

Review Article



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Hemorrhagic Fever with Renal Syndrome: Literature Review, Epidemiology, Clinical Picture and Pathogenesis

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ABSTRACT

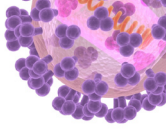
Hantaviruses can cause two types of infections in humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome. The old world hantaviruses, primarily Hantaan virus (HTNV), responsible for causing HFRS occurs endemically in Asia and Europe. *Apodemus agrarius*, a striped field mouse, is being considered as main host reservoir for HTNV. Infection in humans is typically accidental and occurs when virus-containing rodent excretions such as urine, feces, or saliva are aerosolized. The major clinical manifestations includes increased vascular permeability causing vascular leakage, acute kidney injury and coagulation abnormalities. The case fatality rate of HFRS varies around 5.0 - 10.0% depending on the causative viral agent. The direct effects of viral infection on endothelial cells, as well as the immunological response to the viral infection, have been suggested to play a key role in the pathogenesis of HFRS. This article summarizes the current knowledge of HFRS epidemiology in Korea and around the globe, etiology, host transmission, clinical presentation, pathogenesis, diagnostic techniques, treatment, and prevention.

Keywords: *Bunyavirus*; Hemorrhagic fever with renal syndrome; Hantavirus; Pathogenesis; Epidemiology

INTRODUCTION

Hemorrhagic fever with renal syndrome (HFRS), a rodent borne viral illness caused by Hantaviruses [1]. The first outbreak of the hantavirus pandemic was discovered during the Korean War (1950 - 53). More than 3,000 United Nations troops have been diagnosed with Korean hemorrhagic fever since the outbreak during the Korean War [2]. Every year, about 100,000 instances of HFRS are reported, the majority of which occur in China, Korea, and Russia [3]. HFRS has become a major epidemic primarily in Asia and Europe. Among all, China is the most severely impacted country and accounting for around more than 90% of all HFRS cases worldwide in the last few decades [4, 5].

In Korea, HFRS was originally identified in a United Nations (UN) soldier stationed in the center front, often known as the "Iron Triangle". During the Korean War, it finally spread to Cheorwon, Gimhwa, and Pyeongyang. Because this illness looked to be indigenous to Korea,



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United States (US) military officials named to it as Korean hemorrhagic fever. A comparable disease, however, was described in a Chinese medical text published around A.D. 960. During the Second World War, HFRS infected 10,000 Japanese military soldiers stationed in Manchuria, and several hundred Russian soldiers in the Far East also contracted the disease. During the Korean War, American researchers founded an epidemic hemorrhagic fever center in Seoul in 1952, but the pathogen remains mysterious [6].

Professor Ho Wang Lee and his fellow researchers detected an antigen in the lung and kidney tissues of *Apodemus agrarius*, caught in Songnae-dong, Dongducheon-si, and Gyeonggi-do, areas where hemorrhagic fever is common. Using immunofluorescence technique, the antigen was found to react with convalescent phase serum obtained from patients with Korean hemorrhagic fever. In 1978, the team named the antigen as Korean-type antigen and isolated it from blood samples of hemorrhagic fever patients and successfully replicated the virus in A549 cells. This unique virus was termed Hantaan virus (HTNV) after the Hantaan river in 1980 [6]. In 1982, the World Health Organization (WHO) organized a conference with the Working Group on Hemorrhagic Fever with Renal Syndrome in Tokyo, Japan. During this conference, a group of disorders with clinical characteristics comparable to Korean hemorrhagic fever were designated hemorrhagic fever with renal syndrome. In 1984, Hantavirus, a novel genus was identified that includes all pathogens of HFRS [6].

Based on the geographical areas where they found, the Hantaviruses are conventionally divided into two categories: Old world hantaviruses and New world hantaviruses. Amur virus (AMV), Seoul virus (SEOV), HTNV, Dobrava virus (DOBV), Tula virus (TULV), and Puumala virus (PUUV) are pathogenic Old world hantaviruses that cause HFRS in humans [4, 7]. HTNV and DOBV tend to produce the most severe form of disease, with mortality rate of around 5.0 - 10.0% [4], whereas Puumala virus is endemic in northern Europe and usually causes a less severe disease, a milder variant of HFRS, also referred as *nephropathia epidemica* (NE), with a low mortality rate of 0.1 - 0.2% [8]. The first pathogenic of New world hantavirus (Sin Nombre virus) that causes Hantavirus cardiopulmonary syndrome (HCPS), was discovered in the early 1990s in the Four Corners region of the US, resulting in second outbreak of hantavirus [7]. Numerous additional pathogenic New world hantaviruses were identified and characterized [9].

Hantavirus is a virus that primarily infects human vascular endothelial cells (ECs) and causes significant damage to capillaries and small vessels. However, understanding the pathophysiology of HFRS is not sufficient. One of the problems is a scarcity of appropriate animal models. Many scientific and clinical research have recently shed light on the disease's underlying causes and suggested various ways to lessen the severity of the disease. We performed this study to review literature on the pathophysiology of HFRS and predict on future research possibilities. We will start with the basics of Hantaviruses, and then proceed further to rodent reservoirs and human transmission pathways. Afterwards, we will go through the clinical manifestations of HFRS and with its epidemiology and geographical distribution in this region and around the globe. We will further highlight the key pathophysiology causing vascular leakage, coagulation abnormalities, and other symptoms. Finally, we will go through some of the most recent advancements in therapy, with an emphasis on some novel medications that may help to lessen the negative effects of infection on the host.

ETIOLOGICAL AGENT AND MORPHOLOGY

Hantaviruses are enveloped RNA viruses with negative-stranded genomes that belong to the *Bunyaviridae* family and the genus *Hantavirus* [10]. The viral particle has an oval or spherical shape with a diameter of 80 to 120 nm. The HTNV-RNA genome is divided into three main sections: small [S: between 1,696 and 2,083 nucleotide (nt) in length], medium (M: between 3,613 and 3,707 nt) and large (L: between 6,530 and 6,550 nt). The nucleocapsid (N) protein is encoded by the S segment; the envelope glycoproteins (G1 and G2) are encoded by the M segment; and the RNA dependent polymerase protein is encoded by the L segment [11, 12]. The three segments' 3' and 5' termini are preserved and complimentary, permitting the formation of panhandle structures, which are considered to have a function in the viral replication and transcription control [13]. HTNV is quite stable and can remain infectious for two weeks at room temperature and possibly longer at lower temperatures.

NATURAL HOST AND TRANSMISSION IN HUMANS

In Far East Russia, China, and Korea, surveillance efforts revealed the presence of HTNV and HTNV-like viruses in *A. agrarius* and *A. peninsulae* rodents, SEOV and SEOV-like viruses in *Rattus norvegicus* [14, 15]. DOBV, and DOBV-like viruses were found in *A. flavicollis*, *A. agrarius*, and *A. ponticus* in Europe [16, 17]. These reservoir animals are asymptomatic following infection. Because the hantaviruses have evolved distinct escape strategies against the innate immune system throughout their long co-evolution within these diverse hosts species [18].

Infection in humans is typically accidental and occurs when virus-containing rodent excretions such as urine, feces, or saliva are aerosolized. Humans are not the natural host of hantavirus and are considered as dead-end host [19]. More than 70.0% of HFRS cases occur in rural regions with poor housing conditions and high rodent population, with local farmers accounting for the majority of infected patients [3]. People who live or work in close proximity to infected rodents (farmers, woodcutter, hikers, etc.) are at a higher risk of infection [4].

HFRS is most common from late autumn until the following spring, with two incidence peaks [20]. The onset of the HFRS epidemic is determined by the kind of pathogenic hantavirus and correlates with increased human outdoor activity in the spring and fall. The size of rodent populations may have an impact on human disease epidemics [21].

GENERAL CLINICAL CHARACTERISTICS OF HFRS

The disease in humans is clinically characterized by acute onset of fever, headache, abdominal discomfort, acute kidney injury (AKI) and hemorrhage. In Korea, fever (94.0%), abdominal discomfort (64.0%) and headache (50.7%) are the most common early clinical symptoms. Although diarrhea as a major presentation is rarely recognized as early indicator, however, a report in Korea suggested that HFRS might present with gastrointestinal symptoms like acute diarrhea [22]. Another recent report in Korea [23], indicated the association of HTNV infection with appendicitis and confirmed the presence of HTNV antigen in the peripheral nerve bundle of appendix tissue via immunohistochemical staining. The diagnosis was further confirmed by analysis of patient's plasma by immunofluorescence assay and nested reverse transcription-polymerase chain reaction (RT-PCR) [23].

HFRS can show as mild, moderate, or severe illness, depending on the causing virus. DOBV and HTNV cause severe HFRS, SEOV causes moderate HFRS, and Puumala virus causes mild HFRS. The disease has a 1 - 5 week incubation period and starts with a fever and influenza-like symptoms and may progress to more severe symptoms characterized by hemorrhage, hypotension and acute renal failure [24]. Following the incubation period, the illness progresses through a five-phase clinical course: febrile phase (3 - 5 days), hypotensive phase (few hours to few days), oliguric phase (3 - 7 days), and diuretic phase (1 - 2 weeks) leading to convalescent phase (3 - 6 months) [22, 25]. Furthermore, in severe cases, some of these stages may overlap, while in moderate cases, one or two phases may be missing. Anemia, leukocytosis, thrombocytopenia, elevated liver enzymes, serum creatinine (renal dysfunction), proteinuria, and hematuria are all common laboratory observations during the acute stage of the illness. The majority of instances recover successfully, however certain severe cases might still result in headaches, restlessness, excessive sweating, hemorrhage, and hyperdiuresis.

Kidney damage is common in HFRS, with acute tubulointerstitial nephritis being the most common clinical manifestation accompanying inflammatory cell infiltration [26]. AKI is a common cause of mortality in individuals with HFRS, especially during the oliguric phase [27]. AKI is characterized clinically by severe proteinuria, haematuria, and a rapid decrease in the glomerular filtration rate (GFR), leading to edema, electrolyte and acid-base balance disturbances [28]. Individuals with old age are more prone to have severe AKI, as well as shock, hematuria, thrombocytopenia, and leukocytosis. Those with severe AKI typically require dialysis or continuous blood purification and spend more time in hospital than patients without AKI [27].

Thrombocytopenia, one of the variables that increases blood vessel permeability, is associated with severe AKI in individuals with acute HTNV infection. Acute thrombocytopenia is a typical HFRS laboratory finding that lasts throughout the Hantavirus infection. As a result, thrombocytopenia is a significant factor in the diagnosis of HFRS [29].

Central nervous system, endocrine and cardiopulmonary and ocular findings are also major clinical manifestations of HFRS. A report from Korea, indicated the occurrence of central diabetes insipidus (DI) and panhypopituitarism caused by HTNV-associated HFRS [30], and suggested the clinicians to distinguish central DI in HFRS patients with a prolonged diuretic phase even if the pituitary MRI results were normal. In the neurological system, Guillain-Barré syndrome, meningoencephalitis, generalized seizures, acute disseminated encephalomyelitis, and urinary bladder paralysis have been described. Pulmonary edema, shock, and perimyocarditis, may develop in cardiopulmonary system. Multiorgan failure, disseminated intravascular coagulopathy, multiple bleedings, pancreatitis, and have also been noticed, all of which can lead to a fatal outcome [31]. A long-term follow up study showed that non-Caucasian patients with HFRS exhibited statistically higher prevalence rates of transient ischemic attack, diseases of musculoskeletal system and, diabetes than non-Caucasian controls [32].

EPIDEMIOLOGY OF OLD WORLD HANTAVIRUSES CAUSING HFRS WITH ITS GEOGRAPHICAL DISTRIBUTION IN KOREA AND AROUND THE GLOBE

Shortly following the identification of HTNV, epidemiological investigations of HFRS in both human and rodent species advanced dramatically (Table 1).

1. Distribution of hantavirus causing HFRS in host reservoir

The global distribution of HFRS is influenced by the geographic dispersion of their host-reservoirs. The mouse species *A. agrarius*, a field mouse, is the vector of the prototype, HTNV [14]. In Korea, *A. agrarius* is the predominate specie of field mouse. In the years 2014 - 2015, in south-west region of Korea, a high prevalence of HTNV (86.7%) was identified in *A. agrarius* in November (autumn) [33]. *A. peninsulae*, is the second most prevalent field mouse species in Korea and carries Soochong virus (SOOV), a genetically unique HFRS-causing hantavirus [34]. The majority of SEOV circulates in the domestic rats and produces urban cases of HFRS in worldwide, *Rattus norvegicus* is considered as the principal reservoir for SEOV. DOBV is a significant cause of HFRS in the Balkans and in southern Europe. *A. flavicollis* is the primary reservoir [16]. PUUV causes NE, which is a mild form of HFRS, has been discovered throughout Scandinavia and in areas of Europe. *M. glareolus*, a bank vole (subfamily *Arvicolinae*), is the host species. In Korea, the royal vole, *M. regulus*, is thought to be a possible reservoir of a PUUV and Muju virus (MJUV) [35].

2. Distribution of hantavirus causing HFRS in humans

Infection with HTNV-related HFRS is found primarily in the rural areas of China, Korea and the far east of Russia. Every year, over 10,000 - 20,000 cases of HTNV-related HFRS are reported in China, whereas about 300 - 900 cases are reported in Korea [36]. The incidence peaks in late autumn and early winter. SEOV has a mild disease course with 40,000 to 60,000 cases reported each year, the most of which are from China. The reports are frequently found in other countries as well including, Korea, Japan and Hong Kong [4]. Unlike HTNV, the cases of SEOV infection occurs throughout the year. In Europe, over than 9,000 HFRS are recorded each year, with PUUV infections being the most prevalent. Severe cases of HFRS in Europe are caused by DOBV. In Korea, HTNV, SEOV, SOOV, MJUV, Imjin virus and Jeju virus have been discovered, among them HTNV, SEOV, SOOV and MJUV are the recognized human pathogen [6]. A study performed the phylogenetic analysis of HTNV isolates from diverse regions of Korea (Jeju, Boseong-gun and Gwangju) and revealed that these three clusters were distinct from HTNV isolates previously identified in Korea, China and Russia. This suggests the possible emergence of new HTNV strains in the southwest region of Korea [37].

Table 1. Geographical distribution and predominant natural reservoir of pathogenic Old World Hantaviruses causing hemorrhagic fever with renal syndrome (HFRS)

Hantaviruses	Serotype	Disease	Predominant Natural Reservoirs	Geographical Distribution
Old World Hantaviruses	Hantaan	HFRS	<i>Apodemus agrarius</i>	Eastern Asia (Korea, Russia and China), Central Europe [14]
	Seoul	HFRS	<i>Rattus rattus</i> , <i>Rattus norvegicus</i>	Worldwide [15]
	Amur	HFRS	<i>Apodemus peninsulae</i>	China, Japan [4]
	Puumala	NE	<i>Myodes glareolus</i>	Scandinavia, Russia, Europe [8]
	Dobrava	HFRS	<i>Apodemus flavicollis</i>	Balkans, Europe, Syria [16]
	Tula	HFRS	<i>Microtus arvalis</i>	Europe [4]
	Soocheong	HFRS	<i>Apodemus peninsulae</i>	Korea, Russia, China [34]
	Muju	HFRS	<i>Myodes regulus</i>	Korea, China [97]
	Imjin	Unknown	<i>Crocidura lasiura</i>	Korea, China [6]
	Jeju	Unknown	<i>Corcidura shantungensis</i>	Korea [6]

NE, nephropathia epidemica.

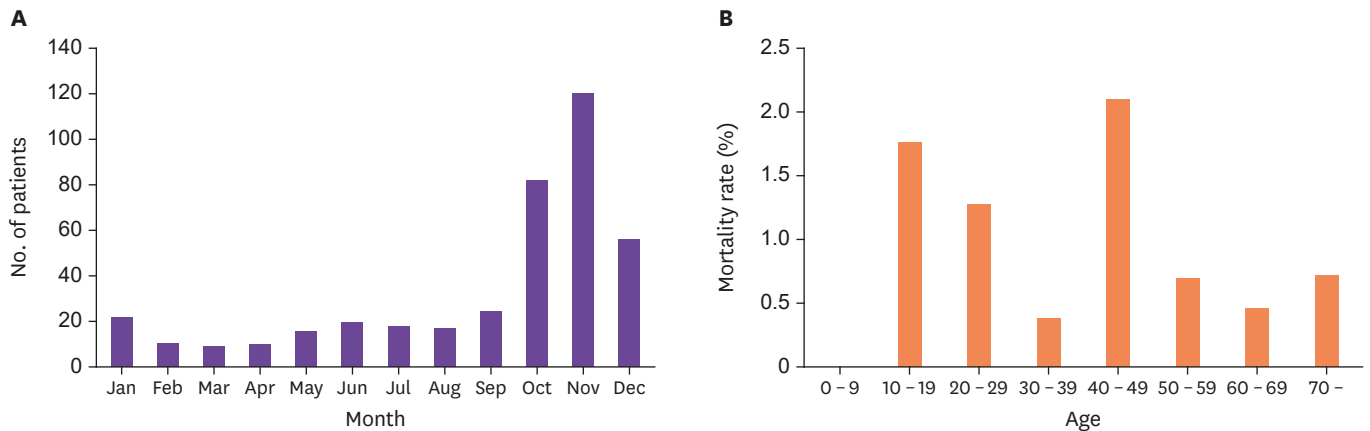
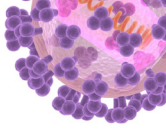


Figure 1. Incidence and death rate of hemorrhagic fever with renal syndrome (HFRS) in Korea (A) Number of patients in each month from 2001 to 2020 (B) Mortality rate by age from 2011 to 2020 (data from Korea Disease Control and Prevention Agency). Number of patients are presented as average in each month. Age of the patients are expressed in years.

The average number of HFRS cases per month in Korea from 2001 - 2020 is shown in **Figure 1**. Peak onset occurred in October, November, and December of each year. The largest number of reported cases were observed in November, with an average of 120 cases in each year. From 2011 - 2020, the age-dependent case fatality rate showed the highest rate in the 10 - 19 year age group, followed by the 20 - 29, 40 - 49, and ≥ 70 year age groups, respectively.

Between 2002 and 2016, a research was conducted in Korea that collected HFRS data in Yeoncheon and around the country. The disease's prevalence in Yeoncheon was significantly greater than the national average. Furthermore, when compared to the national average, the seasonal fluctuation pattern was not detected in Yeoncheon, indicating that HFRS can occur in endemic regions independent of seasonal variations [38]. In contrast, another research [39] found seasonal variation with most instances recorded between October and December, while some cases identified in Yeoncheon were between January and March. As a result, in order to appropriately analyze the seasonal variation, other endemic areas with high HFRS prevalence will need to be studied.

PATHOGENESIS OF HFRS

HFRS caused by Hantavirus infection causes a nonpathogenic, persistent infection in rodents [40]. On the other hand, clinically productive HFRS in humans, is defined by alterations in EC permeability and vascular edema. Plasma exosmosis or even hemorrhage are caused by increased vascular permeability, which is linked to a variety of clinical symptoms in HFRS, including hemoconcentration, hypotension, shock, and abdominal discomfort [41]. While the processes underlying the pathogenesis of HFRS are not fully recognized, the direct effects of viral infection of ECs and the immune response to hantavirus infection have been considered playing a significant role [42, 43].

1. Role of endothelial cells

It was documented that human ECs isolated from adult and fetal veins have been found to be extremely vulnerable to HTNV infection. Increased ECs permeability or direct damage to the vasculature can both produce vascular leakage (**Fig. 2**) Microscopy has revealed extensive

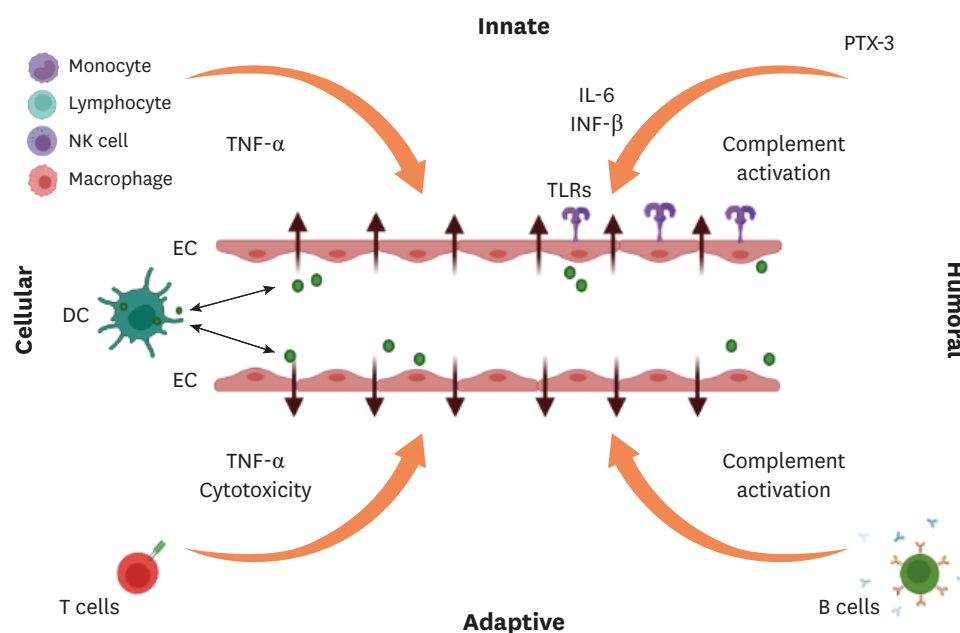


Figure 2. Proposed immune response of hantavirus causing endothelial barrier disruption. Both humoral and cellular components of innate and adaptive immune systems may cause vascular leakage. In response to hantavirus-infected ECs, neutrophils release inflammatory cytokines like TNF- α which enhance vascular permeability directly or indirectly. The humoral pattern recognition receptor PTX3 and antibodies activate complement system. DCs can transport the virus from lung tissue to ECs of the microvasculature in other organs, or they can get infected after interacting with virus-infected ECs. As hantavirus-infected DCs mature, they move to draining lymph nodes, where they provoke an aggressive CD8+ T cell response. Activated complement components causes cytoskeletal modifications in ECs, which contributes to the ECs barrier's dysfunction. TLRs detect hantavirus and trigger immune response. B-cells produce antibodies of various subclass. TNF, tumor necrosis factor; IL, interleukin; INF, interferon; PTX, pentraxin-related protein-3; TLR, toll-like receptor; NK, natural killer; DC, dendritic cell; EC, endothelial cell.

EC swelling, perivascular edema, erythrocyte diapedesis, and mononuclear cell infiltrates in HFRS patients without signs of EC injury. *In vitro* infection with HTNV, shows no distinct cytopathic effect as shown by phase microscopy and electron microscopy [44]. As a result, hantavirus is classified as a non-cytopathogenic virus that predominantly affects vascular ECs [45, 46]. This shows that increased permeability, rather than direct cellular cytotoxicity or vascular damage, causes endothelial barrier function to be lost.

During the acute phase of HFRS, increased levels of soluble EC receptors such as E-Selectin [47], intercellular adhesion molecule [48], and tumor necrosis factor receptor-1 [49] are carried into the circulation. The upregulation of pro-inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)- α , and interferon (IFN)- γ can all result in activation of endothelium [50, 51]. These cytokines cause EC permeability either directly or indirectly through EC activation, resulting in leukocyte recruitment and subsequent EC gap development [52]. Leukocytosis is prominent in hantavirus infections and is most likely related to the inflammatory response to the pathogen. Remarkably, a recent study found that neutrophil activation via extracellular trap formation occurs in the moderate type of HFRS [53]. The pro- or anti-inflammatory responses to hantavirus infection in the rodent host promote viral clearance or tolerance, respectively [54-56]. As a result, while the host's pro-inflammatory response is essential for viral clearance, excessive activation appears to result in EC permeability and consequent vascular leakage.

Integrins have also a crucial role in controlling vascular permeability and endothelial cell migration. It has been established that HTNV, SEOV, and PUUV, the HFRS-causing hantaviruses, gain particular $\alpha\beta 3$ or $\alpha IIb\beta 3$ integrins for cellular entrance [57, 58]. These integrins are heterodimeric receptors made up of α and β subunits that can mediate cell-to-cell adhesion and platelet aggregation [59]. ECs and platelets are important regulators of vascular activities, and integrins play an important role in these cells barrier functions.

2. Role of immune response

HFRS, like many other pathogenic viruses, is predominantly eliminated by the activity of the immune system, both innate and adaptive. As a result, it is widely considered that the etiology of HFRS is mostly immunological, with immune complexes, complement activation, T and B cell responses, and HTNV-induced cytokine release all playing a role [60, 61] (Fig. 2).

1) Innate immune response

a. Toll like receptor

The first line of defense against hantavirus infection is the innate immune system, which is characterized by IFN responses and innate immunocyte activation. Different pathways trigger IFN signaling. Following the identification of different pathogen-associated molecular patterns by various pattern-recognition receptors, innate immunity can be initiated. Toll-like receptors (TLRs) are vital in mediating the innate response among the many receptors that engage in the identification of microbial invaders [62]. TLRs are capable of eliciting efficient immunological responses as well as the production of inflammatory cytokines and type I IFN for host defense [63]. A study also observed that TLR4 may be involved in the upregulation of TNF- α , IFN- β , and IL-6 expression in HFRS [64].

b. Inflammatory Cytokines/chemokines

Overexpression of inflammatory cytokines is frequently documented in HFRS patients, giving rise to the theory that a "cytokine storm" may play a key role in the disease's pathophysiology. Cytokines are regarded to be one of the key causes of hantavirus symptoms.

Increased levels of cytokines and chemokines and an imbalance in their production contribute to increasing vascular endothelial permeability and a severe clinical course in patients with HFRS. According to one study [65], the cytokines are generated by many cells, including macrophages, monocytes, and lymphocytes, in response to pro-inflammatory signals and play a role in inflammation control. Cytokines, particularly TNF, IL-1 and IL-6, have been related to fever, septic shock, and the production of acute-phase proteins. A study reported that [66], the concentrations of TNF- α , IL-6, IFN- γ , IL-8, IP-10, and regulated upon activation, normal T cell-expressed and secreted (RANTES) were significantly higher in patients with HFRS compared to controls, and the highest concentrations found typically during the febrile, hypotensive, and oliguric phases, especially in severe and critical-type HFRS cases. Another study suggested that [67], cytokines like TNF- α , IL-6 and IL-1, were mediators causing synthesis of acute phase protein, fever, and septic shock and, while that of TNF- α , IFN- β , and IL-6 were key cytokines for enhanced ECs permeability.

c. Complement system

The complement system, which facilitates opsonization of microorganisms, lysis of gramnegative bacteria, and clearance of immunological complexes, is also thought to be implicated in hantavirus-induced immunopathology. SC_{5b-9}, a soluble form of the terminal complement membrane attack complex, can bind $\beta 3$ integrin, a possible receptor for the virus,

perhaps responsible for increasing ECs permeability in HFRS [68]. Through the production of bradykinin and plateletactivating factor, SC_{5b-9} may also enhance the permeability of cultured ECs [69]. The complement system activated during the acute phase of PUUV infection, and complement activation levels are associated to disease severity [70, 71]. As a result, complement activation might have a role in the development of vascular leakage. The acute phase protein pentraxin-related protein 3 is generated at the site of inflammation and its levels are observed to be elevated during the acute stage of PUUV infection, with high levels being linked to disease severity [72].

d. Nature killer cell

Natural killer (NK) cells, also known as effector and regulatory cells in innate and adaptive immunity are thought to transport into hantavirus-infected tissues to produce cytotoxic chemicals and secrete cytokines and chemokines. In HFRS, NK cells have a role in the pathophysiology and capillary leak syndrome [73], distinctive of hantavirus induced disease. Macrophages and monocytes serve as a link between innate and adaptive immunity. The immune-mediated pathogenesis is aided by high production of activating cytokines in the early stages of HFRS [74].

e. Dendritic cells and Macrophages

During HTNV infection, dendritic cells (DCs) develop and increase the expression and production of class I and class II major histocompatibility complex molecules, along with costimulatory and adhesion molecules [75]. TNF and IFN- γ release are also increased when DCs are activated.

ANDV was found in alveolar macrophages and submandibular glands in human tissue samples from ANDV fatal cases. It has been postulated that replication in human salivary glands and alveolar macrophage secretions may contribute to person-to-person transmission. As a result, it is critical to comprehend the involvement of macrophages in hantavirus infection, not only just as measure of the immune response against the virus, but also in viral transmission [76].

2) Adaptive Immune Response

The absence of cytotoxicity after hantavirus infection of ECs, along with the expression of activated T cells following hantavirus disease pathogenesis, has led to hypothesis that hantavirus disease pathology is mediated, at least to some extent, by hantavirus specific effector T cells.

a. CD8+ T-cell response

T cells play a dual function in viral infections. On the one hand, they are vital aspects of the host's defense against intracellular infections, but on the other, they are frequently at least partially responsible for the organ dysfunction and clinical disease produced by viruses. Although both functions have been proven in mouse models, data from primary human infections is limited and contradictory [77]. During prolonged SEOV infection, regulatory T cells contribute to elevated TGF- β protein levels in the lungs. As a result, regulatory T cells may have a role in the subclinical pathologic findings in rodents following SEOV infection [61].

Immunopathology of HFRS has also been linked to cell mediated responses. T cell activation has been associated to hantavirus pathogenesis, either through an excess of pro-inflammatory cytokines production or by cytotoxic T lymphocytes (CTLs) mediated death

of infected cells [78]. CTL activation is considered to be facilitated by hantavirus antigens, which have been discovered in HFRS patients' renal tubular cells [79] and they may attract T cells to damage the renal tubular system. CTL concentration in the kidneys might be linked to epithelial cell leakage and disruption, potentially leading to AKI. Furthermore, NP-specific CD8⁺ T cells might survive for far more than 15 years following PUUV infection, indicating powerful, lengthy CD8⁺ T cell responses [80]. With the beginning of symptoms, a robust virus-specific CD8⁺ T-cell response was detected, with high levels of granzyme B and perforin coupled with increasing cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitory receptor expression [81].

b. CD4⁺ T-cell response

In research, CD4⁺ T-cell responses in viral diseases have received less attention than CD8⁺ T-cell responses. Nonetheless, for HFRS in humans, CD4⁺ T cells could be involved as a part of complex immune response in the affected organ. Due to the assumption of an exaggerated immune response implicated in hantavirus pathogenesis, regulatory T cells (T_{regs}) are the most researched subset of CD4⁺ T cells. It has been proposed that Tregs are required for the establishment of chronic hantavirus infection in rodent hosts and have a role in immunopathology modulation [61, 82].

c. B-cell response

IgM antibody. Shortly after hantavirus infection, a significant IgM response arises. IgM antibody is against all the three structural proteins of hantavirus. Patients with HFRS have high levels of hantavirus IgM, which are found concurrently with the beginning of clinical symptoms. IgM serum concentrations will peak 7 - 11 days following the onset of symptoms. During the convalescent phase of HFRS, IgM levels typically decrease while IgG levels increase [21]. As a result, it is frequently employed as an HFRS diagnostic indicator.

IgG antibody. The IgG1 and IgG3 levels frequently rise as the illness progresses. In HFRS patients, however, IgG2 levels often stay stable [83]. IgG3 levels against hantavirus N and G1 proteins generally peak during the convalescent phase of HFRS and then progressively drop over the next few decades. No association has been found between IgG subclass and clinical severity. To further understand the importance of antibody-mediated responses in patient survival, an in-depth study of IgG responses against various hantaviruses is necessary.

IgA antibody. IgA has a key role in mucosal immunity, and aerosol is a major mode of hantavirus transmission. As a result, the existence of neutralizing IgA may play an important role in both acute infection recovery and long-term immunity. The greatest amounts of anti-PUUV IgA may be seen in the serum of acute and early convalescent stage. The levels of IgA will steadily rise as the illness progresses. Therefore, it is considered as one of the marker for early stage of infection [84].

Neutralizing antibodies. During hantavirus infection, G1 and G2 glycoproteins are considered as the potential antigens involved in the production of neutralizing antibodies (nAbs). Increased levels of nAbs were detected in survivors compared to deceased in PUUV-infected patients, suggesting the nAbs production may be directly related to odds of survival [85].

LABORATORY DIAGNOSIS

Human HFRS can be diagnosed using clinical and epidemiological data, along with laboratory testing. Patients with unknown fever, thrombocytopenia, renal failure, or respiratory distress who live in hantavirus disease-endemic areas should undergo laboratory testing. The laboratory diagnosis of hantavirus infection is mostly dependent on four types of tests: serology, molecular techniques, viral isolation and immunochemistry [86, 87] (Table 2).

1. Serological assays

The most practical technique is to use ELISAs to identify IgM/IgG antibodies against the three structural hantavirus proteins (Gn, Gc, and N) of hantavirus. Almost all acute HFRS patients exhibit IgM and IgG antibodies against the N protein at the beginning of symptoms. As a result, serological assays that detect IgM and/or IgG antibodies to hantaviral antigens in serum are the most often used techniques for diagnostic testing of HFRS. Unfortunately, ELISA is not currently available in Korea. The indirect immunofluorescence assay, which employed hantavirus-infected cells preserved as an antigen on microscope slides, was one of the first serological tests used to detect HFRS in Europe and Asia. The use of virus-infected cells for serological testing is limited since cell culture infections necessitate BSL-3 facilities.

Immunoblot and neutralization tests are also used to aid in the serological identification and classification of suspected hantaviral infections. A plaque reduction neutralization test is largely accepted as the most effective approach for hantavirus identification and characterization [88]. However, neutralization tests are time-consuming and need the use of BSL-3 facilities. Nonetheless, these tests remain the gold standard for serologically identifying related hantavirus infections, while early sera may exhibit more wide cross-reactivity than convalescent-phase sera.

Table 2. Laboratory techniques used for the detection of hantaviruses

Methods	Benefits	Shortcomings	Instructions
Serological Techniques			
ELISAs (IgG, IgM)	Sensitive Cross reactivity enables identification of unknown hantaviruses Inexpensive Can be utilized throughout the duration of clinical course	Cannot utilized for serotyping	Most frequently used
ICG	Rapid, sensitive and specific Inexpensive Simple to carry out	Cannot utilized for serotyping	Frequently used Cost-efficient
WB	More sensitive and specific than ELISAs	Costly and time-consuming	Not frequently used
IFA	More specific	Less sensitive and time-consuming	Not frequently used
Neutralization assay	Can be utilized for serotyping	Costly and time-consuming Requires BSL-3	Not frequently used
Molecular Techniques			
Real-time RT-PCR	Highly sensitive and specific Quantitative assay Allow to obtain the sequence of nucleotide	Costly than ELISA and time-consuming Could not show viral detection following the viremic phase	Frequently used Positive earlier than serological assays
NGS	Valuable for genotyping	Costly and complex	Hardly used
Others			
IHC	Valuable for antigen detection in tissues	Time-consuming	Frequently used for biopsy
Viral culture	Permits virological research	Less sensitive and time-consuming Cumbersome and requires BSL-3	Hardly used

ELISA, enzyme linked immunosorbent assay; ICG, immunocromatography assay; WB, western blot; IFA, immunofluorescence assay; BSL, biosafety level 3 laboratory; RT-PCR, reverse transcription polymerase chain reaction; NGS, next generation sequencing; IHC, immunohistochemistry.

2. Molecular assays

Based on the identification of the viral genome, extremely sensitive diagnostic techniques have developed. From the first day of illness, the hantavirus genome may be identified quickly using RT-PCR with clinical samples such as blood, serum, urine or organ segments [89]. The study used urine and saliva specimens to perform RT-nested PCR (RT-nPCR) targeting the L-segment of hantavirus to detect virus in patients during the early phase of infection. Importantly, the virus was detected in urine where as it was not found in serum. The virus was detected in urine and serum specimens up to one month after the initial phase of illness, but not in saliva. Therefore, the urine may serve as an important specimen to detect hantavirus during the early stages of infection and HFRS should not be ruled out based on negative RT-PCR results in serum [89].

It has been reported that viral genomes can be detected in patients before the first day of symptoms [87]. Real-time RT-PCR is a rapid and accurate method for diagnosing HFRS in the laboratory for early stage of infection. Real-time RT-PCR can also be used to determine the viral load in clinical samples. When compared to conventional PCR, RT-nPCR test has a higher degree of sensitivity [89].

3. Viral isolation in cell culture

Because viral isolation from human samples is uncommon, it is not a diagnostic strategy for human hantavirus infection. However, clinical samples inoculated into Vero E-6 cell cultures can be used to isolate hantaviruses for research objectives [90]. Immunofluorescence can be used to identify hantavirus-infected cells one to two weeks after inoculation. The isolation is laborious and time-consuming, poses a significant risk of viral contamination in the laboratory, and necessitates biosecurity precautions to prevent the handler from aerosol transmission.

4. Immunohistochemistry

Immunohistochemistry is useful for detecting viral antigens in tissues, especially in fatal instances where no other types of samples are available.

TREATMENT AND PREVENTION

The treatment of HFRS is mainly supportive and dependent on the clinical manifestations of the illness and may involve hemodialysis, oxygenation, and shock therapy. There is no specific therapy available. The use of ribavirin (1-beta-D-ribofuranosyl 11, 2, 4-triazole-3-carboxamide), an antiviral drug, has resulted in a decline in morbidity and a decrease in mortality among patients with HFRS. A study performed double-blinded clinical trial of intravenous ribavirin in China, and found that mortality was significantly reduced among 242 patients (seven folds decrease in risk) in ribavirin group. The severity of the disease was associated with the occurrence of oliguric and hemorrhagic phase in the placebo group [91], However, intravenous ribavirin treatment is not yet accessible in Korea. If started in the early course of disease, ribavirin has been found in clinical studies to be effective against hantaviruses that cause HFRS [92]. A meta-analysis was conducted to observe if ribavirin therapy for HPS reduces disease severity [92]. Human and animal studies were included in this analysis. The results found no significant reduction in mortality associated with HPS in humans with ribavirin therapy, however, the drug resulted in an increased survival rate for HPS-like disease in animal group.

Other potential novel approaches includes using a bradykinin receptor antagonist (bradykinin is implicated in vasodilation and increases vascular permeability). Icatibant, a drug that inhibits bradykinin binding, might benefit a significant number of individuals with PUUV and other hantavirus infections [93]. In Korea, icatibant is available but used only for the treatment of hereditary angioedema [94].

Monoclonal antibodies (MAbs) have been developed to combat HTNV. The anti-HTNV MAbs have been shown to exhibit anti-HTNV activity both *in vitro* and *in vivo*. As a result, MAbs might be a promising therapy option for HFRS [95]. Passive immune treatment with human plasma, are based mostly on comparable findings in the hamster model, but have not been extensively employed in humans. Several case studies have documented steroid-based anti-inflammatory therapeutic alternatives, notably in individuals with chronic and non-resolving renal failure.

For prevention of infection, it is recommended to avoid areas where high numbers of murid rodents reside in order to prevent getting into contact with virus-laden rat excrement. This includes maintaining dwellings and the surrounding region rodent-free, for example, by removing food sources and crawl spaces to make residences and work locations undesirable to rodents. A significant research attempts have been undertaken in recent years to produce a viable and safe hantavirus vaccine using vaccination techniques ranging from dead virus to recombinant DNA technologies. Hantavax (Korea Green Cross, Seoul, Korea), a formalin-inactivated HTNV vaccine made from rodent brain-derived virus, is commercially accessible in Korea, however, the protective response has been reported to be short-lived [96].

CONCLUSION AND FUTURE PROSPECTIVE

One of biology's biggest unresolved mysteries is the emergence of zoonotic infections. Hantaviruses have found all over the world and are thought to have co-evolved for a long period of time with certain rodent species that serve as their natural reservoir. The precise contribution of these several host response factors to hantavirus pathology is still unknown, and it is uncertain if one component is the major cause of pathogenesis and the others are secondary contributors. The immunological response is commonly considered to have a key role in hantavirus pathogenesis. The progress of hantavirus pathogenesis investigations, as well as vaccines and therapies, will be aided by the introduction of more animal models. This will aid in elucidating the function of host defense components in protective immunity against hantaviruses following infection or vaccination, as well as proving the principle of Hantavirus-induced immunopathogenesis. The development of medication for HFRS is becoming increasingly important. Intense antiviral treatment has improved the prognosis of many types of viral diseases. Therefore, it is necessary to develop potential antiviral therapy against hantavirus.

In the future, it is anticipated that a greater knowledge of viral biology and pathophysiology would lead to more successful and targeted therapy approaches. A greater knowledge of hantavirus ecology would allow for better management of the infection risk for humans, as well as forecasts of future developments that mankind would face. Further study into the phylogenetic relationships and circulation of viral strains, host specificity, viral persistence mechanisms in animals, and variables affecting virus pathogenicity and distribution is also a major priority in scientific field.

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