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Review

Hantavirus Infections: A Review of Pathogenesis, Diagnosis, Treatment, and Vaccine Developments

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Abstract

Hantaviruses are zoonotic RNA viruses belonging to the family Hantaviridae, primarily transmitted to humans through rodent reservoirs. These viruses cause two major clinical syndromes in humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). Due to their high mortality rates, potential for global spread, and the lack of specific antiviral therapies, hantaviruses are regarded as significant public health threats. In recent years, advances in molecular virology, immunology, structural biology, and vaccine technologies have provided important insights into hantavirus pathogenesis and host–virus interactions. Current research has increasingly focused on host-targeted antiviral strategies, TFEB-mediated lysosomal degradation mechanisms, monoclonal antibody therapies, and mRNA-based vaccine platforms. In addition, advanced molecular diagnostic methods and metagenomic surveillance systems have improved opportunities for early diagnosis. This review comprehensively summarizes the current literature regarding the epidemiology, virology, pathogenesis, immune responses, clinical manifestations, diagnostic approaches, current treatment options, and vaccine development strategies for hantavirus infections.

Keywords: Antiviral Therapy, Hantavirus, HCPS, HFRS, Orthohantavirus, Vaccine, Zoonosis

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Hantaviruses are enveloped, negative-sense, single-stranded RNA viruses belonging to the genus Orthohantavirus within the order Bunyavirales. Transmission to humans primarily occurs through inhalation of aerosolized urine, feces, or saliva from infected rodents.[1,2]

Clinically, hantaviruses cause two major syndromes: hemorrhagic fever with renal syndrome (HFRS), which is more common in Europe and Asia, and hantavirus cardiopulmonary syndrome (HCPS), which is predominantly observed in the Americas.[3]

Hantavirus infections first gained attention during the Korean War, when clusters of severe febrile illness were reported. To date, more than fifty hantavirus species have been identified, many of which are capable of causing human disease. Mortality rates vary according to the viral species, ranging from less than 1% in Puumala virus infections to as high as 40% in infections caused by Andes or Sin Nombre viruses.[4–6]

In recent years, climate change, deforestation, urbanization, and increased human–wildlife interaction have renewed epidemiological concern regarding hantaviruses. Furthermore, heightened global awareness of zoonotic diseases following the COVID-19 pandemic has accelerated hantavirus-related research.[1,7]

The aim of this review is to summarize current epidemiological, molecular, and clinical knowledge regarding hantavirus infections and to evaluate emerging therapeutic and vaccine strategies.

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Virology and Classification

The hantavirus genome consists of three segments: small (S), medium (M), and large (L). The S segment encodes the nucleocapsid protein, the M segment encodes the Gn and Gc glycoproteins, and the L segment encodes the RNA-dependent RNA polymerase.[1,8]

Virions are enveloped particles approximately 80–120 nm in diameter and primarily replicate within endothelial cells.[9] One of the distinguishing characteristics of hantaviruses is that they do not exert direct cytolytic effects; instead, they induce immune-mediated endothelial damage.[9,10]

Old World Hantaviruses

Old World hantaviruses are primarily found in Europe and Asia and are mainly associated with HFRS. Major species include:

- Hantaan virus (HTNV)
- Seoul virus (SEOV)
- Puumala virus (PUUV)
- Dobrava-Belgrade virus (DOBV)

Puumala virus is the principal causative agent of nephropathia epidemica in Northern Europe.[11]

New World Hantaviruses

New World hantaviruses occur in North and South America and are associated with HCPS. Major species include:

- Sin Nombre virus
- Andes virus
- Laguna Negra virus

The Andes virus is of particular importance because it has demonstrated limited potential for person-to-person transmission.[12]

Epidemiology

Hantavirus infections are estimated to cause approximately 150,000–200,000 cases annually worldwide. However, the true burden is believed to be considerably higher because of asymptomatic infections and limited diagnostic capacity.[13,14]

China bears the highest global burden of HFRS. In Europe, Puumala virus is especially prevalent in Finland, Sweden, and Germany. HCPS is most frequently reported in Argentina, Chile, Brazil, and the southwestern regions of the United States.[15–17]

Recent studies have demonstrated that temperature fluctuations, rainfall patterns, rodent population density, and habitat alterations significantly influence hantavirus prevalence. Within the framework of the "One Health" concept, the integrated evaluation of human, animal, and environmental health has been strongly emphasized.[7]

Transmission Dynamics

Human infection primarily develops through inhalation of aerosolized rodent secretions. Farmers, forestry workers, laboratory personnel, and military staff are considered high-risk groups.[18,19]

Aerosols generated during the cleaning of enclosed spaces contaminated with rodent excreta represent a major source of transmission. In rare cases, rodent bites may also result in infection.[18,20]

Person-to-person transmission has been documented for Andes virus, particularly during the prodromal phase through close respiratory contact.[12]

Pathogenesis

The hallmark pathological feature of hantavirus infections is increased vascular permeability.[10]

Viral Entry and Tropism

Hantaviruses attach to endothelial cells primarily through β3 integrins, protocadherin-1, and heparan sulfate receptors.[21,22]

Differences in cellular tropism between Old World and New World hantaviruses have been demonstrated and are believed to contribute to variations in clinical virulence.[23]

Endothelial Dysfunction

Hantaviruses do not directly lyse infected cells. Instead, functional impairment develops within infected endothelial cells, leading to increased capillary permeability.[10]

Major mediators implicated in pathogenesis include:

- TNF-α
- IL-6
- VEGF
- Complement activation

These processes may ultimately result in pulmonary edema, hypotension, shock, and acute kidney injury.[24,25]

Immune Response

Innate Immunity

Type I interferon responses play a critical role in controlling hantavirus infection.[1,26] However, the virus can suppress interferon signaling through various viral proteins.

Macrophages and natural killer cells contribute to viral clearance, although excessive inflammatory responses may exacerbate tissue damage.[27]

Adaptive Immunity

CD8+ T lymphocytes are essential for viral clearance; however, excessive activation may aggravate endothelial injury.

Neutralizing antibodies directed against Gn and Gc glycoproteins constitute a key component of protective immunity.[1,28]

Clinical Manifestations

Hemorrhagic Fever with Renal Syndrome (HFRS) HFRS classically progresses through five phases:

1. Febrile phase
2. Hypotensive phase
3. Oliguric phase
4. Diuretic phase
5. Convalescent phase

Major clinical findings include:

- Fever
- Headache
- Myalgia
- Thrombocytopenia
- Proteinuria
- Acute kidney injury[14,15]

Hantavirus Cardiopulmonary Syndrome (HCPS)

HCPS is characterized by rapidly progressive pulmonary edema and respiratory failure.

Major symptoms include:

- Fever
- Dyspnea
- Hypoxemia
- Tachycardia
- Non-cardiogenic shock

Mortality rates may reach 30–40%.[3,13]

Diagnosis

Serological Methods

Detection of hantavirus-specific IgM and IgG antibodies by ELISA remains the most widely used diagnostic approach. Immunoblot and immunofluorescence assays are also employed.[13,29]

Molecular Diagnosis

RT-PCR is particularly useful during the early viremic phase.

The following techniques are increasingly utilized:

- Multiplex PCR systems
- Metagenomic sequencing
- Portable molecular diagnostic platforms[13,30]

Treatment

Currently, there is no universally approved specific antiviral therapy for hantavirus infections.[19]

Supportive Therapy

The cornerstone of management includes:

- Intensive care support
- Oxygen therapy
- Hemodynamic stabilization
- Dialysis
- Extracorporeal membrane oxygenation (ECMO) [3]

Ribavirin

Ribavirin has shown benefit when administered early in HFRS cases; however, its efficacy in HCPS remains limited.

Novel Antiviral Approaches

Favipiravir and several RNA polymerase inhibitors are currently under experimental investigation.[31,32,36]

A significant study published in 2025 demonstrated that apatinib suppresses Hantaan virus replication by enhancing TFEB-mediated lysosomal biogenesis, thereby promoting degradation of viral proteins. This strategy appears promising for host-targeted antiviral therapy. [33,37]

Monoclonal Antibodies

Neutralizing monoclonal antibodies targeting Gn/Gc glycoproteins have demonstrated encouraging results in experimental studies.[38]

Structural Biology and Reverse Genetics

Advances in cryo-electron microscopy (cryo-EM) technologies have enabled the detailed characterization of hantavirus glycoprotein structures.

These studies are important for:

- Identification of neutralizing epitopes
- Rational vaccine design
- Development of novel antiviral targets

Reverse genetics systems have also enabled the laboratory generation of recombinant hantaviruses [1,27]

Vaccine Development

Inactivated Vaccines

Inactivated vaccines against Hantaan and Seoul viruses are currently used in China and South Korea; however, long-term protective efficacy remains variable.[35]

DNA Vaccines

DNA vaccines are considered promising because of their ability to induce robust cellular immune responses.[36]

mRNA Vaccines

Following the COVID-19 pandemic, mRNA technologies have increasingly been applied to hantavirus research.

Studies published in 2025 demonstrated that Gn/Gc-targeted mRNA vaccines are capable of inducing broad neutralizing antibody responses.[1]

Viral Vector Vaccines

Research on recombinant vesicular stomatitis virus (rVSV)-based vaccine platforms is also ongoing.[37]

Animal Models

The principal experimental models include:

- Hamsters
- Mice
- Humanized mouse models
- Non-human primates

In hamster models, Andes virus produces lethal pulmonary disease closely resembling human HCPS.[25]

Public Health Perspective

Rodent control remains the most effective strategy for hantavirus prevention.

Preventive measures include:

- Avoiding aerosolization of rodent excreta
- Proper disinfection of enclosed environments
- Use of personal protective equipment
- Active surveillance systems

Climate change and environmental transformation are expected to influence rodent populations and may increase the future risk of hantavirus outbreaks.[7,38].

Conclusion

Hantaviruses are important zoonotic pathogens with substantial mortality potential. Recent advances in molecular biology, immunology, and structural virology have significantly improved the understanding of hantavirus pathogenesis. Nevertheless, the lack of globally effective antiviral therapies and widely licensed vaccines remains a major challenge.

mRNA vaccine platforms, host-targeted antiviral strategies, monoclonal antibody therapies, and advanced surveillance systems appear highly promising for future hantavirus control. Multidisciplinary global collaboration based on the "One Health" approach will be essential for the effective prevention and control of hantavirus infections.

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