CHAPTER

# 11

# Viral Hemorrhagic Fever

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## INTRODUCTION

Viral hemorrhagic fevers (VHFs) refer to a group of illnesses that are caused by several distinct families of viruses. In general, the term "viral hemorrhagic fever" is used to describe a severe multisystem syndrome (multiple organ systems in the body are affected). Characteristically, the overall vascular system is damaged, and the body's ability to regulate itself is impaired. These symptoms are often accompanied by hemorrhage (bleeding). While some types of hemorrhagic fever viruses can cause relatively mild illnesses, many of these viruses cause severe, life-threatening diseases.

## ETIOLOGY

A wide range of viruses can cause viral hemorrhagic fever (VHF) and hence are designated as hemorrhagic fever viruses.

- The family Arenaviridae include the viruses responsible for Lassa fever and Argentine, Bolivian, Brazilian and Venezuelan hemorrhagic fevers.
- The family Bunyaviridae include the members of the Hantavirus genus that cause hemorrhagic fever with renal syndrome (HFRS), the Crimean-Congo hemorrhagic fever (CCHF) virus from the Nairovirus genus, and the Rift Valley fever (RVF) virus from the Phlebovirus genus.
- The family Filoviridae includes Ebola virus and Marburg virus. Finally, the family Flaviviridae includes dengue, yellow fever, and two viruses in the tick-borne encephalitis group that cause VHF: Omsk hemorrhagic fever virus and Kyasanur Forest disease virus.

## COMMON CHARACTERISTICS

- They are all RNA viruses, and all are covered, or enveloped, in a fatty (lipid) coating.
- Their survival is dependent on an animal or insect host, called the natural reservoir.
- The viruses are geographically restricted to the areas where their host species live.
- Humans are not the natural reservoir for any of these viruses.
- Humans are infected when they come into contact with infected hosts. However, with some viruses, after the accidental transmission from the host, humans can transmit the virus to one another.
- Human cases or outbreaks of hemorrhagic fevers caused by these viruses occur sporadically and irregularly. The occurrence of outbreaks cannot be easily predicted.

With a few noteworthy exceptions, there is no cure or established drug treatment for VHFs.

General characteristics of these viral families can be found in this table below.

## TRANSMISSIONS

Viruses causing hemorrhagic fever are initially transmitted to humans when the activities of infected reservoir hosts or vectors and humans overlap. Some viruses that cause hemorrhagic fever can spread from one person to another, once an initial person has become infected. Ebola, Marburg, Lassa and Crimean-Congo hemorrhagic fever viruses are examples. This type of secondary transmission of the virus can occur directly, through close contact with infected people or their body fluids. It can also occur indirectly, through contact with objects contaminated with infected body fluids. For example, contaminated syringes and needles have played an important role in spreading infection in outbreaks of Ebola hemorrhagic fever and Lassa fever.

## PATHOPHYSIOLOGY

The primary defect in patients with viral hemorrhagic fever (VHF) is that of increased vascular permeability due to multiple cytokines activations. Hemorrhagic fever viruses have an affinity for the vascular system, leading initially to signs such as flushing, conjunctival injection, and petechial hemorrhages, usually associated with fever and myalgias. Later, frank mucous membrane hemorrhage may occur, with accompanying hypotension, shock, and circulatory collapse.

Inadequate or delayed immune response to these novel viral antigens may lead to one hand rapid development of overwhelming viremia and other hand pronounced macrophage activation with extensive damage of affected organs. Hemorrhagic complications are multifactorial and are related to hepatic damage, consumptive coagulopathy, and primary marrow injury to megakaryocytes.

Hepatic involvement varies with the infecting organism and is at times seen with Ebola, Marburg, RVF, CCHF, and yellow fever. Renal failure with oliguria is a prominent feature of HFRS seen in Hantavirus infection and may be seen in other VHFs as intravascular volume depletion becomes more pronounced. Bleeding complications are

**Table 1: Viruses causing Hemorrhagic Fever**

| Virus | Diseases | Incubation Period (Days) | Case Infection ratio | Case Fertility Rate | Natural Distribution | Usual Source of Human Infection | Target Population |
|---|---|---|---|---|---|---|---|
| Arenaviridae: Arena virus | Lassa Fever | 5-16 | Commonly mild infection | 15% | West Africa | Rodent | All ages Both sexes |
| | Argentine HF | 7-14 | >1/2 infections result in Disease | 15-30% | South America | Rodent | All ages Both sex |
| | Bolivian HF | 9-15 | >1/2 infections result in Disease | 15-30% | South America | Rodent | Countryside:Men. Village: All age both sexes |
| | Venezuelans HF | 7-14 | >1/2 infections result in Disease | 15-30% | South America | Rodent | All ages both sexes |
| Bunia viridae i. Phlebo virus | Rift valley Fever | 2-5 | 1:100 | 50% | Sub-Saharan Africa, Madagaskar, Egypt | Mosquito | All age both sex, Men more exposed, Liver disease Predisposed |
| ii. Nairo virus | Crimean-Congo HF | 3-22 | ≥1:5 | 15-30% | Europe, Asia, Africa | Tick | All age both sex, Men more exposed |
| iii. Hanta virus | HF with renal syndrome | 9-35 | Hantan > 1:1.25 Puumala 1:20 | Hantan 5-15% Puumala <1% | Worldwide depending on rodent reservoir | Rodent | Adult male more prone |
| | Hanta virus Pulmonary syndrome | 7-28 | Very high | 40-50% | Americas | Rodent | Adult male more prone |
| Filoviridae Filovirus | Marburg and Ebola virus | 3-16 | High | 25-90% | Sub Saharan Africa | Unknown | All ages both sex, Child less exposed |
| Flavivirus | Yellow fever | 3-6 | 1:2 – 1:20 | 20% | Africa, South America | Mosquito | All ages both sexes adult more exposed, preexisting flaviirus immunity may cross protect |
| New | | | | | | | |
| New Arena virus | Luzo virus (Discovered in 2008) | 2 weeks | Very high | Highly fatal | Lusaka (Zambia), Johannesburg (South Africa) | Rodent, Bat | All ages both sexes |
| New Flavi virus | Alkhumra hemorrhagic fever | Few weeks | Very high | 25% | Saudi Arabia | Sheep, Goat, Rodent. Mosquito | Al ages both sexes |

particularly prominent with Ebola, Marburg, CCHF, and the South American arena viruses.

## COMMON CLINICAL FEATURES

Although clinical features vary somewhat for the various hemorrhagic fever viruses, the clinical presentations overlap substantially. All of the agents cause a febrile prodrome associated with varying degrees of prostration; other notable features include the following.

- Bleeding manifestations occur in variable proportions of patients (eg, in about 30% of patients with Ebola or Marburg hemorrhagic fever and in only about 1% of patients with Rift Valley fever).
- A maculopapular rash may be noted early in the clinical course in some forms of VHF (notably in Ebola and Marburg hemorrhagic fevers)
- Severe exudative pharyngitis is a characteristic early feature of Lassa fever.
- Several agents cause meningoencephalitis in addition to VHF (eg, Rift Valley fever, Kyasanur Forest disease, Omsk hemorrhagic fever viruses).
- Jaundice may be a prominent feature in some infections (eg, Ebola and Marburg hemorrhagic fevers, Lassa fever, Rift Valley fever, yellow fever).

## INVESTIGATIONS

There may be leucopenia, thrombocytopenia with elevated hepatic enzymes, raised prothombin time, activated partial thromboplastin time and fibrin degradation product in patients with hemorrhages and hepatopathy.

Specific viral diagnosis can be made using serologic tests, including enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction. Difficult cases may require tissue cultures. During the 2000-2001 Ebola outbreak in Uganda, reverse transcriptase-PCR (RT-PCR) emerged as a very effective means for detecting Ebola virus in patient serum, plasma, and whole blood. Report all suspected cases of viral hemorrhagic fever (VHF) immediately to local and state public health departments and to the CDC.

Because of the need for specialized microbiologic containment and handling of these viruses, initiate contact with the Centers for Disease Control and Prevention (CDC; Atlanta, GA) as soon as possible and prior to transport of specimens for virus-specific diagnosis. Specific state and federal statutes govern the shipment of highly infectious disease agents.

## TREATMENT

Fluid resuscitation and supportive care are the mainstays of emergency department therapy.

Intravenous crystalloids, oxygen, and cardiac monitoring are the most appropriate initial steps in the treatment of patients in whom viral hemorrhagic fever (VHF) is suggested. Other measures include the following:

- Administer blood and blood products as clinically indicated.
- Avoid intramuscular injections and the use of aspirin or other anticoagulants.
- Minimize invasive procedures because of the risk associated with viral transmission from sharp objects

Infection control measures include the following:

- Prevent nonessential staff and visitors from entering the room
- All staff entering the room should wear gloves and gowns
- Persons coming within 3 feet of the patient should wear face shields or surgical masks with eye
- protection (including side shields); use HEPA filter masks if patients have prominent respiratory, GI, or hemorrhagic symptoms.
- If large amounts of blood or other body fluids are present in the environment, use leg and shoe coverings.
- Before exiting the room, discard all used protective barriers and clean shoes with a hospital disinfectant or solution of household bleach.
- If possible, use an anteroom for putting on and removing protective barriers and for storing supplies.

No specific antiviral therapy is available for Ebola or Marburg virus infection. The use of convalescent serum (ie, sera from patients who have survived infection) is suggested as a possible therapy.

Lassa fever and HFRS due to Hantavirus infection have been treated effectively with intravenous and oral ribavirin. Because of this, ribavirin has been recommended as a potential treatment for other arena viruses and bunya viruses. Treatment is most effective when given early in the clinical course. Ribavirin also is recommended for post exposure prophylaxis. Other potential antiviral therapies against Lassa fever include novel benzimidazole compounds such as ST-193 and other related heterocyclic compounds.

Recently proposed guidelines for the use of ribavirin for post exposure prophylaxis recommend the use of oral ribavirin exclusively for definitive, high-risk exposures, such as contaminated needle stick injury, mucous membrane or no intact skin exposure with contaminated blood or body fluids, participation in emergency resuscitative procedures (eg, intubation, suctioning), or prolonged close contact in an enclosed space with infected patients without appropriate personal protective equipment.

## PREVENSION

1. Because many of the hosts that carry hemorrhagic fever viruses are rodents, disease prevention effort include:

a. Controlling of rodent populations

b. Discouraging rodents from entering and living in homes or workplaces.

c. Encouraging safe cleanup of rodent nest and droppings.

2. Vaccines:

Yellow fever vaccine is readily available and is both safe and effective. A bivalent vaccine is being developed from the preexisting 17D yellow fever vaccine that would express not only yellow fever glycoprotein's but also Lassa glycoprotein's, theoretically stimulating a protective immune response against both viruses.

A recent study evaluating the safety and efficacy of a tetravalent dengue vaccine demonstrated full seroconversion against all WHO dengue serotypes in flavivirus-naive adults.

Argentine HF (Junín) vaccine is also effective and may protect against Bolivian HF as well.

Rift Valley fever and Hantan (HFRS) vaccines are also available.

Although there is no approved vaccine for either Ebola or Marburg virus, significant progress has been made in developing an effective experimental vaccine using a vesicular stomatitis virus-based vaccine.

Other efforts to create a viable (and marketable) Ebola vaccine have led to the development of an experimental bivalent vaccine that confers protection against both rabies and Ebola virus.

## COMPLICATION

Complications from viral hemorrhagic fever (VHF) infection include retinitis, orchitis, encephalitis, hepatitis, transverse myelitis, and uveitis.

In patients who recover from Lassa fever infection, deafness is the most common complication.

Renal insufficiency is associated with HFRS infection.

## DENGUE HEMORRHAGIC FEVER

### Introduction

Dengue virus, belong to a family Flaviviridae and have four serotypes (DEN 1, 2, 3, 4). They are transmitted mainly by Aedes aegypti and Aedes albopictus mosquito. Among the four serotype DEN 2 is more virulent and most of DHF are due to infection of DEN 2.

Dengue is a mosquito borne viral disease, which has raised concern globally, due to alarming 30 fold increase in its incidence in last few decades. Almost 75% of global population exposed to dengue live in Asia-Pacific region. In India first major epidemic of DHF was observed in 1996 involving Delhi, Lucknow, Kolkata and Chennai. In 2015 India also faced a major outbreak affected worstly in Delhi and Punjab followed by West Bengal and Gujarat having total mortality of 90000 with 180 deaths.

### Transmission

Most Dengue epidemic occurs post monsoon, due to increase in vector population. However virus maintenance during inter epidemic period has been attributed to transoverian transmission of Dengue virus. Dengue virus primarily transmitted to human through an infected mosquito bite. Humans are the main amplifying host of the virus. After a blood meal virus infect the mosquito and stays in its gut for 8-12 days of extrinsic incubation period. Virus again reenter the human body after subsequent bite. Aedes aegypti is one of the most efficient vector for arboviruses because it is highly anthrophilic, frequently bites several times before completing oogenesis, and thrives in close proximity to Humans.

### Pathogenesis

Replication of the dengue virus occurs within mononuclear cells including skin dendritic cells, tissue macrophages, peripheral blood monocytes, and hepatocytes. At present, the host cell receptors involved in the viral entry are mostly unknown. Primary or first infection in nonimmune persons usually causes DF. Subsequent dengue infection by a different serotype causes more severe illness, such as DHF/DSS. The key manifestations of DHF/DSS are sudden onset of shock, capillary leakage, and hemorrhagic diathesis/thrombocytopenia occurring at the time of defervescence. Pathogenesis is not well-defined, but it is suggested that during secondary infection with a different serotype, cross-reactive nonneutralizing antibodies bind to DENV and facilitate uptake via Fc receptors, resulting in enhanced viral replication. The resultant higher viral antigen load leads to an exaggerated activation of cross-reactive dengue specific T cells. Biological mediators released by the activated T cells as well as virus-infected cells along with complement activation by viral proteins and immune complexes are implicated in increasing vascular permeability and coagulopathy. This phenomenon is known as antibody-dependent enhancement.

### Clinical features

This model for classifying dengue has been suggested by an expert group (Geneva, Switzerland, 2008) and is currently being tested in 18 countries by comparing its performance in practical settings to the existing WHO case classification (Table 2).

### Diagnosis

The nonspecific nature of the illness mandates laboratory verification for diagnosis.

For confirmation of Dengue infection, Govt of India recommends use of ELISA- based virus specific antigen (NS1) for diagnosing the cases from the first day onwards and antibody detection test IgM capture ELISA (MAC-ELISA) for diagnosing the cases after the fifth day of disease onset.

Govt of India introduced ELISA- based NS1 antigen in 2010 in addition to MAC- ELISA tests which can detect the case during ay 1 to day 5 of illness.

**Table 2: Expert Group Classification for Dengue**

| Criteria For Dengue | Warning Signs | Criteria For Severe Dengue |
|---|---|---|
| **Probable Dengue**<br>Live in or travel to Dengue endemic area.<br>Fever and 2 of the following criteria :<br>1. Nausea, vomiting<br>2. Rash<br>3. Aches and pains<br>4. Tourniquet test positive<br>5. Leucopenia<br>6. Any warning signs<br>7. Liver: AST/ALT> 1000<br>Laboratory confirmed Dengue (important when no signs of plasma leak) | **Warning Signs***<br>Abdominal pain or tenderness<br>Persistent vomiting<br>Clinical fluid accumulation<br>Mucosal bleeding<br>Lethargy, Restlessness<br>Liver enlargement > 2cm<br>Laboratory: Increase in HCT with rapid decrease in platelet count.<br>(*requiring strict observation and medical intervention) | **Severe plasma leakage**<br>Shock<br>Fluid accumulation with severe respiratory distress.<br>Severe bleeding as evaluated by clinician.<br>Severe organ involvement.<br>CNS: Impaired consciousness<br>Heart and other organs |

## Treatment

The management of dengue virus infection is essentially supportive and symptomatic. No specific treatment is available. However, there are Indian studies which have contributed in terms of better management of DHF/DSS. A rapid response to platelet and fresh frozen plasma (FFP) transfusion is reported in a study. Anti-D has been used in children with DHF and severe refractory thrombocytopenia. In experimental study pre-feeding mice with trivalent chromium picolinate (CrP) in drinking water could abolish the adverse effects of DV infection on most of the hematological parameters. *Hippophae rhamnoides* (Sea buckthorn, SBT) leaf extract has been shown to have a significant anti-dengue activity.

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