

HANTAVIRUS INFECTIONS

2/13/2017

History

During the Korean War (1950-1953), U.S. Army troops suddenly began to develop a mysterious, often fatal illness that was termed Korean hemorrhagic fever. Over the next 20 years, this illness was included in the syndrome of hemorrhagic fever with renal syndrome (HFRS) which was shown to occur in many countries.

In 1993, a previously unknown disease, hantavirus pulmonary syndrome (HPS), was identified among residents of the southwestern United States. HPS was subsequently recognized throughout the contiguous United States and the Americas.

Since 1993, researchers have discovered that there is not just one hantavirus causing HPS, but several. In June 1993 a Louisiana bridge inspector who had not traveled to the Four Corners area (CO, UT, AZ, NM) developed the HPS syndrome. An investigation was begun. The patient's tissues were tested for hantavirus. As a result, the Bayou Virus was discovered and linked to a carrier, the rice rat (*Oryzomys palustris*).

The Sin Nombre Virus, (SNV) was first isolated from rodents collected on the premises of one of the initial HPS patients in the Four Corners region. Black Creek Canal virus was isolated from *Sigmodon hispidus* collected near the residence of a human case in Dade County, Florida. Bayou virus was originally identified as the cause of a fatal case of HPS that occurred in northern Louisiana in June, 1993. A second case of HPS caused by Bayou virus was reported in Texas in November, 1995, and another in 1996. Bayou virus is genetically most similar to Black Creek Canal virus, which has caused a single case of HPS in Florida.

Other Hantaviruses : Several members of the Hantavirus genus cause different forms of hemorrhagic fever with renal syndrome (HFRS), an ancient disease first described in Russia in 1913. The four viruses that are associated with HFRS, each named for the region from where they were first isolated: Hantaan virus, Seoul virus, Puumala virus and Dobrava virus.

Seoul virus: During early December 2016, a home-based rat breeder in Wisconsin developed an acute febrile illness. During late December 2016, the CDC tested a blood specimen from the patient and confirmed that the infection was caused by Seoul virus, a member of the hantavirus family of rodent-borne viruses. A family member who worked with rodents also tested positive for Seoul virus. Both people have recovered. A follow-up investigation of rat breeders who supplied the initial patient's rats revealed six additional human cases of Seoul virus infections occurring at two Illinois rat-breeding facilities. Of the eight confirmed cases in Wisconsin and Illinois, two were hospitalized. Rats at these facilities have also tested positive for Seoul virus

Seoul virus is a member of the hantavirus group of rodent-borne viruses. Trace-back and trace-out investigations of possibly infected rodents have identified distribution chains in other states. People who become infected with this virus often exhibit relatively mild or no symptoms, but some will develop a form of hemorrhagic fever with renal syndrome (HFRS) with death in approximately 1% to 2% of HFRS

cases. Although serologic studies have indicated the presence of Seoul virus in wild rats in the U.S., this was the first known outbreak associated with pet rats in the United States.

Hantaviruses belong to the Bunyavirus family. There are five genera within the family: Bunyavirus, Phlebovirus, Nairovirus, Tospovirus, and Hantavirus. Each is made up of negative-sensed, single-stranded RNA viruses. All these genera include arthropod-borne viruses, with the exception of Hantavirus which is rodent-borne.

Epidemiology

People who have become ill with HPS got the disease after having been in frequent contact with rodents and/or their droppings around a home or a workplace. In addition, many people who became ill, reported that they had not seen rodents or their droppings at all.

Aerosols are most likely to be the major route of transmission from rodents to humans. Humans, who are dead-end hosts, may contract the virus when saliva or excreta from infected rodents are inhaled as aerosols, produced directly from the animal. Transmission may also occur when fresh or dried materials contaminated by rodent excreta are disturbed, directly introduced into broken skin, introduced into the eyes, or, possibly, ingested in contaminated food or water. Persons have also become infected after being bitten by rodents.

Ticks, fleas, mosquitoes and other biting insects have not been implicated in the transmission of HPS. In fact, aside from the rodent vectors described above, no other animals are known to have a direct role in the transmission of the previously identified hantaviruses or with any case of HPS. However, domestic cats and dogs may bring infected rodents into contact with humans.

Person-to-person transmission of HFRS in Asia and HPS in the United States has not been reported. In addition, a study of 396 health care workers in the southwestern U.S. failed to show nosocomial transmission. Therefore, CDC guidelines for management of HPS patients in the U.S. recommend standard precautions. Information collected recently in Argentina, however, suggests that person-to-person transmission may have occurred during a 1996 outbreak centered in the towns of El Bolson and Bariloche.

Nosocomial transmission of HFRS or HPS has also never been reported, which is consistent with the difficulty of culturing virus from infected persons. Furthermore, a serosurvey among health care workers who took care of the initial cluster of HPS patients failed to show any seropositive results. Therefore, no additional precaution besides universal precautions is indicated for HPS patients.

Main Natural Hosts

- The deer mouse (*Peromyscus maniculatus*) found almost everywhere in North America
- The white-footed mouse (*Peromyscus leucopus*) found through southern New England, the Mid-Atlantic and Southern states, the Midwest and into the western states and Mexico. It prefers wooded and brushy areas, although sometimes it will live in more open ground.
- The cotton rat (*Sigmodon hispidus*), found in the southeastern United States.
- The rice rat (*Oryzomys palustris*) likes marshy areas and is semi-aquatic. It is found in the Southeastern U.S. and into Central America. It is the main carrier of the Bayou virus.

Sometimes, the "country mouse" becomes a "city mouse". Both the deer mouse and the cotton rat are usually in rural areas, but can also be found in cities when conditions are right, such as easy availability of food, water and shelter.

It appears that other rodents carrying strains of hantavirus that cause HPS are yet to be identified.

The virus is transmitted horizontally among rodents. Transmission from rodent-to-rodent is believed to occur primarily after weaning and through contact, perhaps aggressive contact with accompanying

combat wounds. Although hantaviruses infect their rodent hosts, there is minimal evidence to suggest that they cause illness in the rodents.

The incubation period is two weeks with a possible range of a few days to six weeks.

Clinical Description

Prodromal phase

Patients with HPS typically present in a very nonspecific way with a relatively short febrile prodrome lasting three to five days. In addition to fever and myalgias, early symptoms include headache, chills, dizziness, non-productive cough, nausea, vomiting, and other gastrointestinal symptoms. Malaise, diarrhea, and lightheadedness are reported by approximately half of all patients, with less frequent reports of arthralgias, back pain, and abdominal pain. Patients may report shortness of breath, (respiratory rate usually 26 to 30 times per minute). Typical findings on initial presentation include fever, tachypnea and tachycardia. The physical examination is usually otherwise normal.

The diagnosis is seldom made at this stage, as cough and tachypnea generally do not develop until approximately day seven. Once the cardiopulmonary phase begins, however, the disease progresses rapidly, necessitating hospitalization and often ventilation within 24 hours.

The cardiopulmonary phase which may last two to four days, is marked by sudden onset of a cough, which is often nonproductive. Gradually, patients exhibit increasing dyspnea and early manifestations of shock. Patients often complain of profuse sweating, back and nonpleuritic chest pain, dizziness, and weakness. Noncardiac pulmonary edema develops quickly, with rapid deterioration of lung function, poor tissue perfusion, and hypotension.

During the cardiopulmonary stage, clinicians may confuse HPS with acute respiratory distress syndrome (ARDS), pneumonia, or influenza.

In the convalescent phase acute diuresis is followed by rapid resolution of respiratory and hemodynamic status. Patients recover promptly and are often discharged within one to two days. Nevertheless, abnormal liver function tests and abnormalities in pulmonary function (eg, air trapping and decreased carbon monoxide diffusing capacity) may persist for as long as six months.

Laboratory Tests

A positive serological test result, evidence of viral antigen in tissue by immunohistochemistry, or the presence of amplifiable viral RNA sequences in blood or tissue, with compatible history of HPS, is considered diagnostic for HPS.

Serologic assays

Tests based on specific viral antigens from SNV are now widely used for the routine diagnosis of HPS. The CDC uses an enzyme-linked immunosorbent assay (ELISA) to detect IgM antibodies to SNV and to diagnose acute infections with other hantaviruses. This assay is also available in some state health laboratories.

- IgG test is used in conjunction with the IgM-capture test. Acute- and convalescent-phase sera should reflect a four-fold rise in IgG antibody titer or the presence of IgM in acute-phase sera to be diagnostic for hantaviral disease. Note that acute-phase serum sent as an initial diagnostic specimen may not yet have IgG. IgG antibody is long lasting, and sera of patients retrospectively identified appear to have retained antibody for many years. The SNV IgG ELISA has been used in serologic investigations of the epidemiology of the disease and appears to be appropriate for this purpose. Investigations of selected populations using this assay have confirmed that infections with the virus are not common and that mild or inapparent infections are rare.

- Western blot assay using recombinant antigens and isotype-specific conjugates for IgM-IgG differentiation has also been developed and its results are generally in agreement with those of the IgM-capture format.
- Rapid immunoblot strip assay (RIBA) is an investigational prototype assay to identify serum antibody to recombinant proteins and peptides specific for SNV and other hantaviruses.
- Serologic confirmation of hantaviral infections has traditionally been done with neutralizing plaque assays, which have been recently described for SNV. However, these specific assays are also not commercially available.

Virus isolation

Isolation of hantaviruses from human sources is difficult, and the viruses causing HPS seem to be no exception to this rule. To date, no isolates of SNV-like viruses have been recovered from humans, and therefore virus isolation is not a consideration for diagnostic purposes.

Immunohistochemistry (IHC):

IHC testing of formalin-fixed tissues with specific monoclonal and polyclonal antibodies can be used to detect hantavirus antigens and has proven to be a sensitive method for laboratory confirmation of hantaviral infections. IHC has an important role in the diagnosis of HPS in patients from whom serum samples and frozen tissues are unavailable for diagnostic testing and in the retrospective assessment of disease prevalence in a defined geographic region.

Polymerase Chain Reaction (PCR):

Reverse transcriptase-PCR (RT-PCR) can be used to detect hantaviral RNA in fresh frozen lung tissue, blood clots, or nucleated blood cells. However, RT-PCR is very prone to cross-contamination and should be considered an experimental technique. Differences in viruses in the United States complicate the use and sensitivity of RT-PCR for the routine diagnosis of hantaviral infections.

Currently specimens for detection of Hantavirus and related virus are sent to the CDC Special Pathogens branch for serological and virological testing. Direct questions to the State Laboratory's Virology Section at (504) 568-5374 or the Louisiana Department of Health's Infectious Disease Epidemiology Section (IDePi).

Specimen collection:

Blood for serological testing: Collect one red-topped tube of venous blood. When sending serum samples into the laboratory, it is usually better to hold the acute serum until the convalescent serum has been collected and forward both at the same time. Spin the blood down and separate the sera or the whole blood on cold packs.

Tissue:

Tissue taken from lung, heart, liver or spleen is preferred for testing. The CDC will perform immunohistochemistry (IHC) and/or PCR testing. Tissue may be formalin fixed, paraffin embedded or fresh frozen.

Tests:

- Hantavirus-specific immunoglobulin M or titers of hantavirus-specific immunoglobulin G. Not available at the State Laboratory; available in limited cases, with prior approval, through the CDC.
- Hantavirus-specific ribonucleic acid sequence by polymerase chain reaction in clinical specimens. Not available at the State Laboratory; available in limited cases, with prior approval, through the CDC.
- Hantavirus antigen by immunohistochemistry. Not available at the State Laboratory; available in limited cases, with prior approval, through the CDC.

Surveillance

Hantavirus illness is a condition reportable within one business day of diagnosis.

Case Definition

Clinical description

Hantavirus pulmonary syndrome (HPS), commonly referred to as hantavirus disease, is a febrile illness characterized by bilateral interstitial pulmonary infiltrates and respiratory compromise usually requiring supplemental oxygen and clinically resembling acute respiratory disease syndrome (ARDS). The typical prodrome consists of fever, chills, myalgia, headache, and gastrointestinal symptoms. Typical clinical laboratory findings include hemoconcentration, left shift in the white blood cell count, neutrophilic leukocytosis, thrombocytopenia, and circulating immunoblasts.

Clinical case definition

An illness characterized by one or more of the following clinical features:

- A febrile illness (i.e., temperature greater than 101.0°F [greater than 38.3°C]) characterized by bilateral diffuse interstitial edema that may radiographically resemble ARDS, with respiratory compromise requiring supplemental oxygen, developing within 72 hours of hospitalization, and occurring in a previously healthy person
- An unexplained respiratory illness resulting in death, with an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable cause

Laboratory criteria for diagnosis

- Detection of hantavirus-specific immunoglobulin M or rising titers of hantavirus-specific immunoglobulin G, or
- Detection of hantavirus-specific ribonucleic acid sequence by polymerase chain reaction in clinical specimens, or
- Detection of hantavirus antigen by immunohistochemistry

Laboratory testing should be performed or confirmed at a reference laboratory. Because the clinical illness is nonspecific and ARDS is common, a screening case definition can be used to determine which patients to test. In general, a predisposing medical condition (e.g., chronic pulmonary disease, malignancy, trauma, burn, and surgery) is a more likely cause of ARDS than HPS, and patients who have these underlying conditions and ARDS need not be tested for hantavirus.

Case classification

Confirmed: a clinically compatible case that is laboratory confirmed

Treatment

Aggressive intervention notwithstanding, many patients with HPS succumb rapidly during the cardiopulmonary phase as a result of overwhelming pulmonary compromise and respiratory failure. Thus, supportive care must be initiated quickly, including admission to the critical care unit for oxygenation, intubation, and assisted ventilation. It is crucial to manage fluid and electrolyte imbalances; overhydration can worsen cardiac status. Vasopressors (e.g., dobutamine) should be utilized to prevent poor perfusion, and broad-spectrum antibiotics should be considered until a diagnosis is confirmed.

In preliminary trials, ribavirin was demonstrated to be helpful early in treatment. In 1993, the U.S. Food and Drug Administration approved its use for the entire course of the disease.

Infected patients often develop respiratory failure within 24 hours of admission. Therefore, it is beneficial

to place a pulmonary artery catheter to monitor wedge pressure; maintaining wedge pressure in the low to normal range ensures optimal cardiac output. Extracorporeal membrane oxygenation for HPS patients seems promising, but further studies are warranted. Universal precautions should be followed without fear of human-to-human transmission.

Investigation

- Identify etiologic agent in patients presenting with acute respiratory distress syndrome (ARDS). For suspect Hantavirus diagnosis, obtain specimens (serum or tissue) for testing. Testing at this time is only available at the CDC. In order to submit specimen(s) for testing, consult with the IDEpi Section with the regards to the criteria for testing, such as patient has clinical presentation with ARDS (not related to a predisposing medical condition).
- Determine the source(s) of exposure such as occupation or recent exposure to rodent excreta.
- **Recommend appropriate rodent control and extermination as well as general education regarding activities which pose a significant risk such as occupying or cleaning rodent-inhabited areas (sheds, attics, abandoned dwellings). Safe disposal of rodents and proper cleaning and disinfection of rodent-inhabited areas are keys to minimizing exposure to the hantavirus.**

Prevention of Transmission

Make home, workplace, vacation home or campsite unattractive to rodents. Rodents search for easy-to-get-food and nesting material in a house. If a residence does not offer this, residents are less likely to come into contact with them.

1. Prevention by keeping indoor area clean:

- Keep a clean home, especially kitchen (wash dishes, clean counters and floor, keep food covered in rodent-proof containers).
- Keep tight-fitting lid on garbage, discard uneaten pet food at the end of the day.
- Set and keep spring-loaded rodent traps. Set traps near baseboards because rodents tend to run along walls and tight spaces rather than out in the open.
- Set EPA-approved rodenticide with bait under plywood or plastic shelter along baseboards. These are sometimes known as "covered bait stations." Remember to follow product use instructions carefully, since rodenticides are poisonous to pets and people, too.
- If bubonic plague is a problem in your area, spray flea killer or spread flea powder in the area before setting traps. This is important. If you control rodents but do not control fleas as well, you may increase the risk of infection with bubonic plague, since fleas will leave rodents once the rodents die and will seek out other food sources, including humans.
- Seal all entry holes 1/4 inch wide or wider with steel wool, cement, wire screening or other patching materials, inside and out.

2. Prevention by keeping outdoor area clean:

- Clear brush, grass and junk from around house foundations to eliminate a source of nesting materials.
- Use metal flashing around the base of wooden, earthen or adobe homes to provide a strong metal barrier. Install so that the flashing reaches 12 inches above the ground and six inches down into the ground.
- Elevate hay, woodpiles and garbage cans to eliminate possible nesting sites. If possible, locate them 100 feet or more from your house.
- Trap rodents outside, too. Poisons or rodenticides may be used as well, but be sure to keep them out of the reach of children or pets.
- Encourage natural predators such as non-poisonous snakes, owls and hawks.
- Remember, totally getting rid of all rodents is not feasible, but with ongoing effort you can keep the population very low.

3. Clean-up rodent infected areas:

- Put on latex rubber gloves before cleaning up.
- Don't stir up dust by sweeping up or vacuuming up droppings, urine or nesting materials.
- Instead, thoroughly wet contaminated areas with detergent or liquid to deactivate the virus.

Most general purpose disinfectants and household detergents are effective. However, a hypochlorite solution prepared by mixing 1½ cups of household bleach in one gallon of water may be used in place of commercial disinfectant. When using the chlorine solution, avoid spilling the mixture on clothing or other items that may be damaged.

- Once everything is wet, take up contaminated materials with a damp towel, then mop or sponge the area with disinfectant.

Hantaviruses are surrounded by a lipid (fatty) envelope, so they are somewhat fragile. The lipid envelope can be destroyed and the virus killed by fat solvents like alcohol, ordinary disinfectants and household bleach. That is why one of the most important ways to prevent transmitting the disease is to carefully wet down dead rodents and areas where rodents have been with disinfectant and/or bleach. When you do this, you are killing the virus itself and reducing the chance that the virus will get into the air.

- Spray dead rodents with disinfectant, then double-bag along with all cleaning materials and bury or burn - or throw out in appropriate waste disposal system. If burning or burying isn't feasible, contact your local or state health department about other disposal methods.

- Finally, disinfect gloves with disinfectant or soap and water before taking them off. After taking off the clean gloves, thoroughly wash hands with soap and warm water.

When going into cabins or outbuildings (or work areas) that have been closed for awhile, open them up and air out before cleaning.

4. Special Precautions for Homes of Persons with Confirmed Hantavirus Infection or Buildings with Heavy Rodent Infestations:

The special precautions may also apply to vacant dwellings that have attracted numbers of rodents while unoccupied and to dwellings and other structures that have been occupied by persons with confirmed hantavirus infection.

Workers who are either hired specifically to perform the clean-up or asked to do so as part of their work activities should receive a thorough orientation from the responsible health agency about hantavirus transmission and should be trained to perform the required activities safely.

- A baseline serum sample, preferably drawn at the time these prevention activities are initiated, should be available for all persons conducting the clean-up of homes or buildings with heavy rodent infestation. The serum sample should be stored at -20°C.

- Persons involved in the clean-up should wear coveralls (disposable if possible), rubber boots or disposable shoe covers, rubber or plastic gloves, protective goggles, and an appropriate respiratory protection device, such as a half-mask air-purifying (or negative-pressure) respirator with a high-efficiency particulate air (HEPA) filter or a powered air-purifying respirator (PAPR) with HEPA filters. Respirators (including positive-pressure types) are not considered protective if facial hair interferes with the face seal, since proper fit cannot be assured. Respirator practices should follow a comprehensive user program and be supervised by a knowledgeable person.

- Personal protective gear should be decontaminated upon removal at the end of the day. If the coveralls are not disposable, they should be laundered on site. If no laundry facilities are available, the coveralls should be immersed in liquid disinfectant until they can be washed.

- All potentially infective waste material (including respirator filters) from clean-up operations that cannot be burned or deep buried on site should be double bagged in appropriate plastic bags. The bagged material should then be labeled as infectious (if it is to be transported) and disposed of in accordance with local requirements for infectious waste.

- Workers who develop symptoms suggestive of HPS within 45 days of the last potential exposure should immediately seek medical attention. The physician should contact local health authorities promptly if hantavirus-associated illness is suspected. A blood sample should be obtained and forwarded with the baseline serum through the state health department to the CDC for hantavirus antibody testing.

5. Precautions for Workers in Affected Areas Who are Regularly Exposed to Rodents:

Persons who frequently handle or are exposed to rodents (e.g., mammalogists, pest-control workers) in the affected area are probably at higher risk for hantavirus infection than the general public because of their frequency of exposure. Therefore, enhanced precautions are warranted to protect them against hantavirus infection.

- A baseline serum sample, preferably drawn at the time of employment, should be available for all persons whose occupations involve frequent rodent contact. The serum sample should be stored at -20°C.

- Workers in potentially high-risk settings should be informed about the symptoms of the disease and be given detailed guidance on prevention measures.

- Workers who develop a febrile or respiratory illness within 45 days of the last potential exposure should immediately seek medical attention and inform the attending physician of the potential occupational risk of hantavirus infection. The physician should contact local health authorities promptly if hantavirus-associated illness is suspected. A blood sample should be obtained and forwarded with the baseline serum through the state health department to the CDC for hantavirus antibody testing.

- Workers should wear a half-face air-purifying (or negative-pressure) respirator or PAPR equipped with HEPA filters when removing rodents from traps or handling rodents in the affected area. Respirators (including positive-pressure types) are not considered protective if facial hair interferes with the face seal, since proper fit cannot be assured. Respirator use practices should be in accord with a comprehensive user program and should be supervised by a knowledgeable person.

- Workers should wear rubber or plastic gloves when handling rodents or handling traps containing rodents. Gloves should be washed and disinfected before removing them, as described above.

- Traps contaminated by rodent urine or feces or in which a rodent was captured should be disinfected with a commercial disinfectant or bleach solution. Dispose of dead rodents as described in the section on Eliminating Rodents inside the Home.

6. Precautions for Campers and Hikers in the Affected Areas:

There is no evidence to suggest that travel into areas where HPS has been reported should be restricted. Most usual tourist activities pose little or no risk that travelers will be exposed to rodents or their urine and/or droppings.

However, persons who do outdoor activities such as camping or hiking in areas where the disease has been reported should take precautions to reduce the likelihood of their exposure to potentially infectious materials.

- Avoid coming into contact with rodents and rodent burrows or disturbing dens (such as pack rat nests).

- Air, then disinfect cabins or shelters before using them. These places often shelter rodents.

- Do not pitch tents or place sleeping bags in areas in proximity to rodent droppings or burrows or near areas that may shelter rodents or provide food for them (e.g., garbage dumps or woodpiles).

- If possible, do not sleep on the bare ground. In shelters, use a cot with the sleeping surface at least 12 inches above the ground. Use tents with floors or a ground cloth if sleeping in the open air.

- Keep food in rodent-proof containers.

- Promptly bury (or – preferably - burn followed by burying, when in accordance with local requirements) all garbage and trash, or discard in covered trash containers.

- Use only bottled water or water that has been disinfected by filtration, boiling, chlorination, or iodination for drinking, cooking, washing dishes, and brushing teeth.

•And last but not least, do not play with or handle any rodents that show up at the camping or hiking site, even if they appear friendly.

Hospital Precaution and Isolation:

Standard precautions (Hantavirus pulmonary syndrome is not associated with nosocomial or person-to-person transmission and, therefore, patients with these infections require only standard precautions).