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# Hantavirus Infection and Its Current Information as Emerging Pathogens: A Review

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**Abstract:** *Hantavirus is a rodent-borne pathogen that has been well characterized since 1950s in Asia and Northern Europe. These viruses are responsible for two different types of clinical symptoms viz Hantavirus pulmonary syndrome (HPS) also known as hantavirus cardiopulmonary syndrome (HCPS) caused by New World (Americas) viruses and hemorrhagic fever with renal syndrome (HFRS) caused by Old World (Asia and Europe) viruses in humans. These viruses belong to genus Hantavirus & family Bunyaviridae. The serotypes Hantaan (HTN), Seoul (SEO), Puumala (PUU), and Dobrava (DOB) virus predominantly cause HFRS, a disease characterized by hemorrhages, renal failure and shock. Newer serotypes of Hantavirus which are highly pathogenic to humans are regularly being reported recently. No antivirals, vaccines, or immunotherapeutics approved by FDA exist for these viruses. This review presents a brief overview of Hantavirus biology, structure, functions of the key viral proteins, the medical features of HFRS and HPS, and their prevention.*

**Keywords:** *Hantavirus, Hantavirus pulmonary syndrome (HPS), hemorrhagic fever with renal syndrome (HFRS), N protein, glycoprotein, RNA polymerase*

## I. INTRODUCTION

Hantaviruses belongs to genus Hantavirus & family Bunyaviridae. These are enclosed tri-segmented negative-stranded RNA viruses cause varying disease worldwide. Genome of Hantavirus is comprised of three segments of different size viz small (S), medium (M), and large (L) of single stranded negative sense RNA. Viral polymerase encoded by L segment while S and M segments encode the nucleocapsid (N) protein & a precursor for two viral surface glycoproteins (G1 and G2, or alternatively called Gn and Gc), respectively [1].

Hantaviruses are emerging zoonotic virus & people are incidental hosts. Approximately more than 40 species of Hantavirus are presently recognized.

These viruses are responsible for two different types of clinical symptoms viz Hantavirus pulmonary syndrome (HPS) also known as hantavirus cardiopulmonary syndrome (HCPS) caused by New World (Americas) viruses and hemorrhagic fever with renal syndrome (HFRS) caused by Old World (Asia and Europe) viruses in humans [2,3]. In European and Asian continents HFRS occurred endemically in the 20<sup>th</sup> century, while HPS was clinically recognized since 1993 [2].

Several different Hantaviruses are known to infect humans. Puumala virus (PUUV) is the most common carried by the bank vole and two other genetically close; Saaremaa viruses (SAAV) and Dobrava-Belgrade (DOBV) are carried by Apodemus mice. DOBV causes severe symptoms and high case fatality rate while SAAV and PUUV cause mild disease [4]. In case of HFRS the mortality rate vary from 0.3 to 10% & for HCPS it varies between 30 to 40 % [5,6&7]. In developing countries approximately 150,000 to 200,000 hospitalized cases are found each year worldwide for HFRS. Case fatality rate may be variable from 1% to 12% depending on the virus infection for HFRS. Average 40 % case fatality rate is found in America with nearly 200 HPS cases per year. HFRS is higher in number than HPS.

Now a days Hantavirus is a global health problem as its infection has spread worldwide due to several new strains identified for this virus. Hantavirus showed asymptomatic, non-specific mild infection and the lack of laboratory diagnostics in hospitals especially in developing countries. Rodents of the family Muridae, subfamily Sigmodontinae (rats and mice) hosted the Hantaviruses that cause HPS [8, 9]. During research the incidence of Hantavirus infection in the population who live in the harbor on the Batam island and Makassar has been reported in Indonesia in 2002. [10].

The outbreak of HFRS occurred during Korean War among U. S. soldiers in the 1950 [11,12]. The subsequent appearance of HCPS/HPS in South America is due to complex distribution and diversity of Hantaviruses; around fifty percent are pathogenic to humans from more than 40 Hantavirus genotypes discovered [14]. Pathogenic Hanta viruses cause devastating diseases in humans with mortality rates from 12% HFRS to 40% HCPS [13,14].

## II. HANTAVIRUS PATHOGENESIS

In both human and animal hantavirus infections, the viral antigen is present in many different organs but predominantly in pulmonary or renal endothelial cells and macrophages [15,16]. The pathogenic (Puumala virus PUUV, Sin Nombre virus SNV, Seoul virus SEOV, Hantaan virus HTNV) and non-pathogenic (Prospect Hill virus, Tula virus) Hantaviruses infect human endothelial cells using different integrin receptor. [17,18]. In territory of Poland, there are at least 6 species of rodents, which could act as hosts for Hantaviruses. One of the most common is the bank vole (*Myodes glareolus*), natural reservoir of the PUUV as well as a house mouse (*Mus musculus*). Studies on the prevalence of antibodies against Hantaviruses among mammalogists, who are occupationally exposed to rodents, showed the presence of antibodies in 26% of studied population [19]. Urban cases of HFRS in some Asian cities have been associated with SEOV, including epidemics of the disease. Prospect Hill virus (PHV) or SEOV has not been associated with outbreaks of Hantavirus disease in the United States, but some person got infected with SEOV mild disease [20].

## III. ROLE OF PROTEIN

N protein molecules coat all the viral RNA segments & forms the ribonucleoproteins (RNPs) to protect viral genomic DNA from degradation by cellular nucleases [21]. A lipid bilayer envelope consisting of G1 and G2 surface glycoproteins enclosed N protein. Glycoproteins encoded by the M segment are essential for viral entry into the host cell by interacting with  $\beta_3$ -integrins, specific cell surface proteins followed by endocytosis [21,22].

Surface glycoproteins G1 and G2 of Hantavirus are expressed as a polyprotein precursor, which yield mature G1 and G2 glycoproteins after cleaving by cellular protease during translocation to ER [23,24]. In case of pathogenic hantaviruses the G1 cytoplasmic tail inhibit IFN- $\beta$  transcription by binding to TRAF3. TRAF3 is required for IRF3 (Interferon regulatory factor 3) phosphorylation, which is essential in IFN $\beta$  induction [25]. Glycoprotein Gn tail play a role for virus assembly by binding to the ribonucleoprotein (RNP).

The viral RNA polymerase possesses replicase, endonuclease and transcriptase functions, thus it carries out both virus transcription and replication. Viral RNA polymerase forms capped primers by cleaving cellular mRNA & start transcription of viral mRNAs.

Hantavirus N protein required for encapsidating viral RNA, as well as regulating virus replication and assembly. Hantavirus N protein prevents phosphorylation of protein kinase R (PKR) which is responsible for establishing antiviral state as PKR inhibits virus replication [26].

The N protein interfere the antiviral pathways activation of infected cells by interacting with host proteins [27]. As there is unavailability of matrix protein, it showed a direct interaction between cytoplasmic tails of G1 and G2 and N protein. The zinc finger domain formed by a part of the G1 tail, plays a role in virus assembly [28]. N protein also interacts with one of the glycoproteins & the virus polymerase (L protein).

In order to survive, virus escapes itself from host innate immune response by inhibiting pathways which activate type I IFN transcription. [29,30].

## IV. CASE REPORT OF HANTAVIRUS

In 1993, the route of person-to-person transmission is a rodent-borne zoonosis which was first recognized in the United States [31]. During 1996 the person-to-person transmission of a Hantavirus was first confirmed in the outbreak of HPS in southern Argentina, where Andes virus was endemic. Epidemiologic evidence confirmed the Hantavirus pulmonary syndrome in the outbreak of 20 reported cases in Argentina.

The possibility of initiating secondary cases was 4% for patients who survived than 41% for those who died. Person-to-person transmission of Andes virus infection should be considered even when rodent exposure cannot be excluded [32]. Since 1993 more than 1,080 cases of HPS have been confirmed in Brazil with case-fatality rate 40%. In Minas Gerais state the higher number of HPS cases (209) is reported than in any other state in Brazil [33]. A Hantavirus known as Araraquara virus was identified in molecular biology studies in associated with HPS cases in Minas Gerais state. The wild rodent *Necromys lasiurus* (the hairy-tailed bolo mouse, also named *Bolomys lasiurus*) was implicated as a reservoir of this virus [34].

The outbreak of Hantavirus disease involving 9 human cases was registered in 2007 in Podkarpackie province in Poland [35]. Andes virus-associated HPS outbreak of 25 cases was recognized in southern Chile in between 1997 to January 1998. Person-to-person transmission suggested by epidemiologic studies in two of three family clusters. Some Hantavirus infection with host species worldwide is given in table 1.



Table 1. Hantavirus infection with host species

S.N.	Country	City	Age	Year	Implicated Host Species	References
1	America	Chester Mexico	10 above	1993	Unknown	Galeno et al., 2002 Godoy et al., 2009
2	Argentina	Mendoza	10 above	1993	Unknown	Schmaljohn et al.,1997
3	India	Tamil Nadu Mumbai	12-70	1993	Unknown	Chandy et al., 2008
4	Indonesia	Jakarta	10 above	1994	Rattusnorvegicus Rattusrattus	Jonsson et al., 2008 Plyusnina et al., 2009
5	Sri Lanka	Kandy	13-74	1988	Rattus spp.	Gamage et al, 2011
6	Nepal	Kathmandu	80 below	1993	Unknown	Murphy et al., 2002
7	Singapore	Singapore	20-45	1977	Rattusnorvegicus	Jonsson et al., 2008
8	Myanmar	Yangon	5 above	1994	Unknown	Lee,et al., 1999
9	Malaysia	Kuantan	60 below	1985	Rattus spp.	SK, et al., 2001

## V. DIAGNOSIS AND TREATMENT

HFRS and HCPS diagnosis is depend upon epidemiological & clinical data and laboratory tests.

The symptoms like high fever, abdominal pain, back pains and pathological laboratory findings with increased serum creatinine, haematuria, proteinuria, thrombocytopenia, and leucocytosis confirmed for possible hantavirus infection. In case of moderate & mild infection the early sign of disease are non-specific hence it is difficult to diagnose Hantavirus infection in early stages. [15,2]. The symptomatic treatment of the infection is primarily based on either HCPS or HFRS.

At present, no specific U.S. Food and Drug Administration approved therapy is available. It is recommended that patients should be moved to an intensive care unit for close monitoring and care with HCPS and severe HFRS. Circulatory volume is very important and must be carefully monitored according to the patient's fluid status. The fluid and electrolyte balance must be maintained with amount of diuresis and kidney function to avoid dangerous over hydration (for patients that are anuric and with leaky capillaries). Dialysis treatments may be needed for HFRS patients with severe renal insufficiency, which is associated with severe fluid retention and pulmonary oedema [41,46&47].

## VI. PREVENTIVE MEASURES AND VACCINE SCENARIO

Many efforts have been done to establish a Hantavirus specific vaccine using inactivated Hantaviruses and passive immunization. Extensive experimental approaches were performed for the investigation of hantavirus specific DNA-vaccines, recombinant hantaviral nucleocapsid proteins, recombinant hantaviral glycoproteins, expression of viral nucleocapsid proteins in transgenic plants, and generation of human recombinant neutralizing antibodies against Hanta viral glycoproteins by phage display technology [48]. The drug 1-s-D-Ribafuranosyl-1,2,4-triazol-3-carboxamid known as Ribavirin has shown to be effective as a viral inhibitory factor for hantaviruses. A pharmaceutical research in combination with new facilities for the detection of specific mechanisms determining virus-cell interactions on a molecular level are promising and can lead to the detection of a specific treatment against hantavirus infections in the near future [49].

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