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
• Exanthsms
• 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 VHF\`s 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