Hanta Virus: An Emerging Threat for Public Health

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ABSTRACT

Hantavirus infection, a pervasive zoonosis exacerbated by global warming, intense rainfall, and flooding, poses a substantial public health threat, with an annual incidence of 150,000-200,000 cases globally. Influenced by climate change, the transmission dynamics of hantavirus are intricately linked to the population densities of its reservoir host, rodents, which constitute 42% of mammalian biodiversity. With 28 known hantaviruses causing severe diseases in humans, the infections range from renal dysfunction to pulmonary and cardiac syndromes, resulting in high mortality rates. The etiology involves enveloped RNA viruses belonging to the Bunyavirales order, with distinct genotypes and species identified. Human infections primarily occur through inhaling particles contaminated with rodent excreta or secretions. Epidemiologically, Hantavirus outbreaks have been documented globally, with varying prevalence and dominant strains. Pathogenesis involves the compromise of endothelial barrier integrity, leading to severe organ damage. The transmission, influenced by climate change, occurs through rodents as intermediate hosts, with a potential for limited person-to-person transmission. Clinical manifestations encompass Hemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Pulmonary Syndrome (HCPS), exhibiting diverse symptoms and severity. Managing severe cases relies on supportive care, with no specific antiviral treatment approved. Prevention involves rodent control measures, thorough cleaning, and protective measures during potential exposure. Vaccines against Hantavirus are essential for high-risk populations. Ongoing research explores antiviral agents, DNA-based vaccines, and immunotherapies as potential treatments. Comprehensive prevention and control strategies are imperative to mitigate the global impact of hantavirus infections.

Keywords: Hantavirus, Zoonosis, Climate Change, Hemorrhagic Fever, Rodent-borne Infections

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1. INTRODUCTION

Hantavirus infection is the most widespread zoonosis that is emerging partially due to global warming, intense rainfall, and increased severity of floods resulting in an annual incidence of about 150000-200000 cases (Sunil-Chandra et al. 2015). The mode of transmission and circulation of hantavirus can be influenced by climate change which can impact the population densities of the reservoir host i.e. rodents (Douglas et al. 2021). Rodents make up 42% of the total mammalian biodiversity in the world, consisting of 2,277 species that inhabit every continent except Antarctica. They serve as carriers for a diverse range of infectious agents (Milholland et al. 2018). People can get infected with hantaviruses by breathing in tiny particles of dust that have been contaminated by rodent droppings or urine (Mattar et al. 2015). The particles lead to various types of organ damage due to a temporary increase in pro-inflammatory cytokines, also known as a "cytokine storm" (Clement et al. 2019). Small mammals are the exclusive carriers of bunyaviruses, which are zoonotic agents capable of inducing Hemorrhagic Fever with Renal Syndrome (HFRS), Hantavirus Pulmonary Syndrome (HPS), or Hantavirus Cardiopulmonary syndrome (HCPS); both of which exhibit case fatality rate up to 50% (Witkowski et al. 2015). The exact cause of the disease is not well known, although it is believed that both interfere with blood vessels and strong responses from cytotoxic lymphocytes give rise to the development of the symptoms (Rasmuson et al. 2016). This condition frequently occurs when a person comes into contact with mouse feces or urine within 1 to 3 weeks after the start of symptoms (Moore and Griffen 2022). Hantavirus infections pose a high mortality rate. It is also worth noting that Hantavirus can be transmitted from person to person, underlining the significance of medical interventions for preventing and treating Hantavirus infections (Dheerasekara et al. 2020). Currently, there are more than 28 known hantaviruses that can cause various diseases in humans globally. These illnesses can range from renal dysfunction to fluid overload in the lungs and major bleeding conditions (Avšič-Županc et al. 2019).

2. ETIOLOGY

Hantaviruses, which are enveloped RNA viruses belonging to the Bunyavirales order, are responsible for a range of hemorrhagic fevers transmitted by rodents. Hemorrhagic fevers caused by various viral families within the Bunyavirales order; such as Phenuiviridae, Arenaviridae, Nairoviridae, and Hantaviridae, are characterized by their rodent-borne nature (Mocanu et al. 2023). The diameter of hantaviruses ranges from 80nm to 120nm (Avšič-Županc et al. 2019). The viral particles, which are enclosed in a spherical shape, feature a genome split into three pieces of negative-strand RNA. These segments are referred to as large (L), medium (M), and small (S) genome segments. The L segment encodes an L-protein, the M segment encodes a glycoprotein precursor called GPC, which consists of two envelope glycoproteins (Gn and Gc) and the S segment encodes a nucleocapsid protein (N) (Muthusinghe et al. 2021). A total of 76 strains and 70 isolates from nine rodent species, one bird species, blood samples of patients with HFRS, and sectional materials from deceased HFRS patients were isolated and identified. The identification process led to the discovery of new hantavirus species, namely Khabarovsk, Taimyr-Topografov, and Adler. Additionally, two new genotypes of the Dobrava/Belgrad virus, known as Kurkino and Sochi, were identified (Tkachenko et al. 2016). Hantaviruses like Sin Nombre (SNV) or Andes virus (ANDV) found in

America result in hantavirus cardiopulmonary syndrome. In Asia, Hantaan (HTNV) and Seoul virus (SEOV); and in Europe, Puumala virus (PUUV) and Dobrava-Belgrade virus (DOBV) are the prevailing hantaviruses responsible for causing hemorrhagic fever with renal syndrome (Klempa 2018). Old World hantaviruses such as Hantaan, Puumala, Seoul, and Dobrava result in hemorrhagic fever with renal syndrome (HFRS), which has a mortality rate ranging from 1% to 15%. This condition affects around 100,000 to 150,000 individuals annually. On the other hand, New World hantaviruses like Andes (ANDV) and Sin Nombre (SNV) viruses lead to hantavirus cardiopulmonary syndrome (HCPS), which has a higher case fatality rate of 40%. However, the number of cases for HCPS is relatively lower, with only a few hundred cases reported each year (Engdahl and Crowe Jr 2020). Hantaviruses can cause severe illnesses in people, with mortality rates up to 12% for HFRS and 60% for HPS in certain outbreaks (Jonsson et al. 2010). The reservoir hosts of HTNV, SEOV, PUUV, DOBV, SNV, and ANDV are striped field mouse (*Apodemus agrarius*), Rat (*Rattus*), bank voles (*Myodes galreolus*), field mouse (*Apodemus flaviollis*), Eastern deer mouse (*Peromyscus maniculatus*) and Long-tailed colilargo (*Oligoryzomys longicaudatus*) respectively (Koehler et al. 2022).

Hantavirus virions attach to host cells and enter through endocytosis. They release RNA nucleoprotein complexes into the cytoplasm through membrane fusion. Virus transcription and replication occur in the cytoplasm or at the endoplasmic reticulum–Golgi intermediate compartment (ERGIC). Capped primers for transcription are generated by the viral polymerase from cellular mRNA. Cellular endonucleases may also assist in primer formation. The viral mRNAs produce proteins such as N protein and glycoproteins on the ER membrane-bound ribosomes. The assembly site for Old World hantaviruses is the Golgi, while the plasma membrane for New World hantaviruses assembly. Spike-like projections on the viral envelope aid in virus assembly and cell entry. Finally, the virions are released from the cell through exocytosis (Muyangwa et al. 2015). The risk of human HFRS was six times higher in areas with severe selenium deficiency and two times higher in areas with moderate deficiency than in areas with enough selenium. Thus, Hantavirus infections in both humans and rodents were more common in areas with low selenium levels (Fang et al. 2015).

3. EPIDEMIOLOGY

The discovery of hantaviruses was prompted by two major outbreaks of disease that happened in the past century. The Korean War outbreak (1950-1953) affected over 3,000 United Nations troops, resulting in Korean hemorrhagic fever or hemorrhagic fever with renal syndrome (HFRS). Hantavirus pulmonary syndrome (HPS) or hantavirus cardiopulmonary syndrome (HCPS) was the name given to the second outbreak that occurred in 1993 in the Four Corners region of the United States. It was originally named Four Corners disease (Jonsson et al. 2010). An outbreak of acute pulmonary distress syndrome was reported in the southwestern United States in 1993 (Lundkvist and Plyusnin 2002). In Argentina, there were 29 confirmed cases of hantavirus pulmonary syndrome (HPS) in humans, which occurred in clusters in 1995. A hantavirus named Andes (AND) virus had been partly described from a lethal HPS case in southwestern El Bolson in 1995 before a severe outbreak occurred in the same area in the spring of 1996. The outbreak affected 18 people (Levis et al. 1998). In Germany, hantavirus infections reached a peak in 2012, with over 2,800 reported cases. The majority of these cases were concentrated in the federal state of Baden-Württemberg, which borders Switzerland. Among the reported cases, the most dominant variant was PUUV (and Vial 2014).

Active surveillance for hantavirus pulmonary syndrome (HPS) in Canada started in 1994 and became a reportable disease at the national level in January 2000. By 31 December 2014, there were 109 laboratory-confirmed cases of HPS documented in Canada, while the United States has identified over 600 cases. Notably, there was an increase in HPS cases in 2013 and 2014, with 13 and 10 cases respectively. HPS cases can occur throughout the year, but there is a distinct peak during the spring and

early summer, with more than 60% of cases reported between April and July (Drebot et al. 2015). Hantavirus pulmonary syndrome (HPS) cases in Brazil have been steadily increasing, accompanied by the emergence of new viral variants. Between October 2001 and December 2009, confirmed HPS cases rose from 134 to 1252, marking an over 800% increase in just eight years. While HPS can occur throughout the year, its highest frequency is observed during the winter and spring seasons. Young adult males, with an average age of 30, are primarily affected by HPS in Brazil (Pinto Junior et al. 2014). During the period 2009 to 2017, 533 cases of HPS have been confirmed in Argentina (Alonso et al.2019). From July 1997 to January 1998, a total of 25 cases of hantavirus pulmonary syndrome (HPS) associated with the Andes virus were identified during an outbreak in southern Chile (Toro et al. 1998). HFRS cases are prevalent across eastern Asia, specifically in China, Russia, and Korea. China is the source of approximately 90% of the global case reports. Presently, HFRS is endemic in 28 out of the 31 provinces in mainland China (Wu et al. 2015).

During the 1950s, outbreaks of HFRS occurred in the forest region of northern Inner Mongolia and the mountainous region of southern Shaanxi province. In the following decades, HFRS cases and epidemics emerged along the middle and lower valleys of the Yanze River and in the Sichuan Basin. Throughout the 1970s, HFRS spread further from these areas. The incidence and endemic areas of HFRS significantly increased from 1981 onwards, with the recognition of the Rattus-type of HFRS and major outbreaks along the middle valleys of the Yellow River. By 1986, 1257 counties in 25 provinces were identified as endemic areas of HFRS, with about half of them newly discovered between 1980 and 1986 (Song 1999). During the period of 2014-2015, the southwest region of Korea experienced a high prevalence of HTNV (86.7%) among *A. agrarius* rodents during the autumn month of November. The average monthly HFRS cases in Korea from 2001 to 2020, revealed peak onset in the months of October, November, and December. Notably, November consistently had the highest number of reported cases, averaging around 120 cases per year (Tariq and Kim 2022). In Europe, over 4,000 cases of Hantavirus infection were recorded by the ECDC in 2019, which means that 0.8 out of every 100,000 people were infected. The primary etiologic agent in 98% of these cases was PUUV. Finland and Germany had the highest number of reported cases, accounting for 69% of the total (Koehler et al. 2022).

4. PATHOGENESIS

Hantaviruses exert a significant impact on target cells by inhibiting the apoptotic factor within them. This action leads to the impairment of endothelial barrier integrity, which is a hallmark of hantavirus disease. The underlying mechanism is believed to involve an excessive natural immune response, playing a central role in the pathogenesis of the disease (Munir et al. 2021). The integrity of the endothelial cell barrier is compromised due to an increased response of CD8+ T cells and elevated levels of vascular endothelial growth factor (VEGF). This results in the degradation of VE-cadherin, a crucial molecule responsible for regulating vascular permeability (López et al. 2019). Vascular leakage in microvascular beds that are infected by Hantavirus is caused by cytokines. The accumulation of mononuclear leukocytes is a micro-anatomical feature of Hantavirus infection (Muyangwa et al. 2015). Hantaviruses primarily infect vascular endothelial cells in humans, but they can also target epithelial cells, mononuclear phagocytes (MNP), follicular dendritic cells (DC), and possibly other cell types (Klingström et al. 2019). In individuals with severe HFRS or HCPS, the affected endothelium can lead to lung edema and potential lung failure. This can occur due to hyper-permeability, activation of the kallikrein-kinin system, or alterations in the endothelial glycocalyx (Kitterer et al. 2016). The other factors that contribute to the pathogenesis of both HFRS and HCPS are acute thrombocytopenia and platelet dysfunction. Additionally, the severity of the disease may be influenced by genetic predisposition, particularly related to HLA type (Avšič-Županc et al. 2019).

5. TRANSMISSION

The mode of hantavirus transmission and its circulation in nature can be influenced by climate change, particularly its impact on the population densities of the hantavirus reservoir host rodents (Douglas et al. 2021). Unlike other Bunyaviruses, hantaviruses do not rely on arthropod vectors for transmission. Rodents, insectivores, or bats that have persistent infections carry and transmit them to people, rather than being transmitted directly. Hantaviruses circulate in nature through horizontal transmission among endemically infected natural carrier hosts, such as mice, rats, and voles (Avšič-Županc et al. 2019). HFRS and HPS, which are caused by hantaviruses, are transmitted by rodents of the Muridae family, specifically the Sigmodontinae subfamily. Each hantavirus species is associated with a specific rodent species as its intermediate host. The incidence of these diseases is influenced by environmental factors that contribute to the reproduction and spread of rodents in endemic areas (Toledo et al. 2022). Humans act as spillover hosts, primarily acquiring infection by inhaling aerosolized excreta or secretions from rodents and insectivores that are infected with the virus (Watson et al. 2014).

It is important to consider the additional risk of person-to-person transmission. Unlike other hantaviruses, there is evidence of ANDV transmitting between individuals, although the efficiency of transmission is limited and accounts for a small portion of cases. The specific risk factors for secondary infections, include being a sex partner or sharing a room with a patient, as well as exposure to the patient's body fluids. This highlights the potential for person-to-person transmission of ANDV and sheds light on the factors contributing to secondary infections (Manigold and Vial 2014).

6. CLINICAL SIGNS

The clinical presentation and severity of HFRS varies depending on the hantavirus species involved. HFRS caused by Hantaan virus, Amur virus, and Dobrava-Belgrade virus exhibits a severe clinical course while Puumala virus infections typically lead to milder disease courses known as "nephropathia epidemica" (Koehler et al. 2021). Nephropathia epidemica (NE) is marked by acute kidney injury accompanied by thrombocytopenia and often proteinuria. The disease is also characterized by severe gastrointestinal symptoms, and intense back and abdominal pain, and can vary in severity from mild or asymptomatic cases to severe acute kidney injury, sometimes leading to a fatal outcome (Latus et al. 2015). Cardiac involvement with electrocardiographic (ECG) abnormalities and acute myocarditis has also been observed during NE (Kitterer et al. 2016). Hantavirus pulmonary syndrome is a severe and acute illness marked by respiratory failure, pulmonary edema, and cardiogenic shock. After exposure, there is an incubation period of 14-17 days. Early stages of HP may include gastrointestinal manifestations, headache, and chills (Mattar et al. 2015). Due to the similarities in their clinical presentations, HFRS and HCPS are often perceived as interconnected syndromes (Koehler et al. 2021).

The disease of HFRS has a five-phase clinical course: febrile, hypotensive, oliguric, polyuric, and convalescent. The febrile phase starts after 2 to 4 weeks of incubation and lasts for about 3 to 7 days. In this phase, patients have fever, headache, vomiting, abdominal pain, back pain, and visual problems. Towards the end of this phase, they may develop small red spots on the palate and redness of the eyes. The hypotensive or shock phase has a variable length, ranging from a few hours to 2 days. In severe cases, fulminant irreversible shock can occur, leading to approximately one-third of deaths. This phase is characterized by thrombocytopenia, leucocytosis, and pronounced hemorrhagic manifestations. The oliguric phase, lasting around 3 to 7 days, may lead to acute kidney injury (AKI) and is liable for half of the fatalities. Patients with AKI often require dialysis, and serum creatinine and urea levels become elevated during this phase. The start of renal function recovery is the polyuric phase, and the diuretic phase onset

is a good sign for the prognosis. The convalescent phase can extend up to 6 months. Children with HFRS may present with a clinical picture similar to adults but generally experience a less severe form of the disease. Abdominal manifestations are commonly reported in pediatric cases (Chandy and Mathai 2017). HCPS is considered more severe than HFRS. It typically follows a three-phase course: prodromal, cardiopulmonary, and convalescent. During the prodromal stage, patients may experience flu-like symptoms such as fever, chills, malaise, headache, vomiting, abdominal pain, and diarrhea, which can resemble other viral infections. The cardiopulmonary phase is characterized by a progressive cough, shortness of breath, and tachycardia. Patients is often presented with non-cardiac pulmonary edema and hypotension, and severe cases may require mechanical ventilation due to respiratory failure. Complications like cardiogenic shock, lactic acidosis, and haemoconcentration can lead to rapid deterioration and even death shortly after hospitalization. Survivors enter the polyuric phase, followed by the resolution of pulmonary edema, and most recover fully without any long-term effects (Chandy and Mathai 2017). However, diagnosing hantavirus infections based solely on clinical symptoms is challenging, particularly in cases with mild and moderate symptoms, as the early signs of the disease are nonspecific (Avšič-Županc et al. 2019).

7. TREATMENT

As of the current date, there are no antiviral drugs approved by the US Food and Drug Administration for the treatment of HFRS (Hantavirus Hemorrhagic Fever with Renal Syndrome) or HPS (Hantavirus Pulmonary Syndrome). Therefore, the approach to managing severe cases relies solely on providing supportive care. It is crucial to focus on maintaining proper fluid and electrolyte balance in these patients. In cases where HFRS patients experience severe kidney impairment, they may require extracorporeal blood purification, such as dialysis treatment. On the other hand, HCPS patients may need mechanical ventilation or even extracorporeal membrane oxygenation (Dheerasekara et al. 2020). The absence of FDA-approved drugs or vaccines remains the primary challenge in effectively controlling this lethal virus. Besides supportive care, there is hope in therapeutic approaches such as antiviral agents, DNA-based vaccines, and the use of polyclonal and monoclonal antibodies. These modalities have shown promise in neutralizing the hantaviruses and are being considered as potential treatments for hantavirus disease (Munir et al. 2019). Human ANDV immune plasma intravenous infusion appears safe for HCPS (Vial et al. 2015). Using mAb JL16 or MIB22 alone as monotherapy, or combining both in a cocktail, could be an effective treatment after exposure for patients infected with ANDV-induced HCPS. In small animal models, specific DNA vaccines have demonstrated protective effects against HCPS, as well as passive transfusion of polyclonal serum obtained from rabbit, duck, and human sources. In HCPS patients, the presence of abundant hantavirus-specific immunoglobulin G (IgG) during the early stages of the disease serves as a predictor for survival. Additionally, administering convalescent immune plasma from HCPS survivors to acute HCPS patients has shown to significantly reduce fatality rates. This demonstrates that antibodies make a significant and practical difference in controlling hantaviruses in vivo (Garrido et al. 2018).

8. PREVENTION AND CONTROL

To prevent the disease, the most important thing is to keep rodents away from where people live and work. This means getting rid of anything that rodents can eat or use to make nests, both inside and outside the house. It also means blocking any holes or gaps that rodents can use to get inside the house. Trapping and killing rodents is another way to control them. When cleaning areas that might have rodent droppings or urine, people should be careful not to breathe in the dust. They should wear rubber gloves and masks,

and use disinfectants to clean the area. To protect people from getting infected, especially those who are at high risk, vaccines against Hantavirus are needed (Dheerasekara et al. 2020). GRFT is a lectin that binds to sugars with many mannose units used as a topical microbicide for the prevention of hantavirus infection. It can block ANDV infection very well. It stops the virus from entering the cells by interfering with its envelope protein. 3mGRFT is a modified version of GRFT that works better than the original one against ANDV and SNV infection (Kuenzli et al. 2018).

9. CONCLUSION

Hantaviruses are zoonotic viruses transmitted by rodents and can cause severe illnesses in humans, such as Hantavirus Pulmonary Syndrome (HPS) and Hemorrhagic Fever with Renal Syndrome (HFRS). The diseases have a significant impact on vascular endothelial cells, leading to respiratory failure and kidney injury. Climate change may influence hantavirus transmission, and person-to-person transmission of some hantaviruses has been observed. Diagnosis is challenging based solely on clinical symptoms, and there are no approved antiviral drugs or vaccines. Supportive care remains the main approach to managing severe cases. Preventative measures involve rodent control and proper hygiene to avoid exposure. Potential treatments under investigation include immune plasma infusions and therapeutic approaches like DNA vaccines and monoclonal antibodies.

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