New World hantaviruses

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Since the initial description in 1993 of hantavirus pulmonary syndrome and its novel aetiological agent, Sin Nombre virus, our knowledge of the epidemiology of New World hantaviruses has continued to evolve. After the identifying outbreak in the southwestern US, four hantaviruses have been identified in North America with specific rodent hosts and associated with a number of sporadic cases. This stability of case recognition in North America is in contrast to the multiple outbreaks and endemic cases in South America. Despite a plethora of New World hantaviruses and new evidence of person-to-person transmission, the ecological and personal determinants of this human infection remain a mystery.

Haemorrhagic fever with renal syndrome represents a wide spectrum of illness caused by Old World hantaviruses, transmitted by their respective rodent hosts, that have been recognized for over 40 years. Since the recent discoveries of many pathogenic, and presumably non-pathogenic, hantaviruses in North and South America, it has become apparent that pathogenic hantaviruses causing hantavirus pulmonary syndrome (HPS) existed in the New World long before their initial discovery in 1993. Since the outbreak that year in the southwestern US which led to the recognition of HPS and its associated aetiological agent and reservoir host, we now know that the threat for disease applies to all 48 contiguous states, Canada, Mexico, Central and South America. Hantaviral infection in the US and Canada is characterized by relatively sporadic cases. By contrast, HPS infection in South America has occurred as outbreaks from multiple hantaviral strains with distinct ecological, clinical, and epidemiological features.

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Case definition

The Centers for Disease Control and Prevention (CDC) considers a probable case of HPS to be a febrile illness (fever greater than 38.3°C)

in a previously healthy person, characterized by unexplained acute respiratory distress syndrome or bilateral interstitial pulmonary infiltrates, with respiratory compromise requiring supplemental oxygen; or an unexplained illness resulting in death in conjunction with an autopsy examination demonstrating non-cardiogenic pulmonary oedema without an identifiable specific cause of death. In addition to a compatible clinical illness, confirmed case-patients must have laboratory evidence of hantavirus infection, *i.e.* presence of hantavirus-specific immunoglobulin M (IgM) or IgG, positive reverse transcription-polymerase chain reaction (RT-PCR) results for hantavirus RNA, or positive immunohistochemical results for hantavirus antigen. A febrile illness and laboratory evidence of acute hantavirus infection without objective pulmonary dysfunction is classified as mild hantavirus disease. Detectable hantavirus-specific IgG antibodies without history of clinical disease are classified as other seropositives.

Clinical description of HPS

Patients with HPS typically present with a relatively short nonspecific febrile prodrome. In addition to fever and myalgia, early symptoms include headache, chills, dizziness, nausea, vomiting, and other gastrointestinal symptoms. Malaise, diarrhoea, and light-headedness are reported by approximately half of all patients, with less frequent reports of arthralgias, back pain, and abdominal pain. Cough and tachypnoea generally do not develop until late in the prodrome along with shortness of breath. Typical findings on initial presentation include fever, tachypnoea and tachycardia. Once the cardiopulmonary phase begins, however, the disease progresses rapidly, necessitating hospitalization and often mechanical ventilation within 24 hours. The cardiopulmonary phase is characterized by bilateral interstitial pulmonary infiltrates caused by non-cardiogenic pulmonary oedema and cardiovascular collapse[1,2].

A fall in the serum albumin and a rise in the hematocrit indicates a fluid shift from the intravascular system into the lungs. The leukocyte cell count is often raised, with a marked left shift. The percentage of immature granulocytes may be as high as 50% and immunoblasts, often reported as atypical lymphocytes, are invariably present, usually at the time of onset of pulmonary oedema. The combination of atypical lymphocytes, a significant bandemia, and thrombocytopenia in the setting of pulmonary oedema is strongly suggestive of a hantavirus infection. A dramatic fall in the platelet count may signal a transition from the prodrome to the cardiopulmonary phase of the illness.

The South American HPS prodrome is, for the most part, as described above. However, atypical features such as conjunctival injection and

head and neck suffusion have been noted, especially in the most recent Argentinian epidemic[3]. Haemorrhagic and renal involvement has been found among Argentine cases in the Central region[4] and preliminary clinical review shows similar findings in Chile (M Tapia, personal communication). The possibility of increased renal involvement has also been a feature of North American cases caused by Bayou and Black Creek Canal viruses, which are closely related genetically to the South American viruses. In the Chilean epidemic of 1997, three of the case-patients were children with petechiae, a sign rarely described in North American cases of HPS[5]. One of the children, who had frank haemorrhage, died; blood was present in the endotracheal tube and there was bleeding from puncture sites.

Radiological findings

HPS has a characteristic radiological evolution, beginning with minimal changes of interstitial pulmonary oedema, and rapidly progressing to alveolar oedema with severe bilateral involvement. Pleural effusions are common and are often large enough to be evident radiographically. Heart and cardiac silhouette size on chest radiographs is usually normal.

Approximately one-third of patients show evidence of pulmonary oedema in the initial radiograph. Virtually all patients demonstrate interstitial oedema 48 hours after the initial radiograph, and two-thirds have developed extensive bibasilar or perihilar airspace disease[6].

Key points for clinical practice

Treatment of patients with HPS remains supportive in nature. Since the syndrome is so rare, a broad spectrum of antibiotic coverage should be administered until bacterial infection can be ruled out. Early intensive care with correction of electrolyte, pulmonary, and haemodynamic abnormalities is imperative. Flow-directed catheterization of the pulmonary artery is helpful for intensively monitoring and clinically managing the patient, and can also verify the normal-to-low pulmonary wedge pressure, decreased cardiac index, and increased systematic vascular resistance in patients who progress to shock; this haemodynamic profile is in contrast to that of septic shock.

Fluid management can be difficult and should be determined by clinical and other evidence of intravascular volume depletion or overload. Fluids can be safely administered to reach a pulmonary artery open pressure of 12–15 mm; levels higher than 15 mm have resulted in

pulmonary oedema, which responded poorly to mechanical ventilation. Early use of inotropic agents, such as dobutamine, to augment myocardial contractility is suggested for hypotension in the context of a relatively normal intravascular volume. Vasopressors, such as norepinephrine, are expected to have poor efficacy since systemic vascular resistance is high.

Epidemiology

United States and Canada

As of January 12, 1998, 177 cases of HPS had been confirmed in 29 states. Of these, 79 case-patients have died, giving a case-fatality proportion of 45%. Most cases occurred in a rural setting. Since 1993, the annual case count has been around 25. In Canada, 24 cases, with a case-fatality of 30%, have been confirmed in the three western provinces (Laboratory Center for Disease Control, personal communication).

The primary rodent reservoir for Sin Nombre virus (SNV), the aetiological agent for the 1993 outbreak and the majority of all cases, is *Peromyscus maniculatus* (deer mouse). Surveillance of the disease in the US has lead to the discovery of three other genetically distinct lineages of hantaviruses that cause HPS, each with a distinct rodent host. Bayou virus, whose rodent reservoir is *Oryzomys palustris* (rice rat), has caused illness in three case-patients in Louisiana and Texas. Black Creek Canal virus, hosted by *Sigmodon hispidus* (cotton rat), has caused a single case in Florida. The New York-1 virus, found in *P. leucopus* (white-footed mouse), infected two people in New York. The collective range of these rodents blankets the contiguous US and most of Canada and Mexico. Therefore, almost all of North America is at risk of disease.

South America

Multiple pathogenic hantaviruses have also been identified in South America. HPS epidemics, as well as sporadic cases, have occurred in Argentina, Brazil, Paraguay, and Chile (Fig. 1). The most recent epidemic occurred in Chile in August 1997[5]. Bolivia and Uruguay have also reported sporadic cases. Hantaviruses in South America have affected persons of all ages and both sexes and, as in the US, most infections have occurred in rural settings.

As of January 31, 1998, a total of 133 cases of HPS had been confirmed in Argentina (Ministerio de Salud y Acción Social) where three endemic areas have been described – the northern, central, and southern

Fig. 1 Countries in North and South America that have reported cases of HPS

regions[7]. The northern region includes Salta and Jujuy province; the central region includes Sante Fe, Buenos Aires and Córdoba province; and the southern region comprises Río Negro, Chubut and Neuquen provinces.

In March 1995, a cluster of HPS occurred in the city of El Bolson, Patagonia. Andes virus was subsequently genetically identified and implicated as the cause of illness [8]. Two of the three infected persons died. This virus was genetically most closely related to the Bayou virus found in North America. The rodent host of the Andes virus is *Oligoryzomys longicaudatus*[9]. Another outbreak of HPS occurred in

this area in 1996; 18 cases were identified within 3 months[7]. Two persons who had not visited the area where the epidemic occurred, but had contact with HPS case-patients, contracted HPS, including a physician in Buenos Aires who attended a patient in the emergency room. In all, there were five case-patients who were physicians, three of whom had been responsible for treating an HPS case-patient. The outbreak was unique because of the apparently low rodent population density and because genetic sequences of all epidemiologically linked cases indicated that person-to-person transmission had occurred[3,7,10]. There was also the possibility of person-to-person transmission in the 1997 Chilean epidemic, also caused by Andes virus, which included one family cluster with staggered onset dates over the course of 6 weeks[5]. But rodent densities were high and each family member may have been exposed to a common source.

In early 1996, an investigation lead to the discovery of 23 laboratory-confirmed cases of HPS in Paraguay[11]. Of these case-patients, 17 had been ill between July 1995 and January 1996. The aetiological agent, Laguna Negra virus[12], was subsequently isolated from the presumptive primary host, *Calomys laucha* (vesper mouse), which was the most commonly captured and most frequently antibody-positive rodent[11]. Tests of serum samples collected from the region revealed a high hantavirus antibody prevalence among ethnic populations. The Indian and Mennonite populations, which account for approximately 99% of the residents, were most affected: 61% of confirmed cases were of Mennonite ancestry, whereas 56% of the 48 hantavirus antibody-positive residents and family contacts were indigenous Indians[11].

Brazil has also had six reported cases of HPS, where Juquitiba virus, in addition to other probable new viruses, has been identified in a cluster of cases in 1993 (S Nichol, C J Peters, personal communication). Uruguay has confirmed two HPS cases, including one fatality (P Padula, personal communication).

The epidemiology of South American hantavirus infection differs from that in North America whereas both seroprevalence and the number of children diagnosed with HPS vary. The hantavirus antibody studies are difficult to interpret since the specific viral strains are unknown. However, they suggest that the case infection ratio is much lower in South America than in North America. Studies in the US estimate a seroprevalence of hantavirus antibodies, mainly in high-risk groups, to be about 1%. In South America, the seroprevalence among the human population varies greatly from region to region, but has been reported as high as 40% among central Paraguayan Indians (Ferrer, personal communication). Chile has seen a larger number of pediatric cases than the US and Argentina[13]. Of the 177 reported HPS cases in the US, only 8 (4.5%) were under the age of 16 years.

The virus

Hantaviruses belong to the family *Bunyaviridae*. There are five genera within this family: *Bunyavirus*, *Phlebovirus*, *Nairovirus*, *Tospovirus*, and *Hantavirus*. The genome of each is made up of tri-segmented negative-sense, single-stranded RNA. The genera all include arthropod-borne viruses, with the exception of *Hantavirus*, which is rodent-borne. There are numerous strains of hantaviruses from all over the world, many of which are not known to be pathogenic to humans[14].

SNV was first isolated from rodents collected on the premises of one of the initial HPS patients in the Four Corners region of the US which is the area where New Mexico, Utah, Arizona, and Colorado meet. Isolation was achieved through passage in *P. maniculatus* and subsequent adaptation to growth in Vero E6 cells. Additional virus strains have also been isolated from deer mice associated with a fatal case in California and white-footed mice from the vicinity of probable infection of a New York case. Black Creek Canal virus was isolated from a cotton rat collected near the residence of a human case in Florida[15,16]. Other virus isolates include Bayou virus[17], Rio Mamore virus from Peru (originally named Punchana virus upon isolation, but subsequently identified as the Rio Mamore viral sequence from Bolivia)[18], Caño Delgadito virus in Venezuela[19], and Laguna Negra virus in Paraguay[12].

Genetic characterization of hantaviruses has generally preceded viral isolation, and there are many viruses genetically characterized that have not been isolated. In Argentina, seven different genotypes of hantavirus have been described[9,20]. Four of them have been associated with HPS and include: Lechiguanas virus (reservoir *O. flavescens*) and HU 39694 (reservoir unknown) in the central region; Orán (reservoir *O. longicaudatus*) in the North; and Andes virus (reservoir *O. longicaudatus*) in the South. Viruses from another three viral genotypes have not yet been associated with human disease. These include Maciel (reservoir *Bolomys obscurus*) and Pergamino (reservoir *Akodon azarae*) viruses in the central region and Bermejo virus (reservoir *Oligoryzomys chacoensis*) in the North (Table 1).

Laboratory testing for hantavirus infection

IgM antibodies or seroconversion, evidence of viral antigen in tissue by immunohistochemistry, or the presence of amplifiable viral RNA sequences in blood or tissue, with a compatible clinical history of HPS, is considered diagnostic for HPS.

CDC uses a widely disseminated IgM capture enzyme-linked immunosorbent assay (ELISA) to detect IgM antibodies to SNV and diagnose acute infections. An IgG test is used in conjunction with the IgM-capture

Table 1 New world hantaviruses and their suspected primary rodent host

Rodent host[a]	Virus[b]	Pathogenic to man?[c]
Akodon azarae	Pergamino	Unknown
Bolomys obscurus	Maciel	Unknown
Calomys laucha	Laguna Negra	Yes
Neacomys spinosus	Rio Mamore	Yes
(*Oligoryzomys microtis?*)		
Oligoryzomys longicaudatus	Andes	Yes
Oligoryzomys flavescens	Lechiguanas	Yes
Oligoryzomys longicaudatus	Oran	Yes
Oligoryzomys chacoensis	Bermejo	Unknown
Oryzomys palustris	Bayou	Yes
Peromyscus maniculatus	Sin Nombre	Yes
Peromyscus leucopus	New York-1	Yes
Reithrodontomys megalotis	El Moro Canyon	Unknown
Sigmodon hispidus	Black Creek Canal	Yes
Sigmodon alstoni	Caño Delgadito	Unknown
Unknown (Argentina)	HU 39641	Yes
Unknown (Brazil)	Juquitiba	Yes

[a]Suspected rodent host based on antibody seroprevalence, and/or virus isolation or genetic identification
[b]Based on virus isolate and/or genetic identification
[c]Pathogenicity is based on reported and confirmed cases of HPS

test for diagnosis in convalescence and in serological investigations of the epidemiology of the disease.

An immunoblot assay using recombinant antigens and isotype-specific conjugates for IgM–IgG differentiation has also been developed; its results are generally in agreement with those of the IgM-capture format. Also in use is a rapid immunoblot strip assay, an investigational prototype assay to identify serum antibody to recombinant proteins and peptides specific for SNV and other hantaviruses. The broad cross-reactivity of the SNV antigens in the ELISA format has made this the diagnostic test of choice for identification of HPS cases across the Americas. Assays using Leguna Negra for IgM detection and recombinant Andes antigen for IgG and IgM detection have also been developed (P. Padula, personal communication).

Serological confirmation of hantaviral infections has been done with plaque reduction neutralization assays, which have recently included SNV[21]. However, these specific assays are not commercially available. Isolation of hantaviruses from human clinical materials is difficult. To date, no isolates of SNV-like viruses have been recovered from humans and, therefore, virus isolation is not a consideration for diagnostic purposes.

Immunohistochemistry 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. Such testing 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 occurrence in a defined geographic region[22].

RT-PCR can be used to detect hantavirus RNA in fresh-frozen lung tissue, blood clots, or buffy coats. However, RT-PCR is very prone to cross-contamination and should be considered a research technique. Differences in viruses associated with HPS complicate the use and sensitivity of RT-PCR for the routine diagnosis of hantavirus infections[23].

Ecology

Host associations

The pattern of association between hantaviruses and their hosts involves several consistent features: (i) each virus is usually associated with a single species of rodent host of the family *Muridae*; and (ii) infection in the host is chronic and asymptomatic and involves long-term shedding of infectious virus into the environment in urine, faeces, and saliva. These characteristics, which suggest a highly evolved relationship, are key to viral maintenance within reservoir populations as well as to the occasional infection of other mammal species, including humans. An additional characteristic is the widespread infection by hantaviruses within three subfamilies of the family *Muridae*, the Murinae (Old World rats and mice), the Sigmodontinae (New World rats and mice), and the Arvicolinae (the voles and lemmings, which occur in both the Old and New Worlds). This pattern suggests that hantaviruses have been associated with rodents of *Muridae* since even before these three subfamilial lineages diverged, perhaps 20 million years ago[24]. The implications of this hypothesis include not only the extreme antiquity of the hantaviruses but also an extremely wide potential diversity of hantaviruses among the approximately 1100 species of rodents in these three murid subfamilies.

Evidence of infection with hantavirus has been found in a variety of non-reservoir rodents, including house mice (*Mus musculus*) and chipmunks (*Tamias* spp.). This is especially likely under epizootic conditions such as occurred in the southwestern US in 1993[25,26]. Carnivores that feed on infected rodents may also become infected, as evidenced by the demonstration of antibody in domestic cats in Europe and the US[27] (TG Ksiazek *et al*, unpublished data), and coyotes in the US (C Bond, personal communication). Nevertheless, since only the natural host is generally capable of supporting chronic infection and shedding large quantities of infectious virus, non-host species are unlikely to have an important role in the epidemiology of HPS.

Viral maintenance

Field studies strongly suggest that transmission of hantavirus within reservoir populations occurs via horizontal mechanisms. Antibody is found more frequently among male animals and among older age classes; the presence of antibody may also be correlated with the presence of scars or wounds, suggesting that aggressive encounters among adult males may be an important mechanism of transmission. All or parts of this epizootiological pattern have been observed in field studies of SNV[28], Black Creek Canal (G Glass *et al*, unpublished data), El Moro Canyon[28], Puumala[29], and Seoul[30,31] viruses in their respective hosts.

Geographic and temporal patterns

Evidence of infection may be found throughout much of the range of a host species, as with SNV[32] (TG Ksiazek *et al*, unpublished data), and Seoul virus[33]; or the range of infection may be restricted to a small part of the host range. Laguna Negra virus has only been detected in populations of its host, *Calomys laucha*, in a small area of the Paraguayan Chaco[11]. Although the species is common throughout central and northern Argentina, so far no evidence of infection has been found there. Reasons for the nonconcordance of host and virus ranges may be related to host genetics (differences in susceptibility), or geographic barriers that prevent the introduction (or re-introduction) of virus into isolated populations. On a local scale, infection in reservoir populations may similarly be very patchy. For example, hantavirus antibody prevalence was as high as 48% at some sites on Long Island, but was < 1% in other areas of New York[34].

Prevalence of infection also may be highly variable on a temporal scale. Although antibody was detected in 30% of deer mice captured during the outbreak of HPS in the southwestern US in 1993, the prevalence of infection was only 10% in the same general area 1 year later[28]. Such changes in prevalence of infection may be related to host population dynamics. Arvicoline species (such as the reservoir for Puumala virus, *Clethrionomys glareolus*) are subject to regular population cycles, which are correlated with both prevalence of infection within reservoir populations and the incidence of human disease[29]. Although American sigmodontine rodents are not known to undergo regular population cycling, they are subject to dramatic, temporary increases in population density called irruptions. Rodent irruptions may be related to unusual climatic events, which result in temporary, but highly favourable, conditions. The subsequent high

population densities likely result in increased contact among rodents, more potential virus transmission events and, thus, higher proportions of virus-shedding rodents among already increased numbers of rodents. The HPS outbreak in the American southwest in 1993 was preceded by an El Niño southern oscillation event, which resulted in unusually warm winters with high rainfall in normally dry areas of the southwestern US. Rodent populations in the general area of the outbreak reached very high densities just prior to the outbreak[35]. Trapping at case households during the outbreak confirmed that rodent populations had remained high in affected areas[25]. An outbreak of HPS in southern Chile in 1997 was associated with dramatic increases in the population density of the reservoir for Andes virus. This rodent irruption may have been related to the synchronous flowering and fruiting of a local species of bamboo, an event which occurs approximately every 10–30 years and provides abundant food for the granivorous Andes virus rodent reservoir *Oligoryzomys longicaudatus*[36].

Prevention

Since control of entire wild rodent populations is impractical and probably undesirable, disease prevention strategies must rely upon minimizing human–rodent contact, especially in the peridomestic environment. Prevention of rodent infestations in homes by attention to sanitation, rodent-proofing, and keeping snap-traps set and baited may decrease risk to rural residents. Experiments conducted with remote cabins and trailers in the US National Parks demonstrate that inexpensive modifications can be very effective in keeping these structures free of deer mice[37].

Transmission

Hantaviruses in the western hemisphere are primarily transmitted to humans via aerosolized particles of infected rodent excreta or saliva. Recent studies have verified excretion of Black Creek Canal virus in urine and faeces of experimentally infected *Sigmodon hispidus*[38]. Virus was isolated in urine as long as 70 days after infection.

Many of the confirmed cases of HPS reported contact with rodents, and most of these individuals reported contact with rodents on more than one occasion. Rodent exposures may have occurred on a daily basis in the home, at work, or recreationally. There are few incidences where exposure is well-defined, *i.e.* a single rodent contact. For these cases, one

type of exposure is believed to have occurred when persons entered and cleaned rarely used rodent-infested structures[39], which may help explain the lack of more cases despite the ubiquitous nature of contact to rodents in the environment.

Considering the recent epidemics in Argentina, the exact mechanism by which the Andes virus was spread from person-to-person remains a mystery. Currently, there is a study protocol for contacts of HPS patients to determine the risk and/or probable modes of transmission. Standard precautions are recommended for South America when treating HPS patients with additional transmission-based precautions (contact, droplet and airborne), depending on local resources. However, this rare person-to-person transmission event should not change the focus from rodent contact being the principal means of infection.

Trends/issues

It is not yet understood whether some people are more susceptible to infection and subsequent development of HPS. There have been few reports of more than one case-patient in a household in North America. It is unclear why one household member can contract the disease while the others, who may have had the same exposure, remain well[40]. Genetics has been suggested to be a factor in the clinical course of nephropathia epidemica caused by the Old World Puumala hantavirus[41], but no similar study has been completed in the US.

The mode of transmission of New World hantaviruses is not yet fully understood. Whether from rodent-to-person and definitely for person-to-person, the exact modes of transmission have yet to be verified. The unknown duration of infectivity of the virus in rodent urine, faeces, and saliva leads to the question of whether secondary routes, including food and fomites, play a major role in transmission. Energy is required to form a small-particle aerosol, a condition that is unlikely to be achieved when a rodent urinates. Similarly, a minute amount of virus, if any, would become aerosolized when a rodent coughs (if rodents cough). This suggests that disturbing areas contaminated with infectious material may be an important risk factor for infection.

If infection were efficient, one would expect the prevalence of hantavirus antibodies in the human population, especially in the US, to be much greater given the often-times inevitable human–rodent contact. However, HPS is a very rare infection, even among those who regularly handle rodents[42]. The full spectrum of the disease has not been fully realized and underreporting can be an issue with milder cases of illness. CDC has never confirmed a North American case of HPS in a child under the age of 11 years. However, a 4-year-old boy with mild hantaviral

disease was detected during an investigation of a confirmed fatal case of HPS[43]. In contrast, South American diagnoses of HPS in children are more common. The reasons for this discrepancy are unknown.

No effective therapy has been identified for New World hantaviruses. Ribavirin has been effective in treating haemorrhagic fever with renal syndrome, but despite the *in vitro* sensitivity of Sin Nombre virus to ribavirin, the effectiveness of using it to treat HPS is not clear and does not appear to be evident in open label use. However, a more discerning double-blind study to determine the efficacy of treating HPS patients early in their illness with ribavirin is under way. Other treatment approaches include extracorporeal membrane oxygenation for salvage therapy, and there is a report of one HPS survivor who was treated with inhaled nitric oxide. Physicians are also re-examining the use of steroids in South American patients.

The discovery of so many pathogenic and apparently non-pathogenic hantaviruses in the Americas with distinct clinical features has re-energized the field of hantavirus virology. These discoveries emphasize that we have much to learn from previously unidentified infectious agents.

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