

CARDIO-VASCULAR SYSTEM

1

Microbiology

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Viral hemorrhagic fevers (VHFs)

Overview

Viral hemorrhagic fevers (VHFs) are a group of illnesses caused by four families of viruses: *Arenaviridae*, *Bunyaviridae*, *Flaviviridae*, and *Filoviridae*.

They share -as the name suggests- the ability to cause viral infections, fever, and bleeding (hemorrhage). They are marked by diffuse vascular damage.

-Common features between the four groups:

1. Enveloped: Lipid-encapsulated.
2. Single-stranded RNA.
3. Zoonotic (animal-borne) **(important)**.
4. The geographical distribution of these viruses is restricted to the geographic distribution of the host (+the vector if it is an arbovirus).
5. Persistent in nature (rodents, bats, mosquitoes, ticks, livestock, monkeys, and primates).

Mortality rates in this lecture are not for memorization.

-Survival is dependent on the animal or insect host, which is the natural reservoir.

❖ The different names within each family of these viruses are dependent on the first geographic region they were isolated from.

- VHFs are classified according to the involvement of an arthropod vector in their transmission cycle into 2 groups:

1. Arboviruses (Arthropod-borne): viruses which one of their main routes of transmission is an arthropod (such as mosquitoes and ticks). Examples include: Bunyaviridae -with the exception of Hantaviruses- and Flaviviridae.
2. Non-Arboviruses: viruses that are not transmitted by arthropods. Examples include: Arenaviridae and Filoviridae.

1-Arenaviridae

Non-Arboviruses, their replication takes place in the cytoplasm, and they carry RNA dependent-RNA polymerase.

They have taken their specific name from the “Arena” (The place of competition); because these viruses acquire the host’s ribosomal subunits in their virion state. This feature appears under the electron microscope as a “**Sandy Cytoplasm**”.

The Arenaviridae family is classified into 2 groups according to the geographical distribution:

1. West African: such as Lassa fever (in Nigeria). This one has the highest mortality rate in this family.

2. South American: Argentine hemorrhagic fever (caused by the Junin virus), Bolivian HF (caused by the Machupo virus), Brazilian HF (caused by the Sabia virus), Venezuelan HF (caused by the Guanarito virus).

Arenaviridae Transmission:

Virus transmission and amplification occurs in rodents, they shed the virus through urine, feces, and other excreta.

Humans can be infected by contact with a rodent's excreta, contaminated materials and aerosol transmission. **Person-to-person transmission has been documented** in Lassa fever (one of the members of this family).

NO arthropods are involved as vectors here; that's why they are considered non-Arboviruses.

There are two types of transmission between the infected rodents:

1. Horizontal transmission: It means the transmission of viruses between two organisms, one of them is not a parent of the other (NOT between mother and her progeny for example). So, if one rodent got infected by another infected rodent, it will die at the end and the transmission cycle will not continue (**an important feature of horizontal transmission !**)
2. Vertical transmission: It means the transmission of viruses from the mother to its fetus . So, if an infected rodent transmits the virus to its fetus, then the transmission cycle continues. That is why **vertical transmission is much more dangerous compared to horizontal transmission.**

-The incubation period is less than 2 weeks (10-14) days, and they have an **acute onset** of disease in general.

Arenaviridae have 2 stages of the disease (Biphasic) according to the severity of the infection:

1. Prodromal stage (viremia phase): the first stage that starts after 2-4 days, it is characterized by a high viral load in the blood. It includes constitutional signs and symptoms that are associated with any type of infection; for example: fever, headache, joints pain, malaise, myalgia ,photophobia. It is important to know that these signs and symptoms are NOT specific to this family.
2. Hemorrhagic stage (toxemia phase) :the second stage in which there is bleeding diathesis (tendency).

In this phase, patients are at high risk of **DIC** (Disseminated Intravascular Coagulopathy), also known as **Consumptive Coagulopathy**, in which there is high consumption of clotting factors and platelets in the body, thus the tendency to bleed is higher. Treatment is supportive, by giving the patient clotting factors, platelets, plasma, blood units, etc...

-At the end stage of the infection, some psycho-behavioral changes (neurologic signs) might appear, for example: vision loss, hearing loss, etc...

In between these 2 phases, there is a **window period**, in which signs and symptoms disappear.

It is important to mention here that these 2 phases will be repeated almost the same in Flaviviridae and Filoviridae, except that the second stage can be more severe and common to take place in Flaviviridae and Filoviridae. i.e. DIC is mainly found in Filoviridae not Arenaviridae.

• Lassa Fever

First seen among missionary nurses in Lassa, Nigeria in 1969 . But now the incidence rate is high in all countries of West Africa (5-14% of all hospitalized febrile illnesses).

Transmission

1. Rodent-borne (the initial route of transmission): direct contact with infected (*Mastomys natalensis*) rodent, which is the natural reservoir, or by inhalation of aerosol from its excreta or urine.
2. Interpersonal transmission (person to person): Direct Contact, Sex, Breast Feeding ...

-**Distinguishing Features** include:

Gradual onset of the disease (in contrast with Filoviridae (Marburg and Ebola) which have an acute onset) , Retro-sternal pain ,Exudative pharyngitis, Hepatitis, **Hearing loss "Deafness" in the fetus after birth if he/she was infected from the mother (in 25% may be persistent even after recovery)** and Spontaneous abortion in pregnant women.

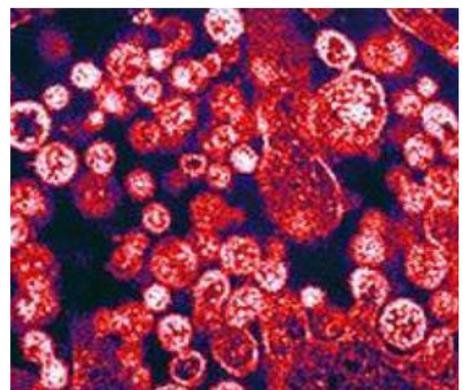
-Mortality rate in sporadic cases is mild (1-3%) because the transmission cycle is not that active, however it might reach 50% in epidemics.

Lassa fever requires biosafety level 4; because they are so dangerous to work on in ordinary laboratories , thus nosocomial infections are so common.

Very important: Lassa fever patients keep shedding the virus from their urine for at least 2 weeks after recovery, so you must isolate the patient for 2 weeks.

Therapy: Ribavirin antiviral is an effective treatment (documented), although supportive treatment is considered as the main therapeutic approach .

The figure to the right shows the **sandy cytoplasm appearance** for Lassa virus under EM.



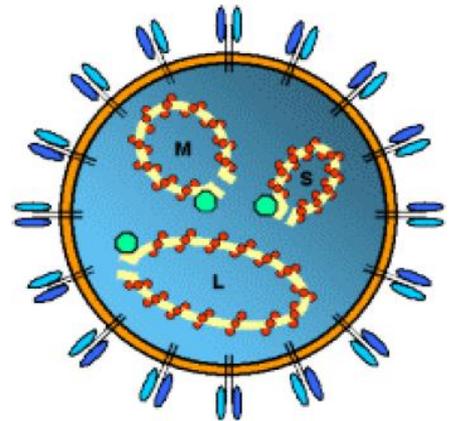
2-Bunyaviridae

They are arthropod-borne viruses **EXCEPT for Hantaviruses**, which are non-arboviruses.

We will talk about 3 viruses: Rift Valley Fever virus (RVF), Crimean-Congo Hemorrhagic Fever virus (CCHF), and Hantavirus.

The RNA of this family is segmented (genes that encode for a certain function are present on different segments). There are 3 segments:

1. **L-segment (Large)** codes for an L-protein (the RNA dependent RNA polymerase).
2. **M-segment (Medium)** codes for two surface glycoproteins G1 and G2, which form the envelope spikes.
3. **S-segment (Small)** codes for an N-protein (nucleocapsid protein).



• Rift Valley Fever

Caused by the simplest virus in this family with the lowest mortality rate (less than 1-5%). It is an asymptomatic or mild illness in humans, but still a fatal disease in cattle or sheep.

However, it has hemorrhagic complications, but they are rare (<5%).

Vision loss “blindness” (due to retinal hemorrhage, vasculitis) in 1-10% of patients.

Very important: The arthropod vector that transmits RVF is the **Aedes aegypti** mosquito.

The incubation period is less than a week (usually 2-5 days).

Treatment: Supportive therapy only. However, Ribavirin is NOT considered an effective documented treatment.

• Crimean-Congo Hemorrhagic Fever (CCHF)

-The virus causing CCHF is an arbovirus, and the **vector** that transmits the virus is the **Ixodid tick (Hyalomma/Haemaphysalis)**.

-**Very important:** Person to person transmission is an effective mode of transmission for CCHF, in addition to aerosols inhalation from laboratories .

-**Distinguishing features:** Abrupt (**acute**) onset, profuse hemorrhage, and most humans infected will develop hemorrhagic fever.

-Mortality rate of CCHF is much higher (15-40%) compared to RVF.

-CCHF has a limited geographical distribution, and this is dependent on the geographical distribution of =the natural reservoir (Host) + the vector if it is an arbovirus (which is the case here).

-Treatment: Ribavirin is an effective documented treatment for CCHF.

• Hantaviruses

They are **non-arboviruses** (The only exception for Bunyaviridae family).

We have two serotypes of Hantaviruses:

1. Old-world Hantavirus: which causes **Hemorrhagic Fever with Renal Syndrome (HFRS)**
2. New-world Hantavirus (Nombro virus): which causes **Hantavirus Pulmonary Syndrome (HPS)**. THIS TYPE IS OUT OF THE SCOPE OF THIS LECTURE.

Transmission to humans:

1. Direct contact or exposure to rodents through: saliva, excreta, inhalation, bites.
2. Ingestion of contaminated food/water: This route of transmission is still controversial and is not evidence-based yet as a well-established route of transmission.
3. Person-to-person transmission: **only found in Andes virus in Argentina.**

-Hemorrhagic Fever with Renal Syndrome (HFRS) :

- 1) Distinguishing Features: **Insidious (chronic) onset**, intense headaches, blurred vision, kidney failure (causing severe fluid overload).
- 2) Mortality rate: 1-15%

3-Flaviviridae

- They are arboviruses, and their replication takes place inside the cytoplasm.

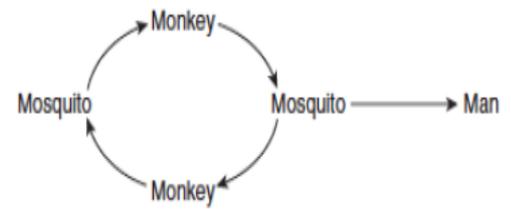
- We will talk about 4 viruses: **Dengue virus, Yellow Fever virus, Omsk Hemorrhagic Fever virus, Kyasanur Forest Disease virus.**

- ALL Flaviviridae are characterized by the **“Biphasic clinical presentation”**:

1. Viremia phase: It is characterized by a high viral load in the blood and high secretion of cytokines. It includes constitutional signs and symptoms; for example: marked fever.
➤ In between the 2 phases, there is a **window period**, in which signs and symptoms disappear.
2. Toxemia phase: Fever returns along with the constitutional symptoms + Hemorrhagic signs and symptoms appear.

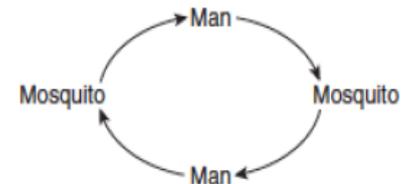
Yellow Fever and Dengue viruses have 3 life cycles:

1. ***Aedes aegypti* cycle:** within the arthropod vector.
2. **Sylvatic cycle:** In jungle forests, between non-human primates like monkeys (natural host) and the vector. Humans are considered accidental hosts. See the figure.



Sometimes sylvatic cycle might refer to tree-cutters in the jungle.

3. **Urban cycle:** between humans and the vector without the need of an intermediate host (the virus is directly transmitted from the mosquito to the human and vice versa). See the figure.



Very important: It is important to mention here that the vector for RVF virus is the same as the vector for yellow fever virus and dengue virus, which is the ***Aedes aegypti***.

Yellow and dengue fevers are common in Africa and South America.

• Yellow Fever

- Distinguishing features: Common hepatic involvement due to hepatocyte necrosis & **jaundice**.
- Mortality rate: high (15-50%) but still low compared to Filoviruses.

-Human-to-human route of transmission can be found in yellow fever but it's very limited. However, this is **not** considered a main route (**not well-documented**). The main mode of transmission is by ***Aedes aegypti***.

• Dengue fever (DF)

Dengue fever has 4 distinct serotypes (DEN 1, DEN 2, DEN 3, DEN 4), **all** are known to cause diseases in humans.

There are 2 types of dengue infections:

1. Dengue Hemorrhagic Fever (DHF): Fatality rate: 5-6%
2. Dengue Shock Syndrome (DSS): has a higher fatality rate (12-44%), patients become hypovolemic, and at higher risk for hypovolemic shock followed by death.

Very important:

1. Onset of dengue fever infections is **sudden (acute)**.
2. Remember the vector is ***Aedes aegypti***.
3. Illness of dengue infection is very severe in younger children (well-documented).

Treatment: supportive treatment only.

Distinguishing Features -not mentioned by the prof-: Eye pain, Rash, Complications: sequelae uncommon.

• Omsk Hemorrhagic Fever

Omsk is a city in Russia.

-It's an arbovirus infection, common in Russia and Europe in general.

-Biphasic infection: viremia → window period → toxemia.

-The hemorrhagic (toxemia) phase starts with hemorrhage under the skin in the form of petechiae and ecchymosis.

The end-stage is characterized by internal and external bleeding from all the body orifices including upper and lower GI bleeding, mouth, nose. In the end, it can progress to DIC followed by hypovolemic shock and death. That is why Omsk fever has a high fatality rate (but less than Filoviruses).

The **Muskrat rodent** is the **natural reservoir** (natural host, not the vector) ☺.

Complications: Hearing loss, Hair loss, Psycho-behavioral difficulties (neurological changes).

• Kyasanur Forest Fever

Kyasanur is an arbovirus infection that is common in India (mainly: Karnataka State), Pakistan, and Bangladesh.

Biphasic infection: viremia → window period → toxemia.

The vector that transmits Kyasanur Forest Fever is the same as the vector for the CCHF, which is the **Ixodid tick**.

(*Hyalomma/Haemaphysalis*). See the picture.

Kyasanur Fever has an **acute onset** of the disease.

Case fatality: 3-5%



4-Filoviridae

They are non-Arboviruses, that have a sudden (acute) onset of the disease with rapidly fatal febrile hemorrhagic illness.

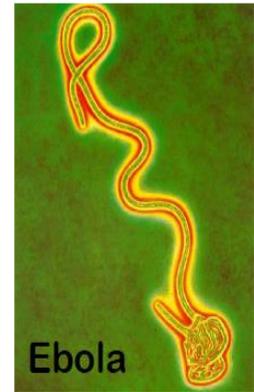
Very important: They are the family with the highest mortality rate (up to 90%), fatality, and morbidity rates, compared to all the previous hemorrhagic fever viruses.

They include **Ebola and Marburg viruses**.

They have a short incubation period (less than a week, usually 1-2 days). In the second week after exposure, patients are at high risk of death. If the patient survives after the second week, he is considered to be recovering. However, this recovery is "**painful**", during which the patient does not feel that he is getting well, but the lab results say that everything is getting better.

Ebola has **5 serotypes** according to the place from where they were first isolated: **Ebola-Zaire, Ebola-Sudan, Ebola-Ivory Coast, Ebola-Bundibugyo, Ebola-Reston.**

First 4 serotypes cause disease in humans (Ebola hemorrhagic fever), whereas the fifth serotype (**Ebola-Reston**) causes illness mainly in **non-human primates**. Although it can establish infection in humans (speaking of the 5th type), it is still not considered a main cause of human disease.



-Human-infectious subtypes are found only in Africa.

-On the other hand, Marburg virus has a single serotype.

***Reservoir is UNKNOWN**, but it is zoonotic. However, bats are a possible reservoir.

Transmission:

1. Person-to-person is an effective route of transmission (**Very important**).
2. Nosocomial:
 - a. Reuse of needles and syringes.
 - b. Exposure to infectious tissues, excretions, and hospital wastes.
3. Aerosol transmission: Primates.

Biosafety level 4 is required to prevent Filoviridae infections.

Patients who died from Filoviridae diseases were burnt in certain countries, and some have had a **safe burying** (approved and applied nowadays in most countries).

Again, they have **biphasic clinical presentation**:

- 1) One in the blood “Viremia phase (Early/Prodromal Symptoms)”: high viral overload → cytokine rush → constitutional symptoms (Fever, Myalgia, Malaise, Fatigue, Headache, Dizziness, Arthralgia, Nausea, Non-bloody diarrhea). These are not specific.
 - 2) The other is in the immune response “Toxemia phase (Progressive Signs)”: endothelial injury → consumption of the clotting factors and platelets; resulting in bleeding under the skin (Ecchymosis, Petechiae), this type of hemorrhage is rarely life-threatening. Severe/End-stage is characterized by DIC, resulting in profuse internal and external bleeding.
- **Very important:** DIC (Disseminated Intravascular Coagulopathy) is a marked (well-established) pathophysiology for Filoviruses (Ebola and Marburg) before severe hemorrhage.

Distinguishing features between Ebola and Marburg:

Ebola: GI involvement, Weight loss.

Marburg: Chest pain, Maculopapular rash on trunk, Pancreatitis, Jaundice.

Lab tests

In order to diagnose patients with VHF, we can use many tests:

- 1) Complete Blood Count: Leukopenia, leukocytosis, thrombocytopenia, hemoconcentration, DIC.
- 2) Liver function test: can be used to detect **yellow fever**.
- 3) Kidney function test: can be used to detect **HFRS**.
- 4) Proteinuria universal.
- 5) Serological tests –Abs are not detected during the acute phase- : Direct examination of blood/tissues in viral Ag enzyme immunoassay.
- 6) Immunohistochemical staining for liver tissue.
- 7) Virus isolation in cell culture.
- 8) RT-PCR sequencing of the virus.
- 9) Electron microscopy specific and sensitive: can be used to show Lassa fever **sandy cytoplasm**.

Treatment for VHF in general

Supportive care: Fluid and electrolyte management, Hemodynamic monitoring, Ventilation and/or dialysis support, Steroids for adrenal crisis, Anticoagulants, IM injections and the Treatment of secondary bacterial infections.

Manage severe bleeding complications: Cryoprecipitate (concentrated clotting factors), Platelets, Fresh Frozen Plasma and Heparin for DIC.

Ribavirin shows activity in vitro (in labs, outside the body) against Lassa fever, New and Old World Hanta-hemorrhagic fevers and the Rift Valley Fever.

- No evidence to support using Ribavirin in Filovirus or Flavivirus infections.

Prevention

- 1) The first step of prevention is by isolation of the patient once diagnosed with one of the VHFs.
- 2) The second step is dependent on the type of the VHF. If it is an arthropod-borne virus, then this step is about arthropod control. If it is a non-arthropod-borne, then it is about controlling the natural host (Rodents control).

Vaccination :

There is only one active vaccine that is approved for VHF and it is against the yellow fever as other vaccines are experimental. It is given for travelers before visiting Africa and South America. There are also passive vaccines for the Argentine and Bolivian Hemolytic Fevers. Active immunization is better than passive if there is enough time. However, passive immunization is a good choice for immunocompromised patients for therapeutic purposes not for prevention. (Remember: Active Immunization is the administration of a pathogen to the body in order for the immune system to develop an immune response that forms a long-

lasting immunity against that pathogen. On the other hand, passive immunization is the administration of preformed antibodies. Because of that, passive immunization doesn't confer a long-lasting immunity, it merely functions as a therapeutic approach not a preventive one)

-All VHF viruses can be used as bioweapons; because transmission can be through aerosol, they need a low infectious dose, no vaccine, as well as they have high mortality and morbidity rates.

Quick recap of the most important information mentioned throughout this lecture:

Documented person-to-person route of transmission is found in all of the following:

- 1) Lassa fever.
- 2) CCHF.
- 3) Andes virus in Argentina (the only one from the Hantaviruses).
- 4) Filoviridae (Ebola + Marburg).

- VHFs that are transmitted by Aedes aegypti vector are:
- 1) RVF
 - 2) Yellow fever
 - 3) Dengue fever

Ixodid tick (*Hyalomma/Haemaphysalis*) is the main vector that transmits:

- 1) CCHF.
- 2) Kyasanur fever.

Biphasic clinical presentation is found in:

1. Arenaviridae
2. Filoviridae
3. Flaviviridae (mainly).

Ribavirin is considered an effective (well-documented) treatment -in vivo- only for:

1. Lassa fever
2. CCHF

Number of serotypes for:

- A. Ebola : five
- B. Dengue : four
- C. Hantaviruses : two
- D. Marburg: one

Lassa fever patients keep shedding the virus from their urine for at least 2 weeks after recovery, so you must isolate the patient for 2 weeks.

Filoviridae (Ebola +Marburg) have the highest mortality, fatality and morbidity rates compared to all other VHFs.

Sandy cytoplasmic appearance under the EM is found in: Arenaviridae (Lassa virus mainly).

DIC or Consumptive Coagulopathy is mainly found in Filoviridae (Ebola +Marburg).

All VHF's are zoonotic

- Lassa fever is transmitted by : (*Mastomys natalensis*)
- Omsk fever natural reservoir is: Muskrat.

Illness of dengue infection is very severe in younger children (well-documented).

Arboviruses	Non-arboviruses
Bunyaviridae (except Hantaviruses)	Arenaviridae
Flaviviridae	Filoviridae

Hearing loss (deafness)	Vision loss (blindness)
Lassa fever	RVF
Omsk	-

Acute (sudden) onset	Chronic (insidious)/ gradual onset
Filoviridae (Ebola +Marburg)	HFRS, caused by old-world hantavirus
Dengue fever	Lassa fever
Omsk fever	-
Kyasanur fever	-

Thank you
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