Viral Hemorrhagic Fever

What is Viral Hemorrhagic Fever?

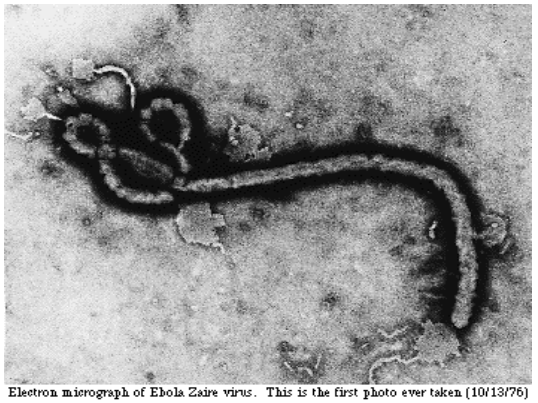
- Severe multisystem syndrome
- Damage to overall vascular system
- Symptoms often accompanied by hemorrhage
  - Rarely life threatening in itself
  - Includes conjunctivitis, petechia, echymosis

Viral Hemorrhagic Fevers

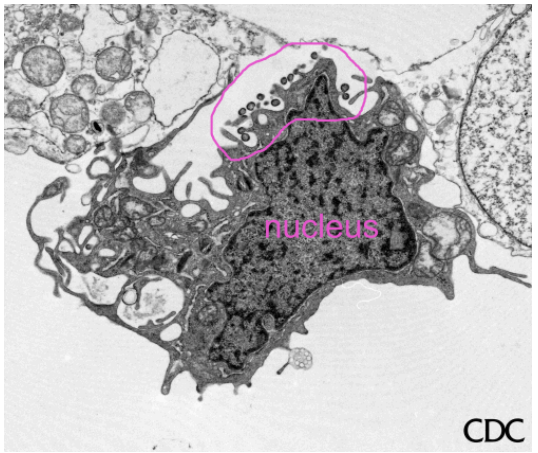
- Diverse group of illnesses caused by RNA viruses from 4 families:
  - Arenaviridae, Bunyaviridae, Filoviridae, Flaviridae
  - Differ by geographic occurrence and vector/reservoir
  - Share certain clinical and pathogenic features
- RNA viruses
  - Enveloped in lipid coating
- Survival dependent on an animal or insect host, for the natural reservoir
- Potential for aerosol dissemination, with human infection via respiratory route (except dengue)
- Target organ: vascular bed
- Mortality 0.5 - 90%, depending on agent

Viral Hemorrhagic Fevers

- Category A agents
  - Filoviruses
  - Arenaviruses
- Category C agents
  - Hantaviruses
  - Tick-borne hemorrhagic fever viruses
  - Yellow fever



Electron micrograph of Ebola Zaire virus. This is the first photo ever taken (10/13/76) by Dr. F.A. Murphy, now at UC Davis, then at CDC. Diagnostic specimen in cell culture at 160,000X magnification.



Viral Hemorrhagic Fevers
Transmission

- Zoonotic diseases
  - Rodents and arthropods main reservoir
  - Humans infected via bite of infected arthropod, inhalation of rodent excreta, or contact with infected animal carcasses
- Person-to-person transmission possible with several agents
  - Primarily via blood or bodily fluid exposure
  - Rare instances of airborne transmission with arenaviruses and filoviruses
- Rift Valley fever has potential to infect domestic animals following a biological attack

Viral Hemorrhagic Fevers
Summary of Agents

Virus Family	Virus/Syndrome	Geographic occurrence	Reservoir or Vector	Human-human transmission ?
Arenaviridae	**Junin (Argentine HF)**	**S.America**	**Rodents**	**Lassa Fever – yes, via body fluids; others – not usually**
	Machupo (Bolivian HF)	**S.America**		
	Guanarito (Brazilian HF)	**S.America**		
	Sabia (Venezuelan HF)	**S.America**		
	Lassa (Lassa Fever)	**West Africa**		
Flaviridae	**Yellow Fever**	**Tropical Africa,Latin America**	**Mosquitoes**	**Yellow Fever – blood infective up to 5d of illness;** **Others - No**
	Dengue Fever	**Tropical areas**		
	Kyanasur Forest Disease	**India**	**Ticks**	
	Omsk HF	**Siberia**		

Viral Hemorrhagic Fevers
Summary of Agents

Virus Family	Virus/Syndrome	Geographic occurrence	Reservoir or Vector	Human-human transmission?
Bunyaviridae	**Congo-Crimean HF**	**Crimea, parts of Africa, Europe & Asia**	**Ticks**	**Congo-Crimean Hemorrhagic Fever – yes, through body fluids; Rift Valley Fever, Hantaviruses – no**
	Rift Valley Fever	**Africa**	**Mosquitoes**	
	Hantaviruses (Hemorrhagic Renal Syndrome/ Hantavirus Pulmonary Syndrome)	**Diverse**	**Rodents**	
Filoviridae	**Ebola HF**	**Africa**	**Unknown**	**Yes, body fluid transmission**
	Marburg HF	**Africa**		

Viral Hemorrhagic Fevers
Clinical Presentation

- Clinical manifestations nonspecific, vary by agent
- Incubation period 2-21 days, depending on agent
- Onset typically abrupt with filoviruses, flaviviruses, and Rift Valley fever
- Onset more insidious (gradual) with arenaviruses

Viral Hemorrhagic Fevers

Initial Symptoms

Prodromal illness lasting < 1 week may include:

- High fever
- Headache
- Malaise
- Weakness
- Exhaustion
- Dizziness
- Muscle aches
- Joint pain
- Nausea
- Non-bloody diarrhea

Viral Hemorrhagic Fevers
Clinical Signs

- Flushing, conjunctival injection (“red eye”)
- Pharyngitis
- Rash
- Edema
- Hypotension
- Shock
- Mucous membrane bleeding

VHF Surveillance:
Clinical Identification of Suspected Cases

- Clinical criteria:
  - Temperature 101° F(38.3° C) for <3 weeks
  - Severe illness and no predisposing factors for hemorrhagic manifestations
  - 2 or more of the following:
    - Hemorrhagic or purple rash
    - Epistaxis
    - Hematemesis
    - Hemoptysis
    - Blood in stools
    - Other hemorrhagic symptoms
    - No established alternative diagnosis

JAMA 2002;287
Adapted from WHO

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
- Ribavirin
  - Not approved by FDA
  - 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
- Correct coagulopathies as needed

- No antiplatelet drugs or IM injections

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”

Viral Hemorrhagic Fevers
Management of Exposed Persons

- Medical surveillance for all potentially exposed persons, close contacts, and high-risk contacts (i.e., mucous membrane or percutaneous exposure) x 21 days
  - Report hemorrhagic symptoms
  - Record fever 2x/day
    - Report temperatures ≥ 101°F(38.3°C)
      - Initiate presumptive ribavirin therapy
- Percutaneous/mucocutaneous exposure to blood or body fluids of infected:
  - Wash thoroughly with soap and water, irrigate mucous membranes with water or saline

Viral Hemorrhagic Fevers
Management of Exposed Persons

- Patients convalescing should refrain from sexual activity for 3 months post-recovery (arenavirus or filovirus infection)
- Only licensed vaccine: Yellow Fever
- Investigational vaccines: AHF, RV, HV
- Possible use of ribavirin to high-risk contacts of CCHF and LF patients

Arenaviridae

- Junin virus
- Machupo virus
- Guanarito virus
- Lassa virus
- Sabia virus
- Chapare
- Lujo

Arenaviridae History

- First isolated in 1933
- 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
- 1989: Guanarito virus – Venezuela
- 1993: Sabia – Brazil
- 2004: Chapare – Bolivia
- 2008: Lujo – S. Africa

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

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

Arenaviridae in Humans

- Incubation period
  - 10–14 days
- Fever, malaise and headache
  - 2–4 days
- Hemorrhagic stage (gums, eyes, or nose)
  - Hemorrhage, leukopenia, thrombocytopenia
  - Neurologic signs (hearing loss, tremors, and encephalitis)

Diagnosis

- ELISA
- RT-PCR
- Virus isolation in cell culture (7- 10 days)
- Immunohistochemistry, performed on formalin-fixed tissue specimens, can be used to make a post-mortem diagnosis.

Treatment

- Supportive care:
  - Appropriate fluid and electrolyte balance
  - Oxygenation and blood pressure maintenance
  - Treatment of any other complicating infections
- Ribavirin, an antiviral drug, has been used with success in Lassa fever patients
- Prevention: by avoiding contact with rodents

Bunyaviridae

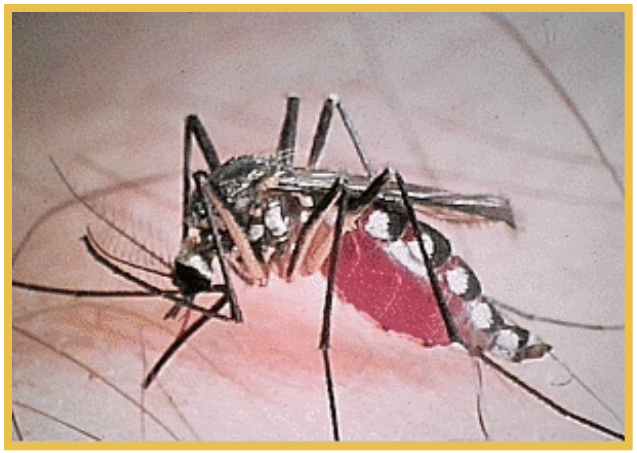
- Rift Valley Fever virus
- Crimean-Congo Hemorrhagic Fever virus
- Hantavirus

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
- 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 - Africa and Arabian Peninsula
  - 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

- RVF
  - Incubation period – 2-5 days
  - 0.5% - Hemorrhagic Fever
- 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
- 1976: Ebola virus
  - Ebola Zaire
  - Ebola Sudan
- 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
- Nosocomial 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
- 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
  - *Aedes aegypti*
  - Sylvatic cycle
  - Urban cycle
- Kasanur Forest Virus
  - Ixodid tick
- Omsk Hemorrhagic Fever virus
  - Muskrat urine, feces, or blood

Flaviviridae Epidemiology

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