

## Hantavirus Infections – Ken Brandt, August 2000

Until the summer of 1993, hantaviruses were known to be a significant cause of disease (and death) in several parts of the world, notably in China, Korea, Russia, and Scandinavia. But while evidence was accumulating that these viruses were much more widespread than originally believed, it was not until the outbreak of pulmonary disease (now called hantavirus pulmonary syndrome) in the Four Corners (New Mexico/Arizona/Utah/Colorado) region was confirmed to be caused by hantaviruses that their present notoriety developed.

Hantavirus is a genus within the family Bunyaviridae and differs from the other four genera in that family in not being transmitted by an insect vector – Bunyaviruses (e.g. La Crosse) are transmitted by mosquitoes, Nairoviruses (e.g. Crimean, Congo haemorrhagic fever) by ticks, Phleboviruses (e.g. Sandfly Fever) by phlebotomine flies and Tospoviruses (e.g. tomato spotted wilt) by thrips. Despite this biological difference, the five genera are very similar in terms of morphology, morphogenesis, genome structure and replication strategy. (1)

Hantaviruses are small (95-110 nm) lipid-enveloped, trisegmented, single-stranded RNA viruses with, it is presumed, a helical nucleocapsid. They differ from most other negative strand viruses in not possessing a matrix protein. The virus replicates in the host cell cytoplasm and is assembled and released by budding into the Golgi apparatus. Primary culture of hantavirus is difficult. It not only requires category 3 containment facilities but also repeated blind passage for up to 3 months. Hantaviruses are therefore usually diagnosed either using a rapid assay (e.g. ELISA or IFA) for IgM and IgG or through RT PCR on blood or tissues. Since IgM is present very early during the course of infections, it is useful in diagnosing acute disease. Use of PCR allows a detailed analysis of the strain type, as well as permitting retrospective assessments of fixed tissues. (2)

Hantavirus infections are zoonoses spread from small rodents. Various rodent populations are persistently and inapparently infected with their own hantavirus, some of which are pathogenic for man. Hantaviruses are classified into serotype and subtypes based upon rodent host, disease produced in man, nucleocapsid protein and membrane glycoprotein antigens, and relatedness of genomic RNA sequences. Most human infections occur in Northern and Eastern Europe, the Far East and South-western USA, but serosurveys have detected evidence of infection in rodents throughout the world. (3) (In Saskatchewan there is a very low incidence of hantavirus disease in mice as <1% of the mice tested were positive).

There are currently two main categories of disease attributable to hantaviruses: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). The former appears to be prevalent in the “Old World”, while HPS seems to be confined to the Americas, at least for the present.

The most severe form of HFRS occurs in Korea, China, Japan and Eastern Russia (Hantaan virus) or the Balkans (Belgrade, Pirogova and Fojnica virus). It evolves through five distinct phases. After an incubation period of 2-3 weeks, the clinical illness begins suddenly with influenza-like symptoms, petechiae and conjunctival haemorrhage. After 3-7 days, the hypotensive phase begins with tachycardia, vomiting, shock and further haemorrhagic signs.

This lasts from 2 hours to 3 days and is accompanied by leucocytosis and thrombocytopenia. The oliguric (or anuric) phase, which lasts 3-7 days, is accompanied by hypotension and severe haemorrhage (epistaxis; gastrointestinal, genitourinary and cerebral bleeding). The diuretic phase lasts from days to weeks, during which the patient may excrete 3-6 litres of urine per day. The convalescent phase may last months as the patient gradually returns to full health. Most deaths occur during the oliguric phase but the high mortality (10 – 15%) seen during the Korean War has fallen to 5% with appropriate management. The Balkan form is very similar but may also have pneumonic complications.

Infection with Seoul virus is usually intermediate in severity. Liver impairment and damage occurs more frequently but the mortality is low (1%). There is an association between hantavirus seropositivity and patients who present with proteinuria and end-stage renal failure.

The mildest form of HFRS in northern Europe is often termed nephropathia epidemica and is due Puumala virus. It presents after an incubation period of 1 – 8 weeks with an abrupt onset of chills and fever. Renal flank pain and polyuria. About one-third of patients have haemorrhagic manifestations (epistaxis, macroscopic haematuria) but symptoms are mild with spontaneous recovery in most cases. Subclinical infection is common with one symptomatic infection to every 14 – 20 cases of subclinical infection. Mortality is <1% but a small proportion of patients may have persistent renal impairment. (2)

Hantavirus pulmonary syndrome (HPS) is considered the “fatal” form of hantavirus disease. In the USA, as of May 28, 1999, CDC had confirmed 217 cases with a case-fatality ratio of 43%. In Canada, LCDC reports 32 cases as of July 26, 1999 and 12 deaths (a case-fatality ratio of 37.5%). In Saskatchewan there have been 5 cases with 1 reported death.

Like HFRS, HPS begins with a rather non-specific prodromal phase that generally lasts for 3-6 days and involves fever, malaise, myalgia, and headaches. This progresses to a cardiopulmonary phase, with shortness of breath, dyspnea, and cough. There are no haemorrhagic signs with HPS nor is there renal failure, although some renal involvement has been seen in some patients. In many cases, death occurs in a few days, with pulmonary edema and respiratory failure. However, unlike HFRS, recovery can be rapid.

People become infected when they stray into habitat of the reservoir host or when the host move to areas of human habitation. In many cases the incidence of human infection is related to fluctuations in the reservoir host population. The 1993 Four Corners HPS outbreak appears to be the result of unusual natural circumstances, in that high rain and snowfall increased the food source for the deer mouse (*Peromyscus maniculatus*), the hantavirus reservoir host. This in turn increased the mouse population and the level of human exposure. How often this type of circumstance has occurred, or may occur in the future, is presently unknown. Man usually becomes infected by inhalation of dust contaminated by the saliva or excretions of infected rodents. It may also be possible that humans are infected after the direct contact with broken skin or eye membranes; by eating or drinking contaminated food or water; and by being bitten by an infected rodent. There is no evidence that the virus can be spread from arthropods (such as insects and ticks), cats, dogs, or infected people.

Avoidance of contact with rodents is the foundation of prevention recommendations. Attempts at controlling the rodent population on a broad scale for prevention of other zoonotic diseases have not been successful, but specific steps can be taken to reduce rodent infestation in areas where people live and work. Rodent control in and around the home can be achieved by the use of traps designed to kill rodents, use of rodenticides, and modification of rodents' habitats. In certain areas the reservoir host species may also be infected with *Yersinia pestis*, the etiologic agent of plague; therefore, rodent trapping and use of rodenticides should be preceded by the use of an insecticide to control fleas and thus reduce the risk of transmission of plague. Rodent food sources can be eliminated from households by placing food (including pet foods) and garbage in rodent-proof containers with tight-fitting lids. Potential shelter for rodent nests, such as wood-piles and dense shrubbery, should be located at least 100 feet from human dwellings, and abandoned vehicles, old tires, and other discarded items should be hauled away. Rodent entry into homes can be discouraged by covering all openings into the house that have a diameter of at least ¼ inch with a steel wool or cement, placing metal flashing around the base of wooden, earthen, or adobe dwellings, and spreading 3 – 4 inches of gravel under the base of homes. (3)  
(4)

During the routine care of patients with HPS and when handling serum and tissue from potentially infected patients, hospital and laboratory staff should use universal precautions; however, the use of a biologic safety cabinet or respiratory-protection equipment is prudent when splashes or generation of aerosol is likely to occur. HPS viruses adapted to cell culture should be manipulated at biosafety level-3 containment facility, and studies of infected host species and viral concentrates should be performed in level-4 (maximum) containment laboratories. (3)

In conclusion, Hantaviruses are responsible for a truly emerging disease (or two diseases, HFRS and HPS). We now appreciate the wide geographic range of hantaviruses and realize that potentially serious hantavirus disease could be encountered virtually anywhere in the world. In the strict sense, however, these hantavirus diseases are not “emerging” (in the way HIV is) since they have likely occurred for a considerable time in the past. Two points are worthwhile noting, however: the first is that knowledge that HFRS and HPS are caused by hantaviruses. This provides diagnostic criteria to eliminate other causes for haemorrhagic fever or dealing with the diseases by vaccination and/or antiviral therapy. The second point is that still unknown hantaviruses are waiting to be found. The more we occupy diverse and unexplained environments the more likely we are to find them. (1)

## References:

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