Hantavirus Pulmonary Syndrome: A Zebra Worth Knowing

KRISTIN L. GRAZIANO, D.O., Tuba City Indian Medical Center, Navajo Area Indian Health Service, Tuba City, Arizona
BRUCE TEMPEST, M.D., Gallup Indian Medical Center, Navajo Area Indian Health Service, Gallup, New Mexico

Hantavirus pulmonary syndrome (HPS) is a severe cardiopulmonary illness most often caused by the Sin Nombre virus, which is transmitted to humans by inhalation of aerosolized particles of rodent excreta or direct rodent contact. Although HPS is more common in the western United States, cases have been identified in 31 states. The illness begins as a nonspecific febrile prodrome, sharing many of its initial symptoms with other more common viral infections. Patients then quickly develop noncardiogenic pulmonary edema, respiratory failure, and shock. Characteristic laboratory findings include thrombocytopenia, a left-shifted leukocytosis, hemoconcentration, and presence of immunoblasts. The overall case fatality rate of HPS is approximately 40 percent. Diagnosis is confirmed by serologic identification of IgM and IgG antibodies to Sin Nombre virus. There is no specific therapy, but early recognition of HPS during the prodromal phase can expedite initiating cardiopulmonary support in an intensive care unit, which is associated with improved survival rates. Prevention of HPS involves avoiding contact with rodents and rodent habitats. (Am Fam Physician 2002; 66:1015-20. Copyright© 2002 American Academy of Family Physicians.)

Hantavirus pulmonary syndrome (HPS) was first recognized during the spring of 1993 after a cluster of young, previously healthy individuals who lived in the southwestern United States acquired an acute, fatal cardiopulmonary illness. The early nonspecific symptoms of these patients uniformly resembled those of other more frequently seen benign viral infections, so the severity of these infections was not initially suspected. However, the febrile prodrome was followed by rapid, diffuse, noncardiogenic pulmonary edema and hemodynamic compromise resulting in an initial case fatality rate of 76 percent.[1]

The etiologic agent was subsequently determined to be a previously unrecognized hantavirus, Sin Nombre virus (SNV), and is now known to be the predominant cause of HPS in the United States.[2] Currently, at least eight species of hantavirus are known to cause HPS in the Western Hemisphere, four of which are found in the United States. Each different virus is associated with a single rodent host species; the reservoir for SNV is the deer mouse *(Per-omyscus maniculatus),* one of the most common small mammals in the United States.[3] Additionally, the cotton rat and rice rat are the rodent vectors in the southeastern United States for the Black Creek Canal and Bayou viruses, respectively; the whitefooted mouse carries the New York virus in the northeast.

Before 1993, illness caused by hantaviral infection had never been documented in the Americas. In Europe and Asia, infection with hantaviruses was known to cause hemorrhagic fever with renal syndrome (HFRS), an entity clinically distinct from HPS. HFRS lacks the severe pulmonary involvement characteristic of HPS and instead exhibits coagulopathies and renal manifestations not usually seen in HPS.

Since the initial outbreak in the United States, there have been more than 280 confirmed cases of HPS, representing approximately 30 cases per year. Contrary to common opinion, HPS is not limited to the southwestern United States and has been reported in 31 states *(Figure 1),*[4] as well as in Canada and South America. This expanding geographic distribution is largely because of increased

Total Cases (N=289 in 31 States)

23
16
7
2
1
1
5
16
2
6
2
3
2
1
1
5
1
RI
12
17
25
14
1
2
1
1
33
1
1
2
1
32
41
1
14
1
1

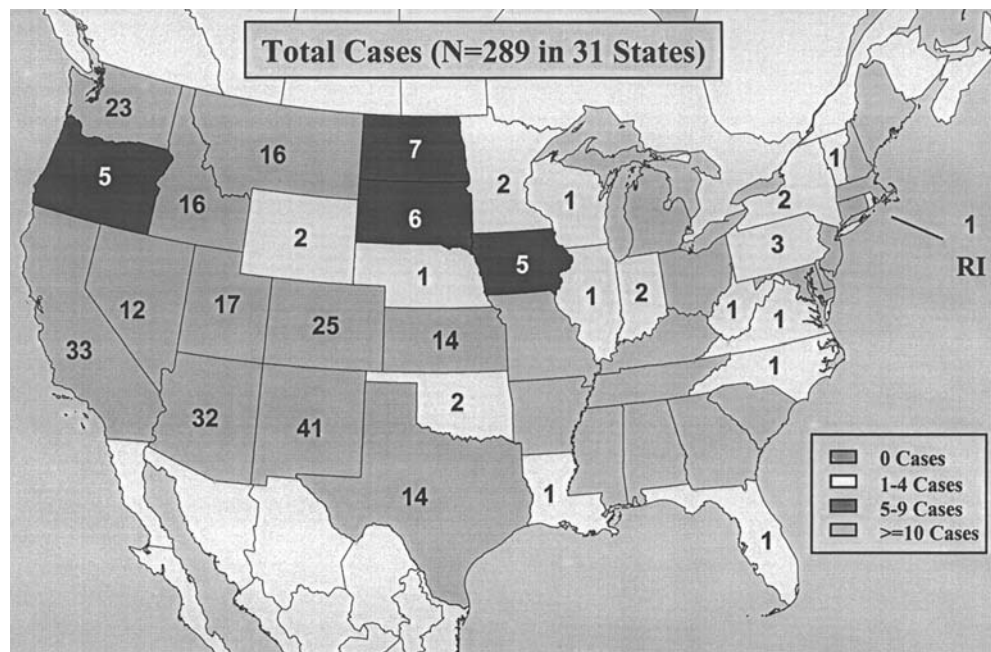| | 0 Cases |
	1-4 Cases
	5-9 Cases
	>=10 Cases

FIGURE 1. Geographic distribution of hantavirus pulmonary syndrome cases in the United States.

Information from Centers for Disease Control and Prevention. Retrieved March 2002, from: www.cdc.gov/ncidod/diseases/hanta/hps/noframes/casemap.htm.

recognition of HPS. Fortunately, HPS remains a rare syndrome. However, because of its mild nonspecific prodrome and fulminant course, family physicians need to be aware of the epidemiology, clinical implications, clues to early diagnosis, and strategies for prevention of HPS.

Epidemiology

The Centers for Disease Control and Prevention (CDC) tracks the latest counts and descriptive statistics of HPS in the United States. CDC data indicate that the infection predominantly affects people in rural areas, is most common in the spring and summer, and carries an overall case fatality rate close to 40 percent. The age range of confirmed case patients is 10 to 75 years, and the mean age is 37 years.[4] HPS is infrequently observed in children.

HPS is not a disease of any one racial group. Whites currently account for the majority of cases, about 77 percent. Native Americans account for about 20 percent, blacks 2 percent, and Asians 1 percent.[4] When considering ethnicity, about 11 percent of HPS cases have been reported among Hispanics.

Although initially regarded as a new infection, an early case of retrospectively identified SNV infection dates back to July 1959.[5] Additionally, reports from Native Americans living in the Southwest suggest similar episodes of illness have occurred for several decades.

VIRAL TRANSMISSION

SNV is transmitted to humans predominantly by inhalation of aerosolized viral particles from rodent excreta or saliva. Other potential mechanisms include direct contact with infected rodents and rodent bites, although these appear to be rare.

Person-to-person transmission of SNV has never been documented in the United States, and nosocomial infection has not occurred.[6,7] However, investigation of an HPS outbreak in Argentina caused by a different hantavirus, the Andes virus, found epidemiologic evidence supporting person-to-person transmission involving health care workers.[8]

RISK FACTORS

Human illness most often results from exposure to infected rodent excreta. In an early case control study,[9] peridomestic cleaning, agricultural activities, and an increased number of rodents in or around households were shown to be associated with HPS. Enter-

ing buildings that are rarely opened or only seasonally opened may also result in exposure to mice and their excretions, contributing to infection. Local increases in precipitation are associated with HPS, presumably by triggering an increase in the rodent population.[10]

Occupationally related HPS appears to be uncommon, and travel to areas where hantavirus illness has been reported is not a risk factor for contracting the disease. The possibility of exposure during recreational activities is small and can be further reduced by limiting contact with rodents.

Clinical Manifestations

It is helpful to think of HPS as having two distinct phases. The first is a prodromal phase characterized by a relatively mild febrile illness, typically lasting three to five days. The second phase, referred to as the cardiopulmonary phase, is manifested by severe, rapidly progressive respiratory failure. Invariably, the transition from mild illness to life-threatening cardiopulmonary compromise is abrupt and dramatic.

PRODROMAL PHASE

Patients in the prodromal phase present with fever and myalgia, making prodromal HPS difficult to distinguish from other more common viral infections. Other early symptoms include gastrointestinal disturbances, headache, chills, and malaise.[4] Physical findings on initial presentation include fever, tachypnea, and tachycardia, but the remainder of the examination is usually normal.

CARDIOPULMONARY PHASE

The cardiopulmonary phase is heralded by the acute onset of pulmonary edema. Increased pulmonary capillary permeability is central to this process and may be caused by endothelial damage in the lung microvasculature.[11] The patient becomes increasingly tachypneic, develops a cough productive of copious, nonpurulent secretions, and progressive hypoxia ensues. Progression of respiratory

The cardiopulmonary phase of hantavirus pulmonary syndrome is manifested by severe, rapidly progressive respiratory failure.

distress is so rapid that patients usually require mechanical ventilation within 24 hours.

In severe cases, significant myocardial depression also occurs, resulting in low cardiac output and hypotension. The HPS-related hypotension has a distinctive hemodynamic profile characterized by a low cardiac index and high peripheral vascular resistance, the opposite of which is seen in septic shock caused by other pathogens.[11] Mortality is related to worsening cardiac depression, progressive respiratory failure, and subsequent acidosis culminating in fatal arrhythmias.

In patients who survive, the recovery occurs almost as quickly as the decompensation. After several days of supportive care, the cardiopulmonary processes quickly resolve, and most patients are discharged within one week of hospitalization. However, most survivors exhibit a modest degree of small airways obstruction even one year after recovery.

ATYPICAL PRESENTATIONS

Early studies indicated that essentially all patients infected with SNV went through the prodromal and cardiopulmonary phases. Recently, there have been confirmed cases of SNV infection in which patients had typical prodromal symptoms but never developed cardiopulmonary involvement.[12] These reports suggest that SNV causes a wider spectrum of disease than previously thought.

Diagnosis

HPS should be considered when patients present with fever and myalgia, especially if they have any of the aforementioned risk factors for exposure to SNV, or have recently encountered areas likely to be contaminated with rodent excretions. A lack of such history,

however, does not eliminate HPS from the differential diagnosis.

Rash, rhinorrhea, pharyngitis, and conjunctivitis are rare in HPS and thus, argue against SNV infection.[13] It is important to note that rash and conjunctivitis are often seen in patients with HPS in South America. If HPS is being considered, a complete blood count (CBC) and chest radiograph should be obtained. Local health departments should be contacted for all suspected cases of HPS.

LABORATORY FINDINGS

Complete Blood Count. Progressive thrombocytopenia is one of the most consistent laboratory findings in HPS, occurring in virtually all patients, and it is frequently present during the prodromal phase. Thrombocytopenia has been shown to be highly discriminatory between patients with HPS and those with other febrile illnesses.[14]

Other important hematologic abnormalities include a left-shifted leukocytosis, presence of immunoblasts, and hemoconcentration. This tetrad (thrombocytopenia, left shift, circulating immunoblasts, and hemoconcentration) is seldom seen in other viral infections. If HPS is suspected and the initial CBC is normal, it should be repeated in eight to 12 hours.

Other Laboratory Findings. Modest impairments of the coagulation profile are seen, but overt disseminated intravascular coagulation is rare. Hypoalbuminemia and lactic acidosis occur late and indicate severe disease. Although it was not reported in the 1993 outbreak, renal impairment can be a component of HPS. Abnormalities of kidney function have been predominant in disease caused by Black Creek Canal and Bayou viruses.[15]

Serologic Diagnosis. The diagnosis is confirmed by serologic identification of IgM and IgG antibodies to SNV. Assays are available at most state public health laboratories and at the CDC.

RADIOLOGIC FINDINGS

HPS has a characteristic radiologic evolution *(Figure 2)*. Initial radiographs are most often normal, but approximately one third will exhibit mild interstitial changes. Heart size is normal, and there are no findings of pulmonary vasculature engorgement. Within 48 hours, basilar or central alveolar flooding occurs and pleural effusions are often seen. These findings differ from those seen in adult respiratory distress syndrome (ARDS), which has a more peripheral distribution and lacks the early prominent interstitial edema.[16,17] A lobar infiltrate is more consistent with bacterial pneumonia.

DIFFERENTIAL DIAGNOSIS

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

Treatment

The probability of survival increases with early recognition and aggressive cardiopulmonary support.[18] A high index of suspicion

The Authors

KRISTIN L. GRAZIANO, D.O., is a family physician on the Navajo Reservation in Tuba City, Ariz. She graduated from the College of Osteopathic Medicine of the Pacific, Pomona, Calif, and she completed a family practice residency at Community Hospital Santa Rosa, a University of California-San Francisco School of Medicine affiliate. Dr. Graziano recently completed a faculty development fellowship through the Department of Family and Community Medicine, University of Arizona College of Medicine, Tucson.

BRUCE TEMPEST, M.D., is a retired commissioned officer in the U.S. Public Health Service. Formerly, he was the chief of internal medicine at the Gallup Indian Medical Center, Gallup, N.M., and the senior clinician in internal medicine for the Indian Health Service. Dr. Tempest received his medical degree from the University of Pennsylvania School of Medicine, Philadelphia, and completed his residency in internal medicine at Philadelphia General Hospital.

Address correspondence to Kristin L. Graziano, D.O., Tuba City Indian Medical Center, Navajo Area Indian Health Service, P.O. Box 600, Tuba City, AZ 86045 (e-mail: docgratz@yahoo.com). Reprints are not available from the authors.
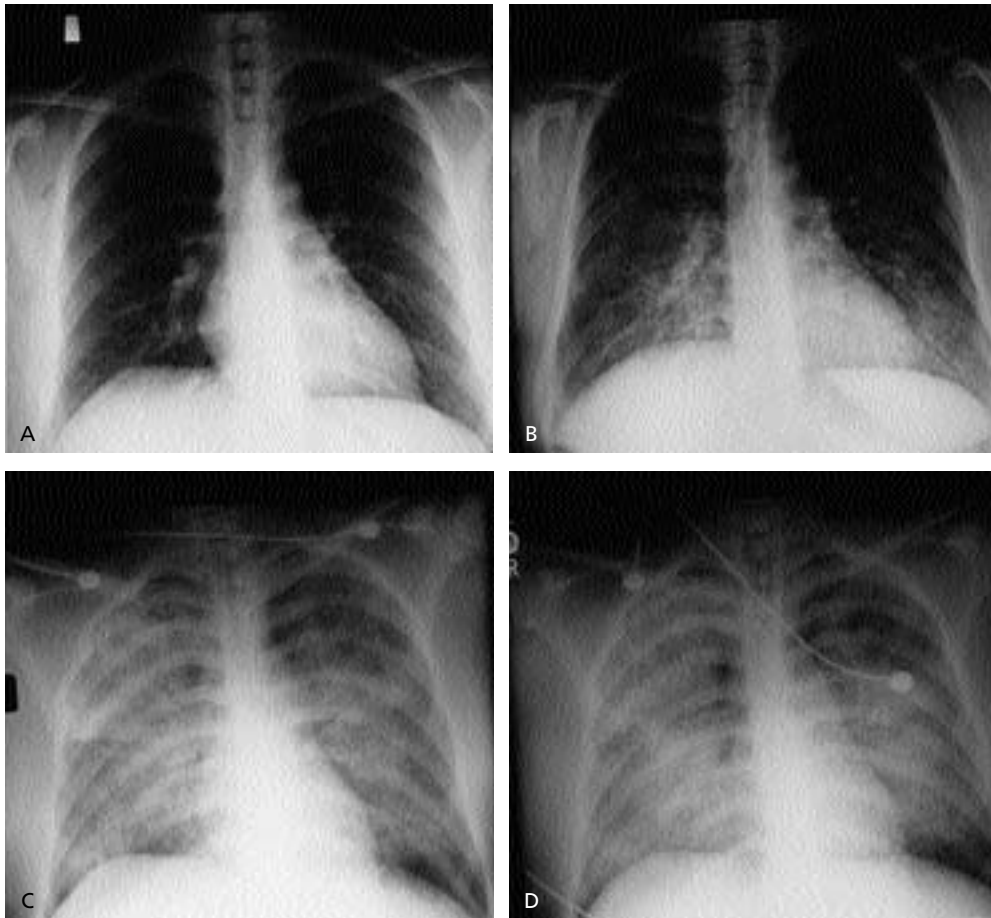
FIGURE 2. Radiographs showing the evolution of hantavirus pulmonary syndrome in a 30-year-old woman. (A) Chest radiograph before onset of illness. (B) Admission radiograph. (C) Radiograph after intubation. (D) Radiograph just before death.

and an awareness of the early manifestations of hantavirus infection are essential to expedite rapid transfer to an intensive care unit. Currently, there is no specific therapy available to treat HPS, therefore the cornerstone of treatment remains supportive measures. Supplemental oxygen, mechanical ventilation when indicated, fluid management, and the appropriate use of pressors are crucial to patient care. Hemodynamic monitoring with a pulmonary artery (Swan-Ganz) catheter will facilitate fluid and pressor management and can aid in establishing a preliminary diagnosis by documenting the characteristic HPS hemodynamic profile. While awaiting serologic confirmation, broad-spectrum antibiotics should be initiated.

Two potential treatments are under investigation. One is the use of extracorporeal membrane oxygenation, which exhibited favorable results in a small study of patients with severe HPS.[19] The second is the antiviral agent riba-virin (Virazole), which is currently being evaluated in a placebo-controlled clinical trial. An earlier open-label trial[20] of ribavirin failed to demonstrate a significant improvement in outcome in patients with HPS. However, this study's design makes it difficult to assess the efficacy of ribavirin.

Prevention

Preventive strategies play a critical role in attempting to limit this lethal disease. The most effective way to decrease risk of HPS is to diminish human exposure to infected rodents; limiting peridomestic exposure is especially important. Measures to prevent HPS include

The tetrad of thrombocytopenia, left-shifted leukocytosis, circulating immunoblasts, and hemoconcentration is seldom seen in viral infections other than hantavirus pulmonary syndrome.

eliminating rodents in and around households by keeping areas clean; rodent-proofing dwellings; controlling rodent populations through traps and rodenticides; properly cleaning areas of infestation; and avoiding rodents in outdoor settings.

Final Comment

Our current knowledge of HPS is in its infancy. We know relatively little about disease spectrum, pathogenesis, and potential therapeutic interventions. As the story continues to unfold, the CDC and state health departments remain excellent resources for new information.

REFERENCES

1. Duchin JS, Koster FT, Peters CJ, Simpson GL, Tempest B, Zaki SR, et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. N Engl J Med 1994; 330:949-55.
2. Nichol ST, Spiropoulou CF, Morzunov S, Rollin PE, Ksiazek TG, Feldmann H, et al. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 1993;262:914-7.
3. Childs JE, Ksiazek TG, Spiropoulou CF, Krebs JW, Morzunov S, Maupin GO, 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 1994;169:1271-80.
4. National Center of Infectious Diseases, Special Pathogens Branch. All about hantavirus. Retrieved May 2002, from: www.cdc.gov/ncidod/diseases/hanta/hps/noframes/caseinfo.htm.
5. Frampton JW, Lanser S, Nichols CR. Sin Nombre virus infection in 1959 [Letter]. Lancet 1995; 346:781-2.
6. Wells RM, Young J, Williams RJ, Armstrong LR, Busico K, Khan AS, et al. Hantavirus transmission in the United States. Emerg Infect Dis 1997;3:361-5.
7. Vitek CR, Breiman RF, Ksiazek TG, Rollin PE, McLaughlin JC, Umland ET, et al. Evidence against person-to-person transmission of hantavirus to health care workers. Clin Infect Dis 1996;22:824-6.
8. Wells RM, Sosa Estani S, Yadon ZE, Enria D, Padula P, Pini N, et al. An unusual hantavirus outbreak in southern Argentina: person-to-person transmission? Emerg Infect Dis 1997;3:171-4.
9. Zeitz PS, Butler JC, Cheek JE, Samuel MC, Childs JE, Shands LA, et al. A case-control study of hantavirus pulmonary syndrome during an outbreak in the southwestern United States. J Infect Dis 1995;171:864-70.
10. Hjelle B, Glass GE. Outbreak of hantavirus infection in the Four Corners region of the United States in the wake of the 1997-1998 El Niño-southern oscillation. J Infect Dis 2000;181:1569-73.
11. Hallin GW, Simpson SQ, Crowell RE, James DS, Koster FT, Mertz GJ, et al. Cardiopulmonary manifestations of hantavirus pulmonary syndrome. Crit Care Med 1996;24:252-8.
12. Kitsutani PT, Denton RW, Fritz CL, Murray RA, Todd RL, Pape WJ, et al. Acute Sin Nombre hantavirus infection without pulmonary syndrome, United States. Emerg Infect Dis 1999;5:701-5.
13. Moolenaar RL, Dalton C, Lipman HB, Umland ET, Gallaher M, Duchin JS, et al. Clinical features that differentiate hantavirus pulmonary syndrome from three other acute respiratory illnesses. Clin Infect Dis 1995;21:643-9.
14. Simonsen L, Dalton MJ, Breiman RF, Hennessy T, Umland ET, Sewell CM, et al. Evaluation of the magnitude of the 1993 hantavirus outbreak in the southwestern United States. J Infect Dis 1995; 172:729-33.
15. Centers for Disease Control and Prevention. Hantavirus pulmonary syndrome—Vermont, 2000. MMWR Morb Mortal Wkly Rep 2001;50:603-5.
16. Ketai LH, Williamson MR, Telepak RJ, Levy H, Koster FT, Nolte KB, et al. Hantavirus pulmonary syndrome: radiographic findings in 16 patients. Radiology 1994;191:665-8.
17. Ketai LH, Kelsey CA, Jordan K, Levin DL, Sullivan LM, Williamson MR, et al. Distinguishing hantavirus pulmonary syndrome from acute respiratory distress syndrome by chest radiography: are there different radiographic manifestations of increased alveolar permeability? J Thorac Imaging 1998;13:172-7.
18. Centers for Disease Control and Prevention. Hantavirus pulmonary syndrome—Colorado and New Mexico, 1998. MMWR Morb Mortal Wkly Rep 1998;47:449-52.
19. Crowley MR, Katz RW, Kessler R, Simpson SQ, Levy H, Hallin GW, et al. Successful treatment of adults with severe Hantavirus pulmonary syndrome with extracorporeal membrane oxygenation. Crit Care Med 1998;26:409-14.
20. Chapman LE, Mertz GJ, Peters CJ, Jolson HM, Khan AS, Ksiazek TG, et al. Intravenous ribavirin for hantavirus pulmonary syndrome: safety and tolerance during 1 year of open-label experience. Antivir Ther 1999;4:211-9.