Classification of hemorrhagic fevers

VHFs-associated Viruses fall into three categories according to reservoir host and the main routes of transporting, which including: rodents-related viruses, arthropods-borne viruses, and those suggested associating with bats.

2.1 Rodents-associating viruses

Arena viruses and hanta viruses were known to cause chronic renal infections in myomorph rodent spp., especially within Muridae family such as rats and mice. These viruses are excreted in urine of infected animals, speeding up the environmental contamination. Human infections are usually getting up via indirect exposure, including ingestion of contaminated foods, touching with household surfaces containing infectious particles, or by inhalating of aerosolized viral matter derived from rodent wastes. Furthermore, exposure may happen via some occupational activity (such as farming, pests control, laboratory works) or recreational encounter (like hike, encampment) in rodent-endemic niches (Swanepoel, 1987).

2.1.1 Lassa fever

This fever is emerged by an arena virus being resident in West Africa (especially in Nigeria, Sierra Leone, Guinea and Liberia). The infection with this virus is ordinarily characterized by a relatively mild disease with fever, where the mortality rate being only 1-2% to each of patients in overall populations, though some cases may evolve VHF and mortality rate could reach to 20% in hospitalized individuals, or override 40% among nosocomial outbreak. Individual-to-individual spreading of infections that happen at houses and hospitals seems to demand direct touch with infected tissue or body fluid (Swanepoel, 1987).

- **The clinical aspects of Lassa fever**

The incubation interval is generally 7-10days (ranging between 3-21days). Approximately, 80% of these infections being asymptomatic or mild, yet in others there are stealthy fever, chill, malady, sore head, and overall myalgia as well general weakness. Within two or three 3 days, the individual develops sores throat, vomit, abdominal or chest (retrosternal) pains, cough, low blood pressure as well as bradycardia. In addition, patient may have distinctive inflammations in pharynx and tonsils alongside vesicular or ulcerative lesions and whitey/yellowed exudates (Alexander et al., 2018). Subsequent to the initial phase, the clinical scanning may detect conjunctival injection, regional lymphadenopathy, spread muscle tenderness, and pulmonary auscultation signs, particularly the rales. A maculopapular exanthema could as well appear in some patients. At 5th-day, the illness development is frequently manifested by constant high-grade fever and systemic toxemia. The complications of hemorrhagic that include the epistaxis, hematemesis, and melaena may arise, which reflected the vascular compromise. In addition, patients may reveal facial and cervical edema, serous effusions like hydrothorax, neurological disruptions, and eventually, hemodynamic instability accompanied with shock.

The severe phase commonly extended from one to three weeks, with fluctuating convalescent scores. Remarkably, sensorineural deafness evolves in nearly 25% of cases, with incomplete or fully auditory recuperation commonly noted within one to three months. Throughout the time of the recovery, patients may as well undergo alopecia and a gait trouble indicated to transitory neuromuscular weakness.

- **Clinical Pathophysiological aspects into Lassa Fever**

Untimely leukopenia maybe succeeded with a transient leukocytosis. Presence of abnormal quantities of protein in the urine (Proteinuria) commonly observed. While abnormality in platelets, prothrombin and clotting time aren't observed; pronounced increasing in serum concentrations of hepatic and muscular biomarkers that including aspartate and alanine transaminases, lactate dehydrogenase, and creatin kinase are frequently occurred. Viremia lasts for approximately 7 days following symptoms onset; however, viral excretion in urine may extended about 3-10 weeks

(Alexander et al., 2018).

2.1.2. Lujo virus

Lujo virus causes a disease called Lujo hemorrhagic fever (LUHF). This virus transport to human via exposure to infected rodents or their urine, dropping, and saliva. This disease is still mysterious and it is not known which type of rodent transmits the virus (Ansari, 2014).

- **Clinical aspects of Lujo virus**

The incubation period for this viral fever ranging between 9-13 days. The prodromal stage commonly characterized with fever, cephalalgia, and myalgia, follow up with gastrointestinal manifestations such as diarrhea and pharyngitis. A morbilliform rash concentrated to face and trunk had been detected in three persons between day 6 and 8 of disease onset. Facial edema was detected in three persons, with one appearing notable pharyngeal ulceration. There is an initial clinical stabilization post-hospital admission was reported in those three patients; however, this was later followed by sudden and severe clinical decline, leading to fatal outcomes for each. Hemorrhagic was not a memorable feature, though one case displayed a petechial rash and another exhibited blood oozing from venipuncture sites. Treatment with intravenous ribavirin to one patient led to his salvation from death.

2.1.3 Hanta virus

In Europe & Asia, a number of hanta viruses are correlated with a set of illnesses, which are overall termed as haemorrhagic fever with renal syndrome (HFRS) (its mortality rate ranging between 1-35%), whilst another set of hanta viruses is causing hanta virus pulmonary syndrome (HPS) (with mortality rates 50%or more) in North & South America. While in Africa, this virus are poorly investigated, and so far there is little evidence of its occurrence here, excepting for Seoul virus, belief to exceedingly, disseminate to seaports by rats that being borne in the ships and occurred in urbanized area (Baize *et al.*, 2009).

- **Clinical aspects of HFRS**

There are four clinical sets of this syndrome, varied in severity (with fatality rate ranges from <1% to 35%), from nephropathia epidemica accompanying with Puumala virus in Scandinavia; via mild or rat-borne HFRS associated with Seoul virus, which had globally dispersed via ship-borne rats; to Far Eastern HFRS associated by Hantaan virus in Asia (as well termed as Korean hemorrhagic fever); and HFRS in Balkan caused by Dobrava virus. The incubation period is nearly 2 to 3 weeks. Typically, the severe cases developed via five featured phases—despite in mild cases, these phases could interfere or be less identifiable. The primary febrile stage continues from three to seven days and could identify by intense fever, chill, malady, myalgia, anorexia, vertigo, sore head, as well as eyes pains, along with ventral and back pains and renal zone tenderness (due to peritoneal and retroperitoneal edema). A distinguished flushing in face, neck and chest occurs, together with injections in eye, palates and pharynx, progressing into rashes as well as conjunctival hemorrhage. Proteinuria is a distinctive consequence. The lowering blood pressure accompanies suddenly and continues from hours up to 2 days, occurring with abnormalities in heart rate and traditional signs of trauma, which including the narrow pressure, cold clammy skin, and dampen sens. About one third of mortal cases evolve to irreversible trauma at this phase. Proteinuria lasts along with mild hematuria, increased hematocrit levels, leukemic reactions and thrombocytopenia. The beginning of an oliguric stage is marked by escalating levels of urea and creatinine. Despite blood pressure is tend to be normalize, yet some heightening may be occur from the hypovolemic condition. Intense nausea and vomit, and bleeding likelihood may be happened. As well, hyperkalemia, hyponatremias and hypocalcaemia may be occurring. Central nervous manifestations along with lungs edema, with 50% of mortality happen at this phase. The diuretic phase might continue from days to weeks, at a diuresis level of 3-6L/day, distinguished beginning of recovery. Convalescence stage continues two or three months with gradual recuperation of glomerular filtering rates (Siegel *et al.*, 2007).

➢ **Clinical aspects of Hantavirus Pulmonary Syndrome**

This syndrome predominantly influences previously healthy persons, frequently young adults, despite the fact that cases could occur in all ages and both sexes. The period of incubation usually spans two or three weeks; the clinical onset is marked by abrupt fever, cephalalgia, intense myalgia, and non-productive or sometimes productive cough. Gastrointestinal manifestations like abdominal pains, nausea, vomit, and diarrhea are happen in a subset of cases. Between days 3 and 6 of sickness, a rapid progression takes place that identified by tachypnea, abnormally rapid heart rate, and low blood pressure, prior appearance of acute respiratory distress syndrome (ARDS) coexist by lung's edema. Hospitalization predominantly takes place at this stage; yet, some patients succumb before to admission. Upon admission, laboratory findings usually including proteinuria, leukocytosis with neutrophilic dominance, an escalated myeloid precursors, unusual lymphocytosis, haemoconcentration, thrombocytopenia, and upraised prothrombin time and partial thromboplastin time. In spite of these hematological abnormalities, no cutaneous manifestations like rash are found, and distinct or internal hemorrhage is extremely rare. Upon 48 hours of hospitalization, nearly all patients evolve spread out bilateral interstitial and alveolar infiltrates and pleural effusions perceptible by radiographic imaging, with resultant hypoxaemia requiting endotracheal intubation, mechanistic ventilation, and supplementary (O_2) therapy. Occasionally, nephritic failure and high creatine kinase levels (confirmed of muscles inflammations). The demise usually happens after six to eight days from starting the disease, overwhelmingly after 48 hrs. of hospitalization. The mortality rate sometimes overrides 40%, and untreatable trauma and myocardial dysfunction may lead to increase these rates. Autopsies expose non-cardiogenic pulmonary oedema and serous pleural effusions, with limited lymphoid infiltrations of the pulmonary tissues. Some survivors exhibited transitory diuresis, but rather they recovered without sequelae.

2.2 Arthropod-borne viruses

Various hemorrhagic fevers are originated from Arthropod-borne viruses (also called arboviruses). These viruses are all similar in that they are transmitted by arthropods that feed on blood (mosquito, midge, sandflies and tick), and numerous terrestrial and local animals serve as a reservoir host. Only some of these viruses led to hemorrhagic disease.

2.2.1 Crimean-Congo hemorrhagic fever

Crimean-Congo virus is causing a viral fever named as Crimean-Congo Hemorrhagic Fever (CCHF), which being transported by Hyalomma (Ixodid Tick). Different terrestrial and local animals include goat, sheep, and hare are serving as reservoirs for viral replication. Nevertheless, human represents the only documented one, in which the clinical illness progresses after viral exposure. Transmission route to humans primarily occurs via biting of an infected tick or by means of exposure to blood of infected animals. Secondary individual-to-individual spreading is facilitated via exposure to contaminated blood or other fluid of body. Outstanding sings involve acute febrile sickness, headache, conjunctival irritation, sensitivity to lights, abdominal pains, emesis, high heart rate, regional lymphadenopathy, and petechial rashes (Leblebicioglu, 2010).

The path of viral entrance and style of infection still doubtful, excepting one study revealed the basolateral entrance of virus in polarizing epithelial cells. The proteins of virus have been found to travel across the endothelial layer via viral glycoprotein (GP) which assists virus to recognize certain receptors such as nucleolin at cell's surface. The replication of viruses occurs in the cytoplasm, and is releasing into the circulation through basolateral layer that is straightly associated with the blood vessels (Xiao et al., 2011; Connolly-Andersen, 2011). The principal attributes of CCHF involving haemorrhage and vessels injury as a result of activating the endothelium, escalated permeabilities, and plasma infiltration. These endothelial cells are directly stimulated via viral proteins or some inducers factors as E-Selectin, Intercellular and Vascular Adhesion Molecules, and augmented adhering of the white blood cells (Weber & Ali, 2008).

Nevertheless, it is not obvious that if these molecules are derived from endothelial cells or white blood cells. Notably, it had revealed that propagation of CCHFV doesn't influence the junctions of epithelium cell, suggesting that hemorrhage presented in affected individuals may belong to its immunological responses rather than by viruses (Connolly-Andersen, 2011). Endothelium destruction was as well found to trigger the assembling of platelets and degranulation come after activating the intrinsic coagulation cascade pathways that leads to continual dissemination intravascular coagulation (DIC) (Schnittler & Heinz, 2003).

Anyway, exact mechanism of platelets assembling and DIC throughout the infection with this virus isn't yet known.

However, a study proposed that no considerable alteration in the levels of mRNA or the proteins of endothelial-specific adhesion molecule named VE-Cadherin in endothelial cells of affected patients and control individuals (Connolly-Andersen, 2011); this makes a knowledge gap to understand the reliable pathway mediates the endothelial induction and vascular permeabilities.

- **Clinical features of Congo fever**

The incubation period often ranging from one to three days after a tick bite, and from five to six days succeeding exposure to infected blood or tissue, even so longer periods may take place. Individuals are frequently ignorant of tick contact; accordingly, close examination for tick or fine bites mark—especially at scalps and among toes—is command. Transmission could as well ocuur from manual smashing of ticks. Contrasting tick-borne rickettsiosis, which is correlated with necrotic eschars at the bite region, CCHF commonly appears with only mild local Hematoma. Unlike other arboviral infections, a considerable percent of patients were clinically symptomatic. The start of disease is typically sudden, with vigorous sore head, cervical pains as well as rigidity, ocular pain, photophobia, fever, chills, and rigor, rapidly progressing to generalized myalgia, intense back and leg pains, nausea, sore throat, and vomit. Early gastrointestinal symptoms may include diffuse abdominal pains and diarrhea. The febrile events are often sporadic, and individuals may experience clear mood fluctuations that ranging from confusion to aggression during the earliest 48 hours. By days 2 to 4, symptoms of lassitude, depression, and somnolence usually appear, go along with by facial flush, conjunctival injection and chemosis. Abdominal pains generally localize to right upper quadrant, sometimes with hepatomegaly. Tachycardia is usual, and patients may have mild hypotension. Lymphadenopathy may be clear, alongside mucosal outcomes like enanthem along with petechia influencing throat, tonsil, together with buccal surfaces. A petechia rashes at trunks as well extremities commonly occur between days three and six and may swiftly developed to intense bruise and ecchymoses, mainly in flexural sites. Hemorrhagic symptoms like blood oozing from injections or venipunctures regions, epistaxis, hematemesis, hematuria, melaena, gingivals hemorrhage, and vaginal orifice hemorrhage predominantly start between days four and five, but scarcely earlier. Internal hemorrhage—inclusive of retroperitoneal and intracranial hemorrhage—may also happen. Critically influenced patients may evolve combined hepatic, kidney, and pulmonary failure starting around day five, with gradual neurological decline causing drowsiness, amazement, and coma. Jaundice may occur at 2nd week. Case-mortalities rates about 30%, with mortality usually occurs between days 5 and 14. Survivors often exhibit abrupt clinical amelioration by days 9 to 10, regardless the residual asthenia, conjunctivitis, mild cognitive impairments, and transitory amnesia may continue for some weeks.

- **Clinical pathology of Congo fever**

Throughout earliest period of sickness, patients might reveal either leukocytosis or leukopenia, along with upraised blood levels of aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, alkaline phosphatase, and creatine kinase. As the disease advances into 2nd week, the laboratory parameters often exhibit escalated bilirubin, creatinine, and urea levels, along with decline in total protein levels. Hematologic abnormalities like thrombocytopenia, prolonged prothrombin time, activating partially thromboplastin interval,

and thrombin times, together with high D-dimer levels and fibrin breakdown outcomes, decreased fibrinogen and hemoglobin levels, are commonly occur at early phase and reflected distributed intravascular coagulation as a fundamental pathogenic mechanism. During the earliest five days, the following laboratory markers substantially correspond with the poor prognosis: leukocytes counts ≥10×10^9/L, platelets counts ≤20×10^9/L, AST ≥200 U/L, ALT ≥150 U/L, APTT ≥60 seconds, and fibrinogen ≤110 mg/dL. Remarkably, leukopenia at this phase is not as robustly correlated with adverse consequences as leukocytosis. After the five day, laboratory markers may seem notably deranged with no necessarily revealing a mortal prognosis. Viremia commonly happens within 1st week of manifestations onset (range 1–13 days), and viral RNA may be detected in serum using RT-PCR for up to 16 days. An absence of noticeable antibodies responses is typical in fatal cases, whilst the existence of antibodies tends to reflect a favorable clinical trajectory.

2.2.2. Rift Valley Fever

Rift Valley Fever Virus (RVFV) is typically found in household livestock like cattle, buffalo, sheeps, goats, and camel, which is lead to Rift Valley Fever (RVF) in both human and ruminants. Man infection mainly occurs via directly or indirectly subjection to blood, organ, and other tissues of infected animals. Transmission routes involve exposing to infected tissue throughout slaughter or butcher, helping with parturition, carrying out veterinary intervention, and disposing of carcass or fetuses. Moreover, utilization of unpasteurized or undercooked milk from infected animals forms a notable risk. Vector-borne transmission is as well reported, especially through bites from infected Aede and Culex mosquitoes, along with other hematophagous flies.

Clinical aspects in humans ranging from moderate to severe. Moderate cases usually include fever, vomiting, headache, and myalgia. The severe cases may include ocular issues like retinal lesions, neurological signs like meningoencephalitis (identified by memory loss, hallucination, disorientation, vertigo, and coma), and bleeding manifestations like hepatic dysfunction, hematemesis, melena, and ecchymosis. Fatal consequences are commonly associated with renal failure or disseminated intravascular coagulation, along with increased Aspartate Aminotransferase, Alanine transaminase, and Lactate Dehydrogenase levels, diminished platelets counts, and encephalitis with coinciding with hepatic and gastrointestinal necrosis (El Imam et al., 2009). These outcomes point out a complex interaction between hepatic and neurological engagement in RVFV pathogenesis, despite the underlying mechanisms still incompletely understood.

RVFV mainly targets dendritic cells (DC) and macrophages. This virus avails DC-SIGN, a C-type lectin receptor expressing on DC, to ease cellular entrance and boost viral binding. Nevertheless, the exact role of DC-SIGN in adjusting the innate immune responses to RVFV infection had yet to be fully explained (Lozach et al., 2011). A previous investigation on Uukuniemi virus (UUKV), a phlebo virus linked to RVFV exhibited that UUKV entrance usually relies on clathrin-independent process. Consequently, majority of other viruses, RVFV and other bunya viruses could invade host cell by means of non-clathrin-mediated entrance pathway (Lozach et al., 2010). Inside host's cell, non-structural protein of RVFV has a key role in virus prevalence by these two independent ways: The 1st mechanism, definite suppression of IFNβ transcription by formation an inhibition complex at IFNβ promotor directly following the infection by associating with SAP30 protein (Le May et al., 2008). The 2nd one is defectively understand, where the non-structural protein has been found to impede the transcriptions of host type 1 interferon mRNA alongside with downregulating of dependent protein kinase, and thus, prohibition expressions of hosts antiviral factors (Ikegami et al., 2009). Nevertheless, mechanisms that underlying the fast accumulating of non-structural proteins at infected cells along with succeeding disturbance in host's innate immunological responses instantly following infection remaining unresolved. Additionally, emerging evidences indicated that non-structural protein could interact with certain genomic DNA regions within host cells, probably causing defects in chromosomes cohesions and segregations. These aberrations could lead to pathophysiological aspects related with RVFV infection (Mansuroglu et al., 2010).

- **Clinical aspects of Rift Valley Fever**

The incubation period of this infection usually ranging between 2-6days. Most cases being either asymptomatic or mild often recognized retrospectively via serological surveys or as incidental laboratory-acquired infection. Symptomatic subjects generally manifest a moderate to severe febrile illness characterized by a sudden onset of intensive retro-orbital pains and headache, photophobia, conjunctival suffusion, myalgia, arthralgia, intense fatigue, nausea, and hepatic tenderness with lacking of hepatomegaly. The febrile stage and related prostration typically take two or three days, despite in some occasion, the illness following a biphasic course extending over nearly two weeks. Ocular issues are documented in 5–20% of cases, typically appearing 1 to 3 weeks following initial onset of manifestations. These manifestations include reduced visual intensity and scotomas, which are recurrently associated with retinal hemorrhage, macular edema, and exudative alterations. Visual functions tend to recover progressively over 1 to 3 months as retinal lesions resolved; however, severe consequences like retinal detachment and lasting blindness may take place in rare cases. Neurological and hemorrhagic issues are rare, affecting only 0.5% or less of patients. If present, these manifestations like encephalitis or heamorrhagic syndromes are correlated with upraised mortality rates. Encephalitis may occur as a complication one or two weeks after the intense febrile infection. The patient may die immediately, recover, or have a delayed recovery. Bleeding fever with or with no neurologic manifestations, may appear within seven days after acute fevered phase. A considerable liver necrosis in these cases may be occurred, also could observe noticeable anemia after enormous epistaxis, hematemesis and melaena. Petechiae, ecchymosis and jaundice may be apparent.

2.2.3 Arboviral zoonosis and Their Roles in Differential identification of Viral Hemorrhagic Fevers

Chikungunya virus, Yellow fever virus, along with Dengue virus are remarkable arboviruses that sustain the enzootic transmission cycles including mosquitoes and non-humans primates, especially within forest ecosystem. Uniquely among arboviruses, these pathogens have the capacity for exploiting human as the exclusive vertebrate hosts throughout urban epidemic outbreak. While all these viruses is capable to induce hemorrhagic manifestations under definite clinical conditions, they have not revealed maintained individual-to-individual transmission. Their primary significance in clinical and epidemiological fields lies in their considerations as differential diagnoses in cases of suspected VHF.

2.2.3.1 Chikungunya

Chikungunya virus (CHIK) is accountable for outbreak of febrile disease associated with arthralgia, in rural area of Africa where non-human primates like baboon and monkeys are found. This virus is most frequently reported in East Africa, but cases have as well been reported in South Africa, especially within Limpopo and Mpumalanga Lowveld, and along northern KwaZulu-Natal coast. A hallmark of infection with CHIK is constant joints pain, which sometimes localized to a certain joint and continues for up to two years after acute phase of infection. Although commonly self-limiting, intense and hemorrhagic signs have been noted in a some cases, exceptionally in Asia and Indian Ocean islands, where CHIK had been correlated with immense urban epidemics. In South Africa, CHIK has been diagnosed in travelers coming back from endemic regions. Theoretically, these imported cases can accelerate local urban transmission, particularly in regions as KwaZulu-Natal, where respective mosquito vectors are spread. Actually, no licensed vaccine is available for CHIK virus.

2.2.3.2 Yellow fever

Yellow fever is caused by a virus borne by mosquitos, which deem as a principle reason for outbreak of fatal illness with hepatic necrosis. Its mosquito vectors present in eastern South Africa. Since there is an effectual vaccine, which is secondhanded for international travelers, the potential for spreading the infection with this virus by tourists is limited, but it is feasible that

patients could be vacated for therapy. Hospital-acquired infection had not ever been reported, even though in endemic regions mosquitos transferral may also influence Healthcare workers.

2.1.2.3.3. Dengue

Dengue virus (DEN) is a mosquito-borne virus responsible for prevalent febrile illness recognized by intense joints and muscles pains, predominantly influencing tropical areas of Asia. The DEN subsists in four discrete serotypes, while most infections are self-limiting, some of cases (particularly young children, older adults, or individuals undergoing sequential infection with a heterologous serotype) could progress to severe symptoms like dengue haemorrhagic fever or dengue shock syndrome. This expanded severity is ascribed to a phenomenon called antibody-dependent enhancement (ADE), where diminishing immunity from a foregoing infection expedites multiplied the viral replication upon subsequent exposure. To present, there is no universally valuable vaccine is found for DEN prevention.

2.3 Bats-Associated Viruses

2.1.3 Ebola virus

Ebola virus (EBOV) is among most lethal pathogens well-known to influence both human and non-human primate, such as monkey, gorilla, and chimpanzee. Despite conclusive natural reservoir of EBOV has never been entirely identified, present evidences suggest that fruit bats or definite primate spp. may act as potential reservoir hosts. Transmission for human commonly happens via direct contact with blood, body fluids, secretion, or organs from infected animals. These zoonotic spillover events are frequently related to hunting, handling, or consuming of bush's meat in endemic zones. In spite of that clinical path of EBOV is described,but a big gap related to the mechanization that implied its pathogenicity. This is for of several purposes (1) owing to the fact that it has a highly pathogenic nature, thus the majority of researches are conducted employing pseudo-set strains that might not precisely mimic pathogenicity's pathways displayed by this virus (2) awkwardness in getting clinical specimens from distant areas where the outbreak had present (3) necessity of a high degree of biohazard thoroughness facilities to process clinical specimens and conducting research.

The entrance route of EBOV into the body of host are including through the mucosal surface, injured skin, abrasion. These viruses are binding with several cells involving monocyte, macrophage, DC, endothelial cells, fibroblast, and hepatocyte (Feldmann and Geisbert, 2011), and tissues tropism has intended by GPs of virus. In addition, various factors such as lectin, immunoglobulin, and tyrosine kinase receptor Ax1 are facilitating the binding process; and internalizing by macropinocytosis. Notably, an investigation had revealed that binding competence is amended by sphingolipid components, especially acid sphingomyelinase and membrane sphingomyelin (Miller et al., 2012). Once enter the body, its particles targeted the late endosome, where they undergone a transition into a fusogenic form, which is a pathway conciliated by faint pH dependent cysteine proteases. Subsequently, via the mechanism that still incompletely understood, the viral nucleocapsid is released into cytoplasm of host cell, commencing the production of progeny virions (Adam et al., 2004; Brecher et al., 2012). Several investigation were revealed a huge releasing of pro-inflammatory cytokines such as IL-1β, IL-1RA, IL-6, IL-8, IL-15, and IL-16; chemokines like MIP-1α, MIP-1β, MCP-1, MIF, IP-10 GRO-α, and eotaxin) owing to infection with EBOV. This is due to the hyper inflammatory responses triggered by host's system that may case to escalate the inflammations and vascular permeabilities (McElroy et al., 2014; Wauquier et al., 2010).

2.1.3 Marburg Hemorrhagic Fever

Marburg virus (MARV) a member of Filoviridae and causes a fever called Marburg Hemorrhage (MHF). Its major host is African fruit bat (*Rousettus aegyptiacus*). Fruit bats infected with MARV remain asymptomatic, displaying no apparent signs of infection. To present, the exact mechanism for transmitting this virus from bats to human has not been conclusively established. Most

Human-to-human transmission cases occur via direct contact with blood, body fluid, and tissue of infected subjects. Clinical symptoms usually including high-level of fever, maculopapular rashes, myalgia, chest pains, sore throat, as well as delirium. In intense severe cases, patients may get pancreatitis, multi-organs disruption, jaundice, as well considerable bleeding symptoms (Paessler and Walker 2013).

- **Clinical manifestations of MHF and EBOV**

The incubation period usually ranging from 7-10days, with a totally span of 2-21days. The duration of acute clinical stage is mainly alike, despite convalescence may be extended. The illness starts suddenly with high fever and intense headache, often limited at frontal region. Early signs involve sore throat, chest and ventral pains, myalgia, arthralgia, malaises, fatigue, nausea, and anorexia. Infected individuals may reveal several clinical signs, such as mouth and pharyngeal lesions, permanent diarrhea and vomit, dryish coughs, conjunctivitis, and a non-pruritic maculopapular rashes influencing the trunks and limbs. These rashes typically appear nearly at the day five of infection and are followed by desquamation between 4-10days. While these rashes may be hard to identify in subjects with darker skin tones, sloughing of skin is marked and might include palm and sole.

Additional consequences might involve splenic enlargement and hepatitis without jaundice, always associated by epigastrium pains. In pregnant women, these infections might lead to spontaneous abortion. In critical and fatal cases, evolvement to a hemorrhagic phase generally happens between 5- 8 days, identified by bleeding from needle puncture site, mucosal haemorrhage (including gingival bleeding), hematemesis, melaena, and nose bleeding. Neurological implication may appear as changed mental status, such as aggressive behavior, confusion, and drowsiness. In the absence of proper fluids management, dehydration could be heavy, engaging to clinical impairment (Swanepoel, 1985).

- **Clinical manifestations of MHF and EBOV**

The clinical manifestations of these viruses including a transitory leucopenia follow by prominent leukocytosis, diminished platelets, augmented transaminases, proteinuria and faint hemoglobin. Viremia was identified until day 17 of disease, but stability of virus was showed in certain organs such as liver, and eyes alongside inflammation of the uvea for many weeks, and releasing in semen was found until 12 weeks following emergence of disease (Swanepoel, 1985).

3. Diagnostic methods for viral hemorrhagic fever

VHFs are identified by detection of specified antibodies (IgM antibody testing paired with acute-convalescent serum serologies), viral antigens (ELISA), immunohistochemistry methods, electron microscopy, and reverse transcriptase polymerase chain reaction (RT-PCR) on blood samples (Mariappan, et al., 2021).

3.1 Virus Culture and Electron Microscopy

One of conventional methods to identify and characterize new or branched viruses is the virus culturing, yet it is challenging with PCR and next-generation sequence techniques since they are fast and further dependable techniques to diagnosis these viruses (Goldsmith *et al*., 2013). Diagnostic electron microscopy deems as a useful technique to identify viruses associated with human disease (Goldsmith *et al*., 2013). Electron microscopy was an essential component of viral diagnosis until highly sensitive nucleic acid amplification techniques (NAT) were developed. It has been instrumental in identifying the causative agent of several disease outbreaks caused by previously unknown viruses based on structural features from clinical or culture material (Möller et al., 2020). However, in many situations, growing live viruses and preparing specimens for EM require accessing to highly specialized laboratory, and these processes being time-consuming, requiring weeks to grow the virus and further time for microscopy. As a result, these methods are no longer used as first-line diagnosis (Racsa,et al,2016).

3.2 Nucleic Acid Detection

This method is one of the common methods used to diagnose VHF. This test is performed to detect DNA and RNA from viruses by polymerase chain reaction (PCR), which is one of the molecular techniques used to diagnose VHF. This test is done by taking a sample of RNA and checking for the presence of the virus. Once the virus is confirmed in the RNA, the person is diagnosed with viral hemorrhagic fever. PCR modifications, such as real-time PCR, can be used to determine viral load in addition to detecting viruses in sera from patients. Real-time PCR as well as reverse transcription PCR being mostly common molecular diagnostic techniques to identification viral infections, like VHF viruses (Mariappan et al., 2021). Since VHF can spread easily, these tests are performed in special laboratories, especially if the symptoms are severe.

3.3 Enzyme-linked immunosorbent assay

It is an immunoassay commonly used for antibody detection (Emmerich et al, 2021).ELISA is used to detect IgM and IgG antibodies in suspected patients. When diagnosing acute VHF, serology is not helpful because IgM antibody levels can indicate various illness stages or presymptomatic or asymptomatic infection. However, sometimes the ELISA may not have specificity and reveal a high level of reactiveness among viruses that are widely related, particularly Flavi virus & Bunya virus (Fajfr & Ruzek, D.2014).

3.4 Immunohistochemistry

Skin biopsy samples were tested for the presence of the Ebola virus using an immunohistochemical assay. Formalin was used to fix the skin biopsy, making the virus non-infectious. It is regarded as an easy, secure, and accurate method for laboratory confirmation of Ebola virus disease (Zaki ,et al,1999) ,Although a quick diagnosis is not possible due to the specialized laboratory procedures needed for this operation, they can be utilized as a monitoring tool or as a substitute for an autopsy on the deceased patient.

4. Treatment for viral hemorrhagic fever

Treatment is based on supportive care such as fluid replacement and symptom control, and antivirals may be used for some types. Viral hemorrhagic fevers are deadly diseases that require early recognition of symptoms and strict preventive measures to limit their spread. Isolation, supportive care, and providing appropriate treatment when available are key factors in improving the chances of survival. Research is ongoing to develop effective vaccines and treatments to combat these serious diseases So far, there are no specialized vaccines, drugs, or therapeutics method present for VHF, excepting EBOV. Presently, Food & Drug Administration had confirmed two medications for Ebola Zaire. The Inmazeb (accepted in October 2020), which is a set of 3 monoclonal antibodies (Commissioner, 2020). The second one is Ebanga (accepted in December 2020), which is single monoclonal antibody. In addition, Merck was manufactured a vaccine against Ebola virus known as rVSVΔG-ZEBOV-GP Ebola vaccine (common name Ervebo), which was accepted by FDA in 2019 (Ebola vaccine, 2021). The researches for evolving novel treatments for VHF have acquired matter at observing of latest series of global viral health crisis. Nevertheless, outcomes from these huge investigation projects have been impeded by some restrictions including: (1) lack of appropriate animal models, (2) Incomplete understanding of the accurate molecular and immunological mechanisms underlying VHF pathogenesis, (3) the presence of various viral serotypes and a broad range of arthropod vectors, (4) Poor clinical diagnosis and rapid diseases progression are often associated with severe outcomes like rapid deterioration of patient status.

5. Prevention

Avoiding close contact with affacted individuals or animals carrying virus, wearing respirators for Lab personnel, gloves for huntsman, masks for farmers in endemic zones, and wear suitable clothing for the general public or nylon clothing for those living in focal site are all ways for

preventing and lower the risk of contracting OHFV. Other preventive means include putting in place infection control procedures, using personal protective equipment, and getting vaccinated when vaccines are available (Diani,et al ,2025)

Conclusions

Hemorrhagic fever is a serious disease that affects humans and causes a high mortality rate due to its pathogenicity. These viruses infect insects or rodents, so the focus is on staying away from rodents or insects that carry the virus. Therefore, it is necessary to adhere to the procedures of Islam and prepare. These procedures allow for preparation for the future. disease outbreaks and preparation reduce the impact of diseases on humans. Scientific research is still ongoing to develop more effective vaccines and treatments that may contribute to reducing the negative effects of these viruses

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