A Comprehensive Review on the Hantavirus Epidemiology and Potential Therapeutic Prospects

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ABSTRACT

Hantaviruses are zoonotic pathogens that have severe harmful effects on humans. They belong to a completely different genus in the *Bunyaviridae* family as they are rodent-borne viruses. They have a persistent life cycle in their primary hosts without causing any infection, however, they can infect humans in case of any contact with rodents or inhalation of aerosolized contaminated rodent droppings or saliva. Hantavirus has a wide geographic dispersal and is found in all the continents except Antarctica. Since their first encounter in the 1950s during the Korean conflict, it has been a threat to humans. Hantavirus syndrome can result in either Hemorrhagic Fever with Renal Syndrome (HFRS), which is more prevalent in America, and Hantavirus Cardiopulmonary Syndrome (HCPS) prevalent in Eurasia. These viruses have caused approximately 2,00,000 infections worldwide in recent years. In this review, we provide a summary of the progress made in understanding the hantavirus epidemiology, different vaccines, drugs, pathogenesis, clinical features, model systems used for hantavirus studies, treatments, and preventions associated with the virus.

Keywords: *Hantavirus, Hemorrhagic fever, Cardiopulmonary syndrome, Pathogens*

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INTRODUCTION

Hantaviruses are rodent-borne, single layer enveloped, negative-sense RNA viruses of the order *Bunyavirales*, family *Hantaviridae* [1, 2]. They are substantially globally uprising pathogens that can cause a varied range of clinical syndromes and lethal fatalities in humans [3]. Hantavirus was first described in Chinese writings approximately 1000 years ago [4]. The earliest prevalence of Hantavirus happened during the Korean conflict (1950-1953) which resulted in more than 3000 United Nations troops falling ill. It was at first named Korean Hemorrhagic Fever (KFH) but was eventually changed to hemorrhagic fever with renal syndrome [5]. The second prevalence of hantavirus took place in Arizona, New Mexico, Colorado, and Utah regions of the southwestern United States (1993) and was named Hantavirus Pulmonary Syndrome (HPS) [3]. Based on clinically established syndromes hantavirus can be distinctly divided into a Hemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Cardiopulmonary Syndrome (HCPS) or HPS [6]. HFRS is resulted by the Prototypic Hantavirus Hantaan Virus (HTNV), Puumala Virus (PUUV), and Dobrav Virus (DOBV), found primarily in Europe and Asia and are termed as the old-world hantaviruses. HPS on the other hand is caused by Andes virus (ANDV), Sin Nombre Virus (SNV), and Choclo Virus (CHOV) found primarily in America and is termed as the new world hantavirus [1]. ANDV is the only hantavirus with reported cases of human-to-human transmission to date [2]. The casualty rates of HFRS vary from <1% to 15% whereas HPS has a casualty rate of up to 40% [1]. Although the genus hantavirus is a specifically rodent-borne virus, Thottapalayam virus (TPM) isolated in Vellore, South India (1964) from an insectivore, *Suncus murinus*, stands as an exception [7]. Around seventy countries report 60,000-100,000 HFRS human cases every year, with the highest number (almost 90%) of these cases prevailing in China [8]. Even though there has been a diligent amount of research carried out

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by various scientists however no WHO-approved vaccine yet available against the virus [9].

Virology

Hantaviruses possess infectious virions that are enveloped, spherical particles with a diameter of 80-120nm [10]. Hantavirus belongs to the Bunyavirus family which contains 5 genera. It is placed so because of the presence of negative-sense, single-stranded RNA, a feature common to all genera of the Bunyavirus family [1, 11]. The composition of hantavirus includes 20-30% fat, >50% protein, 7% carbohydrates, and 2% RNA. At room temperature, these viruses can survive for more than 18 days at 4◦C and -20◦C for 10 days as they are quite stable [12]. These negative sense, single-stranded RNA genomes contain three segments: a 1.8–2.1kb small segment (S), a 3.7–3.8kb medium segment (M), and a 6.5–6.6kb large segment (L) that encode the nucleoprotein (Np), envelope glycoproteins (Gn and Gc) and viral RNA-dependent RNA polymerase (RdRp) [13-15]. Complementary nucleotides are present in each 3′ and 5′ untranslated region, these regions are highly conserved. RNA segments are given a circular appearance by these regions as they form a panhandle structure [14, 16]. Transcription and replication of hantavirus are meditated by RdRp with its transcriptase, replicase, and endonuclease activity [17]. 250-kDa RdRp and 50-kDa nucleocapsid proteins are encoded by L and S segments, respectively. A Glycoprotein Precursor (GPC) of 1133-1158 amino acids is encoded by the M segment [14, 18]. Gn and Gc glycoproteins compose the outer membrane of hantavirus which controls the recognition and entry into host cells [17]. Translating ribosomes are directed towards the Endoplasmic Reticulum (ER) by a signal peptide at the N-terminus of GPC, here the cellular signal peptidase complex at a preserved WAASA sequence cleaves the GPC co-translationally to capitulate Gn and Gc [19]. Before being administered into the viral particles Gn and Gc experience N- and O-glycosylation and cluster along with the Golgi apparatus. The surface of hantavirus virions contains Gn and Gc viral proteins as they also facilitate viral entry into vulnerable cells [17, 20].

Transmission

Transmission of hantavirus can be direct or indirect although there are contradicting studies in this regard. Viruses such as ANDV and SNV are primarily found in saliva and sometimes in urine and feces [21]. This indicates that the immediate contact could be the reason for intraspecies transmission [22]. As per the studies carried out by [23], it has been confirmed that the main reason behind SNV transmission is the direct association of deer mice. Indirect transmission takes place by inhaling contaminated virus particles present in the air. This has been considered as the major mode of transmission of hantavirus. Ingestion of adulterated substances can also be a mode of transmission for the virus [24]. Environmental factors have also contributed towards hantavirus transmission for which various tests and ecological surveys have been carried out [25].

Currently, four rodent genera have been identified to carry old-world hantaviruses responsible for HFRS in Eurasia, mainly Myodes, Microtus, Apodemus, and Rattus [26]. Myodes Glareolus is a reservoir of PUUV throughout Europe except for the Mediterranean region [27]. In Asia, Myodes Rufocanus found in Japan and Myodes Regulus found in Korea have been identified as carriers of Hokkaido virus and Muju virus, respectively [28, 29]. Other than that, these two insectivore families- Soridae and Talpidae have also been found responsible for carrying the old-world hantaviruses in Eurasia [26].

The transmission of Hantavirus and its clinical course has been depicted in **Figure 1**.

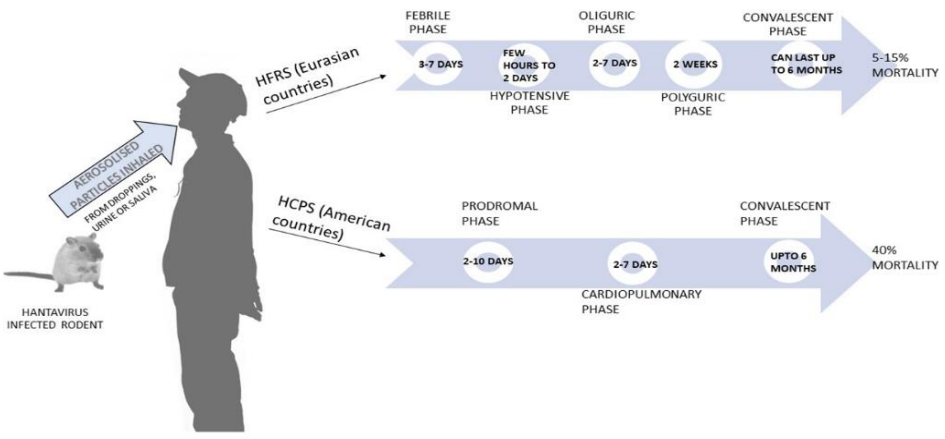

Figure 1. Hantavirus Transmission and Its Different Clinical Course for Eurasian and American Countries.

Epidemiology

Although human beings do not fall under the common host range of hantavirus, they usually get infected by inhaling aerosolized virus particles or by coming into contact with rodents' excreta [30, 31]. Airborne infections are the most common form but there have been cases of getting infected with a rodent bite. People working near rodents have higher risks of contracting the infection [32, 33]. 22 out of 40 hantaviruses are pathogenic and rodents host these pathogenic species. In cases when the host gets severely infected the virus continues replicating although neutralizing antibodies are present. Although the host does not express any signs of infection, it has an impact on the life span of the host [34, 35].

Epidemiology of old world hantaviruses in Eurasia

The first outbreak occurred in Korea about 70 years ago when almost 3000 Korean soldiers were found infected with HFRS, and the infection was known as Korean hemorrhagic fever. Infection by Seoul hantavirus (SEOV) results in mild HFRS and thus accounts for a low fatality rate of 1-2%. During 2006-2012 about 77,558 cases and 866 deaths due to HFRS were reported in China which indicated a seroprevalence of 0.83 per 100,000, casualty rates of 0.01 per 100,000, and a mortality rate of 1.13% [36]. China holds the record for the highest number of HFRS cases in the world, approximately 90% [37]. 29 out of 32 provinces have reported HFRS cases in China [38]. DOBV causes very lethal cases of HFRS in Europe, it is transmitted by *A. flavicollis* and is detected only in the Balkan region. A mild form of HFRS that is resulted from SAAV, carried by *A. agrarius* was also identified. However, there are no severe cases of SAAV causing HFRS unlike DOBV, which has fatality rates up to 12% [33].

Epidemiology of new world hantavirus in America

Before 1993, there seemed to be no evidence of hantavirus existence in America [2]. Cases of HCPS were detected in Argentina, Bolivia, Brazil, Canada, Chile, Panama, Paraguay, and Uruguay, thus it was first identified as a disease in the Four corner area in May 1993. In North and South America about 200 cases of HCPS were reported annually. Although the cases reported for HCPS are less compared to HFRS, the mortality rate of HCPS is approximately 40%. HCPS viruses cause unrecognized, asymptomatic, or subclinical infections like HFRS [2, 33].

The initial locally obtained case of HFRS caused by SEOV was reported in 2008. An outbreak of SEOV infection was reported by US CDC in 2017 that infected 17 rat owners in seven states. Although cases of HCPS are very infrequent in Canada, they indicate a certain seasonal pattern [39]. About 15 hantaviruses have been recognized as pathogenic and are associated with HCPS [2, 40]. ANDV found in South America has higher mortality rates and gets transmitted from person to person [21]. Certain factors affect hantavirus survival and their existence, they include temperature, humidity, UV exposure, and organic material (received from the host). USA is predominated by SNV and in late 2009, about 500 cases were reported in the United States where the maximum cases were from Arizona, Colorado, and New Mexico (63% of the cases were males) [35]. Central America witnessed its first hantavirus outbreak between 1999-2000 in Los Santos province Panama where the affected male to female ratio was 1.2:1 and held a mortality rate of about 26% [41].

Epidemiology in Africa

The first seroepidemiological evidence of hantaviruses in Africa came forth in 1984. This was based on the presence of antibodies discovered by Gonzalez *et al*. in human beings and rodents in Benin, Buriko Faso, Central African Republic, and Gabon. Subsequently, serological surveys were used to demonstrate hantaviral infections in Senegal, Nigeria, Egypt, Djibouti, and Guinea [42, 43]. About 10 hantaviruses have been recognized in Africa inclusive of rodents, shrews, and bats. Sangassou Virus (SANGV) is the first African hantavirus and the only one to be isolated on cell culture. It has been utilized in seroepidemiological studies in Guinea. It was detected in a wood mouse (Hylomyscus simus) that was caught in a forest. Various rodents and shrew-borne hantaviruses were also discovered in sub-Saharan Africa. By molecular identification of viral RNA in wild-living animals, many new shrews and bat-borne hantaviruses were found [44].

The epidemiology of a few important Hantaviruses worldwide along with their mortality rates has been mentioned in **Table 1**.

Table 1. Epidemiology of Some Key Hantaviruses along with their Mortality Rates

Virus	Host	Disease	Mortality (%)	Geographical distribution
Amur/Soochong	*Apodemus peninsulae*	HFRS	5-10	Far East Russia
Dobrava	*Apodemus flavicollis*	HFRS (severe)	5-10	Balkans
Hantaan	*Apodemus agrarius*	HFRS (severe)	5-10	Russia, China, South Korea
Puumala	*Myodes glareolus*	HFRS (NE)	<1	Europe, Asia

Seoul	*Rattus*	HFRS (Moderate)	1-2	South Korea
Bayou	*Oryzomys palustris*	HCPS (Renal variant)	>40	North America
Choclo	*Oligoryzomys fulvescens*	HCPS	>40	Panama
Sin Nombre	*Peromyscus maniculatus*	HCPS (severe)	>40	North America
Andes	*Oligoryzomys longicaudatus*	HCPS (severe)	>40	South America
New York	*Peromyscus leucopus*	HCPS	>40	North America
Itapua	*Oligoryzomys nigripes*	HCPS	>40	South America
Neembucu	*Oligoryzomys chacoensis*	HCPS	>40	South America
Maporal	*Oligoryzomys delicatus*	HCPS	>40	South America
Rio Mamore	*Oligoryzomys microtis*	HCPS	>40	Bolivia, Peru
Paranoa	*Not known*	HCPS	>40	South America
Oran	*Oligoryzomys longicaudatus*	HCPS	>40	Argentina

Note: *HFRS- Haemorrhagic Fever with Renal Syndrome, HCPS- Hantavirus Cardiopulmonary Syndrome

Vaccine development

Vaccination has always been the most successful approach in protecting against any viral infection or disease. Although numerous efforts have been made to produce vaccines, there is no FDA-approved vaccination for hantavirus yet [45].

HFRS vaccines in China and South Korea

HFRS has been reported in 29 of 31 provinces in China. This alarming number of cases led to the development of physically and chemically inactivated HTNV, SEOV, and PUUV based vaccines. These vaccines were developed in cell culture that had evolved to the bivalent vaccines for HTNV and SEOV made in Vero cells [1, 4]. According to the National Expanded Program on Immunization, approximately 2 million vaccines are administered annually. In China and Korea, both cell culture and rodent-brain-derived vaccines have been developed and tested in humans [46].

A formalin-inactivated vaccine was made for HTNV growth in a suckling mouse brain named Hantavax®. Despite the administration of Hantavax®, there was no significant decrease in the number of cases, however, the vaccination along with some preventative measures have proven to be effective [18].

Virus-like particles (VLPs)

VLPs are made of repeating viral structural proteins that lack infectious genetic materials but are similar to natural viral particles [17]. These vaccines have produced elevated antibody responses in humans against viruses [47]. HTNV-specific antibodies and neutralizing antibodies in mice increase when CD40L/GM-CSF is administered into VLPs. GM-CSF and CD40L containing VLPs expressed in eukaryotic expression vector have a stable long-term protective impact, with a high tier neutralizing body for 6 months after immunization [20].

Recombinant proteins

Recombinant vaccines have been efficient in the prevention of hantavirus. PUUV and DOBV possess recombinant N proteins that are expressed in yeast and have been indicated to induce a prophylactic immune response in rodent models [48]. Many methods have been suggested for the formation of recombinant proteins. Among various hantavirus species, the nucleocapsid proteins are more conserved. Therefore, high cross-reactive antibody responses have been said to be induced by nucleocapsid proteins [46].

Sub-unit vaccines

It is easy and safe to produce sub-unit proteins that do not result in any interference between the component of multivalent formation. Here, using PUUV, TOPV, ANDV, and DOBV a recombinant nucleoplasmid (rN) protein is developed to produce an immune response against PUUV. In proliferation examination, T lymphocytes that are immunized with heterogenic r Ns were successfully recollected by PUUV rN *in vitro*, similarly animals T lymphocytes were immunized with homologous proteins. Subunit vaccines hold advantages like safety, easy production, and absence of interference between components of the multivalent formulation [8, 49, 50].

Nucleic acid-base molecular vaccines

Three different vectors are used for constructing DNA vaccines that contain the M or S gene segment of SEOV. These three vectors include DNA-based Sindbis replicon (pSIN2.5), packaged Sindbis replicon vectors (pSINrep5), and naked DNA expression vectors [51]. A DNA vaccine containing the HTNV, M gene was also generated that provided immunity against HTNV, SEOV, and DOBV and produced high values of neutralizing antibodies [52]. PUUV DNA vaccines were developed that had elevated

levels of antibody production in hamsters and non-human primates [52]. Later, two (phase 1) clinical trials were conducted as per vaccine delivery technology to test the efficiency of HTNV and PUUV, M segmented DNA viruses. It was concluded that with the help of vaccine delivery technology immunogenicity can be increased. Further, a second clinical trial (phase 2a) was carried out, on 120 healthy volunteers. To test HTNV, PUUV, and HTNV/PUUV, DNA vaccines were delivered with the help of intramuscular electroporation [1, 9, 53, 54]. HTNV Gn or HTNV Gc targeting DNA vaccines were developed combined with Lysosome-Associated Membrane Protein (LAMP1). Antigen-presenting pathway and stimulated CD4+ T cells are altered by LAMP1 which evokes a strong, humoral, cellular immune response and eternal immune reaction in the body of the organism [46].

Drugs

There are no US Food and Drug Administration (FDA) confirmed antiviral medicines for HFRS or HPS to date. Maintaining the electrolyte and fluid balance of such patients is important and they require intensive care. Taking proper care of the patients till the patient's immune system is completely free from the virus is important [55].

Ribavirin

Suckling mice with clinical signs administered with ribavirin had shown decreased viral load and lethality by 45% in comparison with control animals [1, 56]. 50 mg/kg and 100 mg/kg of ribavirin saved the hamsters from lethal HPS without toxicity [57]. Ribavirin administration on the 14 days after getting infected also provided a lot of shielding against the fatal HPS. However, ribavirin was shown to cause no effects on certain patients suffering from HPS and had subsequently progressed to the cardiopulmonary phase.

Lactoferrin

Lactoferin is an iron-binding glycoprotein [58]. It has antibacterial, antifungal, antiviral activities. As per a study, it was used to prevent HFRS in a suckling mouse. A composition of lactoferin and ribavirin is needed to prevent foci creation, that exhibits the synergetic effects of both the drugs in vitro. In SEOV/suckling mouse model, administration of 40 and 160 mg/kg of lactoferin in vivo as 2 doses caused 85% and 94% survival [46].

Corticosteroids

In Chile, a clinical trial was done to check the effects of methylprednisolone for the therapy of HPS infection which concluded that there was no significant difference in fatality rates, and it did not confer any clinical benefits [1, 46].

Favipiravir

Favipiravir has the potential to inhibit SNV and ANDV in vitro [46]. Favipiravir has no significant effects and can be well tolerated by humans as per the human trials. Consumption of 100 mg/kg/day of favipiravir orally every day has reduced levels of SNV RNA in the blood as well as SNV antigens in the lungs. Daily use of 100mg/kg/day favipiravir also boosts the survival rate to 100%, which is followed by a lower diagnosis of ANDV RNA in the blood and ANDV RNA and antigen in the lung [1].

ETAR

ETAR possesses anti-viral activity against HTNV and ANDV in vitro. It is a nucleoside analog. Mice were given 12.5 mg/kg or 25 mg/kg of ETAR for 15 days and this increased the survival rate [1].

Vandetanib

Vandetanib can reduce VE-cadherin degradation as it is a tyrosine-kinase suppressor that targets the VEGF receptor 2 (VEGFR2) and has the potential to inhibit phosphorylation of VEGFR2 in vitro. Administration of 10, 25,50 mg/kg/day of vandetanib in the hamsters had reduced casualties and increased survival rate by 23% [1].

Immunotherapy

Since there is no treatment for hantavirus, numerous researches have described that neutralizing antibodies can hinder HPS in vivo. Passive transfusion of polyclonal serum and inoculation with recombinant DNA (ANDV M/SNV M) vaccines from geese, ducks, and rabbits have preserved hamsters from HPS [59, 60]. Scholars have shown that two recombinant monoclonal antibodies that were formed from an ANDV convalescent survivor with high neutralizing antibody titers shielded hamsters from fatal ANDV-HPS. In this regard, one source subject was chosen to have high antibody titers after screening 29 convalescent HCPS sera. Using recombinant DNA technology (rDNA) recombinant monoclonal antibodies have been generated from isolated memory B cells. Hence, JL.16 and MIB22, the two resultant monoclonal antibodies have been shown to successfully neutralize ANDV in vitro [46]. Polyclonal antibodies along with DNA vaccines on the other hand are still in the process of development. Standardized polyclonal antibody against ANDV, SNV, PUUV, and HTNV that can be taken towards a Phase 1 clinical test is still undergoing research.

Models systems to study entry of hantavirus

As the procedure and the path to study a virus is extremely risky and full of challenges, surrogate viruses used for the research have made things easier and approachable for scientists. Surrogate viral systems, possessing hantavirus glycoproteins, Gn/Gc, have been developed and these are essential and adequate for the entry of hantavirus and when demonstrated free of other hantavirus proteins, Gn/Gc unite into VLPs. Surrogate viruses have allowed researchers to understand new mechanistic entry techniques of the virus. Although VLPs have manifested to be useful, since the packaging of reporter genes are no longer allowed, VLPs cannot be used for viral entries. To bring a solution to this problem, researchers have essentially come up with many surrogate systems that depend on substituating the naive viral entry proteins of model viruses with hantavirus, Gn/Gc [45, 61]. To understand host factors required for entry of hantavirus vesicular stomatitis virus (VSV's) have been used as they are cytolytic [62]. Due to this approach, the role of the host factors including Protocadherin-1 (PCDH1) [63], the New World hantavirus receptors and cholesterol has been unraveled during the entry and infection of the virus. To measure neutralizing antibodies against both Old World and New world hantavirus pseudo-typed Virus stock pools (VSPs) have permitted the generation of large viral preparations [13, 45, 64]. Replication-competent VSVs were used to locate key mutations in Old World HTNV and DOBV, Gn/Gc that intensifies viral replication. The mentioned studies have found that mutations in the cytoplasmic domains have enhanced Gn/Gc administration in the VSV particles, to increase Gn/Gc cell surface expression [65]. Therefore, such VSVs that are replication-competent can be used to understand mechanisms of action of neutralizing antibodies as well as antiviral drugs by the election of drug- and antibody-neutralization escape mutants.

Hantavirus reservoir hosts

The natural reservoirs of hantavirus have often been regarded to be asymptomatic as the lab experiments that are carried out on them reveal an absence of disease or clinical signs. There were no changes in the host tissue during hantavirus infection as per numerous histopathological analyses [66, 67]. The main natural reservoir hosts of hantavirus come from the subfamily *Murinae* within the family *Muridae* and subfamilies *Arvicolinae*, *Neotominae*, and *Sigmodontinae* within the family *Cricetidae*. Various novel hantaviruses have been discovered from sorcid and talpid insectivores, but neither of these viruses have been correlated with any human disease [48]. Hantavirus can act on the natural reservoir in two ways either they could suppress the immune response of the reservoir or alter it to protect themselves from it [68]. Some experiments had been performed to scrutinize whether hantavirus infections had induced similar kinds of responses in heterologous reservoir species. After performing cross-infection of deer mice with ANDV and MAPV that held SNV infections as the reference model. The results showed that the ANDV infections were short-lived as the virus was removed within a few weeks because the immune gene transcription levels were extremely high in the spleen and strong CD4+ T-cell responses were seen. The infected rodents usually shed their viruses in urine, feces, and saliva. The main route of contamination to humans is virus-contaminated air particles. The closeness of domestic animals such as cats, dogs, pigs, and cattle with rodents could increase the transference of hantavirus to them. The evolution of the species over time could make it more fatal and dangerous to humans [25, 69].

Pathogenesis

The disease gets instigated by the inhalation of infectious aerosolized virus particles. Hantavirus begins its replication on the surface of pulmonary endothelial cells, macrophages, and dendritic cells as it binds to the β3 integrin receptors present on the surface of these cells [48]. Viral replication of hantavirus does not directly damage capillary endothelial cells or the vascular endothelium [70]. The entire array of events from inhaling the infectious virus particles to the pulmonary capillary leakage is very virtually comprehended. The process by which the virus causes capillary pulmonary leakage still needs a lot of research. However, experimental verifications reveal that multiple immunopathological mechanisms rather than cytopathic impacts are responsible for the distortion of vascular endothelium and the consequential capillary leakage is correlated to hantavirus [71]. Endothelial permeability is mainly regulated by Vascular Endothelial Growth Factor (VEGF), also called vascular permeability factor [72]. High values of Lactate Dehydrogenase (LDH), indicating cellular damage, associated with extreme values of serum perforin, granzyme B, and epithelial cell apoptosis markers in PUUV infected patients. This research demonstrates that tissue distortion is caused by the immune reaction and epithelial apoptosis takes part majorly in the damage [73, 74]. To maintain vascular integrity, integrin-directed migration of endothelial cells is necessary which gets interrupted due to the contact of the infected virus with the β3 integrin receptors [75, 76]. Activation of hantavirus special cytotoxic CD8 T lymphocytes (CTLs) is released in high amounts in the blood because of an immune response to the infection. The intensity of the disease was indicated to be associated with the number of CTLs in the blood [77]. The stimulation of CTLs is partially due to the absence of downregulation of T-cell function, in HCPS patients, such

as TGF-β it is indicated by low values of serum of cytokines liberated by regulative T cells.

There can be two potential contributions to the elevated permeability of endothelial cells due to the acute immune response. One being the high values of inflammatory mediators and cytokines, including TNF-α, IL-6, IL-10, liberated within the intense phase of stimulated T cells [78]. The second being, the potential of hantavirus-specific cytotoxic T lymphocytes to lyse human endothelial cells infected with SNV that has been demonstrated in the transwell permeability assays [79]. The annexation of the endothelium is believed to instigate IFN-alpha [11]. Inflammatory cytokines have an important role in initiating the inflammatory reaction and to regulate the host defense against hantaviral pathogenesis mediating the innate immune response.

Elevated levels of cytokine expression and endothelial adhesion molecules in HFRS are mainly located in the distal nephron in the peritubular area [11]. The real process associated with kidney failure in HFRS is still unclear [48]. Viral replication is further activated by immature dendritic cells once they reach the regional lymph nodes, after serving as carriers for the virus through the lymphatic tissue. Immune stimulation is generated by CD8+T cells and macrophages when they get disclosed to the endothelial cells. The maturation of infected dendritic cells is instigated by hantavirus that evokes T-cell responses in the acute infection phase, which is not similar to other hemorrhagic fever viruses that hinder dendritic cell maturation.

Diagnosis and treatment

Hantavirus infection can be diagnosed by detecting the background of rodent exposure, signs that suggest respiratory or renal involvement, blood exams that indicate intense thrombocytopenia, and positive serological tests [48]. The most extensively used serological test to diagnose HCPS is IgM capture and IgG indirect ELISAs, which detect the presence of IgM and IgG [48, 80]. Rapid tests for SNV and SEOV have been developed in the form of strip immunoblot assays. With the help of immunohistochemical detection of hantavirus, detection of HCPS from tissue samples has been successfully done. Although RT-PCR is also used, results must be carefully transcribed as it is prone to cross-contamination and must be followed by constructive results from immunodiagnostic assays as well. Early symptoms of HCPS involve influenza-like symptoms (fatigue, muscle aches, fever, fatigues). If observed symptoms are found with a rodent exposure history and shortness of breath, the patient would strongly indicate HCPS infection. HCPS does not have any specific treatment, therapy, or vaccine to date however early detection and care can increase the survival rate significantly. HCPS patients are given supplementary oxygen treatment to help them overcome the respiratory distress phase. The patient might also require mechanical ventilation and proper fluid management [80].

Treatment of hantavirus involves administration of drugs and therapies post-exposure to the virus. Therapeutics that are administered are used to treat either clinical symptoms or diagnosis of viremia [1]. Maintenance of correct oxygen and blood pressure levels is required. HFRS patients suffering from renal insufficiency are given dialysis treatment [81, 82]. Despite the patients being looked after properly in the Intensive Care Units (ICU) about one-third of the patients lose their lives within 48 hours after getting admitted. Most patients do not require mechanical ventilation if monitored carefully and are given fluids to maintain the fluid balance. Although 40% of patients do require mechanical ventilation which results in respiratory failure. For patients that do not have improved conditions despite the ventilation, Extracorporeal Membrane Oxygenation (ECMO) could be used, however, trials are absent, with regards to this treatment. Ribavirin, an antiviral drug showed positive results for HFRS patients in China during its clinical trials. If ribavirin is taken within the first 5 days after the start of symptoms, then it could decrease the mortality extent significantly in the case of HFRS [83, 84], though, it has not proved to be much effective.

Clinical features

The intensity and effect of hantavirus vary from subclinical, mild (e.g., by PUUV and SAAV) to moderate (by SEOV) or severe (e.g., HTNV, AMRV, SOOV, and DOBV) depending upon the etiological agent. The mortality rate is 1% in cases of mild infection while in cases of severe cases it can take any value between 5 and 15% in cases of HFRS [2, 12, 82]. HCPS is considered more lethal compared to HFRS as it has higher mortality rates [33]. Most of the hantaviruses cause renal failure or respiratory diseases in humans [25]. HFRS is a renal disease that also includes hemorrhagic fever on the other hand HCPS is a pulmonary disease and it involves pulmonary edema, hypoxia, hypotension. Despite numerous efforts, there is no vaccine approved against hantavirus infection worldwide [17].

HFRS has five phases, divided into febrile phase, hypotensive shock phase, oliguric phase, polyuric phase, and convalescent-phase [54]. The symptoms of HFRS include fever, hemorrhage, hyperemia, hypotensive shock, kidney damage hematuria, proteinuria, and disseminated intravascular coagulation (DIS) [53]. The transition from the febrile to hypotensive phase is marked by thrombocytopenia and leucocytosis at the end of the febrile stage along with conjunctival hemorrhages and petechial infection on the skin and mucosa characterizing

the beginning of the hypotensive phase. Irreversible shock at the onset of the hypotensive (shock) phase results in the death of about one-third of the patients. Other severe hemorrhagic symptoms involve headache, insomnia, hyperhidrosis, hemorrhage, and hyper diuresis. The decrement in kidney function leads to the oliguric phase. Blood pressure remains stable however anuria, proteinuria, abnormal urinary sediment, and other oliguric manifestations can be observed. About 50% of fatalities occur during this phase. Serological tests show escalated serum creatinine and urea levels. This is followed by the polyuric phase which includes recuperation of renal function and hence improved urinary outputs. Lastly, there is a convalescent stage associated with the recovery of the patient [82, 85]. During hantavirus infection, acute thrombocytopenia is a common characteristic of HFRS [54]. For HFRS treatment, ribavirin is used as it has anti-viral properties. It is also present in the WHO Model List of medicines used to treat HFRS. Keeping the fluid levels intact is important in HFRS caused by SEOV as well as PUUV [86]. The patient's fluid condition, the extent of diuresis, and kidney function must be observed. To treat HFRS one or two hemodialysis sessions are required [30]. On the other hand, HCPS progresses through only 3 phases- prodromal, cardiopulmonary, and convalescent-phase. The prodromal phase is characterized by non-specific flu-like symptoms, analogous to febrile disease. Progressive cough, shortness of breath, development of acute non-cardiac pulmonary edema, and hypotension mark the onset of the cardiopulmonary phase. Patients become critical during this phase and can die within hours in case of a severe condition. Survival through this phase leads to the polyuric stage. The last phase involves slow convalescence with weakness and fatigue [40]. Even though HFRS is associated with renal problems and HCPS with lung disease, it is now seen that HFRS sometimes shows symptoms of lung problems and HCPS shows renal or hemorrhagic issues as well.

1. High throughput sequencing (HTS) of hantavirus

HTS has major domination on the genomic studies of the viral population. With the advancement of new HTS technologies, lower costs, and higher accuracy they have successfully attained a lot of limelight in recent years. HTS is used in many virus studies [87]. HTS has never been used along with experiments to understand the evolution and diversity of hantavirus during the onset of reservoir infection. The fusion of experimental viral change along with HTS will be regarded as a robust tool to recognize and follow chosen variations in composing replicable experimental setups and to shed light on the viral adaptive pathways [25].

2. Prevention

Hantaviruses can be prevented by controlling rodents, especially where human activities are involved. To get rid of rodent food sources inside and around the house, preventative measures must be taken so that rodents cannot enter the households. Regular cleaning of households, use of rodent traps, destroying nesting sites. Use of rubber gloves, ventilation of the households, cleaning up areas that might contain rodent feces [2, 44]. Such areas should undergo rodent control protocols and humans should avoid such places. If the environment is made discouraging for rodents their activities will substantially decrease.

CONCLUSION

There remains a lot to be understood about hantaviruses. The biology of hantavirus and the entry of the virus into the cell still requires further research and studies. With the advancement in technology, genome editing tools such as CRISPR-Cas9, HTS technology, surrogate viruses, and model animals further research can be done on the virus to understand it on a much broader level. Although a lot of effort has been given to the development of vaccines against the virus, there remain several drawbacks but with the improvement in research methods and introduction of new techniques preferably efficacious antibody therapies may be developed in the future to treat the disease-causing virus.

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REFERENCES

[1] Brocato RL, Hooper JW. Progress on the prevention and treatment of hantavirus disease. Viruses. 2019;11(7):610.
[2] Jonsson CB, Figueiredo LTM, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev. 2010;23(2):412-41.
[3] Tian H, Stenseth NC. The ecological dynamics of hantavirus diseases: From environmental variability to disease prevention largely based on data from China. PLoS Negl Trop Dis. 2019;13(2):e0006901.
[4] Zhang YZ, Zou Y, Fu ZF, Plyusnin A. Hantavirus infections in humans and animals, China. Emerg Infect Dis. 2010;16(8):1195.

[5] Lee HW, Lee PW, Johnson KM. Isolation of the etiologic agent of Korean hemorrhagic fever. J Infect Dis. 1978;137(3):298-308.
[6] Clement J, Underwood P, Ward D, Pilaski J, LeDuc J. Hantavirus outbreak during military manoeuvres in Germany. Lancet. 1996;347(8997):336.
[7] Yadav PD, Vincent MJ, Nichol ST. Thottapalayam virus is genetically distant to the rodent-borne hantaviruses, consistent with its isolation from the Asian house shrew (Suncus murinus). Virol J. 2007;4(1):1-5.
[8] Liang H, Yang R, Liu Z, Li M, Liu H, Jin X. Recombinant Zika virus envelope protein elicited protective immunity against Zika virus in immunocompetent mice. PloS one. 2018;13(3):e0194860.
[9] Jiang F, Wang L, Wang S, Zhu L, Dong L, Zhang Z, et al. Meteorological factors affect the epidemiology of hemorrhagic fever with renal syndrome via altering the breeding and hantavirus-carrying states of rodents and mites: a 9 years' longitudinal study. Emerg Microbes Infect. 2017;6(1):1-9.
[10] McCormick JB, Palmer EL, Sasso DR, Kiley MP. Morphological identification of the agent of Korean haemorrhagic fever (Hantaan virus) as a member of the Bunyaviridae. Lancet. 1982;319(8275):765-8.
[11] Moore RA, Griffen D. Hantavirus Syndrome. StatPearls [Internet]. 2020.
[12] Vaheri A, Henttonen H, Voutilainen L, Mustonen J, Sironen T, Vapalahti O. Hantavirus infections in Europe and their impact on public health. Rev Med Virol. 2013;23(1):35-49.
[13] Iheozor-Ejiofor RP, Levanov L, Hepojoki J, Strandin T, Lundkvist Å, Plyusnin A, et al. Vaccinia virus-free rescue of fluorescent replication-defective vesicular stomatitis virus and pseudotyping with Puumala virus glycoproteins for use in neutralization tests. J Gen Virol. 2016;97(5):1052-9.
[14] Schmaljohn CS, Dalrymple JM. Analysis of Hantaan virus RNA: evidence for a new genus of Bunyaviridae. Virology. 1983;131(2):482-91.
[15] Graham BS, Gilman MS, McLellan JS. Structure-based vaccine antigen design. Annu Rev Med. 2019;70:91-104.
[16] Chizhikov VE, Spiropoulou CF, Morzunov SP, Monroe MC, Peters CJ, Nichol ST. Complete genetic characterization and analysis of isolation of Sin Nombre virus. J Virol. 1995;69(12):8132-6.
[17] Liu R, Ma H, Shu J, Zhang Q, Han M, Liu Z, et al. Vaccines and therapeutics against Hantaviruses. Front Microbiol. 2020;10:2989.
[18] Hantaviruses SC. A global disease problem. Emerg Infect Dis. 1997;3:95-104.
[19] Löber C, Anheier B, Lindow S, Klenk HD, Feldmann H. The Hantaan virus glycoprotein precursor is cleaved at the conserved pentapeptide WAASA. Virology. 2001;289(2):224-9.
[20] Dong Y, Ma T, Zhang X, Ying Q, Han M, Zhang M, et al. Incorporation of CD40 ligand or granulocyte-macrophage colony stimulating factor into Hantaan virus (HTNV) virus-like particles significantly enhances the long-term immunity potency against HTNV infection. J Med Microbiol. 2019;68(3):480-92.
[21] Padula PJ, Edelstein A, Miguel SD, Lopez NM, Rossi CM, Rabinovich RD. Hantavirus pulmonary syndrome outbreak in Argentina: molecular evidence for person-to-person transmission of Andes virus. Virology. 1998;241(2):323-30.
[22] Forbes KM, Sironen T, Plyusnin A. Hantavirus maintenance and transmission in reservoir host populations. Curr Opin Virol. 2018;28:1-6.
[23] Warner BM. Development of a Sin Nombre virus transmission model in deer mice and its use for assessing oral bait vaccine candidates, 2020. Available from: https://mspace.lib.umanitoba.ca/bitstream/handle/1993/34933/Warner_Bryce.pdf?sequence=1
[24] Witkowski PT, Perley CC, Brocato RL, Hooper JW, Jürgensen C, Schulzke JD, et al. Gastrointestinal tract as entry route for hantavirus infection. Front Microbiol. 2017;8:1721.
[25] Madrières S, Castel G, Murri S, Vulin J, Marianneau P, Charbonnel N. The needs for developing experiments on reservoirs in hantavirus research: Accomplishments, challenges and promises for the future. Viruses. 2019;11(7):664.
[26] Avšič-Županc T, Saksida A, Korva M. Hantavirus infections. Clin Microbiol Infect. 2019;21:e6-16.
[27] Brummer-Korvenkontio M, Vaheri A, Hovi T, Von Bonsdorff CH, Vuorimies J, Manni T, et al. Nephropathia epidemica: detection of antigen in bank voles and serologic diagnosis of human infection. J Infect Dis. 1980;141(2):131-4.
[28] Kariwa H, Yoshizumi S, Arikawa J, Yoshimatsu K, Takahashi K, Takashima I, et al. Evidence for the existence of Puumula-related virus among Clethrionomys rufocanus in Hokkaido, Japan. Am J Trop Med Hyg. 1995;53(3):222-7.
[29] Vapalahti O, Mustonen J, Lundkvist Å, Henttonen H, Plyusnin A, Vaheri A. Hantavirus infections in Europe. Lancet Infect Dis. 2003;3(10):653-61.
[30] Bi Z, Formenty PB, Roth CE. Hantavirus infection: a review and global update. J Infect Dev Ctries. 2008;2(01):003-23.

ISSN (Online) 2249-6084 (Print) 2250-1029

[31] Hart CA, Bennett M. Hantavirus infections: epidemiology and pathogenesis. Microbes Infect. 1999;1(14):1229-37.
[32] Heyman P, Vaheri A, Lundkvist Å, Avsic-Zupanc T. Hantavirus infections in Europe: from virus carriers to a major public-health problem. Expert Rev Anti Infect Ther. 2009;7(2):205-17.
[33] Avšic-Zupanc T, Saksida A, Korva M. Hantavirus infections. Clin Microbiol Infect. 2016;30:1e11.
[34] Torres-Pérez F, Wilson L, Collinge SK, Harmon H, Ray C, Medina RA, et al. Sin Nombre virus infection in field workers, Colorado, USA. Emerg Infect Dis. 2010;16(2):308.
[35] Chandy S, Mathai D. Globally emerging hantaviruses: An overview. Indian J Med Microbiol. 2017;35(2):165-75.
[36] Zhang S, Wang S, Yin W, Liang M, Li J, Zhang Q, et al. Epidemic characteristics of hemorrhagic fever with renal syndrome in China, 2006–2012. BMC Infect Dis. 2014;14(1):384.
[37] He J, Christakos G, Wu J, Cazelles B, Qian Q, Mu D, et al. Spatiotemporal variation of the association between climate dynamics and HFRS outbreaks in Eastern China during 2005-2016 and its geographic determinants. PLoS Negl Trop Dis. 2018;12(6):e0006554.
[38] Liu S, Wei Y, Han X, Cai Y, Han Z, Zhang Y, et al. Long-term retrospective observation reveals stabilities and variations of hantavirus infection in Hebei, China. BMC Infect Dis. 2019;19(1):1-10.
[39] Kerins JL, Koske SE, Kazmierczak J, Austin C, Gowdy K, Dibernardo A, et al. Outbreak of Seoul virus among rats and rat owners—United States and Canada, 2017. Morb Mortal Wkly Rep. 2018;67(4):131.
[40] Jonsson CB, Hooper J, Mertz G. Treatment of hantavirus pulmonary syndrome. Antivir Res. 2008;78(1):162-9.
[41] Pini N, Levis S, Calderón G, Ramirez J, Bravo D, Lozano E, et al. Hantavirus infection in humans and rodents, northwestern Argentina. Emerg Infect Dis. 2003;9(9):1070.
[42] Kim S, Kang ET, Kim YG, Han JS, Lee JS, Kim YI, et al. Localization of Hantaan viral envelope glycoproteins by monoclonal antibodies in renal tissues from patients with Korean hemorrhagic fever H. Am J Clin Pathol. 1993;100(4):398-403.
[43] Wang W, Zhang Y, Li Y, Pan L, Bai L, Zhuang Y, et al. Dysregulation of the β3 integrin-VEGFR2 complex in Hantaan virus–directed hyperpermeability upon treatment with VEGF. Arch Virol. 2012;157(6):1051-61.
[44] Krüger DH, Ulrich R, Lundkvist Å. Hantavirus infections and their prevention. Microbes Infect. 2001;3(13):1129-44.
[45] Mittler E, Dieterle ME, Kleinfelter LM, Slough MM, Chandran K, Jangra RK. Hantavirus entry: Perspectives and recent advances. Adv Virus Res. 2019;104:185-224.
[46] Dheerasekara K, Sumathipala S, Muthugala R. Hantavirus Infections—Treatment and Prevention. Curr Treat Options Infect Dis. 2020:1-2.
[47] Mohsen MO, Zha L, Cabral-Miranda G, Bachmann MF. Major findings and recent advances in virus–like particle (VLP)-based vaccines. InSeminars in immunology, Elsevier. 2017;32:123-32.
[48] Hussein IT, Haseeb A, Haque A, Mir MA. Recent advances in hantavirus molecular biology and disease. Adv Appl Microbiol. 2011;74:35-75.
[49] Nicacio CD, Lundkvist Å, Sjölander KB, Plyusnin A, Salonen EM, Björling E. A neutralizing recombinant human antibody Fab fragment against Puumala hantavirus. J Med Virol. 2000;60(4):446-54.
[50] Sun J, Li M, Wang Y, Hao P, Jin X. Elaboration of tetravalent antibody responses against dengue viruses using a subunit vaccine comprised of a single consensus dengue envelope sequence. Vaccine. 2017;35(46):6308-20.
[51] Hooper JW, Kamrud KI, Elgh F, Custer D, Schmaljohn CS. DNA vaccination with hantavirus M segment elicits neutralizing antibodies and protects against Seoul virus infection. Virology. 1999;255(2):269-78.
[52] Hooper JW, Custer DM, Thompson E, Schmaljohn CS. DNA vaccination with the Hantaan virus M gene protects Hamsters against three of four HFRS hantaviruses and elicits a high-titer neutralizing antibody response in Rhesus monkeys. J Virol. 2001;75(18):8469-77.
[53] Lu DH, Jiang H, Lian JQ. Hantavirus Infection during Pregnancy. Virol Sin. 2020:1-9.
[54] Jiang H, Du H, Wang LM, Wang PZ, Bai XF. Hemorrhagic fever with renal syndrome: pathogenesis and clinical picture. Front Cell Infect Microbiol. 2016;6:1.
[55] Abbas AA, Ali HA, Alagib MA, Salih HF, Elkhidir IM, El Hussein AR, et al. Prevalence and risk factors of Hantavirus infection in patients undergoing hemodialysis in Khartoum, Sudan, in 2019: a cross-sectional study. Trans R Soc Trop Med Hyg. 2020.
[56] Perley CC, Brocato RL, Wu H, Bausch C, Karmali PP, Vega JB, et al. Anti-HFRS human IgG produced in transchromosomic bovines has potent hantavirus neutralizing activity and is protective in animal models. Front Microbiol. 2020;11:832.

[57] Ogg M, Jonsson CB, Camp JV, Hooper JW. Ribavirin protects Syrian hamsters against lethal hantavirus pulmonary syndrome—after intranasal exposure to Andes virus. Viruses. 2013;5(11):2704-20.

[58] Murphy ME, Kariwa H, Mizutani T, Tanabe H, Yoshimatsu K, Arikawa J, et al. Characterization of in vitro and in vivo antiviral activity of lactoferrin and ribavirin upon hantavirus. J Vet Med Sci. 2001;63(6):637-45.

[59] Haese N, Brocato RL, Henderson T, Nilles ML, Kwilas SA, Josleyn MD, et al. Antiviral biologic produced in DNA vaccine/goose platform protects hamsters against hantavirus pulmonary syndrome when administered post-exposure. PLoS Negl Trop Dis. 2015;9(6):e0003803.

[60] Custer DM, Thompson E, Schmaljohn CS, Ksiazek TG, Hooper JW. Active and passive vaccination against hantavirus pulmonary syndrome with Andes virus M genome segment-based DNA vaccine. J Virol. 2003;77(18):9894-905.

[61] Betenbaugh M, Yu M, Kuehl K, White J, Pennock D, Spik K, et al. Nucleocapsid-and virus-like particles assemble in cells infected with recombinant baculoviruses or vaccinia viruses expressing the M and the S segments of Hantaan virus. Virus Res. 1995;38(2-3):111-24.

[62] Kleinfelter LM, Jangra RK, Jae LT, Herbert AS, Mittler E, Stiles KM, et al. Haploid genetic screen reveals a profound and direct dependence on cholesterol for hantavirus membrane fusion. MBio. 2015;6(4):e00801.

[63] Jangra RK, Herbert AS, Li R, Jae LT, Kleinfelter LM, Slough MM, et al. Protocadherin-1 is essential for cell entry by New World hantaviruses. Nature. 2018;563(7732):559-63.

[64] Levanov L, Iheozor-Ejiofor RP, Lundkvist Å, Vapalahti O, Plyusnin A. Defining of MAbs-neutralizing sites on the surface glycoproteins Gn and Gc of a hantavirus using vesicular stomatitis virus pseudotypes and site-directed mutagenesis. J Gen Virol. 2019;100(2):145-55.

[65] Slough MM, Chandran K, Jangra RK. Two point mutations in old world hantavirus glycoproteins afford the generation of highly infectious recombinant vesicular stomatitis virus vectors. MBio. 2019;10(1).

[66] Compton SR, Jacoby RO, Paturzo FX, Smith AL. Persistent Seoul virus infection in Lewis rats. Arch Virol. 2004;149(7):1325-39.

[67] Hutchinson KL, Rollin PE, Peters CJ. Pathogenesis of a North American hantavirus, Black Creek Canal virus, in experimentally infected Sigmodon hispidus. Am J Trop Med Hyg. 1998;59(1):58-65.

[68] Easterbrook JD, Zink MC, Klein SL. Regulatory T cells enhance persistence of the zoonotic pathogen Seoul virus in its reservoir host. Proc Natl Acad Sci. 2007;104(39):15502-7.

[69] McGuire A, Miedema K, Fauver JR, Rico A, Aboellail T, Quackenbush SL, et al. Maporal hantavirus causes mild pathology in deer mice (Peromyscus maniculatus). Viruses. 2016;8(10):286.

[70] Nolte KB, Feddersen RM, Foucar K, Zaki SR, Koster FT, Madar D, et al. Hantavirus pulmonary syndrome in the United States: a pathological description of a disease caused by a new agent. Hum Pathol. 1995;26(1):110-20.

[71] Borges AA, Campos GM, Moreli ML, Souza RL, Aquino VH, Saggioro FP, et al. Hantavirus cardiopulmonary syndrome: immune response and pathogenesis. Microbes Infect. 2006;8(8):2324-30.

[72] Rahimi N. Defenders and challengers of endothelial barrier function. Front Immunol. 2017;8:1847.

[73] Klingström J, Hardestam J, Stoltz M, Zuber B, Lundkvist Å, Linder S, et al. Loss of cell membrane integrity in puumala hantavirus-infected patients correlates with levels of epithelial cell apoptosis and perforin. J Virol. 2006;80(16):8279-82.

[74] Klingström J, Hardestam J, Lundkvist Å. Dobrava, but not Saaremaa, hantavirus is lethal and induces nitric oxide production in suckling mice. Microbes Infect. 2006;8(3):728-37.

[75] Gavrilovskaya IN, Gorbunova EE, Mackow NA, Mackow ER. Hantaviruses direct endothelial cell permeability by sensitizing cells to the vascular permeability factor VEGF, while angiopoietin 1 and sphingosine 1-phosphate inhibit hantavirus-directed permeability. J Virol. 2008;82(12):5797-806.

[76] Gavrilovskaya IN, Peresleni T, Geimonen E, Mackow ER. Pathogenic hantaviruses selectively inhibit β 3 integrin directed endothelial cell migration. Arch Virol. 2002;147(10):1913-31.

[77] Kilpatrick ED, Terajima M, Koster FT, Catalina MD, Cruz J, Ennis FA. Role of specific CD8+ T cells in the severity of a fulminant zoonotic viral hemorrhagic fever, hantavirus pulmonary syndrome. J Immunol. 2004;172(5):3297-304.

[78] Linderholm M, Tärnvik A, Groeneveld PH. Increased production of nitric oxide in patients with hemorrhagic fever with renal syndrome—relation to arterial hypotension and tumor necrosis factor. Infection. 1996;24(5):337-40.

[79] Hayasaka D, Maeda K, Ennis FA, Terajima M. Increased permeability of human endothelial cell line EA. hy926 induced by hantavirus-specific cytotoxic T lymphocytes. Virus Res. 2007;123(2):120-7.

[80] Kallio ER, Voutilainen L, Vapalahti O, Vaheri A, Henttonen H, Koskela E, et al. Endemic hantavirus

infection impairs the winter survival of its rodent host. Ecology. 2007;88(8):1911-6.

[81] Schönrich G, Rang A, Lütteke N, Raftery MJ, Charbonnel N, Ulrich RG. Hantavirus-induced immunity in rodent reservoirs and humans. Immunol Rev. 2008;225(1):163-89.

[82] Linderholm M, Elgh F. Clinical characteristics of hantavirus infections on the Eurasian continent. Hantaviruses. 2001:135-51.

[83] Huggins JW, Kim GR, Brand OM, McKee KT. Ribavirin therapy for Hantaan virus infection in suckling mice. J Infect Dis. 1986;153(3):489-97.

[84] Huggins JW, Hsiang CM, Cosgriff TM, Guang MY, Smith JI, Wu ZO, et al. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. J Infect Dis. 1991;164(6):1119-27.

[85] McCaughey C, Hart CA. Hantaviruses. J Med Microbiol. 2000;49(7):587-99. doi:10.1099/0022-1317-49-7-587

[86] Goeijenbier M, Aron G, Anfasa F, Lundkvist Å, Verner-Carlsson J, Reusken CB, et al. Emerging viruses in the Republic of Suriname: retrospective and prospective study into chikungunya circulation and suspicion of Human Hantavirus Infections, 2008–2012 and 2014. Vector Borne Zoonotic Dis. 2015;15(10):611-8.

[87] Pérez-Losada M, Arenas M, Galán JC, Bracho MA, Hillung J, García-González N, et al. High-throughput sequencing (HTS) for the analysis of viral populations. Infect Genet Evol. 2020;80:104208.

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