MICROBIOLOGY

بسم الله الرحمن الرحيم

MID | Lecture 1

Viral Hemorrhagic Fevers

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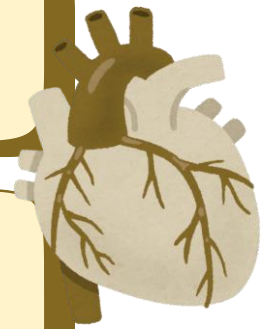
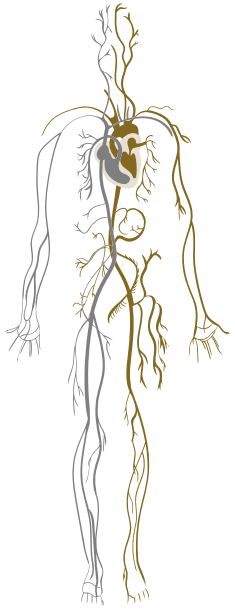


وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

اللهم إنّا نعوذ بك من شرور أنفسنا ومن سيئات أعمالنا



المحاضرة طويلة بس إن شاء الله سهلة
يفضل تكونوا حاضرين المحاضرة قبل دراسة الملف
استعينوا بالله

Viral hemorrhagic fevers (VHFs)

By: Assis. Prof Nader Alaridah MD, PhD

Overview

أستغفر الله العظيم وأتوب إليه

- Viral hemorrhagic fevers (VHFs) are a group of illnesses caused by four families of viruses. *Arenaviridae*, *Bunyaviridae, Filoviridae and Flaviviridae*
- VHF are characterized by **viral infection, fever, and bleeding**.
- The **fever**, primarily resulting from a cytokine storm, most commonly occurs during the viremia phase.
- **Bleeding** develops in stages. Early in the disease, bleeding appears under the skin as petechiae and ecchymoses.
- In the late stage of VHF, patients may experience bleeding from all body orifices, occurring both internally and externally.
- VHF pathology is marked by 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

Ebola and Marburg viruses are the most significant due to their **extremely high mortality rates (up to 90%).**

Arboviruses & Non-arboviruses

- **Arboviruses** are viruses whose **main transmission route involves arthropod vectors**. Transmission can occur from animals to humans, from humans to humans, or via a vector that carries the virus between infected animals and humans.
- **Non-arboviruses** do **not require arthropod vectors** for transmission; they are transmitted directly, either from animals to humans or from humans to humans.
- **Bunyaviridae** and **Flaviviridae** families are generally arboviruses. **Hantavirus (a member of the bunyaviridae family)**, however, is a non-arbovirus. It is **transmitted directly from infected animal feces, or urine to humans**, without the involvement of arthropod vectors.

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

- Not all viral groups that cause viral hemorrhagic fevers (VHFs) are capable of **person-to-person transmission**; in some viruses it has been documented, while in others it has not.
- The doctor emphasized to **note which viruses have documented person-to-person transmission.**

Common features of all four families:

- **Enveloped, Lipid-encapsulated**
- **Single-strand RNA**
- **Zoonotic (animal-borne)**, meaning that the virus infects animals and can be passed from them to humans
- **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

- **Lassa virus** originates from **West Africa**, whereas other arenaviruses are from **South America.**

- Junin virus : Argentine hemorrhagic fever
- Machupo virus : Bolivian hemorrhagic fever
- Guanarito virus : Venezuelan hemorrhagic fever
- Lassa virus : Lassa fever - Nigeria (highest mortality rate)
- Sabia virus : Brazilian hemorrhagic fever

Arenaviridae

- **Arenaviridae** (as any RNA virus, such as other VHF-causing viruses) replicate in the **cytoplasm** and carry their own **RNA-dependent RNA polymerase**.
- Arenaviridae RNA is segmented.
- They are named “arenaviruses” because, under the microscope, their cytoplasm appears **“sandy”**. This is due to the virus incorporating **host ribosomal subunits** into the virion, giving the cytoplasm a granular appearance reminiscent of the floor of an arena.
- Arenaviridae viruses are Non-arboviruses.

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 has been documented.

Arenaviridae Transmission

- Arenaviridae are **not transmitted by arthropods**; there is **no vector involvement** such as mosquitoes or ticks. The initial infection in humans occurs through **direct exposure to infected animals**, primarily small rodents, or their **excreta, urine, or other secretions**.
- Transmission among rodents can be **horizontal** or **vertical**. In **horizontal transmission**, an infected adult rodent cannot sustain the virus—it dies and the virus cycle does not continue. In contrast, **vertical transmission**, from an infected mother to her fetus, allows the virus to persist, ensuring the continuation of its transmission cycle.

Arenaviridae in Humans

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

Clinical Course (not specific for Arenaviridae)

Slides 38-41 discuss the same concepts as in this slide. You can read through them fast and then return here.

1. Short incubation period (less than 2 weeks), with varying onset, but generally acute.
2. Prodromal stage: fever, malaise, myalgia, arthralgia, photophobia. (non-specific)
3. Progressive stage: more severe signs - see slide 40 for more details.
4. End-stage disease: neurological signs, hearing and vision loss, shock and death.

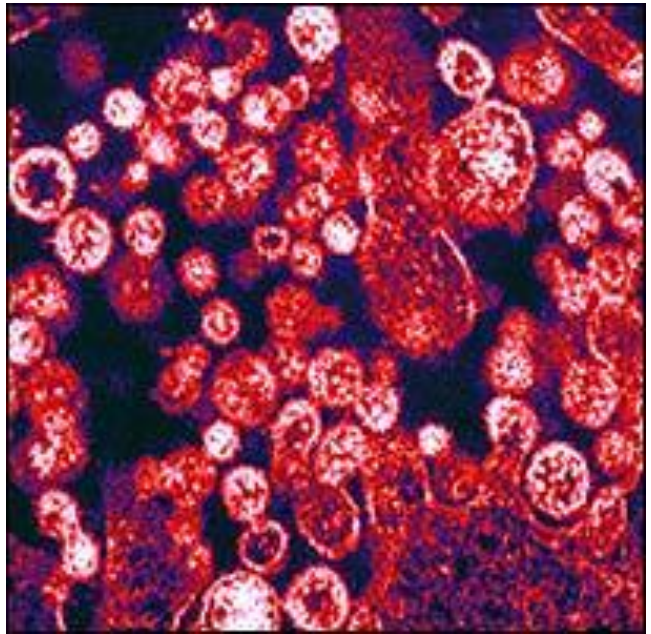
Pathogenesis:

Biphasic Illness (seen in many viruses in this lecture):

- First phase (initial **"viremic" phase**): constitutional symptoms.
- **Second phase ("toxemic" phase)** is associated with:
  - Worsening systemic symptoms
  - Vascular-endothelial dysfunction
  - Hemorrhagic manifestations
  - Consumptive coagulopathy, such as **DIC**, in severe illness (most seen in **filoviridae**).

Arenaviridae: Lassa Fever

- The incidence is high within its geographic range, primarily in West Africa, and Nigeria specifically.
- 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)*
- The rodent is the natural reservoir
- Interpersonal transmission can occur by:
  - Direct Contact
  - Sex
  - Breast Feeding



➢ Notice the sandy cytoplasm

Lassa Fever

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

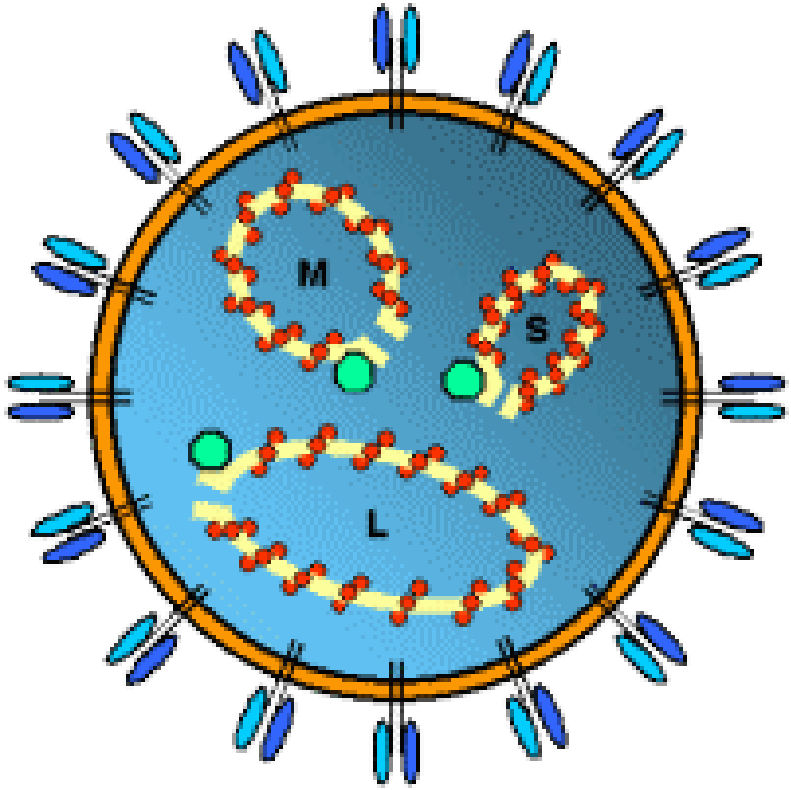
Lassa Fever

- In arenaviruses with a **gradual onset**, such as **Lassa fever**, the clinical course begins with the **incubation period**, followed by the **prodromal stage**, then the **progressive stage**, and finally the **end stage**. The end stage is characterized by **marked hemorrhage**, **organ failure**, **hypovolemia**, **shock**, and potentially **death**.
- Lassa fever may cause **pharyngitis** and **hepatitis**.
- Infants infected **in utero** may develop **deafness after birth**, and the resulting **hearing loss often persists even after recovery**.
- Mortality in **sporadic cases** is approximately **1–3%**, largely due to the **inactive or limited transmission cycle** in such settings.
- **Important:** Lassa fever patients can continue to **shed the virus in their urine for at least two weeks after recovery**, meaning they must remain **isolated even after clinical improvement**.

Bunyaviridae

- Rift Valley Fever virus
- Crimean-Congo Hemorrhagic Fever virus
- Hantavirus
- All are arboviruses except hantaviruses

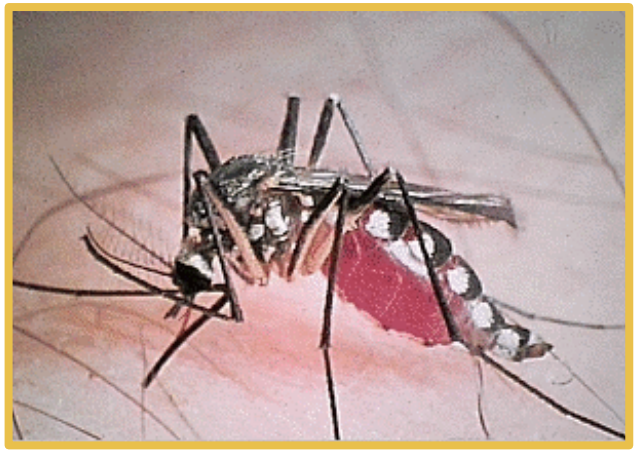
RNA is segmented into three parts:
L-segment codes for an L-protein (the RNA dependent RNA polymerase);
M segment codes for two surface glycoproteins G1 and G2 which form the envelope spikes;
S segment codes for an N-protein (nucleocapsid protein).



L: Large, M: Medium, S: Small

Bunyaviridae Transmission

- Arthropod vector
  - Exception – Hantaviruses
- RVF – *Aedes* mosquito *[top picture]*
  - This mosquito is also a vector in yellow and dengue fever.
- CCHF – Ixodid tick (*Hyalomma)* *[bottom picture]*
- Hantavirus – Rodents (non-arboviruses)
- 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 has been documented

Rift Valley Fever

- Asymptomatic or mild illness in humans
- Short incubation period (2 to 5 days)
- Distinguishing Characteristics
  - Hemorrhagic complications rare (<5%)
  - Vision loss (retinal hemorrhage, vasculitis) in 1-10%
- Overall mortality 1%, least mortality rate
- Fatal disease in animals
- Therapy: Ribavirin?

There are no clear guidelines recommending ribavirin for these patients, and its effect on prognosis is uncertain; management is mainly supportive.

Crimean-Congo Hemorrhagic Fever

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

In the case of CCHF, ribavirin is a documented treatment and is considered effective.

Bunyaviridae: Hantaviruses

- **Hantavirus** is **not transmitted by vectors**; infection occurs through **direct contact with infected animals**, typically rodents.
- There are **two main types of hantaviruses**:
- **Old World hantaviruses** – cause **Hemorrhagic Fever with Renal Syndrome (HFRS)**.
- **New World hantaviruses** – cause **Hantavirus Pulmonary Syndrome (HPS)**; this topic is outside the scope of this lecture.
- In this lecture, we will focus on **HFRS caused by Old World hantaviruses**.

Bunyaviridae: Hantaviruses

- Transmission to humans:
  - Exposure to rodent saliva and excreta
    - Inhalation
    - Bites
    - Ingestion in contaminated food/water (?),
      This route of transmission is not well-established or supported by strong evidence.
    - Person-to-person transmission (only in Andes virus in Argentina)

Hemorrhagic Fever with Renal Syndrome (HFRS)

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

Flaviviridae

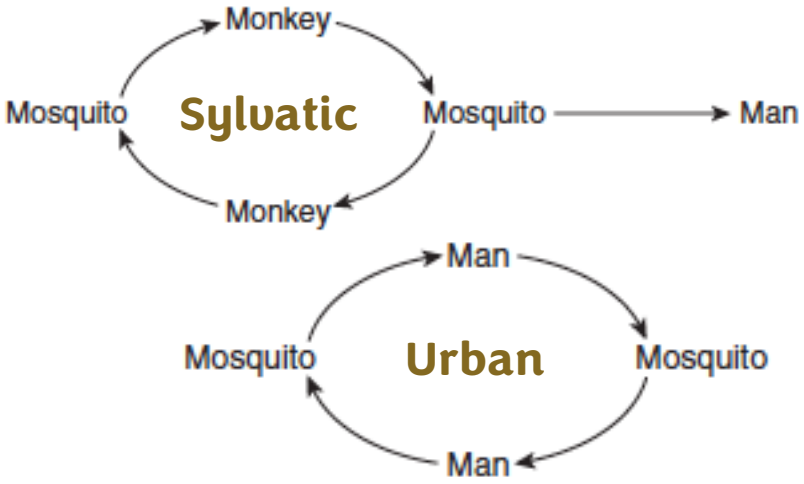
- Dengue virus (West Africa/South America)
- Yellow Fever virus (West Africa/South America)
- Omsk Hemorrhagic Fever virus (Russia/Europe)
- Kyassnur Forest Disease virus (India)

It is a large family that contains these 4 viruses demonstrated to cause VHF, but also includes the following:

- West Nile virus (causes encephalitis)
- St. Louis virus (causes encephalitis)
- Hepatitis C virus
- *Many Others…*

Flaviviridae Transmission

- Arthropod vector (below are the reservoirs for each virus):
- Yellow Fever and Dengue viruses (3 life cycles):
  1. *Aedes aegypti* – inside the vector:
  2. Sylvatic cycle – in the "jungle/forest": (between the vector and non-human primates; humans are accidental hosts in this cycle)
  3. Urban cycle – in human-occupied areas: (directly between the vector and human, without the need for an intermediate host, unlike sylvatic)



- Kasanur Forest Virus
  - Ixodid tick
- Omsk Hemorrhagic Fever virus: Fever Lasting sequela
  - Muskrat urine, feces, or blood

Biphasic Clinical Presentation

A common feature in Flaviviridae (and other viruses):

1. Viremia phase
   - With cytokine storm, marked by fever and constitutional symptoms

➢ Window period
   - Symptoms decline and the patient improves

2. Toxemia phase
   - Return of symptoms seen in the viremic phase
   - Additionally, hemorrhagic symptoms appear, first as petechiae and ecchymoses, and later as internal and external bleeding, in which DIC is implicated. Bleeding can develop into hypovolemic shock, which is fatal.

Yellow Fever

- Distinguishing features
  - Biphasic infection
  - Common hepatic involvement & jaundice (thus the name)
- Mortality: 15-50%

Flaviviridae: Dengue

- Dengue Fever (DF) / Fatality: <1%
- Dengue Hemorrhagic Fever (DHF) / Fatality: 5-6%
- Dengue Shock Syndrome (DSS) / Fatality 12-44%
  - Hypovolemic shock causes increased mortality rate
- Four distinct serotypes
  - DEN-1, DEN-2, DEN-3, DEN-4 (all 4 cause human disease)
- Distinguishing Features
  - **Sudden onset**
  - Eye pain
  - Rash
  - Complications/sequelae uncommon
- Illness is severe in younger children (important note)

Omsk Hemorrhagic Fever

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

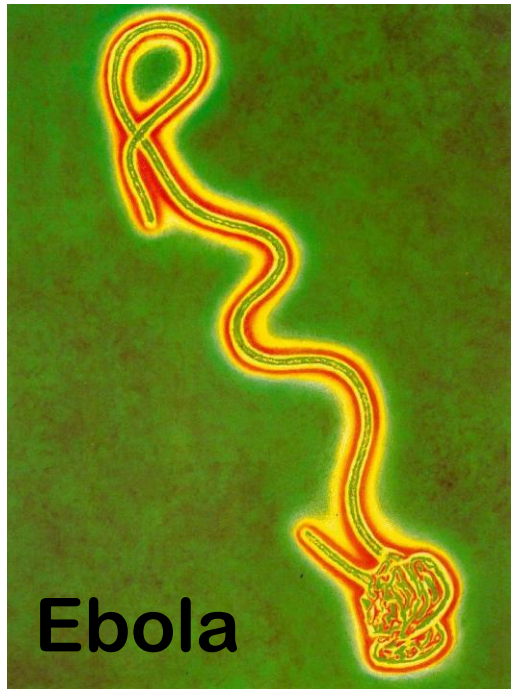
Flaviviridae: Kyanasur Forest

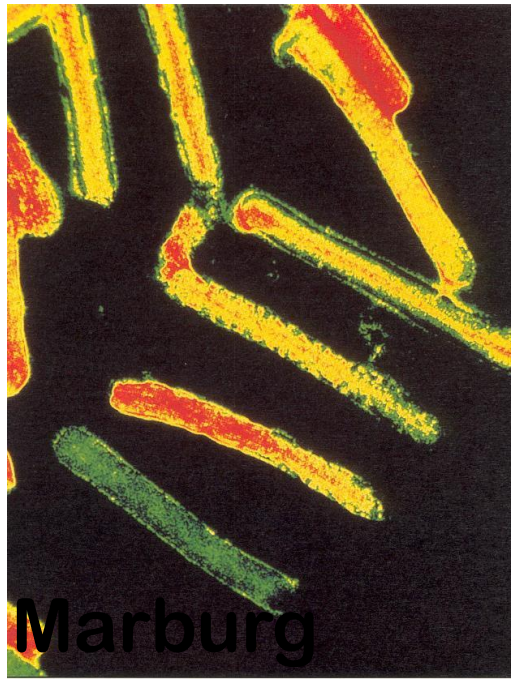
- Distribution: limited to Karnataka State, India
- Haemaphysalis vector (of the family Ixodidae)
- Distinguishing Features
  - Acute onset
  - Biphasic

- Case-fatality: 3-5% (400-500 cases annually)

Filoviridae

- Ebola (from Ebola river in Africa)
  - Ebola-Zaire
  - Ebola-Sudan
  - Ebola-Ivory Coast
  - Ebola-Bundibugyo
  - (Ebola-Reston) - not in humans
- Marburg (from Germany)





Filoviridae Transmission

- Reservoir is UNKNOWN
  - Bats implicated with Marburg and Ebola
- Non-arboviruses
- Intimate contact
- Nosicomial transmission
  (whether in medical personnel/patient interaction or in labs)
  - Reuse of needles and syringes
  - Exposure to infectious tissues, excretions, and hospital wastes
- Aerosol transmission
  - Primates

In Filoviruses, it is unknown from where did humans first contact the infection, but the most acceptable theory is that the reservoir is fruit bats.

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

- Distinguising 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** (the doctor mentioned 2 days)
- **Abrupt onset (faster than the other 3 families)**
  - Fever, chills, malaise, and myalgia
- Hemorrhage and **DIC (well-established in filoviridae)**
- **Death** around day 7–11 **(second week of infection)**
- **Painful recovery**
- After the second week, the patient is considered recovering, but the recovery is painful – lacking subjective patient improvement.
- As explain in slide 13, filoviridae have devastating end-stage symptoms, so while the pathogenesis is similar among all VHF viruses, filoviridae involve the most severe sequelae.

Common Pathophysiology

- Small vessel involvement **(toxemia phase)**
  - Increased vascular permeability
    - Multiple cytokine activation
  - Cellular damage
  - Abnormal vascular regulation:
    - Consumptive coagulopathies (e.g., DIC)
    - Severe bleeding
    - Early -> mild hypotension
    - Severe/Advanced -> Shock
- Viremia **(initial viremic phase + persists later)**
  - Macrophage involvement
    - Inadequate/delayed immune response

Common Clinical Features: Early/Prodromal Symptoms

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

These are general and <u>not</u> specific for VHF-causing viruses, and they can be seen in any type of viral or non-viral infection.

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.

Hemorrhage in this phase is not life threatening.

Common Clinical Features: Severe/End-stage

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

Bleeding in this phase is fatal since it involves severe internal and external hemorrhage. DIC is a major player because it causes depletion of coagulation factors.

Lab studies

- Complete Blood Count
  - Leucopenia, leucocytosis, thrombocytopenia, hemoconcentration, DIC
- Bleeding time
- Liver enzymes in yellow fever virus
- Proteinuria universal
- Kidney function tests are most used in hantavirus with renal syndrome

- 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 (such as in arenaviridae) is specific and sensitive

All the viruses discussed in this lecture are highly dangerous. They cannot be handled in regular hospital laboratories. Dealing with these pathogens requires **Biosafety Level 4 (BSL-4)** facilities.

Patients infected with these viruses must be **strictly isolated**, and strict **infection-control precautions** are mandatory to prevent **nosocomial transmission**. Medical personnel are at significant risk of acquiring these infections if proper protective measures are not followed.

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 (in labs, not inside human bodies)** **is active** against:
  - Lassa fever
  - Crimean-Congo Hemorrhagic fever
  - Old and New World Hantavirus Hemorrhagic fevers
  - Rift Valley Fever (questionable for clinical use as mentioned)

  No evidence to support use in Filovirus or Flavivirus infections

Prevention

- Nosocomial: Complete equipment sterilization & protective clothing
- House to house rodent trapping
- If vector-borne, another layer of prevention is added to control the vectors (remember malaria)
- 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 (only approved vaccine)**
  - ACTIVE IMMUNIZATION
    - Travelers to Africa and South America

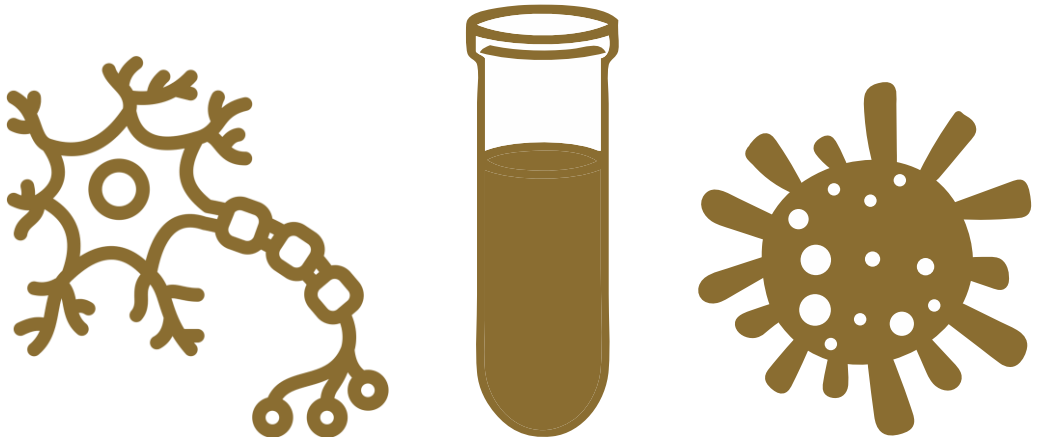
- Experimental vaccines under study
  - Argentine HF, Rift Valley Fever, Hantavirus and Dengue HF

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

It has been controversial whether published research on these viruses should be done, as results are available for everyone and can be used for harmful acts.

The END



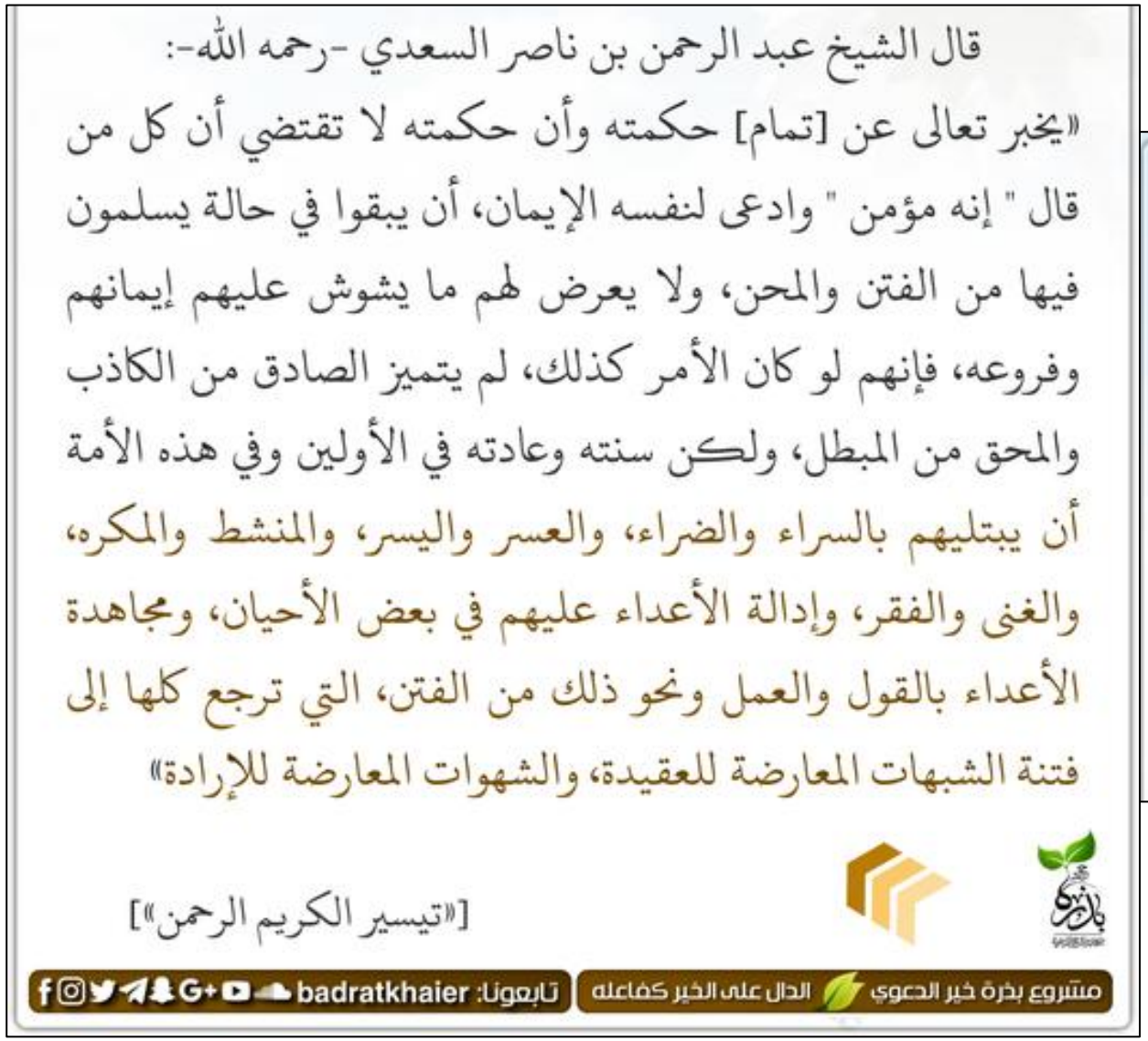
MICROBIOLOGY QUIZ LECTURE 1

رسالة من الفريق العلمي

قال الشيخ عبد الرحمن بن ناصر السعدي -رحمه الله-:

«يخبر تعالى عن [تمام] حكمته وأن حكمته لا تقتضي أن كل من قال " إنه مؤمن " وادعى لنفسه الإيمان، أن يبقوا في حالة يسلمون فيها من الفتن والمحن، ولا يعرض لهم ما يشوش عليهم إيمانهم وفروعه، فإنهم لو كان الأمر كذلك، لم يتميز الصادق من الكاذب والمحق من المبطل، ولكن سنته وعادته في الأولين وفي هذه الأمة أن يبتليهم بالسراء والضراء، والعسر واليسر، والمنشط والمكره، والغنى والفقر، وإدالة الأعداء عليهم في بعض الأحيان، ومجاهدة الأعداء بالقول والعمل ونحو ذلك من الفتن، التي ترجع كلها إلى فتنة الشبهات المعارضة للعقيدة، والشهوات المعارضة للإرادة»

[«تيسير الكريم الرحمن»]



قَالَ تَعَالَىٰ:

﴿أَحَسِبَ ٱلنَّاسُ أَن يُتْرَكُوٓاْ أَن يَقُولُوٓاْ ءَامَنَّا وَهُمْ لَا يُفْتَنُونَ﴾

[العنكبوت: ٢]

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			