HANTAVIRUSES

AETIOLOGY

Classification of the causative agent

There are more than 20 viral species within the genus *Hantavirus* - the only pathogens of the family *Bunyaviridae* (enveloped, negative-sense single-stranded RNA) in vertebrates not associated with arthropod vectors. Instead, they are maintained in persistently infected rodents. Each virus is associated with a specific reservoir host (see ***Hosts*** for further information).

Hantaviruses are divided into two broad categories: Old World and New World viruses. In humans, Old World hantaviruses generally cause what is referred to as “haemorrhagic fever with renal syndrome” (HFRS) and New World hantaviruses cause “hantavirus pulmonary syndrome” (HPS). It should be noted, however, that both are multisystemic diseases and there can be significant overlap between these syndromes.

These viruses are notoriously difficult to study and isolate; molecular techniques have proven to be absolutely critical for scientific understanding and classification. The most pathologically significant hantaviruses will be discussed in this technical card: Hantaan virus, Dobrava-Belgrade virus, Seoul virus, Puumala virus, Sin Nombre virus, New York virus, Black Creek Canal virus, Bayou virus, and Andes virus.

Hantaviruses are zoonotic and are classified as Biosafety Level 4 (BSL4) agents. They are not listed by the OIE but voluntary reporting is requested.

Resistance to physical and chemical action

Temperature: Inactivated at 56°C/15 minutes or 2 hours if dried

pH: Generally susceptible to pH<5 but some species tolerate a pH of 3

Chemicals/Disinfectants: 70% ethanol, 1-10% sodium hypochlorite (higher concentrations for more soiled areas)

Survival: Can persist for days to weeks in the environment, but become rapidly nonviable if desiccated

EPIDEMIOLOGY

Hosts

- Humans (*Homo sapiens*)
- Old World hantaviruses
    - Hantaan virus - striped field mouse (*Apodemus agrarius*)
    - Dobrava-Belgrade virus - yellow-necked mouse (*Apodemus flavicollis*)
    - Seoul virus - brown rat (*Rattus norvegicus*)
    - Puumala virus - bank vole (*Clethrionomys glareolus*)
- New World hantaviruses
    - Sin Nombre virus - deer mouse (*Peromyscus maniculatus*)
    - New York virus - white-footed mouse (*Peromyscus leucopus*)
    - Black Creek Canal virus - cotton rat (*Sigmodon hispidus*)
    - Bayou virus - rice rat (*Oryzomys palustris*)
    - Andes virus - long-tailed pygmy rice rat (*Oligoryzomys longicaudatus*)
- Other relevant hosts include:

    - *Akodon* spp.
    - *Microtus* spp.
    - *Bolomys obscurus*
    - Other species of *Oligoryzomys, Peromyscus, Apodemus, Microtus,* and *Rattus*
- Hantaviral nucleic acid and positive viral titers have been detected in many species not believed to play an important role in disease transmission or maintenance. Bats, birds, and other mammalian insectivores and carnivores are among those identified, and it is believed shared habitat and/or ingestion of infected prey are responsible for these transiently positive tests.

Transmission

- Contact with rodent excretions or via rodent bite
    - Hantaviruses are shed in excreta for long periods of time. Episodes of shedding may be intermittent but are generally believed to occur for the life of the host.
- Inhalation of aerosols or dust carrying infective material
- Human-to-human transmission is rare but has been demonstrated for Andes virus
- Rodent-to-rodent transmission occurs via biting or scratching; vertical transmission is not believed to occur due to maternal antibody protection
- There is insufficient evidence to suggest arthropod vectors transmit virus, but Bayou virus RNA has been identified in mites and ixodid ticks

Sources

- Rodent blood, saliva, urine, and faeces

Occurrence

Old World hantaviruses tend to organize in rural, urban, and laboratory-associated patterns. Rural disease is commonly caused by Hantaan, Dobrava-Belgrade, and Puumala viruses, whereas urban disease is often caused by Seoul virus. Hantaan virus is widespread in China, Russia, and the Korean Peninsula, Dobrava-Belgrade virus in the Balkans and Greece, and Puumala virus in northern Europe with a particular focus around Scandinavia. Seoul virus can be identified globally due to the popularity of pet rats in many parts of the world, but is most common in Japan, the Korean Peninsula, China, and the Americas. There have been many instances where wild-caught rodents have been utilised for laboratory research and transmitted disease to personnel. Most cases are typically seen in the winter, when mice seeking shelter are most likely to contact humans, and when rodent density is highest.

New World hantaviruses were unappreciated until 1993, when outbreaks of Sin Nombre virus occurred in the southwestern United States. It is largely believed that the two preceding winters, which were unusually wet, allowed for a surplus of grain and vegetation to grow. The subsequent boom in mouse populations is considered a major contributing factor to the sudden development of human cases. Disease in humans tends to be most common throughout the spring and summer, which corresponds with seasons of increased rodent activity and times of the year during which people are often more active outdoors.

Additional members of this genus are often identified, but the understanding of their pathogenicity remains poor; few are well-characterised.

For more recent, detailed information on the occurrence of this disease worldwide, see the OIE World Animal Health Information System - Wild (WAHIS-Wild) Interface [http://www.oie.int/wahis_2/public/wahidwild.php/Index].

DIAGNOSIS

The pathogenesis of Hantaan virus, the “prototype” hantavirus, in its reservoir host has been well documented. After inoculation, mice rapidly mount a neutralising antibody response that coincides with a declining viraemia. During the first week post-inoculation, 100-1000 times more virus is identifiable in urine and throat swabs, and

mice appear to have a greater ability to transmit the virus. There is viral persistence in the lung and kidney, among other organs.

Clinical diagnosis

Hantaviruses are not believed to cause disease in their reservoir hosts. Rats infected with Seoul virus show no demonstrable difference in health or lifespan in comparison to uninfected individuals.

Clinical disease is believed to be limited to humans and can manifest as HFRS (includes “nephropathia epidemica” description specific to Puumala virus in Scandinavia) or HPS. Reservoir hosts are not believed to be affected.

HFRS infections in humans are characterized by 2-3 weeks of incubation followed by five well-described phases of clinical disease. Less severe cases are generally shorter in duration and have less distinct phases. HPS generally begins with nonspecific signs and rapidly progresses to respiratory distress over hours or days.

Lesions

- Hantaviruses are not believed to cause lesions in rodent reservoir hosts
- Particularly young rodents and atypical host species infected in experimental settings have developed meningoencephalitis or pulmonary and renal disease. Studies typically utilise high doses of inoculum that are not always representative of a natural infectious dose, so these findings may not be representative of natural infections.

Differential diagnoses

- In humans:
    - Viral or bacterial interstitial pneumonia
    - Other viral haemorrhagic fever viruses (*Arenaviridae, Filoviridae, Flaviviridae,* and other *Bunyaviridae*)
    - Leptospirosis
    - Complicated streptobacillary rat-bite fever
    - Pneumonic tularemia or plague (*Francisella tularensis, Yersinia pestis*)

Laboratory diagnosis

Due to zoonotic potential and public health risks, tests should be performed in laboratories suitable for handling BSL4 agents whenever possible.

Samples

For isolation of agent

- Whole blood
- Kidney
- Lung
- Blood, saliva, urine, or feces of infected rodent

Serological tests

- Whole blood
- Serum

Procedures

Identification of the agent

- Viral isolation is consistently difficult and rarely performed outside of a laboratory setting
- Reverse-transcriptase polymerase chain reaction (RT-PCR)
- Immunohistochemistry (IHC)

Serological tests

- Antibody capture enzyme-linked immunosorbent assays (ELISAs) are the preferred method of assessing hantavirus exposure in rodents due to the risk of working with infectious samples
    - Spot cards are often used by veterinarians to assess the serologic status of pet rats, otherwise 100µL of blood collected in EDTA can be used for serologic testing
- Immunofluorescent assay (IFA)
- Enzyme immunoassay (EIA)
- Cross-reactivity between hantaviruses occurs, which facilitates the clinical diagnosis of undetermined species in ill patients but does not always yield a specific aetiologic diagnosis

PREVENTION AND CONTROL

Sanitary prophylaxis

- Rodent control is the primary mechanism by which human infections can be prevented
    - Seal and rodent-proof residences and food stores to prevent the entry of rodents
    - Reduce or destroy suitable rodent dwellings near homes
    - Remove rodent faeces or excreta in areas that humans frequent; ensure the area is well-ventilated while cleaning and consider wearing goggles and a particulate respirator; while cleaning, wear clothing that is easily removed and washed upon finishing
    - Wetting down dust and dirt with detergent or disinfectant can reduce aerosol generation when cleaning; mopping or wiping surfaces with damp cloths is preferential to sweeping
    - If the rodent density is particularly high, baiting and trapping may be necessary
- Researchers and laboratory staff should avoid utilising wild rodents trapped in endemic areas whenever possible
    - If their collection is necessary, protective clothing, gloves, and respirators are recommended. Drawing blood and obtaining tissue samples are activities that warrant a great level of caution - these tissues may be infectious, and stressed animals may bite.
    - Ensure access to disinfectants and media/packaging that minimises transport risk
    - Isolate and test all rodents before introduction to or establishment of a laboratory colony

Medical prophylaxis

- Inactivated vaccines (human use) exist for Hantaan and Seoul virus and are predominantly used in Asia

POTENTIAL IMPACTS OF DISEASE AGENT BEYOND CLINICAL ILLNESS

Risks to public health

- Many hantaviruses are zoonotic and highly lethal with mortality rates ranging from 5-15% or greater depending on the viral species. While they are not typically transmissible person-to-person, morbidity is serious and recovery may take weeks to months.
- Domestic pet rats are capable of harboring and spreading Seoul virus without the knowledge of the owner. In the event of a local outbreak or if an individual in the household develops disease that resembles or is diagnosed as Seoul virus, rat owners should have their animals tested by a veterinarian. In the meantime, cages should be cleaned regularly in agreement with published recommendations.

- All veterinary staff should handle the animal with appropriate personal protective equipment and follow published guidelines.

Risks to agriculture

- Hantaviruses are not believed to be direct risks to agriculture.
- Many farm buildings such as barns and sheds are desirable habitats for mice and staff should take care to keep these areas clean and well-ventilated if rodent-proofing is not feasible.

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The OIE will periodically update the OIE Technical Disease Cards. Please send relevant new references and proposed modifications to the OIE Science Department (scientific.dept@oie.int). Last updated 2020. Written by Samantha Gieger and Erin Furmaga with assistance from the USGS National Wildlife Health Center.