

Human hantavirus infections: epidemiology, clinical features, pathogenesis and immunology

Tobias Manigold^a and Pablo Vial^{b,c}

^a Internal Medicine, University Hospital Basel, Switzerland

^b Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago de Chile, Chile

^c Clínica Alemana de Santiago, Santiago de Chile, Chile

Summary

In humans, hantaviruses can cause haemorrhagic fever with renal syndrome (HFRS) or hantavirus cardiopulmonary syndrome (HCPS). Currently it is estimated that 150,000 to 200,000 cases of hantavirus disease occur each year, the majority being reported in Asia. 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. Despite the high morbidity and case-fatality rates of HFRS and HCPS, respectively, no vaccine or drug is currently proven to be preventive or therapeutic. This review summarises clinical features and current epidemiological findings, as well as concepts regarding the immunology, pathogenesis and intervention strategies of human hantaviral diseases.

Key words: hantavirus; HCPS; HFRS; immunology; pathogenesis

Introduction

Hantaviruses can cause two distinct illnesses in humans: haemorrhagic fever with renal syndrome (HFRS) caused

by so-called “Old World hantaviruses”, or hantavirus cardiopulmonary syndrome (HCPS) caused by “New World hantaviruses”. Figure 1 demonstrates the geographical distribution of pathogenic hantaviruses and principal associated pathologies in humans.

Human disease caused by hantaviruses has been recognised for more than 80 years. However, the various causative hantaviruses were mostly identified decades later, and the first virus isolate, from the field mouse *Apodemus agrarius*, was achieved only in 1976 by Lee et al., who named it Hantaan virus (HTNV) [1]. Nephropathia epidemica (NE) had already been described in Sweden in the 1930s and was later shown to be due to Puumala virus (PUUV) infection. In the early 1950s, Hantaan virus caused HFRS in more than 3,000 United States troops in Korea [2, 3]. In 1993, a previously unrecognised syndrome characterised by respiratory failure and shock (HCPS) was reported in the south-western United States (Four Corners region). Subsequently, Sin Nombre virus (SNV) and the deer mouse, *Peromyscus maniculatus*, were identified as the aetiological agent and natural reservoir, respectively [4, 5]. In 1995, South American hantaviruses with genetic similarity to SNV were identified. The *Oligoryzomys*-borne hantavirus, Andes virus (ANDV), was implicated in the first recognised HCPS cases in Argentina [6]. Later, other pathogenic hantaviruses and their associated rodent reservoirs were discovered in Central and South America [7, 8]. Currently, it is estimated that 150,000 to 200,000 cases of hantavirus disease occur per year, of which 70% to 90% correspond to HFRS cases in China. However, reported cases in the known endemic areas in Asia, Scandinavia and the Americas seem to be on the rise. For instance, in Germany an all-time peak of hantavirus infections was noted during 2012 [9]. Also, the 2012 outbreak in Yosemite Park, a formerly unaffected area, involved ten patients, three of whom died [10]. Additionally, the number of countries in which hantavirus in rodents and HCPS cases in humans have been identified has progressively increased [11–15]. Thus, clinicians should be reminded to consider hantavirus infections among the possible diagnoses in patients with fever, thrombocytopenia, respiratory symptoms and/or signs of renal failure.

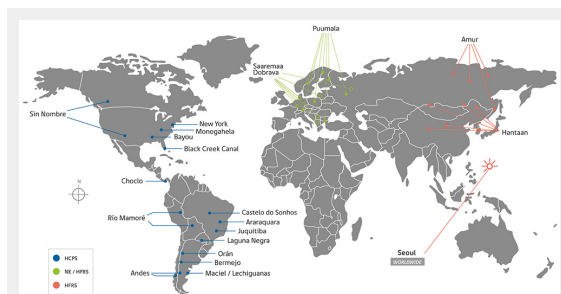


Figure 1

Geographical distribution of pathogenic hantaviruses and principal associated pathologies in humans.

HCPS = hantavirus cardiopulmonary syndrome; HFRS = haemorrhagic fever with renal syndrome; NE = nephropathia epidemica

Virus and epidemiology

Hantaviruses are negative-sense single-strand ribonucleic acid (RNA) viruses, which belong to the family of Bunyaviridae. In contrast to the other members of the Bunyaviridae family, the genus hantavirus is not transmitted to humans by arthropods (e.g., mosquitoes), but directly by small mammals that are the natural reservoir. In total, over 40 hantavirus species are currently known and 22 of them are considered pathogenic for humans. Each of these is strictly associated with a unique rodent host, which belongs to one of three rodent subfamilies. Consequently, the geographical distribution of the different hantavirus strains is determined by the distribution of the respective rodents.

Importantly, moles, shrews and bats are also increasingly described as natural hosts of new members of the hantavirus genus (e.g., Huangpi virus, Lianghe virus, Longquan virus, Yakeshi virus, Seewis virus). However, the pathogenicity of these viruses for humans is unclear. Also, there are reports of seropositive domestic animals such as dogs and cats, suggesting that these become infected from contact with infected primary hosts. However, there is neither evidence of disease in these species nor of a role as a reservoir for human infection.

Chronically infected rodent hosts show substantial levels of viral replication despite the presence of neutralising antibodies, but no clinical signs of illness; however, the virus may affect their lifespan [16]. It is believed that the incidence of infected rodents is influenced by several factors, including climate and land cover, both of which affect food availability and, in turn, changes in population density. Increases in the rodent population density usually lead to an increase in hantavirus infection and transmission among rodents, followed by an increase of human infections [17]. Transmission to man occurs via inhalation of aerosols derived from the vector's urine, faeces or saliva, but may possibly also be due to bites by infected animals [18, 19]. Hantavirus survival in the environment is very important for transmission. Wild-type PUUV remains infective in contaminated bedding at room temperature for 12–15 days and is inactivated after 24 hours at 37 °C [20]. Globally, the main factors that affect survival of hantavirus outside the rodent host are temperature, humidity, exposure to ultraviolet light and sunlight, and the organic content of the contaminated fluid. Optimal conditions for survival in the environment may vary for different hantaviruses and explain the differential infection dynamics in rodents and humans. Peridomestic exposure occurs in human settlements in rural areas close to natural reservoirs of the rodents. Exposure may also occur when humans invade the rodent's natural habitat (e.g., forestry workers, camping tourists, soldiers). Conversely, reservoir rodents may enter abandoned human housing (e.g., summer residences) in their search for food and leave contaminated droppings, urine and nesting material to which humans are exposed upon their return. In Chile, approximately 25% of the cases of HCPS are associated with recreational activities and 75% are acquired by residents in rural areas through peridomestic or occupational exposure. Importantly, very recent reports indicate Seoul virus (SEOV) infection in United Kingdom-derived pet rats of the *Rattus norvegicus* species [21–23]. Thus, distribu-

tion of infected pets may further extend the risk of exposure even to persons who did not cross the rodent's natural habitat. In the future, testing of pet rats before sale could become necessary in order to diminish such cases.

In the case of the South American ANDV, an additional risk factor has to be considered: ANDV is the only hantavirus for which person-to-person transmission has been consistently documented [24, 25], albeit with limited efficiency and accounting for a low proportion of cases. An elegant study by Ferres et al. showed that, among 476 household contacts of 76 ANDV-infected index cases, 16 contacts (3.4%) developed HCPS [26]. It was shown that being a sex partner of, or sleeping in the same room as a patient, as well as exposure to a patient's body fluids, were significant risk factors for secondary infections. Importantly, an earlier study did not find increased incidences of ANDV infection among healthcare workers who had been in contact with acutely ill ANDV-infected patients [27]. However, one report from Argentina and one from Chile suggest that patient care during the prodromal phase of the infection may be a risk factor for hantavirus acquisition [28, 29].

Seroprevalence in endemic Chilean regions was found to be 1.9% [27] and could be as high as 7.5% in certain areas and populations (e.g., farmers and forestry workers) with elevated risk for exposure [30]. However, the highest reported seropositivity rates of 15% to 60% come from rural areas of Panama, Paraguay and Argentina [31–33]. In the Four Corners region, the United States' endemic site for SNV infections, studies have revealed up to 1% seropositivity, whereas the general United States population probably shows less than 0.1%. In China, the world's most endemic region for hantavirus diseases, it is estimated that seroprevalence in the general population is <5%. In a recent study in German forestry workers, 8.2% of men and 15.6% of women were seropositive [34], mostly specifically for Tula virus and Dobrava virus.

In Switzerland, in Canton St. Gallen the first survey of hantavirus-specific immunoglobulin G (IgG) in populations of eastern Switzerland revealed low seroprevalence rates which did not differ significantly between populations at higher risk for hantavirus infection (0.0%–1.9%) and the average adult population (0.5%) [35]. In addition, in Switzerland, infection with PUUV was shown in a patient without a history of travel during the incubation period, suggesting that infection may be endemic and independent of migration [36]. In the future, incidences in Switzerland may, become similar to those in neighbouring countries. For instance, in 2012 in Germany, reports of hantavirus infections reached an all-time high, with more than 2,800 cases [9]. The majority of these cases had been reported in the federal state of Baden-Württemberg, neighbouring Switzerland, with PUUV being the most prevalent strain [37]. Thus, although exposure to hantaviruses is currently not perceived to be a public health problem, these numbers indicate that it may be or become more frequent than suggested by the low incidence of reported cases and the low seroprevalence.

The clinical expression of the infection may vary with different hantaviruses, and in areas with high seroprevalence a high proportion of infections may be asymptomatic or have

only mild symptoms (febrile illness without HCPS). In one prospective study in Panama, the ratio of infection detected by seroconversion to infection resulting in HCPS was 14:1 [31].

Incidence rates of infection and HCPS may vary significantly in different areas: in rural areas of Panama the finding of 70 seroconversions in 857 person-years of observation was equivalent to 8 infections per 100 person-years [31]. In contrast, in Chile, which represents the most endemic region for HCPS, the mean incidence rate is 0.29 cases per 100,000 inhabitants/year and in the United States the rate is 0.009/100,000.

Clinical characteristics

Following infection of target cells, hantaviruses may lead to two zoonotic diseases in humans: haemorrhagic fever with renal syndrome (HFRS) or hantavirus cardiopulmonary syndrome (HCPS). Both clinical entities are caused by subsequent breakdown of the endothelial barrier function in capillary vessels, but clinical development and fatality rates are very different.

For HFRS, as well as NE, an incubation period ranging from 10 days to 6 weeks followed by a febrile phase with nonspecific signs, such as myalgia, headache, abdominal pain and malaise, and also neurological, cardiovascular and gastrointestinal symptoms [38]. In addition, ocular symptoms such as refraction abnormalities, which do not seem to occur as a result of central nervous system involvement, may occur during PUUV infection [39]. Haemorrhage may occur as injection of the conjunctiva and mucosa. Subsequently, patients enter a hypotensive phase with symptoms of vascular leakage, which is often associated with thrombocytopenia, shock and, in a proportion of cases, mental confusion. The following oliguric phase may last up to 5 days with risk for hypertension, pulmonary oedema and renal insufficiency, and often determines the patient's fate, with approximately 50% of all fatalities occurring in this phase. After the subsequent diuretic phase, which may last months, the convalescent phase starts. Severity and case-fatality rates of HFRS depend on the causative strain, with DOBV and HTNV reaching approximately 10% and 5%, respectively [40, 41]. HFRS due to SEOV may reach a case-fatality rate of 2%, whereas PUUV-induced NE leads to death in 0.08% to 0.4% [41] of patients.

For HCPS, the incubation period is usually up to 17 days for SNV infection, but may be as long as 38 days for ANDV [42]. As with HFRS, the febrile phase may last up to 5 days and mostly consists of nonspecific, influenza-like symptoms: fever, myalgia, headache, malaise and arthralgia. Gastrointestinal and neurological signs may also occur in this phase. Abdominal pain may be severe and is occasionally misdiagnosed as an acute abdomen, with some patients undergoing surgery. Laboratory findings include thrombocytopenia, leucocytosis or leucopenia, a high haematocrit (due to extravasation of fluid), peripheral immunoblasts (a sign of massive immune stimulation), usually a differential lymphocyte count of over 10%, abnormal liver function tests, a mild increase in creatinine, hyponatraemia and proteinuria [43–47].

When patients present at the hospital with more specific symptoms, such as cough and dyspnoea, tachycardia and hypotension, HCPS is usually already at an advanced stage. Even though disease expression may vary with different viruses, approximately 50% of the infections evolve to a cardiopulmonary phase characterised by dyspnoea, cough, tachycardia and hypotension, which reflect rapidly progressive pulmonary oedema caused by capillary leakage and low cardiac output. Consequently, cardiogenic shock is the main cause of death. Thrombocytopenia and intravascular coagulation syndrome are commonly reflected in haemorrhagic manifestations in various sites (haematuria, intestinal bleeding, metrorrhagia) and indicate negative prognosis. Renal failure may occur in up to 50% of the patients. Elevation of pancreatic enzymes may occur in some patients and encephalitis has also been reported incidentally [48].

Severity and case-fatality rates of HCPS vary considerably between geographical regions; acute infection by most New World hantaviruses, including Sin Nombre, Andes, Araraquara and Juititaba, result in case-fatality rates of 25% to 40%, whereas in Panama (Choclo virus) the case-fatality rate is 10%, and in Paraguay (Laguna Negra virus) it is 15%. It should be noted that these lower mortality rates occur in areas of unusually high seroprevalence [49]. One hallmark of HCPS is the fulminant development of respiratory failure, followed by shock, which often makes mechanical ventilation, vasoactive drug support or extracorporeal membrane oxygenation necessary. Owing to the rapid onset and progression of the disease most deaths (90%) occur during the first 48 hours of the clinical course of HCPS [46, 50]. In contrast to the adult acute respiratory distress syndrome seen in other systemic infections, respiratory failure in HCPS resolves within a few days and is followed by a polyuric phase. Of note, patients may not fully recover from symptoms associated with hantavirus infection (fatigue, myalgia, dyspnoea) for months; one study reported that survivors remained with exertional dyspnoea for 1 to 2 years after acute infection in 43% (Panama) and 77% (New Mexico) of cases [51].

Because of the high mortality, the absence of any proven antiviral treatment or vaccine and the virtual absence of protective immunity in the general western population, HCPS-causing hantaviruses are considered Biodefense Category A pathogens within the antibioterrorism programme of the National Institutes of Allergy and Infectious Diseases (NIAID). Consequently, major research funding had been invested in the search for preventive and therapeutic methods during the last two decades. In Chile, this, in combination with large national programmes and extended research, has led to improved prevention, faster diagnosis and optimised intervention. As a consequence, the fatality index has been lowered from 60% to around 30% among the approximately 60 HCPS cases per year. Similar learning-curve phenomena with significant reductions of case-fatality rates have been observed in other countries. As disease awareness and availability of diagnostic tests increase, earlier diagnosis, prompter transportation to centres with intensive care units and more aggressive management of the complications are pursued.

Diagnosis

IgG/IgM responses against hantavirus nucleocapsid antigen (N-antigen) represent the standard diagnostic tool. B-cell N-antigen epitopes are largely conserved among hantaviruses, thus often not allowing differentiation between the various hantavirus strains. However, sensitivity and specificity of clinical serological assays for detection of hantaviruses in specific areas may vary according to the virus N-antigen used as capture antigen. Assays for simultaneous detection of antibodies against clinically important Old and New World hantaviruses have been developed, as well as assays for viruses circulating in specific areas using homologous N-antigen to improve the detection and diagnostic capabilities [52–57].

Most of the tests currently use recombinant nucleocapsid protein, and the most common types of tests are based on an enzyme-linked immunosorbent assay, indirect immunofluorescence or strip immunoblot. Close to 100% of the patients have IgM and IgG antibodies detected upon onset of the symptoms of vascular leakage (acute phase); however, sensitivity to detect these antibodies may be lower during the prodromal phase of the infection, thus hindering early diagnosis.

Antibody responses against glycoproteins Gn and Gc (formerly known as G1 and G2) are not considered of major diagnostic importance, as they develop later in the course of infection and are much less conserved among different strains. Because of the low seroprevalence in the population in Europe and the United States, diagnosis is usually made by detection of IgM and IgG against hantaviral N-antigen in these countries. Reverse transcriptase–polymerase chain-reaction (RT-PCR) not only offers direct detection of the viral genome, but also allows identification of the underlying hantaviral genotype, thus bypassing limitations of serological tests. On the other hand, RT-PCR technology is technically more complex and its availability, therefore, is limited. Most interestingly, testing of whole blood samples rather than serum may provide an important advantage. In a prospective study on household contacts of ANDV-infected index cases, Ferrer et al showed that quantitative PCR on whole blood samples turned positive up to 5 to 15 days (median 11) before serological diagnosis and onset of HCPS, whereas seropositivity coincided with clinical symptoms [26]. Thus, in cases with high pretest probability (e.g., a contact of an index patient or documented source of exposure) quantitative RT-PCR testing of nucleated peripheral blood cells may be more suitable than antibody detection.

In Switzerland, patients are most likely to be either PUUV-infected residents or returning travellers who are already symptomatic. Thus, testing for anti-N antibodies should be sufficient to confirm the diagnosis in most cases. However, in Switzerland samples can be referred to “Zentrum für Labormedizin” in St. Gallen for both serological and PCR (PUUV) testing.

Immunology and pathogenesis of human disease

The primary target cells of hantavirus infection are endothelial cells of capillaries of various organs, primarily of the lung and kidneys, although infection occurs in a variety of other organs and cell types (endothelial and epithelial cells, macrophages, follicular dendritic cells, lymphocytes, neutrophils and platelets). The main receptor in endothelial cells for pathogenic hantavirus is beta-3-integrin. Infection is followed by impairment of the barrier function of endothelial cells, fluid extravasation and subsequent organ failure. However, although appearance of neutralising antibodies (NAbs) seems to impair the development of disease (see below), the mechanisms for the so-called “vascular leak” are largely unknown. Notably, infection of endothelial cells by hantavirus is noncytopathic *in vitro* and *in vivo*, which has led to the hypothesis that a strong cellular immune response, elicited by cytotoxic CD8⁺ T cells, may be responsible for hantavirus pathogenesis in man. However, the absence of necrotic endothelial cells despite presence of inflammatory T cells in lung tissue of HCPS patients [58] seemed to argue against T-cell mediated organ damage. A recent paper showing that the N-antigen of hantaviruses protects infected cells from caspase-3–dependent apoptosis [59] may explain this discordant finding. In line with the hypothesis of T-cell mediated immunopathogenesis, early studies in a small number of acute HCPS patients (with SNV infection) pointed towards human leucocyte antigen (HLA) B*35 as a risk factor for a severe HCPS outcome [60]. Likewise, analysis of peripheral blood cells showed higher frequencies of SNV-specific CD8⁺ T cells in patients with a severe outcome, as compared with those with a mild/moderate outcome. However, the differences between severely and mildly/moderately affected patients were based on data from two out of seven patients and on frequencies of tetramer-positive cells only. Furthermore, Ferrer et al. and investigations at our lab on the T-cell memory pool of Chilean survivors of ANDV seem to argue against a T-cell mediated immunopathogenesis: firstly, the HLA-B*35 allele was more frequent in patients with mild HCPS [61]; secondly, HLA-B*35 associated memory T-cell responses were stronger in patients with mild outcome of HCPS [62]; thirdly, T-cell dynamics and differentiation in a prospectively studied patient emphasised the role of T cells in viral clearance after the acute phase of HCPS [63]. Finally, compelling evidence arguing against a T-cell mediated pathogenesis of HCPS derives from two recent studies in ANDV-infected Syrian hamsters, the sole animal model of HCPS [64, 65]. Both studies showed that depletion of T cells (either before or 6–8 days after ANDV infection, respectively) did not impact disease onset or outcome of HCPS.

As cellular immune responses may not be sufficient to explain hantavirus pathogenesis, mechanisms based on direct virus-cell interactions come more into focus. In this regard, important contributions come from the group of Mackow et al., who compared pathogenic and nonpathogenic hantaviruses [66, 67]. Whereas pathogenic hantaviruses seem to inhibit innate type I interferon (IFN) responses by infected cells, nonpathogenic viruses, such as Prospect Hill vir-

us, are not capable of doing so. This may be relevant for the pathogenicity of hantaviral infections, since IFN- β protects from vascular leakage by upregulation of CD73 on endothelial cells [68]. This finding was recently confirmed in an *in-vitro* model of Dengue 2 virus infection [69]. Moreover, *in vitro* pathogenic hantaviruses initiate viral entry by binding to the $\alpha V\beta 3$ integrin, whereas nonpathogenic viruses use $\alpha V\beta 1$ [67, 70]. Since inactivation of virus-bound $\beta 3$ -integrins contributes to deregulation of vascular endothelial growth factor receptor-2 (VEGFR2) and diminished antagonism of vascular endothelial growth factor (VEGFA), this may lead to impairment of vascular endothelial (VE) cadherin expression and subsequent loss of endothelial barrier function.

However, direct virus-cell interactions may not explain why onset of clinical symptoms occurs so late during infection, usually at a time-point when viral load is already falling, at least in plasma. Likewise, the aetiology of thrombocytopenia, a common feature in hantaviral diseases, is far from being clarified. Several authors have suggested that thrombocytopenia could be due to platelet consumption in response to the damage to the endothelial layer. Others suggested that this may be the direct consequence of the virus interaction with $\beta 3$ -integrin receptor on platelets [71].

During the acute phase, the dynamics of the development of neutralising antibodies against the surface antigens Gn and Gc is considered to be of crucial importance for clinical outcome. Bharadwaj et al showed that SNV-infected patients with mild HCPS showed significantly higher NAb titres at the time of disease onset than those patients with severe HCPS [72]. Similar results have been found for patients with acute ANDV infection [7]. After convalescence from hantaviral disease, humans are considered to be protected for life against reinfection and to date there are no reports of reinfection. Immunity is mediated by NAb at high titres, which can readily be detected up to 35 years after infection. Conversely, passive immunisation with both patient-derived or vaccine-induced NAb was capable of protecting Syrian hamsters from HCPS even 5 days after otherwise lethal ANDV infection [73].

It is, however, unclear how NAb titres can be maintained for decades if one assumes that hantaviruses are usually cleared within days at the time of clinical presentation [74]. As shown by Pinschewer et al. titres of NAb usually require permanent stimulus in order to be maintained [75]. Intriguingly, our study in convalescent ANDV-infected patients showed that even in patients who had never returned to ANDV endemic areas since their primary infection, NAb titres were either maintained or even rising up to 11 years after acute infection [62]. These findings, together with those of high frequencies of nonproliferative, terminally differentiated CD8⁺ T cells, suggest latent antigen exposure in ANDV patients, which may not be explained by extrinsic re-exposure. In this context, it is noteworthy that prospective follow-up data from Ferres et al. [26] and Vial et al. [29] in patients with severe HCPS indicate that viral genome can be detected in blood cells as early as 15 days before and as late as 90 days after the onset of clinical symptoms. These data alter our previous view that in humans hantaviruses are present and cleared within several days. In fact, it may indicate the propensity of the virus to

establish latency in certain tissues. However, to date, and despite several attempts, virus could not be cultivated from convalescent patients. Nevertheless, to our knowledge immune-privileged sites (such as testes, brain) of convalescent patients are not being systematically examined post mortem for viral antigens.

Although the importance of NAb for immunity to hantaviruses is being extensively investigated in several studies, the protective role of antiviral T cells is much less defined. As pointed out above, there is probably more evidence against than in favour of the hypothesis of T-cell mediated immunopathogenesis. Indeed, indirect evidence of the memory T cell pool of ANDV-infected patients as well as T-cell dynamics in a prospectively studied patient, seem rather to emphasise a role of T cells in viral clearance and survival after HCPS [62, 63]. An association between strong T-cell responses and favourable disease outcome was especially true in HLA-B*35-positive survivors of ANDV infection. Interestingly, the same association has recently been confirmed in HTNV infected patients, especially when they were HLA-A*2 and HLA-B*35-positive [76].

Given that the fatality rate of ANDV infection in Syrian hamsters is much higher than in humans, it is rather difficult to study what impact T cells have on viral clearance and survival. However, data from Martinez et al. in the Syrian hamster model showed that T cells might be able to confer protective, not sterilising, immunity. Hamsters vaccinated with the ANDV N-antigen were protected from homologous challenge with ANDV but less towards Seoul Virus [77]. Since NAb against glycoproteins Gn and Gc were not detected, these data suggest that a preventive T-cell based vaccine might be possible.

Current treatments, trials and outlook

Several studies have indicated that ribavirin is capable of inhibiting replication of SNV and ANDV *in vitro*, as well as in *in-vivo* models. However, although in a randomised study of HFRS patients ribavirin led to decreased morbidity and mortality [78], acute HCPS patients (with SNV infection) did not benefit from the treatment [79, 80]. This is consistent with observations in a recent study, in which ribavirin was capable of protecting 100% of ANDV-infected Syrian hamsters if administered either before or up to 3 days after infection with ANDV [81], whereas protection was markedly decreased when it was administered 5 or 7 days after infection. Given that the clinical presentation (and earliest possible treatment with ribavirin) of HCPS usually occurs 1–5 weeks after the supposed infection, these data may explain why ribavirin was not effective in acute HCPS patients. Nevertheless, it is tempting to speculate that prospective treatment of household contacts of index cases with acute HCPS could benefit from ribavirin treatment [81].

As outlined above, pathogenic hantaviruses may disrupt the VE-cadherin-VEGFR2 interaction by both binding to $\alpha V\beta 3$ integrins and inducing VEGF. Consistent with this finding, *in-vitro* inhibitors of the VEGFR2 or Src kinase could abolish ANDV-induced hyperpermeability [82]. It will be interesting to see which effects small or

large molecules blocking the VEGF-VEGFR interaction or downstream signalling pathways (e.g., vandetanib or aflibercept) may show in future *in-vitro* and *in-vivo* studies. However, even if significant effects were seen in these models, it remains doubtful whether therapeutic intervention along the VEGF-VEGFR2 pathway will lead to clinically relevant improvement in patients who are already symptomatic.

Based on the hypothesis that HFPS and HCPS are caused by an exaggerated host immune response, there have been attempts to prevent severe HCPS by the use of steroids during the acute phase. However, only recently it was shown in a randomised trial in ANDV-infected patients that the use of high doses of methylprednisolone upon hospitalisation is not beneficial and therefore not recommended [50]. The basis for these disappointing results is not clear, but it is likely that the underlying immune mechanisms of HCPS are already too advanced to be influenced by steroids once patients become symptomatic.

Given the importance of NABs for disease outcome, passive immunotherapy could represent a possible treatment for acute HCPS. Currently one clinical trial is underway to assess safety and efficacy of transfusion of serum from convalescent patients (containing high titres of NABs) into patients with acute HCPS. Despite the currently small sample size of around 40 patients, preliminary results are encouraging, as they indicate a markedly reduced fatality index in the treatment group as compared with usual fatality of around 30% [83].

In addition to minimisation of the risk of exposure and rodent control as prevention strategies, the demand for preventive vaccines for hantavirus infections is steadily increasing. In Chile alone, around 5 million people live in endemic areas. It is estimated that the demand for vaccines lies in the tens of millions in Europe and probably more than 100 million in Eurasia [84]. Vaccine development needs to take the different epidemiological settings and causative hantaviruses into account. However, there are attempts to develop a “one-size-fits-all” solution by pan-hantavirus vaccines covering both HCPS- and HFPS-causing hantaviruses [85].

Taken together, very different concepts are currently pursued to either prevent or treat human hantavirus infections. It remains challenging and interesting to see which of the current concepts will finally prevail.

Funding / potential competing interests: This work was supported by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, Grant Number 5U19AI045452.

Correspondence: Tobias Manigold, MD, Internal Medicine, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland, [tobias.manigold\[at\]usb.ch](mailto:tobias.manigold[at]usb.ch)

References

- Lee HW, Lee PW, Johnson KM. Isolation of the etiologic agent of Korean Hemorrhagic fever. *J Infect Dis.* [Internet]. 1978;137:298–308. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24670>.
- Smadel JE. Epidemic hemorrhagic fever. *Am J Public Health Nations Health.* [Internet]. 1953 Oct [cited 2013 Oct 13];43(10):1327–30. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1620469&tool=pmcentrez&rendertype=abstract>.
- Schmaljohn C, Hjelle B. Hantaviruses: a global disease problem. *Emerg Infect Dis.* [Internet]. 1997;3:95–104. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2627612&tool=pmcentrez&rendertype=abstract>.
- Nichol ST, Spiropoulou CF, Morzunov S, Rollin PE, Ksiazek TG, Feldmann H, et al. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. *Science.* 1993;262:914–7.
- Ksiazek TG, Peters CJ, Rollin PE, Zaki S, Nichol S, Spiropoulou C, et al. Identification of a new North American hantavirus that causes acute pulmonary insufficiency. *Am J Trop Med Hyg.* [Internet]. 1995;52:117–23. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7872437.
- López N, Padula P, Rossi C, Lázaro ME, Franze-Fernández MT. New hantaviruses causing hantavirus pulmonary syndrome in central Argentina. [Internet]. *Virology.* 1997;349:998–9. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9100632.
- Padula PJ, Colavecchia SB, Martínez VP, Gonzalez Della Valle MO, Edelstein A, Miguel SDL, et al. Genetic Diversity, Distribution, and Serological Features of Hantavirus Infection in Five Countries in South America. *J Clin Microbiol.* [Internet]. 2000;38:3029–35. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=87178&tool=pmcentrez&rendertype=abstract>.
- Vincent MJ, Quiroz E, Gracia F, Sanchez AJ, Ksiazek TG, Kitsutani PT, et al. Hantavirus pulmonary syndrome in Panama: identification of novel hantaviruses and their likely reservoirs. *Virology.* [Internet]. 2000;277:14–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11062031>.
- Krüger DH, Ulrich RG, Hofmann J. Hantaviruses as zoonotic pathogens in Germany. *Dtsch Arztebl Int.* [Internet]. 2013 Jul [cited 2013 Oct 13];110(27–28):461–7. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3722641&tool=pmcentrez&rendertype=abstract>.
- Hantavirus pulmonary syndrome in visitors to a national park--Yosemite Valley, California, 2012. *MMWR Morb Mortal. Wkly Rep* [Internet]. 2012 Nov 23 [cited 2013 Oct 13];61(46):952. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23169317>.
- Puerta H, Cantillo C, Mills J, Hjelle B, Salazar-Bravo J, Mattar S. The New-World Hantaviruses. Ecology and epidemiology of an emerging virus in Latin America. *Med Aires.* 2006;66:343–56.
- Mátta S, Parra M. Serologic evidence of hantavirus infection in humans, Colombia. *Emerg Infect Dis* [Internet]. 2004 Dec [cited 2013 Oct 13];10(12):2263–4. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3323398&tool=pmcentrez&rendertype=abstract>.
- Alemán A, Iguarán H, Puerta H, Cantillo C, Mills J, Ariz W, et al. First serological evidence of Hantavirus infection in rodents in Colombia. *Rev Salud Publica Bogota Colomb* [Internet]. 2006;8 Suppl 1:1–12. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16925117.
- Rosa EST, Mills JN, Padula PJ, Elkhoury MR, Ksiazek TG, Mendes WS, et al. Newly recognized hantaviruses associated with hantavirus pulmonary syndrome in northern Brazil: partial genetic characterization of viruses and serologic implication of likely reservoirs. *Vector borne zoonotic Dis Larchmont NY* [Internet]. 2005;5:11–9. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15815145.
- Casapia M, Mamani E, García MP, Miraval ML, Valencia P, Quino AH, et al. [Hantavirus pulmonary syndrome (Rio Mamore virus) in the Peruvian Amazon region]. *Rev Peru Med Exp Salud Publica* [Internet]. [cited 2013 Oct 13];29(3):390–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23085803>.
- 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;88:1911–6.

- 17 Olsson GE, Dalerum F, Hörnfeldt B, Elgh F, Palo TR, Juto P, et al. Human hantavirus infections, Sweden. *Emerg Infect Dis*. 2003;9:1395–401.
- 18 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* [Internet]. 2010;16:308–10. Available from: <http://www.cdc.gov/eid/content/16/2/308.htm>.
- 19 Merino C, Arias A, Castillo C. First Case of Hantavirus Cardiopulmonary Syndrome Occurring after a Rodent Bite. *Rev Chil Enf Respir*. 2002;18:199–205.
- 20 Kallio ER, Klingström J, Gustafsson E, Manni T, Vaehri A, Henttonen H, et al. Prolonged survival of Puumala hantavirus outside the host: evidence for indirect transmission via the environment. *J Gen Virol*. 2006;87:2127–34.
- 21 Jameson LJ, Taori SK, Atkinson B, Levick P, Featherstone C a, van der Burgt G, et al. Pet rats as a source of hantavirus in England and Wales, 2013. *Euro Surveill* [Internet]. 2013 Jan;18(9):8–10. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23470018>.
- 22 Taori SK, Jameson LJ, Campbell A, Drew PJ, McCarthy ND, Hart J, et al. UK hantavirus, renal failure, and pet rats. *Lancet* [Internet]. 2013 Mar 23 [cited 2013 Oct 13];381(9871):1070. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23668557>.
- 23 Lundkvist A, Verner-Carlsson J, Plyusnina A, Forslund L, Feinstein R PA. Pet rat harbouring Seoul hantavirus in Sweden, June 2013. *Euro Surveill* [Internet]. 2013 [cited 2013 Oct 13];Jul 4(18(27)):pii: 20521. Available from: <http://www.eurosurveillance.org/images/dynamic/EE/V18N27/art20521.pdf>.
- 24 Martinez VP, Bellomo C, San Juan J, Pinna D, Forlenza R, Elder M, et al. Person-to-person transmission of Andes virus. *Emerg Infect Dis* [Internet]. 2005;11:1848–53. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16485469>.
- 25 Martinez VP, Bellomo CM, Cacace ML, Suarez P, Bogni L, Padula PJ. Hantavirus pulmonary syndrome in Argentina, 1995–2008. *Emerg Infect Dis* [Internet]. 2010 Dec [cited 2013 Oct 13];16(12):1853–60. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3294556&tool=pmcentrez&rendertype=abstract>.
- 26 Ferres M, Vial P, Marco C, Yanez L, Godoy P, Castillo C, et al. Prospective evaluation of household contacts of persons with hantavirus cardiopulmonary syndrome in Chile. *J Infect Dis* [Internet]. 2007;195:1563–71. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17471425>.
- 27 Castillo C, Villagra E, Sanhueza L, Ferres M, Mardones J, Mertz GJ. Prevalence of antibodies to hantavirus among family and health care worker contacts of persons with hantavirus cardiopulmonary syndrome: lack of evidence for nosocomial transmission of Andes virus to health care workers in Chile. *Am J Trop Med Hyg* [Internet]. 2004 Mar;70(3):302–4. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15031521>.
- 28 Padula PJ, Edelstein A, Miguel SD, López NM, Rossi CM, Rabinovich RD. Hantavirus pulmonary syndrome outbreak in Argentina: molecular evidence for person-to-person transmission of Andes virus. *Virology* [Internet]. 1998;241:323–30. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9674243>.
- 29 Martinez-Valdebenito C, Calvo M, Ferres M, Vial C, Mansilla R, Marco C, et al. Andes hantavirus case-cluster with household and first nosocomial transmission in Southern Chile. *Submitt Publ*.
- 30 Täger Frey M, Vial PC, Castillo CH, Godoy PM, Hjelle B, Ferrés MG. Hantavirus prevalence in the IX Region of Chile. *Emerg Infect Dis*. 2003;9:827–32.
- 31 Armién B, Pascale JM, Muñoz C, Lee S-J, Choi KL, Avila M, et al. Incidence rate for hantavirus infections without pulmonary syndrome, Panama. *Emerg Infect Dis* [Internet]. 2011 Oct [cited 2013 Oct 13];17(10):1936–9. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3310655&tool=pmcentrez&rendertype=abstract>.
- 32 Ferrer JF, Jonsson CB, Esteban E, Galligan D, Basombrio M a, Peralta-Ramos M, et al. High prevalence of hantavirus infection in Indian communities of the Paraguayan and Argentinean Gran Chaco. *Am J Trop Med Hyg* [Internet]. 1998 Sep;59(3):438–44. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9749641>.
- 33 Williams RJ, Bryan RT, Mills JN, Palma RE, Vera I, De Velasquez F, et al. An outbreak of hantavirus pulmonary syndrome in western Paraguay. *Am J Trop Med Hyg* [Internet]. 1997 Sep [cited 2013 Oct 13];57(3):274–82. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9311636>.
- 34 Mertens M, Hofmann J, Petraityte-Burneikiene R, Ziller M, Sasnauskas K, Friedrich R, et al. Seroprevalence study in forestry workers of a non-endemic region in eastern Germany reveals infections by Tula and Dobrava–Belgrade hantaviruses. *Med. Microbiol. Immunol*. 2011;200(4):263–8.
- 35 Schultze D, Fierz W, Matter HC, Bankoul S, Niedrig M, Schmiedl A. Cross-sectional survey on hantavirus seroprevalence in Canton St. Gallen, Switzerland. *Swiss Med Wkly Off J Swiss Soc Infect Dis Swiss Soc Intern Med Swiss Soc Pneumol*. 2007;137:21–6.
- 36 Fontana-Binard L, Schultze D, Rojanavisut BS, Krüger DH, Dollenmaier G, Zanetti G, et al. [First case of nephropathia epidemica acquired in Switzerland]. *Rev. Med. Suisse*. 2008;4(163):1572–5. French.
- 37 Boone I, Wagner-Wiening C, Reil D, Jacob J, Rosenfeld UM, Ulrich RG, et al. Rise in the number of notified human hantavirus infections since October 2011 in Baden-Württemberg, Germany. *Euro Surveill* [Internet]. 2012 May 24 [cited 2014 Jan 1];17(21). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22687824>.
- 38 Lednicky JA. Hantaviruses: a short review. *Arch Pathol Lab Med* [Internet]. 2003 Jan [cited 2013 Oct 13];127(1):30–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12521363>.
- 39 Hautala N, Kauma H, Rajaniemi S-M, Sironen T, Vapalahti O, Pääkkö E, et al. Signs of general inflammation and kidney function are associated with the ocular features of acute Puumala hantavirus infection. *Scand. J. Infect. Dis*. 2012;44(12):1–7.
- 40 Nichol ST. Bunyaviruses. In: Knipe DM, Howley PM, eds. *Field's Virology Vol 2, 4th ed Philadelphia, Pa Lippincott Williams Wilkins*. 2001. p. 1603–33.
- 41 Vaehri A, Strandin T, Hepojoki J, Sironen T, Henttonen H, Mäkelä S, et al. Uncovering the mysteries of hantavirus infections. *Nat Rev Microbiol* [Internet]. 2013 Aug [cited 2013 Oct 13];11(8):539–50. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24020072>.
- 42 Vial PA, Valdivieso F, Mertz G, Castillo C, Belmar E, Delgado I, et al. Incubation period of hantavirus cardiopulmonary syndrome. *Emerg Infect Dis* [Internet]. 2006 Aug [cited 2013 Oct 13];12(8):1271–3. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3291207&tool=pmcentrez&rendertype=abstract>.
- 43 Riquelme R, Riquelme M, Torres A, Rioseco ML, Vergara JA, Scholz L, et al. Hantavirus pulmonary syndrome, southern Chile. *Emerg Infect Dis* [Internet]. 2003 Nov [cited 2013 Oct 13];9(11):1438–43. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14718088>.
- 44 Hallin GW, Simpson SQ, Crowell RE, James DS, Koster FT, Mertz GJ, et al. Cardiopulmonary manifestations of hantavirus pulmonary syndrome. *Crit Care Med* [Internet]. 1996 Feb [cited 2013 Oct 13];24(2):252–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8605797>.
- 45 Duchin JS, Koster FT, Peters CJ, Simpson GL, Tempest B, Zaki SR, et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. The Hantavirus Study Group. *N Engl J Med* [Internet]. 1994 Apr 7 [cited 2013 Oct 13];330(14):949–55. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8121458>.
- 46 Campos GM, Borges AA, Badra SJ, Figueiredo GG, Souza RLM de, Moreli ML, et al. [Pulmonary and cardiovascular syndrome due to hantavirus: clinical aspects of an emerging disease in southeastern Brazil]. *Rev Soc Bras Med Trop* [Internet]. 2009 [cited 2013 Oct 13];42(3):282–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19684976>.
- 47 Castillo C, Naranjo J, Sepúlveda A, Ossa G, Levy H. Hantavirus pulmonary syndrome due to Andes virus in Temuco, Chile: clinical experience with 16 adults. *Chest* [Internet]. 2001 Aug [cited 2013 Oct 13];120(2):548–54. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11502657>.
- 48 Talamonti L, Padula PJ, Canteli MS, Posner F, Marczeski FP, Weller C. Hantavirus pulmonary syndrome: encephalitis caused by virus Andes. *J Neurovirol* [Internet]. 2011 Apr [cited 2013 Oct 13];17(2):189–92. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21240581>.

- 49 Armien B, Pascale JM, Muñoz C, Mariñas J, Núñez H, Herrera M, et al. Hantavirus fever without pulmonary syndrome in Panama. *Am J Trop Med Hyg* [Internet]. 2013 Sep [cited 2014 Jan 1];89(3):489–94. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23836565>.
- 50 Vial PA, Valdivieso F, Ferrer M, Riquelme R, Rioseco ML, Calvo M, et al. High-dose intravenous methylprednisolone for hantavirus cardiopulmonary syndrome in Chile: a double-blind, randomized controlled clinical trial. *Clin Infect Dis* [Internet]. 2013 Oct [cited 2013 Oct 13];57(7):943–51. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23784924>.
- 51 Gracia F, Armien B, Simpson SQ, Munoz C, Broce C, Pascale JM, et al. Convalescent pulmonary dysfunction following hantavirus pulmonary syndrome in Panama and the United States. *Lung* [Internet]. 2010 Oct [cited 2013 Oct 13];188(5):387–91. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2939327&tool=pmcentrez&rendertype=abstract>.
- 52 Feldmann H, Sanchez A, Morzunov S, Spiropoulou CF, Rollin PE, Ksiazek TG, et al. Utilization of autopsy RNA for the synthesis of the nucleocapsid antigen of a newly recognized virus associated with hantavirus pulmonary syndrome. *Virus Res* [Internet]. 1993 Dec [cited 2013 Oct 13];30(3):351–67. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8109165>.
- 53 Elgh F, Lundkvist A, Alexeyev OA, Stenlund H, Avsic-Zupanc T, Hjelle B, et al. Serological diagnosis of hantavirus infections by an enzyme-linked immunosorbent assay based on detection of immunoglobulin G and M responses to recombinant nucleocapsid proteins of five viral serotypes. *J Clin Microbiol* [Internet]. 1997 May [cited 2013 Oct 13];35(5):1122–30. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=232715&tool=pmcentrez&rendertype=abstract>.
- 54 Hjelle B, Jenison S, Torrez-Martinez N, Herring B, Quan S, Polito A, et al. Rapid and specific detection of Sin Nombre virus antibodies in patients with hantavirus pulmonary syndrome by a strip immunoblot assay suitable for field diagnosis. *J Clin Microbiol* [Internet]. 1997 Mar [cited 2013 Oct 13];35(3):600–8. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=229635&tool=pmcentrez&rendertype=abstract>.
- 55 Schmidt J, Meisel H, Capria SG, Petrailyte R, Lundkvist a, Hjelle B, et al. Serological assays for the detection of human Andes hantavirus infections based on its yeast-expressed nucleocapsid protein. *Intervirology* [Internet]. 2006 Jan [cited 2013 Sep 26];49(3):173–84. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16428893>.
- 56 Lederer S, Lattwein E, Hanke M, Sonnenberg K, Stoecker W, Lundkvist Å, et al. Indirect immunofluorescence assay for the simultaneous detection of antibodies against clinically important old and new world hantaviruses. *PLoS Negl Trop Dis* [Internet]. 2013 Jan [cited 2013 Oct 13];7(4):e2157. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3617148&tool=pmcentrez&rendertype=abstract>.
- 57 Padula PJ, Rossi CM, Della Valle MO, Martínez P V, Colavecchia SB, Edelstein A, et al. Development and evaluation of a solid-phase enzyme immunoassay based on Andes hantavirus recombinant nucleoprotein. *J Med Microbiol* [Internet]. 2000 Feb [cited 2013 Oct 13];49(2):149–55. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10670565>.
- 58 Mori M, Rothman AL, Kurane I, Montoya JM, Nolte KB, Norman JE, et al. High levels of cytokine-producing cells in the lung tissues of patients with fatal hantavirus pulmonary syndrome. *J Infect Dis* [Internet]. 1999 Feb [cited 2013 Oct 13];179(2):295–302. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9878011>.
- 59 Gupta S, Braun M, Tischler ND, Stoltz M, Sundström KB, Björkström NK, et al. Hantavirus-infection confers resistance to cytotoxic lymphocyte-mediated apoptosis. *PLoS Pathog* [Internet]. 2013 Mar [cited 2013 Oct 13];9(3):e1003272. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3610645&tool=pmcentrez&rendertype=abstract>.
- 60 Koster F, Vigil J, Olson D, Terajima M, Ennis F, Al. E. *Am J Trop Med* 65: (Abstr.). CI I, II III HLA alleles Assoc with Sev hantavirus Cardiopulm Syndr southwest US. 2001.
- 61 Ferrer C P, Vial C PA, Ferrés G M, Godoy M P, Culza V A, Marco C C, et al. Genetic susceptibility to Andes Hantavirus: Association between severity of disease and HLA alleles in Chilean patients. *Rev Chil Infectol organo Of la Soc Chil Infectol* [Internet]. 2007;24:351–9. Available from: http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0716-10182007000500001&lng=en&nrm=iso.
- 62 Manigold T, Mori A, Graumann R, Llop E, Simon V, Ferrés M, et al. Highly Differentiated, Resting Gn-Specific Memory CD8+ T Cells Persist Years after Infection by Andes Hantavirus. *PLoS Pathog* [Internet]. 2010;6:16. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2824805&tool=pmcentrez&rendertype=abstract>.
- 63 Manigold T, Martínez J, Lazcano X, Ye C, Schwartz S, Cuiza A, et al. Case report: T-cell responses during clearance of Andes virus from blood cells 2 months after severe hantavirus cardiopulmonary syndrome. [Internet]. *J. Med. Virol.* 2008. p. 1947–51. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18814258.
- 64 Hammerbeck CD, Hooper JW. T cells are not required for pathogenesis in the Syrian hamster model of hantavirus pulmonary syndrome. *J Virol* [Internet]. 2011 Oct [cited 2013 Oct 13];85(19):9929–44. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3196444&tool=pmcentrez&rendertype=abstract>.
- 65 Prescott J, Safronetz D, Haddock E, Robertson S, Scott D, Feldmann H. The adaptive immune response does not influence hantavirus disease or persistence in the Syrian hamster. *Immunology* [Internet]. 2013 Oct [cited 2013 Oct 13];140(2):168–78. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23600567>.
- 66 Matthys V, Mackow ER. Hantavirus regulation of type I interferon responses. *Adv Virol* [Internet]. 2012 Jan [cited 2013 Oct 13];2012:524024. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3423653&tool=pmcentrez&rendertype=abstract>.
- 67 Mackow ER, Gavrilovskaya IN. Cellular receptors and hantavirus pathogenesis. *Curr Top Microbiol Immunol* [Internet]. 2001 Jan [cited 2013 Oct 13];256:91–115. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11217408>.
- 68 Kiss J, Yegutkin GG, Koskinen K, Savunen T, Jalkanen S, Salmi M. IFN-beta protects from vascular leakage via up-regulation of CD73. *Eur J Immunol* [Internet]. 2007 Dec [cited 2013 Oct 13];37(12):3334–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18034430>.
- 69 Patkar C, Giaya K, Libraty DH. Dengue virus type 2 modulates endothelial barrier function through CD73. *Am J Trop Med Hyg* [Internet]. 2013 Jan [cited 2013 Oct 13];88(1):89–94. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3541750&tool=pmcentrez&rendertype=abstract>.
- 70 Gavrilovskaya IN, Brown EJ, Ginsberg MH, Mackow ER. Cellular entry of hantaviruses which cause hemorrhagic fever with renal syndrome is mediated by beta3 integrins. *J Virol* [Internet]. 1999 May [cited 2013 Oct 13];73(5):3951–9. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=104173&tool=pmcentrez&rendertype=abstract>.
- 71 Ma Y-Q, Qin J, Plow EF. Platelet integrin alpha(IIb)beta(3): activation mechanisms. *J Thromb Haemost* [Internet]. 2007 Jul [cited 2013 Sep 22];5(7):1345–52. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17635696>.
- 72 Bharadwaj M, Nofchissey R, Goade D, Koster F, Hjelle B. Humoral immune responses in the hantavirus cardiopulmonary syndrome. *J Infect Dis* [Internet]. 2000 Jul [cited 2013 Oct 13];182(1):43–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10882580>.
- 73 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 Active and Passive Vaccination against Hantavirus Pulmonary Syndrome with Andes Virus M Genome Segment-Based DNA Vaccine. 2003;
- 74 Terajima M, Hendershot JD, Kariwa H, Koster FT, Hjelle B, Goade D, et al. High levels of viremia in patients with the Hantavirus pulmonary syndrome. *J Infect Dis* [Internet]. 1999 Dec [cited 2013 Oct 13];180(6):2030–4. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10558964>.
- 75 Pinschewer DD, Perez M, Jeetendra E, Bächli T, Horvath E, Hengartner H, et al. Kinetics of protective antibodies are determined by the viral surface antigen. *J Clin Invest* [Internet]. 2004 Oct [cited 2013 Oct

- 13];114(7):988–93. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=518669&tool=pmcentrez&rendertype=abstract>.
- 76 Ma Y, Wang J, Yuan B, Wang M, Zhang Y, Xu Z, et al. HLA-A2 and B35 restricted hantaan virus nucleoprotein CD8+ T-cell epitope-specific immune response correlates with milder disease in hemorrhagic fever with renal syndrome. *PLoS Negl Trop Dis* [Internet]. 2013 Jan [cited 2013 Oct 8];7(2):e2076. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3585118&tool=pmcentrez&rendertype=abstract>.
- 77 Martinez VP, Padula PJ. Induction of Protective Immunity in a Syrian Hamster Model Against a Cytopathogenic Strain of Andes Virus. *Cell*. 2012;95:87–95.
- 78 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* [Internet]. 1991 Dec [cited 2013 Oct 13];164(6):1119–27. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1683355>.
- 79 Chapman LE, Ellis BA, Koster FT, Sotir M, Ksiazek TG, Mertz GJ, et al. Discriminators between hantavirus-infected and -uninfected persons enrolled in a trial of intravenous ribavirin for presumptive hantavirus pulmonary syndrome. *Clin Infect Dis* [Internet]. 2002 Feb 1 [cited 2013 Oct 13];34(3):293–304. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11774075>.
- 80 Mertz GJ, Miedzinski L, Goade D, Pavia AT, Hjelle B, Hansbarger CO, et al. Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. *Clin Infect Dis* [Internet]. 2004 Nov 1 [cited 2013 Oct 13];39(9):1307–13. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15494907>.
- 81 Safronetz D, Haddock E, Feldmann F, Ebihara H, Feldmann H. In vitro and in vivo activity of ribavirin against Andes virus infection. *PLoS One* [Internet]. 2011 Jan [cited 2013 Oct 13];6(8):e23560. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3154477&tool=pmcentrez&rendertype=abstract>.
- 82 Gorbunova EE, Gavrilovskaya IN, Pepini T, Mackow ER. VEGFR2 and Src kinase inhibitors suppress Andes virus-induced endothelial cell permeability. *J Virol* [Internet]. 2011 Mar [cited 2013 Oct 13];85(5):2296–303. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3067787&tool=pmcentrez&rendertype=abstract>.
- 83 Vial P et al. Treatment of hantavirus cardiopulmonary syndrome with human immune plasma. *Submiss Prep*.
- 84 Hjelle B. Vaccines against hantaviruses. *Expert Rev Vaccines* [Internet]. 2002 Oct [cited 2013 Oct 13];1(3):373–84. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12901576>.
- 85 Hooper JW, Joselyn M, Ballantyne J, Brocato R. A novel Sin Nombre virus DNA vaccine and its inclusion in a candidate pan-hantavirus vaccine against hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS). *Vaccine* [Internet]. 2013 Sep 13 [cited 2013 Oct 13];31(40):4314–21. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23892100>.

Figures (large format)

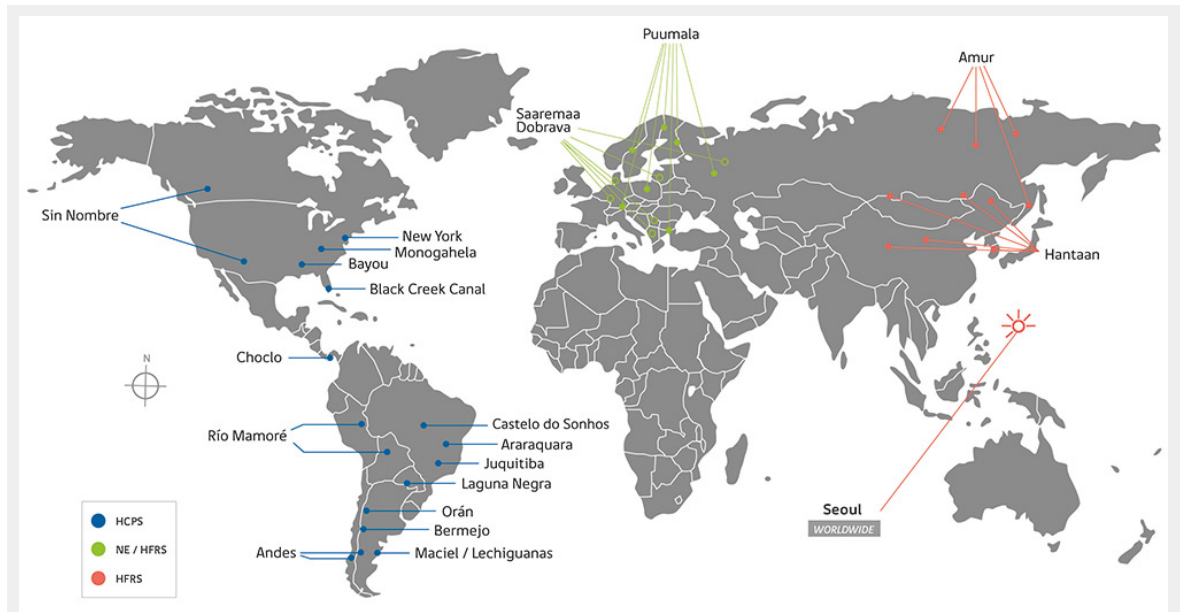


Figure 1

Geographical distribution of pathogenic hantaviruses and principal associated pathologies in humans.

HCPS = hantavirus cardiopulmonary syndrome; HFRS = haemorrhagic fever with renal syndrome; NE = nephropathia epidemica