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Hantaviruses

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In 1978, the etiologic agent of Korean Hemerologic fever was isolated from small infected field rodent *Apodemus agrarius* near Hantan river in South Korea. The virus was named as Hantaan virus, after the name of the river Hantan. This initial discovery dates back to scientific approaches that were initiated after the Korean war (1951-1953), during which more than 3000 cases of Korean hemorrhagic fever were reported among UN troops. In 1981, Hantaan virus strain 76-118, isolated from *Apodemus agrarius* was grown in A549 cell line, and its electron microscopic images revealed that the virus was a new member of the Bunyaviridae family. It was observed that hantaviruses unlike other members of this family do not have an arthropod vector, and exclusively establish a persistent infection in the population of their specific rodent hosts. In 1981, a new genus termed as “hantavirus” was introduced in the Bunyaviridae family, which included the viruses that cause hemorologic fever with renal syndrome (HFRS) (Fig1). It was initially thought that pathogenic hantaviruses are restricted to old world. Until 1993, the only native hantavirus found in new world was non pathogenic Prospect Hill virus (PHV). This myth ended after the hantavirus outbreak in the four corner region of Southwestern United States that caused serious respiratory distress in infected patients and lead to the discovery of a new hantavirus disease called hantavirus cardiopulmonary syndrome (HPS). An examination of frozen stored samples of lung tissue from people who had died of unexplained lung disease in the past revealed that HPS is an old disease with conformed cases dating to at least 1959. Within a very short period the virus causing HPS was isolated from common deer mouse (*Peromyscus maniculatus*, Fig 1) and was later named as Sin Nombre virus (SNV). Later on, it became clear that other hantaviruses similar to SNV, such as Andes virus (ANDV), are present through out the united states. Currently, the hantavirus genus includes more than twenty one species and more than 30 genotypes (Table 1).

Hantaviruses have coevolved for millions of years with their rodent and insectivore reservoirs. Rodent reservoirs include both Cricetidae rodents (subfamilies Arvicolinae, Neotominae and Sigmodontinae) and Muridae rodents (subfamily Murinae). Cricetidae rodents include voles, lemmings of the northern hemisphere and new world mice and rats. Muridae rodents include old world mice and rats (Fig 2). Hantavirus phylogeny follows closely that of their rodent hosts, suggesting long term co-evolution, although there are evidences of occasional host switches in the past. The phylogenetic tree suggests that co-speciation of hantavirus with their host animals of four different rodent subfamilies appears to influence their ability to cause a specific clinical manifestation in humans. For example, a majority of viruses in Neotominae and Sigmodontinae subfamilies are known to cause severe HPS with high mortality rate (40-50%). These viruses are distributed throughout North and South America in different rodent species of New World Neotominae and Sigmodontinae rodents. Old world hantaviruses that have co-evolved with Murinae rodents cause severe HFRS that primarily affects kidney function with a mortality of 0-15%. Although the disease caused by Murinae viruses has less mortality rate,

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it still poses a significant threat to human health due to severity of the disease and the ability of the viruses to cause large scale epidemics. Among Arvicolinae-borne hantaviruses, only puumala virus (PUUV) causes a mild form of human disease often referred as nephropathic epidemia with a mortality rate of less than 1%. Interestingly, most other members of this subfamily are non-pathogenic to humans. Until recently, the only exception that did not have a confirmed rodent connection is Thottapalayam virus (TPMV), which was isolated from an Asian house shrew or musk shrew (*Suncus murinus*) captured in 1964 during a survey for Japanese encephalitis virus in southern India (4).

Microbiology

Electron microscopy revealed that hantaviruses are spherical or oval particles with a diameter of 80 to 210 nm (Fig 3). They have tripartite negative sense RNA genome (13,28). The large (L) segment genomic RNA encodes viral RNA dependent RNA polymerase (RdR), the medium size (M) segment encodes viral glycoprotein precursor (GPC) which is later cleaved into two glycoproteins G1 and G2, and the small (S) segment encodes the viral nucleocapsid protein (N). The nucleotide sequence at 5' and 3' termini of each genome segment is complementary and undergoes base pairing to form panhandle structures (Fig 3). Inside the virus particle the three genomic RNAs are complexed with N protein and form three individual nucleocapsids, which along with RdRp are packaged within a lipid envelop. Two glycoproteins G1 and G2 remain embedded within the lipid envelop (Fig 3).

Like many other viruses, hantaviruses enter the host cells by the interaction between viral glycoproteins and cell surface integrin receptors (Fig 3). Interestingly, pathogenic and non pathogenic hantavirus use different integrin receptors to enter their host cells. Human integrins α IIa β 3 expressed by platelets, and α v β 3 expressed by endothelial cells mediate the cellular entry for HFRS and HCP causing hantaviruses (10). In contrast, non pathogenic hantaviruses, such as, PHV and TULV use α 5 β 1 receptor for cellular entry. Once engaged on the host cell surface, hantaviruses enter the cells by clathrin-dependent endocytosis. Upon internalization, the three nucleocapsids are released into the cell cytoplasm along with viral RdRp. Subsequently, RdRp initiates transcription and viral mRNAs encoding three viral proteins are synthesized. Viral mRNAs are around 100 nucleotides shorter than parent genomic viral RNAs, and lack poly A tails. Viral RdRp uses a novel "cap snatching" mechanism for transcription initiation. During cap snatching 10-14 nucleotide long 5' capped oligonucleotides are cleaved from host cell transcripts and used as primers by viral RdRp to initiate the viral mRNA synthesis, following a prime-and-realign mechanism (7,21). Viral mRNAs are translated in the cell cytoplasm by the host cell translation machinery. Viral RdRp also replicates the genome via complementary cRNA synthesis. Complementary cRNAs are exact complement of genomic viral RNA (vRNA), and serve as templates for the synthesis of negative sense viral genome. Viral assembly and maturation takes place either on the cell surface or on the Golgi. Virions that mature on the Golgi are transported to cell surface via vesicular secretory pathways. Ultimately, new virions bud off the host cells from plasma membrane.

Nucleocapsid protein

N protein is the most abundant hantavirus protein found in the cytoplasm of infected cells. Its transcript is detected in infected cells six hours post infection. N protein is responsible for encapsidation and packaging of the viral genome. However, recent studies have shown that N is a multifunctional protein involved in diverse viral functions, including its role in the transcription and translation initiation of viral mRNA (21,22). Trimeric N also recognizes vRNA panhandle with specificity and likely facilitates the selective incorporation of viral genomic RNA into virions. N has also been found to interact with multiple host cell proteins and the nature of such interaction remains unclear.

Glycoproteins

Glycoprotein precursor (GPC) is synthesized on ribosomes associated with endoplasmic reticulum (ER) and is translocated to ER lumen by an endogenous signal peptide. In ER, GPC is post translationally cleaved at a conserved WAASA site, and two glycoproteins G1 and G2 are generated which are later glycosylated and translocated to the Golgi. Glycoproteins facilitate the attachment of virions with the integrin receptors located on the host cell surface.

RdRp

Hantavirus RdRp is a huge protein with a molecular weight of 250-280 KD. Because of its large molecular weight RdRp is difficult to express in bacteria, and thus remains the most uncharacterized protein in hantaviruses. RdRp mediates both transcription and replication of viral genome. During transcription RdRp synthesizes viral mRNA from negative sense vRNA template. During replication RdRp replicates vRNA genome via a cRNA intermediate. Thus it is likely that hantavirus RdRp has multiple activities, including endonuclease, replicase, transcriptase and RNA helix unwinding activities. However, recent studies have shown that viral RdRp requires N protein for function. For example, short capped primers generated from host cell mRNAs by the process of cap snatching are used by RdRp to initiate the transcription. Hantavirus N protein has been found to be involved in the generation of such capped primers (21).

Epidemiology

The geographic distribution of hantavirus hosts mirrors the hantavirus epidemiology and geographic distribution (Table 1). Hantavirus infection to humans is considered a spill over infection that causes two types of serious illnesses, HFRS and HPS. The primary root of infection for both these illnesses is the inhalation of live virus through lungs. In general humans get hantavirus infection by direct contact with infected rodents or their aerosolized excreta; although there are reports documenting the spread of Andes virus (ANDV) from human to human (8,23). HFRS is caused by old world hantaviruses and most of its cases are found in Eastern Asia (China, Korea and Eastern part of Russia) and Europe, including the European part of Russia). Annually more than 100,000 HFRS cases are reported in China alone (15), and over 900 cases are reported in Korea and Eastern Russia (19). In Europe majority of HFRS cases are registered in Russia, Finland and Sweden (Fig 4, table 1). Majority of HFRS patients are males with age of 20 to 50 years. HFRS mortality rate depends upon the type of virus and in general varies from 0.1 to 10%. HFRS patients mostly belong to rural areas where the hantaviral rodent hosts are thickly inhabited. The only hantavirus that causes diseases in urban areas is the Seoul virus (SEOV) because its host is a domestic rat (*Rattus norvegicus* and *Rattus rattus*). HPS has a mortality of 40-50% and is caused by new world hantaviruses, including SNV, ANDV, Monongahela virus, New York virus, Black Creek Canal virus, Bayou virus, Oran virus and numerous other newly identified strains. Although HPS is found throughout United States, the majority of cases are registered in western region and are caused by SNV. In fact SNV is the predominantly found viral species that causes HPS in patients. HPS outbreaks in North America are associated with increased population of host deer mouse (*peromyscus maniculatus*). HPS has also been reported in other countries in south and central America, including Argentina, Brazil, Chile, Bolivia, Paraguay, Uruguay and Panama.

Pathogenesis

It is not yet exactly clear how hantaviruses spread the human body after their inhalation through lungs. However, immature Dendritic cells (DCs) likely play a significant role in their dissemination. Immature DCs express $\beta 3$ integrins, the receptors that hantaviruses use for attachment and entry. In the airways and alveoli of lungs, the DCs located in the vicinity of

epithelial cells serve as primary targets for pathogen pick up. Hantaviruses infect both immature and mature DCs, which likely serve as vehicles for the transport of virions through the lymphatic vessels to the regional lymph nodes, where they get opportunity to infect other immune cells, such as, macrophages and monocytes. After further replication the free or cell bound virions can infect the endothelial cells, the ultimate targets for viruses causing hemorrhagic fever (20).

Increased vascular permeability and decreased platelet count are the hallmarks of hantavirus associated disease, and the mechanics of such pathogenesis is poorly understood. Unlike other hemorrhagic fever viruses such as Ebola virus, the hantaviruses do not increase the permeability of endothelial cell monolayers *in vitro*, nor do they cause any cytopathic effects in the host endothelial cells. This points towards the role of host immune system in hantavirus pathogenesis.

Invading viruses are detected early during infection by non immune cells as well as DCs located at host pathogen interface (2). Pathogen recognition receptors (PRRs) for virus detection in host cells include TLRs and RIG-I like helicases (RIG-I and MDA5). RIG-I detects viruses from multiple families, including *Orthomyxoviridae*, *paramyxoviridae*, *Rhabdoviridae* and *Flaviviridae*. However, the PRRs that sense hantaviruses in host cells remains to be identified. Type I INF and other pro-inflammatory responses triggered by PRR signaling induce host resistance for viral infection and activation of innate immune cells, such as, natural killer (NK) cells or NKT cells for host defense. These early responses are aimed to reduce the viral dissemination during lag phase before adaptive immune response is ready to strike. It is well established that treatment of cells with type I INF induces the expression of several hundred INF stimulating genes (ISGs), including the well characterized MxA protein that has antiviral activity against the viruses of the Bunyaviridae family (9,17). Interestingly, most pathogenic hantaviruses have evolved the strategies to sabotage the INF induced host defense mechanisms. For example, pathogenic hantaviruses (HTNV, NYV) delay the type-I INF response, including MxA expression in endothelial cells. This virus programmed delay in the establishment of antiviral state in host cells generates a window of opportunity for rapid replication and spread of pathogenic hantaviruses through endothelial cell layer.

Inflammatory cytokines/chemokines produced by antiviral innate immune response represent a double edged sword. On one hand, they play a role in virus elimination, but on other hand, if not properly regulated they can facilitate a virus associated disease. For example, TNF α can purge viruses from infected cells with out causing cell lysis. However, at the same time TNF α can modulate the endothelial barrier functions by promoting vascular leakage by increasing leukocyte adhesion and transendothelial migration (3). TNF α and other cytokines are suspected to play role in Ebola virus (EBOV) mediated septic shock during EBOV hemorrhagic fever. Although hantavirus infection to DCs *in vitro* produces substantial amount of TNF α , which is consistent with increased plasma levels of this cytokine in hantavirus infected patients during acute phase of HFRS. However, there is no evidence of such a harmful innate immune response, producing a “cytokine storm” similar to 1918 strain of influenza virus, that could contribute to the hantavirus immunopathogenesis.

In general, DCs are the prime targets for viruses to evade immune system. For example, human cytomegalovirus and herpes simplex viruses (DNA viruses) impair the function of DCs and induce their apoptosis by different mechanisms (18). Filoviruses, such as, EBOV and Marburgvirus infect immature human DCs and inhibit their transition to antigen presenting cells and also impair their ability to produce T-cell stimulatory cytokines (25). On the other hand, hantaviruses infect immature DCs and activate their maturation and transition into antigen presenting cells with out causing any cytopathic effects. Mature DCs after hantavirus infection had increased T-cell stimulatory capacity, explaining the elicitation of vigorous T-

cell response with long lasting memory in patients during acute phase of hantavirus infection (35). Although epitopes are defined for all three hantavirus proteins, N protein is the major viral target antigen recognized by T cells, likely due to its higher comparative abundance in infected cells. In recent years the concept that CTL response directed against hantavirus infected endothelial cells mediates increased capillary permeability is gaining more and more support from multiple indirect evidences. For example, T cell attracting chemokines CCL5 and CXCL10 are secreted by human lung microvascular endothelial cells after infection by either HTNV or SNV *in vitro* (31). Hantavirus specific CTLs efficiently lyse human endothelial cells leading to the increased vascular permeability (12). In addition, PUUV infected patients show a peak CTL response at the onset of disease with increased serum levels of perforin, granzyme B, and the epithelial cell apoptosis marker caspase-cleaved cytokeratin-18 (16,32). The number of CD8⁺ T cells in PUUV infected patients strongly increase during the acute phase of HFRS, and leave a strong long-lived CTL memory against the PUUV N protein (35). It is likely that a strong unusual primary response accounts for such a long-lived hantavirus specific CTL memory. These observations suggest that the strength of antiviral CTL response and the number of available CTL targets in endothelial cell layer could determine the severity of damage to the vascular bed in hantavirus infected patients. An interesting question that how do the reservoir host rodents escape the vascular damage during persistent hantavirus infection remains to be answered. However, recent studies have suggested that regulatory T cells may play an important role in limiting immunopathology in the natural reservoir host, but this response may interfere with viral clearance. It is hypothesized that in humans the immune mechanisms that downregulate the hantavirus specific CTL response and facilitate the viral clearance by non-cytolytic means are missing, leading to a CTL storm for rapid elimination of virus at the expense of costly damage to the endothelial barrier that causes fatal capillary leakage. In contrast, rodent hosts have elevated regulatory T cell response that controls the CTL activity, leading to viral persistence without immunopathology (Fig 5). The quality of T cell response triggered against hantaviruses is determined by DCs, which are programmed through PRRs during early stages of infection. Thus, further investigation is required to identify the PRRs that detect hantaviruses in rodent hosts and humans. It is probable that PRRs for hantaviruses in humans and rodents are different and program DCs differently that leads to a fatal disease in humans and viral persistence in rodent hosts. Similar to cellular immunity, hantaviruses induce a stable and long lasting humoral immune response involving antibodies of all Ig subclasses (IgA, IgM, IgG). Antibodies against N protein appear soon after the onset of the disease and antibodies against G1 and G2 appear later during the progress of the disease. High titers of antibodies have been found in individuals that have experienced HCPS years ago. Humans infected with PUUV show the presence of neutralizing antibodies in blood decades post infection, suggesting that previously infected individuals are protected life long from the infection. Tables 2 and 3 summarize the immune response in humans and rodents by hantavirus infection.

Clinical presentation

As described by the Centers for Disease Control and Prevention (CDC), Patients with HCPS typically present a short febrile prodrome of 3-5 days (31). In addition to fever and myalgias, early symptoms include headache, chills, dizziness, non-productive cough, nausea, vomiting, and other gastrointestinal symptoms. Malaise, diarrhea, and lightheadedness are reported by approximately half of all patients, with less frequent reports of arthralgias, back pain, and abdominal pain. Patients may report shortness of breath, (respiratory rate usually 26 - 30 times per minute). Typical findings on initial presentation include fever, tachypnea and tachycardia, with usually a normal physical exam.

The analysis of clinical, laboratory, and autopsy data of seventeen patients with confirmed hantavirus infection during 1993 hantavirus outbreak revealed the mean duration of symptoms

before hospitalization is 5.4 days. The most common symptoms at the time of hospitalization were fever, myalgia, headache, cough, and nausea or vomiting (Tables 4 and 5), with myalgia being the most frequently reported initial symptom. The most common physical findings were tachypnea and tachycardia (Tables 6 and 7). Fifty percent of the patients had a respiratory rate of 28 or more breaths per minute, and 50 percent had a heart rate of 120 or more beats per minute. No patient had conjunctival hemorrhage, petechial rash, clinical signs of internal hemorrhage (including a guaiac-positive stool specimen), or peripheral or periorbital edema. Notable hematologic findings included an elevated white-cell count with increased neutrophils, myeloid precursors, and atypical lymphocytes

The partial-thromboplastin time was 40 seconds or longer in 67 percent of the patients at the time of admission (Tables 8 and 9). Although minimal abnormalities of renal function were common, the serum creatinine levels did not rise above 2.5 mg per deciliter (220 μ mol per liter) in any patient (Tables 8 and 9). The mean specific gravity of urine at the time of admission was 1.024 ± 0.010 . Forty percent of patients had proteinuria on admission. Urine dipstick tests for blood were positive in fifty seven percent of tested patients at the time of admission.

The initial chest radiograph showed interstitial or interstitial and alveolar infiltrates (Fig 6) in sixty five percent, fluffy alveolar infiltrates in twelve percent, and no abnormalities in twenty four percent of the patients. Subsequently, ninety four percent had rapidly evolving, bilateral, diffuse infiltrates, and six percent had interstitial infiltrates confined to the lower lobes. Pleural effusions were noted during the course of the illness in four patients. Eleven of twelve patients (ninety two percent) who underwent chest radiography and arterial measurement of oxygen saturation at the time of admission had either pulmonary infiltrates or arterial oxygen saturation under 90 mm Hg. Similar observations were made in other hantavirus infected cases (1,24)

Since the emergence of HCPS in United States in 1993, only 5.5% of the cases reported to CDC were children less than sixteen years of age. Due to minimum causalities in younger children and adolescents, it is hypothesized that hantavirus infection in children is less likely to develop into serious illness as compared to adults. The analysis of clinical data of ten SNV pediatric cases is presented in Tables 4-9.

Diagnostics

Hantavirus infection is diagnosed on the basis of a positive serological test and the confirmation of viral antigen in the tissue of infected patient or the presence of viral RNA sequences in patient's blood or tissue, along with a compatible history of the disease.

Serologic assays

During 1993 hantavirus outbreak, cross-reactive antibodies to the previously known hantaviruses, such as, Hantaan, Seoul, Puumala, and Prospect Hill virus were found in the acute- and convalescent-phase sera of some HPS patients. Since then, tests based on specific viral antigens from SNV have been developed and are widely used for the routine diagnosis of HPS. Enzyme-linked immunosorbent assay (ELISA) is the popular test for the detection of IgM antibodies in patient's blood that are raised against Hantaviruses during infection.

An IgG test in conjunction with the IgM-capture test is also used for the diagnosis of Hantavirus disease. Acute and convalescent-phase sera should reflect a fourfold rise in IgG antibody titer or the presence of IgM in acute-phase sera for a positive hantavirus infection. It may be noted that acute-phase serum used as an initial diagnostic specimen may not yet have IgG. IgG is a long lasting antibody, retained for many years after infection. Thus, SNV IgG ELISA has been used in serologic investigations of the epidemiology of the disease and appears to be appropriate

for this purpose. Rapid immunoblot strip assay (RIBA) is an investigational prototype assay for the identification of serum antibodies to recombinant proteins and peptides specific for SNV and other hantaviruses. Also, neutralizing plaque assays have recently been performed for the serological confirmation of SNV infections. However, these specific assays are not commercially available. Isolation of hantaviruses from human sources is difficult and no isolates of SNV-like viruses have been recovered from humans. Thus, isolation of hantavirus is not considered for diagnostic purposes.

Immunohistochemistry (IHC)

IHC testing of formalin-fixed tissues with specific monoclonal and polyclonal antibodies can be used to detect hantavirus antigens and has proven to be a sensitive method for laboratory confirmation of hantaviral infections. IHC has an important role in the diagnosis of HPS in patients from whom serum samples and frozen tissues are unavailable for diagnostic testing and in the retrospective assessment of disease prevalence in a defined geographic region.

Polymerase Chain Reaction (PCR)

Reverse transcriptase polymerase chain reaction (RT-PCR) is a very sensitive assay and can be used for the detection of hantaviral RNA in infected samples, such as, lung tissues and blood clots from infected patients. However, RT-PCR is very prone to cross-contamination and should be considered an experimental technique with a limited use for diagnostic purposes of hantavirus infections.

Differential diagnosis

A variety of Infectious etiologies, such as, pneumonia, sepsis with ARDS, and acute bacterial endocarditis can often be confused with HPS. Other conditions commonly found in the southwest United States have presentations similar to HPS, such as, septicemic plague, tularemia, histoplasmosis, and coccidioidomycosis. In addition, noninfectious conditions, including myocardial infarction with pulmonary edema and Goodpasture's syndrome should also be considered.

Treatment

Apart from supportive care there is no treatment for hantavirus infection at present. Patients receive broad spectrum antibiotics while awaiting the results of laboratory diagnostic tests for the confirmation of hantavirus associated disease. Initial supportive care includes the use of antipyretics and analgesics. Patients are immediately transferred to intensive care unit (ICU) if preliminary symptoms indicate the higher probability of HPS. ICU management should include careful assessment, monitoring and adjustment of volume status and cardiac function, including inotropic and vasopressor support if needed. Fluids should be administered carefully due to higher chances of capillary leakage. Supplemental oxygen is necessary for hypoxic patients. Due to high risks of respiratory failure, ICU management should keep equipment and materials for intubation and mechanical ventilation readily available. Patients with severe HPS quickly progress to respiratory failure, and in absence of ECMO (extracorporeal membrane oxygenation) almost all patients die within 24-48 hours of the onset of this severe phase.

Antiviral therapy including the use of ribavirin, a guanosine analogue, has not been shown to be effective for the treatment of HPS. However, efficacy trials in HFRS patients in China have shown significant beneficial effects of ribavirin if started early in the disease course. Although ribavirin perturbs SNV replication in vitro, neither an open-label trial conducted during the 1993 outbreak nor an attempted placebo-controlled trial demonstrated clinical benefit for HPS. However, it has been suggested that ribavirin efficacy may depend on phase of infection and

the severity of the disease at the time of administration. Ribavirin is not recommended for treatment of HPS and is not available for this use.

Examination of neutralizing antibody titers in patients at the time of admission has revealed low antibody titers for the patients with severe disease and higher antibody titers for patients with mild disease. These observations provide clues towards the use of human neutralizing antibodies during the acute phase of HPS that might prove effective for the treatment and / or prophylaxis of hantaviral infections.

There is no FDA-approved vaccine for hantavirus infection in USA. A killed-virus vaccine against hantavirus infection has been developed in Korea and China. However, such approaches are not persuaded in USA due to many reasons. Efforts are underway to develop a DNA vaccine, based on the gene gun approach for the transport of an expression plasmid containing M segment gene to the individual, which upon expression will generate neutralizing antibodies against glycoproteins G1 and G2.

Immunity and reinfection

High titers of neutralizing antibodies have been found in individuals who have experienced HPS years ago (34,36). Neutralizing antibodies against PUUV have been detected in individuals decades after infection (30). These observations suggest that previously infected individuals are protected life-long from reinfection. There are no known re-infections with the homologous hantavirus. Closely related hantaviruses, such as Seoul and Hantaan viruses, seem to cross-protect against re-infection in experimental animals, and one might expect cross-protection among the hantaviruses derived from sigmodontine rodents.

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Figure 1. Classification of negative stranded RNA viruses and the rodent reservoirs for the hantavirus genus

Left panel shows the classification of negative stranded RNA viruses in two groups, Mononegavirales and segmented negative stranded RNA viruses. Mononegavirales have a single copy of negative sense RNA genome and segmented RNA viruses have multiple copies of negative sense RNA genome. Segmented RNA viruses have been further classified into three families, Orthomyxoviridae, Bunyaviridae and Arenaviridae. Viruses in the Bunyaviridae family have been classified into five genera, Bunyavirus, Hantavirus, Nairovirus, Phlebovirus and Tospovirus. Right panel show the rodent reservoirs for hantaviruses. (A) *Apodemus agrarius* (Reservoir for hantaan virus that cause HFRS); (B) deer mouse (*Peromyscus maniculatus*), (C) The Cotton Rat (*Sigmodon hispidus*); (D) The Rice Rat (*Oryzomys palustris*); (E) The White-footed Mouse (*Peromyscus leucopus*). Rodents in B, C, D and E cause HPS. All pictures in the right panel were obtained from the CDC web site; <http://www.cdc.gov/NCIDOD/DISEASES/HANTA/HPS/noframes/rodents.htm>

Figure 2.

Phylogenetic tree of hantaviruses carried by the different rodents (Family Muridae, subfamily Murinae and Family Cricetidae, subfamilies Arvicolinae, Sigmodontinae and Neotominae) and insectivores. The tree is based on the complete coding region of the S segment. HTNV, Hantaan virus; SEOV, Seoul virus; DOBV, Dobrava virus; SAAV, Saaremaa virus; PUUV, Puumala virus; TULV, Tula virus; PHV, Prospect Hill virus; BLLV, Blood Land Lake virus; ISLAV, Isla Vista virus; KHAV, Khabarovsk virus; TOPV, Topografov virus; SNV, Sin Nombre virus; NYV, New York virus; MGLV, Monongahela virus; ELMCV, El Moro Canyon virus; RIOSV, Rio Segundo virus; MULV, Muleshoe virus; BAYO, Bayou virus; BCCV, Black Creek Canal virus; LANV, Laguna Negra virus; RIOMV, Rio Mamore virus; ANDV, Andes virus; TPMV, Thottapalayam virus. In the figure, viruses causing HFRS are in red type and those causing HCPS in blue type. Viruses not associated with disease are in black type. This picture was obtained from reference (33)

Figure 3. Hantaviral genome

(a) Hantaviral genome comprises of three negative sense RNAs, S segment encodes nucleocapsid protein (N), M segment encodes glycoproteins G1 and G2, and L segment encodes viral RdRp. (b) Panhandle structures of three hantaviral genomic RNAs are formed by the base pairing of complementary bases at 5' and 3' terminus of each genome segment. (c) Pictorial representation of hantavirus particle, showing three nucleocapsids enveloped in a lipid bilayer. (d) Thin-section electron micrograph of Sin Nombre virus isolate, a causative agent of hantavirus pulmonary syndrome (HPS) <http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/hpsem.htm>. (e) Pictorial representation of hantavirus life cycle.

Distribution of hantavirus species world wide

Figure 4.
World wide distribution of hantavirus species

Figure 5.

Working hypothesis of differential regulation of hantavirus-specific immune responses in rodent reservoir hosts and humans. During their encounter with viruses DCs integrate different signals received through several PRRs (PRR 1, PRR 2, PRR3, etc.) which determine the quality of the ensuing T-cell response. (A) In their rodent reservoir host, hantavirus-associated PRR signaling could program DCs to stimulate Treg cells that can suppress virus-specific CTLs, leading to viral persistence and at the same time preventing virus-induced immunopathology. (B) In humans, who are not adapted to hantaviruses, PRR signaling in DCs results in a dominant antiviral CTL response. As a consequence, hantavirus-infected endothelial cells (EC) are immediately eliminated leading to immunopathology.

Note: This picture was obtained from Ref (29)

Figure 6. Radiographs showing the evolution of hantavirus pulmonary syndrome in a 30-year-old woman. (A) Chest radiograph before onset of illness. (B) Admission radiograph. (C) Radiograph after intubation. (D) Radiograph just before death.
Note: This picture was obtained from Ref (11)

Table 1Members of the genus *Hantavirus*, family *Bunyaviridae*

Species	Disease	Principal Reservoir	Distribution of Virus	Distribution of Reservoir
Hantaan (HTN)	HFRS ^a	<i>Apodemus agrarius</i> (striped field mouse)	China, Russia, Korea	C Europe south to Thrace, Caucasus, & Tien Shan Mtns; Amur River through Korea to E Xizang & E Yunnan, W Sichuan, Fujiau, & Taiwan(China)
Dobrava-Belgrade (DOB)	HFRS	<i>Apodemus flavicollis</i> (yellow-neck mouse)	Balkans	England & Wales, from NW Spain, France, S Scandinavia through European Russia to Urals, S Italy, the Balkans, Syria, Lebanon, & Israel
Seoul (SEO)	HFRS	<i>Rattus norvegicus</i> (Norway rat)	Worldwide	Worldwide
Puumala (PUU)	HFRS	<i>Clethrionomys glareolus</i> (bank vole)	Europe, Russia, Scandinavia	W Palearctic from France and Scandinavia to Lake Baikal, south to N Spain, N Italy, Balkans, W Turkey, N Kazakhstan, Altai & Sayan Mtns; Britain & SW Ireland
Thailand (THAI)	nd ^b	<i>Bandicota indica</i> (bandicoot rat)	Thailand	Sri Lanka, peninsular India to Nepal, Burma, NE India, S China, Laos, Taiwan, Thailand, Vietnam
Prospect Hill (PH)	nd	<i>Microtus pennsylvanicus</i> (meadow vole)	U.S., Canada	C Alaska to Labrador, including Newfoundland & Prince Edward Island, Canada; Rocky Mountains to N New Mexico, in Great Plains to N Kansas, & in Appalachians to N Georgia, U.S.
Khabarovsk (KHB)	nd	<i>Microtus fortis</i> (reed vole)	Russia	Transbaikalia Amur region; E China
Thottapalayam (TPM)	nd	<i>Suncus murinus</i> (musk shrew)	India	Afghanistan, Pakistan, India, Sri Lanka, Nepal, Bhutan, Burma, China, Taiwan, Japan, Indomalayan Region
Tula (TUL)	nd	<i>Microtus arvalis</i> (European common vole)	Europe	Throughout Europe to Black Sea & NE to Kirov region, Russia
Sin Nombre (SN)	HPS ^c	<i>Peromyscus maniculatus</i> (deer mouse)	U.S., Canada,	Alaska Panhandle across N Mexico Canada, south through most of continental U.S., excluding SE & E seaboard, to southernmost Baja California Sur and to NC Oaxaca, Mexico
New York (NY)	HPS	<i>Peromyscus leucopus</i> (white-footed mouse)	U.S.	C and E U.S. to S Alberta & S Ontario, Quebec & Nova Scotia, Canada; to N Durango & along Caribbean coast to Isthmus of Tehuantepec & Yucatan Peninsula, Mexico
Black Creek Canal (BCC)	HPS	<i>Sigmodon hispidus</i> (cotton rat)	U.S.	SE U.S., from S Nebraska to C Virginia south to SE Arizona & peninsular Florida; interior & E Mexico through Middle America to C Panama; in South America to N Colombia & N Venezuela
El Moro Canyon (ELMC) ^d	nd	<i>Reithrodontomys megalotis</i> (Western harvest mouse)	U.S., Mexico	British Columbia & SE Alberta, Canada; W and NC U.S., S to N Baja California & interior Mexico to central Oaxaca
Bayou (BAY) ^d	HPS	<i>Oryzomys palustris</i> (rice rat)	U.S.	SE Kansas to E Texas, eastward to S New Jersey & peninsular Florida

Species	Disease	Principal Reservoir	Distribution of Virus	Distribution of Reservoir
Topografov (TOP)	nd	<i>Lemmus sibiricus</i> (Siberian lemming)	Siberia	Paleartic, from White Sea, W Russia, to Chukotski Peninsula, NE Siberia, & Kamchatka; Nearctic, from W Alaska E to Baffin Island & Hudson Bay, S Rocky Mtns to C B.C., Canada
Andes (AND)	HPS	<i>Oligoryzomys longicaudatus</i> ^f (long-tailed pygmy rice rat)	Argentina	NC to S Andes, approximately to 50 deg S latitude, in Chile & Argentina
Isla Vista (ISLA) ^d	nd	<i>Microtus californicus</i> (California vole)	U.S.	Pacific coast, from SW Oregon through California, U.S., to N Baja California, Mexico
Bloodland Lake (BLL) ^d	nd	<i>Microtus ochrogaster</i> (prairie vole)	U.S.	N & C Great Plains, EC Alberta to S Manitoba, Canada, S to N Oklahoma & Arkansas, E to C Tennessee & W West Virginia, U.S.; relic populations elsewhere in U.S. & Mexico
Muleshoe (MUL) ^d	nd	<i>Sigmodon hipidus</i> (cotton rat)	U.S.	See Black Creek Canal
Rio Segundo (RIOS) ^d	nd	<i>Reithrodontomys mexicanus</i> (Mexican harvest mouse)	Costa Rica	S Tamaulipas & WC Michoacan, Mexico, S through Middle American highlands to W Panama; Andes of W Colombia & N Ecuador
Rio Mamore (RIOM) ^d	nd	<i>Oligoryzomys microtis</i> (small-eared pygmy rice rat)	Bolivia	C Brazil south of Rios Solimoes-Amazon & contiguous low lands of Peru, Bolivia, Paraguay, & Argentina.
Oran virus	HPS	" <i>Oligoryzomys longicaudatus</i> "* (Northern Argentina)	South America	South America
Hu39694	HPS	<i>Oligoryzomys</i> ^f . <i>flavescens</i>	South America (Argentina)	South America (Argentina)
Laguna Negra virus	HPS	<i>Calomys laucha</i>	South America	South America
Choclo virus	HPS	<i>Oligoryzomys fulvescens</i>	South America	South America
Juquitiba virus	HPS	<i>Oligoryzomys nigripes</i>	South America (Brazil)	South America (Brazil)
Araraquara virus	HPS	<i>Bolomys lasiurus</i>	South America (Brazil)	South America (Brazil)
Castelo Dos Sonhos virus	HPS	<i>Oligoryzomys</i> <i>ssp</i> ^f .	South America (Brazil)	South America (Brazil)
Araucaria virus	HPS	<i>Bolomys lasiurus</i> or <i>Akodon</i> <i>ssp</i> ^f .	South America (Brazil)	South America (Brazil)

Note: The table contents are from references (14,27)

^a HFRS, hemorrhagic fever with renal syndrome

^b nd, none documented

^c HPS, hantavirus pulmonary syndrome

^d not yet isolated in cell culture

^e viruses for which incomplete characterization is available, but for which there is clear evidence indicating that they are unique

f suspected host, but not confirmed

Table 2

Summary of immune response in humans during hantavirus infection

Categorical Response	Immune Marker	Effect on infection	Virus species ^a	In vitro / In vivo	Tissue or Cell type ^b Phase of infection ^c
Innate	RIG-I	Elevated	SNV	In vitro	HUVEC, ≤ 24 h p.i
		Reduced	NY-1	In vitro	HUVEC, ≤ 24 h p.i
	TLR3	Elevated	SNV	In vitro	HUVEC, ≤ 24 h p.i
	IFN-β	Elevated	PUUV, PHV, ANDV	In vitro	HSVEC, HMVEC, , ≤ 24 h p.i
		Reduced	TULV, PUUV NSs	In vitro	COS-7 and MRC5 cells, ≤ 24 h p.i
	INF-α	Elevated	PUUV, HTNV	In vitro	Mφ, DCs, 4 days p.i
		No change	HTNV	In vitro	Blood, acute
	IRF-3, IRF-7	Elevated	SNV, HTNV, PHV	In vitro	HMVEC-L, , ≤ 24 h p.
	MxA	Elevated	HTNV, NY-IV, PHV, PUUV, ANDV, SNV,	In vitro	Mφ, HUVEC, HMVEC-L, 6h-4 days p.i
	MCH I & II	Elevated	HTNV	In vitro	DCs, 4 days p.i
Proinflammatory / Adhesion	CD 11b	Elevated	PUUV	In vitro	Blood, acute
	CD-40, CD80, CD86	Elevated	HTNV	In vitro	Des, 4 days p.i
	Nk cells	Elevated	PUUV	In vitro	Bal, acute
	IL-1β	Elevated	SNV, HTNS	In vitro	Blood, lungs, acute
	IL-6	Elevated	SNV, PUUV	In vitro	Blood, lungs, acute
	NF-α	Elevated	PUUV, SNV, HTNV	In vitro	Blood, lungs, acute, kidney
	CCL5	Elevated	SNV, HTNV	In vitro	HMVEC-L, HUVEC, 3-4 days p.i
	CXCL8	Elevated	PUUV	In vitro	Blood, acute
		Elevated	PUUV	In vitro	Men, blood, acute
	CXCL10	Elevated	TULV, PHV, HTNV	In vitro	HUVEC, Mφ, 4-2 days p.i
		Elevated	SNV, HTNV, PHV	In vitro	HUVEC-L, HUVEC, 3-4 days p.i
		Elevated	PUUV	In vitro	Men, blood, acute

Categorical Response	Immune Marker	Effect on infection	Virus species ^a	In vitro / In vivo	Tissue or Cell type ^b Phase of infection ^c
CD8+ and CD4+ T cells	IL-2	Elevated	SNV, HTNV, PUUV	In vitro	Blood, lungs, acute
	Nitric Oxide	Elevated	PUUV	In vitro	Blood, acute
	GM-CSF	Elevated	PUUV	In vitro	Women, blood, acute
	ICAM, VCAM	Elevated	PUUV	In vitro	Kidney acute
	E- selectin	Elevated	HTNV, PHV	In vitro	HUVEC, 3-4 days p.i
		Elevated	PUUV	In vitro	Blood, acute
		Elevated	HTNV, SNV	In vitro	Blood, CD4+, CD8+, lungs, acute
	INF- γ	Elevated	DOBV, PUUV, HTNV	In vitro	Blood, BAL, acute
	CD8+	Elevated	PUUV, SNV	In vitro	PBMC, acute
	Virus specific INF- γ +CD8+ Perforin, GranzymeB	Elevated	PUUV	In vitro	Blood acute
Regulatory	CD4+CD25+ "activated"	Elevated	DOB, PUUV	In vitro	PBMC, acute
	IL-4	Elevated	SNV	In vitro	Lungs, acute
	Suppressor T cells ^d	Reduced	HTNV	In vitro	Blood, acute
	IL-10	Elevated	PUUV	In vitro	Blood, acute
Humoral	TGF- β	Elevated	PUUV	In vitro	Kidney, acute
	IgM, IgA, IgG, IgE	Elevated	All hantaviruses	In vitro	Blood

Note: Contents of this table are from reference (6)

^aSNV, Sin Nombre virus; NY-IV, New York -1; PUUV, Puumala virus; PHV, Prospect Hill virus; ANDV, Andes virus; TULV, Tula virus; HTNV, Hantaan virus; DOBV, Dobrava virus

^bHUVEC, human umbilical vascular endothelial cells, HSVEC, human saphenous vein endothelial cells; HMVEC-L, human lung microvascular endothelial cells; COS-7, African green monkey kidney fibroblast transformed with Siman virus 40; MRC5, human fetal lung fibroblasts; M ϕ , Macrophages; DCs, dendritic cells; Bal, bronchoalveolar lavage; PMBC, human peripheral blood mononuclear cells.

^cAcute infection is during symptomatic disease in patients.

^dSuppressor T cells likely represent cells currently referred to as regulatory T cells

Table 3

Summary of immune response in rodents during hantavirus infection

Categorical Response	Immune Marker	Effect on infection	Virus species ^a	Host, Tissue or Cell type ^b	Phase of infection ^c
Innate	TLR7	Reduced	SEOV	Male Norway rats, lungs	Acute, Persistent
	RIG-I	Elevated	SEOV	Female Norway rats, lungs	Acute, Persistent
		Elevated	SEOV	Female Norway rats, lungs	Acute, Persistent
	TLR3	Elevated	SEOV	Norway rats, Thalamus	Acute
		Elevated	SEOV	Male Norway rats, lungs	Acute, Persistent
	INF- β	Reduced	SEOV	Male Norway rats, lungs	Acute, Persistent
		Elevated	SEOV	Female Norway rats, lungs	Acute
	MX2	Reduced	SEOV	Male Norway rats, lungs	Acute, Persistent
		Elevated	SEOV	Female Norway rats, lungs	Acute, Persistent
	JAK2	Elevated	HTN, SEOV	Mice ^d , fibroblast transfected with MX2	3-4 days p.i
Elevated		SEOV	Female Norway rats, lungs	Acute	
	MHC II	Elevated	PUUV, SEOV	Bank Voles	Genetic susceptibility
Proinflammatory / Adhesion	IL-1 β	Reduced	SEOV,	Male Norway rats, lungs	Persistent
	IL-6	Reduced	SEOV	Male & female Norway rats, lungs	Acute, Persistent
		Elevated	SEOV	Male rats spleen	Acute
	TNF- α	Reduced	HTNV	Newborn mice ^d , CD8+, Spleen	Acute
		Reduced	SEOV	Male Norway rats, lungs	Acute persistent
	CXCL1 / CXCL10	Elevated	SEOV	Female Norway rats, lungs	Acute
		Reduced	SEOV	Male Norway rats, lungs	Acute persistent
	CCL2 / CCL5	Elevated	SEOV	Male Norway rats, Spleen	Acute
		Elevated	SEOV	Male Norway rats, Spleen	Acute
	NOS2	Reduced	SEOV	Male Norway rats, lungs	Acute persistent
		Elevated	SEOV	Male Norway rats, spleen	Acute
		Elevated	HTNV	Mouse M ϕ ^d In vitro	6 h p.i

Categorical Response	Immune Marker	Effect on infection	Virus species ^a	Host, Tissue or Cell type ^b	Phase of infection ^c
	VCAM / VGF	Elevated	SEOV	Male Norway rats, spleen	Acute
CD8+ and CD4+ T cells	CD8+	Reduced	HTNV,	Newborn mice ^d , spleen	Persistent
		Elevated	HTNV,	SCID mice ^d , CD8+ transferred	Persistent
		Elevated	SEOV	Female Norway rats, lungs	Persistent
	INF- γ	Elevated	SEOV	Female Norway rats, lungs	Acute
		Elevated	SEOV	Male Norway rats, lungs	Acute
		Elevated	SEOV	Female & male Norway rats	Acute
		Elevated	SNV	Deer mice, CD4+ T cells	Acute
		Elevated	HTNV	Newborn mice ^d CD4+ T cells	Acute
		Reduced	HTNV	Newborn mice ^d CD4+ T cells	Persistent
	INF- γ R	Elevated	SEOV	Female Norway rats, lungs	Acute, persistent
		Reduced	SEOV	Male Norway rats, lungs	Persistent
		Elevated	SEOV	Nude rat	Persistent
	T cells	Elevated	HTNV	Nude mice ^d	Persistent
		Reduced	SEOV	Male Norway rats, lungs	Acute, persistent
		Elevated	SNV	Deer mice, CD4+ T cells	Acute
Regulatory		Elevated	SEOV	Female & male Norway rats	Acute
	Regulatory T cells	Elevated	SEOV	Male Norway rats, lungs	Persistent
	FoxP3	Elevated	SEOV	Male Norway rats, lungs	Persistent
	TGF- β	Elevated	SNV	Deer mice, CD4+ T cells	Persistent
	IL-10	Reduced	SEOV	Male Norway rats, lungs, spleen	Persistent
		Elevated	SNV	Deer mice, CD4+ T cells	Persistent
Humoral	IgG	Elevated	SNV	Deer mice	Persistent
		Elevated	SEOV	Norway rats	Persistent
		Elevated	HTNV	Field mice	Persistent
		Elevated	PUUV	Bam Voles	Persistent

Categorical Response	Immune Marker	Effect on infection	Virus species ^a	Host, Tissue or Cell type ^b	Phase of infection ^c
		Elevated	BCCV	Cotton rats	Persistent

Note: Contents of this table are from reference (6)

^a SEOV, Seoul virus; SNV, Sin Nombre virus; HTNV, Hantaan virus; PUUV, Puumala virus; BCCV, Black Creek Canal virus.

^b Mφ, Macrophages.

^c Acute infection is < 30 days p.i and persistent infection is ≥ 30 days p.i.

^d Mus musculus, non-natural reservoir host for hantaviruses

Table 4**Symptoms in 17 Patients with Hantavirus Infection**

Symptom	No of patients (%)
Fever	17(100)
Myalgia	17(100)
Headache	12(71)
Cough	12(71)
Nausea or vomiting	12(71)
Chills	11(65)
Malaise	10(59)
Diarrhea	10(59)
Shortness of breath	9(53)
Dizziness or lightheadedness	7(41)
Arthralgia	5(29)
Back pain	5(29)
Abdominal pain	4(24)
Chest pain	3(18)
Sweats	3(18)
Dysuria or frequent urination	3(18)
Rhinorrhea or nasal Congestion	2(12)
Sore throat	2(12)

Note: Contents of this table are from reference (5)

Table 5Symptoms in 10 pediatric patients (age ≤ 16 years) with SNV Infection

Symptom	No of patients (%)
Fever	10(100)
Myalgia	8(80)
Headache	10(100)
Cough	9(90)
Nausea or vomiting	9(90)
Chills	3(30)
Diarrhea	4(40)
Shortness of breath	8(80)
Dizziness or lightheadedness	3(30)
Back pain	5(50)
Abdominal pain	5(50)
Chest pain	3(30)
Sore throat	4(40)

Note: Contents of this table are from reference (26)

Table 6

Clinical findings at the time of admission in 17 Patients with hantavirus Infection

Sign	Percentage of patients	Median (Range)
Respiratory rate $\geq 20/\text{min}$	100	28 (20-70)
Heart rate ≥ 100 bpm	94	120 (90-150)
Temperature ≥ 38.1 °C	75	38.8 (35.4-40.4)
Systolic or rales on lung examination	31	
Abdominal tenderness	24	
Cool, Clammy, or mottled skin	18	
Injection or suffusion of conjunctiva	18	

Note: Contents of this table are from reference (5)

Table 7

Clinical findings at the time of admission in 9 pediatric patients with SNV infection.

Sign	Percentage of patients
Tachypnea*	67
Fever (temperature ≥ 38.0 °C)	56
Crackles or rales on lung exam	44
Abdominal tenderness	44
Hypotension [@]	33
Tachycardia (heart rate >120 bpm)	22
Cool, Clammy, or mottled skin	11

Respiratory rate >25 breaths / min (10-13 years old). Respiratory rate > 20 breaths / min (≥ 14 years old). Includes 2 patients mechanically ventilated before admission.

Note: Contents of this table are from reference (26)

[@] Systolic blood pressure <95 mm Hg (10-13 years old). Systolic blood pressure <100 mm Hg (≥ 14 years old)

Table 8

Results of laboratory studies during hospitalization in patients with hantavirus Infection

Test*	Admission value	Maximal [Minimal] Value
White cells- $\times 10^3$ /mm ³	10.4(3.1-65.3)	26.0 (5.6-65.3)
Band forms - %	22 (8-62)	27 (4-67)
Hematocrit -%		
Men	51.3 (49.9-60.0)	56.3 (49.9-67.7)
Women	46.4 (35.0-55.8)	48.5 (36.5-60.3)
Platelets – $\times 10^3$ /mm ³	84 (26-320)	[64] (12-148)
Prothrombin time – sec	13.0 (11.2-21.1)	14 (12.6-21.1)
Partial-thromboplastin time – sec	42.5 (30.0-150.0)	54.4 (31.0-150.0)
Bicarbonate – mmol / liter	18 (12-25)	[14] (8-20)
Lactate dehydrogenase IU / liter	362 (209-1525)	568 (324-1525)
Aspartate aminotransferase IU / liter	112 (28-432)	148 (62-432)
Alanine aminotransferase IU / liter	55 (25-148)	63 (27-149)
Albumin – g / dl	3.0 (1.5-4.6)	[2.5] (1.5-3.5)
Blood urea nitrogen – g / dl	11 (3-23)	17 (8-32)
Creatinine – mg / dl	1.1 (0.6-2.5)	1.4 (0.6-2.5)
Lactate – mmol / liter	4.4 (2.2-11.0)	-
Creatine kinase – IU / liter	46 (19-1026)	-

Note: Contents of this table are from reference (5)

* Maximal normal values: Lactate dehydrogenase, 180 to 232 IU per liter; aspartate aminotransferase, 35 to 40 IU per liter; alanine aminotransferase, 35 to 60 IU per liter, Lactate, 2.2 mmol per liter; and creatine kinase, 180 to 269 IU per liter. To convert values from creatinine to micro moles per liter, multiply by 88.4

@ Two of ten patients tested had elevated creatine kinase concentrations: 1026 IU per liter with an MB fraction of 16 (2 percent) in 1 patient, and 814 IU per liter with an MB fraction of 87 (11 percent) in another patient, who was undergoing cardiopulmonary resuscitation when the sample was obtained.

Table 9

Results of laboratory studies at the time of admission in pediatric patients with Sin Nombre hantavirus infection.

Test	Admission value (Median [Range])
White cells $\times 10^3 / \text{mm}^3$	9.0 (3.4-59.2)
Mematocrit %	
Patients 10-12 y (n = 5)	42.0 (34.9-45.2)
Males 13-16 y (n = 2)	54.3 (47.6-61)
Females 13-16 y (n = 4)	41.9 (40-48.4)
Platelets $\times 10^3 / \text{mm}^3$	67 (43-98)
Creatinine (mg / dl)	0.7 (0.4-3.9)
Prothrombin time (sec)	13.1 (11.0-29.8)
Partial thromboplastin time (sec)	38(27-212)
Carbon dioxide (mmol / liter)	20 (15-27)
Blood urea nitrogen (mg / dl)	10 (8-26)
Aspartate aminotransferase (IU / L)	98 (39-129)
Albumin (g / dl)	2.8 (1.2-3.5)
Alanine aminotransferase (IU / L)	55 (21-80)
Lactate dehydrogenase (IU / L)	1243 (382-1724)
Lactate (mmol / L)	2.5 (1.5-18.4)

Note: Contents of this table are from reference (26)