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Hantavirus Pulmonary Syndrome

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Introduction

Hantavirus pulmonary syndrome (HPS) was first recognized in May 1993 when two young, healthy adults who lived together in the New Mexican desert near the Four Corners, died within 5 days of one another of rapidly progressive respiratory failure (Duchin et al., 1994; Hjelle et al., 1994b). The precipitous nature of their illnesses, which were clinically identical and which appeared to be infectious, led local physicians to notify health authorities of the two deaths. Within a month, more than a dozen people in the southwestern United States died from similar clinical syndromes that began with nonspecific viral symptoms. Early mortality rates were as high as 76%, and all of the patients were identified because of their need for critical care. By mid-June investigators in the Special Pathogens Branch of the U.S. Centers for Disease Control and Prevention (CDC) determined that sera from the disease victims contained antibodies with reactivity to several species of hantavirus.

Using reverse transcription-polymerase chain reaction (RT-PCR), researchers at the CDC and at the University of New Mexico (UNM) were able to identify and characterize the virus by amplifying viral gene sequences taken from human and animal tissues (Elliott et al., 1994; Feldman et al., 1993; Spiropoulou et al., 1994). Sequencing of major portions of the viral genome demonstrated that the virus was a unique member of the hantavirus genus. The agent responsible for the initial outbreak was eventually named the *Sin nombre* virus, or the "virus without a name," although over a dozen viruses are now known to cause the syndrome throughout North and South America. Before 1993, no hantaviruses were known to cause human disease in the Americas, although hantaviruses were known for causing hemorrhagic fevers accompanied by renal insufficiency in Europe and in Asia. For the most part, victims of HPS have not suffered hemorrhage or renal failure.

HPS is named for its dramatic effects on cardiopulmonary function. In HPS, nonspecific influenza-like symptoms lead to increased pulmonary capillary permeability and pulmonary edema, which can progress over a few hours to a severe state similar to adult respiratory distress syndrome (ARDS), and to shock due to low cardiac output (Hallin et al., 1996). Effective treatment requires supportive care in an intensive care unit and frequently includes mechanical ventilation, intravenous hydration, hemodynamic support, and even extracorporeal membrane oxygenation (Crowley et al., 1998; Hallin et al., 1996).

Hantaviruses

The hantaviruses constitute a genus of negative-sense RNA viruses belonging to the family Bunyaviridae (McCormick, 1991; Peters, 1994, 1995). A number of species of the genus have been identified, including Hantaan virus, Seoul virus, Puumala virus, and Dobrava virus. The Bunyaviridae share a common viral structure. The viral genome, encased within a nucleocapsid shell, typically consists of three segments: the S segment or small segment

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codes for the nucleocapsid protein (N protein), the M or medium segment codes for the viral envelope glycoproteins (two proteins: G_1 and G_2), and the L or large segment codes for a viral transcriptase. The hantaviruses, including those that cause HPS, conform to this basic structural pattern.

The hantaviruses are also similar to other bunyaviruses in that each virus is predominantly associated with a specific rodent reservoir, usually rural field mice, voles, or rats. When a rodent becomes infected the virus disseminates throughout the host's body during a period of viremia that lasts several days. Following the viremic period hantavirus antigens are detectable in lungs, kidneys, and other organs; these tissues appear to remain antigen-positive for the duration of the host's life. The rodents remain apparently healthy but shed virus in urine, feces, and saliva. Unlike other bunyaviruses, infection by hantavirus species is not transmitted via an arthropod vector but appears to be transmitted via aerosols of urine and feces from the infected animal. The hosts harbor and shed live virus in spite of developing neutralizing IgM and IgG antibodies. Sin nombre virus and Black Creek Canal virus appear to follow this pattern in their rodent hosts (Green et al., 1998; Hutchinson et al., 1998).

Hemorrhagic Fever with Renal Syndrome

The prototype virus of the genus is the Hantaan virus, named for the Hantaan river on the Korean peninsula, where it was first encountered by western physicians during the Korean conflict (McKee, 1991). However, both the virus and its host, the rural field mouse *Apodemus agrarius,* are found throughout northeastern Asia. The Hantaan virus causes a life-threatening illness that was originally named Korean hemorrhagic fever but is now known as hemorrhagic fever with renal syndrome (HFRS). The clinical manifestations of HFRS are classically described in five relatively distinct phases. Their description is germane to this discussion because they are strikingly similar to the clinical phases of HPS. During the febrile or prodromal phase, the patient experiences high fevers and myalgias for an average of 4 to 5 days. Just as patients defervesce, they develop severe vascular leak, especially notable in the peritoneum, which leads to ascites and retroperitoneal edema and causes severe back and abdominal pain. This phase may also be accompanied by profound hypotension and shock. The patients then develop a severe oliguria that may be accompanied by severe pulmonary edema, which is exacerbated by volume resuscitation. During the shock and oliguric phases of the illness, disseminated intravascular coagulation results in severe bleeding complications that may include exsanguination or intracranial hemorrhage. One third of deaths from HFRS result from such bleeding complications. Patients who survive these severe phases of the illness develop a pronounced diuresis and tend to recover. Convalescence from this illness requires a number of months for patients with severe disease. The current mortality rate of HFRS is 5% to 15%.

The Dobrava virus of eastern Europe causes a severe form of HFRS with a mortality rate of 5% to 35%. Seoul virus, which is distributed worldwide in its host *Rattus norvegicus,* and Puumala virus, which is found in Scandinavia and eastern Europe, cause mild forms of HFRS with low mortality. The first hantavirus recognized to be indigenous to the western hemisphere, Prospect Hill virus, was discovered in the early 1980s in the meadow vole of the northeastern United States but has not caused known human disease. Nucleotide sequence analysis indicates that Sin nombre virus is a novel hantavirus that is most closely related to the Prospect Hill and Puumala viruses (Hjelle et al., 1994c).

Hantavirus Pulmonary Syndrome

Since the initial outbreak in 1993, Sin nombre virus has been detected in humans and in rodents in nearly every geographical area of the continental United States and in Canada (CDC, 1993, 1994a,b,c; Hjelle et al., 1995a; Morzunov et al., 1995). Several other hantaviruses that are closely related to Sin nombre virus have been identified in California, Louisiana, Texas, and Florida and are associated with HPS. Additionally, outbreaks of HPS have occurred in Uruguay and in the Patagonian Andes of Argentina and Chile (Enria et al., 1996). The Patagonian outbreaks were caused by the Andes virus, a hantavirus isolated from the long-tailed rice rat, *Oligoryzmus longicaudatus,* in 1996 (Lopez et al., 1996). Table 1 shows the New World hantaviruses and their geographic locations.

Genetic linkage analysis demonstrates that Sin

TABLE 1. Hantaviruses in the Americas

Virus	Rodent host	Geographic location	Clinical syndrome	Mortality	Reference
Sin nombre/Muerto Canyon/Convict Creek/Four Corners	Deer mouse *Peromyscus maniculatus*	Western North America, Mexico, Canada	HPS	50%	Li et al., 1995
New York/Shelter Island/Rhode Island	White-footed mouse *Peromyscus leucopus*	Eastern North America, Canada	HPS	1 fatal case	Hjelle et al., 1995a,b
Black Creek Canal	Cotton rat *Sigmodon hispidus*	United States, Venezuela, Peru	HPS with hemorrhage	1 case	Khan et al., 1996
Muleshoe	Cotton rat *Sigmodon hispidus*	West Texas, United States	None known	—	Rawlings et al., 1996
Bayou	Rice rat *Oryzomys palustris*	Louisiana, United States	HPS with hemorrhage	1 fatal case	Khan et al., 1995; Morzunov et al., 1995
Prospect Hill	Meadow vole *Microtus pennsylvanicus*	Eastern North America, Canada	None known	—	Lee et al., 1985
Leakey	Grey mouse *Mus musculus*	Texas	None known		Baek et al., 1988
Bloodland Lake	Prairie vole *Microtus ochrogaster*	Southern Canada, Midwestern United States	None known	—	
Isla Vista	California meadow mouse *Microtus californicus*	California and Oregon, United States; Baja California, Mexico	None known	—	Song et al., 1994
El Moro Canyon	Western harvest mouse *Reithrodontomys megalotis*	Western states of United States, Central Mexico, Canada	None known	—	Torrez-Martinez et al., 1995
Rio Segundo	Mexican harvest mouse *Reithrodontomys mexicanus*	Mexico and Costa Rica, South America	None known	—	Hjelle et al., 1994a
Cano Delgadito	Cotton rat *Sigmodon alstoni*	Venezuela	None known	—	Fulhorst et al., 1997
Rio Mamoré	Pygmy rice rat *Oligoryzomys microtis*	Bolivia	None known	—	Bharadwaj et al., 1997; Hjelle et al., 1996a
Andes	Coli largo *Oligoryzomys longicaudatis*	Argentina, Chile	HPS	70%	Lopez et al., 1996

HPS, Hantavirus pulmonary syndrome.

nombre virus and other, closely related hantaviruses are not recent variants of the genus, but have existed in their present forms for many years (Hjelle et al., 1994c). Because each of these hantaviruses survives in its own unique rodent reservoir, it is possible that they all coevolved with their respective hosts. Cases of HPS as early as 1959 have been retrospectively diagnosed by serum antibody titers, indicating that the disease itself existed unrecognized for years (Hjelle et al., 1994c; Yamada et al., 1995). Furthermore, Native American mythology in the Four Corners area relates that humans should avoid close contact with mice or they risk illness or even death, possibly reflecting a prior experience of these peoples with HPS (Simpson et al., 1995).

Epidemiology

Because the data are more complete and accessible, this discussion of the epidemiology and clinical features of HPS is largely restricted to the syndrome that is caused in North America by the Sin nombre virus and other closely related viruses. Forty-eight cases of HPS were reported in the United States during 1993, the year in which HPS was first recognized; the overall case fatality rate was 56% in that outbreak year. The majority of cases occurred in the region known as the Four Corners area, the boundary common to the states of New Mexico, Arizona, Utah, and Colorado. As of October 30, 1998, 200 cases were identified in 30 states in the United States and additional cases have been found in Canada. The disease seems to have a predilection for affecting healthy adults; the median age of patients confirmed to have HPS is 37 years, with a range of 11 to 69 years. Remarkably, preadolescent children have suffered only mild illnesses and have not required mechanical ventilation. Sixty percent of patients have been male and 40% female. The overall case-fatality rate now stands at 43%, although the mortality among patients diagnosed since January 1, 1994, is slightly lower, at 34%. The initial cluster of HPS cases was unusual for an outbreak of infection in that it occurred in an area of sparse population, and HPS remains a disease that is contracted in the rural setting. The Four Corners area continues to have the highest case rate, and all but 15 of the cases have been identified west of the Mississippi River.

Clinical Features

Clinical Course

In those patients whose exposure to the virus can be identified, the incubation period for HPS induced by Sin nombre virus averages 7 to 10 days. However, incubation periods up to 50 days' duration have been observed. After the onset of symptoms, HPS resulting from Sin nombre virus infection is characterized by 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 (Duchin et al., 1994). This phase typically lasts 3 to 6 days, at which time the onset of respiratory symptoms and shock is abrupt. Mortality is greatest 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, they may have urine flow rates ranging from 300 to 500 ml per hour, simultaneous with rapid resolution of respiratory and hemodynamic abnormalities (Hallin et al., 1996). Following diuresis and extubation, patients enter the convalescent phase of the illness, which may last 6 months or longer. During the convalescent phase, they experience gradually resolving malaise and weakness, along with fibromyalgia-like symptoms. Some patients have mild pulmonary function abnormalities that persist as long as a year. Rarely, hearing loss and impaired mental functioning have been reported as long-term sequelae of HPS, though the latter is likely no more frequent than in other forms of acute respiratory failure and shock (Hopkins et al., 1998; Javer et al., 1998).

Symptoms and Physical Signs

Differentiating HPS from other, less severe viral illnesses is difficult during the prodromal phase, because the most common signs and symptoms are identical to those of milder illnesses. Nearly all patients complain of subjective fever or chills upon presentation, and most patients have myalgias or headache. Eighty-nine percent of patients initially have nausea/vomiting, diarrhea, or abdominal pain. In fact, several patients have been admitted for treatment of gastroenteritis before the diagnosis of HPS became clear.

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 have been confused with purulent sputum. 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. Table 2 shows presenting symptoms of HPS, as well as symptoms that are uncommon in the syndrome. These latter symp-

TABLE 2. Presenting Symptoms in Hantavirus Pulmonary Syndrome

Frequent[a]	Common[b]	Uncommon[c]	Essentially absent
Fever	Nausea/ vomiting[d]	Sweats	Sore throart
Chills	Dyspnea	Dizziness	Meningismus
Myalgia	Cough	Arthralgia	Rash
Headache	Diarrhea[d]	Chest pain	Sinusitis
		Back pain	Pleuritic pain
		Abdominal pain[d]	

[a]Frequent, present in >50% of cases.
[b]Common, present in 20%–50% of cases.
[c]Uncommon, present in <20% of cases.
[d]One or another of these abdominal symptoms is present in >85% of cases.

toms have been helpful in distinguishing HPS from other viral syndromes.

The most frequent initial physical findings in HPS are tachypnea, fever, and tachycardia (Duchin et al., 1994; Hallin et al., 1996). Examination of the lungs reveals fine rales. 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 most patients are thrombocytopenic, no petechiae are seen. Several findings seen commonly in HFRS, such as conjunctival hemorrhage, flushing, or peripheral edema, are not present in HPS.

Laboratory Findings

Thrombocytopenia, leukocytosis with a left shift, and circulating immunoblasts constitute a triad of findings that is unique to HPS in North America (Duchin et al., 1994; Dull et al., 1994). Thrombocytopenia is present in 79% of patients at presentation and in all patients during their hospital course. Hemoconcentration is common, with hemalocrits as high as 77% (Zaki et al., 1995). While 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 ARDS (Jenison et al., 1995; Nolle el al., 1995). The immunoblasts are characterized by deeply basophilic cytoplasm, enlarged nuclei, and variably prominent nucleoli, and they vary in size, with mature circulating plasma cells at the upper extreme. Most patients have elevated prothrombin times and partial thromboplastin times at some point during their illness. Disseminated intravascular coagulation may develop in patients with severe disease, but it is far less common in HPS than in HFRS.

Liver enzymes, including aspartate aminotransferase and alanine aminotransferase, tend to be increased but not dramatically so. Hypoalbuminemia is a common finding, but bilirubin and alkaline phosphatase typically are normal (Nolte et al., 1995). Serum lactate dehydrogenase (LDH) level is frequently increased with an electrophoretic pattern that indicates lung and liver injury (Hallin et al., 1996). Analysis of pleural fluid can demonstrate either transudative or exudative levels of protein and LDH (Bustamante et al., 1997). The findings likely depend on the degree of intravascular to extravascular fluid shift and the time during disease evolution at which the pleural fluid specimen is obtained.

Serum lactate levels help to establish the severity of the disease. An increased serum lactate level identifies patients in whom poor tissue perfusion is present, and who require immediate resuscitative efforts. In an early series all patients with a serum lactate level of 4.0 mmol/L or higher died in spite of aggressive treatment, with the exception of two patients who were treated with extracorporeal membrane oxygenation (ECMO) (Crowley et al., 1998; Hallin et al., 1996). Arterial blood gases demonstrate a decreased ratio of PaO_2 to FiO_2 in all cases, and frank hypoxemia is frequently present on initial presentation.

Radiographic Findings

Chest radiographic abnormalities are noted on admission in most patients, even when dyspnea is not present. The major findings are those of interstitial edema and include Kerley B lines, hilar indistinctness, and peribronchial cuffing (Ketai et al., 1994, 1998). Many patients progress to develop severe air space disease and progressive hypoxemia. Air space 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 the time of 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.

Diagnosis

Clinical Evaluation and Differential Diagnosis

Diagnosis of HPS is difficult early in the course of disease or in patients with mild disease. Certainly, a high degree of awareness must be maintained in areas of relatively high incidence, such as the Four Corners area, but it is equally important for physicians in other areas to be vigilant, because of the rapidly progressing nature of the illness (Duchin et al., 1994; Dull et al., 1994; Hallin et al, 1996). A history of rodent exposure may be helpful. Typically, the history may be one of cleaning a dusty closet or outbuilding and encountering significant amounts of mouse excreta or mice (Armstrong et al., 1995). Unfortunately, such a history is frequently absent. The minimum requirement for clinical diagnosis should include some elements of the prodrome, since all patients have had the prodrome, and either evidence of pulmonary edema or the typical hematological changes described above. Although thrombocytopenia and interstitial infiltrates on chest radiograph are often found at presentation, in several patients these elements have been absent for up to 2 days (chest radiograph) and 4 days (thrombocytopenia) after admission. The presence of a lobar infiltrate or of symptoms not included in the usual prodrome should prompt the physician to consider etiologies other than Sin nombre virus infection (Moolenaar et al., 1995). If the diagnosis of HPS is suspected after the history and physical examination, initial screening should include a complete blood count, including platelets; a peripheral smear examined for immature neutrophil precursors and immunoblasts; serum LDH, AST, and albumin levels; coagulation studies; a chest radiograph; and either an oxygen saturation or arterial blood gases (Dull et al., 1994).

A differential diagnosis for more severe disease is shown in Table 3. In the Four Corners area *Yersinia pestis* is endemic among rodent species, especially prairie dogs, and pneumonic plague must be considered in any patient with severe respiratory illness, especially in the summer months. Patients with pneumonic plague have disease that mimicks HPS and have been admitted for diagnosis and treatment of potential HPS (Whitten et al., 1997). Tularemia is also endemic in the western United States, including the Four Corners area, and needs to be considered in patients who present with rapidly progressive illness. Infection with *Legionella* species is so rare as to be reportable in the Four Corners area, but it must be considered in the differential diagnosis of severe respiratory illness in many areas of the United States. At this time virtually all of the infections listed in Table 2 are more common than HPS and severe, rapidly progressive respiratory illness in any individual patient is much more likely to be the result of infection with one of these agents than the result of infection with a hantavirus. However, the pan-American distribution of HPS makes it a legitimate consideration when the differential includes others listed diseases.

TABLE 3. Differential Diagnosis of Rapidly Progressive ARDS-Like Illness in the Febrile Patient

Bacterial	Viral
Plague	Influenza
Tularemia	Adenovirus
Anthrax	Parvovirus
Legionella	Coxsackie
Chlamydia	Respiratory syncytial virus
Mycoplasma	Hemorrhagic fevers
Brucella	
Q fever	
Rocky Mountain spotted fever	
Pneumococcus	
Meningococcus	

ARDS, adult respiratory distress syndrome.

Serologic Testing

The diagnosis of HPS is confirmed by identification of antibodies to Sin nombre virus antigens in serum or by detection of Sin nombre genetic material in blood mononuclear cell preparations via

RT-PCR (Hjelle et al., 1994d; Jenison et al., 1994). The diagnosis can also be confirmed at autopsy by RT-PCR analysis of infected tissues or by immunologic staining of these tissues for Sin nombre antigens (Feldmann et al., 1993; Schwarz et al., 1995). During the initial months of the Four Corners outbreak in 1993, RT-PCR assumed a crucial role in the rapid diagnosis of patients with suspected Sin nombre virus infection. However, this form of diagnosis is labor-intensive and therefore expensive. Additionally, false-positive results may result from minor contamination in the laboratory. PCR also lacks the ability to diagnose remote infection, because Sin nombre virus is cleared from the circulation within 2 to 4 weeks after the onset of clinical symptoms (Hjelle et al., 1994d). These drawbacks of PCR analysis limit its usefulness as a mainstay of diagnosis, so immunologic assays were developed very soon after the initial HPS outbreak.

A western blot assay was developed at UNM that is based on recombinant N and G proteins expressed in *E. coli* (Jenison et al., 1994). Patients who are acutely ill have both IgG and IgM antibodies to the viral nucleocapsid protein, as well as IgG antibody to the glycoprotein-1 (G1) protein of the Sin nombre virus. Most patients also have IgM antibody to the G1 protein. The enormous number of specimens tested at the CDC necessitates a simpler serologic test that is more suitable for large-scale screening, so the CDC principally uses enzyme immunoassay for serologic diagnosis. The ELISA uses recombinant Sin nombre nucleocapsid antigens in the solid phase to capture antibodies in patient serum. The most important limitation of the serologic tests is the delay before a result is obtained, owing to the need to send a specimen to UNM or to the CDC.

Not every clinical laboratory, especially in the rural locations where HPS tends to develop, has the equipment and expertise to perform Western blotting or to maintain reagents for an ELISA that would be used only rarely. To deal with this problem a recombinant immunoblot assay in the form of a test strip has been developed that is both accurate and speedy (Hjelle et al., 1997). Unfortunately, initial industry support for the test has waned, and it is not yet available for widespread use.

At present, one may obtain serologic testing in patients with an appropriate clinical syndrome through both the CDC and UNM. Since HPS is a reportable disease, all patients must eventually be tested by the CDC laboratories. The diagnosis of HPS is based on the presence of IgM antibodies in an acute-phase serum or a 4-fold rise in IgG titer from the acute phase to the convalescent. At the CDC specimens are batched and run on a weekly basis. At UNM specimens are assayed as needed and results are reported within 24 hours of receipt of the serum specimen. One may obtain testing from the CDC by contacting one's state health department. HPS testing at UNM is coordinated by the infectious diseases physician on call.

Treatment

Emergency Department and Pre-Intensive Care Unit

Because of the extreme severity of the illness, and because HPS progresses very rapidly, patients with suspected HPS should be transferred immediately to a facility with experience and expertise in managing severe shock (Hallin et al., 1996). Since HPS tends to be acquired in rural areas, air ambulance to a major center is frequently the best mode of transport. Intravenous access with large-bore catheters should be established prior to transfer. Crystalloid or colloid fluids should be administered to hypotensive patients. However, volume administration should be limited if signs of pulmonary edema develop. If pulmonary edema develops, an inotropic agent, such as dobutamine 5 to 20 μg/kg/min or dopamine 4 to 10 μg/kg/min, should be administered, even if a pulmonary artery catheter is not yet available. It is advisable to avoid agents with principally vasoconstrictor effects.

Because other infections that cause severe respiratory failure are more common than HPS, all patients with suspected HPS should be empirically treated with antibiotics to cover agents shown in Table 2. During the initial HPS outbreak in 1993, patients were treated with very broad-spectrum coverage that included erythromycin, an extended-spectrum penicillin or imipenem/cilastatin, and an aminoglycoside. In patients with severe disease that includes respiratory and/or circulatory failure, such a combination still has merits, in that the severity of

the illness dictates that all possible agents are well covered. In patients with early disease or with mild disease, antibiotics are directed to organisms causing atypical pneumonias (Moolenaar et al., 1995). Reasonable agents include intravenous macrolides or one of the newer, extended-spectrum fluoroquinolones. Appropriate specimens should be collected for the diagnosis of an atypical pneumonia. Such specimens should include sputum, if available, for direct immunofluorescence of appropriate agents and serum for measurement of appropriate antibodies and antigens.

Intensive Care Unit Management

HPS poses a dilemma for those who attempt to treat it. As patients develop a severe pulmonary capillary leak, they simultaneously develop myocardial insufficiency and shock that demands increased cardiac filling pressures. As pulmonary capillary pressures increase during volume administration, fluid pours indiscriminately into the alveolar space. This is a similar circumstance to that encountered when treating patients with ARDS, but the consequences are much more dramatic. The situation is best managed via a flow-directed pulmonary artery catheter, which should be placed at the first sign of pulmonary edema or decreasing PaO_2/FiO_2 in patients with suspected Sin nombre infection. Pulmonary artery occlusion pressures higher than 10 to 12 mm Hg lead to severe flooding of the alveolar space with edema fluid, and this knowledge must temper the desire to administer volume to a patient who may be hypotensive. Simultaneously with volume resuscitation, patients should be given an inotropic agent. Since nearly all patients who enter this shock phase of the illness demonstrate decreased cardiac output and increased systemic vascular resistance, dobutamine is the most logical choice for inotropic support.

Patients whose interstitial edema progresses to alveolar disease nearly always require mechanical ventilation (Hallin et al., 1996). For this reason one may consider early, elective intubation of patients whose oxygen requirements are not met by nasal cannula oxygen. As stated above, currently accepted modes of mechanical ventilation, with precautions against alveolar overdistension, repetitive alveolar collapse and reexpansion, and oxygen toxicity are effective in most patients. In a series of 30 patients cared for in New Mexico and in Kansas, only one failed to respond to mechanical ventilation according to these principles; that is, adequate, if not ideal, oxygenation and ventilation were achieved in all but one patient.

Salvage Therapy

Because of the combination of cardiogenic shock and pulmonary capillary leak, which seemed to resolve quickly in recovering patients, it was hypothesized that ECMO might be an appropriate therapy for some patients with HPS, since the modality could address both problems simultaneously (Crowley et al., 1998). Additionally, the rapid recovery of surviving patients led the investigators to believe that the duration of ECMO would be shorter than had been observed in patients with ARDS, and that the risk of nosocomial sepsis would for that reason be reduced. The ECMO protocol was initially designed to treat patients with serum lactate levels greater than 4 mmol/L or a cardiac index less than 2.0 $L/min/m^2$ (normal value, 2.5–3.5 $L/min/m^2$) while on full inotropic support, because, at the time, all such patients had died.

Two patients who met these criteria were treated. The first patient, who was suffering pulseless electrical activity at the time of ECMO institution, died. The second patient, whose cardiac index was 0.8 $L/min/m^2$ at the time of ECMO institution, survived. A third patient, who could not be adequately oxygenated or ventilated using standard mechanical ventilation, also survived. Both survivors required ECMO treatment for less than 96 hours. ECMO appears to be a viable mode of salvage therapy for certain critically ill HPS patients who would otherwise die. One patient with severe HPS has also been successfully treated with inhaled nitric oxide (Rosenberg et al., 1998). The rationale for its use is quite similar to the rationale for ECMO. Both of these intensive therapeutic measures require transport of the HPS patient to a tertiary-level center.

Isolation Precautions

A final issue in the therapy of HPS is the potential for nosocomial transmission to other pa-

tients or to healthcare workers. There is no evidence that Sin nombre infection can be spread person to person; all cases in North America can be adequately explained by rodent exposure. A study of nosocomial transmission during the 1993 Four Corners outbreak involved 266 health care workers with varying degrees of exposure to HPS patients or to their blood and body secretions (Vitek et al., 1996; Wells et al., 1997b). No serologic evidence of infection by Sin nombre virus was found in any of the healthcare workers. Until late in 1996 there was no evidence for human-to-human transmission of any hantavirus. However, during the Patagonian outbreak in October and November 1996, such transmission appears to have occurred. Traditional epidemiological techniques suggest that some patients in this outbreak, including at least three physicians and one nurse, had no rodent exposure and contracted the illness from exposure to other patients (Enria et al., 1996; Wells et al., 1997a). Some of these exposures may have been blood-borne, but others appear to have been respiratory in nature.

The possibility of respiratory transmission from human to human potentially could be refuted by molecular epidemiological techniques. In this approach viral specimens could be obtained from each infected patient and the RNA sequences from each patient's virus would be determined. While the sequences of all viruses within a species are largely identical, viruses from geographic locations separated by more than 100 meters should have minor base substitutions (substitutions that have minimal, if any, effect on protein structure) that distinguish them from one another (Hjelle et al., 1996b). For any pair of patients in whom viral sequences differ, person-to-person transmission has not occurred. If the viral sequences are identical between two patients, human-to-human transmission is not confirmed, but such transmission is likely if classical epidemiology fails to reveal a potential common exposure. Viral sequences obtained from patients during the Patagonian outbreak of 1996 in fact demonstrate identical sequences in both the M segment and noncoding regions of the S segment in 16 patients who were linked by classical epidemiology (Padula et al., 1998). Some of these HPS patients had no potential exposure to the virus other than caring for other hospitalized HPS patients.

It is difficult to say what effect the information from Argentina should have on the isolation of HPS patients in North America. The epidemiological evidence argues against a requirement for respiratory isolation, although universal precautions clearly are prudent. At UNM, where the largest series of patients has been treated, patients with suspected HPS are placed in respiratory isolation only because *Yersinia pestis* is endemic in the area and the pneumonic form of plague can appear similar in many ways to HPS. Routinely, only universal precautions are used, once HPS is confirmed. Personal communications with physicians and health officials in Argentina suggest that universal precautions may not be adequate to prevent nosocomial transmission of the responsible hantavirus. In South America it appears prudent to use respiratory isolation unless further epidemiological studies rule out the possibility of human-to-human transmission.

Summary

The number of known HPS cases in the United States is now >200, and the illness has occurred in all geographic areas of the country. Though the incidence of the disease is low, the mortality rate remains at 50%, owing to the difficulty in treating a simultaneous severe pulmonary capillary leak syndrome and cardiogenic shock. Adequate treatment of severe cases requires experienced critical care physicians and nurses, as well as advanced facilities. Although nosocomial transmission appears unlikely in North America, universal precautions must be used and some consideration may be given to the use of respiratory isolation.

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