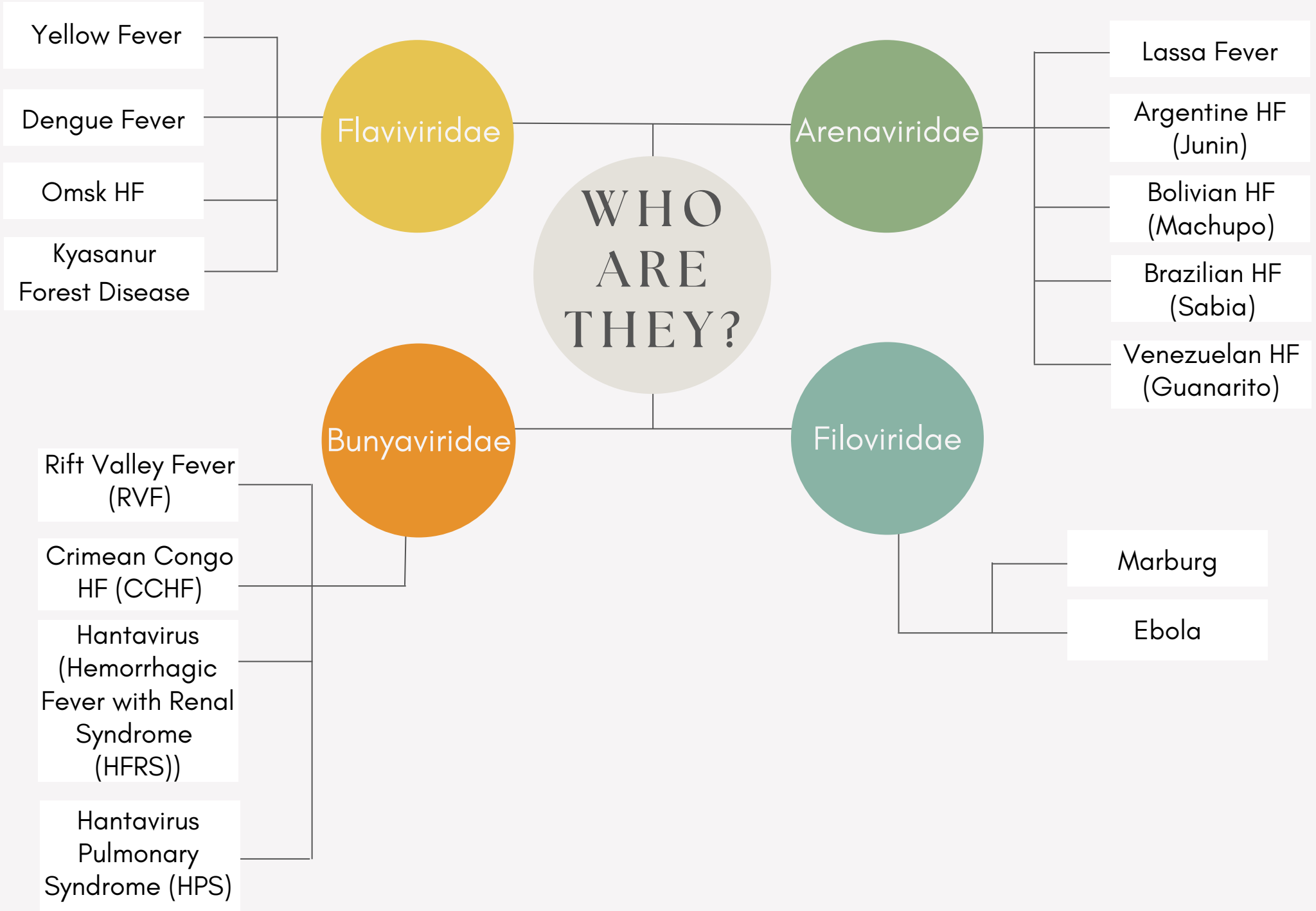
Viral hemorrhagic fevers



General features

Arboviruses

Any virus that is transmitted by arthropod vectors, Such as:
1. Flaviviridae
2. Bunyaviridae (except Hantavirus)

Structure

-Enveloped Lipid-encapsulated
-All of them -sRNA (replicate in the cytoplasm) except Flaviviridae +sRNA (replicate in the nucleus)

Common pathophysiology

Diffuse Damage to overall vascular system characterized by hemorrhage

Transmission

-Zoonotic (animal-borne)
-Geographically restricted by the host
- Persistent in nature (rodents, bats, mosquitoes, ticks, monkeys)

Reservoir

Rodents & Arthropods

How do we get infected?

1.Rodents: inhalation or Contact with excreta
2.Arthropods (Bites of infected mosquito or tick)
3.person to person:
Airborne potential for some arenaviridae, filoviridae

Statistics

Ebola and Marburg have the highest mortality rate

Interpersonal transmission rout is well documented in:

1. Lassa Fever
2. Crimean Congo HF (CCHF)
3. Filoviridae (Marburg & Ebola)

	Transmission	Clinical features	Example
Arenaviridae	▪ Non-arboviruses. ▪ Rodent-borne. ▪ Virus transmission & amplification occurs in **rodents** →then they shed virus through urine, feces, & other excreta →Human infection ▪ How the human get infected? 1. Contact with rodent's excreta 2. Contaminated materials 3. **Person-to-person transmission** **(only in case lassa fever)**	▪ Incubation period 10-14 days. ▪ Fever and malaise 2-4 days. ▪ Mild Hemorrhage in form of petechiae or purpura. ▪ Leukopenia &thrombocytopenia ▪ Neurologic signs	**Lassa Fever (west Africa)** ▪ Highest mortality rate in this group ▪ Reservoir: Rodent-borne (Mastomys natalensis) ▪ Can transmit from person to person (intrapersonal rout) via direct contact, sex, breastfeeding. ▪ Distinguishing clinical Features: - Gradual onset - Myocarditis → Retro-sternal pain - Exudative pharyngitis - **Hearing loss** in 25% may be persistent - **Spontaneous abortion** ▪ Morphology under EM: Sandy Cytoplasm
Bunyaviridae	▪ Arthropod vector (arboviruses), except Hantaviruses. ▪ Contact with animal blood or products of infected livestock. ▪ Rodents (Hantavirus) ▪ Person-to-person transmission with CCHF	RNA morphology ▪ Have a segmented RNA: 1. L segment: codes for an Lprotein (the RNA dependent RNA polymerase) 2. M segment: codes for two surface glycoproteins G1 and G2 which form the envelope spikes 3. S segment: codes for an N-protein (nucleocapsid protein).	**Rift Valley Fever** ▪ Mild illness in humans so usually asymptomatic ▪ Arthropod vector: Aedes mosquito ▪ Distinguishing clinical Features: - Hemorrhagic complications rare - **Vision loss** "blindness" due to retinal hemorrhage,vasculitis **Crimean-Congo Hemorrhagic Fever** ▪ Arthropod vector: Ixodid tick ▪ Distinguishing clinical Features: - Abrupt (sudden) onset - hemorrhagic fever + significant hemorrhagic complication - Profuse hemorrhage (internally & externally) - May develop GI symptoms like hematemesis and melena **Hantaviruses** ▪ Non-arboviruses ▪ Transmission: Exposure to rodent saliva and excreta ▪ There are two serotypes of Hantaviruses: 1. New-world Hantavirus → cause Hantavirus Pulmonary Syndrome (HPS) 2. Old-world Hantavirus → Hemorrhagic Fever with Renal Syndrome (HFRS) ▪ Distinguishing clinical Features of HFRS: - Insidious onset - Intense headaches - Blurred vision - kidney failure; causing severe fluid overload & periorbital edema

	Transmission	Clinical features	Example
Flaviviridae	▪ Arthropod vector	▪ Characterized by the "Biphasic clinical presentation": 1. Viremia phase: high viral load in the blood and high secretion of cytokines and constitutional signs and symptoms (marked fever) 2. Toxemia phase: Fever returns along with the constitutional symptoms + Hemorrhagic signs and symptoms *In between the 2 phases, there is a window period, in which signs and symptoms disappear ▪ Yellow Fever and Dengue have two cycles: 1. Sylvatic cycle: The cycle between nonhuman primates and humans are considered accidental hosts 2. Urban cycle: between humans and the vector without the need of an intermediate host	**Yellow Fever** ▪ Arthropod vector: Aedes aegypti ▪ Distinguishing clinical Features: - Common hepatic involvement & jaundice (cause lytic necrosis of hepatocyte). **Dengue** ▪ Arthropod vector: Aedes aegypti ▪ 3 levels: 1. Dengue Fever (Lowest Fatality) 2. Dengue Hemorrhagic Fever 3. Dengue Shock Syndrome (Highest Fatality) ▪ Four distinct serotypes: DEN-1, DEN-2, DEN-3, DEN-4 ** The infection by one of these serotypes will develop a lifelong immunity for that serotype but if get infected later by anther serotype the patient will develop a severe illness ▪ Distinguishing clinical Features: - Sudden onset - Eye pain - Rash - Arthralgia - Illness is severe in younger children **Omsk Hemorrhagic Fever** ▪ Reservoir: Muskrat ▪ Arthropod vector: Dermacentor reticulatus tick ▪ Distinguishing clinical Features: - Acute onset ▪ Complications - **Hearing loss** - **Hair loss** - Psycho-behavioral difficulties **Kyanasur Forest** ▪ Arthropod vector: Ixodid tick (Haemaphysalis) ▪ Distinguishing clinical Features: - Acute onset
Filoviridae	▪ Non-arboviruses ▪ Nosicomial transmission ▪ Aerosol transmission ▪ Reservoir is UNKNOWN (but it is zoonotic) ▪ Interpersonal transmission (Intimate contact)	▪ Most severe hemorrhagic fever ▪ Incubation period: 4-10 days ▪ Aerosol transmission ▪ Abrupt onset ▪ Hemorrhage and DIC ▪ Death around day 7-11 (in the second week) ▪ Painful recovery; the patient does not feel that he is getting well. ▪ Filament like under EM	**Ebola** ▪ Five subtypes: Ebola-Zaire, Ebola-Sudan, Ebola-Ivory Coast, EbolaBundibugyo, **Ebola-Reston (illness in nonhuman primates / US)** ▪ Human-infectious subtypes found only in Africa ▪ Distinguishing clinical Features: - Acute onset - GI involvement / Weight loss **Marburg** ▪ Distinguishing clinical Features: Sudden onset/ chest pain/ Maculopapular rash on trunk/ Pancreatitis/ Jaundice

COMMON PATHOPHYSIOLOGY

- Small vessel involvement (Increased vascular permeability)
- Multiple cytokine activation & Inadequate/delayed immune response
- Cellular damage
- Abnormal vascular regulation (mild hypotension in early stage)
- Viremia (Macrophage involvement)

LAB STUDIES

- Complete Blood Count
- Liver enzymes
- Proteinuria universal
- Serological tests - Ab not detected acute phase
- EM specific and sensitive

GENERAL INFORMATION

EARLY/PRODROMAL SYMPTOMS

- Flu-like symptoms
- Fever, Myalgia, Headache, ...
- Non-bloody diarrhea.
- Arthralgia

PROGRESSIVE SIGNS

- Conjunctivitis, Periorbital edema
- Subconjunctival hemorrhage
- Ecchymosis, Petechiae
- But the hemorrhage itself is rarely lifethreatening.

SEVERE/END-STAGE

- Multisystem compromise
- Profuse bleeding
- Consumptive coagulopathy & DIC mainly in Filoviridae
- Encephalopathy
- Shock
- Death

Treatment	Prevention	Vaccination
▪ Ribavirin is considered an effective treatment -in vivo- only for: 1. Lassa Fever 2. Rift Valley Fever 3. CCHF ▪ Supportive care: - Fluid and electrolyte management - Ventilation and/or dialysis support - Steroids for adrenal crisis - Anticoagulants, IM injections - Hemodynamic monitoring	▪ Isolation of infected individuals ▪ House to house rodent trapping ▪ Sterilization ▪ Vector control in arboviruses	▪ Passive immunization: Argentine and Bolivian HF ▪ Active immunization: **Yellow fever** -the only- **(live attenuated vaccine)** **For pregnant & immunocompromised: Passive immunization

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