

A Brief Overview Of Hantavirus Infections

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DOI: 10.47750/pnr.2023.14.502.202

Abstract

Hantaviruses belong to the Bunyaviridae family as a separate genus. It is currently known that there are over 20 serogenotypes/seroserotypes and that a number of new types are under investigation. The types of Hantaviruses which infect rodents tend to be specific to specific hosts and are primarily found in specific rodent species. As a result of the various types of Hantaviruses and their target organs, Hantaviruses can cause a variety of diseases. There are two major diseases in the world: hemorrhagic fever with renal syndrome (HFRS) and hemorrhagic fever with the syndrome (HPS). A new strain of Hantavirus has been observed in progressively increasing numbers within the world as a result of an accelerating increase in Hantavirus cases throughout the world, which represents an issue of public health of great concern across the globe. Hantavirus disease is a relatively new disease, however, its spectrum continues to expand as the number of recognized virus types continues to rise. It has been reported that Hantavirus causes human disease in the British Isles, but at this point, the disease is largely unknown. Hanta viral infection may be underestimated, especially in developing countries, due to its mild asymptomatic nature and lack of standardized laboratory diagnosis in hospitals. There are no simple standardized laboratory diagnoses in hospitals due to its asymptomatic and non-specific nature. Presented is an overview of what is currently known about hantaviruses and hantavirus infections, including their properties, classification, laboratory diagnostics, treatment, and prevention.

Keywords: hemorrhagic fever, renal syndrome, Hantavirus, rodent

INTRODUCTION:

An enveloped single-stranded negative-sense RNA virus, Hantavirus belongs to the Bunyaviridae family. Rodent excreta are normally inhaled by humans when they are transported between rodents and inhaled by rodents.¹ The hantavirus breeds recurrent infections in the rodents of the families Muridae and Cricetidae, which are naturally infected by the virus.² It causes several diseases in humans, including the Hantavirus (cardio) pulmonary syndrome and hemorrhagic fever with renal syndrome. Each year, there are between 60,000 and 100,000 cases of HFRS reported in China.³

Generally speaking, Seven Hantavirus sero/genotypes have been reported in China, out of which 2 of these viruses are responsible for HFRS, namely the Hantaan virus carried by *Apodemus agrarius* mice and the Seoul virus transmitted by *Rattus norvegicus* rats.⁴ A serious public health issue continues to plague China with HFRS. The rodents usually become infected with them, but they are not afflicted with any diseases by them. It was first identified in Russian clinical records from far eastern Siberia in 1913 that hemorrhagic fever with renal syndrome (HFRS) was a human viral disease. An account of a similar disease written by Ho Wang Lee (1982) dates back to the year 960. *Apodemus agrarius*, a murid rodent, has been found to get chronic infections with urinary excretion caused by HFRS as part of its unique renal complications.⁵

There are many areas in Central and Northern Asia where this mouse is one of the more commonly found wild rodents, and it can sometimes be found in cultivated fields, gardens, haystacks, even in humans' homes. There has been considerable work done to understand how social conflict is associated with HFRS and how it evolved clinically, epidemiologically, and ecologically in recent decades.⁶ The Hantavirus that has now been found in western Europe and Scandinavia may have caused both Allied and German field nephritis in Flanders during World War I (Bradford 1916; Arnold 1944). As a result of their invasion of Manchuria (Kitano 1944), Japanese military doctors discovered the disease in the mid-1930s, and during World War II, Finnish and German troops contracted the disease (Stuhlfauth 1943; Hortung 1944), and during the Korean Conflicts in 1951 (Smadel 1953), UN forces discovered the original and actual hantavirus.⁷

A LIST OF HANTAVIRUS PROPERTIES IS AS FOLLOWS:

As a structure:

These are negative-sense trisegmented RNA viruses with enveloped structures. RNA-dependent RNA polymerase (L), medium (M) and small (S) segments encode for glycoprotein precursor (GPC) and nucleocapsid (N) proteins, which are respectively processed into the envelope glycoprotein (G_{nan}G_c) and the nucleocapsid (N) protein.⁸

Protein N of the Hantavirus:

It is the Hantavirus N protein that forms the largest proportion of viral proteins in infected cells and virions. The immune system responds strongly and rapidly to this protein. N proteins contain 100 amino acids at their amino-terminus, making them extremely antigenic¹⁴. Proteins have B-cell epitopes at their N-termini, while T-cell epitopes are randomly distributed throughout the protein. A given Hantavirus strain of a particular serotype tends to maintain its amino acid sequence in relation to different strains of the same serotype of Hantavirus. Several expression systems can be used to develop recombinant N proteins for commercial use, including *Escherichia coli*, baculovirus and yeast expression systems. Whenever diagnostic tests are carried out, recombinant proteins are used instead of native proteins.⁹

Glycoprotein of the Hantavirus:

G1 and G2 surface glycoproteins are composed of polyprotein precursors, GPCs, that are degraded by proteases within the cell. In addition, these glycoproteins interact with the surface receptors, β_3 integrins and promote entry of hantaviruses.¹⁰

There are several types of Hantaviruses:

Based on the phylogenetic analysis of their N protein, hantaviruses can be divided into four main groups:

- ❖ The following viruses are classified into Group A: Murinae (HFRS-causing species), HTNV, Seoul virus (SEOV), Thailand virus (THAIV), and Dobrava/Belgrade virus (DOBV).
- ❖ Group B: *Arvicolinae*-borne species such as Puumala virus (PUUV), a mild form of HFRS in Europe caused by *Nephropathia epidemica* (NE).
- ❖ Group C: *HCPS-causing species in the Americas that are from the Sigmodontinae and Neotominae*

The species borne by shrews, moles, and bats are included in Groups D and E.

TPMV occupies a special place in the history of Hantavirus research. In 1964, Vellore, South India, discovered the first Hantavirus isolate from an inspector. Hantaviruses, originally thought to be arboviruses, were finally recognized to be not only rodent-borne.¹¹

CLINICAL SYNDROMES ASSOCIATED WITH HANTAVIRUS:

Hemorrhagic fever associated with renal syndrome

Five stages of clinical manifestation were identified: febrile, hypotensive, oliguric, polyuric, and convalescent. Incubation period of this virus can last anywhere between 2-4 days, and from there, it can manifest itself into symptoms such as aches and pains in the abdomen, headaches, vomiting, nausea, stomach pains, backaches and vision disturbances that can last up to 3-7 days. There may be conjunctival suffusion as well as petechiae on the palate at the end of this process. For the hypotensive (shock) period, the time range can range from a few hours to two days.¹²

Hantavirus cardiopulmonary syndrome:

The severity of this condition is greater than that of HFRS. Fever, chills, malaise, headaches, gastrointestinal discomfort, vomiting, stomach pain and diarrhea are some of the prodromal symptoms. Cardiopulmonary and convalescent symptoms are described as convalescent.¹³

Diagnosis by laboratory tests:

It is important to understand that HFRS and HCPS29S exhibit the same significant laboratory findings. These include: thrombocytopenia, leukocytosis, elevating hematocrit, haematuria, proteinuria, and serum creatinine. The early clinical signs of Hantavirus infections cannot be diagnosed, since these infections are nonspecific. Serology is the principal method of diagnosing Hantavirus infections. It is almost always the case that anti-hantavirus IgM and/or IgG antibodies are present when symptoms first begin to appear.¹⁴

Transmission and Epidemiology:

Insectivores (*Suncus murinus*) and rodents from the subfamilies Murinae, Arvicolinae, and Sigmodontinae all tested positive for Hantaviruses. HNTV, DOBV, SAAV, SEOV and Amur viruses are the most common hantaviruses related to HFRS and non-human diseases.³¹ Murinae are the most common rodent species of the Old World. As with Prospect Hill virus and other viruses in the United States, there is a correlation between PUUV and HFRS in Europe, but not for human infections.¹⁵

There are several viruses from the New World that are transmitted through the species of rats and mice called Sigmodontinae, which are widespread throughout the New World. In each subfamily of rodents, there is a phylogenetically distinct virus, some of which may be human pathogens, while others may not be.¹⁶ There is a significant concordance between the phylogenetic relationships between the viruses and those of their dominant host (with rare exceptions), which shows a close association between the two. The majority of hantaviruses under study have their own

murid rodents host, except for TPMV, along with other newly discovered hantaviruses such as AVG, Ripley virus (RPLV), Tanganya virus (TGNV), and Cao Bang virus (CBNV). Hantaviruses, however, are not just found in insectivores like *Suncus murinus*; they have also been identified in bats, cats and birds, as well as other species of insectivores.¹⁷

The presence of hantavirus infection in dogs and pigs was also demonstrated by serological tests.¹⁸ The presence of these species is unclear and it is unclear whether they are persistently infected or if they are just spilling over infected secondary hosts after contacting the primary host.¹⁹

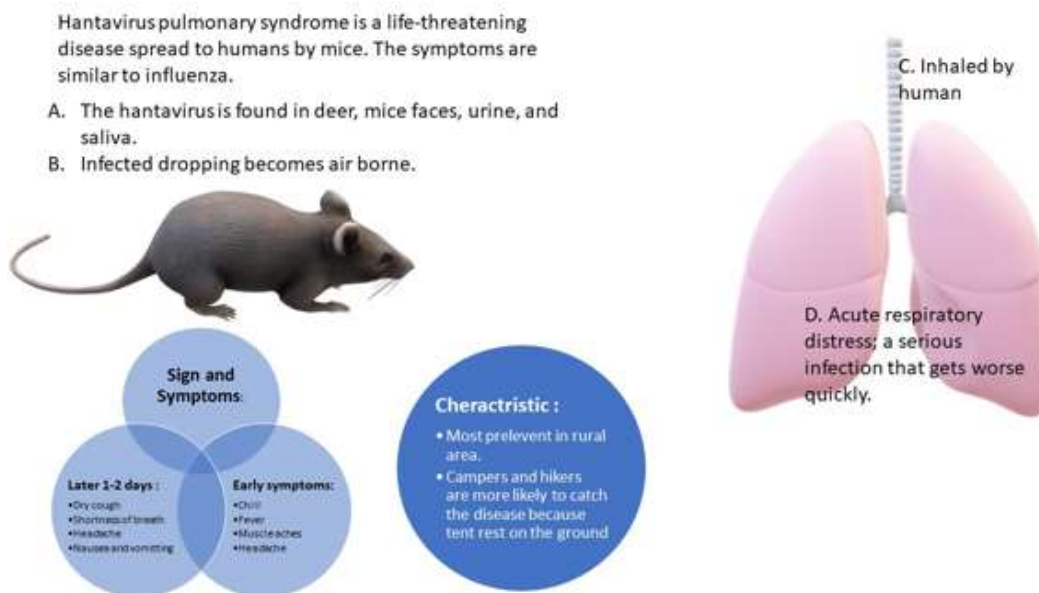
Transmitting:

Animal excreta, such as saliva, urine, and feces, are believed to be the primary transmission source of Hantavirus.²⁰ It is undoubtedly true that rodents and humans, as well as rodent rodents, are most commonly infected by aerosols. However, virus transmission by bite can also occur among rodents.²¹

The epidemiological features are as follows:

Rural areas have a greater prevalence of hantavirus infections, but urban areas have an increased prevalence of SEOV-induced HFRS. Hantavirus infections are underestimated due to asymptomatic or nonspecific mild infections.²² Some Hantaviruses can be found in Europe to have a ratio of 14:1 to 20:1 between subclinical and clinical infection. In Finland, HFRS cases averaged 13% per year in an eight-year study (ranging from 4% to 30% depending on the region).²³ According to these findings, as many as 70% of all cases of PUUV infection are underdiagnosed because of mild or subclinical symptoms that are associated with the infection.²⁴

Fig No. 1: Rodent borne disease



Management of clinical cases:

HFRS and HPS do not currently have specific treatments; therefore, supportive measures remain the cornerstone of treatment. Intensive care units that can monitor vital signs such as blood and tissue oxygenation, cardiac output, central blood pressure, and cerebral pressure must be immediately accessed. The balance of fluids must be maintained at all times.²⁵

The dosage of haemodialysis for HFRS patients normally requires one to two sessions, while for HPS patients, mechanical ventilation is considered to be essential when high pressures are indicated and sufficient ventilation is needed.²⁶ As a rescue therapy for severe HPS, extracorporeal membrane oxygenation has proven effective. In severe cases of HFRS and HPS, corticosteroids were used, although they are not standard treatment for hanta virus infection.²⁷

Diagnostic testing in laboratories:

Laboratory tests and clinical information are used to diagnose hantavirus infections. Hantavirus infection can be difficult to diagnose in individuals with mild to moderate symptoms.²⁸ In addition to native or purified virus preparations, the detection of hantavirus antibodies has also been accomplished using recombinant proteins produced by bacteria, yeast, and insects. Identifying IgM antibodies or low-avidity IgG antibodies usually involves indirect fluorescent analysis (IFA) and enzyme immunoassays (EIA).²¹ There are several methods for detecting IgM that can be used to detect acute infections, particularly in endemic areas where IgG is highly prevalent due to previous infections, which is highly useful for diagnosis of acute infections.²⁹

Studies conducted in laboratories:

The following serological techniques, PCR techniques, and immune histochemistry studies can support the diagnosis of Hantavirus pulmonary syndrome (HPS):

- Real-time PCR is one of the most commonly used tools to detect viral RNA in blood and tissues, and it is a standard of diagnosis. There has been reported a 100% specificity and a 94% specificity for diagnostic sensitivities, respectively.³⁰

The prevention and control of disease:

Vaccines for Hantavirus do not exist. You can reduce your HPS risk by taking the following steps:

- Make sure not to get into areas where rodents leave droppings.
- Protect your face and nose with latex gloves and goggles when exposed to mouse droppings.
- Sanitizing mouse dropping areas with disinfectants is one method that can be used to prevent the spread of contaminated dust into the air.
- Stop rodents from entering your home by sealing holes
- Capture rodents around your house in order to reduce the population
- Don't forget to take food with you when you go camping.
- Ventilate spaces suspected of containing rodents before entering them.³¹

CONCLUSION

There is no specific treatment for hantavirus infection, and the best way to prevent infection is to avoid contact with rodent droppings and to take precautions when cleaning areas where rodents have been present. The hanta virus infected patients if receive medical attention in an intensive care unit early and are diagnosed, we know they will do well.³² To assist patients undergoing extreme respiratory distress, intensive care facilities use incubators and oxygen therapy.³³

REFERENCES

1. Easterbrook JD, Klein SL. Immunological mechanisms mediating hantavirus persistence in rodent reservoirs. *PLoSPathog.* 2008; 23: 68-72. doi: 10.1371/journal.ppat.1000172
2. Bi Z, Formenty PB, Roth CE. Hantavirus infection: A review and global update. *J Infect Dev Ctries* 2008; 2: 3-23. DOI: 10.3855/jidc.317
3. Zeier M, Handermann M, Bahr U, Rensch B, Müller S, Kehm R, et al. New ecological aspects of Hantavirus infection: a change of a paradigm and a challenge of prevention—a review. *Virus Genes.* 2005; 30: 157–80. doi: 10.1007/s11262-004-5625-2.
4. Plyusnin A, Morzunov SP. Virus evolution and genetic diversity of Hantaviruses and their rodent hosts. *Curr Top Microbiol Immunol.* 2001; 256: 47–75. DOI: 10.1007/978-3-642-56753-7_4
5. Arthur RR, Lofts RS, Gomez J, Glass GE, LeDuc JW, Childs JE (1992) Grouping of hantaviruses by small (s) genome segment polymerase chain reaction and amplification of viral RNA from wild-caught rats. *Am J Trop Med Hyg* 47: 210–224. DOI: 10.4269/ajtmh.1992.47.210
6. Jonsson CB, Hooper J, Mertz G. Treatment of hantavirus pulmonary syndrome. *Antiviral Res.* 2008; 78: 162-9. DOI: 10.1016/j.antiviral.2007.10.012
7. Dhadde G.S, Yadav J.P., Sapate R.B, Mali H.S, Raut I.D, In vitro Anthelmintic Activity of crude extract of flowers of *Bougainvillea Spectabilis* Wild against *Pheretima Posthuma*, *International Journal of Pharmacy and Pharmaceutical Research*, 2020; 17: 1-18.
8. Dhadde Gurunath S.*, Mali Hanmant S., Sapate Rohit B., Vakhariya Rohan R., Raut Indrayani D., Nitalikar Manoj M., Investigation of In-Vitro Anthelmintic Activity of Methanolic Extract of *Tylophora Indica* Leaves Against *Haemonchus Contortus*, *Journal of University of Shanghai for Science and Technology*, 2021; 23(2): 37-42. DOI: 10.52711/2231-5691.2022.00023
9. Aitichou M, Saleh SS, McElroy AK, Schmaljohn C, Ibrahim MS. Identification of Dobrava, Hantaan, Seoul, and Puumala viruses by one-step real-time RT-PCR. *J Virol Methods.* 2005; 124: 21-26. DOI: 10.1016/j.jviromet.2004.10.004
10. Loginova SIa, Koval'chuk AV, Borisevich SV, Kopylova NK, Pashchenko IuI, Khamitov RA, Maksimov VA, Shuster AM. Antiviral effectiveness of the combined use of amixine and virasole in experimental hemorrhagic fever with renal syndrome in sucking albino mice. *Vopr Virusol.* 2005; 50: 30-32.
11. 2011 Dec;162(1-2):138-47. doi: 10.1016/j.virusres.2011.09.017. Epub 2011 Sep 17. DOI: 10.1016/j.virusres.2011.09.017
12. *South Med J.* 2009 Jun;102(6):620-5. doi: 10.1097/SMJ.0b013e3181a4eeda DOI: 10.1097/SMJ.0b013e3181a4eeda
13. Hjelle B, Goade D, Torrez-Martinez N, Lang-Williams M, Kim J, Harris RL, et al. Hantavirus pulmonary syndrome, renal insufficiency, and myositis associated with infection by Bayou hantavirus. *Clin Infect Dis.* 1996; 23: 495-500. doi: 10.1093/clinids/23.3.495.
14. Plyusnin A., Mustonen J., Asikainen K., Plyusnina A., Niemimaa J., Henttonen H., Vaheri A. Analysis of puumala hantavirus genome in patients with nephropathia epidemica and rodent carriers from the sites of infection. *J Med Virol.* 1999; 59: 397-405. DOI: 10.1002/(sici)1096-9071(199911)59:3<397::aid-jmv21>3.0.co;2-#
15. Kramski M, Meisel H, Klempa B, Krüger DH, Pauli G, Nitsche A. Detection and typing of human pathogenic hantaviruses by real-time reverse transcription-PCR and pyrosequencing. *Clin Chem.* 2007; 53: 1899-905. DOI: 10.1373/clinchem.2007.093245
16. Hujakka H, Koistinen V, Kuronen I, Eerikäinen P, Parviainen M, Lundkvist A, Vaheri A, Vapalahti O, Näränen A. *J Virol Methods.* 2003 Mar;108(1):117-22. doi: 10.1016/s0166-0934(02)00282-3.
17. Dieterle ME, Solà-Riera C, Ye C, Goodfellow SM, Mittler E, Kasikci E, Bradfute SB, Klingström J, Jangra RK, Chandran K. *Elife.* 2021 Jul 6;10:e69708. doi: 10.7554/eLife.69708.
18. Yashina LN, Panov VV, Abramov SA, Smetannikova NA, Luchnikova EM, Dupal TA, Krivopalov AV, Arai S, Yanagihara R. *Viruses.* 2022 Feb 2;14(2):309. doi: 10.3390/v14020309.
19. Bellomo C, Alonso DO, Ricardo T, Coelho R, Kehl S, Periolo N, Azogaray V, Casas N, Ottonelli M, Bergero LC, Cudós MC, Previtali MA, Martinez VP. *PLoS Negl Trop Dis.* 2021 Nov 17;15(11):e0009842. doi: 10.1371/journal.pntd.0009842.
20. Williams EP, Taylor MK, Demchyshyna I, Nebogatkin I, Nesterova O, Khuda I, Chernenko L, Hluzd OA, Kutseva VV, Glass GE, Yanko N, Jonsson CB. *Viruses.* 2021 Aug 18;13(8):1640. doi: 10.3390/v13081640.
21. Jeske K, Jacob J, Drewes S, Pfeffer M, Heckel G, Ulrich RG, Imholt C. *Epidemiol Infect.* 2021 Feb 22;149:e97. doi: 10.1017/S0950268821000443.
22. Sheela Thorat S, Gurunath D, Swapnali A, Mohite, Rohan Kumar R, Chavan, Mr, Ramling D, Mali, Comparative Study of Antibacterial Activity of *Tamarindus indica* and *Tagetes erecta*, *Research Journal of Pharmacognosy and Phytochemistry*, 2019; 11(3): 186-188.
23. Glass GE, Johnson JS, Hodenbach GA, Disalvo CL, Peters CJ, Childs JE, Mills JN. Experimental evaluation of rodent exclusion methods to reduce hantavirus transmission to humans in rural housing. *Am J Trop Med Hyg.* 1997; 56: 359-364.
24. Mills JN. Regulation of rodent-borne viruses in the natural host: implications for human disease. *Arch Virol Suppl.* 2005; 19: 45-57.
25. Ahn C, Cho JT, Lee JG, Lim CS, Kim YY, Han JS, Kim S, Lee JS (2000) Detection of Hantaan and Seoul viruses by reverse transcriptase-polymerase chain reaction (RT-PCR) and restriction fragment length polymorphism (RFLP) in renal syndrome patients with hemorrhagic fever. *Clin Nephrol* 53: 79-89.

26. Biel SS, DonosoMantke O, Lemmer K, Vaheri A, Lundkvist A, Emmerich P, Hukic M, Niedrig M (2003) Quality control measures for the serological diagnosis of hantavirus infections. *J Clin Virol* 28: 248-256.
27. Plyusnin A., Mustonen J., Asikainen K., Plyusnina A., Niemimaa J., Henttonen H., Vaheri A. Analysis of puumala hantavirus genome in patients with nephropathiaepidemica and rodent carriers from the sites of infection. *J Med Virol*. 1999; 59: 397-405.
28. Chapman LE, Mertz GJ, Peters CJ, Jolson HM, Khan AS, Ksiazek TG, Koster FT, Baum KF, Rollin PE, Pavia AT, Holman RC, Christenson JC, Rubin PJ, Behrman RE, Bell LJ, Simpson GL, Sadek RF. Intravenous ribavirin for hantavirus pulmonary syndrome: safety and tolerance during 1 year of open-label experience. *Antivir Ther*. 1999; 4: 211-219.
29. Jonsson CB, Hooper J, Mertz G. Treatment of hantavirus pulmonary syndrome. *Antiviral Res*. 2008; 78: 162-9.
30. . McCaughey C, Hart CA. Hantaviruses. *J Med Microbiol*. 2000; 49: 587-99. Krüger DH, Ulrich R, Lundkvist AA. Hantavirus infections and their prevention. *Microbes Infect*. 2001; 3: 1129-44.
31. Childs JE, Korch GW, Glass GE, LeDuc JW, Shah KV (1987) Epizootiology of hantavirus infections in Baltimore: isolation of a virus from Norway rats, and characteristics of infected rat populations, *Am J of Epi* 126: 55–68.
32. Childs JE, Ksiazek TG, Spiropoulou CF, Krebs JW, Morzunov S, Maupin GO, Gage KL, Rollin PE, Sarisky J, Ensore RE, Frey JK, Peters CJ, Nichol ST (1994) Serologic and genetic identification of *Peromyscus maniculatus* as the primary rodent reservoir for a new hantavirus in the southwestern United States. *J Infect Dis* 169: 1271–1280.
33. McCaughey C, Hart CA. Hantaviruses. *J Med Microbiol*. 2000; 49: 587-99. Krüger DH, Ulrich R, Lundkvist AA. Hantavirus infections and their prevention. *Microbes Infect*. 2001; 3: 1129-44
34. Cho HW, Howard CR Antibody responses in humans to an inactivated hantavirus vaccine (Hantavax). *Vaccine*. 1999; 17: 2569–2575.