

The Cardio-

VASCULAR

System

- Anatomy
- Histology
- Pathology
- Pharmacology
- Physiology
- Microbiology

Lec #: 1- Viral Hemorrhagic Fever

Dr. Name: Dr Ashraf Khasawneh

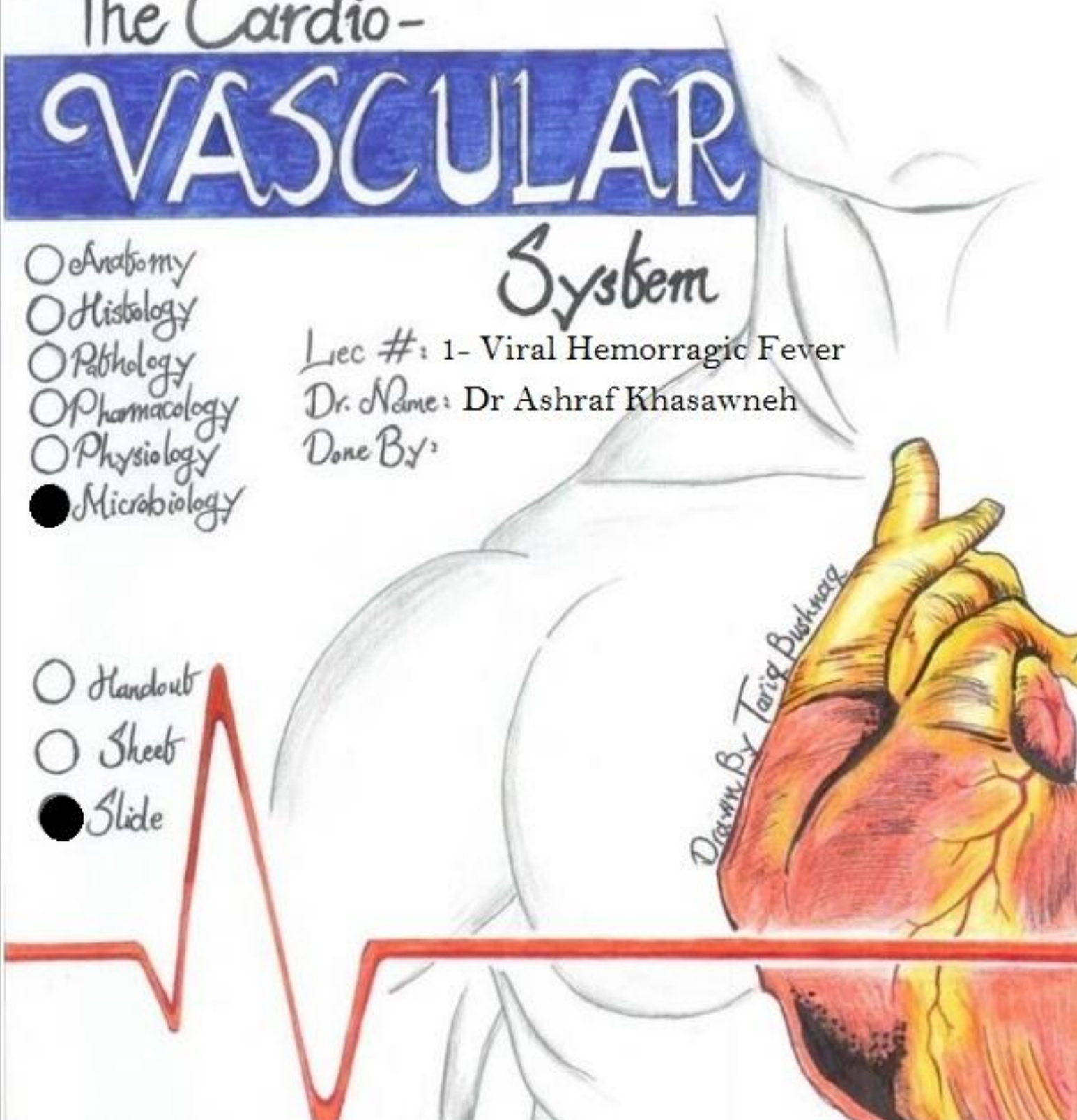
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Handout

Sheets

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Drawn by Tariq Bushnaq



Viral Hemorrhagic Fever

What is Viral Hemorrhagic Fever?

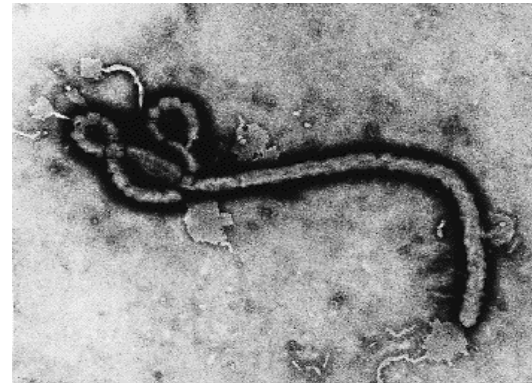
- Severe multisystem syndrome
- Damage to overall vascular system
- Symptoms often accompanied by hemorrhage
 - Rarely life threatening in itself
 - Includes conjunctivitis, petechia, echymosis

Viral Hemorrhagic Fevers

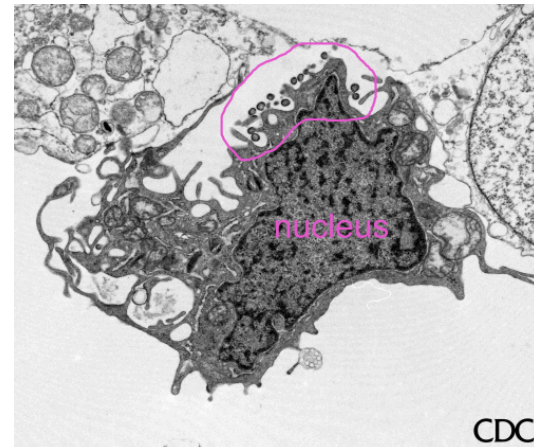
- Diverse group of illnesses caused by RNA viruses from 4 families:
 - Arenaviridae, Bunyaviridae, Filoviridae, Flaviridae
 - Differ by geographic occurrence and vector/reservoir
 - Share certain clinical and pathogenic features
- RNA viruses
 - Enveloped in lipid coating
- Survival dependent on an animal 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		
	Kyasanur 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

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 $\geq 101^{\circ}\text{F}(38.3^{\circ}\text{C})$
 - 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
- 17th–20th 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
- Kananur 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 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