Original Research Article

Hantavirus Diseases - A Comprehensive Review

Abstract

Hantaviruses are a diverse group of infectious agents which are zoonotic in nature and transmitted to humans through rodent reservoir. Hantaviruses are enveloped RNA viruses that persistently infect rodent hosts without ill-effect. The host persistently excretes virus in urine and saliva. Man becomes infected from the rodents when one enters the ecological niche of the other. Hantaviruses can cause two types of diseases in humans: hemorrhagic fever with renal syndrome (HFRS) and Hantavirus cardiopulmonary syndrome (HCPS). The number of reported Hantavirus infections is increasing worldwide, and new Hantaviruses are being discovered in many countries, making them a global public health concern. Hantavirus infections are thought to be under diagnosed due to the fact that they frequently cause asymptomatic and nonspecific mild infections, as well as a lack of simple standardized diagnostic laboratory methods. This review summarizes current knowledge on Hantaviral infections, including virology, epidemiology, clinical manifestations, laboratory diagnostics, treatment, and prevention.

Keywords: Hantavirus; HCPS; HFRS; Rodent infection; Hemorrhagic fever; pulmonary syndrome.

Introduction:

Hantaviruses are rodent-borne viruses causing clinical illness in humans of varying severity. It is named for the Hantan River area in South Korea where an early outbreak of one of its species was observed (1). There are several different Hantaviruses, with a different geographical distribution and causing different clinical diseases. Each Hantavirus is specific to a different rodent host (2). Transmission of the virus to humans occurs through the inhalation of infected rodent urine, droppings, or saliva. Two main clinical syndromes can be distinguished after Hantavirus infection: HFRS mainly caused by Seoul, Puumala and Dobrava viruses; nephropathia epidemica (NE), a mild form of HFRS caused by Puumala virus; and HCPS, which may be caused by Andes virus, Sin Nombre virus, and several others. This article will review the

effects of HPS and HFRS, how physicians or other healthcare professionals manage these conditions against Hantavirus infections. HFRS, which was first described clinically at the turn of the twentieth century, occurs endemically in the Asian and European continents, whereas HCPS, which has been recognized as a clinical entity since 1993, is the prototype of emerging diseases in the Western hemisphere. HFRS case fatality rates range from 1% to 12% depending on the virus (3). It is estimated that 40% of the cases of HCPS in America are fatal, despite the number of cases being much lower than that of HFRS. Hantaviruses in the Americas are known as “New World” Hantaviruses and cause HPS. Other Hantaviruses, known as “Old World” Hantaviruses, are found mostly in Europe and Asia and cause HFRS (4). The most important Hantavirus in the United States that can cause HPS is the Sin Nombre virus, spread by the deer mouse (5).

Currently it is estimated that 150,000 to 200,000 cases of Hantavirus disease occur each year, the majority being reported in Asia (6). However, human Hantavirus infections are increasingly reported in the Americas and Europe. Although many of the underlying pathogenic mechanisms still remain unclear, recent evidence rather argues against a purely immune-mediated pathophysiology of human disease. This article will review the effects of HPS and HFRS, and how physicians or other healthcare professionals manage these conditions against Hantavirus infections.

Hantaviruses:

The genus Hantaviruses: family Bunyaviridae renamed as the order Bunyavirales, family Hantaviridae, and genus Orthohantavirus (7). Currently, International Committee on Virus Taxonomy (www.ictv.online.org) recognized approximately 41 Hantaviruses worldwide. Hantavirus infections are emerging diseases worldwide. These viruses are single-stranded ribonucleic acid (RNA) viruses that are enclosed. The genome is divided into three segments encoding, the nucleocapsid protein (N), small (S) segment, and M (medium) segment. The M segment encodes the glycoprotein precursor (GPC) which is cleaves into the Gn and Gc glycoproteins (N- and C- terminal). The RdRp (RNA-dependent RNA polymerase) is encoded by the L (large) gene (8).

Two hantavirus-related disorders include haemorrhagic fever with renal syndrome (HFRS) and Hantavirus cardiopulmonary syndrome (HCPS) or Hantavirus pulmonary syndrome (HPS). HFRS is characterized by a hemorrhagic rash and renal failure as a clinical manifestation. The HFRS virus is widespread throughout Asians and Europeans, mortality around 5% to 15%. HCPS causes cardiac failure more commonly than the pulmonary syndrome and fatality rates range from 40% to 50% occurring in America (9). From its inception until now, HFRS has been entwined with military operations. This should not come as a surprise, given that the conditions of war typically force military people to come into closer proximity to rats than they would under normal circumstances. Infections with the Hantavirus are considered to have been the cause of some "trench nephritis" that occurred during World War I (10).

Haemorrhagic Fever with Renal Syndrome

The incubation period is 1-6 weeks in HFRS signs. Clinical signs of HFRS may vary from asymptomatic to mild, moderate to severe, based on the causal agent of the illness (11). The generalized high-fatality respiratory syndrome (HFRS) produced by Hantaan orthohantavirus (HTNV), Seoul orthohantavirus (SEOV), Dobrava-Belgrade orthohantavirus (DOBV), and Amur virus (AMRV) is more acute, with mortality between 5–15 per cent, whereas SEOV causes mild sickness. Puumala virus (PUUV) and Saaremaa virus (SAAV) both induce a minor variant of the illness with a less than 1% death rate (12). The feverish, hypotensive, oliguric, polyureic, and convalescent phases are all considered different stages of the illness. The development of a high temperature and chills, as well as headaches, backaches, stomach pain, nausea, and vomiting, are all symptoms of the febrile phase. The most common symptoms are sedation and visual abnormalities. This febrile phase might last up to one week. Atypical conjunctival haemorrhages and fine petechiae are often seen on the palate near the conclusion of the febrile phase. The hypertensive phase can last for up to two days (13). Hypotension and shock may be seen in severe cases. About 30% of HFRS deaths during this phase are linked to fulminant irreversible shock. The oliguric phase may last up to one week, during which oliguria, proteinuria, and abnormal urinary sediment are seen (14). About 50% of deaths occur in this phase. In the polyureic phase, the kidney function starts to recover, and the output of urine increase. During the convalescence phase, which may extend up to 6 months, the patient recovers completely; the clinical and laboratory markers get normalized (15, 16). NE is generally producing milder

symptoms than HFRS. On the other hand, most patients experience fever, headache, back pain, gastrointestinal symptoms, and chronic kidney disease, which results in oliguria. Symptoms of multi-organ failure are common (17).

Hantavirus Cardiopulmonary Syndrome

Hantavirus Pulmonary Syndrome (HPS) is a severe, sometimes fatal, respiratory disease in humans caused by infection with Hantaviruses (18). It damages cells that compose blood vessel capillaries, causing them to leak fluids. This fluid leak, if it is profound in the lungs, causes life-threatening pulmonary syndrome. The virus spreads from rodents to humans (19). Although outbreaks seem like there is person-to-person transfer, outbreaks are usually noted among groups of people exposed to the same infected rodent population while those with Hantavirus infections do not transfer them to other uninfected individuals. The incubation period for HPS can vary from a few days to several weeks. Early symptoms include fever, fatigue, and muscle aches, particularly large muscle aches in the thighs, hips, back and even the shoulder (20). Other manifestations of HPS can include headache, dizziness, chills and gastro-intestinal problems like nausea, vomiting, diarrhea, abdominal pain and a dry cough can also occur. After this early phase, patients become severely short of breath because their lungs fill with fluid. The heart is also affected and lungs filled with fluids. This condition is known as Acute Respiratory Distress Syndrome (ARDS) and often requires mechanical ventilation. It can also lead to multi-organ failure, including the kidneys, and is associated with high mortality (21). However, if the patient can be successfully support through this phase, recovery can be quite rapid with no long-term consequences. In the United States, deer mice, cotton and rice rats (in the Southeast), and the white-footed mouse (in the Northeast), are the known rodent carriers of Hantaviruses causing HPS. Most HPS has occurred in the western states where the deer mouse is common (22).

Among the agents of HCPS, the most severe forms are associated with Sin Nombre virus and the southern (prototypical) form of Andes virus; slightly milder forms are caused by the northern form of Andes virus (Andes-Nort), Laguna Negra virus, and Choclo virus (23). Other South American genotypes such as Rio Mamore virus, Maripa virus, Juquitiba virus, and Castelo de Sonhos virus have emerged sporadically or in small outbreaks. In general, case-fatality ratios of HCPS range from 30 to 50 percent for severe forms and 10 to 30 percent for milder forms. The

illness caused by Choclo virus (Panama) is the mildest form of HPS in that it nearly always or always lacks a significant component of cardiac insufficiency and is associated with a markedly lower case-fatality ratio (24).

Structure and Morphology of Hantavirus

Hantavirus is circular or ovoid. The size ranges from 80-180 nanometres, containing three segments (25). The virus is composed of the small, medium, and large genomic portions that code for nucleocapsid protein (N), the glycoprotein precursor (GPC), and the RNA-dependent RNA polymerase (RdRp), respectively. These three segments are covalently linked with the N protein to produce ribonucleocapsid proteins. On the other hand, glycoproteins have a role in viral adhesion to host cells, host cell invasion, and pathogenicity. At the same time, RdRp and N proteins are essential in viral genome duplication and transcription (26).

Around 1800 nucleotides (nt) are in the S segment genome, which codes for approximately 430 amino acids. The M segment has a length of around 1140 amino acids and 3700 nucleotides. The L segment is about 6500 nucleotide length and codes for 2150 amino acids in total (27). Each segment of 3' and 5' termini are mostly preserved and complimentary. It is possible to make a "panhandle" hairpin arrangement by folding the terminal ends of segments in a certain way. The N protein binds to Hantavirus RNA and encapsulates viral and complementary RNA but not messenger RNA. Encapsidation occurs when a specific panhandle terminal structure is essential for genome synthesis and translation (28).

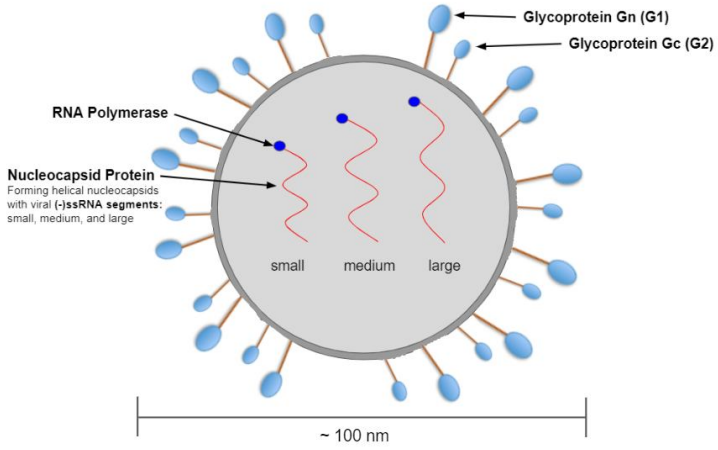

Figure 1. Hantavirus structure

Pathogenesis

Hantavirus infections are most common in the lungs and kidneys of humans and animals, respectively (29). Animals, more than humans, are more likely to stay infected throughout their lifetimes and to transfer the virus to other animals and people. Increased vascular permeability and acute thrombocytopenias are two pathophysiologic features of both HCPS and HFRS (30). Despite the replication of Hantavirus in the vascular endothelium, no cytopathological consequences are detected. Inflammatory cell infiltrations and tubular damage are linked to viral antigens in kidney tissues, implying that viral replication, in concert with the immune response, contributes to tissue degradation (31). During acute NE, renal involvement is characterized by a significantly decreased glomerular filtration rate and a markedly decreased adequate renal plasma flow (32).

The infection occurs when Gn (dark cyan) and Gc (light cyan) surface proteins connect with the 3-integrin receptor, a key receptor molecule on the body's endothelial cells (33). Because integrin receptor 3 in immature dendritic cells probably has an essential factor in transmitting the Hantavirus (34). In vitro investigations showed that Hantavirus replication in infected cells causes no cytopathic harm to the cells. Infections with HTNV, Sin Nombre orthohantavirus (SNV), and DOBV viruses have been associated with an essential difference between a high Hantavirus viral load and illness severity in various investigations (35, 36, 37). During viral pathogenesis, Hantaviruses induce the synthesis of vascular endothelial growth factor (VGEF), a vascular permeability factor that acts through the VGEF-R2 receptor. This protein interacts with the vascular endothelial (VE)-cadherin and is responsible for maintaining endothelial cell barrier functions in the body (38).

Increased vascular permeability is a result of the immunological response. Toll-like receptors (TLRs) are thought to have a role in the innate immune response by boosting the production of pro-inflammatory cytokines and type 1 interferon (IFN). In HTNV-infected vascular endothelial cells, five TLRs have been identified. Increased expression of tumor necrosis factor (TNF), IFN, and (IL-6) may occur as a consequence of TLR4 up regulation in HFRS (39).

The increased production of inflammatory cytokines is a crucial factor in the pathogenesis of Hantavirus. TNF-α, IL-6, IFN-a, IL-8, and interferon-inducible protein (IP)-10 blood concentrations were considerably more significant in HFRS patients than in control participants in an in vitro research. TNF-α and IL-6 are believed to have a role in developing fever and septic shock, and increased endothelial cell permeability results from interferon-gamma (40). The HLA-DRB1*0301 haplotype and HLA B8 allele have been linked to a severe form of HFRS induced by PUUV infection (41).

Hantavirus Transmission

It is thought that inhaling aerosolized rat faeces can transmit Hantaviruses from one individual to another. It is believed that transmission takes place when infected and uninfected mice come into close contact with one another. Additionally, it has been speculated that transmission occurs when infected rats fight, gnaw on one another, or engage in sexual behavior. Extensive catch and discharge ponder was used with Peromyscus maniculatus (deer mice) populations that were already well-established and SNV-infected to show that the disease does not manifest in newborns. Infection with the Hantavirus has recently been documented in various domestic animal species, including pigs, cats, rabbits, and dogs (42, 43).

Hantavirus replication occurs in vascular endothelial cells and macrophages, primarily in the lung and kidneys. According to a study, pathogenic Hantaviruses enter host cells by interacting with beta-3 integrins and causing endocytosis (44). Viral RdRp starts the essential transcription that results in the creation of small, medium, and large messenger RNAs. The N protein, the most prevalent viral protein for Hantaviruses, is generated sooner in the infection than any other protein. Within the endoplasmic reticulum, glycoprotein precursors undergo a proteolytic process that forms Gc and Gn. After undergoing a further glycosylation process in the endoplasmic reticulum (ER), Gc and Gn proteins are transferred to the Golgi complex. RNPs are formed when newly produced viral RNAs are encased by the N protein (45).

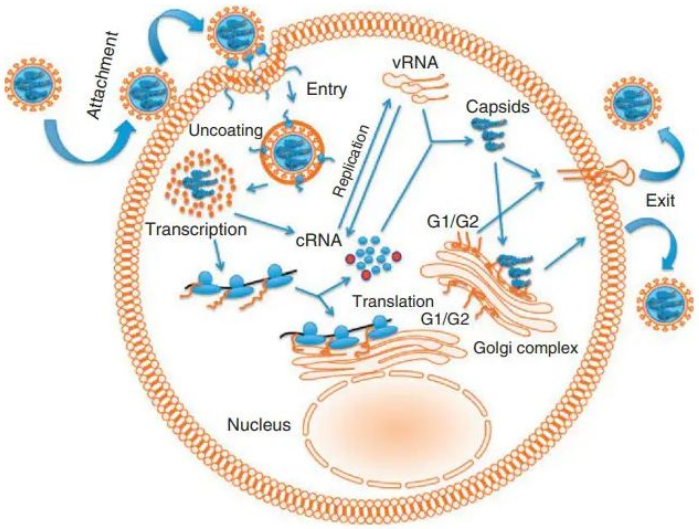

Figure 2. Hantavirus Replication

Diagnosis of Hantavirus infections

Diagnosing HFRS and HCPS needs epidemiological data and clinical and laboratory tests. Identifying an illness based on signs and symptoms, incredibly mild to moderate, might be challenging. The use of serology, molecular tests, immunochemistry, and cell culture techniques in diagnosing Hantavirus infection are all critical components (46).

Serological tests

Serological test is a commonly used method for the diagnosis of viral infection. The ELISA test is the most often used method for Hantavirus sero-diagnosis because it can detect IgM antibodies throughout the severe phase of the disease and IgG antibodies at the beginning of the sickness. Indirect IgM and IgG ELISAs and IgM capture ELISAs were employed to identify antibodies in the serological testing. The sensitivity of IgM capture ELISA has been demonstrated to be higher than that of indirect ELISA. HCPS seroconversion was reported in paired samples collected from a suspected HCPS patient in northwestern Colombia (47, 48). When the samples were tested for the Sin Nombre virus using an ELISA, it was discovered that IgG and IgM seroconversion between them-using sera collected from patients suffering from acute febrile illness in Brazil. Vieira *et al.*, conducted a retrospective analysis of the data. Anti-Hantavirus antibodies were detected in the samples using an ELISA test (49). A total of 13.6 per cent of the sera tested were positive for IgG antibodies among the samples tested. However, IgM was negative in all tested

samples, indicating that Hantaviruses are in circulation in specific regions. According to Yoshimatsu *et al*., the use of the N protein of Hantaviruses as a diagnostic antigen for screening and serotyping has been extensively studied (50). The authors discovered that the N protein was widely distributed among the Hantaviruses and that the immunodominant amino-terminal region was a valuable motif for describing Hantavirus ecology.

The European Network for the Diagnosis of "Imported" Viral Diseases (ENIVD) carried out its first external quality assurance (EQA) program in 2002. The program's goal was to assess the quality and efficiency of Hantavirus diagnostics to improve the diagnostic process (51). Unlike HCPS, the prevalence of HFRS was minimal in Europe, with the World Health Organization reporting annual incidences ranging from 100 in Eastern and Southern Europe to 1000 in Finland. In some outbreaks, the case fatality rate for HFRS was 12 per cent and HCPS 50 per cent. In Europe, most Hantavirus infections were triggered by the Hantaviruses Puumala, Dobrava-Belgrade, and Saaremaa. As a follow-up to this, conducted a second EQA study as part of their research (52). By exchanging a panel of sera, researchers gathered information on the efficacy and specificity of various serological tools. It has been reported that the efficiency of both commercial and in-house assays is the same. When compared to enzyme immunoassays, it was discovered that immunoblot assays were more efficient.

Recombinant antigens are often used in enzyme immunoassays (EIAs). Full-length proteins or shortened forms of these antigens can be expressed in bacteria, insect cells, or yeast cells. Screening and serotyping of Hantavirus in the ELISA platform, *E. coli*, and Baculovirus expression methods were used (53). Antigenically, the cross-reactive area has viruses belonging to similar categories but not viruses belonging to different categories. However, conformation-dependent epitopes were discovered in the C-terminal portion of the N protein. They were eliminating the N-terminal immunologically dominant region after multimerization is expected to reduce cross-reactivity while maintaining serotype-specific antibody reactivity (54).

In Turkey, a research study looked at the indicators that help diagnose Hantavirus infection. Investigations were conducted on 100 individuals from rural Turkey hospitalized with a preliminary diagnosis of Hantavirus infection. Twenty patients (Group 1) who had Hantavirus

infection had it confirmed using immunofluorescence and immunoblot assays. The serum of the remaining 80 patients tested negative for Hantaviruses, but additional infectious and non-infectious illnesses were identified in this group (Group 2). According to this analysis, serum CRP showed a 100% negative predictive value for the Diagnosis of Hantavirus infection, but platelet and creatinine had 75% and 70% positive predictive values. In conclusion, laboratory indicators utilized in clinical practice are crucial for Hantavirus infection prediction (55).

Based on the results of the ICG strip test and recombinant antigen-based ELISA, the study provided the following approaches for Hantavirus infection diagnosis. HTNV, PUUV, SEOV, and Andes orthohantavirus (ANDV) would be selected as representative viruses. An alternative method for the neutralization test is to retest positive sera for group A or group C antigens by ELISA using trN50 or trN100 antigens to check for serotyping. Because the N protein structure is consistent across the Hantaviruses that have been previously described, a serological inquiry focusing on the N-terminal immunodominant region may be a more effective strategy for understanding Hantavirus ecology (56).

In the immunochromatographic (ICG) technique, nanoparticle mobility across a membrane is detected using a strip. The immunodominant regions of the N protein were used to build an ICG test for the Diagnosis of human and animal antibody samples. Protein A has a strong affinity for human IgG antibody molecules and a moderate affinity for human IgM antibody molecules. As a result, the ICG test that used Protein A-labeled colloidal gold could identify both Hantavirus IgG and IgM antibodies to a lower level (57).

Using recombinant antigens expressed by *E. coli* at the amino-terminal end of N protein, a pilot study was conducted to evaluate a novel rapid immune-chromatography (ICG) test for detecting IgG antibodies in acute and convalescent samples from different Hantaviruses. Additionally, the ICG test was assessed for its capacity to differentiate between the three major Hantavirus groups. Instead of serum specimens, the ICG test might be used on diluted whole blood. This permits the ICG test to be utilized in field monitoring or in surroundings where suitable laboratory equipment is inadequate. Three-line strips exhibited superior sensitivity when tested with convalescents than single-antigen and mixed-line strips (58).

The SEOV is the cause of laboratory rat-associated HFRS at Asian and European institutes and universities. An ICG test was developed mainly to identify SEOV IgG antibodies in urban and laboratory rats. Because the N-terminal 103 amino acid of HTNV generated by *E. coli* is virtually identical to that of SEOV, it was used as an antigen in the ICG test. The ICG test had virtually similar sensitivity for detecting antibodies as the ELISA test and was a better sensitivity result than the IFA test. The sensitivity and specificity were 100% and 99.8% compared to ELISA and ICG. Consequently, the ICG test provides an efficient, simple, and safe technique for diagnosing SEOV infection in rats, particularly during field observations (59).

Neutralization test

Regarding serotyping viruses, plaque reduction neutralization tests (PRNTs) or focal reduction neutralization tests (FRNTs) are the gold standard. This is accomplished by determining serum antibody-neutralizing capability. Hantaviruses grow slowly in mammalian cells and have a weak cytopathic effect in the widely used VeroE6 cell line (60). As a result, the FRNT method, which does not require cell lysis, could be a viable option. The FRNT works using a virus with a known titer combined with serially diluted patient serum samples. The virus-antibody complex is washed away, and the cells can proliferate, preventing newly generated virions from freely diffusing in the cell culture. It is calculated by staining infected foci with fluorescent or enzymatically labeled antibodies and counting the spots (61).

Cell culture for FRNT must be done in a BSL-3 facility. However, the test is time-consuming and labour-intensive. Different strategies for serological typing of Hantaan and Seoul viruses were investigated. Micro neutralization test (MNT), pseudo particle neutralization test (PPNT), and immunofluorescence assay-supported viral glycoproteins (IFA-GP) were created by the author and compared to the Plague reduction neutralization test (PRNT). Both MNT50 and PPNT50 tests were discovered to be inexpensive alternatives to PRNT50 (62).

Neutralization assays may separate Hantaviruses into antigenically diverse species by determining the antigenic differences in glycoproteins. Although Hantaviruses have been classified into three antigenic groups, a group I (HTNV, SEOV, and DOBV), group II (PUUV,

Tula virus, and Prospect Hill virus), and group III (SNV and ANDV) based on antigenic cross-reactivity of the N protein. Three antigens are required from each group to screen for all Hantavirus infections transmitted by rodents (63).

Molecular Diagnosis

Molecular diagnostic methods are also often used to diagnose Hantavirus infections. The advantage of polymerase chain reaction is that the PCR result may be analyzed to identify the viral genotype PCR allows for quick disease detection within 24 hours, which is especially useful in the acute stage. For diagnosing Hantaviruses, reverse transcription nested polymerase chain reaction (RT-nPCR) with genus and species-specific primers was created. The primer sets were designed to complement highly homologous portions of Hantavirus genomes and the nucleotide sequence of the Araraquara virus N gene (64). The practical test for diagnosing HCPS is ELISA's more widespread serological approach. In Brazil, the nested RT-PCR for Hantavirus could be employed as an early genomic characterization of circulating Hantaviruses and a better diagnosis of acute Hantavirus infection. Before developing IgM antibodies, real-time PCR is a helpful method for identifying Hantavirus RNA (65). The one-step RT-PCR was developed for detecting DOBV, HTNV, PUUV, and SEOV viruses. The RT-PCR sensitivity assays for these viruses were 98 per cent, 96 per cent, 92 per cent, and 94 per cent, respectively, while the specificity was more than 98 per cent (66).

The Hantaan and Seoul virus in the Far East were tested by nested reverse transcriptase-PCR (nRT-PCR) and restriction fragment length polymorphism (RFLP). Primers specific for G1 segments of Hantaan and Seoul viruses were utilized in the test. The use of a combination of nRT-PCR and RFLP for Hantavirus serodiagnosis was found to be a quick and easy procedure (67). A nested RT-PCR approach was used to identify novel viruses responsible for HFRS, SFTS, and flaviviruses. Apodemusagrarius (n = 39) were collected and evaluated using serological and molecular methods. Nested RT-PCR revealed a significant positive rate of Hantavirus (46 per cent), but serological techniques revealed only 17 per cent (68). A recent study used polymerase chain reaction (PCR) to type Hantaviruses from five continents. Five different sets of oligonucleotide primers were employed. One set of primers targeted a conserved region of the S segment, while the remaining four targeted the M segment. The PCR results were

100 per cent consistent with serological typing, indicating that PCR may be used in conjunction with serological methods or as a standalone test for Hantavirus typing. Researchers have demonstrated that real-time RT-PCR can reliably detect HFRS in Sweden (69). The most common diagnostic procedures were serological tests, which were equivocal, particularly during the viraemic period. The assay can detect 98 per cent of verified clinical cases of puumala virus-induced HFRS. Molecular approaches may replace serological testing in the early infection phases. They developed real-time RT-PCR and pyrosequencing to detect European and Asian Hantaviruses. The former had a detection limit of 10 plasmid copies per reaction, whereas the latter had a detection limit of ten to one hundred plasmid copies per response. The PCR tests can detect, differentiate, and quantify Hantaviruses in human and rodent hosts (70).

An RT-LAMP test has been developed to detect the New Bunya virus in China promptly. The assay was validated using 138 samples from patients with clinical suspicion of SFTS and 40 samples from patients with laboratory-confirmed Hantavirus cases. Both sets of samples were used to test the assay (71). The test results showed that real-time RT-PCR and classical RT-PCR agree with one another 97% of the time. The sensitivity of the RT-LAMP test is 99 per cent, and its specificity is 100 per cent. Consequently, the RT-LAMP test has been reported to be an effective alternative method for diagnosing SFTS brought on by the New Bunya virus, particularly in environments where resources are limited. Combining molecular and immunological techniques is an effective way to gain a better knowledge of viral pathogenesis and potential treatments (72).

Cell culture

Hantaviruses were cultured using Vero E6 cell lines obtained from monkeys of African and are a standard continuous mammalian cell line used in microbiology laboratories (73). Characterization, prevention, and vaccine strategy rely heavily on culture isolation and whole genome sequencing. The virologic and genomic characteristics of the wild-type (wt) and Vero E6 cell-cultured strains of the Puumala virus strain were studied. It was discovered that the S and M segments of the Hantavirus had different effects on the adaptation process and that the S segment's non coding sequences have changed. The Hantavirus isolated in cell culture was shown to be phenotypically and genotypically changed. In the laboratory, cell cultivation is

arduous, time-consuming, and fraught with the potential of virus contamination. Because Hantaviruses are dangerous, culture work must be carried out in a BSL 3 laboratory (74).

Available Treatment and Prevention for Hantaviral infection

Currently, no particular FDA-approved therapy for Hantavirus infection is available in America, and the primary therapeutic option is supportive care (75). It is suggested that HCPS or HFRS patients be admitted to an ICU for careful monitoring and treatment. When individuals with HFRS have severe renal impairment, fluid retention, and pulmonary oedema, dialysis may be necessary to alleviate their symptoms. For severe thrombocytopenia and bleeding, transfusions may be necessary. Transfusions can be done in case of severe thrombocytopenia and bleeding. In severe HCPS cases, respiratory failure and shock may occur at the onset of the cardiopulmonary phase (76).

Anti-hanta viral activity of ribavirin medication was demonstrated in suckling mice that had been infected with Hantaan viral type. A research test was carried out in China; ribavirin was administered to HFRS patients. The research results indicate that ribavirin can significantly lower the death rate if administered soon after the beginning of symptoms in HFRS patients. Intravenous ribavirin has been shown to reduce oliguria and the degree of renal failure early onset of HFRS. In addition, intravenous ribavirin was utilized to treat HCPS patients. On the other hand, few clinical trials on ribavirin treatment demonstrated that the patients received no clinical benefit from the drug (77).

The virus sticks to the receptor on the host cell. After getting inside, the virus unwraps itself and makes copies of it. N protein binds to the end caps of the host mRNA. C-terminus is the part of RdRp that binds to the N protein. The capped RNA primer is made when the N-terminal endonuclease domain of RdRp cuts the host cell mRNA at a "G" residue 14 nucleotides after the 5′ caps.

Conclusion:

Global understanding and awareness of Hantavirus infections have improved significantly in the last few decades. The number of viruses detected continues to increase, and so does the extent of

Hantavirus infections. Despite its recent discovery, Hantavirus is an old disease. Environmental changes can affect the geographic distribution, frequency and dynamics of rodent carriers and thus the epidemiology of Hantavirus infection. Hantaviruses are widely believed to be found worldwide, but more research is needed on specific viral epidemics. With the development of faster and more sensitive tests and improved clinical awareness, human Hantavirus infections are likely to be detected in new areas, and new species of rodents carrying hitherto unknown viruses have been discovered. There is still a long way to go before an effective treatment for Hantavirus infection is found and the long-term prognosis of Hantavirus infection and the pathogenicity of specific virus species are unknown true protection requires safe and effective multivalent vaccines or vaccines tailored to local conditions.

References:

1. Mir MA. Hantaviruses. Clin Lab Med. 2010 Mar; 30(1):67-91. doi: 10.1016/j.cll.2010.01.004. PMID: 20513542; PMCID: PMC2880890.
2. Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev. 2010 Apr; 23(2):412-41. doi: 10.1128/CMR.00062-09. PMID: 20375360; PMCID: PMC2863364.
3. Bi Z, Formenty PB, Roth CE. Hantavirus infection: a review and global update. J Infect Dev Ctries. 2008 Feb 1; 2(1):3-23. doi: 10.3855/jidc.317. PMID: 19736383.
4. Akram SM, Mangat R, Huang B. Hantavirus Cardiopulmonary Syndrome. 2023 Feb 25. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 29083610.
5. Netski D, Thran BH, St Jeor SC. Sin Nombre virus pathogenesis in Peromyscus maniculatus. J Virol. 1999 Jan; 73(1):585-91. doi: 10.1128/JVI.73.1.585-591.1999. PMID: 9847363; PMCID: PMC103864.
6. Manigold T, Vial P. Human hantavirus infections: epidemiology, clinical features, pathogenesis and immunology. Swiss Med Wkly. 2014 Mar 20; 144:w13937. doi: 10.4414/smw.2014.13937. PMID: 24652684.
7. Kuhn JH, Schmaljohn CS. A Brief History of Bunyaviral Family Hantaviridae. Diseases. 2023 Feb 28; 11(1):38. doi: 10.3390/diseases11010038. PMID: 36975587; PMCID: PMC10047430.

8. Chaitanya KV. Structure and Organization of Virus Genomes. Genome and Genomics. 2019 Nov 18:1–30. doi: 10.1007/978-981-15-0702-1_1. PMCID: PMC7119911.
9. Akram SM, Mangat R, Huang B. Hantavirus Cardiopulmonary Syndrome. 2023 Feb 25. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 29083610.
10. Walf AA, Frye CA. The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. Nat Protoc. 2007; 2(2):322-8. doi: 10.1038/nprot.2007.44. PMID: 17406592; PMCID: PMC3623971.
11. Vial PA, Valdivieso F, Mertz G, Castillo C, Belmar E, Delgado I, Tapia M, Ferrés M. Incubation period of hantavirus cardiopulmonary syndrome. Emerg Infect Dis. 2006 Aug; 12(8):1271-3. doi: 10.3201/eid1208.051127. PMID: 16965713; PMCID: PMC3291207.
12. Connolly-Andersen AM, Ahlm K, Ahlm C, Klingström J. Puumala virus infections associated with cardiovascular causes of death. Emerg Infect Dis. 2013 Jan;19(1):126-8. doi: 10.3201/eid1901.111587. PMID: 23260342; PMCID: PMC3557968.
13. Koehler FC, Di Cristanziano V, Späth MR, Hoyer-Allo KJR, Wanken M, Müller RU, Burst V. The kidney in hantavirus infection-epidemiology, virology, pathophysiology, clinical presentation, diagnosis and management. Clin Kidney J. 2022 Jan 29;15(7):1231-1252. doi: 10.1093/ckj/sfac008. PMID: 35756741; PMCID: PMC9217627.
14. Clement J, Maes P, Van Ranst M. Hemorrhagic Fever with Renal Syndrome in the New, and Hantavirus Pulmonary Syndrome in the Old World: paradi(se)gm lost or regained? Virus Res. 2014 Jul 17;187:55-8. doi: 10.1016/j.virusres.2013.12.036. Epub 2014 Jan 17. PMID: 24440318.
15. McCAUGHEY C, Hart CA. Hantaviruses. J Med Microbiol. 2000 Jul;49(7):587-599. doi: 10.1099/0022-1317-49-7-587. PMID: 10882083.
16. Rasche FM, Uhel B, Krüger DH, Karges W, Czock D, Hampl W, Keller F, Meisel H, von Müller L. Thrombocytopenia and acute renal failure in Puumala hantavirus infections. Emerg Infect Dis. 2004 Aug;10(8):1420-5. doi: 10.3201/eid1008.031069. PMID: 15496243; PMCID: PMC3320406.
17. Settergren, B. (2000), 'Clinical aspects of nephropathiaepidemica (Puumala virus infection) in Europe: a review', Scandinavian Journal of Infectious Diseases 32(2), 125–132.

18. Moore RA, Griffen D. Hantavirus Syndrome. 2022 May 15. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 30020615.
19. Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on Hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev. 2010 Apr; 23(2):412-41. doi: 10.1128/CMR.00062-09. PMID: 20375360; PMCID: PMC2863364.
20. Avšič-Županc T, Saksida A, Korva M. Hantavirus infections. Clin Microbiol Infect. 2019 Apr; 21S:e6-e16. doi: 10.1111/1469-0691.12291. Epub 2015 Jun 22. PMID: 24750436.
21. Diamond M, Peniston HL, Sanghavi D, Mahapatra S. Acute Respiratory Distress Syndrome. 2023 Feb 6. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 28613773.
22. Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev. 2010 Apr; 23(2):412-41. doi: 10.1128/CMR.00062-09. PMID: 20375360; PMCID: PMC2863364.
23. Mir MA. Hantaviruses. Clin Lab Med. 2010 Mar;30(1):67-91. doi: 10.1016/j.cll.2010.01.004. PMID: 20513542; PMCID: PMC2880890.
24. Armien B, Pascale JM, Muñoz C, Mariñas J, Núñez H, Herrera M, Trujillo J, Sánchez D, Mendoza Y, Hjelle B, Koster F. Hantavirus fever without pulmonary syndrome in Panama. Am J Trop Med Hyg. 2013 Sep;89(3):489-94. doi: 10.4269/ajtmh.12-0334. Epub 2013 Jul 8. PMID: 23836565; PMCID: PMC3771286.
25. Battisti, A. J., Chu, Y. K., Chipman, P. R., Kaufmann, B., Jonsson, C. B. and Rossmann, M. G. (2011), 'Structural studies of Hantaan virus', Journal of Virology 85(2), 835–841.
26. Hussein, I. T., Haseeb, A., Haque, A. and Mir, M. A. (2011), 'Recent advances in hantavirus molecular biology and disease', Advances in Applied Microbiology 74, 35–75.
27. Nelson R, Cañate R, Pascale JM, Dragoo JW, Armien B, Armien AG, Koster F. Confirmation of Choclo virus as the cause of hantavirus cardiopulmonary syndrome and high serum antibody prevalence in Panama. J Med Virol. 2010 Sep; 82(9):1586-93. doi: 10.1002/jmv.21864. PMID: 20648614; PMCID: PMC2927102.
28. Mir MA. Hantaviruses. Clin Lab Med. 2010 Mar; 30(1):67-91. doi: 10.1016/j.cll.2010.01.004. PMID: 20513542; PMCID: PMC2880890.

29. Mackow, E. R. and Gavrilovskaya, I. N. (2001), 'Cellular receptors and hantavirus pathogenesis, Current Topics in Microbiology and Immunology 256, 91–115.
30. Vapalahti, O., Lundkvist, A. and Vaheri, A. (2001), 'Human immune response, host genetics, and severity of disease', Current Topics in Microbiology and Immunology 256, 153–169.
31. Terajima, M., Hayasaka, D., Maeda, K. and Ennis, F. A. (2007), 'Immunopathogenesis of hantavirus pulmonary syndrome and haemorrhagic fever with renal syndrome: Do CD8+ T cells trigger capillary leakage in viral haemorrhagic fevers?' Immunology Letters 113(2), 117–120.
32. Ala-Houhala, I., Koskinen, M., Ahola, T., Harmoinen, A., Kouri, T., Laurila, K., Mustonen, J. and Pasternack, A. (2002), 'Increased glomerular permeability in patients with nephropathiaepidemica caused by Puumala hantavirus', Nephrology, Dialysis, and Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association 17(2), 246–252.
33. Gavrilovskaya, I. N., Peresleni, T., Geimonen, E. and Mackow, E. R. (2002), 'Pathogenic hantaviruses selectively inhibit beta3 integrin directed endothelial cell migration', Archives of Virology 147(10), 1913–1931.
34. Peebles, R. S. and Graham, B. S. (2001), 'Viruses, dendritic cells and the lung', Respiratory Research 2(4), 245–249.
35. Xiao, R., Yang, S., Koster, F., Ye, C., Stidley, C. and Hjelle, B. (2006), 'Sin nombre viral RNA load in patients with hantavirus cardiopulmonary syndrome', The Journal of Infectious Diseases 194(10), 1403–1409.
36. Saksida, A., Duh, D., Korva, M. and Avsic-Zupanc, T. (2008), 'Dobrava virus RNA load in patients who have haemorrhagic fever with renal syndrome', The Journal of Infectious Diseases 197(5), 681–685.
37. Yi, J., Xu, Z., Zhuang, R., Wang, J., Zhang, Y., Ma, Y., Liu, B., Zhang, Y., Zhang, C., Yan, G., Zhang, F., Xu, Z., Yang, A. and Jin, B. (2013), 'Hantaan virus RNA load in patients having haemorrhagic fever with renal syndrome: Correlation with disease severity', Journal of Infectious Disease 207, 1457–1461.
38. Wang, W., Zhang, Y., Li, Y., Pan, L., Bai, L., Zhuang, Y., Huang, C. X., Wang, J. P., Yu, H. T., Wei, X., Jiang, W., Nan, Y. Y., Yang, D. Q., Su, W. J., Wang, P. Z. and Bai, X. F.

(2012), 'Dysregulation of the β3 integrin-VEGFR2 complex in hantaan virus-directed hyperpermeability upon treatment with VEGF', Archives of Virology 157(6), 1051–1061.

39. Jiang H, Du H, Wang LM, Wang PZ, Bai XF. Hemorrhagic Fever with Renal Syndrome: Pathogenesis and Clinical Picture. Front Cell Infect Microbiol. 2016 Feb 3; 6:1. doi: 10.3389/fcimb.2016.00001. Erratum in: Front Cell Infect Microbiol. 2016 Dec 08; 6:178. PMID: 26870699; PMCID: PMC4737898.
40. Shin OS, Song GS, Kumar M, Yanagihara R, Lee HW, Song JW. Hantaviruses induce antiviral and pro-inflammatory innate immune responses in astrocytic cells and the brain. Viral Immunol. 2014 Aug;27(6):256-66. doi: 10.1089/vim.2014.0019. Epub 2014 Jun 17. PMID: 24937036; PMCID: PMC4076983.
41. Korva M, Saksida A, Kunilo S, Vidan Jeras B, Avsic-Zupanc T. HLA-associated hemorrhagic fever with renal syndrome disease progression in slovenian patients. Clin Vaccine Immunol. 2011 Sep;18(9):1435-40. doi: 10.1128/CVI.05187-11. Epub 2011 Jul 20. PMID: 21775516; PMCID: PMC3165220.
42. Zhang YZ, Zou Y, Fu ZF, Plyusnin A. Hantavirus infections in humans and animals, China. Emerg Infect Dis. 2010 Aug;16(8):1195-203. doi: 10.3201/eid1608.090470. PMID: 20678311; PMCID: PMC3298307.
43. Liu S, Wei Y, Han X, Cai Y, Han Z, Zhang Y, Xu Y, Qi S, Li Q. Long-term retrospective observation reveals stabilities and variations of hantavirus infection in Hebei, China. BMC Infect Dis. 2019 Sep 2; 19(1):765. doi: 10.1186/s12879-019-4402-8. PMID: 31477045; PMCID: PMC6721381.
44. Muranyi W., Bahr U., Zeier M. and van der Woude FJ. (2005), 'Hantavirus infection', Journal of American Society of Nephrology 16(12), 3669-3679.
45. Ramanathan, H. N. and Jonsson, C. B. (2008), 'New and old world hantaviruses differentially utilize host cytoskeletal components during their life cycles', Virology 374(1), 138–150.
46. Mattar, S., Guzman, C. and Figueiredo, L. T. (2015), 'Diagnosis of hantavirus infection in humans', Expert Review of Anti-Infective Therapy 13, 939–946.
47. Stefic K, Mahjoub N, Desouche C, Néré ML, Thierry D, Delaugerre C, Barin F, Chaix ML. Difficulties of Identifying the Early HIV Antibody Seroconversion Period

Depending on the Confirmatory Assay. Open Forum Infect Dis. 2020 Apr 21; 7(5):ofaa140. doi: 10.1093/ofid/ofaa140. PMID: 32478120; PMCID: PMC7246347.

48. Mattar S, Garzon D, Tadeu L, Faccini-Martínez AA, Mills JN. Serological diagnosis of hantavirus pulmonary syndrome in a febrile patient in Colombia. Int J Infect Dis. 2014 Aug;25:201-3. doi: 10.1016/j.ijid.2014.03.1396. Epub 2014 Jun 23. PMID: 24970702.
49. Vieira CJ, Silva DJ, Barreto ES, Siqueira CE, Costa VG, Lourenço FJ, Moreli ML, Bronzoni RV. Serological evidence of hantavirus infection in an urban area in Mato Grosso State, Brazil. Rev Soc Bras Med Trop. 2016 May-Jun;49(3):348-50. doi: 10.1590/0037-8682-0026-2016. PMID: 27384832.
50. Yoshimatsu, K. and Arikawa, J. (2014), 'Serological diagnosis with recombinant N antigen for hantavirus infection', Virus Research 187, 77–83.
51. Vial C, Martinez-Valdebenito C, Rios S, Martinez J, Vial PA, Ferres M, Rivera JC, Perez R, Valdivieso F. Molecular method for the detection of Andes hantavirus infection: validation for clinical diagnostics. Diagn Microbiol Infect Dis. 2016 Jan;84(1):36-39. doi: 10.1016/j.diagmicrobio.2015.07.019. Epub 2015 Jul 29. PMID: 26508102; PMCID: PMC4754785.
52. Vapalahti O, Mustonen J, Lundkvist A, Henttonen H, Plyusnin A, Vaheri A. Hantavirus infections in Europe. Lancet Infect Dis. 2003 Oct;3(10):653-61. doi: 10.1016/s1473-3099(03)00774-6. PMID: 14522264.
53. Kumar N, Pandey D, Halder A. Preventive, Diagnostic and Therapeutic Applications of Baculovirus Expression Vector System. Trends in Insect Molecular Biology and Biotechnology. 2017 Nov 16:163–91. doi: 10.1007/978-3-319-61343-7_9. PMCID: PMC7115001.
54. Lebani K, Jones ML, Watterson D, Ranzoni A, Traves RJ, Young PR, Mahler SM. Isolation of serotype-specific antibodies against dengue virus non-structural protein 1 using phage display and application in a multiplexed serotyping assay. PLoS One. 2017 Jul 6;12(7):e0180669. doi: 10.1371/journal.pone.0180669. PMID: 28683141; PMCID: PMC5500353.
55. Sevencan F, Gözalan A, Uyar Y, Kavakli I, Türkyilmaz B, Ertek M, Lundkvist A. Serologic Investigation of Hantavirus Infection in Patients with Previous Thrombocytopenia, and Elevated Urea and Creatinine Levels in an Epidemic Region of

Turkey. Jpn J Infect Dis. 2015; 68(6):488-93. doi: 10.7883/yoken.JJID.2014.405. Epub 2015 Apr 10. PMID: 25866109.

56. Solà-Riera C, Gupta S, Ljunggren HG, Klingström J. Orthohantaviruses belonging to three phylogroups all inhibit apoptosis in infected target cells. Sci Rep. 2019 Jan 29; 9(1):834. doi: 10.1038/s41598-018-37446-1. PMID: 30696898; PMCID: PMC6351540.
57. Amada T, Yoshimatsu K, Koma T, Shimizu K, Gamage CD, Shiokawa K, Nishio S, Ahlm C, Arikawa J. Development of an immunochromatography strip test based on truncated nucleocapsid antigens of three representative hantaviruses. Virol J. 2014 May 14; 11:87. doi: 10.1186/1743-422X-11-87. PMID: 24885901; PMCID: PMC4047433.
58. Amada, T., Yoshimatsu, K., Yasuda, S. P., Shimizu, K., Koma, T., Hayashimoto, N., Gamage, C. D., Nishio, S., Takakura, A. and Arikawa, J. (2013), 'Rapid, whole blood diagnostic test for detecting anti-hantavirus antibody in rats', Journal of Virological Methods 193(1), 42–49.
59. Amada T, Yoshimatsu K, Yasuda SP, Shimizu K, Koma T, Hayashimoto N, Gamage CD, Nishio S, Takakura A, Arikawa J. Rapid, whole blood diagnostic test for detecting anti-hantavirus antibody in rats. J Virol Methods. 2013 Oct; 193(1):42-9. doi: 10.1016/j.jviromet.2013.04.021. Epub 2013 May 15. PMID: 23684845.
60. Rissanen I, Stass R, Zeltina A, Li S, Hepojoki J, Harlos K, Gilbert RJC, Huiskonen JT, Bowden TA. Structural Transitions of the Conserved and Metastable Hantaviral Glycoprotein Envelope. J Virol. 2017 Oct 13; 91(21):e00378-17. doi: 10.1128/JVI.00378-17. PMID: 28835498; PMCID: PMC5640846.
61. Payne S. Methods to Study Viruses. Viruses. 2017:37–52. doi: 10.1016/B978-0-12-803109-4.00004-0. Epub 2017 Sep 1. PMCID: PMC7149989.
62. Li W, Cao S, Zhang Q, Li J, Zhang S, Wu W, Qu J, Li C, Liang M, Li D. Comparison of serological assays to titrate Hantaan and Seoul hantavirus-specific antibodies. Virol J. 2017 Jul 18;14(1):133. doi: 10.1186/s12985-017-0799-0. PMID: 28720142; PMCID: PMC5516384.
63. Koma, T., Yoshimatsu, K., Pini, N., Safronetz, D., Taruishi, M., Levis, S., Endo, R., Shimizu, K., Yasuda, S. P., Ebihara, H., Feldmann, H., Enria, D. and Arikawa, J. (2010), 'Truncated hantavirus nucleocapsid proteins for serotyping Sin Nombre, Andes, and

Laguna Negra hantavirus infections in humans and rodents', Journal of Clinical Microbiology 48(5), 1635–1642.

64. Moreli, M. L., Sousa, R. L. and Figueiredo, L. T. (2004), 'Detection of Brazilian hantavirus by reverse transcription polymerase chain reaction amplification of N gene in patients with hantavirus cardiopulmonary syndrome', Memorias do Instituto Oswaldo Cruz 99(6), 633–638.
65. Galeno, H., Mora, J., Villagra, E., Fernandez, J., Hernandez, J., Mertz, G. J. and Ramirez, E. (2002), 'First human isolate of hantavirus (Andes virus) in the Americas', Emerging Infectious Diseases 8(7), 657–661.
66. Pang Z, Li A, Li J, Qu J, He C, Zhang S, Li C, Zhang Q, Liang M, Li D. Comprehensive multiplex one-step real-time TaqMan qRT-PCR assays for detection and quantification of hemorrhagic fever viruses. PLoS One. 2014 Apr 21;9(4):e95635. doi: 10.1371/journal.pone.0095635. PMID: 24752452; PMCID: PMC3994070.
67. Fetzer C, Pesch S, Ohlinger VF. High risk of false positive results in a widely used diagnostic test for detection of the porcine reproductive and respiratory syndrome virus (PRRSV). Vet Microbiol. 2006 Jun 15; 115(1-3):21-31. doi: 10.1016/j.vetmic.2006.01.001. Epub 2006 Feb 3. PMID: 16458457.
68. Nunes BTD, de Mendonça MHR, Simith DB, Moraes AF, Cardoso CC, Prazeres ITE, de Aquino AA, Santos ADCM, Queiroz ALN, Rodrigues DSG, Andriolo RB, Travassos da Rosa ES, Martins LC, Vasconcelos PFDC, Medeiros DBA. Development of RT-qPCR and semi-nested RT-PCR assays for molecular diagnosis of hantavirus pulmonary syndrome. PLoS Negl Trop Dis. 2019 Dec 26;13(12):e0007884. doi: 10.1371/journal.pntd.0007884. PMID: 31877142; PMCID: PMC6932758.
69. Kramski M, Meisel H, Klempa B, Krüger DH, Pauli G, Nitsche A. Detection and typing of human pathogenic hantaviruses by real-time reverse transcription-PCR and pyrosequencing. Clin Chem. 2007 Nov;53(11):1899-905. doi: 10.1373/clinchem.2007.093245. Epub 2007 Aug 23. PMID: 17717126.
70. Guterres A, de Oliveira RC, Fernandes J, Schrago CG, de Lemos ER. Detection of different South American hantaviruses. Virus Res. 2015 Dec 2;210:106-13. doi: 10.1016/j.virusres.2015.07.022. Epub 2015 Jul 26. PMID: 26220480.

71. Huang XY, Hu XN, Ma H, Du YH, Ma HX, Kang K, You AG, Wang HF, Zhang L, Chen HM, Dumler JS, Xu BL. Detection of new bunyavirus RNA by reverse transcription-loop-mediated isothermal amplification. J Clin Microbiol. 2014 Feb;52(2):531-5. doi: 10.1128/JCM.01813-13. Epub 2013 Dec 4. PMID: 24478484; PMCID: PMC3911317.
72. Srikiatkhachorn, A. and Spiropoulou, C. F. (2014), 'Vascular events in viral haemorrhagic fevers: a comparative study of dengue and hantaviruses', Cell and Tissue Research 355(3), 621–633.
73. Ammerman NC, Beier-Sexton M, Azad AF. Growth and maintenance of Vero cell lines. Curr Protoc Microbiol. 2008 Nov;Appendix 4:Appendix 4E. doi: 10.1002/9780471729259.mca04es11. PMID: 19016439; PMCID: PMC2657228.
74. Montoya-Ruiz C, Díaz FJ, W MJ, Xiaofeng Z, Levis S, Zapata JC, Muskus CE, Álvarez CM, Rodas JD. Development of a serosurveillance assay for detection of Necoclí virus exposure. Arch Virol. 2018 Dec;163(12):3291-3301. doi: 10.1007/s00705-018-4015-3. Epub 2018 Sep 6. PMID: 30191374.
75. Brocato RL, Hooper JW. Progress on the Prevention and Treatment of Hantavirus Disease. Viruses. 2019 Jul 4;11(7):610. doi: 10.3390/v11070610. PMID: 31277410; PMCID: PMC6669544.
76. Hamid K, Sathyanarayanan SP, Naim T, Hamza M, Mahmood Baig MO, Sitta EA. Hantavirus Cardiopulmonary Syndrome and Diffuse Alveolar Hemorrhage in the Era of COVID-19. Case Rep Infect Dis. 2021 Sep 24;2021:8800500. doi: 10.1155/2021/8800500. PMID: 34603804; PMCID: PMC8486545.
77. Dheerasekara K, Sumathipala S, Muthugala R. Hantavirus Infections-Treatment and Prevention. Curr Treat Options Infect Dis. 2020;12(4):410-421. doi: 10.1007/s40506-020-00236-3. Epub 2020 Oct 29. PMID: 33144850; PMCID: PMC7594967.