Hantavirus

Hemorrhagic Fever with Renal Syndrome (HFRS), Hantavirus Pulmonary Syndrome (HPS), Hemorrhagic Nephrosonephritis, Epidemic Hemorrhagic Fever, Korean Hemorrhagic Fever, Nephropathia Epidemica (NE)

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Importance

Hantaviruses are a large group of viruses, carried in rodents and insectivores worldwide, which can cause disease in people who become accidental hosts. Each virus appears to have co-evolved with its reservoir host, and does not usually cause illness in this animal. In humans, the consequences of infection depend with the virus. Although some hantaviruses tend to be associated with asymptomatic infections or mild disease, others have case fatality rates of 50% or greater. Hantavirus infections are fairly common in parts of Asia and Europe. Although hantavirus-associated disease was first reported in the United States in the 1990s during an outbreak in the Four Corners region, these viruses are not new to the U.S. Since the 1990s, they have been reported in rodents and insectivores throughout the country, and additional human cases have been found. There is serologic evidence that some domesticated animals may also become accidental hosts for hantaviruses, but little or no evidence of disease.

Etiology

Hantaviruses (genus *Hantavirus*, family Bunyaviridae) are a group of antigenically distinct viruses carried in rodents and insectivores (shrews and moles). Each hantavirus is endemic in one, or at most, a few specific rodent or insectivore hosts, to which it is well adapted. At least 20 hantaviruses have been identified, but estimates of the exact number of viruses vary. Newly identified hantaviruses are often named for the location where the virus is found; however, some of these viruses are later reclassified. The Laguna Negra, Rio Mamore, Oran, Lechiquanas and Pergamino viruses, which were once thought to be separate hantaviruses, are now considered to be variants of Andes virus, and the New York virus and Monongahela virus are currently classified as variants of Sin Nombre virus. One variant of Dobrava virus (DOBV-Aa) is also called Saaremaa virus; whether this is a separate virus or a less pathogenic variant of Dobrava virus is controversial. Some hantaviruses have not yet been named.

Different hantaviruses cause hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS), the two syndromes seen in humans. Hemorrhagic fever with renal syndrome is a group of clinically similar diseases that occur mainly in Europe and Asia. The most important hantaviruses causing HFRS are Hantaan virus, Puumala virus, Dobrava virus and Seoul virus. Other hantaviruses such as Amur virus are also associated with this disease. HFRS includes several diseases that formerly had other names, including Korean hemorrhagic fever and epidemic hemorrhagic fever. "Nephropathia epidemica" is sometimes used for a mild form of HFRS, which is often caused by Puumala virus or Saaremaa virus.

Hantavirus pulmonary syndrome is caused by a number of hantaviruses in North and South America. In the United States and Canada, the Sin Nombre virus (with its Monongahela and New York variants) is responsible for most cases. HPS can also result from infection by the Muleshoe, Black Creek Canal and Bayou viruses , as well as other named or unnamed hantaviruses. In South and Central America, Andes virus and its variants are important causes of HPS, and Choclo, Castelo Dos Sonhos, Juquitiba, Bermejo, Maciel and other hantaviruses can also cause this syndrome. Some hantaviruses have yet been not been linked to human disease, either because they are not pathogenic for humans or because their rodent hosts are unlikely to pass the virus to humans.

Geographic Distribution

Hantaviruses are found worldwide in rodents and insectivores. The distribution of each virus is usually limited by the geographic range of its specific host(s).

The viruses that cause hantavirus pulmonary syndrome seem to occur only in North, Central and South America. Confirmed human cases have been reported in the United States, Canada, and some countries in Central and South America. In the U.S., most cases are seen in the western states, but infections have been reported throughout the country. Hantaviruses reported to cause HPS in North America include Sin Nombre, Black Creek Canal, Muleshoe and Bayou viruses. Hantaviruses that have been associated with HPS in South and Central America include Andes, Bermejo, Choclo, Araraquara, Juquitiba, Maciel and Castelo dos Sonhos viruses.

HFRS is mainly seen in Europe and Asia; however, one agent, the Seoul virus, can be found worldwide in its rat host, and has been associated with a few cases of HFRS in the United States. In addition to Seoul virus, HFRS is caused by Hantaan virus in Asia, and by Dobrava and Puumala viruses in Europe. Other viruses are also associated occasionally with cases of HFRS.

Although clinical cases have not been reported from Africa or the Middle East, antibodies to hantaviruses have been reported among humans in both regions, and a hantavirus was recently discovered in the African wood mouse (*Hylomyscus simus*).There is currently no evidence for hantavirus-associated disease in Australia, but it is likely that hantaviruses are carried in some Australian rodents or insectivores.

Transmission

Each hantavirus has one or possibly a few specific rodent or insectivore hosts. In these host populations, infections can be spread in aerosols and via bites. Other routes of exposure may also be possible. Rodents can shed hantaviruses in saliva, feces and urine. Infected animals carry these viruses for weeks to years, and sometimes for life. Transient infections are also possible. Recently infected animals tend to shed larger amounts of virus; generally, virus shedding decreases significantly by approximately 8 weeks after infection. Transmission routes may vary with the specific virus; for example, some hantaviruses are more readily isolated from the urine than others. Rodents do not appear to transmit Hantaan or Puumala viruses vertically.

Humans can become incidental hosts when they contact infected rodents or their excretions. Often, rodent urine, droppings or nests are disturbed in enclosed areas; the viruses are then inhaled in aerosolized dust. Infection can sometimes occur after only a few minutes of exposure to aerosolized virus. Hantaviruses can also be transmitted through broken skin, the conjunctiva and other mucous membranes, by rodent bites and possibly by ingestion. Vertical transmission is generally thought to be negligible or nonexistent; however, data suggesting the possibility of hantavirus transmission in breast milk have been reported from South America. Person-to-person spread has not been seen in HPS cases in North America or HFRS in Eurasia, but occurs occasionally with the Andes virus in Argentina.

In the environment, hantaviruses are susceptible to drying, but can remain viable for longer periods if they are protected by organic material. At room temperature (23°C; 73°F), both Puumala and Tula viruses lose viability within 24 h when they are dried, but can remain infectious for more than 5 days if their environment remains moist. In cell culture medium, these two viruses lose their infectivity within 5–11 days at 23°C, but can survive up to 18 days at 4 °C (39°F). Both viruses are completely inactivated within 24 hours when they are kept at 37°C (98.6°F). Puumala virus can remain infectious in the bedding of voles for 12-15 days at room temperature. Hantaan virus also appears to remain viable for several days at room temperature.

Whether animals other than rodents, shrews and moles can shed hantaviruses is uncertain. Studies from China suggest that hantavirus-infected pigs can excrete antigens in urine and feces, and may also pass the virus to their offspring across the placenta. Antibodies to hantaviruses have been reported in other species, but they have not been reported to shed these viruses. No infected animals have been linked to human cases.

Most sources state that hantaviruses are not transmitted by arthropods. However, experimental evidence for the transmission of Hantaan virus by trombiculid mites (chiggers, i.e., *Leptotrombidium* sp.), as well as evidence for the occurrence of this virus in chiggers and gasmid mites has been reported from China. RNA from Bayou virus has been reported in mites and an ixodid tick in Texas. The significance of these findings is unknown.

Disinfection

Hantaviruses are susceptible to many disinfectants including 1% sodium hypochlorite, 2% glutaraldehyde, 70% ethanol and detergents. A 10% sodium hypochlorite solution has been recommended for heavily soiled areas. Hantaviruses are also susceptible to acid (pH 5) conditions. In addition, they can be inactivated by heating to 60° C for at least 30 minutes

Infections in Humans

Incubation Period

The incubation period for HFRS is 1-6 weeks. Incubation periods of one week to 39 days and nine to 33 days have been reported in patients with HPS from Andes virus and Sin Nombre virus, respectively.

Clinical Signs

Hantaviruses usually cause one of two diseases, HFRS and HPS; however, other syndromes may also be possible. Depending on the virus, hantavirus infections vary from asymptomatic to severe.

Hemorrhagic fever with renal syndrome

The severity of HFRS varies with the causative agent. Hantaan, Dobrava and Amur virus infections usually cause severe symptoms. Seoul virus generally results in more moderate disease, while Puumala and Saaremaa (Dobrava Aa) virus infections are typically mild. Classically, the course of the disease has been divided into febrile, hypotensive/ proteinuric, oliguric, diuretic and convalescent stages; these stages are usually more evident in severe disease, and may not be seen in mild cases.

The onset of HFRS is usually abrupt; the initial clinical signs may include fever, chills, prostration, headache and backache. Gastrointestinal signs including nausea, vomiting and abdominal pain may also be seen; in some cases, the

pain can be severe enough to mimic appendicitis. Patients may also develop injected mucous membranes, photophobia, temporary visual impairment, a flushed face and conjunctivae, or a petechial rash, which usually occurs on the palate or trunk. This prodromal stage typically lasts for a few days to a week, and is followed by the onset of renal signs. The first stage is the proteinuric stage. Hypotension may develop during this phase of the disease and can last for hours or days. Nausea and vomiting often occur, and death may result from acute shock. In severe cases, this is typically followed by an oliguric phase then a diuretic/polyuric phase as kidney function improves. Death can occur at any point, but it is particularly common during the hypotensive or oliguric phases. In severe cases, kidney failure may be seen. Some cases have lung involvement (to a lesser extent than in HPS) or neurological signs. Hemorrhagic signs or tendencies including petechiae, hematuria or melena may also be seen, particularly in more severe cases. Disseminated intravascular coagulation can occur. Full recovery may take weeks or months, but patients usually recover normal kidney function. Rare complications may include chronic renal failure and hypertension.

Hantavirus pulmonary syndrome

Hantavirus pulmonary syndrome is usually characterized by pulmonary rather than kidney disease. The initial phase usually lasts for 3 to 5 days; the clinical signs during this period are similar to the prodromal stage of HFRS, and may include fever, myalgia, headache, chills, dizziness, malaise, lightheadedness, nausea, vomiting and sometimes diarrhea. Arthralgia, back pain and abdominal pain are occasionally seen. Respiratory distress and hypotension usually appear abruptly, with cough and tachypnea followed by pulmonary edema and evidence of hypoxia. Cardiac abnormalities can occur, and may include bradycardia, ventricular tachycardia or fibrillation. After the onset of the cardiopulmonary phase, the disease usually progresses rapidly; patients may be hospitalized and require mechanical ventilation within 24 hours. Kidney disease can also be seen, but it tends to be mild; kidney damage occurs more often with the Andes, Bayou and Black Creek viruses. Hemorrhagic signs are rare in patients with HPS in North America, but more common in South America. Although recovery is rapid and patients usually recover full lung function, convalescence may last for weeks or months. Asymptomatic or mild infections appear to be rare with Sin Nombre virus, but may be more common with some South American hantaviruses. Andes virus infections tend to cause severe disease, while Choclo virus infections are usually milder.

Other syndromes

Mild cases can have a variety of signs and symptoms that do not necessarily resemble HPS or HFRS. Hantavirus infections have been suspected in fever of unknown origin in some Asian countries. In Europe, Tula virus infections were found in two patients. One case occurred in a 12-year-old boy in Switzerland who had been bitten by a rodent and developed paronychia, recurrent febrile episodes, a slightly enlarged spleen and a macular, nonpruritic rash on his torso and proximal limbs. The other patient was an adult with fever, renal disease and pneumonia. The Tula virus infection was suspected but not proven to be the cause of the disease in both cases.

Communicability

Although viruses can be found in the blood and urine of HFRS patients, person-to-person transmission has not been seen in cases of HPS in North America or HFRS in Eurasia. Person-to-person transmission has been reported during at least two outbreaks of Andes virus in South America. One study suggested that transmission might take place during the prodromal stage of illness or shortly afterward.

Diagnostic Tests

A definitive diagnosis can be made if the hantavirus is isolated from the patient; however, recovery is not always successful. In addition, some hantaviruses (including Sin Nombre virus) have never been isolated in cell culture. If viruses are found, they can be identified by virus neutralization.

Hantavirus infections are often diagnosed by serology. Either the presence of specific IgM in acute phase sera or a rise in IgG titer is diagnostic. Serological tests include the immunofluorescent antibody test (IFA), enzyme-linked immunosorbent assays (ELISA), immunoblotting and virus neutralization. Commercial ELISA and/or immunoblot assay kits have been developed for Dobrava, Hantaan, Puumala, Seoul, Sin Nombre and some other viruses. Rapid immunochromatographic IgM antibody tests have been described in the literature for acute Dobrava, Hantaan and Puumala virus infections. Hantaviruses can cross-react in some serologic assays.

Hantavirus infections can also be diagnosed by finding antigens in tissues with immunohistochemistry. Viral RNA can be detected in blood or tissues with reverse transcriptase-polymerase chain reaction assays (RT-PCR). PCR assays that can differentiate some hantaviruses have been described; one published assay identifies Dobrava, Hantaan, Seoul and Puumala viruses. Real-time RT-PCR has been described for some viruses.

Treatment

Supportive care is the mainstay of treatment. Intensive care may be required. Ribavirin may be helpful in cases of HFRS, but has not been effective for HPS to date.

Prevention

Hantavirus infections can be prevented by avoiding exposure to rodents and their excretions. Many cases of HPS and HFRS occur after living or working in an enclosed, rodent-infested space; however, some patients

have reported no known contact with rodents or their feces. HFRS has also been associated with agricultural activities, such as harvesting crops or working with hay. Homes, sheds and other buildings should be rodent-proofed, and food should be stored securely to avoid attracting these pests. When complete rodent-proofing is impossible, traps or rodenticides should also be used for control.

The Centers for Disease Control and Prevention (CDC) website has information on the safe cleaning of rodent-infested areas and droppings. Precautions include airing out the room before starting clean-up, and wetting the area with commercial disinfectant or bleach. Infested areas should be cleaned with paper towels, followed by mopping or sponging. Procedures that might aerosolize the virus, such as sweeping, should be avoided, and protective clothing and gloves should be worn while cleaning. Special precautions must be taken when cleaning heavily infested areas; a local, state or federal health department should be contacted for detailed guidelines.

People who are occupationally exposed to rodents should take additional precautions to prevent infection. Depending on the circumstances and type of exposure, this may include gloves, goggles, rubber boots or disposable shoe covers, coveralls or gown, and/or a respirator (as of 2008, the CDC recommends a N-100 filter type respirator). In the U.S., detailed precautions for a variety of situations, including exposure to rodent blood and organs, are available from the CDC. Anyone who develops a febrile illness consistent with the early signs of HPS or HFRS should seek medical attention promptly, and inform the attending physician of the occupational risk. Hospitals should follow universal precautions when treating patients with Andes virus infections. People who have been in contact with these patients should be monitored for prodromal symptoms.

Vaccines for hantaviruses are in development, but are not yet available in the U.S. One commercial inactivated vaccine for HFRS (Hantavax) is available in Korea, but some studies suggest the protection is incomplete.

Morbidity and Mortality

Hantavirus outbreaks are often associated with increased rodent populations or environmental factors that lead to increased human exposure to rodents. HPS tends to peak in late spring or early summer. HFRS tends to peak with human agricultural activities in spring and fall. Occupations that may be at higher risk of infection include rodent control workers, field biologists/ mammalogists, farmers, forestry workers and military personnel. Activities such as camping or staying in rodent-infested cabins can also increase the risk.

Approximately 1-8% of the population has antibodies to hantaviruses in Europe; the seropositivity rate varies with the country and specific virus. Worldwide, approximately 150,000 to 200,000 people are hospitalized with HFRS each year, mainly in Asia. In Europe, HFRS is most common in

Russia (3000 cases), Finland (1000 cases) and Sweden (300 cases), with 100 or fewer cases seen annually in other countries. In the U.S., 0.2-0.5% of the general population is seropositive for hantaviruses. One study reported that 0.5% (4 of 757) of active mammalogists working in the field had antibodies to Sin Nombre virus; one of the four seropositive individuals reported being hospitalized for an illness suggestive of HPS. As of March 2007, fewer than 500 cases of HPS have been reported in the U.S. since the Sin Nombre virus was discovered. In South America, 1-40% of the population has antibodies to hantaviruses, and HPS is also more common.

Different hantaviruses tend to cause mild, moderate or severe disease. The mortality rate also varies with the availability of healthcare services. The case fatality rate is approximately 0.1% to 0.4% for Puumala virus (the most commonly reported infection in Europe), 1-5% for Seoul virus, 7-12% for Dobrava virus, and 10-15% for Hantaan virus. The estimated case fatality rate is 40-60% for HPS caused by Sin Nombre virus. The case fatality rate for Muleshoe, Black Creek Canal and Bayou viruses is also greater than 40%. Andes virus infections have a similar case fatality rate (43-56%), but the mortality rates for some variants may be lower: the case fatality rate is 9-29% for Laguna Negra virus and 8-40% for Lechiguanas virus and Oran virus. Choclo virus infections have a case fatality rate of approximately 25%.

Infections in Animals

Hantaviruses in Rodents and Insectivores

Hantaviruses are found naturally in various species of rodents and insectivores (shrews and moles). Each virus is thought to be carried mainly by one species of animal; however, sometimes a species can carry more than one hantavirus, and some hantaviruses may infect more than one host. The infection rate varies between sites and over time, but in some cases, up to 50% of a rodent population can be seropositive. On average, approximately 10% of deer mice are seropositive for Sin Nombre virus.

Hantaviruses can be carried lifelong, and are not usually associated with overt disease in their reservoir hosts. However, studies have reported decreased survival in bank voles (*Myodes glareolus*) infected with Puumala virus and deer mice infected with Sin Nombre virus, as well as lower weight gains in infected male deer mice. Domesticated rodents can develop clinical signs when they are infected with some hantaviruses. Hamsters infected with Andes virus may develop fatal pulmonary disease similar to HPS. Hantavirus infections can also kill neonatal rodents. Fatal meningoencephalitis occurs in infant laboratory mice (*Mus musculus*) experimentally infected with Hantaan virus, as well as rats infected with Seoul virus. Maternal antibodies seem to be protective during the period of susceptibility. Rats and mice over the age of 2-3-weeks do not usually develop clinical signs. Infant mice do not seem

to be susceptible to disease caused by Puumala or Sin Nombre viruses.

To prevent infections in laboratory colonies, wild rodents should be quarantined and tested for hantaviruses. This may be particularly important in some regions. One study from Korea reported serologic evidence for hantaviruses in 12% of rats and 23% of mice in conventional facilities, and 3% of mice in barrier facilities. Serology, immunoblotting of lung or other tissues for antigens, and RT-PCR can be used to detect hantavirus infections in rodents.

Hantaviruses in Other Mammalian Species

Species other than rodents and insectivores can be infected by hantaviruses, but there is little or no evidence that these animals become ill. Antibodies to some hantaviruses have been found in cats, dogs, swine, horses, cattle, deer, rabbits/ hares, chipmunks and moose. In one study, 10% of healthy cats in the United Kingdom and 23% of cats with chronic diseases were seropositive. Other studies have reported lower rates. Horses, cattle and coyotes were seronegative in one U.S. survey.

Pigs were reported to be systemically infected with hantaviruses in China. Hantavirus antigens were found in the heart, liver, lung, spleen, kidney, blood, urine and feces, as well as in wastes from pigpens. A Russian study reported that hantavirus antigens could be found in the lungs of several avian species (including passerine birds, pheasants, doves, herons and owls) in the far eastern region of the country; this finding remains to be confirmed.

Cynomolgus macaques (*Macaca fascicularis*) that were experimentally infected with Puumala virus became lethargic and developed kidney disease with proteinuria and microhematuria. When cynomolgus macaques were infected with Andes virus, they did not have clinical signs but did have transient decreases in lymphocyte numbers. Disease has not been associated with hantaviruses in other species.

Internet Resources

Centers for Disease Control and Prevention (CDC). Rodent Control.
http://www.cdc.gov/rodents/

CDC. All About Hantavirus. Technical Information Index.
http://www.cdc.gov/ncidod/diseases/hanta/hps/noframes/phys/technicalinfoindex.htm

Public Health Agency of Canada. Material Safety Data Sheets
http://www.phac-aspc.gc.ca/msds-ftss/index.html

Medical Microbiology
http://www.ncbi.nlm.nih.gov/books/NBK7627/

The Merck Manual
http://www.merck.com/pubs/mmanual/

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Table 1: Selected hantaviruses and their major rodent hosts

Virus	Rodent Host(s)
Amur	*Apodemus peninsulae*
Andes	*Oligoryzomys longicaudatus* (long-tailed pygmy rice rat)
Laguna Negra (Andes virus variant)	*Calomys laucha*
Lechiguanas (Andes virus variant)	*Oligoryzomys flavescens*
Oran (Andes virus variant)	*Oligoryzomys longicaudatus*
Rio Mamore (Andes virus variant)	*Oligoryzomys microtis* (small-eared pygmy rice rat)
Araraquara virus	*Bolomys lasiurus*
Asama virus	*Urotrichus talpoides* (Japanese shrew mole)
Ash River	*Sorex cinereus* (masked shrew)
Bayou	*Oryzomys palustris* (rice rat)
Black Creek Canal	*Sigmodon hispidus* (cotton rat)
Bloodland Lake	*Microtus ochrogaster* (prairie vole)
Camp Ripley	*Blarina brevicauda* (northern short-tailed shrew)
Choclo	*Oligoryzomys fulvescens* (fulvous pygmy rice rat)
Dobrava	*Apodemus flavicollis* (yellow-necked field mouse)
El Moro Canyon	*Reithrodontomys megalotis* (Western harvest mouse)
Hantaan	*Apodemus agrarius* (striped field mouse)
Hu39694	*Oligoryzomys flavescens* (?)
Isla Vista	*Microtus californicus* (California vole)
Jemez Springs	*Sorex monticolus* (dusky shrew)

Virus	Rodent Host(s)
Juquitiba	*Oligoryzomys nigripes*
Khabarovsk	*Microtus fortis* (reed vole)
Muleshoe	*Sigmodon hispidus* (cotton rat)
Prospect Hill	*Microtus pennsylvanicus* (meadow vole)
Puumala	*Myodes glareolus* (bank vole)
Rio Segundo	*Reithrodontomys mexicanus* (Mexican harvest mouse)
Saaremaa (or DOBV-Aa)	*Apodemus agrarius* (striped field mouse)
Seewis	*Sorex araneus* (Eurasian common shrew)
Seoul	*Rattus norvegicus* (Norway rat); *Rattus rattus* (black rat)
Sin Nombre	*Peromyscus maniculatus* (deer mouse)
Monongahela (Sin Nombre virus variant)	*Peromyscus maniculatus* (deer mouse)
New York (Sin Nombre virus variant)	*Peromyscus maniculatus* (deer mouse); *P. leucopus* (white-footed mouse)
Soochong	*Apodemus peninsulae*
Tanganya	*Crocidura theresae* (Therese shrew)
Thailand	*Bandicota indica* (bandicoot rat)
Thottapalayam	*Suncus murinus* (musk shrew)
Topografov	*Lemmus sibiricus* (Siberian lemming)
Tula	*Microtus arvalis* (European common vole)