INTERNATIONAL SCHOOL OF MEDICINE

Department of Infectious Diseases

The topic of the lecture:

Viral Hemorrhagic Fever

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Overview

- Organism
- History
- Epidemiology
- Transmission
- Disease in Humans
- Disease in Animals
- Prevention and Control

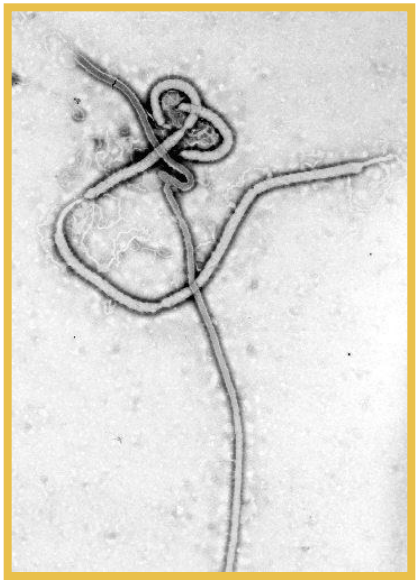
What is Viral Hemorrhagic Fever?

- Severe multisystem syndrome
- Damage to overall vascular system
- Symptoms often accompanied by hemorrhage
  - Rarely life threatening in itself
  - Includes conjunctivitis, petechia, echymosis

The Organisms

Viral Hemorrhagic Fever

- Viruses of four distinct families
  - Arenaviruses
  - Filoviruses
  - Bunyaviruses
  - Flaviviruses
- RNA viruses
  - Enveloped in lipid coating
- Survival dependent on an animal or insect host, for the natural reservoir



Classification

Arenaviridae	Bunyaviridae	Filoviridae	Flaviviridae
Junin	Crimean-Congo H.F.	Ebola	Kyasanur Forest Disease
Machupo	Hantavirus	Marburg	Omsk H.F.
Sabia	Rift Valley fever		Yellow Fever
Guanarito			Dengue
Lassa			

Arenaviridae

Junin virus
Machupo virus
Guanarito virus
Lassa virus
Sabia virus

Arenaviridae History

- 1933: The first arenavirus was isolated
- 1958: Junin virus - Argentina
  - First to cause hemorrhagic fever
  - Argentine hemorrhagic fever
- 1963: Machupo virus – Bolivia
  - Bolivian hemorrhagic fever
- 1969: Lassa virus – Nigeria
  - Lassa 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 Epidemiology

- West Africa
  - Lassa
- South America
  - Junin, Machupo, Guanarito, and Sabia
- Contact with rodent excreta
- Case fatality: 5 – 35%
- Explosive nosicomial outbreaks with Lassa and Machupo

Arenaviridae in Humans

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

Bunyaviridae

Rift Valley Fever virus

Crimean-Congo Hemorrhagic Fever virus

Hantavirus

Bunyaviridae History

- 1930: Rift Valley Fever – Egypt
  - Epizootic in sheep
- 1940s: CCHF - Crimean peninsula
  - Hemorrhagic fever in agricultural workers
- 1951: Hantavirus – Korea
  - Hemorrhagic fever in UN troops
- The family now consists of 5 genera with over 350 viruses

Bunyaviridae Transmission

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

Bunyaviridae Epidemiology

- RVF - sub-Saharan Africa and Saudi Arabia and Yemen
  - 1% case fatality rate
- CCHF - Africa, Eastern Europe, Asia
  - 30% case fatality rate
- Hantavirus - North and South America, Eastern Europe, and Eastern Asia
  - 1-50% case fatality rate

Bunyaviridae Humans

- **Rift Valley Fever**
  - Incubation period – 2-5 days
  - 0.5% - Hemorrhagic Fever
  - 0.5% - retinitis or encephalitis 1 to 4 weeks
- **CCHF**
  - Incubation period – 3-7 days
  - Hemorrhagic Fever - 3–6 days following clinical signs
- **Hantavirus**
  - Incubation period – 7–21 days
  - HPS and HFRS

Bunyaviridae Animals

- RVF
  - Abortion – 100%
  - Mortality rate
    - >90% in young
    - 5-60% in older animals
- CCHF
  - Unapparent infection in livestock
- Hantaviruses
  - Unapparent infection in rodents

Filoviridae

Marburg virus

Ebola virus

Filoviridae History

- 1967: Marburg virus
  - European laboratory workers in Germany and former Yugoslavia
- 1976: Ebola virus
  - Ebola Zaire
  - Ebola Sudan
  - Mortality rates greater than 50%.
- 1989 and 1992: Ebola Reston
  - USA and Italy
  - Imported macaques from Philippines
- 1994: Ebola Côte d'Ivoire

Filoviridae Transmission

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

Filoviridae Epidemiology

- **Marburg** – Africa
  - Case fatality – 23-33%
- **Ebola** - Sudan, Zaire and Côte d'Ivoire – Africa
  - Case fatality – 53-88%
- **Ebola** – Reston – Philippines
- Pattern of disease is UNKOWN

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

Filoviridae Animals

- Hemorrhagic fever
  - Same clinical course as humans
- Ebola Reston
  - High primate mortality - ~82%

Flaviviridae

Dengue virus

Yellow Fever virus

Omsk Hemorrhagic Fever virus

Kyassnur Forest Disease virus

Flaviviridae History

- 1648 : Yellow Fever described
- Outbreaks in tropical Americas 17^{th}–20^{th} century
  - Yellow Fever and Dengue outbreaks
- 1927: Yellow Fever virus isolated
- 1943: Dengue virus isolated
- 1947
  - Omsk Hemorrhagic Fever virus isolated
- 1957: Kyasanur Forest virus isolated

Flaviviridae Transmission

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

Flaviviridae Epidemiology

- Yellow Fever Virus – Africa and Americas
  - Case fatality rate – varies to 50%
- Dengue Virus – Asia, Africa, Australia, and Americas
  - Case fatality rate – 1-10%
- Kyasanur Forest virus – India, Mysore State
  - Case fatality rate – 3–5%
- Omsk Hemorrhagic Fever virus – Europe
  - Case fatality rate – 0.5–3%

Flaviviridae Humans

- Yellow Fever
  - Incubation period – 3–6 days
  - Short remission
- Dengue Hemorrhagic Fever
  - Incubation period – 2–5 days
  - Infection with different serotype
- Kyasanur Forest Disease
- Omsk Hemorrhagic Fever
  - Lasting sequela

Flaviviridae Animals

- Yellow Fever virus
  - Non-human primates – varying clinical signs
- Dengue virus
  - Non-human primates – No symptoms
- Kyasanur Forest Disease Virus
  - Livestock – No symptoms
- Omsk Hemorrhagic Fever Virus
  - Rodents – No symptoms

Disease in Humans

Clinical Symptoms

- Differ slightly depending on virus
- Initial symptoms
  - Marked fever
  - Fatigue
  - Dizziness
  - Muscle aches
  - Exhaustion

Clinical Symptoms

- More severe
  - Bleeding under skin
    - Petechiae, echymoses, conjunctivitis
  - Bleeding in internal organs
  - Bleeding from orifices
  - Blood loss rarely cause of death

Diagnosis

- Specimens must be sent to
  - CDC
  - U.S. Army Medical Research Institute of Infectious Disease (USAMRIID)
    - Serology
    - PCR
    - IHC
    - Viral isolation
    - Electron microscopy

Treatment

- Supportive treatment: maintaining fluid and electrolyte balance, circulatory volume, BP and treating for any complicating infections.
- Ribavirin
  - Effective in some individuals
  - Arenaviridae and Bunyaviridae only
- Convalescent-phase plasma
  - Argentine HF, Bolivian HF and Ebola
- Strict isolation of affected patients is required
- Report to health authorities

Prevention and Control

Prevention and Control

- Avoid contact with host species
  - Rodents
    - Control rodent populations
    - Discourage rodents from entering or living in human populations
    - Safe clean up of rodent nests and droppings
  - Insects
    - Use insect repellents
    - Proper clothing and bed nets
    - Window screens and other barriers to insects

Prevention and Control

- Vaccine available for Yellow fever
- Experimental vaccines under study
  - Argentine HF, Rift Valley Fever, Hantavirus and Dengue HF
- If human case occurs
  - Decrease person-to-person transmission
  - Isolation of infected individuals

Prevention and Control

- Protective clothing
  - Disposable gowns, gloves, masks and shoe covers, protective eyewear when splashing might occur, or if patient is disoriented or uncooperative
- WHO and CDC developed manual
  - “Infection Control for Viral Hemorrhagic Fevers In the African Health Care Setting”

Prevention and Control

- Anyone suspected of having a VHF must use a chemical toilet
- Disinfect and dispose of instruments
  - Use a 0.5% solution of sodium hypochlorite (1:10 dilution of bleach)

VHF Agents as Biological Weapons

- Outbreak of undifferentiated febrile illness 2-21 days following attack
  - Could include
    - Rash, hemorrhagic diathesis and shock
- Diagnosis could be delayed
  - Unfamiliarity
  - Lack of diagnostic tests
- Ribavirin treatment may be beneficial

VHF Agents as Biological Weapons

- Most are not stable in dry form
- Most have uncertain stability and effectiveness in aerosol form
  - Arenaviruses have tested effectiveness in aerosol form
- Marburg and Ebola have high case fatality rates
- Rift Valley is the most stable VHF in liquid or frozen state
- VHFs do pose a threat as aerosolized agents