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# Hantavirus Pulmonary Syndrome (HPS): A Concise Review based on Current Knowledge and Emerging Concept

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**ABSTRACT**

Hantaviruses are rodent-borne bunyaviruses transmitted from the rodents. Today numerous rodent species are carrying hantaviruses throughout the world. These group of viruses can cause one of two types of viral hemorrhagic fever (VHF) in human beings namely hemorrhagic fever with renal syndrome (HFRS), and hantavirus pulmonary syndrome (HPS). In the spring of 1993, an unknown group of hantaviruses emerged in the United States as the cause of an acute respiratory disease currently termed as Hantavirus pulmonary symdrome (HPS), also referred to as hantavirus cardiopulmonary syndrome (HCPS). HPS is characterized by an acute onset of headache, fever, hypovolemic hypotension, myalgia and respiratory failure. This review covers the distribution, virology, epidemiology, pathophysiology, symptoms, treatment and prevention of hantavirus causing HPS/HCPS.

## INTRODUCTION

Hantavirus was first identified in 1993, causing a disease similar to adult respiratory distress syndrome (Hjelle, 1995). Later many unique hantaviruses were identified throughout the America. Due to which the taxonomy of these viruses had become very complex and tedious to maintain. Presently, more than 20 distinct New World hantaviruses has been identified. All of these viruses are associated with a unique rodent as their host. Viral hemorrhagic fever (VHF) includes variety of diseases. There are 12 different VHF causing enveloped RNA viruses belonging to four families: Arenaviridae, Bunyaviridae, Filoviridae and Flaviviridae. The extreme diseased conditions of these viruses include increased vascular permeability, circulatory instability, and diffuse hemorrhage (Enria *et al.,* 2001). For several VHFs, person-to-person transmission may occur due to the direct contact with infected persons, their blood, and their excretions. Generally rodents like rats or mice are the animal reservoirs of these viruses, but some intermediate hosts are also there like domestic livestock, monkeys and other primates (Vinh and Embil, 2009). Viruses are generally transmitted to humans with urine, saliva, fecal matter or other body excretions from infected rodents reservoir (figure 1). Mostly, these viruses spread when the vector mosquitoes or tick bites a human, or when ticks are crushed by human. In some cases, the humans may get infected when they care for or slaughter these animals (Figueiredo *et al.*, 2009).

In some cases, hemorrhagic fever causing viruses are spread from person to person, if once an initial person has become infected. This type of transmission is called as the secondary transmission of the virus (simpson *et al.,* 2010). The secondary transmission of these viruses through contaminated syringes and needles had played a major role in spreading these infections. Hantaviruses, have a worldwide distribution, are broadly split into the New World hantaviruses and the Old World hantaviruses (associated with a different disease, (HFRS)). Sin Nombre virus (SNV) and Andes virus (ANDV) are the most common causes of HPS in North and South America, respectively. The mortality of HPS is approximately 40% (Jonsson *et al.*, 2010). It was reported that the hantaviruses infect the lung microvascular endothelium without causing any virus induced cytopathic effect. This viral infection leads to microvascular leakage, which is the fingerprint of HPS (Schmaljohn and Hjelle, 1997, MacNeil *et al.,* 2011).

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This article concisely reviews the recent progress in our understanding of the molecular and cell biology of HPS-associated hantaviruse and epidemiology, pathophysiology with an emphasis on the effects of viral iterations with host cells and with the immune system, treatment and prevention.

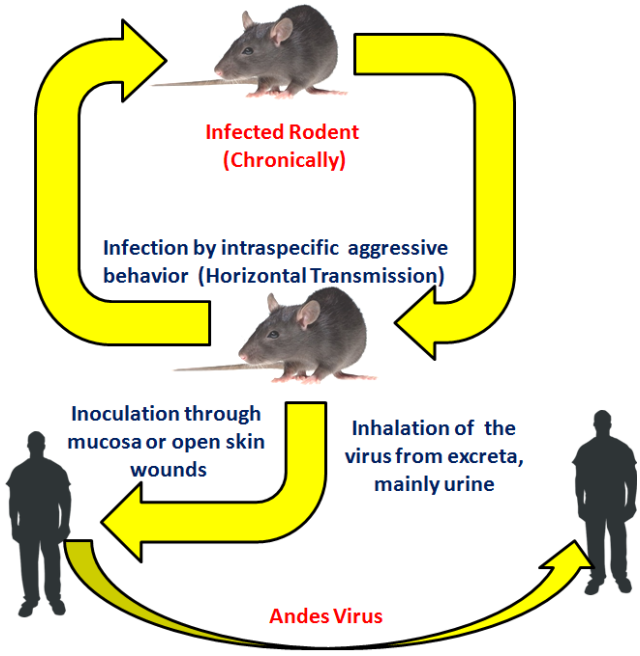


**Fig. 1:** Transmission route of hantavirus.

**Hantavirus Pulmonary Syndrome (HPS)**

Hantavirus pulmonary syndrome (HPS), a pan-American viral zoonosis, also referred to HCPS, is a rare but frequently fatal disease (Hallin *et al.*, 1996). It is characterized by a febrile prodrome followed by sudden onset of severe pulmonary edema and cardiogenic shock (Safronetz *et al.*, 2011). The white-footed mouse (Peromyscusleucopus) is a reservoir for virus that is either a variant of Sin Nombre virus (SNV) or a closely related virus. The cotton rat (Sigmodonhispidus) is the rodent reservoir for BCCV in southern Florida and the rice rat (Oryzomyspalustris) appears to be the rodent reservoir for Bayou virus. The deer mouse (Peromyscus maniculatus) is the primary rodent reservoir for SNV in the southwestern United States (Childs *et al.*, 1994).

**Virology of Hantaviruses**

***The viral genome and virion structure***

As member of the family Bunyaviridae, HPS causing hantavirus is generally negative-sense single-stranded RNA virus with a trisegmented genome (Schmaljohn, 1985, Schmaljohn and Nichol, 2007). At the 3′ and 5′ ends of each segment of the viral RNA (vRNA) contains an ORF flanked by non-coding regions (NCRs). The three ORFs of the genome segments, which are small, medium and large, encode three different proteins nucleocapsid (N) protein, glycoprotein precursor (GPC; which eventually matures into the glycoproteins Gn and Gc (previously known as G1 and G2, respectively)) and RNA-dependent RNA-polymerase (RdRp) respectively (Vaheri *et al.*, 2013). The terminal region of the NCRs contain a panhandle like structure, a complementary nucleotides, which functions as the viral promoter and is crucial for replication and transcription (Spiropoulou, 2011, Hussein *et al.*, 2011). The outermost part of the virion is covered by spikes comprising of each glycoprotein, Gn and Gc (Figure 2). The height of spike is invariably 12 nm, and the virion median diameter is 135 nm. The trisegmented viral genome is generally replicated and transcribed by RdRp.

***The life cycle and replication of hantaviruses***

Hantaviruses generally infect the epithelial, endothelial, macrophage, lymphocyte and follicular dendritic cells. They infect via the attachment of viral glycoprotein to the receptor(s) present on the host's cell surface (Zaki *et al.*, 1995, Mackow *et al.*, 2001, Spiroloulou, 2001, Raftery *et al.*, 2002, Markotic *et al.*, 2007). For entry the receptors interact with the larger viral glycoprotein (Gn) are integrins: β1 integrin considered to be apathogenic and β3 integrin for pathogenic hantaviruses causing HPS (Gavrilovskaya *et al.*, 1995, Gavrilovskaya *et al.*, 1998, Larson *et al.*, 2005). Generally hantaviruses enters via clathrin-coated pits, followed by movement to early endosomes and subsequent delivery to late endosomes or lysosomes (Jin *et al.*,2002). In the case of clathrin-mediated endocytosis, the clathrin coat present on vesicle is diassembled and the virion-harbouring vesicle enters the early endosome which matures into a late endosome. Fusion between the viral and endosomal memebranes is driven by acid-induced conformation changes in the viral fusion protein in the late endosome. This results in the release of the three viral ribonucleoproteins (RNPs) into the cytoplasm within the endolysosomal compartments. Primary transcription takes place due to viral RdRp and give rise to the S, M and L mRNAs. On the free ribosome, translation of the S and L mRNA transcript occurs and on the membrane-bound ribosomes, M-segment transcript occurs which is co-translated on rough endoplasmic reticulum (RER). For hantaviruses, N protein plays key roles in several important steps in the virus life cycle including translation, trafficking and assembly (Betenbaugh *et al.*, 1995, Severson *et al.*, 1999, Jonsson and Severson *et al.*, 2001, Schmaljohn, 2001, Ramanathan *et al.*, 2007, Mir *et al.*, 2008, Ramanathan and Jonsson, 2008, Panganiban and Mir, 2009) and is most abundant viral protein and synthesized early in infection (Schmaljohn and Hooper, 2001). During import into the ER, the glycoprotein precursor is proteolytically precessed into Gn and Gc (Ruusala *et al.*,1992, Spiropoulou, 2001). At the end of Gn, a conserved amino acid motif, WAASA, is presumed to be the proteolytic cleavage site (Lober *et al.*, 2001). In the ER, Gc and Gn proteins are glycosylated and subsequently transported to the Golgi complex (Vapalahti *et al.*, 1995, Schmaljohn, 1996, Antic *et al.*, 1992, Ruusala *et al.*, 1992, Ravkov *et al.*, 1998). The viral polymerase switches from transcription to the replication and then amplification of S, M, and L genomic RNAs soon after the initial burst of transcription. The newly synthesized vRNAs are encapsidated by the N protein to form the RNPs (Schmaljohn and Hooper, 2001), and transported to the golgi apparatus. Finally

virus egression occurs via the fusion of the golgi vesicle harboring the mature virion particles with the plasma membrane with the help of transport vesicles (Figure 2).

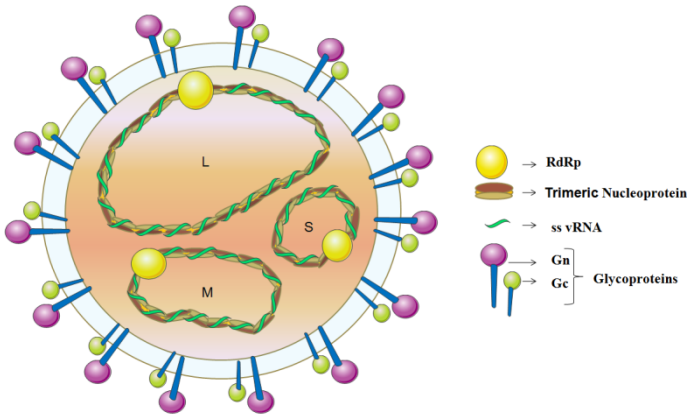


**Fig. 2:** Hantavirus particle, genes and proteins. Schematic representation of the virion, containing the RdRp (RNA-dependent RNA polymerase), (-) ss viral RNA (vRNA), Trimeric Nucleoprotein and Spike complex glycoproteins (Gn and Gc)

## Epidemiology

In human populations the epidemiology of hantavirus infections is based largely on incidences of peridomestic exposure of humans to rodents in endemic areas. In the United States, hantavirus-associated disease was not recognized prior to May 1993. The initial HPS outbreak was recognized by the Medical Investigator of the New Maxico Office and Indian Health Service. They had identified a newly recognized hantavirus, SNV, and reservoir, *Peromyscus maniculatus*, approximately two weeks after receiving laboratory diagnostic specimens (Chapman and Khabbaz, 1994). Centers for Disease Control and Prevention (CDC) established an emergency phone hotline and was successful in rapidly identifying the widespread sporadic geographic distribution of HPS cases throughout the United States (Tappero *et al.*, 1996). In United States, 465 HPS cases have been reported to the CDC in March 2007, and 35% of these resulted in death (37% female and 64% male), with a mean age of patients of 38 years (range, 10 to 83 years). In 30 U.S. states, many HPS cases have been reported with the majority in the western half of the country occurring in residents of rural areas. For New Maxico, number of cases have been reported (Chu *et al,* 2003).

Hantavirus infections have been found in Latin America, North America, including Canada and eastern Asia. However, HPS seems to be restricted to North and South America (Table 1). While in the United States, transmission from human to human has not been reported, HPS outbreaks reported from Argentina were possibly associated with the transmission from one human to another one (Enria *et al.*, 1996). Clinical and pathological findings has been suggested by a report of 3 cases of severe European Puumala hantavirus infection were similar to those found in American hantavirus patients and met the HPS case definition (Rasmuson *et al.*, 2011). In the United States the main reason of HPS is the infection with the SNV. But in some isolated locations, a handful of other Hantaviruses have also been implicated. Since 1993, when the HPS was described, in other countries of western hemisphere discovery of several new hantaviruses has been done because of the awareness and heightened surveillance. Sigmodontinae rodents are reservoirs of Hantavirus, which cause HPS, however they are asymptomatically infected.

**Table 1:** Geographical distribution and their rodent hosts of Hantavirus (These data adapted from Muranyi *et al.*, 2005)

| Types | Serotypes of virus | Rodent reservoir | Geographical distribution |
|---|---|---|---|
| **New world Hantavirus (North America)** | SNV | *Peromyscus maniculatus* | North America |
| | Black Creek Canal (BCCV) | *Sigmodon hispidus* | North America |
| | New York | *Peromyscus leucopus* | North America |
| | Bayou (BAYV) | *Oryzomys palustris* | North America |
| **New world Hantavirus (South America)** | Araraquara | *Bolomys lasiurus* | South America |
| | Choclo | *Oligoryzomys fulvescens* | South America |
| | Leguna Negra | *Calomys laucha* | South America |
| | Oran | *Oligoryzomys longicaudatus* | South America |
| | Lechiguanas | *Oligoryzomys flavescens* | South America |
| **Old World Hantaviruses** | PUUV | *Clethrionomys glareolus* | Europe ,Russia, Scandinavia |
| | HTNV | *Apodemus agrarius* | Russia, Korea |
| | Tula (TULV) | *Microtus arvalis* | Europe |
| | Thottapalayam (TPMV | *Suncus murinus* | South India |
| | Amur | *Apodemus peninsulae* | South east Siberia, China, Japan |

In Argentina, the first outbreak of HPS cases was reported since September through December of 1996 in the southern Andean city of El Bolson, a ski resort nestled in the Andes Mountains. During this outbreak, 18 cases occurred and 3 of these were three doctors who treated patients with the disease and who became ill (Wells *et al.*, 1997). During the period of 1996 to 2001, 324 cases of HPS had been reported by the Argentina Health Ministry. Of these, 138 cases came from provinces of the north (Salta and Jujuy), 124 were from the central region (Buenos Aries and Santa Fe), and 62 were from the south of the country (Chubut, Neuquen and Rio Negro). The mortality rate reached 30 % between 1996 and 2001 (Calderon *et al.*, 1999).

Outside the United States, the first cluster of HPS cases occurred in Paraguay from July 1995 through January 1996. In the western part of Paraguay, 17 cases of HPS caused by Laguna Negra Virus (LANV) were confirmed. In Paraguay, there have been over 125 cases since the first outbreak of HPS in 1996 and 1997 (Williams *et al.*, 1997).

In Coyhaique Health District of the Aysen region of Chile, a cluster of 25 HPS cases was recognized between July 1997 and January 1998 (Toro *et al.*, 1997). There were three children with petechiae, one of whom died from hemorrhagic pulmonary secretions and bleeding from puncture sites (Ferres and Vial, 2004). In Chile, the first HPS case was described in 1995 (Baro *et al.*, 1999). In different zones of Chile, 485 cases have been reported through 2006, with a 37% mortality rate, which confirms the prediction that the disease may appear throughout the geographic distribution of the rodent reservoir (Navarrete *et al.*, 2007).

The first outbreak of HPS in Panama, with 12 cases and a 25% case fatality rate, occurred in 1999 to 2000 in Los Santos (Bayard *et al.*, 2004, Vincent *et al.*, 2000). Sequence analysis of virus genome showed that this virus to be a novel hantavirus, Choclo virus. In Uruguay, the first three HPS cases were reported in the area bordering Brazil (Ministry of Health of Uruguay) in 2004. Lechiguanas virus (LECV) and Andes Central Plata virus, two closely related hantaviruses, are associated with HPS (Delfraro *et al.*, 2003) and carried by *Oligoryzomys flavescens*. However, a Juquitiba virus (JUQV) in Uruguay, carried by two rodent species, *Oligoryzomys nigripes and Oxymycterus nasutus* (Delfraro *et al.*, 2008).

In Brazil, the first HPS case, caused by JUQV, occurred in the southeast in 1993, and about 66% of the patients had a fatal outcome (Vesconcelos *et al.*, 1997). Through April 2009, about 1,145 HPS cases were reported in Brazil with a 39.5% fatality rate and were caused mostly by 5 lineage of hantaviruses: Araraquara, Araucaria strain, LANV, Castelo dos Sonhos, and Anajatuba viruses (Johnson *et al.*,1999, Mendes *et al.*, 2004) . In the central plateau and southeastern regions, the fatality rate for HPS caused by Araraquara virus (ARAV) (44.5%) was significantly higher than the southern regions caused by JUAV (32.5%, 126 death out of 387 cases). These results suggest that ARAV strain may have higher virulence than JUQV or other hantaviruses in Brazil (Figueiredo *et al.*, 2009). In the cerrado region, 70 Brazilian patients were having HPS caused by ARAV, the disease inflicted mostly males (75.7%), 35.8 years old with a 54.3% case fatality. In other places of northwestern and northeastern Brazil, the HPS cases and serological evidence of human hantavirus infection have been reported and are likely to be caused by other novel genotypes of hantaviruses (Figueiredo *et al.*, 2003, Suzuki *et al.*, 2004, Figueiredo *et al.*, 2009).

*Hantaviruses research in India*

In 1966, the first hantavirus species, Thottapalayam virus (TPMV) was isolated from the spleen of a shrew (Suncus murinus). Initialy it was suspected as an arbovirus but later stage proved as a member of the Bunyaviridae family based on serological studies and electron microscopic observation (Zeller *et al.*, 1989). Later during a case study, it has been found that 14.7% of individuals with febrile illness were positive for anti-hantavirus IgM and 5.7% of healthy blood donor samples tested were positive out of 152 serum samples (Chandy *et al.*, 2005). These findings suggested the presence of Hantavirus infection as symptomatic or asymptomatic infections in the Indian population. In a case study from Western India, hantavirus infection has been reported as ocular involvement which include transient myopia, conjunctival hemorrhages, low intraocular pressure and intraocular dimension changes. Eleven patients (ten males and one female, mean age 37.6 years) had been subjected to the intensive care for pyrexia or hemorrhagic fever following exposure to flood water. Five male patients (mean age 31.6 years) had been identified as having hantavirus infection. In one patient, dot and blot intraretinal hemorrhages had been observed in the macula of one eye and streak hemorrhages of the disc in the other. No eye abnormalities had been observed in the remaining four male patients (Mehta *et al.*, 2007).

**Clinical course and Serological diagnosis of HPS**

The clinical course of the hantavirus affecting the host, passes through different stages with peculiar symptoms. The clinical course is divided into three periods: the febrile prodrome, cardiopulmonary stage and convalescence (Figure 3). After exposure it shows the 14 to 17 days incubation period followed by the 3-6 days prodrome phase with myalgia, malaise and fever of adrupt onset in the absence of coryza and cough.

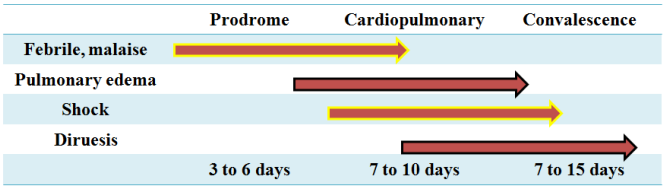


**Fig. 3:** Clinical course of hantavirus pulmonary syndrome.

The detection of the acute hantavirus infection and laboratory tests have to be primarily based on serology, since the viremia of this type of infections is short-termed and vRNA cannot be regularly detected in the blood or urine of patients in hospitals. Different types of serological diagnosis have been summarized in table 2.

**Table 2:** Laboratory test of Hantavirus pulmonary syndrome.

| | Platelets ⇧ | Hematocrit ⇩ | Aspartate amino transferase ⇧ | Lactic dehydrogenase ⇧ |
|---|---|---|---|---|
| **Prodrome (3 to 6 days)** | ± | ± | ± | ± |
| **Cardiopulmonary (7 to 10 days)** | ++++++ | +++++ | +++++++++ | ++++++++ |
| **Convalescence (7 to 15 days)** | | +±± | | |

**('±'** = not significant, '+' = significant)

**Pathophysiology and Immune response in HPS**

In HPS, hantavirus virion attacks the host cells to replicate itself. The virion attaches to a receptor on the cell surface and the binding event induces endocytosis signaling, after which the virion enters the cell in clathirin-coated vesicles (Vaheri *et al.*, 2013). They replicate inside the cell and via transport vesicle they are transported to the plasma membrane for release (figure 4). At the plasma membrane the egress of progeny virions takes place. Finally progeny virions leave the cell and get ready to attack other cells.

HPS is characterized by hantavirus-induced vascular leakage due to alterations of the endothelium barrier. The pathogenesis models have been focused either on the influx of immune cells and release of cytokines or on increased adherens junction protein degradation, vascular endothelial (VE)-cadherin, due to hantavirus-mediated hypersensitization of endothelial cells (EC) to vascular endothelial growth factor-A (VEGFA). Novel mechanism of vascular leakage involves the plasma kallikrein-

kinin system (KKS) activation. In a experiment, it has been found that the incubation of the plasma proteins factor XII (FXII), prekallikrein (PK), and high molecular weight kininogen (HK) with hantavirus-infected EC results in increased HK cleavage, higher enzyme activities of FXIIa/kallikrein (KAL) and increased bradykinin (BK) liberation, then identified dramatic increase in EC permeability after KKS activation and liberation of BK (Figure 5) (Vaheri *et al.*, 2013, Taylor *et al.*, 2013).

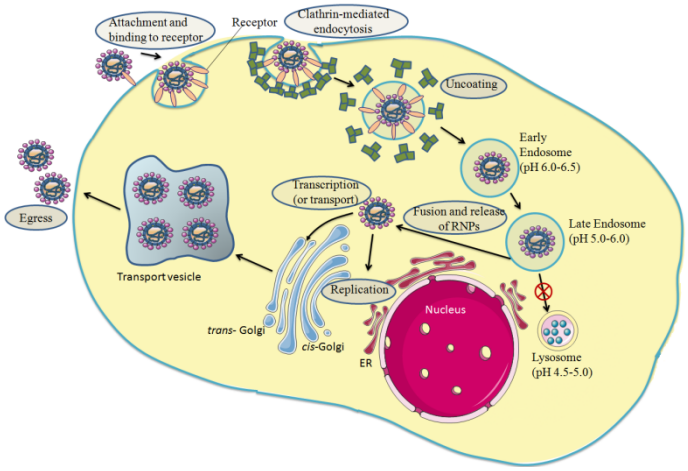


**Fig. 4:** The life cycle and replication of hantavirus.

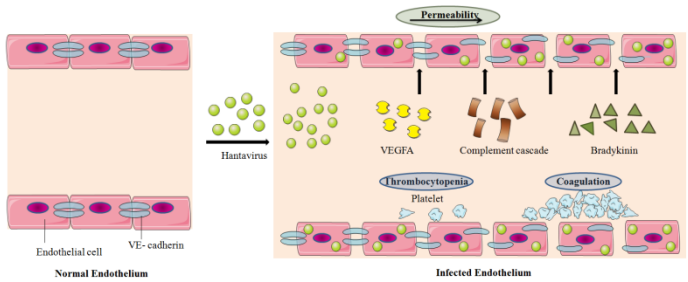


**Fig. 5:** Vasculopathy in hantavirus-mediated diseases.

In hantavirus-mediated diseases, various hypothesis have been presented to explain the thrombocytopenia, intravascular coagulation and vascular permeability. A hantavirus infected endothelial monolayer owing to vascular endothelial growth factor A (VEGFA) upregulation, which downregulates the adherens junction protein, VE-cadherin. The platelets interact with infected endothelial cells and hantavirus glycoproteins, and this might be the cause of thrombocytopenia. Systemic intravascular coagulation, caused by hantavirus infection , may also contribute to thrombocytopenia (Taylor *et al.*, 2013).

The basic lesion is increased pulmonary capillary permeability which is the major cause for the severe pulmonary edema. Here, an immunologic mechanism is considered to play a very important role (figure 6). The macrophages and lymphoblasts cells recruits to pulmonary tissue can provoke a lymphokine-mediated activation of vascular endothelium by the high viral burden. The endothelium forms the primary barrier within the vasculature, and dysregulation of endothelial cell functions can cause a wide variety of vascular effects that lead to changes in vascular permeability. In order to enumerate cytokine-producing cells (interleukin [IL-1α, IL-1β, IL-6] and tumor necrosis factor [TNF-α], lymphokines [interferon-γ, IL-2, IL-4, and TNF-β]) in tissues obtained at autopsy from subjects with HPS, a technique i.e. Immunohistochemical staining is generally used (Mori *et al.*, 1999).

The tissues of lung and spleen of HPS patient possesses high numbers of cytokine-producing cells. These results suggest that local cytokine may play an important role in the pathogenesis of HPS. The patient's lung CD8+T cells are present in infiltrated alveolar walls. Patients with severe disease have shown higher frequencies of viral-specific CD8+T cells than the patients with moderate disease in their peripheral blood mononuclear cell (PBMC) samples (Kilpatrick *et al.*, 2004). The impairment of the defense mechanism of endothelial cells against cytotoxic CD8+T cells may be the mechanism of capillary leakage (Terajima *et al.*, 2007).

Probably active suppression of immune T regulatory cells is involved in HPS pathogenesis. Hantaviral antigen has been observed in the cardiac endothelium and interstitial macrophages in association with atypical myocarditis in HPS. These findings support the statement that myocardial depression and HPS shock may be caused by structural changes (Saggioro *et al.*, 2007). HPS shock is may be related to an exacerbated immune response of CD8+T cells producing cytotoxicity on the infected endothelial cells (Abel and Figueiredo, 2008).

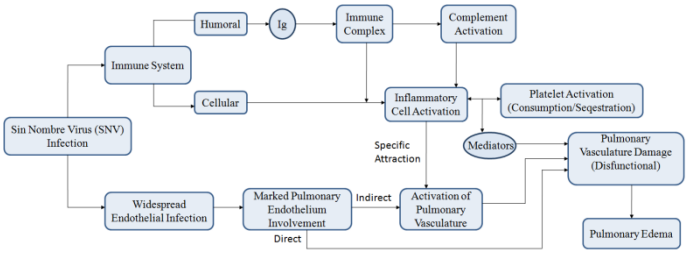


**Fig. 6:** Flow Diagram of possible mechanism of pulmonary edema in patients with HPS.

## Symptoms

HPS begins after about two weeks of initial infection. Rodent exposure is most commonly observed as peridomestically. The illness starts with fever and severe myalgia involving the muscles pain particularly in the thighs and lower back. Gastrointestinal disturbances and abdominal discomfort may be noticed in some of the cases. Generally dizziness is reported as early symptom.

Various typical symptoms such as pharyngitis and rhinorrhea are generally absent in this case. The patient develops respiratory symptoms after about 4-5 days later (range of 1-10 days) that usually consist of modest cough and dyspnea and then can leads to hospitalization because of rapid deterioration (Armstrong *et al.*,1995).

HPS is a severe disease characterized by pulmonary edema followed by cardiogenic shock and respiratory failure. In some patient, the tachycardia may be found occasionally.

Tachypnea is common in HPS. Patients having full-blown HPS appear ill with severe ventilatory insufficiency (Raboni *et al.,* 2005).

**Treatment**

Treatment of HPS requires invasive hemodynamic monitoring with an arterial line and a pulmonary artery catheter and intensive support (Jonsson *et al.,* 2008). Treatment initiated after the onset of severe respiratory distress is less likely to favorably impact the outcome. During the period of severe respiratory insufficiency mechanical ventilation could be necessary to survive. Excess fluid administration should be avoided despite the fact that patients may be hypotensive and hemo-concentrated. Because of increased vascular leak of fluid into the lungs overzealous fluid administration can aggravate respiratory insufficiency. To correct hypotension, early use of pressors is recommended.

For patients with refractory shock extracorporeal membrane oxygenation may be considered. In a report, about two third of the patients having severe HPS, with predicted mortality of 100%, were supported with extracorporeal circulation survived and completely recovered (Dietl *et al.,* 2008).

For HPS no specific treatment is available. Treatment with intravenous ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) i.e. a guanosine analog, did not confirm the promosing results (Chapman *et al.,* 1999, Chapman *et al.,* 2002, Maes *et al.,* 2004) Recently, it has been found that ribavirin inhibits the hantavirus progeny production in vitro. Incorporation of ribavirin into nascent RNA results in high mutation frequencies (9.5/1000 nucleotides) and hence synthesize the transcriptionally defect vRNA ( Severson *et al.,* 2003).

The study showed that the susceptibility of hantavirus RdRp to drugs leads to error catastrophes during the viral replication cycle. These insights allow new strategies for the therapeutic procedures development which comprise the incorporation of lethal mutations during hantavirus replication (Jonsson *et al.,* 2005). Hyperimmune serum may offers a promising future therapy because survival is correlated with higher neutralizing antibody titers at admission.

As previously described hantavirus-infected endothelial cell (EC) are responsible for KKS activation resulting in liberation of BK, an inflammatory peptide, have the potential to induce vascular permeability, edema formation, and hypotension. Excess liberation of BK causes the alterations in EC permeability. Furthermore, the EC permeability alterations could be prevented using inhibitors that directly block BK binding, the KAL activity, or the FXIIa activity. Through *in-silico* drug designing, those inhibitors could be designed using different tools and data collected from previous experiments could have profound implications for treatment of hantavirus infections (Kleinberg and Wanke, 1995, Taylor *et al.,* 2013).

**Prevention**

To limit this fatal disease, preventive strategies play a critical role. To decrease the risk of HPS, the foremost effective approach is to check human exposure to infected rodents and peridomestic exposure should be limited. Other approaches include eliminating rodents in and around households by controlling rodent populations using traping box and rodenticides, keeping areas clean; rodent-proofing dwellings; cleaning areas of infestation; and avoiding rodents in outdoor settings. In epidemic areas, vaccines are being studied for the prevention of Hantavirus infection (Park *et al.,* 2004).

According to a study of an inactivated Hantavirus vaccine, a significant Hantavirus antibody titer was developed in 79% of the 64 human volunteers after 30 days of vaccination (Cho and Howard, 1999). One month after the booster dose, Seroconversion rates increased to 97%. By one year, antibody titers were declined, but in almost all subjects, a vigorous immine response occurred with revaccination. However, neutralizing antibodies were produced in only 50% of the subjects one year after the booster dose. For HPS, improved vaccination is needed.

Now days, drugs for the treatment of this deadly disease can be developed by using various tools, databases, softwares and methods under *"in silico"* drug designing. *In silico* methods can help in identifying drug targets via bioinformatics tools (Kleinberg and Wanke, 1995). They can also be used to analyze the target structures, generate candidate molecules, check for their likeness for drugs, dock these molecules with the target, rank them according to their affinities regarding binding, further optimize the molecules to improve binding characteristics (Wanke and DuBose, 1998).

## CONCLUSION

HPS "emerged" as a new deadly viral hemorrhagic disease during the spring of 1993, caused by hantaviruses, and within weeks, the clinical illness and etiologic agent were characterized, the rodent host was identified and new diagnostic assays were developed. The retrospective diagnosis of case-patients from early as 1959 reveals that human hantavirus infections occurred previously and resulted in HPS, indicates that it is not new to the United States but went unrecognized until May 1993.

The extreme manifestations include increased capillary permeability (causing vascular leakage), circulatory instability, diffuse hemorrhage and thrombocytopenia. Virus infects the endothelial cells but does not disrupt the endothelium but leads to dramatic changes in both the function of infected endothelial cells and barrier function of endothelium. It has also been observed that capillary leakage is triggered by cytotoxic CD8+T cells (CTLs) and that cytokines contribute to the increased capillary permeability.

Vascular permeability can also be increased by terminal soluble complement complex and this complement activation is linked to severity of hantavirus infection. There is still a long way to go to find an effective treatment for this deadly disease, and the long-term prognosis of hantavirus infection and the pathogenicity

of certain virus species remain to be established. A better understanding of viral biology and pathophysiology could lead to more specific and effective therapeutic modalities in the future.

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