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ORTHOHANTAVIRUS: ANOTHER CONTAGION NEMESIS ON A HUNT

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ABSTRACT
Orthohantavirus is a genus of single-stranded, enveloped, negative-sense RNA viruses in the family Hantaviridae of the order Bunyaviral. Members of this genus may be called orthohantaviruses or simply hantaviruses. They normally cause infection in rodents, but do not cause disease in them. Human may become infected with hantaviruses through contact with rodent urine, saliva, or feces. Some strains cause potentially fatal diseases in humans, such as hantavirus hemorrhagic fever with renal syndrome (HFRS), or hantavirus pulmonary syndrome (HPS), also known as hantavirus cardiopulmonary syndrome (HCPS), while others have not been associated with known human disease. HPS (HCPS) is a "rare respiratory illness associated with the inhalation of aerosolized rodent excreta (urine and feces) contaminated by hantavirus particles." Human infections of hantaviruses have almost entirely been linked to human contact with rodent excrement; however, in 2005 and 2019, human-to-human transmission of the Andes virus was reported in South America. Hantavirus is named for the Hantan River area in South Korea where an early outbreak was observed, and was isolated in 1976 by Ho Wang Lee.

KEYWORDS: Rodent-borne, Hantaviridae, virion, transcription-translation, glycosylation, co- evolution, ribavirin, nephropathia, epidemica.

INTRODUCTION
Hantaviruses are rodent-borne viruses that cause hemorrhagic fever in humans. These viruses are associated with diverse disease syndromes with varying degrees of severity. Diseases caused by hantaviruses are generally manifested as either hemorrhagic fever with renal syndrome (HFRS) or hantavirus pulmonary syndrome (HPS). The most prevalent and lethal HFRS-associated hantavirus is Hantaan virus (HTNV) (20,000–50,000 cases per year, mostly in Asia) with a case-fatality rate of 5–15% (Fang et al., 2006). The most prevalent hantavirus in Central Europe, northern Europe/Scandinavia, and western Russia is Puumala virus (PUUV); whereas in southern Europe and the Balkans, both PUUV and Dobrava virus (DOBV) cause disease. The most prevalent and lethal HPS-associated hantaviruses are Andes virus (ANDV) in South America and Sin Nombre virus (SNV) in North America. There have been close to 2000 cases of HPS between 1993 and 2007 with an overall mortality rate of approximately 40%, despite state-of-the-art treatment in modern intensive care units. The mechanisms underlying the pathogenesis of the vascular leak syndromes associated with HFRS and HPS remain unknown. There are no vaccines or specific antiviral drugs licensed by the U.S. Food and Drug Administration to treat or prevent HFRS or HPS.[1]

Figure-1: Rodent the carrier of hantavirus.

Taxonomy: Orthohantaviruses belong to the Hantaviridae family and members of both the family and of the genus are called hantaviruses. The genus also belongs to the subfamily Mammantavirinae, the mammalian hantaviruses, with three other genera. Orthohantaviruses specifically are mammalian hantaviruses that are transmitted among rodents. The genus has 36 recognized species as of 2019. The type species of the genus is the *Hantaan orthohantavirus*.

Characteristics Structure: Hantavirus virions are about 120–160 nanometers (nm) in diameter. The lipid bilayer of the viral envelope is about 5 nm thick and is embedded with viral surface proteins to which sugar residues are attached. These glycoproteins, known as Gn and Gc, are encoded by the M segment of the viral genome. They tend to associate (heterodimerize) with each other and have both an interior tail and an exterior domain that extends to about 6 nm beyond the envelope surface. Inside the envelope are the nucleocapsids. These are composed of many copies of the nucleocapsid protein N, which interact with the three segments of the viral genome to form helical structures. By mass, the virion is greater than 50% protein, 20–30% lipid and 2–7% carbohydrate. These features are common to all members of the Hantaviridae family.[2]

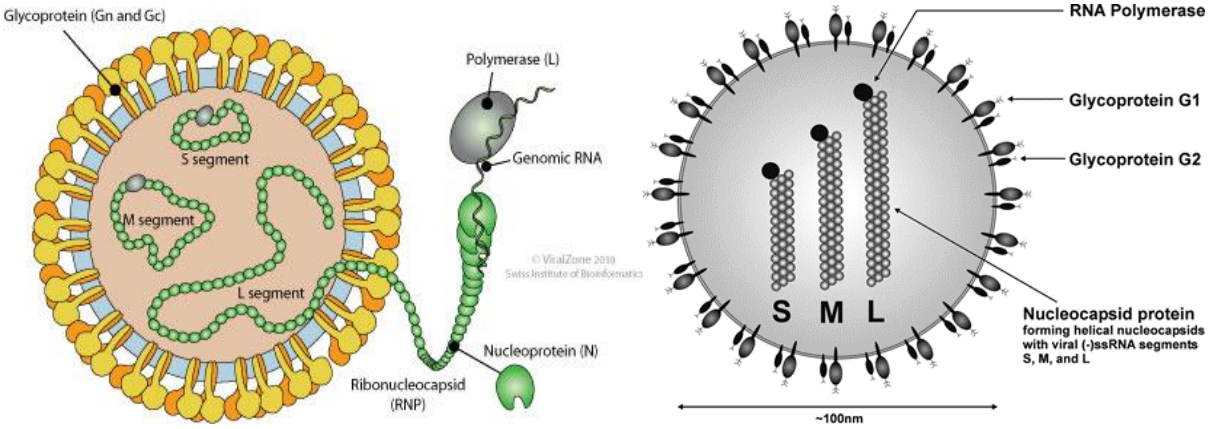


Figure-2: Hantavirus genome.

Genome: Their genomes are single stranded & RNA which is composed of three segments: the small (S), medium (M), and large (L) segments. The S segment, 1-3 kilobases (kb) in length, encodes for the nucleocapsid (N) protein. (A) The M segment, 3.2-4.9 kb in length, encodes a glycoprotein precursor polyprotein that is co-translationally cleaved into the envelope glycoproteins Gn and Gc, alternatively called G1 and G2. The L segment, 6.8-12 kb in length, encodes the L protein which functions primarily as the viral RNA-dependent. RNA polymerase used for transcription and replication. In hantavirus transcription, it occurs through a prime and realign mechanism. Cellular mRNA is cleaved by either Hantavirus RNA-dependent RNA polymerase (RdRp) or cellular endonucleases in a process called cap snatching, thus forming a capped primer (m7GpppNn). It is this capped primer that initiates transcription by aligning its guanidine to the 3′ cytosine of the vRNA. After synthesis of several nucleotides, the nascent RNA slips back and realigns. Final elongation then takes place, producing an extra copy of viral mRNA. (B) Replication of Hantavirus RNA. Replication takes place in cytoplasm of the infected cell, using prime and realign mechanism. RdRp attached to the 3′ end of vRNA aligns guanidine triphosphate (pppG) residue to the first cytosine of the virus RNA and synthesizes the first three nucleotides of the new cRNA strand. The nascent RNA slips back and realigns after successive addition of bases. Then, final elongation takes place, resulting in production of the full length cRNA. In turn, this positive strand anti-genomic cRNA serves as a template for producing a large amount of the new strands of vRNA. (C) Hantavirus transcription and template for the viral RdRp, which initiates transcription by cap-snatching mechanism and generates viral mRNA. Viral mRNAs are translated producing N protein, glycoprotein precursor (which is cleaved to form G1 and G2 glycoproteins), and RdRp from the small (S), medium (M), and large (L) segment-originated mRNA, respectively.[3]

Life cycle: Viral entry into host cells initiates by binding to surface cell receptors. Viral particles are then transported to late endosomes. Gc-mediated membrane fused with endosomal membrane, releases the nucleocapsid into the cytoplasm. After their release the complexes are targeted to the ER–Golgi Intermediate compartments (ERGIC) through microtubular -associated movement resulting in the formation of viral factories. These factories then facilitate transcription and translation of the viral proteins. Transcription of viral genes must be initiated by L protein with the three nucleocapsid species. The viral L protein cleaves cellular messenger RNAs (mRNAs) for the production of capped primers. As a result of this cap-snatching the mRNAs of hantaviruses are capped and contain nontemplated 5'-terminal extensions. The G1 (or Gn) and G2 (Gc) glycoproteins are then transported from the endoplasmic reticulum to the Golgi complex, where glycosylation is completed. Hanta virus virions are believed to assemble by association of nucleocapsids with glycoproteins embedded in the membranes of the Golgi, followed by budding into the Golgi cisternae. Nascent virions are

then transported in secretory vesicles of plasma membrane and released by exocytosis.[4]

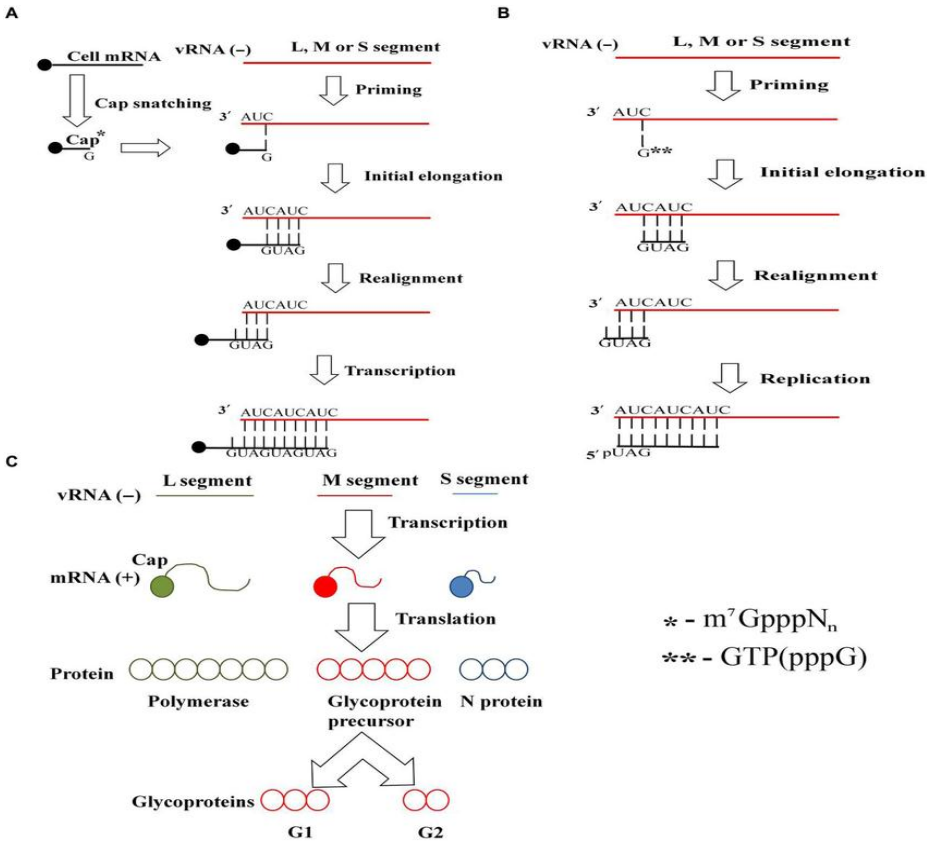


Figure-3: Virus transcription.

Pathogenesis: The pathogenesis of hantavirus infections is unclear as there is a lack of animal models to describe it (rats and mice do not seem to acquire severe disease). While the primary site of viral replication in the body is not known, in HFRS the main effect is in the blood vessels while in HPS most symptoms are associated with the lungs. In HFRS, there are increased vascular permeability and decreased blood pressure due to endothelial dysfunction and the most dramatic damage is seen in the kidneys, whereas in HPS, the lungs, spleen, and gall bladder are most affected. Early symptoms of HPS tend to present similarly to the flu (muscle aches, fever and fatigue) and usually appear around 2 to 3 weeks after exposure. Later stages of the disease (about 4 to 10 days after symptoms start) include difficulty breathing, shortness of breath and cough.

Phylogenetic Analysis: Phylogenetic analysis of Old World and American hantaviruses indicates that the relationship among hantaviruses corresponds with the phylogeny of their rodent hosts. Viruses of rodents belonging to the subfamily Murinae are monophyletic as are hantaviruses of arvicoline and sigmodontine rodents, suggesting that long-term virus-rodent coevolution is taking place. Hantavirus evolution is best understood as co-evolution within specific lineages in the rodent family Muridae. The apparent coupling between hantaviruses and their rodent hosts suggests that viruses of sigmodontine rodents share a common ancestor, as do viruses of the subfamily Arvicolinae and Murinae. This coupling also has a geographic and clinical correlate: viruses found in Old World murine rodents, including Hantaan virus (HTNV), Seoul virus (SEOV) and Dobrava virus, are associated with HFRS in Eurasia. By contrast, viruses carried by New World sigmodontine rodents, including SNV Black Creek Canal virus (BCCV) and Bayou virus (BAYV), are associated with HPS in the Americas. This distinction can narrow the search for a rodent host for newly discovered HPS- like diseases and suggest disease implications for the various new viruses being genetically amplified from rodents.[5]

Diseases: Hantavirus pulmonary syndrome Human disease: Hantavirus pulmonary syndrome (HPS) is one of two potentially fatal syndromes of zoonotic origin caused by species of hantavirus. These include Black Creek Canal virus (BCCV), New York orthohantavirus (NYV), Monongahela virus (MGLV), Sin Nombre orthohantavirus (SNV), and certain other members of Hantavirus genera that are native to the United States and Canada. Specific rodents are the principal hosts of the hantaviruses including the hispid cotton rat (*Sigmodon hispidus*) in southern Florida, which is the principal host of Black Creek Canal virus. The deer mouse (*Peromyscus maniculatus*) in Canada and the Western United States is the principal host of Sin Nombre virus.

The white-footed mouse (*Peromyscus leucopus*) in the eastern United States is the principal host of New York virus. In South America, the long-tailed mouse (*Oligoryzomys longicaudatus*) and other species of the genus Oligoryzomys have been documented as the reservoir for Andes virus.

Signs, symptoms and disease progression: Initially, HPS has an incubation phase of 2-4 weeks, in which patients remain asymptomatic. Subsequently, patients can experience 3-5 days of flu-like prodromal phase symptoms, including fever, cough, muscle pain, headache, lethargy, shortness of breath, nausea, vomiting and diarrhea. In the following 5-7-day cardiopulmonary phase, the patient's condition rapidly deteriorates into acute respiratory failure, characterized by the sudden onset of shortness of breath with rapidly evolving pulmonary edema, as well as cardiac failure, with hypotension, tachycardia and shock. It is often fatal despite mechanical ventilation and intervention with diuretics. After the cardiopulmonary phase, patients can enter a diuretic phase of 2-3 days characterized by symptom improvement and diuresis. Overall, patient mortality from HPS is 36%.

Transmission: The hispid cotton rat, indigenous to southern Florida, is the carrier of the Black Creek Canal virus. The virus can be transmitted to humans by a direct bite or inhalation of aerosolized virus, shed from stool, urine, or saliva from a natural reservoir rodent. In general, droplet and/or fomite transfer has not been shown in the hantaviruses in either the pulmonary or hemorrhagic forms.[6]

Prevention: Rodent control in and around the home or dwellings remains the primary prevention strategy, as well as eliminating direct contact with rodents in the workplace and at campsites ,with rodent droppings and thereby wearing a mask while cleaning such areas to avoid inhalation of aerosolized rodent secretions is one of the key of prevention.

Treatment: There is no cure or vaccine for HPS. Treatment involves supportive therapy, including mechanical ventilation with supplemental oxygen during the critical respiratory-failure stage of the illness. Although ribavirin can be used to treat hantavirus infections, it is not recommended as a treatment for HPS due to unclear clinical efficacy and likelihood of medication side effects. Early recognition of HPS and admission to an intensive care setting offers the best prognosis.

Hantavirus hemorrhagic fever with renal syndrome: Hantavirus hemorrhagic fever with renal syndrome (HFRS) is a group of clinically similar illnesses caused by species of hantaviruses from the family Hantaviridae, in the order Bunyavirales. It is also known as Korean hemorrhagic fever and epidemic hemorrhagic fever. The species that cause HFRS include Hantaan orthohantavirus, Dobrava-Belgrade orthohantavirus, Saaremaa virus, Seoul orthohantavirus, Puumala orthohantavirus and other orthohantaviruses. It is found in Europe, Asia, and Africa. Of these species, Hantaan River virus and Dobrava-Belgrade virus cause the most severe form of the syndrome. When caused by the Puumala virus, it is also called nephropathia epidemica. This infection is known as sorkfeber in Swedish and myyräkuume in Finnish (vole fever). In Norway, it is called musepest (mouse plague). Both hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) appear to be immunopathologic, and inflammatory mediators are important in causing the clinical manifestations.[7]

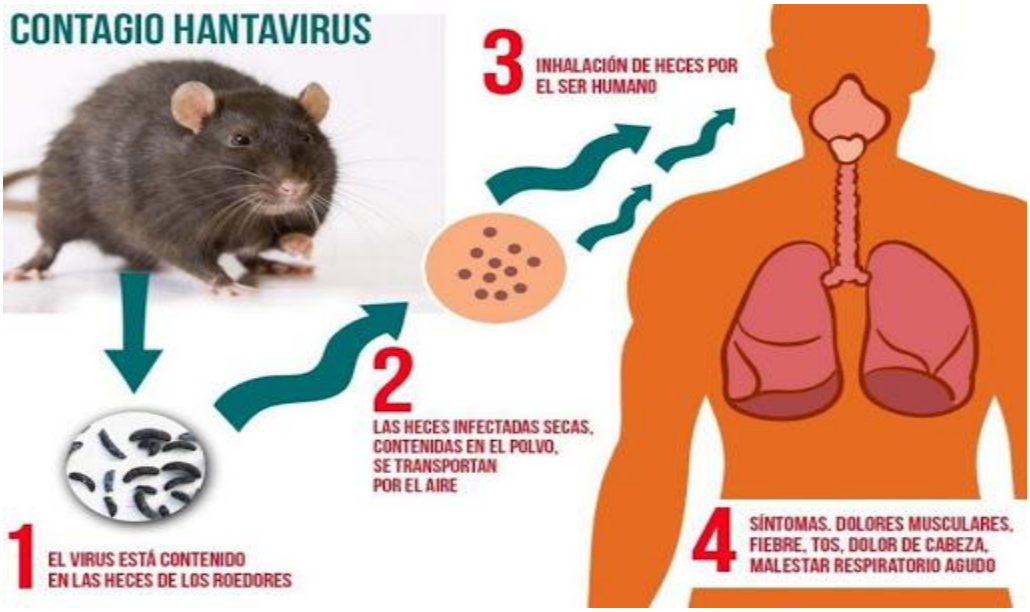


Figure-4: Virus cycle.

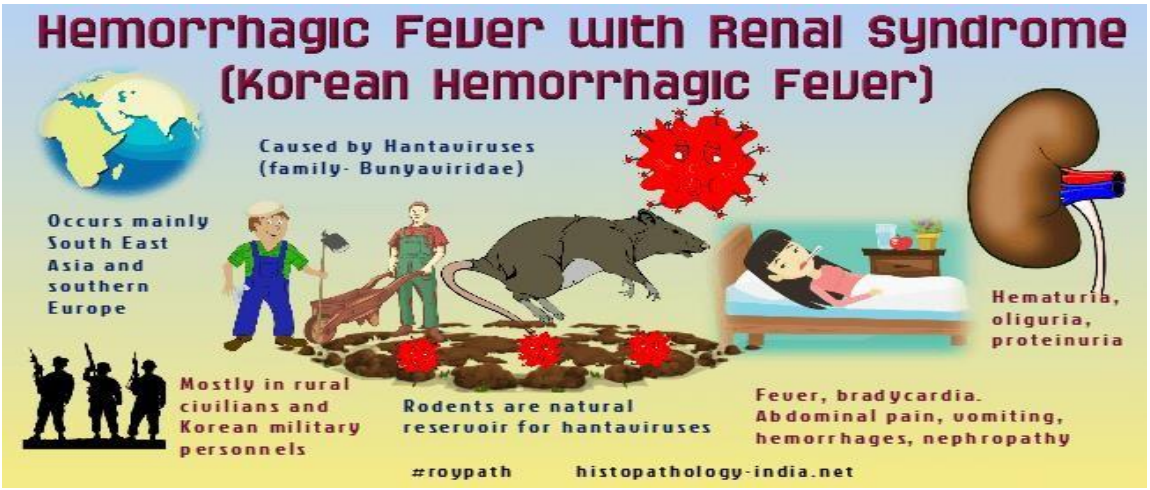
Signs and symptoms: Symptoms of HFRS usually develop within 1 to 2 weeks after exposure to infectious material, but in rare cases, they may take up to 8 weeks to develop. In *Nephropathia epidemica*, the incubation period is three weeks. Initial symptoms include intense headaches, back and abdominal pain, fever, chills, nausea, and blurred vision. Individuals may have flushing of the face, inflammation or redness of the eyes, or a rash. Later symptoms can include low blood pressure, acute shock, vascular leakage, and acute kidney failure, which can cause severe fluid overload. The severity of the disease varies depending upon the virus causing the infection. Hantaan and Dobrava virus infections usually cause severe symptoms, while Seoul, Saaremaa, and Puumala virus infections are usually more moderate. The course of the illness can be split into five phases: 1) Febrile phase Symptoms include: redness of cheeks and nose, fever, chills, sweaty palms, diarrhea, malaise, headaches, nausea, abdominal and backpain, respiratory problems such as the ones common in the influenza virus, as well as gastro-intestinal problems. These symptoms normally occur for three to seven days and arise about two to three weeks after exposure. 2) Hypotensive phase: this occurs when the blood platelet levels drop and symptoms can lead to tachycardia and hypoxemia. This phase can last for 2 days. 3) Oliguric phase: This phase lasts for three to seven days and is characterized by the onset of renal failure and proteinuria. 4) Diuretic phase: This is characterized by diuresis of three to six liters per day, which can last for a couple of days up to weeks. 5) Convalescent phase: This is normally when recovery occurs and symptoms begin to improve.[8]

Transmission: Transmission by aerosolized rodent excreta still remains the only known way the virus is transmitted to humans. In general, droplet and/or fomite transfer has not been shown in the hantaviruses in either the pulmonary or hemorrhagic forms. For *Nephropathia epidemica*, the bank vole is the reservoir for the virus, which humans' contract through inhalation of aerosolized vole droppings.

Diagnosis: HFRS is difficult to diagnose on clinical grounds alone and serological evidence is often needed. A fourfold rise in IgG antibody titer in a 1-week interval and the presence of the IgM type of antibodies against hantaviruses are good evidence for an acute hantavirus infection. HFRS should be suspected in patients with acute febrile flu-like illness, kidney failure of unknown origin and sometimes liver dysfunction.

Treatment: There is no cure or vaccine for HFRS. Treatment involves supportive therapy including renal dialysis. Treatment with ribavirin in China and Korea, administered within 7 days of onset of fever, resulted in a reduced mortality as well as shortened course of illness.[9]

Prevention: Closed storage sheds and cabins are often ideal sites for rodent infestations. Airing out of such spaces prior to use is recommended. Avoid direct contact with rodent droppings and wear a mask to avoid inhalation of aerosolized.



A difference can be drawn accordingly

Table-1: Comparison table between HFRS (hantavirus hemorrhagic fever with renal syndrome) & HPS (hantavirus pulmonary syndrome)

Comparison of HFRS and HPS

Feature	HFRS	HPS
Major target organ	Kidney	Lung
First phase	Febrile	Febrile "prodrome"
Second phase	Shock	Shock, pulmonary edema
Evolution	Oliguria, diureses, convalescence	Diureses, convalescence
Mortality	1-15%	50%

Epidemiology: Hantavirus infections have been reported from all continents except Australia. Regions especially affected by hemorrhagic fever with renal syndrome include China, the Korea Pensinsula, Russia (Hantaan, Puumala and Seoul viruses), and northern and western Europe (Pulaama and Dobrava virus). Regions with the highest incidences of hantavirus pulmonary syndrome include Argentina, Chile, United States, Canada, Panama.[10]

Table-2: Hantavirus characteristics.

Characteristics of Some Known Hantaviruses

Hantaviruses	Geographic Region	Reservoir	Pathology	Mortality
Hantaan	Asia	Field mouse	Renal	5-15%
Seoul	Worldwide	Domestic rat	Renal	1%
Puumala	Northern Europe	Bank vole	Renal	1%
Prospect Hill	United States	Meadow vole	No known human disease	N/A
Sin Nombre	North America	Deer mouse	Pulmonary	50%

CONCLUSION

The results conclude that the Hantavirus is maintained within the rodent population, specifically the deer mouse. The information presented in this paper shows that there needs to be a greater awareness of the possible public health impact. Hantavirus is not only deadly but may have a very simple reservoir. Diagnosing HPS in an individual who has only been infected a few days is difficult, because early symptoms such as fever, muscle aches, and fatigue are easily confused with influenza. However, if the individual is experiencing fever and fatigue and has a history of potential rural rodent exposure, together with shortness of breath, would be strongly suggestive of HPS. If the individual is experiencing these symptoms, they should see their physician immediately and mention their potential rodent exposure. There is no specific treatment, cure, or vaccine for hantavirus infection. However, we do know that if infected individuals are recognized early and receive medical care in an intensive care unit, they may do better. In intensive care, patients are intubated and given oxygen therapy to help them through the period of severe respiratory distress. The earlier the patient is brought in to intensive care, the better. If a patient is experiencing full distress, it is less likely the treatment will be effective. Therefore, if you have been around rodents and have symptoms of fever, deep muscle aches, and severe shortness of breath, see your doctor immediately. Be sure to tell your doctor that you have been around rodents—this will alert your physician to look closely for any rodent-carried disease, such as HPS.

REFERENCES

1. Drebot, Jones S.; Grolla, A.; Safronetz, D.; Strong, J. E.; Kobinger, G.; Lindsay, R. L. (2015). Hantavirus pulmonary syndrome in Canada: An overview of clinical features, diagnostics, epidemiology and prevention. Canada Communicable Disease Report (Report). Vector-borne diseases in Canada. 41-06. Winnipeg, MB: National Microbiology Laboratory, Public Health Agency of Canada. p. 40. ISSN 1481-8531.

2. Gravinatti ML, Barbosa CM, Soares RM, Gregori F (2020). "Synanthropic rodents as virus reservoirs and transmitters". Rev Soc Bras Med Trop., 53: e20190486.
3. Jiang H, Zheng X, Wang L, Du H, Wang P, Bai X (2017). "Hantavirus infection: a global zoonotic challenge". Virol Sin., 32(1): 32–43.
4. Klempa B (2018). "Reassortment events in the evolution of hantaviruses". Virus Genes, 54(5): 638–646.
5. Elliott RM (1990). "Molecular biology of the Bunyaviridae". The Journal of General Virology, 71(3): 501–522.
6. Mir MA, Panganiban AT (2005). "The Hantavirus Nucleocapsid Protein Recognizes Specific Features of the Viral RNA Panhandle and is Altered in Conformation upon RNA Binding". Journal of Virology, 79(3): 1824–1835.
7. Brocato RL, Hooper JW (2019). "Progress on the Prevention and Treatment of Hantavirus Disease". Viruses, 11(7): 610.
8. Vapalahti O, Mustonen J, Lundkvist A, Henttonen H, Plyusnin A, Vaheri A (2003). "Hantavirus infections in Europe". The Lancet Infectious Diseases, 3(10): 653–661.
9. Kariwa H, Yoshida H, Sánchez-Hernández C, Romero-Almaraz Mde L, Almazán-Catalán JA, Ramos C, Miyashita D, Seto T, Takano A, Totani M, Murata R, Saasa N, Ishizuka M, Sanada T, Yoshii K, Yoshimatsu K, Arikawa J, Takashima I (2012). "Genetic diversity of hantaviruses in Mexico: Identification of three novel hantaviruses from Neotominae rodents". Virus Research, 163(2): 486–494.
10. Ramsden C, Holmes EC, Charleston MA (2008). "Hantavirus Evolution in Relation to Its Rodent and Insectivore Hosts: No Evidence for Codivergence". Molecular Biology and Evolution, 26(1): 143–153.