

Viral hemorrhagic fevers (VHFs)

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Overview

- Viral hemorrhagic fevers (VHFs) are a group of illnesses caused by four families of viruses. *Arenaviridae* , *Bunyaviridae*, *Filoviridae* and *Flaviviridae*
- Diffuse Damage to overall vascular system.
- Symptoms often accompanied by hemorrhage
- Some VHFs cause mild disease, but some, like Ebola or Marburg, cause severe disease and death.

Quick Overview: Who are they?

- **Arenaviridae**

- Lassa Fever
- Argentine HF (Junin)
- Bolivian HF (Machupo)
- Brazilian HF (Sabia)
- Venezuelan HF (Guanarito)

- **Bunyaviridae**

- Rift Valley Fever (RVF)
- Crimean Congo HF (CCHF)
- Hantavirus (Hemorrhagic Fever with Renal Syndrome (HFRS))
- Hantavirus Pulmonary Syndrome (HPS)

- **Filoviridae**

- Marburg
- Ebola

- **Flaviviridae**

- Yellow Fever
- Dengue Fever
- Omsk HF
- Kyasanur Forest Disease

Quick Overview: How do we get infected?

- **Rodents & Arthropods, both reservoir & vector**
 - Bites of infected mosquito or tick
 - Inhalation of rodent excreta
 - Infected animal product exposure
- **Person-to-Person**
 - Blood/body fluid exposure
 - Airborne potential for some arenaviridae, filoviridae

Common features

- **Enveloped Lipid-encapsulated**
- **Single-strand RNA**
- **Zoonotic (animal-borne)**
- **Geographically restricted by host**
- **Persistent in nature (rodents, bats, mosquitoes, ticks, livestock, monkeys, and primates)**
- Survival dependent on an animal or insect host, for the natural reservoir

Arenaviridae

- Junin virus : Argentine hemorrhagic fever
- Machupo virus : Bolivian hemorrhagic fever
- Guanarito virus : Venezuelan hemorrhagic fever
- Lassa virus : Lassa fever- Nigeria
- Sabia virus : Brazilian hemorrhagic fever

Arenaviridae Transmission

- Virus transmission and amplification occurs in rodents
- Shed virus through urine, feces, and other excreta
- Human infection
 - Contact with excreta
 - Contaminated materials
 - Aerosol transmission
- Person-to-person transmission

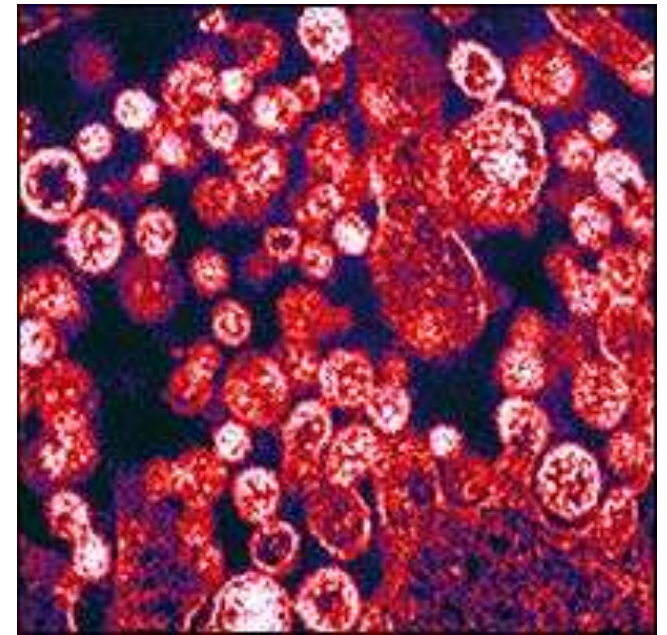


Arenaviridae in Humans

- Incubation period 10–14 days
- Fever and malaise 2–4 days
- Hemorrhagic stage
 - Hemorrhage, leukopenia, thrombocytopenia
 - Neurologic signs

Arenaviridae: Lassa Fever

- First seen in Lassa, Nigeria in 1969.
- Now in all countries of West Africa
 - 5-14% of all hospitalized febrile illness
- Rodent-borne (*Mastomys natalensis*)
- Interpersonal transmission
 - Direct Contact
 - Sex
 - Breast Feeding



Lassa Fever

- Distinguishing Features
 - Gradual onset
 - Retro-sternal pain
 - Exudative pharyngitis
 - Hearing loss in 25% may be persistent
 - Spontaneous abortion
- Mortality 1-3% overall (up to 50% in epidemics)
- Therapy: Ribavirin

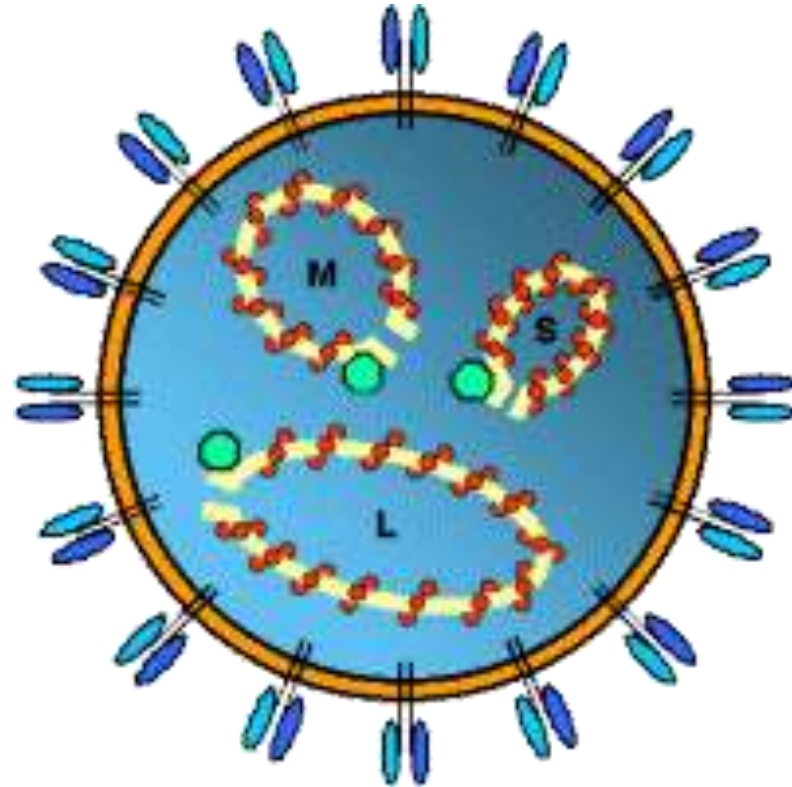
Bunyaviridae

- Rift Valley Fever virus
- Crimean-Congo Hemorrhagic Fever virus
- Hantavirus

L-segment codes for an L-protein (the RNA dependent RNA polymerase);

M segment codes for two surface glycoproteins G1 and G2 which form the envelope spikes;

S segment codes for an N-protein (nucleocapsid protein).



Bunyaviridae Transmission

- Arthropod vector
 - Exception – Hantaviruses
- RVF – *Aedes* mosquito
- CCHF – Ixodid tick (*Hyalomma*)
- Hantavirus – Rodents
- Less common
 - Aerosol
 - Exposure to infected animal tissue



Bunyaviridae

- **Transmission to humans**
 - Arthropod vector (RVF, CCHF)
 - Contact with animal blood or products of infected livestock
 - Rodents (Hantavirus)
 - Laboratory aerosol
 - Person-to-person transmission with CCHF

Rift Valley Fever

- Asymptomatic or mild illness in humans
- Distinguishing Characteristics
 - Hemorrhagic complications rare (<5%)
 - Vision loss (retinal hemorrhage, vasculitis) in 1-10%
- Overall mortality 1%
- Therapy: Ribavirin?

Crimean-Congo Hemorrhagic Fever

- Distinguishing features
 - Abrupt onset
 - Most humans infected will develop hemorrhagic fever
 - Profuse hemorrhage
- Mortality 15-40%
- Therapy: Ribavirin

Bunyaviridae: Hantaviruses

- Transmission to humans:
 - Exposure to rodent saliva and excreta
 - Inhalation
 - Bites
 - Ingestion in contaminated food/water (?)
 - Person-to-person (Andes virus in Argentina)

Hemorrhagic Fever with Renal Syndrome (HFRS)

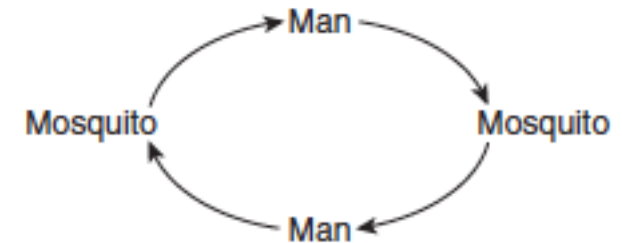
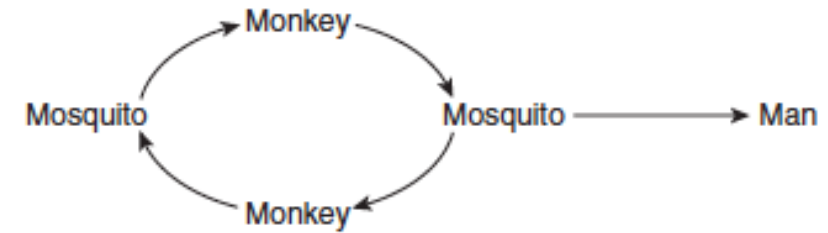
- Distinguishing Features
 - Insidious onset
 - Intense headaches,
 - Blurred vision
 - kidney failure
 - (causing severe fluid overload)
- Mortality: 1-15%

Flaviviridae

- Dengue virus
- Yellow Fever virus
- Omsk Hemorrhagic Fever virus
- Kyassnur Forest Disease virus

Flaviviridae Transmission

- Arthropod vector
- Yellow Fever and Dengue viruses
 - *Aedes aegypti*
 - Sylvatic cycle
 - Urban cycle
- Kasanur Forest Virus
 - Ixodid tick
- Omsk Hemorrhagic Fever virus : Fever Lasting sequela
 - Muskrat urine, feces, or blood



Yellow Fever

- Distinguishing features
 - Biphasic infection
 - Common hepatic involvement & jaundice
- Mortality: 15-50%

Flaviviridae: Dengue

- Dengue Fever (DF) /Fatality: <1%
- Dengue Hemorrhagic Fever (DHF)/ Fatality: 5-6%
- Dengue Shock Syndrome (DSS) /Fatality 12-44%
- Four distinct serotypes
 - DEN-1, DEN-2, DEN-3, DEN-4
- Distinguishing Features
 - Sudden onset
 - Eye pain
 - Rash
 - Complications/sequelae uncommon
- Illness is severe in younger children

Omsk Hemorrhagic Fever

- Distinguishing Features
 - Acute Onset
 - Biphasic infection
 - Complications
 - Hearing loss
 - Hair loss
 - Psycho-behavioral difficulties
 - Mortality: 0.5 – 3%

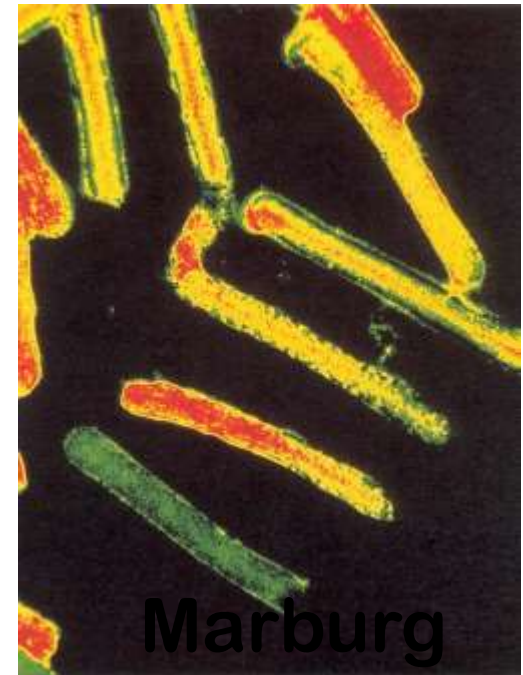
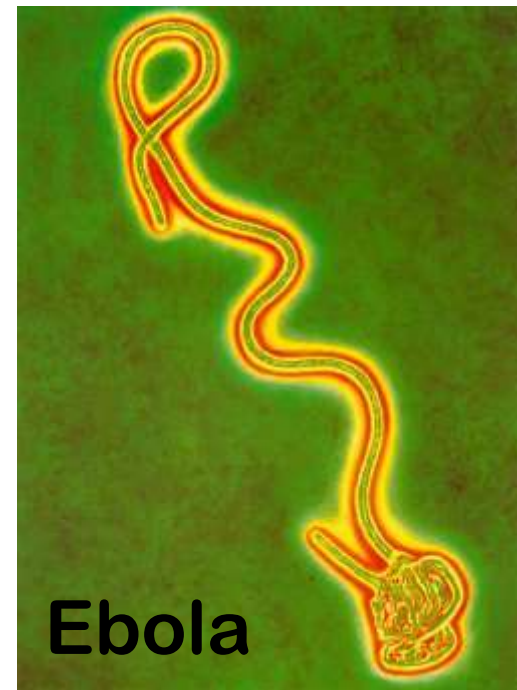
Flaviviridae: Kyanasur Forest

- Distribution: limited to Karnataka State, India
- Haemaphysalis vector
- Distinguishing Features
 - Acute onset
 - Biphasic
- Case-fatality: 3-5% (400-500 cases annually)



Filoviridae

- Ebola
 - Ebola-Zaire
 - Ebola-Sudan
 - Ebola-Ivory Coast
 - Ebola-Bundibugyo
 - (Ebola-Reston)
- Marburg



Filoviridae Transmission

- Reservoir is UNKNOWN
 - Bats implicated with Marburg
- Intimate contact
- Nosocomial transmission
 - Reuse of needles and syringes
 - Exposure to infectious tissues, excretions, and hospital wastes
- Aerosol transmission
 - Primates

Filoviridae: Ebola

- Rapidly fatal febrile hemorrhagic illness
- Transmission:
 - bats implicated as reservoir
 - Person-to-person
 - Nosocomial
- Five subtypes
 - Ebola-Zaire, Ebola-Sudan, Ebola-Ivory Coast, Ebola-Bundibugyo, Ebola-Reston
 - Ebola-Reston imported to US, but only causes illness in non-human primates
- Human-infectious subtypes found only in Africa

Filoviridae: Ebola

- Distinguishing features:
 - Acute onset
 - GI involvement / Weight loss
 - 25-90% case-fatality

Filoviridae: Marburg

- Distinguishing features
 - Sudden onset
 - Chest pain
 - Maculopapular rash on trunk
 - Pancreatitis
 - Jaundice
- 21-90% mortality

Filoviridae Humans

- Most severe hemorrhagic fever
- Incubation period: 4–10 days
- Abrupt onset
 - Fever, chills, malaise, and myalgia
- Hemorrhage and DIC
- Death around day 7–11
- Painful recovery

Common Pathophysiology

- Small vessel involvement
 - Increased vascular permeability
 - Multiple cytokine activation
 - Cellular damage
 - Abnormal vascular regulation:
 - Early -> mild hypotension
 - Severe/Advanced -> Shock
- Viremia
 - Macrophage involvement
 - Inadequate/delayed immune response

Common Clinical Features: Early/Prodromal Symptoms

- Fever
- Myalgia
- Malaise
- Fatigue/weakness
- Headache
- Dizziness
- Arthralgia
- Nausea
- Non-bloody diarrhea

Common Clinical Features: Progressive Signs

- Conjunctivitis
 - Facial & thoracic flushing
 - Pharyngitis
 - Exanthems
 - Periorbital edema
 - Pulmonary edema
- Hemorrhage
 - Subconjunctival hemorrhage
 - Ecchymosis
 - Petechiae
 - But the hemorrhage itself is rarely life-threatening.

Common Clinical Features: Severe/End-stage

- Multisystem compromise
- Profuse bleeding
- Consumptive coagulopathy/DIC
- Encephalopathy
- Shock
- Death

Lab studies

- Complete Blood Count
 - Leucopenia, leucocytosis, thrombocytopenia, hemoconcentration, DIC
- Liver enzymes
- Proteinuria universal
- Serological tests – Ab not detected acute phase; Direct examination blood/tissues for viral Ag enzyme immunoassay.
- Immunohistochemical staining liver tissue
- Virus isolation in cell culture
- RT-PCR sequencing of virus
- Electron microscopy specific and sensitive

Treatment

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

Treatment

- Manage severe bleeding complications
 - Cryoprecipitate (concentrated clotting factors)
 - Platelets
 - Fresh Frozen Plasma
 - Heparin for DIC
- Ribavirin in vitro activity vs.
 - Lassa fever
 - New World Hemorrhagic fevers
 - Rift Valley Fever
 - No evidence to support use in Filovirus or Flavivirus infections

Prevention

- Nosocomial: Complete equipment sterilization & protective clothing
- House to house rodent trapping
- Better food storage & hygiene
- Cautious handling of rodent if used as food source
- If human case occurs
 - Decrease person-to-person transmission
 - Isolation of infected individuals

Vaccination

- Argentine and Bolivian HF
 - PASSIVE IMMUNIZATION
 - ✓ Treat with convalescent serum containing neutralizing antibody or immune globulin
- Yellow Fever
 - ACTIVE IMMUNIZATION
 - ✓ Travelers to Africa and South America
- Experimental vaccines under study
 - Argentine HF, Rift Valley Fever, Hantavirus and Dengue HF

Why do VHFs make good Bioweapons?

- Disseminate through aerosols
- Low infectious dose
- High morbidity and mortality
- Cause fear and panic in the public
- No effective vaccine
- Available and can be produced in large quantity
- Research on weaponization has been conducted

The END