HANTAVIRUS INFECTIONS IN THE UNITED STATES: DIAGNOSIS AND TREATMENT

Gregory Mertz, Louisa Chapman

In volume three of *Antiviral Chemotherapy: New Directions for Clinical Application and Research*, Dr. Karl Johnson described the spectrum and mechanism of action, pharmacokinetics, and toxicity of ribavirin. Clinical data supporting the use of intravenous ribavirin for several forms of viral hemorrhagic fever, including Lassa fever and hemorrhagic fever with renal syndrome (HFRS), are presented in detail elsewhere and will not be repeated in this chapter.

The etiologic agent of Lassa fever is an arenavirus (family *Arenaviridae*, genus *Arenavirus*), Lassa fever virus. HFRS results from infection caused by at least four recognized hantaviruses (family *Bunyaviridae*, genus *Hantavirus*). Both Lassa fever virus and hantaviruses are maintained in nature through chronic infections in rodent reservoir hosts. Although differing markedly in pathophysiology and clinical presentation, severe human cases of Lassa fever or HFRS share the common features of increased capillary permeability, hypovolemic shock and hemorrhagic manifestations.

In May 1993, Dr. Bruce Tempest, an Indian Health Service (IHS) physician in Gallup, New Mexico and Richard Malone and Dr. Patricia McFeeley at the New Mexico Office of Medical Investigator (OMI) noted a cluster of unexplained deaths in previously healthy, young adults from rural region of the Four Corners region of New Mexico and Arizona. After a febrile prodrome, patients rapidly developed shortness of breath and non-cardiogenic pulmonary edema. Those with the most severe form of the disease had lactic acidosis, shock and cardiac arrhythmias and died.

A working group, which included representatives from the IHS, OMI, New Mexico State Health Department, University of New Mexico (UNM), and Navajo Division of Health, met and defined the clinical syndrome and pathology and excluded most known causes for the syndrome. In late May, the Centers for Disease Control and Prevention (CDC) was invited to assist in the investigation, and a field team traveled to the Southwest. In early June, Dr. Thomas Ksiazek and other investigators in the Special Pathogens Branch (SPB) at CDC found antibodies in patients' sera in patterns suggesting cross-reactivity (but not identity) with previously known hantaviruses. Other investigators at SPB identified a new hantavirus by genetic studies of autopsy tissue, using reverse transcription-polymerase chain reaction (RT-PCR).

Intravenous ribavirin was made available from June 1993 to September 1994 under an open CDC protocol for treatment of individual patients with suspected hantavirus pulmonary syndrome (HPS). A controlled trial of ribavirin, sponsored by the National Institute of Allergy
and Infectious Diseases (NIAID) - Collaborative Antiviral Study Group (CASG), will begin in 1995. This chapter will describe the etiologic agents, epidemiology, pathology, clinical course and management of hantavirus infection in the United States.

HANTAVIRUSES AND THEIR RODENT RESERVOIRS

Nucleotide sequence analysis of viral genetic material amplified from autopsy tissue by RT-PCR indicated that the agent causing the New Mexico outbreak was a previously unrecognized hantavirus.\(^7\)\(^11\) It is more closely related to the previously described New World hantavirus, Prospect Hill virus, and to Puumala virus than to Hantaan virus and Seoul virus (Figure 1). More recently, the agent has been isolated in cell culture.\(^12\)\(^13\) The agent has been described in the literature under several names, including Four Corners virus, Muerto Canyon virus, Sin Nombre virus and HPS-associated hantavirus; the formal name will be decided by the International Committee on the Toxomany of Viruses.

Figure 1. Parsimony tree analysis comparing HARDS-related virus G2 sequences (alleles FCV-3H226 and FCV-MHAR) with other hantavirus sequences. FCV: Four Corners Virus. PHV: Prospect Hill Virus. HV: Haatan Virus. Insert shows a simplified tree analysis for Haatan virus, Seoul virus, Puumala virus, Prospect Hill virus and Four Corners virus. From Reference 9, with permission.

As hantaviruses all have a rodent reservoir, rodents living around the homes of patients were trapped, speciated and studied for hantavirus infection. The predominant rodent species trapped near patients' homes and work areas was the deer mouse, *Peromyscus maniculatus*. Hantavirus antibodies were detected in *P. maniculatus* and related species. Nucleotide sequence analysis of RT-PCR-amplified viral genetic material from patients and from *P. maniculatus* showed that nucleotide sequences were highly related, indicating that the deer mouse is the primary rodent reservoir.\(^14\) More recently, several other hantaviruses have been identified, in part through investigation of hantavirus cases occurring outside the range of the deer mouse.

Mapping of nucleotide sequences from a man who died in Louisiana revealed another related hantavirus, but no rodent reservoir for this virus has been identified\(^15\). In October 1993, a man in Florida contracted an illness similar to HPS, and hantavirus IgG and IgM antibodies were detected in an acute-phase serum sample. No *Peromyscus sp.* were trapped near his home but a third hantavirus, now tentatively named Black Creek Canal virus, was detected in cotton rats, *Sigmodon hirsutus*, trapped at the site.\(^16\) The range of the *P.*