VIRAL HEMORRHAGIC FEVERS AND HANTAVIRUS INFECTIONS IN THE AMERICAS

Timothy J. Doyle, MPH, Ralph T. Bryan, MD, and Clarence J. Peters, MD

In 1958, Junin virus emerged into the scientific consciousness as the causative agent of Argentine hemorrhagic fever (AHF).[55] Three other members of the arenavirus family have subsequently been implicated in South American hemorrhagic fevers (SAHF): Machupo virus, first isolated in 1963,[34] causes Bolivian hemorrhagic fever (BHF); Guanarito virus, first isolated in 1990,[63] causes Venezuelan hemorrhagic fever (VHF); and Sabiá virus, first isolated in 1990,[15] is a causative agent of hemorrhagic fever in Brazil. All SAHF viruses are associated with a primary rodent reservoir and are transmitted to humans primarily via inhalation of aerosolized virus found in rodent excreta.

In 1993, a previously unknown hantavirus, later referred to as *Sin Nombre virus* (SNV), was identified as the causal agent of a severe, life-threatening respiratory disease now known as *hantavirus pulmonary syndrome* (HPS), which first appeared in dramatic fashion during an outbreak in the Southwestern United States.[9, 52] Subsequent work has uncovered at least eight additional distinct hantaviruses throughout the Western hemisphere associated with HPS.[64] All hantaviruses are associated with a primary rodent reservoir, and their transmission to humans is believed to involve mechanisms similar to human infection with South American hemorrhagic fever viruses.

This article describes laboratory, epidemiologic, and clinical features of the SAHF and hantavirus disease in the Americas, and points out common features of their emergence. Because of their vastly different ecology and epidemiology as mosquito-borne diseases, yellow fever and dengue hemorrhagic fever, which

From the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Albuquerque, New Mexico (TJD, RTB); and the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia (CJP)

also exist as viral hemorrhagic diseases in the Western Hemisphere, are not discussed.

SOUTH AMERICAN HEMORRHAGIC FEVERS

The South American arenavirus hemorrhagic fevers (SAHFs) are caused by members of the New World Tacaribe complex of the family Arenaviridae (Table 1). The Tacaribe complex was named for its prototype member, Tacaribe virus, which was first isolated in 1956 from *Artibeus* bats in Trinidad, and is not known to cause human disease. There are at least nine other members of the Tacaribe complex in the Western hemisphere not known to cause disease in addition to the four that are recognized human pathogens (Fig. 1).[57]

Prominent Old World members of the Arenaviridae family include the prototype lymphocytic choriomeningitis virus (LCMV), an important cause of aseptic meningitis in the United States that is only rarely associated with hemorrhagic manifestations, and Lassa virus, the causal agent of Lassa fever, a hemorrhagic fever common in tropical West Africa that does not exist in the Western hemisphere. Despite being an Old World virus, LCMV is sustained in the Western hemisphere by the presence of its predominant rodent host, *Mus musculus*, which was introduced to the New World from Europe. Monoclonal and polyclonal antibody studies,[6] as well as molecular phylogeny,[4] support the division of the arenavirus family into Old World and New World lineages, notwithstanding their current distribution.

Virology

All members of the Arenaviridae family are round, oval, or pleomorphic, with a diameter averaging 110 to 130 nm, but ranging from 50 to 300 nm.[59] Virions bud from the host cell membrane and generally contain 20 nm particles that are cellular ribosomes. The RNA genome consists of two single-stranded (occasionally diploid) segments: the small, or S, segment (22S, mol wt. 1.6×10^6) and the large, or L, segment (31S, mol wt. 3×10^6); both gene segments use an ambisense coding strategy. The S segment encodes the GPC glycoprotein, which is cleaved into two glycoproteins, GP1 and GP2, after translation. These two proteins are the surface structural units of the virus. The S segment also

Table 1. HEMORRHAGIC FEVER VIRUSES OF THE WESTERN HEMISPHERE (FAMILY ARENAVIRIDAE)

Virus Species	Disease	Disease Distribution	Primary Reservoir
Junin	Argentine hemorrhagic fever (AHF)	Argentine pampas	*Calomys musculinus*
Machupo	Bolivian hemorrhagic fever (BHF)	Bolivia; Beni Department	*Calomys callosus*
Guanarito	Venezuelan hemorrhagic fever (VHF)	Venezuela; Portuguesa State	*Zygdontomys brevicauda*
Sabiá	Unnamed	Brazil; São Paulo State	Unknown

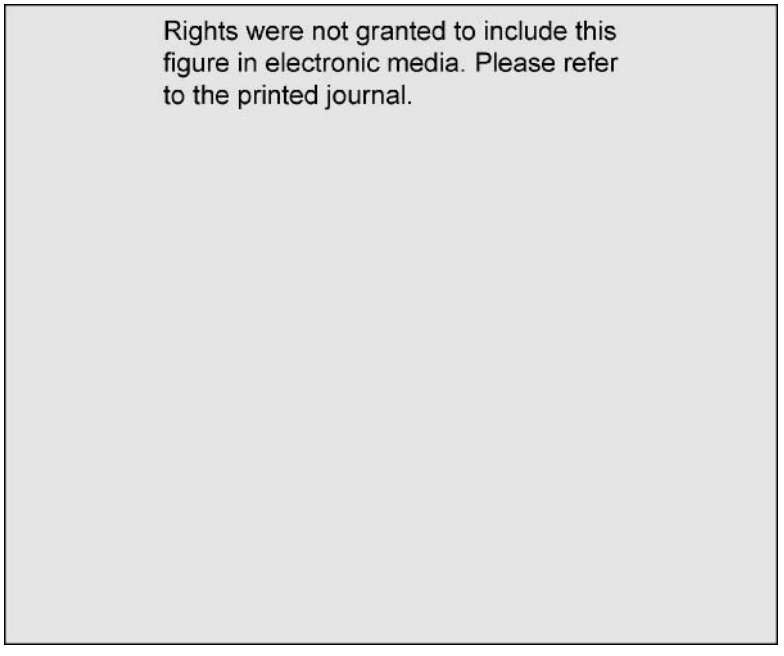

Figure 1. New World arenaviruses and their rodent reservoirs in the Americas. Circles denote the place of isolation, with known human pathogens underlined. (Courtesy of A. Sanchez and M. D. Bower.)

encodes the nucleocapsid, or N, protein. The different arenaviruses generally share 40% to 60% amino acid homology in the GPC or N genes. Different strains of the same virus are often more than 90% related at the amino acid level.

Arenaviruses infect a wide variety of cells in vitro, with little obvious cell damage or cytopathic effect. Rodents are known to be the natural host and reservoirs of arenaviruses, with the exception of Tacaribe virus. The geographic distribution of each arenavirus is limited by that of its reservoir rodent; however, arenaviruses often do not extend over the entire range of their host, and their distribution in some cases is quite focal or restricted.[14] The development of persistent arenavirus infection in the natural rodent host depends on the maturity of the immune system, genetic susceptibility, route of exposure, and strain of the infecting virus, and is accompanied by prolonged virus shedding in rodent urine, feces, and saliva.[59]

Epidemiology

Argentine hemorrhagic fever (AHF) was first recognized in 1955 in the primarily agricultural region of West Buenos Aires Province. Since then the annual incidence of AHF has fluctuated between 100 and 4000 cases, with disease occurring among all ages and both sexes. There is a seasonal pattern to AHF, with cases beginning in late summer and peak incidence occurring in autumn. Male agricultural workers are at greatest risk of infection, and the case

fatality rate of untreated AHF is 15% to 30%. Several instances of transmission from recovering husbands to their wives have been documented with AHF, but the mechanism is not known. The predominant rodent host of Junin virus is *Calomys musculinus*, with spillover into other rodent species commonly reported.[47] The endemic area of AHF has expanded to the north and west, and now encompasses more than 120,000 square km and 2 million inhabitants in Eastern Argentina.

Bolivian hemorrhagic fever (BHF) was first recognized in 1959 in the Beni Department of Bolivia.[32] An epidemic of BHF consisting of more than 500 cases occurred during 1963 and 1964 in the towns of San Joaquin, Orobayaya, and the surrounding area, with peak incidence in the fall and winter months corresponding to the dry season.[44] Cases occurred in all age groups and both sexes. Case fatality rates during the outbreak exceeded 15%, and there was no serologic evidence of asymptomatic infection. *Calomys callosus* was determined to be the primary rodent reservoir,[34] and the epidemic quickly subsided following aggressive rodent abatement efforts within the municipalities.[40]

A second outbreak of BHF occurred in the highland Cochabamba region of Western Bolivia in 1971. This area is outside the range of *Calomys callosus*, although the causal agent was found to be a strain of the Machupo virus.[60] Another unusual feature of this outbreak was evidence of person-to-person transmission. From 1976 to 1992 there were no reported cases of BHF in Bolivia, although unconfirmed cases likely occurred during that interval. Then, from 1993 to 1994, several sporadic cases were confirmed in the Beni region, including an outbreak with intrafamilial transmission that once again showed the potential for this rodent-borne virus to occasionally spread from person to person.[38]

Venezuelan hemorrhagic fever (VHF) was first recognized in 1989 in the rural areas of the Guanarito municipality, Portuguesa State, in northwestern Venezuela. Between May 1990 and March 1991, 104 cases of VHF were reported to the Ministry of Health, with a case fatality rate of 25%.[63] Adult males were most commonly affected, but cases included women and children. Rates of asymptomatic human infection were found to be very low in the general population, and there was no evidence of person-to-person transmission. The causal agent for VHF was named *Guanarito virus*, and its principal reservoir was initially thought to be the cotton rat, *Sigmodon alstoni*, with spillover to other species, most notably the cane rat, *Zygdontomys brevicauda*.[63] Subsequent studies showed two different arenaviral species circulating in the region, and *S. alstoni* was concluded to be the host for the Pirital virus, not known to cause human disease.[21, 57]

Of note, due to agricultural colonization activities in the region, the human population in the endemic zone had doubled in the 10 years leading up to the recognition of VHF as a distinct clinical entity. Sporadic cases occurring prior to 1989 were explained as dengue hemorrhagic fever, which is endemic in Venezuela. Only migration and population growth with resultant deforestation and land use alteration allowed what was probably a low-level, endemic disease to reach the epidemic proportions often required for detection.

Brazilian hemorrhagic fever is the presumptive name for an illness caused by Sabiá virus, and was first recognized in 1990 in a fatal case in São Paulo State, Brazil. The index case, a 25-year-old woman, died after a 4-day hospitalization characterized by signs, symptoms, and laboratory findings consistent with yellow fever.[15] Two laboratory workers were later infected while working with the virus, and survived.[2] No other cases have been reported, and limited studies have failed to ascertain the natural reservoir for this virus.

Little is known about the health consequences to humans of other New

World arenaviruses. Aerosol infections are common when these viruses are manipulated in the laboratory, and in the case of some arenaviruses, have resulted in seroconversions with minimal clinical consequences.[59]

Clinical Features

AHF is the best characterized of the SAHFs, and both BHF and VHF are quite similar.[33, 63] Both untreated Sabiá virus infections resembled the other SAHF, although the first case had extensive liver damage in addition to the usual findings. Following an incubation period of 6 to 16 days, onset of SAHF is gradual, with fever and malaise being the first symptoms noted. Headache, myalgia, arthralgia, and dizziness typically appear next whereas gastrointestinal symptoms, such as nausea, vomiting, constipation and diarrhea, are also frequently present. Neurologic abnormalities, including tremor of the tongue and extremities, disorientation, hyporeflexia, or ataxia may also appear.

Early signs of impaired vascular regulation, such as flushing of the face, conjunctival injection, and hypotension, may give way to more severe involvement, including petechiae, periorbital edema, pulmonary edema, and shock. Bleeding disorders appear in roughly one half of patients and include bleeding gums, hematemesis, and melena. Leukopenia, thrombocytopenia, and proteinuria are almost always present within the first few days of illness. Severely ill patients develop multiple hemorrhages in the gastrointestinal mucosa, uterus, and other mucosal surfaces. Most patients have tremors, dizziness, decreased tendon reflexes, and other modest neurologic findings. Severe neurologic complications appear in a small number of patients, and may completely overshadow the vascular and hemostatic abnormalities. CNS abnormalities such as delirium, convulsions, and coma are associated with an extremely poor prognosis.

The suspected pathogenesis of arenavirus hemorrhagic fevers is through an effect on macrophages that induce cytokine activation.[58] Interferon-α and tumor necrosis factor (TNF)-α are abundant in serum, and their levels correlate with the severity of disease, supporting the idea that soluble mediators are important in the pathogenesis of SAHF. Fatal outcomes occur in 15% to 30% of patients, usually within 2 to 14 days of hospitalization. Circulating antibodies appear 10 to 12 days after illness onset and coincide with clinical improvement, suggesting that humoral immunity, in addition to a cellular response, is important in recovery. Survivors usually experience a very gradual improvement, with diffuse hair loss and transverse furrowing of the nail beds being common features of recovery. There are no known long-term sequelae, but convalescence may be prolonged, lasting up to several months.[32]

Diagnosis and Treatment

Diagnosis of SAHF can be strongly suspected on clinical grounds based on geography, rodent exposure history, initial signs and symptoms, and clinical laboratory abnormalities. Specific causal diagnosis of arenavirus infection can be made by isolating the virus in cell cultures, such as vero cells. Rapid diagnosis can be obtained by antigen detection ELISA or by finding IgM in serum by ELISA. The usual serologic tests also yield rising titers, with the IgG ELISA being the most useful general diagnostic test and plaque reduction neutralization being the best test to differentiate different arenaviruses.[59]

Arenaviruses are sensitive to ribavirin in vitro, and this antiviral agent is an established treatment for Lassa fever. No clinical trials of ribavirin therapy for SAHF have been conducted, but work in animal models and early human experience suggest its usefulness in treating SAHF.[2, 17]

Administration of convalescent plasma is an established treatment for Junín virus infection. When the proper dose is administered early, taking into account the patient's weight and the concentration of antibody in the plasma, AHF mortality is reduced to less than 1%.[19] About 10% of plasma recipients experience a relapse of neurologic complications 3 to 6 weeks after treatment, which resolves without sequelae. The efficacy of convalescent plasma therapy in BHF and VHF is less well established, but the similarities of these diseases with AHF suggest that convalescent plasma would be useful.[56]

Prevention

Minimizing human–rodent interactions is the cornerstone of preventing naturally occurring infection by SAHF viruses. Rodent control has been effective in controlling BHF outbreaks in towns,[44] but sporadic disease continues after exposure in rural settings.[38] A live attenuated vaccine has been used to successfully immunize over 170,000 high-risk people against Junín virus in the endemic region of Argentina. A double-blind, placebo-controlled field trial showed greater than 95% vaccine efficacy,[45] and subsequent results have supported these findings. The Junín vaccine protects against Machupo virus inoculation of guinea pigs and nonhuman primates, but no human studies are available.

Very little nosocomial or interhuman disease transmission has been seen in the endemic areas for South American arenavirus hemorrhagic fevers. Nevertheless, patients are viremic, the viruses are consistently aerosol infectious in the laboratory (hence, the need for Biosafety Level 4 precautions), and occasional episodes have shown the potential of these viruses to be transmitted from person to person. Therefore, strict isolation procedures should be practiced, and clinical laboratory samples should be identified and handled with caution.[8, 10]

HANTAVIRUS DISEASE IN THE AMERICAS

Hantavirus is a genus in the family Bunyaviridae, and takes its name from the Hantaan river in Korea, where the prototype member, Hantaan virus, was first isolated from the striped field mouse in 1978.[42] Hantaan virus is the causal agent of Korean hemorrhagic fever, which first became a United States health concern when affecting thousands of soldiers in the Korean conflict during the 1950s. Other pathogenic Old World members of the hantavirus genus include Seoul virus, Dobrava virus, and Puumala virus, each of which causes a spectrum of human illness collectively referred to as *hemorrhagic fever with renal syndrome* (HFRS). The distribution of HFRS is widespread and includes large portions of Asia and Europe. Each hantavirus is associated with a primary rodent reservoir, and human infection occurs via the inhalation of aerosolized virus excreted in rodent urine, feces, and saliva.

Although much evidence of rodent infection with hantaviruses in North America existed,[72] clinical illness due to hantavirus infection in humans was not noted prior to the 1990s. The rodent reservoir of Seoul virus *(Rattus norvegicus)* was introduced to the Western Hemisphere from Europe by cargo ship, and exists in many port cities in the eastern United States. Enhanced surveillance for

hantavirus infection in humans eventually suggested the occasional presence of HFRS due to Seoul infection in the United States.[23]

In the spring of 1993, an outbreak of severe respiratory illness in the southwestern United States led to the isolation of a previously unknown hantavirus as the causal agent of hantavirus pulmonary syndrome (HPS).[39] The virus was eventually called *Sin Nombre virus* (SNV), and represented a distinct New World lineage of hantaviruses. Subsequent events have revealed at least eight additional New World hantaviruses that cause HPS (Table 2) and several additional New World hantaviruses not known to cause disease in the Western Hemisphere (Fig. 2). Due to Seoul virus infection, HFRS in the United States represents an Old-World hantavirus disease occurring primarily outside the Western hemisphere, and is not discussed extensively here.

Virology

All hantaviruses are lipid, enveloped, spherical viruses of 80 to 110 nm in diameter. The RNA genome is trisegmented with the large, or L, segment approximately 6500 nucleotides in length, the middle, or M, segment approximately 3600 to 3800 nucleotides in length, and the small, or S, gene approximately 1700 to 2100 nucleotides in length.[51] The M segment encodes G1 and G2 envelope glycoproteins, and the S segment encodes the N nucleocapsid protein.

No evidence of genetic reassortment with previously recognized Old World hantaviruses was found in the initial characterization of SNV,[66] and SNV is routinely 90% homologous across geographic and temporal variation of iso-

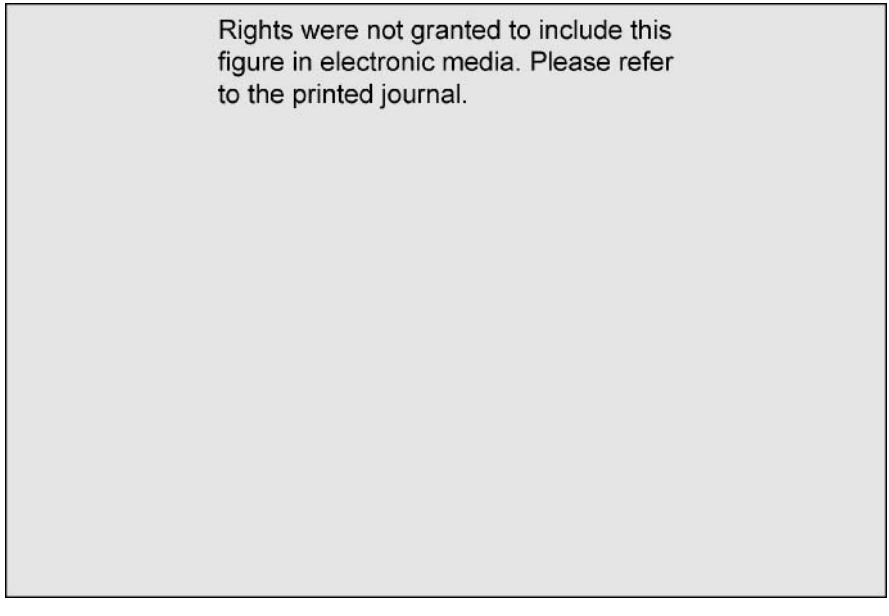

Figure 2. New World hantaviruses and their rodent reservoirs in the Americas, with known human pathogens underlined. (Courtesy of B. Ellis and J. Mills.)

Table 2. HANTAVIRUSES ASSOCIATED WITH HUMAN DISEASE IN THE WESTERN HEMISPHERE (FAMILY BUNYAVIRIDAE, GENUS HANTAVIRUS)

Virus Species	Disease	Disease Distribution	Primary Reservoir	Reservoir Distribution
Seoul	HFRS	United States, particularly eastern urban centers	*Rattus norvegicus*	Worldwide
Sin Nombre	HPS	North America, predominantly western United States and western Canada	*Peromyscus maniculatus*	North America
New York	HPS	Eastern United States	*Peromyscus leucopus*	North America
Black Creek Canal	HPS	Southeastern United States	*Sigmodon hispidus*	Southeastern United States, Central America, Northern South America
Bayou	HPS	Southeastern United States	*Oryzomys palustris*	Southeastern United States
Laguna Negra	HPS	Paraguay	*Calomys laucha*	South America
Andes	HPS	Argentina	*Oligoryzomys longicaudatus*	Chile, Argentina
HU39694	HPS	Argentina	Unknown	Unknown
Lechiguanas	HPS	Argentina	*Oligoryzomys flavescens*	Argentina
Juquitiba	HPS	Brazil	Unknown	Unknown

lates.[64] Serum antibodies in HPS patients cross-react strongly with other New World antigens, but only weakly with Old World hantavirus antigen.

Rodents are the natural hosts and reservoirs of hantaviruses and show no apparent ill effects as a result of infection. As in the case of arenaviruses, hantaviruses are highly selective toward a single or limited number of rodent host species. Spillover to other rodent species is commonly reported, particularly during periods of high rodent population density and high virus transmission, but chronic infection or further transmission to other hosts are not believed to be significant. There is no convincing evidence of chronic viremia in hantavirus-infected rodents as is often seen in arenavirus infections; the persistence of virus is managed through chronic virus shedding. The distribution of any particular hantavirus also appears to be less focal than that of arenaviruses, with antibody-positive rodents readily detected throughout their natural range.[11]

Epidemiology

North America

In North America, four distinct hantaviruses are known to cause HPS. Of the more than 180 confirmed cases in the United States and Canada (CDC, unpublished data),[41] the majority are believed to have been the result of SNV infection; however, New York virus,[26] Bayou virus,[50] and Black Creek Canal virus[61] are known to have caused a total of six cases of HPS in the eastern and southeastern United States. The deer mouse, *Peromyscus maniculatus*, is recognized as the primary rodent reservoir of SNV[13] whereas the white-footed mouse *(Peromyscus leucopus)*,[27] the rice rat *(Oryzomys palustris)*, and the cotton rat *(Sigmodon hispidus)*[62] are believed to be the primary rodent reservoirs for New York, Bayou, and Black Creek Canal viruses, respectively.

In North America, HPS occurs primarily west of the Mississippi river, with an annual incidence in nonepidemic years of 20 to 30 cases and a mortality rate of approximately 50%. Cases have occurred in all months, but are less common during the winter. Following the outbreak in the Southwest in 1993, several previously fatal cases of HPS were identified from stored autopsy tissue[73] whereas the earliest retrospectively identified survivor was ill in 1959.[20] The age range of confirmed cases in the United States is 11 to 69 years old (mean age 36), with a slight male preponderance. HPS in children is less common, yet has been reported, particularly in postpubertal adolescents.[5] Asymptomatic infection is generally thought to be uncommon,[65] and there is no evidence of person-to-person transmission.[67, 70]

Risk factors for HPS include handling or trapping rodents and peridomestic cleaning of food storage areas or rarely used outbuildings.[1, 75] There have been several cases that were thought to have been occupationally exposed as farmers or utility workers (D. Werker, personal communication).[30]

Rodent studies indicate a background seroprevalence of SNV antibodies ranging from 4% to 17% in captured deer mice[48] whereas case investigations often reveal a seroprevalence exceeding 25% near case homes.[12, 29] Increased rodent seroprevalence is thought to be correlated with greater rodent densities.

South America

In South America the presence of hantavirus-infected rodents has been known since the 1980s.[68] Sporadic cases of HPS were reported in Argentina[53]

and Brazil[74] following the 1993 outbreak in the United States. In 1995 an outbreak of HPS occurred in an agricultural community in western Paraguay, affecting at least 17 people.[71] Six additional cases occurring in the region between 1987 and 1994 were also serologically confirmed. The case fatality rate during the outbreak period was 12%, but this may have been underestimated due to the relative infrequency of autopsies performed in the region. The background human seroprevalence was found to be between 12% and 15% among case contacts and community residents, suggesting either circulation of more than one virus or a milder illness, and a much higher rate of asymptomatic infection than seen in North America. The causal agent was named Laguna Negra virus, and the vesper mouse, *Calomys laucha*, was found to be the primary rodent reservoir.[31]

In 1996 an outbreak of HPS occurred in southern Argentina, affecting at least 18 people in Rio Negro Province. Circumstances suggested interhuman transmission, particularly when two additional people outside the region became infected after coming in contact with HPS patients.[18, 69] No explanation for this unique episode has been found, nor is the mode of transmission known. The causal agent, Andes virus, had been identified earlier,[43] and the rodent reservoir was found to be the long-tailed pygmy rice rat, *Oligoryzomys longicaudatus*.

Overall, there have been more than 108 confirmed HPS cases in Argentina, 34 in Paraguay, 27 in Chile, and 6 in Brazil. There are currently five hantavirus species in South America recognized as causing HPS; seven other species are not known to cause human disease.

Clinical Features

The early clinical features of HPS resemble those of the SAHF. After an incubation period believed to be 1 to 4 weeks, a prodromal phase ensues. Fever, headache, and myalgia, commonly of 3 to 5 days' duration, are often accompanied by gastrointestinal symptoms of vomiting, diarrhea, or abdominal pain.[16] The neurologic symptoms seen in SAHF are absent, except for dizziness in some patients.

Progression to the cardiopulmonary phase of HPS is heralded by increasing shortness of breath and onset of nonproductive cough, often accompanied by shock.[24] Common physical findings include tachypnea, tachycardia, hypotension, and rales or crackles on respiratory auscultation examination. Important clinical laboratory findings include leukocytosis with a left shift, thrombocytopenia, hemoconcentration, mildly elevated hepatic transaminases, marked elevations in serum lactate dehydrogenase levels, and moderately prolonged partial thromboplastin times. Pulmonary edema develops rapidly, and almost all cases require supplemental oxygen. Approximately three fourths of patients require mechanical ventilation.

Hemodynamic profiles in patients with HPS are distinct from those with sepsis. Although hemodynamic findings in patients with septic shock include elevated cardiac index (CI) and decreased systemic vascular resistance (SVR), patients with HPS typically have a normal pulmonary wedge pressure (PWP), decreased CI, and an elevated SVR, which is indicative of cardiac suppression.[46] Fatal outcomes are usually preceded by rapid respiratory failure and the abrupt onset of lactic acidosis, and occur after relatively short hospitalizations of 1 to 2 days.

Although rare in SNV-associated HPS, infection with Bayou and Black Creek Canal viruses has been associated with acute renal insufficiency (serum

creatinine > 3.0 mg/dL, BUN > 40 mg/dL), hypertension, and serum creatine kinase (CK) levels more than 1000 U/L.[25, 36, 37]

Resolution of the cardiopulmonary stage of HPS, which often lasts only 24 to 48 hours, is heralded by the onset of diuresis. Once diuresis begins, clinical improvement is usually rapid. Survivors generally require intubation for only 2 to 4 days, and many patients are ready for discharge after hospitalizations of less than 1 week. There are no known chronic sequelae associated with HPS, although this has not been systematically assessed.

The pathogenesis of HPS is related to a profound abnormality in vascular permeability; however, hemorrhagic manifestations are rare. The capillary leak syndrome is confined to the lungs, and chest radiograph series typically chronicle the rapid onset of diffuse, bilateral interstitial, and later alveolar, pulmonary edema.[35] Microscopic studies of lung tissue show scant to moderate numbers of hyaline membranes, intact pneumocytes, and scarce neutrophils. The absence of a marked pulmonary response of acute inflammatory cells distinguishes HPS from most other infectious pneumonias.[16]

In contrast to SAHFs, circulating antibodies appear much sooner in the clinical course of HPS, and often correspond to clinical decline rather than improvement.[39, 58] Thus, the impaired vascular permeability is believed to be immunologically mediated. Circulating IgG antibodies appear early, persist indefinitely, and have been detected more than 30 years after illness.[20]

Diagnosis and Treatment

Clinicians should consider HPS in patients with fever and myalgias, particularly of the larger muscle groups, such as shoulders, thighs, and lower back. The addition of gastrointestinal complaints (nausea, vomiting, abdominal pain) should raise the index of suspicion and prompt the clinician to inquire about potential rodent exposures. The absence of certain signs and symptoms can help to distinguish HPS from other acute viral syndromes; rash, conjunctivitis, sinusitis, otitis, rhinorrhea, exudative pharyngitis, and arthritis are rare in HPS.[49] Initial laboratory work-up in suspected cases should include pulse oximetry, a chest radiograph, and a complete blood count. The likelihood of HPS is high in those with a compatible clinical history plus an oxygen saturation measurement less than 90%, interstitial infiltrates or other indications of pulmonary edema on chest radiograph and thrombocytopenia, particularly if the latter is accompanied by left-shifted leukocytosis and an elevated hematocrit.

Given the nonspecific prodromal symptoms and rapid, fulminant progression of disease, timely laboratory diagnostic confirmation is essential in HPS. Virus isolation in cell culture is far more difficult for hantaviruses than for arenaviruses; therefore, serology is a more timely diagnostic modality. Western blot and ELISA are suitable serologic assays whereas immunohistochemistry is a sensitive and reliable assay for detecting tissue antigen in biopsy or necropsy tissue. In the United States, ELISA assays are available at most state public health laboratories or by state health department referral at CDC. Viral isolation and molecular diagnostic techniques are available at selected research laboratories, and have thus far been most useful for epidemiologic rather than clinical purposes.

There is no known effective pharmacologic therapy for HPS, though ribavirin has shown a treatment effect in reducing HFRS mortality.[28] Open-label ribavirin treatment had no obvious effect in a limited number of HPS patients, and a placebo-controlled clinical trial is currently underway. In the absence of a

proven pharmacologic treatment and in light of the rapid progression of HPS, effective clinical management depends heavily on careful fluid management, hemodynamic monitoring, and ventilatory support. Therapeutic responses to shock in patients with HPS must be guided by an understanding of the underlying pathophysiology of this disorder; that is, profound pulmonary capillary leak in the presence of primary myocardial pump dysfunction.

Prevention

As with SAHFs, minimizing human–rodent contact is the bedrock of HPS prevention. Rodent eradication is impractical and unfeasible, as *Peromyscus* are among the most common and widespread mammals of North America. Appropriate prevention strategies include minimizing rodent habitat near the home by clearing away brush and potential nesting sites, minimizing rodent entry opportunities into the home by sealing all openings and properly storing food supplies, and taking precautions when cleaning rodent droppings or emptying rodent traps by wetting the area with a disinfectant to kill the virus and minimize aerosolization.[7] These prevention practices have been shown to be effective in significantly reducing the number of rodents captured in and around dwellings.[22]

Universal precautions should be followed when caring for hospitalized patients. Laboratory infection is uncommon, and Biosafety Level 2 (BSL-2) precautions are recommended when handling patient sera whereas BSL-3 precautions should be used for cell-culture virus propagation. There are no human vaccines against New-World hantaviruses, although prototype human vaccines against Hantaan virus are being tested.

COMMON FEATURES IN DISEASE EMERGENCE

Their highly selective association with a predominant rodent host species, their genomic sequence conservation across a wide geographic and temporal range, and the within-species clinical homogeneity of resultant human disease all support the ancient presence of arenaviruses and hantaviruses in the Americas. Indeed, it is likely that these New World viruses coevolved with their rodent hosts in the Western Hemisphere.[3] Therefore, it is reasonable to suspect that human disease caused by these viruses has occurred in the Western Hemisphere for as long as humans have come in contact with rodents in the region.

The perceived emergence of human disease caused by these viruses may represent improvements in ability to diagnose these infections. There are, however, several additional factors that have likely contributed to an actual increase in incidence of these diseases. Firstly, both the SAHF and HPS affect predominately rural populations. Changing human demographic patterns in previously uninhabited regions of the Americas and the resultant changes in land use have contributed to outbreak circumstances, allowing for increased detection of disease.

Secondly, the human epidemiology of SAHF and HPS in the Americas is heavily dependent on rodent ecology. Therefore, factors that encourage increases in rodent population densities, such as anomalous weather patterns typified by recurrent El Niño Southern Oscillation weather events or the less well understood effects of global warming and global climate change, may contribute to epidemic conditions.[46, 54]

CONCLUSION

The plethora of New World arenaviruses and hantaviruses recently isolated is a harbinger for the detection of additional viruses that may or may not be pathogenic to humans, but which satisfy the common feature of an association with a single predominant rodent host species. Against this backdrop, the limiting factor in the number of potential viruses to be detected is the number of murid rodent species in the Western hemisphere. In the future, if ecological, human demographic, and land use patterns conspire to create a situation in which many people come into contact with many rodents, it is not unreasonable to expect additional arena- and hantavirus microbes to emerge and be detected as new human pathogens.

ACKNOWLEDGMENTS

The authors thank Jim Mills, PhD, Michael Bowen, PhD, Darcy Wolsey, and Joni Young for their assistance in the preparation of this manuscript.

References

1. Armstrong LR, Zaki SR, Goldoft MJ, et al: Hantavirus pulmonary syndrome associated with entering or cleaning rarely used, rodent-infested structures [letter]. J Infect Dis 172:1166, 1995
2. Barry M, Russi M, Armstrong L, et al: Treatment of a laboratory-acquired Sabiá virus infection. N Engl J Med 333:294–296, 1995
3. Bowen MD, Peters CJ, Nichol ST: Phylogenetic analysis of the Arenaviridae: Patterns of virus evolution and evidence for cospeciation between arenaviruses and their rodent hosts. Mol Phylogenet Evol (in press) 1997
4. Bowen MD, Peters CJ, Nichol ST: The phylogeny of New World (Tacaribe complex) arenaviruses. Virology 219:285–290, 1996
5. Bryan RT, Doyle TJ, Moolenaar RL, et al: Hantavirus pulmonary syndrome. Seminars in Pediatric Infectious Diseases 8:44–49, 1997
6. Buchmeier MJ, Lewicki HA, Tomori O, et al: Monoclonal antibodies to lymphocytic choriomeningitis and Pichinde viruses: Generation, characterization, and cross-reactivity with other arenaviruses. Virology 113:73–85, 1981
7. Centers for Disease Control and Prevention: Hantavirus infection—southwestern United States: Interim recommendations for risk reduction. MMWR 42(RR-11):2–13, 1993
8. Centers for Disease Control and Prevention: Management of patients with suspected viral hemorrhagic fever. MMWR 37(S-3):1–15, 1988
9. Centers for Disease Control and Prevention: Outbreak of acute illness—southwestern United States, 1993. MMWR 42(22):421–424, 1993
10. Centers for Disease Control and Prevention: Update: Management of patients with suspected viral hemorrhagic fever—United States. MMWR 44:475–479, 1995
11. Childs JE, Bryan RT: The epidemiology of hantavirus pulmonary syndrome. (Submitted for publication)
12. Childs JE, Krebs JW, Ksiazek TG, et al: A household-based, case-control study of environmental factors associated with hantavirus pulmonary syndrome in the southwestern United States. Am J Trop Med 52:393–397, 1995
13. Childs JE, Ksiazek TG, Spiropoulou CF, et al: Serologic and genetic identification of *Peromyscus maniculatus* as the primary rodent reservoir for a new hantavirus in the southwestern United States. J Infect Dis 169:1271–1280, 1994
14. Childs JE, Peters CJ: Ecology and epidemiology of arenaviruses and their hosts. *In* Salvato MS (ed): The Arenaviridae. New York, Plenum Press, 1993, pp 331–392

15. Coimbra TLM, Nassar ES, Burattini MN, et al: New arenavirus isolated in Brazil. Lancet 343:391–392, 1994
16. Duchin JS, Koster FT, Peters CJ, et al: Hantavirus pulmonary syndrome: A clinical description of 17 patients with a newly recognized disease. N Engl J Med 330:949–955, 1994
17. Enria D, Maiztegui JI: Antiviral treatment of Argentine hemorrhagic fever. Antiviral Res 23:23–31, 1994
18. Enria D, Padula P, Segura E, et al: Hantavirus pulmonary syndrome in Argentina: Possibility of person-to-person transmission. Medicina (B Aires) 58:709–711, 1995
19. Enria DA, Briggiler AM, Fernandez NJ, et al: Importance of dose of neutralising antibodies in treatment of Argentine haemorrhagic fever with immune plasma. Lancet 2:255–256, 1984
20. Frampton JW, Lanser S, Nichols CR, et al: Sin Nombre virus infection in 1959 [letter]. Lancet 346:781–782, 1995
21. Fulhorst CF, Bowen MD, Salas RA, et al: Isolation and characterization of Pirital virus, a newly discovered South American arenavirus. Am J Trop Med (in press), 1997
22. Glass GE, Johnson JS, Hodenbach GA, et al: Experimental evaluation of rodent exclusion methods to reduce hantavirus transmission to humans in rural housing. Am J Trop Med 56:359–364, 1997
23. Glass GE, Watson AJ, LeDuc JW, et al: Domestic cases of hemorrhagic fever with renal syndrome in the United States. Nephron 68:48–51, 1994
24. Hallin GW, Simpson SQ, Crowell RE, et al: Cardiopulmonary manifestations of hantavirus pulmonary syndrome. Crit Care Med 24:252–258, 1996
25. Hjelle B, Goade D, Torrez-Martinez N, et al: Hantavirus pulmonary syndrome, renal insufficiency, and myositis associated with infection by Bayou hantavirus. Clin Infect Dis 23:495–500, 1996
26. Hjelle B, Krolikowski J, Torrez-Martinez N, et al: Phylogenetically distinct hantavirus implicated in a case of hantavirus pulmonary syndrome in the northeastern United States. J Med Virol 46:21–27, 1995
27. Hjelle B, Lee S-W, Song W, et al: Molecular linkage of hantavirus pulmonary syndrome to the white-footed mouse, *Peromyscus leucopus*: Genetic characterization of the M genome of New York virus. J Virol 69:8137–8141, 1995
28. Huggins JW, Hsiang CM, Cosgriff TM, et al: Prospective, double-blind concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. J Infect Dis 164:1119–1127, 1991
29. Jay M, Ascher MS, Chomel BB, et al: Seroepidemiologic studies of hantavirus infection among wild rodents in California. Emerging Infectious Diseases 3:183–190, 1997
30. Jay M, Hjelle B, Davis R, et al: Occupational exposure leading to hantavirus pulmonary syndrome in a utility company employee. Clin Infect Dis 22:841–844, 1996
31. Johnson AM, Bowen MD, Ksiazek TG, et al: Laguna Negra virus associated with HPS in western Paraguay and Bolivia. Virology 238:115–127, 1997
32. Johnson KM: Arenavirus, Viral Infections of Humans. New York, Plenum Press, 1991
33. Johnson KM, Halstead SB, Cohen SN: Hemorrhagic fevers of Southeast Asia and South America: A comparative appraisal. Prog Med Virol 9:105–158, 1967
34. Johnson KM, Kuns ML, Mackenzie RB, et al: Isolation of Machupo virus from wild rodent *Calomys callosus*. Am J Trop Med 15:103–106, 1966
35. Ketai LH, Williamson MR, Telepak RJ, et al: Hantavirus pulmonary syndrome (HPS): Radiographic findings in 16 patients. Radiology 191:665–678, 1994
36. Khan AS, Gaviria M, Rollin PE, et al: Hantavirus pulmonary syndrome in Florida: Association with the newly identified Black Creek Canal virus. Am J Med 100:46–48, 1996
37. Khan AS, Spiropoulou CF, Morzunov S, et al: Fatal illness associated with a new hantavirus in Louisiana. J Med Virol 46:281–286, 1995
38. Kilgore PE, Peters CJ, Mills JN, et al: Prospects for the control of Bolivian hemorrhagic fever. Emerging Infectious Diseases 1:97–100, 1995
39. Ksiazek TG, Peters CJ, Rollin PE, et al: Identification of a new North American hantavirus that causes acute pulmonary insufficiency. Am J Trop Med 52:117–123, 1995

40. Kuns ML: Epidemiology of Machupo virus infection. II: Ecological and control studies of hemorrhagic fever. Am J Trop Med 14:813–816, 1965
41. LCDC: Hantavirus pulmonary syndrome in Canada. Canada Communicable Disease Report 21:77–80, 1995
42. Lee HW, Lee PW, Johnson KM: Isolation of the etiologic agent of Korean hemorrhagic fever. J Infect Dis 137:298–308, 1978
43. Lopez N, Padula P, Rossi C, et al: Genetic identification of a new hantavirus causing severe pulmonary syndrome in Argentina. Virology 220:223–226, 1996
44. Mackenzie RB: Epidemiology of Machupo virus infection. I: Pattern of human infection, San Joaquin, Bolivia, 1962–1964. Am J Trop Med 14:808–813, 1965
45. Maiztegui JI, McKee KT, Enria DA, et al: Eficacia protectora de la cepa atenuada Candid 1 de virus junín contra la fiebre hemorragica argentina (FHA). Medicina (B Aires) 51:467, 1991
46. Mertz GJ, Hjelle B, Bryan RT: Hantavirus infection. *In* Schrier RW (ed): Advances in Internal Medicine. Chicago, Mosby-Year Book, 1997, pp 369–421
47. Mills JN, Ellis BA Jr, McKee KT, et al: Junín virus activity in rodents from endemic and nonendemic loci in central Argentina. Am J Trop Med 44:589–597, 1991
48. Mills JN, Ksiazek TG, Ellis BA, et al: Patterns of association with host and habitat: Antibody reactive with Sin Nombre virus in small mammals in the major biotic communities of the southwestern United States. Am J Trop Med 56:273–284, 1997
49. Moolenaar RL, Dalton C, Lipman HB, et al: Clinical features that differentiate hantavirus pulmonary syndrome from three other acute respiratory illnesses. Clin Infect Dis 21:643–649, 1995
50. Morzunov SP, Feldmann H, Spiropoulou CF, et al: A newly recognized virus associated with a fatal case of hantavirus pulmonary syndrome in Louisiana. J Virol 69:1980–1983, 1995
51. Nichol ST, Ksiazek TG, Rollin PE, et al: Hantavirus pulmonary syndrome and newly described hantaviruses in the United States. *In* Elliott RM (ed): The Bunyaviridae. New York, Plenum Press, 1996, pp 269–280
52. Nichol ST, Spiropoulou CF, Morzunov S, et al: Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 262:914–917, 1993
53. Parisi M, Enria DA, Pini NC, et al: Deteccion retrospectiva de infecciones clinicas por hantavirus en la Argentina. Medicina (B Aires) 56:1–13, 1996
54. Parmenter R, Brunt J, Moore D, et al: The hantavirus epidemic in the Southwest: Rodent population dynamics and the implications for transmission of hantavirus-associated adult respiratory distress syndrome (HARDS) in the Four Corners region. Albuquerque, University of New Mexico, 1993
55. Parodi AS, Greenway DJ, Rugiero HR: Sobre la etiologia del brote epidemico de Junín. El Dia Medico 30:2300–2301, 1958
56. Peters CJ: Arenavirus diseases. *In* Porterfield JS (ed): Exotic Viral Infections. London, Chapman & Hall, 1995, p 19
57. Peters CJ: Arenaviruses. *In* Richman DD, Whitley RJ, Haydon FG (eds): Clinical Virology. New York, Churchill Livingstone, 1997, pp 973–996
58. Peters CJ: Pathogenesis of viral hemorrhagic fevers. *In* Nathanson N, Ahmed R, Gonzalez-Scarano F (eds): Viral Pathogenesis. Philadelphia, Lippincott-Raven, 1996
59. Peters CJ, Buchmeier MJ, Rollin PE, et al: Arenaviruses. *In* Fields BN, Knipe DM, Howley PM, et al (eds): Fields Virology. Philadelphia, Lippincott-Raven, 1996
60. Peters CJ, Kuehne RW, Mercado RR, et al: Hemorrhagic fever in Cochabamba, Bolivia, 1971. Am J Epidemiol 99:425–433, 1974
61. Ravkov EV, Rollin PE, Ksiazek TG, et al: Genetic and serologic analysis of Black Creek Canal virus and its association with human disease and *Sigmodon hispidus* infection. Virology 210:482–489, 1995
62. Rollin PE, Ksiazek TG, Elliott LH, et al: Isolation of Black Creek Canal virus, a new hantavirus from *Sigmodon hispidus* in Florida. J Med Virol 46:35–39, 1995
63. Salas R, Manzione ND, Tesh RB, et al: Venezuelan haemorrhagic fever. Lancet 338:1033–1036, 1991
64. Schmaljohn C, Hjelle B: Hantaviruses: A global disease problem. Emerging Infectious Diseases 3:95–104, 1997

65. Simonsen L, Dalton MJ, Breiman RF, et al: Evaluation of the magnitude of the 1993 hantavirus outbreak in the southwestern United States. J Infect Dis 172:729–733, 1995
66. Spiropoulou CF, Morzunov S, Feldmann H, et al: Genome structure and variability of a virus causing hantavirus pulmonary syndrome. Virology 200:715–723, 1994
67. Vitek CR, Breiman RF, Ksiazek TG, et al: Evidence against person-to-person transmission of hantavirus to health care workers. Clin Infect Dis 22:824–826, 1996
68. Weissenbacher M, Merani MS, Hodara VL, et al: Hantavirus infection in laboratory and wild rodents in Argentina. Medicina (B Aires) 50:43–46, 1990
69. Wells RM, Estani SS, Yadon ZE, et al: An unusual hantavirus outbreak in southern Argentina: Person-to-person transmission? Emerging Infectious Diseases 3:171–174, 1997
70. Wells RM, Young J, Williams RJ, et al: Hantavirus transmission in the U.S. Emerging Infectious Diseases 3:361–365, 1997
71. Williams RJ, Bryan RT, Mills JN, et al: An outbreak of hantavirus pulmonary syndrome in western Paraguay. Am J Trop Med 57:274–282, 1997
72. Yanagihara R: Hantavirus infection in the United States: Epizootiology and epidemiology. Rev Infect Dis 12:449–457, 1990
73. Zaki SR, Khan AS, Goodman RA, et al: Retrospective diagnosis of hantavirus pulmonary syndrome, 1978–1993: Implications for emerging infectious diseases. Arch Pathol Lab Med 120:134–139, 1996
74. Zaparoli MA, Iversson LB, Rosa MD, et al: Investigation on case-contacts of human disease caused by hantavirus in Juquitiba, State of São Paulo, Brazil [abstract No. 440]. Am J Trop Med 53:232–233, 1995
75. Zeitz PS, Butler JC, Cheek JE, et al: A case-control study of hantavirus pulmonary syndrome during an outbreak in the southwestern United States. J Infect Dis 171:864–870, 1995

Address reprint requests to

Clarence J. Peters, MD
CDC/NCID/DVRD/SPB
Mailstop A-26
1600 Clifton Road NE
Atlanta, GA 30333