**HANTAVIRUS**

BOM-12:  Sec.  35.2  Hantavirus Syndromes  p. 1,005-1,007

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**What is a Bunyavirus?**

Bunyaviruses include all the viruses in the Family *Bunyaviridae* (boon ya vir’ i day).

*Bunyaviridae* is the largest family of viruses, with 350 recognized "species".

The family is divided into 5 "genera":

- **Bunyavirus**
- **Nairovirus**
- **Phlebovirus**
- **Tospovirus**
- **Hantavirus**

(other *Bunyaviridae* unassigned to existing genera)

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**Why do these viruses have such funny names?**

Many viruses are named for the geographic location in which they were first discovered. These are often exotic locales unfamiliar to North Americans.

For example, the first virus in the Family *Bunyaviridae* was isolated from a species of *Aedes* by Smithburn in 1946, pursuant to studies of Yellow Fever in *Bunyamwera*, Uganda.

The first *Hantavirus* was isolated following an outbreak of "Korean Hemorrhagic Fever" among UN troops in the Korean War (1951-1953). It was named after the *Hantaan River* in Korea.

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**What diseases are caused by Bunyaviruses?**

Bunyaviruses are the agents of several important zoonoses (plural of zoonosis):

<table>
<thead>
<tr>
<th><em>Bunyavirus</em></th>
<th>LaCross Encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nairovirus</strong></td>
<td>Crimean-Congo hemorrhagic fever (CCHF) is caused by a Nairovirus. Outbreaks of CCHF infection occur sporadically in Africa, south-eastern Europe, and in the former Soviet Union. CCHFV is mainly transmitted by ticks, but has also caused severe hospital outbreaks.</td>
</tr>
<tr>
<td><strong>Phlebovirus</strong></td>
<td>Rift Valley fever (RFV)</td>
</tr>
<tr>
<td><strong>Tospovirus</strong></td>
<td>plant viruses</td>
</tr>
</tbody>
</table>
| **Hantavirus**        | Hantavirus Pulmonary Syndrome (HPS)  
                       | Korean Hemorrhagic Fever (KHF)  
                       | Hemorrhagic Fever with Renal Syndrome (HFRS) |
HANTAVIRUS OUTBREAKS

<table>
<thead>
<tr>
<th>HANTAVIRUS STRAIN</th>
<th>ANIMAL RESERVOIR</th>
<th>LOCATION</th>
<th>SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hantaan</td>
<td>Striped field mouse</td>
<td>Central and Eastern Asia</td>
<td>HFRS (KHF)</td>
</tr>
<tr>
<td>Seoul</td>
<td>Rat</td>
<td>World-wide</td>
<td>HFRS</td>
</tr>
<tr>
<td>Dobrava</td>
<td>Yellow-necked field mouse</td>
<td>Eastern Europe</td>
<td>HFR</td>
</tr>
<tr>
<td>Puumala</td>
<td>Bank vole</td>
<td>North and central Europe</td>
<td>HFRS (NE)</td>
</tr>
<tr>
<td>Sin Nombre</td>
<td>Deer mouse</td>
<td>USA</td>
<td>HPS</td>
</tr>
</tbody>
</table>

What is a zoonosis?

Your text has an index and a glossary.

What is a "hemorrhagic fever"?

A Viral Hemorrhagic Fever (VHF) is one of a group of illnesses caused by several distinct families of viruses (Filoviruses, Arenaviruses, Flaviviruses, and Bunyaviruses). While some types of hemorrhagic fever viruses cause relatively mild illnesses, many of these viruses cause severe, life-threatening disease.

In general, the term VHF is used to describe a severe syndrome in which multiple organ systems in the body are affected. Characteristically, the vascular system is damaged, and the body's ability to regulate itself is impaired. Patients with severe cases of VHF often show signs of bleeding under the skin, in internal organs, or from body orifices like the mouth, eyes, or ears. As dramatic as the bleeding appears, the bleeding is rarely life-threatening by itself. Severely ill patient cases may also show shock, nervous system malfunction, coma, delirium, and seizures. Some types of VHF are associated with renal (kidney) failure.

Unlike the other Bunyaviruses implicated in human outbreaks, Hantaviruses are not "Arboviruses". What is an Arbovirus, and why does this make Hantaviruses particularly scary?

Arboviruses are transmitted from animal to human hosts by arthropod vectors (ticks, fleas, mosquitoes, etc.) Hanta viruses do not require a vector because they can be transmitted by aerosols.
What is the geographic distribution of cases of human Hantavirus infection in the US?

What is the mortality rate for Hantavirus Pulmonary Syndrome (HSP)?

In the Four Corners Outbreak in 1993 the mortality rate was 60%.

What is the structure of the Hantavirus virion?

The virion is spherical, 80-120nm in diameter.

All Bunyaviruses have enveloped virions.

Within the envelope one finds a 3-part "Nucleocapsid", with each part being composed of an RNA molecule and a structural protein.

What does it mean to say that a virus is "enveloped"?

It means that the viral genome and capsid are surrounded by a lipid bilayer membrane derived from the plasma membrane of the host cell.
What does it mean to say that Hantavirus (Bunyaviridae) genomes are "tripartite segmented minus-strand RNA"?

The Hantavirus genome is encoded in three separate (tripartite) ss RNA molecules named "Small", "Medium", and "Large"

All 3 RNA's are linear, but in the virion they appear to be circular because the ends are held together by base-pairing. The three RNA's are not present in equimolar amounts within a virion. The 5' ends are not capped; 3' ends are not polyadenylated. Isolated genomic RNA is not infectious.

How large are the Hantavirus RNA's, and what proteins do they code for?

L 8.5kb / RNA-dependent RNA Polymerase (L Protein). Also cleaves 5' meG caps from host mRNA to use as primer.

M 5.7kb / encodes a polyprotein precursor that is cleaved to generate two envelope glycoproteins (G1 and G2) and also the NSm polypeptide of unknown function.

S 0.9kb: / encodes the nucleocapsid (N) and a nonstructural protein (NSs) from overlapping open reading frames (ORFs) on a single mRNA. The N protein forms a trimer that specifically encapsidates the viral -RNA's to form the nucleocapsid. The NSs protein acts as an interferon antagonist.

i.e. the hantavirus genome codes for a total of 6 proteins.

What does it mean to say that the virion RNA's are "minus (-) strand"?

It means they are complementary to mRNA.

How are viral mRNA's synthesized?

The virion-associated minus-RNA is copied by virion-associated RNA replicase.

Replication of Hantavirus (Bunyavirus) genomes requires the unique enzyme RNA-dependent RNA polymerase, which is not found in uninfected animal host cells. How is it possible for Hantavirus infections to initiate if the virion contains the -strand and must be copied to produce a + strand before gene expression???

Each of the three virus RNA molecules is already associated with a molecule of RNA Replicase in the virion. This pre-positioned RNA replicase copies the -strands to +strands before any expression of the viral genome in the new host.
But how can the newly synthesized + RNA's be translated without methyl guanine caps?

The + strand RNA's somehow capture, or cannibalize, the 5' m7G caps of pre-existing host mRNA's.

How do the viral proteins G1 and G2 become part of the envelope?

The + strand M-mRNA has a eukaryotic signal sequence for attachment to the rough ER. The proteins are inserted in the membrane of the Golgi apparatus. The virus nucleocapsids bud into cisternae of the Golgi; this is how they pick up their envelopes.

How are mature viruses released from the infected host cells?

Hantavirus proteins G1 and G2 are made from a polyprotein precursor that is cleaved at a conserved site.

The polyprotein precursor is synthesized by ribosomes attached to the rough endoplasmic reticulum (rER).

G1 and G2 are inserted in the rER membrane.

Sugar groups are added (glycosylation) to the proteins while they are in the ER and G1 and G2 associate to form heterodimers.

G1/G2 heterodimers are then transported to the Golgi where further glycosylation occurs.

The G1/G2 are retained in the Golgi until virion assembly.

The N protein forms homotrimers that then interact with each other to form a chain. The multimerization of N protein allows RNA encapsidation to proceed rapidly once the process has been initiated. The nucleocapsid assembly probably occurs in the perinuclear region.

It is not known why + strand vRNA is excluded from association with N protein.

The nucleocapsids are then transported to the virion assembly site at the Golgi. This transport may be conducted by interaction with actin filaments.

At the virus assembly site the N protein interacts with the cytoplasmic tail of G1 bringing together all of the virion components: glycoproteins G1 and G2, N protein, L protein, and the three vRNAs: S, M, and L.

Virion assembly is immediately followed by budding into the Golgi cisternae. Nascent virions are then transported in secretory vesicles to the plasma membrane and released by exocytosis.

Electron microscopy studies of the Sin Nombre virus suggested that New World hantaviruses assemble and bud at the plasma membrane, in contrast to the Old World hantaviruses that bud into the Golgi.
How long do hantavirus particles remain infective outside a host animal?
What allows human-human transmission of Hantavirus?

???

**What treatments have been developed for HSP?**

There is no specific therapy, but early recognition of HPS can expedite initiating cardiopulmonary support in an intensive care unit, which is associated with improved survival rates. Two potential treatments are under investigation. One is the use of extracorporeal membrane oxygenation.

The second is the antiviral chemical agent ribavirin (Virazole). Ribavirin has been shown to be effective in HFRS caused by the Hantaan virus. One trial of the use of ribavirin in treating HPS showed little effect. This may have been because of the rapidity of death in the most acutely ill patients. Further controlled trials are being conducted.

**What is Ribavirin and how does it work?**

Ribavirin is a ribonucleoside analog that acts as an RNA mutagen and has demonstrated effectiveness against infections by several RNA viruses. Currently it is thought that Ribavirin may act by inducing "viral error catastrophe".
What is viral error catastrophe?

![Error Catastrophe Graph](image)

*Fig. 4 Model of error catastrophe. The majority of viruses in a normal picornavirus population are viable [87]. However, a small increase in mutation frequency is predicted to push the virus population into error catastrophe (the mutagenized population on the right), where the number of errors per viral genome is sufficiently high to lethally mutate a majority of the virus population. This is predicted to be the case for most RNA viruses. White Live virus; grey dead virus.*

What is the incubation period for HSP?

The incubation period of HPS has a range of 9-33 days, but is usually between 14-17 days in length.

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CDC Special Pathogens Branch HV Website: [http://www.cdc.gov/ncidod/diseases/hanta/hps/](http://www.cdc.gov/ncidod/diseases/hanta/hps/)