



Review Article

Hantavirus Diseases: A Review of Virology, Clinical Features, and Therapeutic Approaches

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Hantaviruses are worldwide zoonotic infections that cause two main human diseases: Hemorrhagic Fever with Renal Syndrome (HFRS) in Eurasia and Hantavirus Pulmonary Syndrome (HPS) in the Americas. These diseases are acquired mostly by inhaling aerosolized excreta from infected rodent reservoirs but transmission may also occur by direct contact or, rarely, person-to-person transmission with some South American strains. Hantaviruses produce severe morbidity and mortality, the severity of which depends on the viral species, the host immunological response, and the timeliness of medical assistance. Much has been learned over the last several decades from large-scale studies on the distribution of reservoir hosts, environmental determinants of virus persistence, and spillover into human populations that provide essential insight into hantavirus ecology. Significant progress has also been achieved in understanding molecular virology and immunopathogenesis, revealing that much of the clinical severity is due to immune-mediated vascular leakage rather than direct viral cytopathic effects. Yet despite the scientific improvements, there are still big gaps. There are no licensed vaccines for global use and antiviral treatments are limited in scope and efficacy with supportive care being the mainstay of clinical management. Diagnostic methods are improving, but species-specific identification is problematic in locations where numerous hantaviruses cocirculate. Furthermore, environmental change, urbanization, and changing rodent population dynamics are providing more opportunities for viral development and global spread. This review covers the present state of knowledge about hantavirus biology, illness features, clinical management, diagnostic methods, prevention efforts, and research objectives to reduce the global burden of hantavirus disease.

Keywords: Hantavirus; Hemorrhagic Fever with Renal Syndrome; Hantavirus Pulmonary Syndrome; Zoonotic transmission; Rodent reservoirs; Viral pathogenesis.

INTRODUCTION

Hantaviruses are negative-sense RNA viruses enclosed in the family Hantaviridae and transmitted predominantly by rats. Humans are typically infected by inhalation of contaminated aerosols from rodent urine, saliva, or feces (1). Hantavirus disorders occur in two main clinical forms: HFRS, common in China,

Russia and portions of Finland, and HPS, documented mostly in the United States and Argentina (2,3). The importance of hantaviruses as emerging pathogens in the Americas was recognized in 1993 with the identification of the Sin Nombre virus in a large epidemic in the Four Corners region (4). Since

then, many hantavirus species have been characterized, each linked with different rodent hosts (5).

2. Molecular Biology and Virology:

The hantavirus genome is tripartite, consisting of S, M, and L segments encoding for nucleocapsid (N) protein, glycoproteins (Gn/Gc), and RNA-dependent RNA polymerase (6). $\beta 3$ integrins on endothelial cells facilitate viral entry, contributing to the vascular leakage observed in HPS and HFRS (7). Recent structural studies have pointed to the importance of glycoprotein spikes in receptor binding and immune evasion (8). Replication occurs in the cytoplasm, with the virus being assembled in the Golgi apparatus (9). Chronic infection and viral shedding result from mechanisms that restrict inflammation and prevent host immune activation (10) in persistent viral infections in rodents.

3. Epidemiology:

The distribution of hantavirus depends on the ecology of the rodent hosts. HFRS-causing species, such as Hantaan virus and Seoul virus, are endemic in China, South Korea and Russia (11). Milder to moderate illness severity has been reported for Puumala and Dobrava virus infections in Europe (12). HPS-associated viruses such as Sin Nombre virus in North America and Andes virus in South America have much greater fatality rates, up to 35-40% (13). Andes virus is unique in having confirmed person-to-person transmission (14). Environmental factors that influence disease onset include climatic change, rodent population cycles, and human encroachment on rodent habitats (15,16). Human cases have increased with rodent population increases, which can be stimulated by increased precipitation and food availability (17).

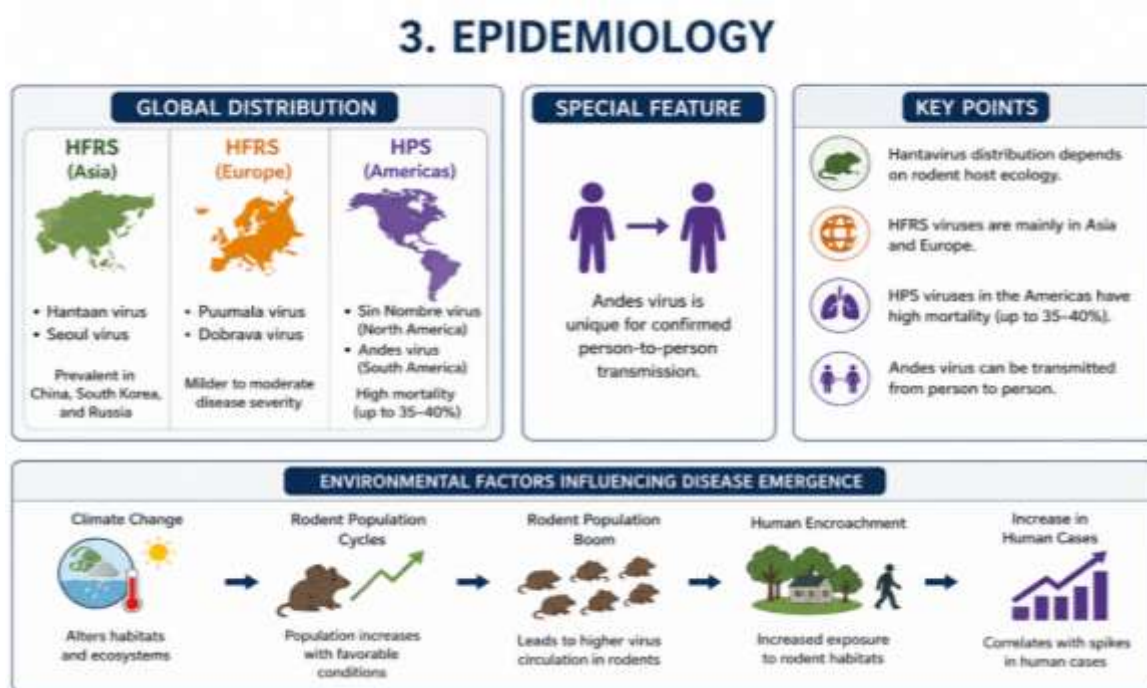


Figure 1: Epidemiology of Hanta Virus

4. Transmission and Reservoir:

Hosts Rodents are natural reservoirs, where chronic infection is maintained without overt disease (18). Transmission to people is by aerosolized excreta or direct touch (19). Arthropods and domestic animals are not important in transmission; In most cases each hantavirus species is linked to only one rodent

species, a phenomenon referred to as host-virus co-evolution (20). Examples are Hantaan virus and *Apodemus agrarius* and Sin Nombre virus and *Peromyscus maniculatus* (21). Spillover infections do occur, but seldom establish sustained transmission cycles.

5. Pathogenesis:

The hallmark of hantavirus disease is increased vascular permeability. This has been linked to immune-mediated endothelial dysfunction rather than cytopathic impact (22). High levels of cytokines such TNF- α , IL-6 and interferons cause capillary leakage and organ dysfunction (23). In HFRS the damage is predominantly to the kidneys with proteinuria,

hematuria and acute renal failure (24). In HPS there is gross non-cardiogenic pulmonary oedema of the lungs leading to respiratory failure (25). Autopsy studies reveal mononuclear cell infiltration without significant tissue damage, supporting an immunopathogenic mechanism over direct viral cytotoxicity (26).

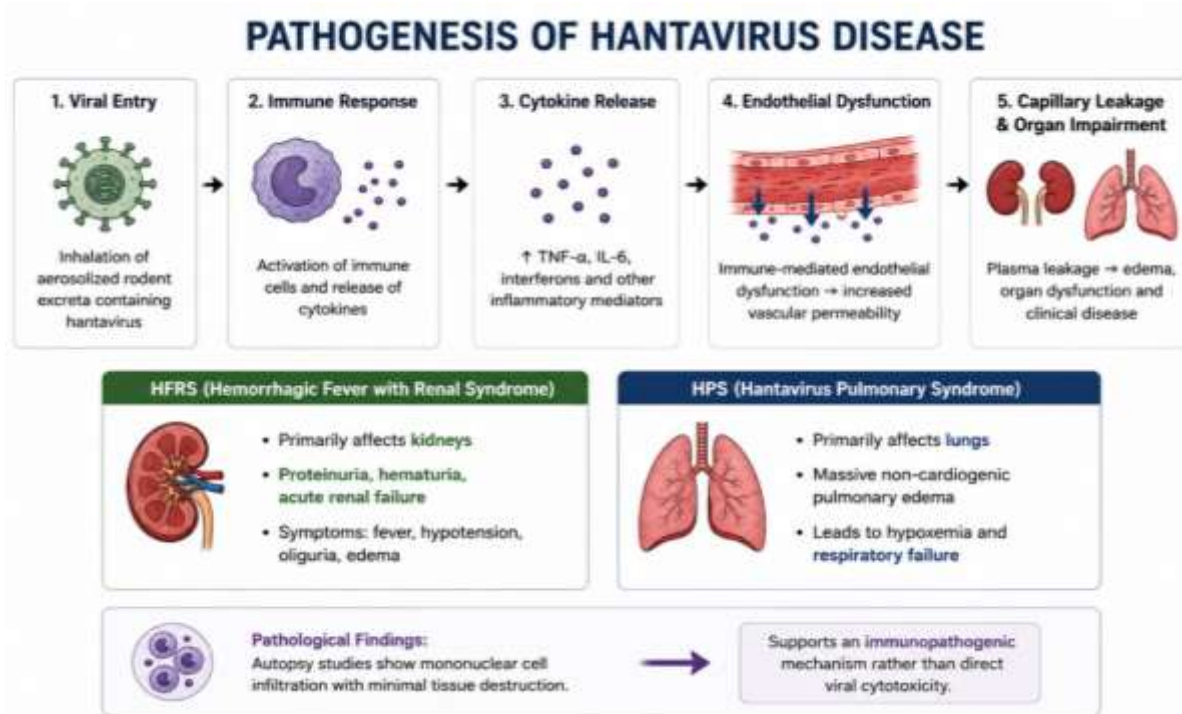


Figure 2: Pathogenesis

6. Clinical Features:

The presentation of disease associated with hantavirus infections varies widely according to the virus involved. Old World hantaviruses generally cause Hemorrhagic Fever with Renal Syndrome (HFRS), and New World hantaviruses typically produce Hantavirus Pulmonary Syndrome (HPS). Renal function and vascular integrity have different underlying pathophysiologic changes during each of the five components in the clinical course of HFRS, which include: fever, hypotension, oliguric, diuretic, and convalescent phases (27). Fever, petechiae, abdominal pain, and varying degrees of renal failure are commonly seen with this disease (27). HPS, on the other hand, begins with a prodromal phase of nonspecific flu-like symptoms (e.g., fever), myalgia, and malaise, followed by rapid development into a cardiopulmonary phase in the majority of patients requiring intensive care support with cough,

tachypnea, hypoxia, and acute respiratory failure within days after onset of illness (28). The early symptoms of HPS can be nonspecific, and the majority of individuals experiencing these symptoms present with viral illnesses that mimic HPS until rapid onset of lung impairment occurs, making early diagnosis extremely difficult. Mortality rates for HPS and HFRS are also very different; for example, the mortality rate for HPS is approximately 30-40%, while the mortality rate for HFRS ranges from 1-15% depending upon which hantavirus was contracted and the availability of supportive medical care (29).

7. Diagnostic Approach:

The diagnosis of hantavirus infection relies on a mixture of serological, molecular, and histopathological techniques, which assist in surveillance activity and also to confirm cases. The primary method for diagnosing acute infections is still

serology (specifically, the use of enzyme immunoassay [ELISA] tests for IgM and IgG) which are widely available, highly sensitive, and may detect either new or previous exposure to the virus (30). Molecular detection using reverse transcription polymerase chain reaction (RT-PCR) is an excellent complementary method and can also differentiate between hantavirus species when sequence data is available, and may also assist with clinical diagnosis of hantavirus infection prior to seroconversion (4). Immunohistochemistry is useful for detecting viral antigens in tissues during postmortem examinations or in retrospective epidemiologic studies to provide definitive identification of cases where death was due to hantavirus (9). However, the high level of cross-reactivity between closely related species makes the interpretation of serological results difficult in those geographic regions where multiple hantaviruses are currently circulating. This presents a challenge to accurate diagnosis, and emphasizes the need for the development of species-specific tests, and improved characterization of antigens, in order to improve diagnostic accuracy (11).

8. Treatment:

Current Hantavirus infections are mainly treated symptomatically through hemodynamic monitoring, resuscitation of fluids, and treatment for shock,

respiratory failure, and renal dysfunctions; therefore, clinical management aims to stabilize the patient by monitoring these 3 critical physiological processes (25). Further evidence has demonstrated that admission to an intensive care unit (ICU) early in the course of the illness and the start of advanced supportive therapies, such as mechanical ventilation and careful fluid management, greatly reduce mortality rates among HPS patients, suggesting that early diagnosis and intervention can lead to better outcomes (28). Ribavirin is one of the antiviral therapies that has been shown to be effective against several hantaviruses that cause HFRS but historically has demonstrated efficacy at the early stages of infection; however, there is limited evidence to support the use of ribavirin for treating patients with HPS due to the differences in the pathogenesis of Old World and New World hantaviruses and the differences in their susceptibility to treatment with antivirals (12). In addition, the inconsistent and frequently inconclusive results of various other treatment modalities have demonstrated the need for more targeted and evidence-based therapies; for instance, the use of extracorporeal membrane oxygenation (ECMO) to provide life support for patients with refractory respiratory failure or adjunctive corticosteroid therapy to lessen immune-mediated pathologies associated with HPS. (29)

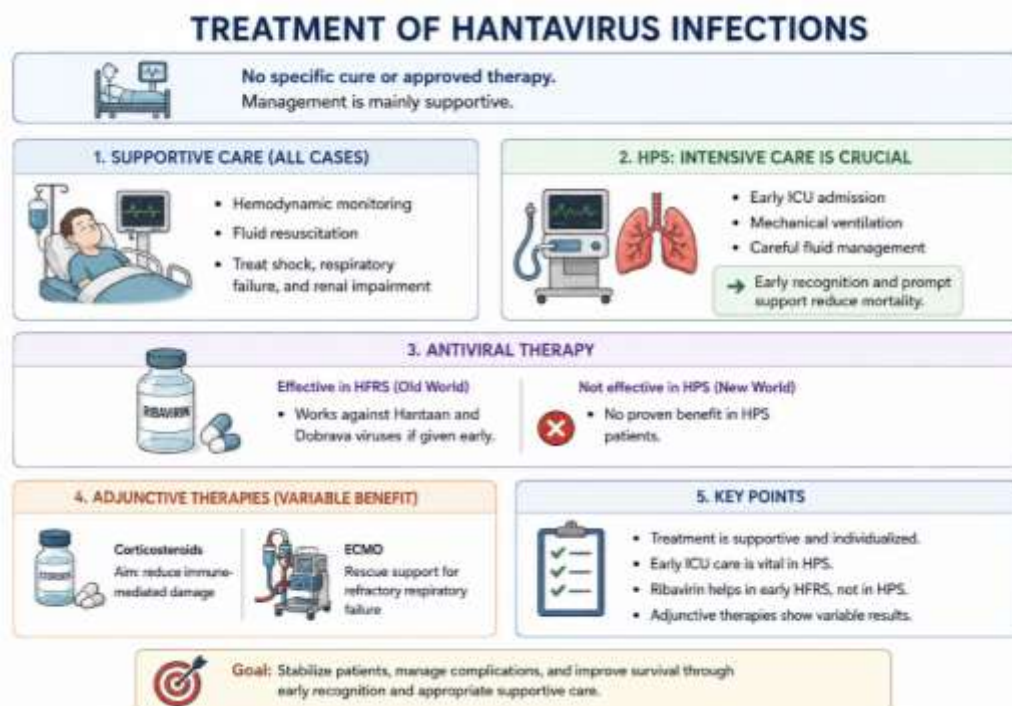


Figure 3: Therapeutic approaches for Hantavirus infections

9. Prevention and Control:

Combining environmental management, public health infrastructure, and more vaccine development can effectively prevent and control hantavirus infections. Prevention is the key to rodent control, as decreasing rodent numbers in residential, agricultural and public areas greatly reduces human exposure to infectious excreta and polluted aerosols (15). This must be complemented with safe cleanup measures such as wet disinfection treatments, use of personal protective equipment, and avoidance of dry sweeping, to limit unintended aerosolization of virus particles (19). In order to enable targeted treatments and resource allocation, public health surveillance systems are particularly crucial for tracking rodent reservoir populations, human cases, and early identification of emergent hantavirus strains (2). Some regions, including South Korea and China, have adopted a formalin-inactivated Hantaan virus vaccine, which has demonstrated moderate protective efficacy and decreased the incidence of hemorrhagic fever with renal syndrome. (11). Novel genetic vaccine platforms, such as DNA-based constructions and mRNA technologies, are now being explored and offer promise to elicit larger and more persistent immune responses across numerous hantavirus species beyond previous techniques (16).

FUTURE RESEARCH:

Directions Future research directions for hantavirus must address numerous important gaps that remain in the way of effective disease control and prevention. First, development of widely protective vaccines is an essential goal as current candidates exhibit low cross-protection across multiple hantavirus species and require enhanced antigen design and modern vaccine platforms (13). Equally crucial is the search for antiviral medicines targeting the machinery of viral replication such as the polymerase complex and nucleocapsid protein interactions, which are promising but underexplored therapeutic approaches (7). There is also the need for better understanding of hantavirus immunopathogenesis, including dysregulated immune responses leading to severe clinical symptoms such as capillary leakage and pulmonary edema (23). Furthermore, predictive ecological modelling that may incorporate climate

variables, rodent population dynamics and human behavioural aspects will be essential to forecast and mitigate risk of outbreaks in both endemic and newly impacted areas (17). Finally, new diagnostic assays to increase species specificity and early identification are required to aid timely clinical intervention and surveillance efforts (30). Hantaviruses are likely to remain a major, growing emerging infectious disease hazard as environmental change, urbanization and socioeconomic factors continue to drive changes in worldwide rodent distribution patterns.

CONCLUSION:

Hantaviruses are a major growing class of zoonotic diseases that have a significant effect on global public health. Over the past several decades considerable progress has been made in understanding their ecology, molecular virology, host-pathogen relationships, and immune-mediated disease processes. These advances have clarified the mechanisms involved in persisting infection by some rodent reservoirs, viral spillovers, and the immune response associated with causing death in people, rather than direct cytotoxic effects of the virus. Despite these advances, several gaps still remain in the knowledge of how to understand, manage and control these deadly zoonotic agents, particularly with regard to the degree of morbidity/mortality associated with Hantavirus Pulmonary Syndrome (HPS) and moderate to severe degrees of Hemorrhagic Fever with Renal Syndrome (HFRS). The lack of approved vaccines for mass use in humans appears to be the existing obstacle for prevention of severe disease caused by hantaviruses. In addition, rodent reservoirs of hantaviruses and associated hantavirus infections are becoming increasingly prevalent globally as a result of urban sprawl, alterations in the environment, and increased contact between people and wildlife. These changes highlight the urgent need for real-time ecological dynamic monitoring capabilities to better characterization of novel hantavirus strains through improved surveillance methods. Various methods of research should be used together to obtain an effective understanding of how to decrease the risk of transmitting hantavirus. These will include using high-elevation ecosystems and studying associated viruses through genetic research, immunological mechanisms, structural studies, and predictive

modeling. To reduce the risk of transmitting hantavirus, scientists must use these scientific methods in conjunction with improved public health infrastructure and targeted community education. The scientific and medical communities need to continue working together to combat the increasing threat posed by hantavirus infections. There is a requirement to develop vaccines, antiviral drugs, and monitoring systems at the global level to prevent future outbreaks; therefore, it can only be done by working together collaboratively.

CONFLICT OF INTEREST:

The authors have no any conflicts of interest concerning this investigation.

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