Hantavirus pulmonary syndrome (HPS), a disease now known to have been present for centuries, if not millennia, in the Americas was discovered only 16 years ago in the southwestern United States.² Two young long-distance runners who lived together in the New Mexican desert fell victim in early May, 1993, to what seemed to be a rapidly progressive pulmonary infection, and both of them died within days. The unusual circumstance of two highly fit individuals succumbing in this manner, especially in the spring, led health officials to investigate the cause and initiate surveillance for other, similar cases. It soon became evident that they were in the midst of an outbreak of a seriously deadly infectious agent and that the syndrome was one that had not been previously described by the medical community.

The causative agent for the illness was soon (<6 weeks after the index cases were identified) determined to be an unidentified North American member of the Hantavirus genus. The clinical syndrome caused by this agent, ultimately named Sin Nombre virus (SNV), came to be called the hantavirus pulmonary syndrome. This designation distinguished it from previously described hantaviral illnesses, which were characterized as hemorrhagic fever with renal syndrome (HFRS). Early in the course of events it became evident that cardiac function, and respiratory function, are markedly impaired by infection with this virus. For that reason, some authors have adopted the moniker Hantavirus cardiopulmonary syndrome. Although that name certainly has logic, the Centers for Disease Control and Prevention (CDC) continue to refer to the illness as HPS, as does this article.

HANTAVIRUSES

The hantaviruses are an enveloped genus of the family Bunyaviridae. Virions are spherical and encapsulated by a bilayered phospholipid membrane. The composition of each virion is greater than 50% protein, 20% to 30% lipid, and 2% to 7% carbohydrate,
making them easily disrupted with heat, detergents, organic solvents, and hypochlorite solutions.\textsuperscript{2} Diameters range from 71 to 200 nm, with an average of approximately 100 nm.\textsuperscript{3} The genome consists of three single-stranded, negative-sense RNA segments: long (L), medium (M), and short (S). Each of the segments encodes only one protein. The S segment codes for the nucleocapsid protein (N protein), the M segment codes for the viral envelope glycoproteins (two proteins, G1 and G2), and the L segment codes for viral transcriptase.\textsuperscript{4} The 3' terminal and 5' terminal end are complementary sequences, resulting in the RNA strand forming “pan-handle” structures that seem to be important in viral transcription and replication.\textsuperscript{5} Each segment also has short noncoding regions, the function of which is yet to be elucidated. \textbf{Fig. 1} shows a schematic of SNV based on CDC electron micrographs.\textsuperscript{6}

Hantaviruses principally target vascular endothelial cells, but also infect alveolar macrophages and follicular dendritic cells. Renal tubular epithelium can also be a site for infection. Cell entry of hantaviruses is mediated by binding to $\beta3$ integrins.\textsuperscript{7} Sin Nombre and New York viruses enter human cells by way of $\alpha v\beta3$ and $\alpha IIb\beta3$

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{snv_schematic.png}
\caption{Schematic diagram of Sin Nombre virus, based on Centers for Disease Control and Prevention electron micrographs. Structures are not drawn to scale. G1 and G2 represent glycoproteins that mediate attachment of virions to human cells by way of $\beta3$ integrins. The virus consists of a phospholipid bilayer envelope surrounding a nucleocapsid protein. Three strands of negative sense RNA constitute the viral genome. (Courtesy of N. Simpson, Fairway, KS.)}
\end{figure}
integrins, whereas Prospect Hill, a nonpathogenic hantavirus, does not, suggesting a role for these particular molecules in human pathogenesis. Uptake of these viruses is inhibited by various competitive ligands. SNV glycoprotein is processed through the Golgi apparatus, where virions likely are packaged, but later in the course of in vitro infection glycoprotein antigens can be found at the cell surface of human pulmonary endothelial cells. Likewise, SNV and Black Creek Canal viruses localize to the apical membrane of polarized Vero cells.

**EPIDEMIOLOGY AND ECOLOGY**

**Reservoirs**

Like other members of the Bunyavirus family, each hantavirus is closely associated with a specific rodent reservoir. The hantaviruses chronically infect rodents that are members of subfamilies of the family Muridae without causing illness in the rodents. Table 1 shows known pathogenic hantaviruses, their rodent hosts, and their geographic locations. The Murinae subfamily hosts the Old World hantaviruses Hantaan and Dobrava, and other nonpathogenic strains.

The Arvicolinae, or voles, are hosts to Puumala virus, which causes HFRS in Scandinavia, and to Prospect Hill virus which is found in the Ohio River valley but does not cause disease. The pathogenic New World hantaviruses chronically infect rodents of the Sigmodontinae subfamily. The single interloper in this relationship between the Muridae and the hantaviruses is Seoul virus, whose host is *Rattus norvegicus*. In keeping with the travel habits of that host, Seoul virus–induced HFRS has been diagnosed throughout Asia and the Americas, mostly in coastal areas, and infected rodents have been identified on every continent, except Antarctica. Indigenous hantaviruses had not been identified in Africa until 2006, when the Sangassou virus was detected in the wood mouse *Hylomyscus simus*, a member of the Murinae subfamily; no human infections with this virus have yet been detected.

In the United States, the principal virus causing HPS is SNV, which chronically infects the deer mouse, *Peromyscus maniculatus*. The deer mouse habitat occupies a huge swath of the North American continent, sparing only areas nearing the Arctic Circle, a few states in the southeastern United States, and southern Mexico. Approximately 10% of tested deer mice in this range are infected with SNV. Additionally, closely related hantaviruses are hosted by other sigmodontine rodents in areas where deer mice are sparse, including Black Creek Canal virus, hosted by the cotton rat *Sigmodon hispidus* in Florida, and the Bayou virus, hosted by the swamp rat *Oligoryzomus palustris* in Louisiana and Texas.

In November of 1996, an outbreak of HPS was detected in the Neuquen region of southern Patagonia, and the source was traced to yet another sigmodontine rodent, the “coli largo” or long-tailed rice rat, *Oligoryzomus longicaudatus*. The hantavirus detected in both patients and rats was named the Andes virus. Heightened awareness of the disease, its causative agents, and its presenting features led to the identification of HPS cases, along with new strains of hantaviruses and newly identified hosts, in multiple South American countries, including Bolivia, Brazil, Chile, Paraguay, and Uruguay. By 1999, HPS caused by Choclo virus was identified in Central America (Panama), carried by the pygmy rice rat *Oligoryzomus fulvescens*. Based on the broad distribution of sigmodontine rodents throughout the Americas, the CDC estimates that it is only a matter of time before HPS is detected in every American country.

**Mode of Transmission**

In contrast to other Bunyaviridae, transmission of hantaviruses does not involve an arthropod intermediate. Transmission largely occurs through inhalation of aerosolized
<table>
<thead>
<tr>
<th>Hantaviruses</th>
<th>Host</th>
<th>Geographic Range</th>
<th>Syndrome</th>
<th>Yearly Incidence/ Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eurasian</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobrava-belgrade (DOB)</td>
<td><em>Apodemus flavicollis</em> (yellow-necked field mouse)</td>
<td>Balkans</td>
<td>HFRS</td>
<td>100/15%</td>
</tr>
<tr>
<td>Hantaan (HTN)</td>
<td><em>Apodemus agrarius</em> (striped-field mouse)</td>
<td>China, Korea, Russia</td>
<td>HFRS</td>
<td>100,000/1%–5%</td>
</tr>
<tr>
<td>Puumala (PUU)</td>
<td><em>Clethrionomys glareolus</em> (red bank vole)</td>
<td>Europe</td>
<td>NE</td>
<td>30,000/1%</td>
</tr>
<tr>
<td>Saaremaa (SAA)</td>
<td><em>Apodemus agrarius</em> (Striped field mouse) <em>Microtus arvalis</em> (European common vole)</td>
<td>Northern Europe</td>
<td>HFRS</td>
<td>Unknown/0%</td>
</tr>
<tr>
<td>Seoul (SEO)</td>
<td><em>Rattus norvegicus</em> (Norway [brown] rat); <em>Rattus rattus</em> (black rat)</td>
<td>Worldwide</td>
<td>HFRS</td>
<td>Unknown/1%–2%</td>
</tr>
<tr>
<td>Tula (TUU)</td>
<td><em>Microtus arvalis</em> (European common vole)</td>
<td>Europe</td>
<td>HFRS</td>
<td>Unknown/0%</td>
</tr>
<tr>
<td><strong>North American</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayou (BAY)</td>
<td><em>Oryzomys palustris</em> (rice rat)</td>
<td>Southeastern United States</td>
<td>HPS</td>
<td>5 cases/1 fatality</td>
</tr>
<tr>
<td>Black creek canal (BCC)</td>
<td><em>Sigmodon hispidus</em> (cotton rat)</td>
<td>Florida</td>
<td>HPS</td>
<td>1 case/0 fatality</td>
</tr>
<tr>
<td>New York (NY)</td>
<td><em>Peromyscus leucopus</em> (white-footed mouse)</td>
<td>Eastern United States</td>
<td>HPS</td>
<td>3 cases/1 fatality</td>
</tr>
<tr>
<td>Sin Nombre (SN)</td>
<td><em>Peromyscus maniculatus</em> (deer mouse)</td>
<td>Western United States</td>
<td>HPS</td>
<td>20–80/35%–40%</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td><strong>Central and South American</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andes (AND)</td>
<td><em>Oligoryzomys longicaudatus</em> (long-tailed pygmy rice rat)</td>
<td>Argentina and Chile</td>
<td>HPS</td>
<td>50–200/35%–40%</td>
</tr>
<tr>
<td>Araraquara (ARA)</td>
<td><em>Bolomys lasiurus</em> (hairy-tailed bolo mouse)</td>
<td>Central Brazil</td>
<td>HPS</td>
<td>20–50/25%</td>
</tr>
<tr>
<td>Bermejo (BMJ)</td>
<td><em>Oligoryzomys chacoensis</em> (Chacoan pygmy rice rat)</td>
<td>Northern Argentina</td>
<td>HPS</td>
<td>Unknown/20%</td>
</tr>
<tr>
<td>Castelo dos sonhos (CAS)</td>
<td>Unknown</td>
<td>Central Brazil</td>
<td>HPS</td>
<td>Unknown/25%</td>
</tr>
<tr>
<td>Choclo (CHO)</td>
<td><em>Oligoryzomys fulvescens</em> (pygmy rice rat)</td>
<td>Western Panama</td>
<td>HPS</td>
<td>2–30/10%</td>
</tr>
<tr>
<td>Juquitiba (JUQ)</td>
<td><em>Oligoryzomys nigripus</em> (black-footed pygmy rice rat)</td>
<td>Southern Brazil</td>
<td>HPS</td>
<td>Unknown/25%</td>
</tr>
<tr>
<td>Laguna Negra (LN)</td>
<td><em>Calomys laucha</em> (vesper mouse)</td>
<td>Northwestern Argentina, Bolivia, and Paraguay</td>
<td>HPS</td>
<td>2–30/9%</td>
</tr>
<tr>
<td>Lechiguanas (LEC)</td>
<td><em>Oligoryzomys flavescens</em> (yellow pygmy rat)</td>
<td>Central Argentina</td>
<td>HPS</td>
<td>Unknown/30%</td>
</tr>
<tr>
<td>Oran (ORN)</td>
<td><em>Oligoryzomys longicaudatus</em> (long-tailed rice rat)</td>
<td>Northwestern Argentina and Bolivia</td>
<td>HPS</td>
<td>Unknown/35%</td>
</tr>
</tbody>
</table>

Abbreviations: HFRS, hemorrhagic fever with renal syndrome; HPS, hantavirus pulmonary syndrome; NE, Nephropathia epidemica (a form of HFRS).
urine, feces, or saliva of the rodent host. Within species, the viruses are also commonly transmitted through aggressive behavior, such as biting, especially among males, and males have a higher prevalence of infection than females. Both HFRS and HPS are predominantly rural diseases, with associated risk factors of farming, land development, hunting, and camping, because each of these activities brings humans into closer contact with the natural rodent reservoirs, which are all sylvan or agrarian in their choice of habitat. However, HPS is nearly always acquired indoors or within closed spaces, such as peridomestic buildings on farms or ranches, livestock feed containers, or the cabs of abandoned pickup trucks.

Several factors contribute to the propensity for indoor acquisition by humans. Animals captured in the peridomestic environment have a higher prevalence of active infection than those captured in a sylvan environment (25% vs. 10%), likely because of greater supplies of foodstuffs and higher murine population densities. Higher population densities lead to more interaction among mice and higher rates of intraspecies transmission. Likewise, humans are more likely to encounter rodent excreta when population densities are higher.

Although SNV and other hantaviruses are capable of withstanding desiccation for days, they are inactivated by ultraviolet light, which is less plentiful in the indoor environment. Humans are prone to cleaning and other activities that stir up virus-carrying dust particles, and without the diluting effect of outdoor air they are subject to inhaling higher concentrations of virus.

Incidence and Prevalence

Since 1993, approximately 465 cases of HPS have been documented in the United States, a few of which were retrospectively identified. The overwhelming majority (>90%) of these infections are isolated, not in clusters. Although SNV-induced HPS has occurred throughout the range of the deer mouse, the incidence is highest in the western United States, and SNV accounts for the vast majority of North American disease. Canada reports approximately 10% to 15% of the North American cases each year. In the United States, approximately two thirds of HPS cases have been among men. The average age of patients who have HPS is 38 years, with a range of 10 to 83 years. There has been a striking absence of severe HPS among prepubertal individuals in the United States, although disease in 11 children aged 10 to 16 years had clinical courses similar to those described in adults. The United States mortality rate is 35%.

The incidence of HPS in Latin America is largely unknown but cases have been reported from Central America to southern Patagonia. The Andes virus was responsible for outbreaks in Argentina and Chile and is closely related to the Bayou virus. Although most North American cases have been sporadic and isolated, most South American cases have occurred in clusters. The Patagonian outbreak in 1996 was unique in that it occurred in an area with a relatively low rodent population density, and human-to-human transmission was suspected when physicians treating infected patients became ill themselves. Gene sequencing of virus recovered from cases with rodent exposure and from their contacts who had no possibility of rodent exposure confirmed human-to-human transmission. As of this writing, human-to-human transmission of hantaviruses has been shown only for the Andes virus.

The seroprevalence of IgG antibodies to hantaviruses differs between North and South American populations. In the United States, the Four Corners area has the highest incidence of infection; however, presence of antibodies among tested individuals in that region is less than 1%. Childhood infection in North America is also rare. In contrast, some endemic areas in South America have a much higher rate of infection,
including in children, with seroprevalence as high as 42.7% in areas of Paraguay. In all areas studied, the seroprevalence is higher in South America than in North America, suggesting the occurrence of mild and asymptomatic infections.

**CLINICAL FEATURES**

Although the dramatic and well-publicized feature of HPS is its effect on cardiopulmonary function, the disease actually comprises four clinical phases: prodrome, pulmonary edema and shock, diuresis, and convalescence. During the initial prodromal phase, symptoms are virtually identical to the febrile phase of HFRS. This phase typically lasts 3 to 6 days, at which time the onset of respiratory symptoms and shock is abrupt. Mortality most commonly occurs in the first 24 hours of the pulmonary edema and shock phase of the illness, which also tends to last from 3 to 6 days. Patients who survive the shock phase enter the diuretic phase of the illness. In this phase, patients may have urine flow rates ranging from 300 to 500 mL/hr, simultaneous with rapid (24–48 hours) resolution of respiratory and hemodynamic abnormalities. After diuresis and extubation, patients enter the convalescent phase of the illness, which typically lasts for a few months, but some patients have taken up to 2 years for full recovery.

**Presentation**

The most common signs and symptoms in the prodromal phase are identical to those of other, less-severe viral illnesses. Nearly all patients complain of subjective fever or chills on presentation, and most have myalgias or headache. Many patients initially have nausea/vomiting, diarrhea, or abdominal pain. In fact, several patients have been admitted to the hospital for treatment of gastroenteritis before HPS is diagnosed. Cough is present in nearly two thirds of patients on presentation. The cough is most often nonproductive, but occasionally a patient produces amber-colored pulmonary secretions that are confused with purulent sputum. This sputum is actually alveolar edema fluid and manifests at the onset of the shock phase of illness. Despite the central role that pulmonary problems play in HPS, dyspnea is not a common early complaint. Dyspnea is associated with advanced disease and often is a sign of impending respiratory failure. Box 1 shows presenting symptoms of HPS, and symptoms that are uncommon in the syndrome. These latter symptoms have been helpful in distinguishing HPS from other acute febrile illnesses.

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The most frequent initial physical findings in HPS are tachypnea, fever, and tachycardia. The pulmonary examination is unrevealing early in the illness, but with the onset of pulmonary edema, fine rales are present, which become more pronounced with progression of disease. Severe abdominal tenderness is present in approximately 10% of patients and may mimic appendicitis. Hypotension is unusual on presentation, but when it is present indicates advanced disease and requires aggressive resuscitation. Although many patients are thrombocytopenic, petechiae are rare in North American HPS. Several findings that are common in HFRS, such as conjunctival hemorrhage, flushing, and peripheral edema, are virtually never present in people who have North American HPS but are relatively more prevalent among people who have Andes virus infection.

**Laboratory Findings**

A trio of hematologic findings, including thrombocytopenia, leukocytosis with a left shift, and circulating immunoblastoid lymphocytes, is unique to HPS in the Americas, although these findings are reported in HFRS in Asia. Thrombocytopenia is present in 79% of patients at presentation and is the most common initial laboratory...
abnormality; it develops in all patients during their hospital course. The white blood cell count is increased, and immature neutrophils such as myelocytes and promyelocytes are frequently present. All patients have a lymphocyte population that includes at least 10% immunoblasts and plasma cells, a finding not seen in similar disorders such as acute respiratory distress syndrome (ARDS). These immunoblasts may often be reported as atypical lymphocytes by laboratory personnel. Hemoconcentration is common, with hematocrits as high as 77%; this finding is believed to result from massive capillary leaking of plasma but not cells.32

Liver enzymes, including aspartate aminotransferase and alanine aminotransferase, tend to be increased, but not dramatically so. Hypoalbuminemia is a common finding, possibly caused by resuscitation with crystalloid solutions, but bilirubin and alkaline phosphatase are typically normal.33 Serum lactate dehydrogenase level is frequently increased with an electrophoretic pattern consistent with lung and liver injury. Creatinine rises mildly in most North American cases, but only 20% of patients achieve creatinine levels greater than 2.0 mg/dL in North America, and only a couple of renal failure cases have been reported.34–36 Case series from South America indicate a 48% prevalence of renal insufficiency.37–39

Serum lactate levels help establish disease severity. An increased serum lactate level identifies patients who have poor tissue perfusion and those who require immediate resuscitative efforts. In early series, all patients who had a serum lactate level of 4.0 mmol/L or higher died despite aggressive treatment, except some patients who were treated with extracorporeal membrane oxygenation (ECMO).28,40,41

**Radiographic Findings**

Chest radiographic abnormalities are noted on admission in most patients, even in the absence of dyspnea. Major findings are interstitial edema, and include Kerley’s B lines,
hilar indistinctness, and peribronchial cuffing. Many patients develop severe airspace disease and progressive hypoxemia. Airspace flooding typically begins in dependent areas of the lung and progresses to involve all lung fields. This progression may be as rapid as 4 to 6 hours from presentation. Cardiac silhouettes are not enlarged, and pleural effusions develop in all patients as the disease progresses. Lobar infiltrates are not seen in HPS, and their presence should strongly suggest another diagnosis.

**Respiratory Function**

Disease often progresses abruptly from prodrome to full-blown HPS, and patients presenting with dyspnea typically require intubation and mechanical ventilation within 1 to 6 hours. All patients who have HPS develop pulmonary edema, with severity ranging from mild interstitial edema to diffuse alveolar flooding with profound hypoxemia. \( \text{PaO}_2 \) to fraction of inspired oxygen (FiO\(_2\)) ratios may be as low as 28 during mechanical ventilation with high levels of positive end-expiratory pressure (normal \( \text{PaO}_2/\text{FiO}_2 \) range is 350–500, dependent on elevation), which would equate to a \( \text{PaO}_2 \) of 28 mm Hg while breathing 100% oxygen. Chest radiography demonstrates diffuse interstitial or alveolar infiltrates, and low respiratory system compliance is evident. Alveolar flooding seems to result from a very low reflection coefficient in the alveolar capillaries; in other words, the barrier between capillary blood and alveolar gas is porous. The result is that relatively low intracapillary hydrostatic pressures can cause massive fluid flux across the membrane. In this disease, pulmonary artery occlusive pressures (wedge pressures) exceeding 10 to 12 mm Hg result in profound alveolar edema (S.Q. Simpson, unpublished data, 1997). Pleural effusions develop in most patients and can be massive; the mechanisms for accumulation of pleural fluid are believed to be similar to those for alveolar fluid formation.

In patients who survive an initial crisis period of 24 to 72 hours, recovery is often nearly as rapid as the decline, and these patients are most frequently extubated in less than a week. After hospital discharge, pulmonary function testing may show air trapping or diminished carbon monoxide diffusing capacity for up to 6 months, during which most patients have returned to their pre-HPS activities. However, patients who remain dyspneic for more than a year after recovering from the acute illness have been reported.

**Hemodynamics**

Nearly all patients who have HPS fit accepted criteria for the diagnosis of severe sepsis, having serologic evidence of infection, fever, tachypnea, tachycardia, and evidence of organ dysfunction. However, the hemodynamic parameters in HPS are unique compared with other forms of septic shock and are closely associated with mortality. Shock caused by other viruses, bacteria, and fungi has been associated with an increased cardiac index and low systemic vascular resistance. Patients who have HPS nearly uniformly have a diminished cardiac index and normal or increased systemic vascular resistance. At presentation, many patients who have HPS have intravascular volume depletion, as evidenced by increased hematocrit and decreased pulmonary artery occlusive pressures. Patients who have hypotension have a low cardiac stroke volume and low cardiac output because of inadequate left ventricular preload. However, intravascular volume repletion does not improve cardiac output, suggesting the presence of myocardial depression. Echocardiography also shows poor left ventricular systolic function. Death, when it occurs, is caused by progressive myocardial insufficiency, and the terminal event is almost uniformly progressive hypotension, which evolves to pulseless electrical activity.
Pathology

At autopsy, the lungs of patients who have HPS are grossly edematous and have an average combined weight nearly twice normal. Pleural effusions are uniformly present, with volume ranging from 200 to 8400 mL. Histologically, variable amounts of alveolar and septal edema are found. Hyaline membranes with little cellular debris are usually present, the respiratory epithelium is intact, and type II pneumocytes appear nonactivated. An interstitial infiltration of mononuclear cells is present and many of the mononuclear cells are enlarged and have the characteristics of immunoblasts. Intravascular neutrophils are common, but only rarely in the interstitium, alveoli, and bronchioles. No vasculitis has been identified in pulmonary vessels, and no viral inclusions or cytopathic effects are seen on light microscopy, although immunologic staining shows viral antigens in the pulmonary endothelium. Electron microscopy shows rare endothelial inclusions of 90 to 110 nm particles consistent in appearance with hantavirus virions. These histopathologic findings distinguish HPS from diffuse alveolar damage or ARDS, in which the infiltrate is predominantly neutrophilic, type II pneumocytes are activated, and extensive cellular debris is present. Immunohistochemistry shows abundant staining of pulmonary endothelial cells. A fine, granular-appearing stain localizes in the pulmonary microvascular endothelium and is rarely seen in the endothelium of larger veins and arteries. When sections of multiple lung segments are available, the microvascular staining appears uniform throughout the lungs.

The heart of patients who have fatal SNV infection is grossly and histologically normal, with no evidence of significant coronary artery disease or recent myocardial infarction. Neither myocarditis nor cardiomyopathy are found. However, myocarditis was present in fatal cases of HPS in both Argentina and Brazil. A small pericardial effusion was seen in one patient. Myocardial capillaries contain SNV antigens in most specimens, with antigen loads ranging from focal involvement to extensive, diffuse staining. In the Brazilian series myocytes stain for hantaviral antigens, a finding that has not been seen in North American HPS.

Examination of the liver shows a portal triaditis in approximately half of the cases, with expanded pools of lymphocytes, including large immunoblasts, but without necrosis. The spleen and lymph nodes typically contain an infiltrate of immunoblasts. Lymphocytes within splenic lymphoid follicles typically contain SNV antigens, and macrophages in several tissues, including the lungs, also stain positively. The brain, kidneys, adrenals, pancreas, skeletal muscle, and skin are normal both macroscopically and histologically. SNV antigens are seen in multiple other tissues, including skeletal muscle, adrenal glands, intestine, and brain, although these tissues stain less intensely and less consistently than the lungs.

DIAGNOSIS AND TREATMENT

The key to treatment of HPS lies in recognition of the illness, but that can be a challenge for clinicians, because the prodromal phase of the illness is nondistinctive. One must have a high index of suspicion, especially in rural locales, and it would be wise to query all patients who have fever, chills, myalgias, and gastrointestinal symptoms for recent history of dust exposure in enclosed spaces or exposure to rodents. Such recent activities as cleaning closets, garages, feed bins, or other outbuildings in rural locations must raise the index of suspicion and should prompt further investigation. In Patagonia it is clearly wise to obtain any history of HPS in close contacts, because of the prospect of human-to-human transmission. However, family members are frequently exposed to common risk factors in their home environment,
and therefore this bit of history-taking can also be useful in other regions of the Americas.

If the patient’s history is compatible with appropriate rodent exposure, a complete blood cell count should be obtained to evaluate for thrombocytopenia, which is the earliest laboratory abnormality in HPS. The combination of a compatible history and thrombocytopenia should prompt hospitalization, especially if atypical lymphocytes are present. Commercial laboratories can serologically confirm or rule out the diagnosis of HPS within 24 hours; IgM antibodies to nucleocapsid antigen are universally present in symptomatic patients, and IgG antibodies are present in most. The state health department should also be contacted and a blood specimen submitted for in-state testing or testing at the CDC. If the patient has cough, dyspnea, or other respiratory symptoms, a chest radiograph should be obtained. If there is evidence of pulmonary interstitial edema, the patient should be moved to an intensive care unit. Careful consideration must be given to transferring any patient who has HPS or suspected HPS to a facility with expertise in the management of shock and severe acute respiratory failure. Patients can and do deteriorate extremely rapidly, and waiting for the onset of shock to initiate transfer is often futile.

Patients transitioning into the shock/respiratory failure stage of illness should have a flow-directed pulmonary artery catheter placed, and an arterial catheter for continuous blood pressure monitoring. Pulmonary artery occlusive pressure should be optimized between 8 and 12 mm Hg, but no higher. If the patient is hypotensive with these cardiac filling pressures, then a cardiac inotrope, preferably dobutamine, should be initiated. Vasopressor agents should be avoided, if possible, because they increase cardiac afterload. If pulse oximetry or serial arterial blood gases show a downward trend in arterial oxygenation, patients should be intubated early in their course.

The University of New Mexico (UNM) has extensive experience with ECMO in the treatment of patients who have HPS. Because ECMO replaces or augments the function of both heart and lungs, it may offer the best hope of survival for patients for whom more conventional intensive care unit therapies fail. UNM reported on a series of 38 patients treated in this manner, with a mortality rate of 40%. Unfortunately, the descriptive nature of this study makes it difficult to draw conclusions regarding the efficacy of ECMO. The mortality rate in the study is roughly equivalent to the 35% overall mortality rate in the United States. However, patients in the study were chosen because they met criteria that in 1994 were believed to be associated with 100% mortality. A randomized trial of ECMO probably will not be undertaken. Instituting ECMO at a moment’s notice, especially among adults, is not possible even in most tertiary hospitals, and therefore more conventional therapies will remain the mainstay of HPS treatment.

As of this writing, no specific therapy exists for hantaviral diseases in the Americas. A multicenter randomized trial of intravenous ribavirin was closed because of a low rate of enrollment. No clear effect of ribavirin was detected, in either direction. Although the possibility of passive immunization has been discussed for 15 years, and neutralizing antibodies remain present for years in survivors, no cases of administering immune human sera have been reported. For now, cautious supportive care remains preferred treatment.

**PREVENTION**

With a case fatality rate of 35% to 40% and no proven effectiveness of antiviral therapy, preventing viral transmission and augmenting viral immunity in appropriate individuals are critical. Satellite imagery allows evaluation of ecologic conditions...
and prospective prediction of areas of high rodent population, thereby enabling measurement of rodent infection rates to predict times of extraordinary risk.\textsuperscript{55}

Less predictable is human to rodent contact; hence the need for measures aimed at decreasing rodent-to-human transmission, including those that decrease the risk for inhalation of aerosolized rodent excreta. To this effect, CDC recommends the “Seal Up! Trap Up! Clean Up!” approach: seal up holes inside and outside the home to prevent entry by rodents, trap rodents, and take precautions before and while cleaning rodent-infested areas. Before cleaning a space or an unused building, ventilate the area by opening doors and windows for at least 30 minutes to diffuse potentially infectious aerosolized material. Do not stir up dust by sweeping or vacuuming up droppings, urine, or nesting materials. Wear rubber, latex, vinyl, or nitrile gloves when cleaning excreta and handling dead rodents or rodent nests.\textsuperscript{54}

Although evidence for human-to-human transmission of HPS in Argentina led the CDC to conduct a comprehensive review of the HPS registry, it found that SNV infection rarely, if ever, transmits from person-to-person, and that existing guidelines for preventing HPS remain appropriate for North America.\textsuperscript{21,22,56,57} However, exercising contact and airborne precautions in the hospital and clinic is appropriate if infection with the Andes strain is suspected, as is remaining vigilant for new evidence of human-to-human transmission of other hantaviruses.\textsuperscript{58}

Effective, though expensive, recombinant vaccines against Hantaan (HTNV), Puumala (PUUV), Dobrava (DOBV), and Seoul (SEOV) strains, causative agents of HFRS, have been tested in clinical trials and are selectively used in Asia.\textsuperscript{58,59} An inactivated bivalent HTNV/PUUV vaccine protected hamsters against subsequent infection by HTNV, SEOV, DOBV, and PUUV, but not SNV or New York Virus.\textsuperscript{58} In a recent study, Rhesus macaques vaccinated with nucleic acid vaccine (Gene Gun method) containing M genome segment of Andes virus developed neutralizing antibodies that also cross-neutralized other HPS-associated hantaviruses, including SNV. Sera from the vaccinated monkeys delayed the onset of HPS and death when injected into hamsters 1 day before challenge. Injection on day 4 or 5 after challenge provided 100% protection.\textsuperscript{60} No human vaccination trials for the New World hantaviruses are currently in progress.

REFERENCES


