
SUSPECTED HANTAVIRUS CASES
MEDICAL EVACUATION UNIT

OLD WORLD AND NEW WORLD HANTAVIRUSES

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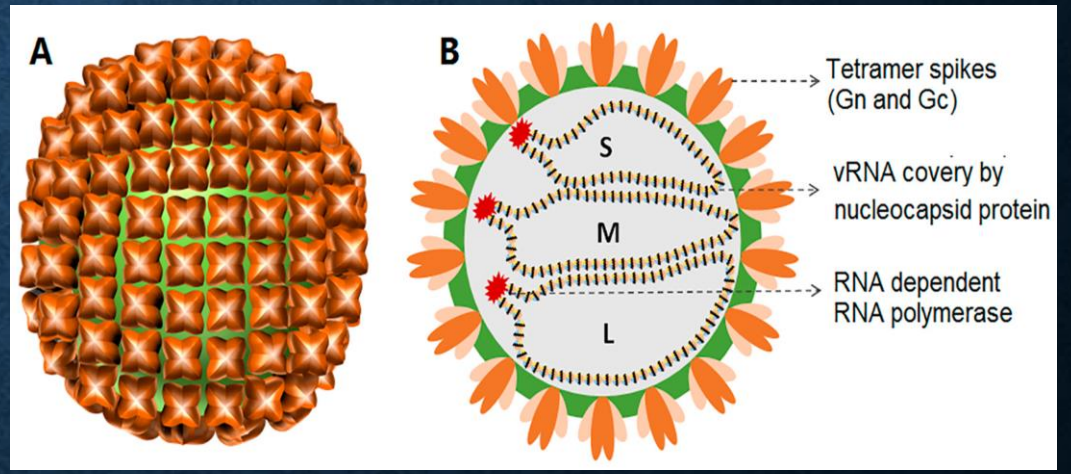
STRUCTURE

- The infectious virions of hantaviruses are enveloped spherical particles with a diameter of 80–120 nm.
- The negative-strand RNA genomes of hantaviruses comprise three segments: a 1.8–2.1 kb small segment (S), a 3.7–3.8 kb medium segment (M), and a 6.5–6.6 kb large segment (L).
- The envelope membrane is composed of bilayer of exterior lipids secreted from Golgi complex.



STRUCTURE

- The L segment encodes the RNA-dependent RNA polymerase (RdRp), which is responsible for viral genome replication and transcription.
- The M segment encodes a glycoprotein precursor, which is post-translationally cleaved into the two envelope glycoproteins, Gn and Gc, involved in host cell attachment and membrane fusion.
- The S segment encodes the nucleocapsid (N) protein, which binds viral RNA to form ribonucleoprotein (RNP) complexes. The ribonucleoprotein arranged within the virion interior.
- Unlike some other bunyaviruses, hantaviruses generally lack a matrix protein, and virion organization depends largely on glycoprotein-capsid interactions.

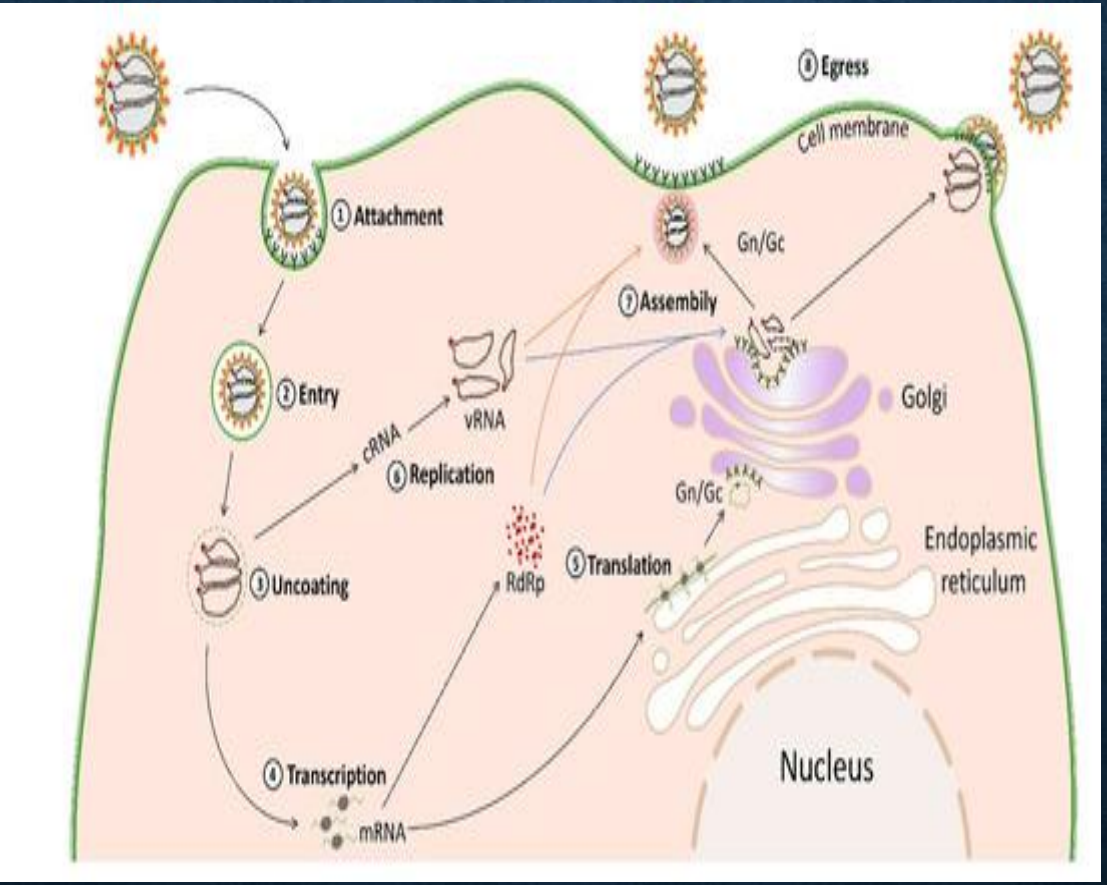
CLASSIFICATION

- Orthohantaviruses (also known as hantaviruses (HTVs)) (order *Bunyavirales*, family *Hantaviridae*, subfamily *Mammantaivirnae*, genus *Orthohantavirus*)
- Generally, hantaviruses are classified into New World hantaviruses (NWHVs) and Old World hantaviruses (OWHVs) according to the geographic location of their respective rodent reservoir and the type of clinical manifestation upon infection of humans.
- NWHVs, such as Sin Nombre orthohantavirus (SNV) or Andes orthohantavirus (ANDV), mainly affect the human lung, causing a disease called hantavirus cardiopulmonary syndrome (HCPS), and circulate in North and South America.
- OWHVs, such as Dobrava-Belgrade orthohantavirus (DOBV), Hantaan orthohantavirus (HTNV) and Puumala orthohantavirus (PUUV), mainly affect human kidneys, causing a disease called hemorrhagic fever with renal syndrome (HFRS).

REPLICATION

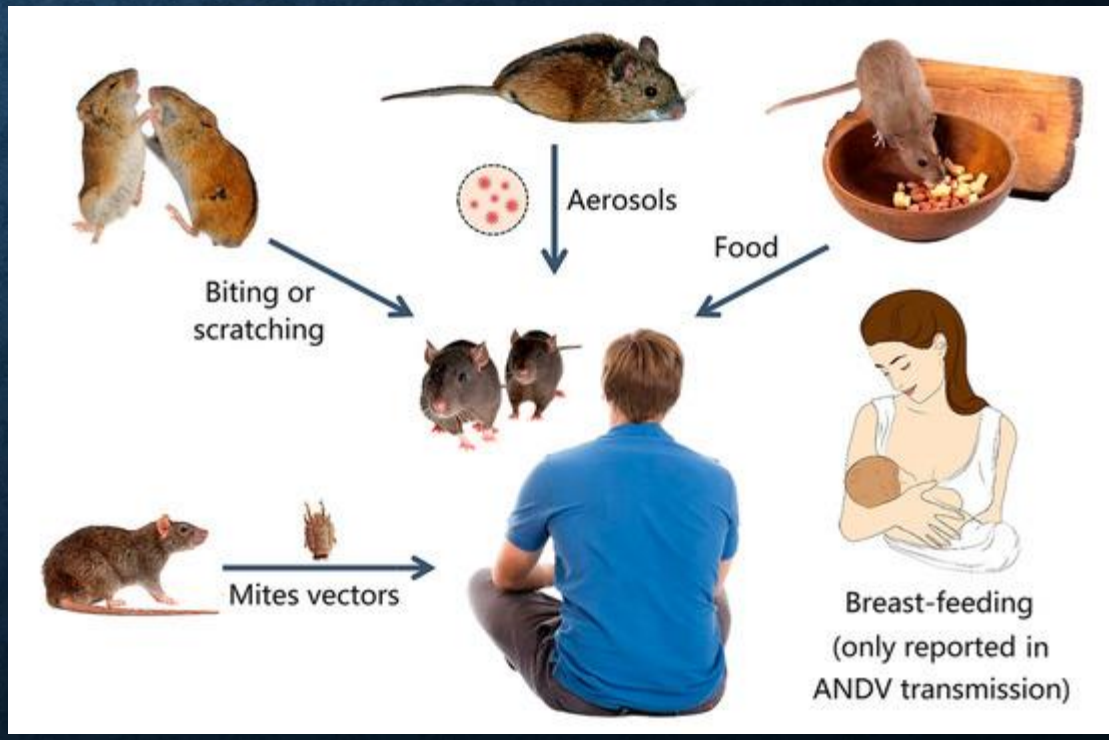
- Vascular endothelial cells and macrophages are the primary sites of hantavirus replication and might use integrins to enter cells.
- Following entry, the virus synthesizes viral mRNA to produce viral proteins and replicate the genome (comprising small, medium and large segments), although the exact details of these processes remain unclear.
- The viral genome is encapsided by nucleocapsid protein to form ribonucleoproteins, which interact with viral glycoprotein to form virus particles.

REPLICATION CYCLE



TRANSMISSION

- Although hantaviruses can be inactivated by heating at 60 °C for 30 min, organic solvents, hypochlorite solvents, or ultraviolet light, they are relatively stable in the external environment. They can survive for 10 days at room temperature and more than 18 days at low temperatures (e.g., 4 °C). This facilitates the transmission of hantaviruses.
- Hantaviruses usually cause asymptomatic and persistent infections in rodents, except that Syrian hamsters infected with ANDV can show typical symptoms of HCPS/HPS. Rodents, shrews, moles, and bats are the reservoirs of some hantaviruses, which can transmit the virus horizontally and vertically.



TRANSMISSION

- Unlike other members of the order Bunyavirales, hantaviruses are not transmitted via obligate intermediate vectors, such as ticks, mosquitoes, flies or arthropods. However, they are directly or indirectly transmitted via hosts during close interactions, via inhalation of infectious aerosols or via contact with droppings or urine of infected animals. It has been shown that hantaviruses are more infectious via parental injection than aerosol transmission, thus, bite wounds and scratches caused by rodents present a risk for transmission that needs to be taken into account. Furthermore, observations of experimental ANDV and PUUV infections in Syrian hamsters indicate a potential transmission via the intragastric route.
- Two major outbreaks of Hantavirus disease, reported in the last century, were the first to catch global attention. The first, HFRS outbreak, occurred during the Korean War (1950–1953), affected more than 3,000 US troops. The second, HPS outbreak, was documented in the southwestern regions of the US in 1993.

PATHOGENESIS

- The main pathogenesis of HFRS and HCPS/HPS covers increased vascular permeability and acute thrombocytopenia. The infection begins with the interaction between hantavirus glycoproteins (Gn and Gc) and β-integrin receptors (e.g., αvβ1 and αvβ3) on target cell membranes. Immature dendritic cells located near ECs transport virions from lymphatic vessels to local lymph nodes to infect more ECs.
- based on in vitro studies hantavirus infection of ECs does not induce direct cytopathic effects.
- However, virus-induced general inflammation may compromise the barrier function of the endothelium and induce vascular leakage. If so, similar mechanisms could be behind the hemorrhages seen in other viral infections. On the other hand, the infection of ECs might lead to virus-specific promotion of permeability.

PATHOGENESIS

- It seems active virus replication could produce increased permeability and decreased the integrity of the endothelial cell barrier.
- Increased coagulation is associated with hemorrhages especially in HFRS. Laboratory findings such as increased bleeding time, prothrombin time, activated partial thromboplastin time, and thrombin time together with decreased plasma activity of several coagulation factors, and the presence of fibrin degradation products are indicative of DIC in severe HFRS.
- Endothelial cell infection could lead to viremia, which has been postulated to play an important role in the vascular dysfunction, it seems actual amount of infecting virus could be an important factor for pathogenesis. This is also supported by in vitro infections where the initial viral load negatively correlates with cell survival.

PATOGENESIS

- Host genetic factors influence the clinical outcome:
    - Endothelial cells and platelets are prominent regulators of vascular functions and integrins play key roles in barrier functions of these cells.
    - Most interestingly, pathogenic and non-pathogenic hantaviruses use different integrin receptors.

PATHOGENESIS

- Individual susceptibility to hantavirus:
  - The severity of HFRS infected by HTNV is positively correlated to the age of the patients. It was reported that most deaths from the hantavirus disease NE occurred in older persons, especially the patients >70 years of age. In China, it was demonstrated that the case fatality rate was higher among individuals ≥50 years of age than that among the younger individuals .
  - Nephropathia epidemica (NE) is a mild form of HFRS , and is caused by Puumala virus, the most common hantavirus, present in most countries in north-western Europe. NE has an abrupt onset with fever and myalgia, thrombocytopaenia (low blood platelet count) and sometimes myopia (short-sightedness).

OVERVIEW

- Hantaviruses are zoonotic viruses that naturally infect rodents and are occasionally transmitted to humans. Infection in people can result in severe illness and often death, although the diseases vary by type of virus and geographical location. In the Americas, infection has been known to lead to hantavirus cardiopulmonary syndrome (HCPS), a rapidly progressive condition affecting the lungs and heart, while in Europe and Asia hantaviruses have been known to cause haemorrhagic fever with renal syndrome (HFRS), which primarily affects the kidneys and blood vessels.
- While there is no specific treatment that cures hantavirus diseases, early supportive medical care is key to improve survival and focuses on close clinical monitoring and management of respiratory, cardiac and kidney complications. Prevention depends largely on reducing contacts between people and infected rodents.