Hantavirus infections

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Summary
Hantaviruses are the causative agents of the zoonotic diseases known as haemorrhagic fever with renal syndrome (HFRS) in Europe and Asia, and hantavirus pulmonary syndrome (HPS) in the Americas. These pathogens are maintained in the wild by rodent reservoirs and are mainly transmitted via the aerosol route. The infection is chronic and apparently asymptomatic in host animals. Whilst HFRS is caused by Hantaan, Seoul, Dobrava and Pumala hantaviruses, HPS is associated with Sin Nombre-like viruses. Common clinical features of HFRS and HPS include fever, myalgia, thrombocytopenia, leukocytosis and a capillary leak syndrome associated with shock in most severe cases. Outbreaks of HFRS and HPS are generally observed during years with dense rodent populations resulting from favourable climatic and environmental conditions. Human activities, such as rodent trapping, farming, cleaning rodent-infested areas, construction work, camping and hunting, are also implicated in the occurrence of hantavirus disease. Prophylactic measures in endemic areas rely essentially on information campaigns and rodent control.

Keywords

Introduction and history
Hantaviruses, members of the family Bunyaviridae, are rodent-borne viruses causing the human diseases known as haemorrhagic fever with renal syndrome (HFRS) in Europe and Asia, and more recently, as hantavirus pulmonary syndrome (HPS) in the Americas (28, 32, 132).

Outbreaks of illnesses characterised by haemorrhagic fever associated with a renal syndrome were reported in the early 1930s, notably in Russia and among Japanese troops in Manchuria (16, 32). A milder clinical form was also described in Sweden (89, 141). According to the geographical occurrence of the disease, HFRS was given different denominations such as Songo fever (People's Republic of China), epidemic haemorrhagic fever (People's Republic of China, Japan, eastern Europe), Korean haemorrhagic fever (KHF) (Republic of Korea), haemorrhagic nephroso-nephritis (Union of Soviet Socialist Republics) and nephropathia epidemica (NE) (Scandinavia) (33). Western physicians started to consider HFRS as a serious medical problem during the Korean War when over 3,000 United Nations soldiers presented a febrile illness characterised by myalgia, haemorrhagic manifestations, acute renal failure and by a mortality ranging between 10% and 15% (32, 119).

The viral aetiology of HFRS was suggested in the early 1940s when researchers from Russia and Japan reproduced the disease in 'volunteers' injected with filtered urine or serum from naturally infected patients (32). However, not until 1978 did Lee and colleagues report the isolation of Hantaan (HTN) virus, the aetiological agent of KHF, from tissues of striped field mice (Apodemus agrarius) trapped near the Hantaan river in the Republic of Korea (66). In 1982, the same research group reported a milder form of HFRS which developed in people from cities in the Republic of Korea, after contact with commensal rats (Rattus rattus and R. norvegicus) (67). The causative virus, named Seoul (SEO), was also detected in rat populations of port cities world-wide (19, 59, 60, 61). In the United States of America (USA), SEO variants such as Tchoupitoulas and Girard Point viruses were found in R. norvegicus trapped in harbours located in Louisiana and Pennsylvania, respectively (60, 123).
In Europe, the causative agent of NE was first isolated in the early 1980s from the lungs of red bank voles (Clethrionomys glareolus) and was named Puumala (PUU) virus, after the south-eastern region of Finland where the infected rodents were trapped (12, 91). In the 1990s, viruses genetically related to PUU have been isolated from eastern and central Europe but have not been associated with a human disease. These hantaviruses, named Tula (TUL), Topografov (TOP) and Khabarovsk (KBR) are carried by European common voles (Microtus arvalis and M. rossiaemeridionalis), Siberian lemmings (Lemmus sibiricus) and reed voles (M. fortis), respectively (49, 105, 106, 126).

In the Balkans, the isolation of a hantavirus serologically related to HTN was reported in 1992 from the lungs of a yellow-necked field mouse (A. flavicollis) captured in a region of Slovenia in which severe cases of HFRS had occurred (8). Later, the virus, named Dobrava (DOB), appeared to be distributed widely in south-eastern Europe (51, 77, 99). The presence of human cases associated with DOB virus was also recently reported in Russia and Estonia where viral genome sequences were detected in A. agrarius (76, 78, 109). More recently, DOB infection was reported in Germany, in a 19-year-old man from a rural region in the east of the country (82).

The first isolation of an indigenous New World hantavirus was reported in 1982 (70). The virus was called Prospect Hill (PH) and was isolated from the tissues of a meadow vole (M. pennsylvanicus) captured near Frederick, Maryland, USA. No human disease associated with PH virus was reported. However, in 1993, another virus which was indigenous to America and genetically was closely related to PH was identified as the causative agent of a syndrome first referred to as unexplained adult respiratory distress syndrome (UARDS) (28, 90). The disease, later renamed HPS, was characterised by a prodromal phase of fever, chills and myalgia and evolved into a fatal syndrome of shock and pulmonary oedema in 40% to 50% of the cases. The outbreak of HPS occurred in the Four Corners region where the borders of Utah, Colorado, New Mexico and Arizona meet; the outbreak principally involved the Navajo American Indian population. The causative agent, initially named Four Corners and later Muerto Canyon virus, was finally called Sin Nombre (SN) virus. The deer mouse (Peromyscus maniculatus) was rapidly identified as the natural reservoir of the virus (21).

Several epidemics and sporadic cases of HPS, associated with viruses genetically related to SN, have also been reported in South America (46, 73, 100, 104, 131, 140). In some cases, the natural reservoir of the virus has not yet been determined. Person-to-person transmission of the disease was reported during an outbreak in southern Argentina in 1996 (97, 130). Further investigations to improve understanding of the epidemiology of the infection are in progress.

Importance for animal and public health

The hantaviruses known to be pathogenic for humans include HTN and SEO in Asia (with a world-wide distribution of sporadic cases for SEO), PUU and DOB in Europe, SN, Bayou (BAY), Black Creek Canal (BCC), Monongahela and New York (NY) in North America, and Andes (AND), Oran, Laguna Negra, Rio Mamore (RIOM), Lechiguanas and Juquitoiba in South America (83, 102, 138).

The mortality rate for HFRS ranges from 0.1% to 0.2% for PUU to 10% to 13% for HTN and DOB infections (65). Hantaviruses responsible for HPS in the Americas are associated with a higher fatality rate, averaging 45% (138).

The geographical distribution of the rodent hosts generally determines the area in which hantavirus disease occurs. In many countries, HFRS and HPS constitute a significant public health problem. Between 150,000 and 200,000 cases of HFRS are observed annually in the People's Republic of China (65). The Republic of Korea and Russia report hundreds to thousands of cases each year (65). Several pathogenic hantavirus strains co-circulate in the Samara and Bashkirtostan regions which are the areas of western Russia in which HFRS is most endemic (4). In northern Europe where NE is highly endemic, the annual incidence ranges from 100 to 300 cases in Sweden, to 1,000 cases in Finland (88). The seroprevalence of hantavirus infection averages 5% in the population of Finland and may reach 20% in some areas (88). A serological survey from northern Sweden showed infection rates as high as 30% to 40% in the older age groups tested (2). In France, Germany, the Netherlands and Belgium, serological studies of the population reported a seroprevalence of PUU virus ranging between 1% and 2% (25, 40, 58, 142). Several hundreds of cases of NE were recorded in both France and Belgium during two consecutive outbreaks that occurred from 1992 to 1993 and from 1995 to 1996 (26, 41, 57). The epidemiological situation is more complex in the Balkans due to the co-circulation of DOB, HTN, SEO and PUU viruses. An HFRS outbreak was reported in Bosnia-Herzegovina and Croatia in 1995 with between 300 and 400 cases recorded; both PUU and DOB viruses were implicated (51, 77, 81). Seroprevalence rates of 4% and 2.5% were recorded among the populations of Greece and Bosnia-Herzegovina, respectively (88, 99).

In North America, HPS cases have been documented in twenty-nine States of the USA and in three Provinces of Canada (98). The most significant outbreak occurred in 1993 in the Four Corners region of south-western USA. In South America, outbreaks and sporadic cases of HPS have been reported in Argentina, Brazil, Chile, Faray, Bolivia and Uruguay (98, 138).
Although rodents constitute the natural reservoir of hantaviruses, infected animals have also been detected in several domestic species. Antibodies to hantavirus have been found in cats living outdoors in the People's Republic of China, Austria, the United Kingdom (UK) and the USA (10, 20, 79, 95). An epidemiological survey in the USA showed reactivity to SN virus in the sera of 2.8% and 3.5% of tested cats and dogs, respectively (80). Seropositive chickens and swine have also been detected in the Republic of Korea (62). Seropositive cats, dogs, guinea-pigs and rabbits have been reported in laboratories where the animals were kept together with infected rodents (125). Antibodies have also been detected in wild-living animals such as moose (Alces alces) in Sweden and long-tailed weasels (Mustela frenata) in the USA (3, 56).

Hantaviruses have not been associated with a pathology in any non-rodent species other than humans. Further investigations would be necessary to determine whether heterologous hosts are capable of shedding hantaviruses; however the scarcity of spill-over events suggests that the role of these hosts in the spread of infection is limited.

Aetiological agent

Hantaviruses constitute a genus of antigenically, genetically and epidemiologically related viruses of the family Bunyaviridae (114, 115). Other members of this family are arthropod-borne viruses classified in four genera named Bunyavirus (e.g. Bunyamwera, California encephalitis, La Crosse, Akabane), Nairovirus (e.g. Crimean-Congo haemorrhagic fever, Nairobi sheep disease), Phlebovirus (e.g. sandfly fever, Rift Valley fever, Uukuniemi) and Tospovirus (e.g. tomato spotted wilt) (14). All Bunyaviridae share the common feature of being enveloped viruses with a three-segmented genome of negative-strand ribonucleic acid (RNA). The virions are spherical or oval, with a diameter between 90 nm and 120 nm and contain three nucleocapsids each consisting of an RNA segment and nucleocapsid and polymerase proteins. The genome consists of a large (L), medium (M) and small (S) segment (7, 29). The L segment, approximately 6,500 nucleotides long, encodes an RNA-dependent RNA polymerase. The M segment, 3,600 to 3,800 nucleotides in length, encodes the glycoproteins (G) G1 and G2 that form a grid-like pattern on the surface of the lipoprotein envelope. The S segment, between 1,600 and 2,100 nucleotides in length, encodes the nucleocapsid protein. The 3' and 5' termini of the three segments are conserved and complementary, allowing the formation of panhandle structures which are thought to play a role in the regulation of viral replication and transcription (113). Budding of hantaviruses occurs in the Golgi compartment, in the endoplasmic reticulum, and for SN virus, on the surface of the plasma membrane (113, 37).

Based on patterns of neutralisation, immunofluorescence and immunoprecipitation, the hantaviruses were initially differentiated into four main serotypes, namely, HTN, SEO, PUU and PH (71, 115, 118). Six additional hantaviruses have been isolated in cell culture and serologically differentiated as DOB, KBR, Thailand (THAI), Thottapalayam (TPM), SN and BCC serotypes (9, 22, 49, 112). The isolation of hantaviruses is slow, laborious and generally requires biosafety level 3 facilities. The use of reverse transcriptase-polymerase chain reaction (RT-PCR) and the subsequent genetic analysis of amplified deoxyribonucleic acid (DNA) sequences has facilitated the differentiation of hantaviruses; approximately thirty different genotypes have been recognised using this method. The principal hantaviruses described to date are presented in Table I. In common with other RNA viruses, hantaviruses are maintained in rodent populations in the form of a mixture of genetic variants; this may complicate the differentiation of viral strains. Morzunov et al. have proposed three essential criteria for the evaluation of a new hantavirus species, as follows:

- immunological evidence with a four-fold or greater two-way difference between viruses in plaque reduction neutralisation assays;
- ecological evidence with a clear association of the new hantavirus species with a different rodent host;
- molecular evidence with a significant nucleotide difference (more than 25% variation in the glycoprotein open-reading frame [ORF] sequence) and amino acid difference (minimum 5% to 6% variation in the nucleoprotein sequence) compared to previously characterised hantaviruses (85).

Epidemiology of infection

Hantavirus disease in humans generally results from the inhalation of excreta that have spread by the aerosol route from infected rodents or, more rarely, is associated with rodent bites. No arthropod vector has been proved to be implicated in the transmission of the virus. The occurrence of human cases is often seasonal and depends on the fluctuations of rodent densities and on human activities which increase the risk of exposure to contaminated materials. According to the likelihood of contact with rodents or excreta, 'groups at risk' have been defined, including animal room workers, animal breeders, rodent control officers, mammalogists, soldiers, farmers, construction workers, hunters, hikers and campers (65). Hantavirus disease is more frequent in males than in females and the incidence generally peaks within the twenty-to fifty-year-old age group for HFRS and from twenty-five to forty-five years of age for HPS (83, 111, 121). The main epidemiological and clinical features associated with hantavirus infections are presented in Table II. In Asia and Europe, HTN, SEO, DOB and PUU are known to cause HFRS with varying degrees of severity. Infection with HTN causes a severe clinical form of HFRS and is found mainly in the rural areas of the People's Republic of China, the Republic of Korea...
Table I
Principal hantaviruses recognised to date: reservoir, pathogenicity for humans and distribution (83, 98, 107, 117)

<table>
<thead>
<tr>
<th>Hantavirus</th>
<th>Main host</th>
<th>Disease</th>
<th>Distribution of detected virus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subfamily Murinae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hantaan (HTN)</td>
<td>Apodemus agrarius (striped field mouse)</td>
<td>Severe HFRS</td>
<td>Asia (People's Republic of China, Republic of Korea, Japan, central and eastern Europe)</td>
</tr>
<tr>
<td>Seoul (SEO)</td>
<td>Rattus rattus, R. norvegicus (common rat, Norway rat)</td>
<td>Moderates HFRS</td>
<td>World-wide</td>
</tr>
<tr>
<td>Dobrava (DOB)</td>
<td>Apodemus flavicollis (yellow-necked field mouse)</td>
<td>Severe HFRS</td>
<td>Balkans, Russia, Estonia</td>
</tr>
<tr>
<td>Thaiand (THAI)</td>
<td>Bandicota indica (bandicoot rat)</td>
<td>Unknown</td>
<td>Thailand</td>
</tr>
<tr>
<td><strong>Subfamily Arvicolinae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puumala (PJJU)</td>
<td>Clethrionomys glareolus (red bank vole)</td>
<td>Mild HFRS/NE</td>
<td>Northern, western, central Europe, Balkans, Russia</td>
</tr>
<tr>
<td>Tula (TUL)</td>
<td>Microtus arvalis, M. rossiaemeridionalis (European common vole)</td>
<td>Unknown</td>
<td>Europe (Czech Republic, Slovakia, Russia)</td>
</tr>
<tr>
<td>Topagrafov (TOP)</td>
<td>Lemmus sibiricus (Siberian lemming)</td>
<td>Unknown</td>
<td>Siberia</td>
</tr>
<tr>
<td>Khararosiv (KBR)</td>
<td>Microtus fortis (reed vole)</td>
<td>Unknown</td>
<td>Russia (extreme east)</td>
</tr>
<tr>
<td>Prospect Hill (PH)</td>
<td>Microtus pennsylvanicus (meadow vole)</td>
<td>Unknown</td>
<td>United States of America, Canada</td>
</tr>
<tr>
<td>Isla Vista (ISLA)</td>
<td>Microtus californicus (California vole)</td>
<td>Unknown</td>
<td>United States of America, Mexico</td>
</tr>
<tr>
<td><strong>Subfamily Sigmodontinae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sin Nombre (SN)</td>
<td>Peromyscus maniculatus (deer mouse)</td>
<td>HPS</td>
<td>United States of America, Mexico</td>
</tr>
<tr>
<td>New York (NY)</td>
<td>Peromyscus leucopus (white-footed mouse)</td>
<td>HPS</td>
<td>United States of America</td>
</tr>
<tr>
<td>Bayou (BAY)</td>
<td>Oryzomys palustris (rice rat)</td>
<td>HPS</td>
<td>United States of America</td>
</tr>
<tr>
<td>Black Creek Canal (BCC)</td>
<td>Sigmodon hispidus (cotton rat)</td>
<td>HPS</td>
<td>United States of America</td>
</tr>
<tr>
<td>Monongahale (MOL)</td>
<td>Peromyscus maniculatus (deer mouse)</td>
<td>HPS</td>
<td>United States of America</td>
</tr>
<tr>
<td>El Mero Canyon (ELMC)</td>
<td>Reithrodontomys megalotis (western harvest mouse)</td>
<td>Unknown</td>
<td>United States of America, Mexico</td>
</tr>
<tr>
<td>Mulikowsi (MUL)</td>
<td>Sigmodon hispidus (cotton rat)</td>
<td>HPS</td>
<td>United States of America</td>
</tr>
<tr>
<td>Rio Segunda (RIO)</td>
<td>Reithrodontomys mexicanus (Mexican harvest mouse)</td>
<td>Unknown</td>
<td>Costa Rica</td>
</tr>
<tr>
<td>Andes (AND)</td>
<td>Oligoryzomys longicaudatus (long-tailed pygmy rice rat)</td>
<td>HPS</td>
<td>Argentina</td>
</tr>
<tr>
<td>Laguna Negra (CHP)</td>
<td>Calomys laucha (vesper mouse)</td>
<td>HPS</td>
<td>Paraguay</td>
</tr>
<tr>
<td>Dorn</td>
<td>Oligoryzomys longicaudatus (long-tailed pygmy rice rat)</td>
<td>HPS</td>
<td>Argentina</td>
</tr>
<tr>
<td>Lachigunsas (LEC)</td>
<td>Oligoryzomys flavescens (long-tailed mouse)</td>
<td>HPS</td>
<td>Argentina</td>
</tr>
<tr>
<td>Rio Maruna (RIOM)</td>
<td>Oligoryzomys microtis (small-eared pygmy rice rat)</td>
<td>Unknown</td>
<td>Bolivia</td>
</tr>
<tr>
<td>Cama Delgardito (CANO)</td>
<td>Sigmodon aleti (cotton rat)</td>
<td>Unknown</td>
<td>Venezuela</td>
</tr>
<tr>
<td>Juquitiba</td>
<td>Unknown</td>
<td>HPS</td>
<td>Brazil</td>
</tr>
<tr>
<td><strong>Order Insectivora</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thottapalayam (TPM)</td>
<td>Suncus murinus (musk shrew)</td>
<td>Unknown</td>
<td>India</td>
</tr>
</tbody>
</table>

HFRS : haemorrhagic fever with renal syndrome
HPS : hantavirus pulmonary syndrome
NE : nephropathia epidemica

and the extreme east of Russia (65). The incidence of HFRS cases in Asia generally presents a major peak in late autumn and early winter and is associated with the harvest activities which increase the risk of contact with striped field mice, the reservoir of HTN virus (111). An epidemiological survey during an outbreak of HFRS in the Anhui province in the People's Republic of China showed notably that sleeping on the ground or heavy farm work, such as threshing, constituted a significantly higher risk of illness than did sleeping on wooden beds or light work (133). Biotic and climatic conditions were also shown to influence the occurrence of hantavirus disease. Lower precipitations in the Huai River region in the People's Republic of China, which provide more arable farmlands and a favorable micro-environment for mice, were found to increase the opportunity of exposure to infected rodents and therefore to increase the incidence of cases of HFRS (11).

The milder form of HFRS associated with SEO virus has been mainly reported in urban areas in the Republic of Korea, the People's Republic of China, Japan and Hong Kong (63). Sporadic cases have also been recorded in South America where patients were first suspected of developing an acute leptospirosis (42). Unlike the incidence of HFRS caused by HTN, human cases associated with SEO virus occur throughout the year. Wild rats infected with SEO virus have also been detected in the US, Africa, India and several Pacific
islands in addition to several European countries (e.g. Greece, Germany, Serbia, Croatia, Slovenia and Northern Ireland) (27, 63, 135). In addition, laboratory outbreaks due to SEO virus infection have been reported in Japan, the Republic of Korea, the People’s Republic of China, Russia, France, Belgium, the Netherlands and the UK (65).

The DOB virus causes a severe form of HFRS in the Balkans. The disease generally occurs in late spring, summer and early autumn and is mainly associated with farming and forestry activities, sheep herding and military operations (36, 83).

The PUU virus, which is the aetiological agent of the mildest form of HFRS called NE, is distributed in most countries of Europe where red bank voles prevail. The highest incidence of human cases occurs in northern Europe where the density of these voles varies in a cyclic pattern over periods of three to four years. Outbreaks of NE coincide with the years when rodent populations reach a peak. Human cases in northern Europe are mainly reported in rural areas and the occurrence of the disease follows a seasonal distribution with a major peak in late autumn and early winter, due to the movement of bank voles into houses and outbuildings. This is followed by a minor peak during the summer months, coinciding with increased human outdoor activities (59, 92). Infection with PUU virus was also found in the grey-sided vole (Clethrionomys rujocanus) in Hokkaido, Japan, but was not associated with disease in man (53).

In the USA, the outbreak of HPS in 1993 occurred after the El Niño-associated heavy precipitations that had significantly increased the production of pine nuts, allowing the proliferation of *P. maniuculatus*, the natural reservoir of SN virus (28, 90). In total, over two hundred cases of HPS were reported between 1993 and the end of 1998 in North America (98). According to epidemiological surveys, infected patients generally resided in rural areas and were engaged in agricultural activities or reported a recent history of cleaning or working in closed buildings with evidence of rodent infestations (44). Information about the likely sites of patient exposure have often been derived from the characterisation of hantavirus genotypes among rodents trapped at suspected sites and the comparison of these data with the viral genome sequences obtained from blood or tissues of the infected patients (44).

In South America, 239 cases of HPS were reported in five different countries during 1998. More than a quarter of all recognised cases occurred in clusters, mainly during the spring and summer (98).

The absence of hantavirus disease in nurses and doctors involved in caring for more than 3,000 United Nations military personnel infected with HTN virus during the Korean War (68), and in 266 medical staff exposed to patients with HPS during the outbreak in 1993 (128), suggests that hantaviruses in Asia and North America are not subject to

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**Table II**

**Epidemiology of hantavirus infections**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Hantavirus strain</th>
<th>Distribution</th>
<th>Epidemiology</th>
<th>Seasonality</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe HFRS</td>
<td>HTN</td>
<td>Asia</td>
<td>Agricultural activities: - harvesting, threshing - planting</td>
<td>Late autumn, early winter (major peak)</td>
<td>Fever, haemorrhage, renal failure, myalgia, hypotension, thrombocytopenia, leukocytosis, abdominal pain, backache</td>
</tr>
<tr>
<td></td>
<td>DOB</td>
<td>Europe</td>
<td>Farming, forestry activities, herding, military operations</td>
<td>Late spring, summer (minor peak)</td>
<td></td>
</tr>
<tr>
<td>Moderate HFRS</td>
<td>SEO</td>
<td>World-wide</td>
<td>Urban exposure to rats, laboratory-acquired infections</td>
<td>Throughout the year</td>
<td>Fever, renal failure, thrombocytopenia, leukocytosis, backache</td>
</tr>
<tr>
<td>NE</td>
<td>PUU</td>
<td>Europe</td>
<td>Movement of voles into houses and out-buildings, wood cutting</td>
<td>Late autumn, early winter (major peak)</td>
<td>Fever, renal failure, thrombocytopenia, leukocytosis, backache</td>
</tr>
<tr>
<td>HPS</td>
<td>SN, BAY, NY, BCC, MGL</td>
<td>North America</td>
<td>Cleaning or working in buildings infected with rodents, agricultural and recreational activities</td>
<td>Throughout the year (less frequent during the winter)</td>
<td>Fever, hypotension, pulmonary capillary leak, leukocytosis, thrombocytopenia, cough. BAY, BCC, AND, renal failure</td>
</tr>
<tr>
<td></td>
<td>AND, CHN, SNP, CL, ACQ</td>
<td>South America</td>
<td>House exposure to rodents, person-to-person transmission</td>
<td>Throughout the year (more frequent in spring and summer)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations**

- AND : Andes
- BAY : Bayou
- BCC : Black Creek Canal
- CHN : Laguna Negra
- CL : Puumala
- Coach : Seoul
- DOB : Dobrava
- HFRS : Hemorrhagic Fever Renal Syndrome
- HPS : Hantavirus Pulmonary Syndrome
- HTN : Hantaan
- MGL : Monongahela
- NE : Nephropathia Epidemica
- NY : New York
- SEO : Seoul
- SN : Sin Nombre

**Clinical Characteristics**

- Fever, haemorrhage, renal failure, myalgia, hypotension, thrombocytopenia, leukocytosis, abdominal pain, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, hypotension, pulmonary capillary leak, leukocytosis, thrombocytopenia, cough. BAY, BCC, AND, renal failure

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**Infections**

- Infection with hantaviruses in Asia and North America are not subject to

**Abnormalities**

- Fever, haemorrhage, renal failure, myalgia, hypotension, thrombocytopenia, leukocytosis, abdominal pain, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, hypotension, pulmonary capillary leak, leukocytosis, thrombocytopenia, cough. BAY, BCC, AND, renal failure

**Transmission**

- Throughout the year (less frequent during the winter)
- Throughout the year (more frequent in spring and summer)

**Disease Distribution**

- Scandinavia: 3-4 year cyclicity (outbreaks correspond to peaks in vole populations)
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, hypotension, pulmonary capillary leak, leukocytosis, thrombocytopenia, cough. BAY, BCC, AND, renal failure

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**Clinical Symptoms**

- Fever, thrombocytopenia, leukocytosis, backache
- Fever, haemorrhage, renal failure, myalgia, hypotension, thrombocytopenia, leukocytosis, abdominal pain, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, renal failure, thrombocytopenia, leukocytosis, backache
- Fever, hypotension, pulmonary capillary leak, leukocytosis, thrombocytopenia, cough. BAY, BCC, AND, renal failure

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**Conclusion**

- The absence of hantavirus disease in nurses and doctors involved in caring for more than 3,000 United Nations military personnel infected with HTN virus during the Korean War (68), and in 266 medical staff exposed to patients with HPS during the outbreak in 1993 (128), suggests that hantaviruses in Asia and North America are not subject to
hantavirus and was isolated in India in 1971 from a shrew. After a short viraemia and the development of antibodies that persist for the lifetime of the host, the virus replicates in different organs, such as the lungs, kidneys, liver, spleen, intestines and salivary glands (39, 136). The virus is shed persistently or sporadically in urine, faeces and saliva (34, 122, 136). Transmission of hantaviruses occurs through horizontal routes and results in a higher frequency of infection in males of heavier weight ranges (18, 84, 93). New-born rodents appear to be protected by maternal antibodies (34). Social behaviour, such as grooming, biting, scratching and exposure to nesting materials are important for the maintenance of the enzootic cycle. After a short viraemia and the development of antibodies that persist for the lifetime of the host, the virus replicates in different organs, such as the lungs, kidneys, liver, spleen, intestines and salivary glands (39, 136). The virus is shed persistently or sporadically in urine, faeces and saliva (34, 122, 136). Transmission of hantaviruses occurs through horizontal routes and results in a higher frequency of infection in males of heavier weight ranges (18, 84, 93). New-born rodents appear to be protected by maternal antibodies (34). Social behaviour, such as grooming, biting, scratching and exposure to nesting materials are important for the maintenance of the enzootic cycle.

Ecological factors, such as climatic conditions, food supply, predators or diseases, influence rodent population dynamics and thus the occurrence of hantavirus disease in humans. Epidemic years are generally associated with favourable climatic conditions and heavy seed crops leading to improved survival and breeding of reservoir rodents. The higher population densities, coupled with a higher prevalence of hantavirus infection in rodents, increases the risk of contact with infected animals and therefore the occurrence of human cases. During non-epidemic periods, infection rates in rodents may be independent of population size and the virus activity may be focal and unevenly distributed in the host species (1, 38, 127, 129).

An epidemiological survey of red bank voles during a non-epidemic year reported that the majority of seropositive rodents showed no evidence of current infection. In contrast, SN viral RNA and specific antibodies were concomitantly detected in more than 90% of deer mice trapped during the 1993 outbreak of HPS (5, 21, 96). These observations suggest that the virus is spread during the early stage of an outbreak and that animals are much less contagious during other periods.

Pathogenesis and lesions

Five phases of illness, designated febrile, hypotensive, oliguric, diuretic and convalescent, characterise the clinical course of HFRS and are particularly distinct in the severe form of the disease (24, 44, 83, 102). After an incubation period of two to three weeks (ranging from five to forty-two days), the disease commences with headache, myalgia, malaise, back and abdominal pain, nausea and vomiting. Dizziness and blurred vision may also be observed. Haemorrhagic manifestations, such as flushing of the face, neck and anterior chest, and injection of the eyes, are also present in the febrile phase. Thrombocytopenia, an elevated white blood cell count and haemoconcentration are usual laboratory findings. The hypotensive phase develops after three to seven days and is mainly characterised by the classical signs of shock (tachycardia, narrowed pulse pressure, hypotension) which may be irreversible in one third of patients. This phase lasts for two to three days. Laboratory data show increased haemoconcentration, leucocytosis with left shift, marked thrombocytopenia, proteinuria and haematuria. During the oliguric phase, patients stabilise haemodynamically but may become hypertensive as a rebound effect of the previous hypotensive state. Persistent oliguria is associated with epistaxis and severe gastrointestinal, genitourinary, retroperitoneal and central nervous system bleeding. Pulmonary oedema occurs in most severe cases. Elevated levels of blood urea and creatinine, acidosis and metabolic disturbances related to the renal failure are commonly reported. The diuretic phase commences three to seven days after the oliguric phase and corresponds to the beginning of clinical recovery. This phase can continue for a few days or several weeks and is mainly characterised by polyuria that can lead to severe fluid and electrolyte imbalances. The convalescent phase extends for two to three months and recovery is complete in most patients. Although sequelae are rare for HFRS, anaemia and hypopithonuria may persist for months in some cases. An association between seropositivity to SEO virus and a chronic hypertensive renal disease has also been reported in Baltimore, USA (35).

In NE, renal failure predominates and haemorrhagic manifestations are generally absent. The fatality rate is inferior to 1% and in many cases the infection may be asymptomatic.
Nonetheless, severe complications, such as pulmonary oedema, haemorrhages and Guillain-Barré syndrome have been documented in some patients (26, 30, 83, 103).

In comparison with HFRS, HPS has a more severe clinical course with an average mortality rate of 45%, haemorrhagic manifestations are absent and most of the pathogenic events occur in the thoracic cavity (44, 83, 102, 117). However, a renal involvement has been reported with BAY, BCC and AND infection (45, 54, 117). Onset of HPS is abrupt with prodromal symptoms of fever, myalgia, headache, nausea, vomiting, abdominal pain and sometimes dizziness and coughing. After three to six days, the cardiopulmonary phase commences with coughing, dyspnoea, shortness of breath, tachycardia, fever and hypotension. A pulmonary oedema develops rapidly and generally requires intubation and mechanical ventilation. Severe cardiopulmonary dysfunctions correlate with a poor prognosis. Haemoconcentration, thrombocytopenia, left-shift leukocytosis and mild to moderate proteinuria are observed frequently. Clinical improvement is usually rapid and sequelae for HPS have not been reported.

Necropsy findings from fatal cases of HFRS include focal haemorrhages in the kidneys, pituitary gland, pancreas, skin and meninges, retroperitoneal oedema and in some cases, pulmonary oedema (83). Congestion and haemorrhages are observed in the renal medulla, with the tubular epithelium showing varying grades of degeneration. Changes observed in renal biopsy of NE cases are consistent with an acute tubulo-interstitial nephritis (86).

Macroscopic examination of patients who have died of HPS show oedematous and heavy lungs, large bilateral pleural effusion and splenomegaly. Histological findings include interstitial infiltrates with mononuclear cells in the lungs, spleen and lymph nodes and sparse to moderate hyaline membranes in the lungs (83).

Most symptoms observed during infection with HFRS or HPS are related to capillary leak. Although hantaviruses replicate in vascular endothelium, the viruses do not cause any cytopathic effect. This observation, in addition to the early immune response at the onset of symptoms, the activation of cluster of differentiation antigen (CD8+) thymus (T) cells and the increased levels of cytokines (e.g. interferon-γ [IFNγ], tumour necrosis factor α [TNFα], interleukin [IL]-2, IL-6) reported in HFRS and HPS patients, suggest an immunopathological basis of hantavirus disease (17, 72, 94, 139). Moreover, in HFRS, activation of complement and circulation of immune complexes have also been documented and is a useful tool for rapid differentiation of viral strains (43, 48, 90).

Diagnosis

The diagnosis of HFRS and HPS is based on clinical and epidemiological information and is confirmed by specific serological tests. In some cases, the detection of viral antigens or viral RNA may also be successful. Immunoglobulin M (IgM) antibodies are detected in the early phase of the disease and may persist in patient sera for several months. Immunoglobulin G (IgG) antibodies appear slightly later than IgM and are detectable for decades. Cross-reactivity occurs between hantaviruses which are genetically closely related, such as the HTN/SEO/DOB and PUU/TUL/SN groups. Classically, hantavirus-specific antibodies were detected by immunofluorescence assay and enzyme-linked immunosorbent assay (ELISA), using native antigens (68). Haemagglutination inhibition and complement fixation methods have also been described. Due to the hazardous nature of hantaviruses and the fact that production is slow, with low yields, tests using recombinant antigens and synthetic peptides have been developed. The nucleoprotein is the major antigen target in the early stages of infection and assays based on baculo- and E. coli-expressed nucleoprotein are good diagnostic tools (13, 31). Neutralisation tests are also used to provide reliable evidence of the serotype incriminated in the infection.

Successful antigen detection by immunohistochemical methods has been reported in biopsies and post-mortem samples from patients with severe HFRS or HPS (110, 139). More recently, the use of RT-PCR for the detection of viral RNA in body fluids and tissues of patients has also been documented and is a useful tool for rapid differentiation of viral strains.

Treatment

No specific treatment is available against the primary viral aetiology of HFRS and HPS. Severe cases of HFRS require hospitalisation, monitoring during the acute phase, fluid and electrolyte therapy and inotropic agents to support the blood pressure (24, 44). Dialysis may be employed in case of severe acute renal failure. Analgesics, tranquilisers and antibiotics for secondary bacterial infections may also be administered. In the People’s Republic of China, intravenous injection of ribavirin in the early stages of the disease was shown to reduce mortality and the severity of symptoms (50).

Management of HPS includes hospitalisation and intensive care, fluid therapy, administration of vasopressors and antibiotics, and close monitoring of oxygenation (44, 102). Ribavirin has failed to show efficacy in HPS.
Table III
General guidelines for prevention of hantavirus infection (83, 98)

<table>
<thead>
<tr>
<th>Prevention of infection</th>
<th>Precautionary measure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General household precautions</strong></td>
<td></td>
</tr>
<tr>
<td>a) preventing rodents from entering houses and outbuildings</td>
<td>Cover holes and openings</td>
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<tr>
<td></td>
<td>Discourage rodent burrowing and nesting</td>
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<tr>
<td></td>
<td>Cut grass around buildings</td>
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<td></td>
<td>Avoid woodpiles</td>
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<td></td>
<td>Remove food sources, elevate garbage containers</td>
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<tr>
<td></td>
<td>Use traps and rodenticides</td>
</tr>
<tr>
<td>b) cleaning rodent-infested areas</td>
<td>Wear gloves and a mask</td>
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<tr>
<td></td>
<td>Avoid aerosols</td>
</tr>
<tr>
<td></td>
<td>Use disinfectant (e.g. 10% bleach solution)</td>
</tr>
<tr>
<td></td>
<td>Properly dispose of contaminated materials and dead animals</td>
</tr>
<tr>
<td><strong>Precautions for outdoor activities</strong></td>
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<tr>
<td></td>
<td>Avoid contact with rodents</td>
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<tr>
<td></td>
<td>Wear a mask (for workers at high risk of exposure)</td>
</tr>
<tr>
<td></td>
<td>Place campsites away from burrows or rodent shelters</td>
</tr>
<tr>
<td><strong>Precautions for rodent trapping and collection of samples</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wear protective clothing and equipment (gloves, mask)</td>
</tr>
<tr>
<td></td>
<td>Choose an adequate processing site for collection of samples</td>
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<tr>
<td></td>
<td>Anaesthetise animals before manipulation</td>
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<tr>
<td></td>
<td>Decontaminate working surfaces and items used for handling and dissecting rodents</td>
</tr>
</tbody>
</table>

Vaccines and prophylaxis

Vaccines

Development of inactivated vaccines for HFRS has been documented in Asia (69, 74, 120). Vaccinia and baculovirus recombinant vaccines expressing the glycoproteins G1 and G2 of HTN and SEO viruses have been found to induce a neutralising and protective antibody response in rodents (23, 116). The nucleoprotein expressed in bacteria or baculovirus, and as chimeric hepatitis B virus core particles, was also shown to induce protection in rodents, despite the absence of neutralising antibodies (75, 116, 124, 137). Recently, a successful vaccination strategy, based on the administration of naked DNA expressing the M segment of SEO virus, has been reported in rodents (47).

Prevention

The risk of contracting hantavirus infection is highest when exposure to rodents or rodent droppings occurs. Results of studies on the viability of HTN virus suggest that the virus may remain infectious in an aerosol for several days after excretion by rodents into the environment (113).

Preventive measures for all hantaviruses include rodent control in and around houses and outbuildings, elimination of food sources and possible nesting sites (Table III). When cleaning rooms infested with rodents, the wearing of gloves and a mask is recommended and a disinfectant should be used. Hantaviruses are labile notably to acid (pH<5), ether, chloroform, sodium hypochlorite, 70% ethanol, heat (60°C for 30 minutes), formalin, ultraviolet and most general-purpose household disinfectants (52). Clinical samples from patients constitute a limited biohazard. In contrast, tissues and excreta from wild rodents must be manipulated in a biosafety hood. Personnel trapping rodents or collecting blood and tissue samples should wear protective equipment, properly anaesthetise animals and carefully disinfect contaminated working spaces, equipment and clothing. Monitoring of laboratory rodents for hantavirus infection may be performed by serological screening; positive animals should be disposed of upon detection.

Conclusion

Hantavirus infection in humans has been recognised as an emerging zoonosis in the Americas and in some European countries. The infection represents an important public health concern in many countries throughout the world. Changes in the environment due to human activities and specific climatic and biotic conditions influencing densities of the rodent host populations are determinant factors for the occurrence of hantavirus disease. Long-term reservoir studies and integration of remote sensing with geographic information systems may provide clues for a better understanding of the epidemiology of hantavirus infection and for the development of predictive models concerning the emergence of the disease. Further investigations concerning the phylogenetic relationship and distribution of viral strains, the host specificity, the mechanisms of viral persistence in rodents, the factors influencing the pathogenicity and the transmission of viruses are also a high priority in the research field. Finally, general information campaigns related to the clinical aspects, diagnosis, treatment, prevention and control of hantavirus infection should be addressed to the community and particularly to medical professionals and groups at risk in endemic areas.
Les hantaviroses

S. Escutenaire & P.-P. Pastoret

Résumé
Les hantavirus sont les agents responsables de zoonoses connues sous le nom de « fièvre hémorragique avec syndrome rénal » (FHSR) en Europe et en Asie et « syndrome pulmonaire à hantavirus » (SPH) en Amérique. Les rongeurs sauvages constituent le réservoir des hantavirus qui sont transmis principalement par inhalation. L’infection est chronique et apparemment asymptomatique chez les animaux hôtes. La FHSR est due aux virus Hantaan, Séoul, Dobrava et Puuma tandis que le SPH est associé au virus Sin Nombre et aux souches apparentées. La FHSR et le SPH présentent des signes cliniques communs dont l’hyperthermie, la myalgie, la thrombocytopénie, la leucocytose et une fuite plasmatique associée au syndrome de choc dans les cas les plus graves. Les épidémies de FHSR et de SPH surviennent généralement pendant les années où les densités de populations des rongeurs atteignent un pic suite à des conditions climatiques et environnementales favorables. Certaines activités humaines, telles que la capture de rongeurs, l’élevage, le nettoyage de zones infestées par les rongeurs, les travaux de construction, le camping et la chasse jouent également un rôle dans l’apparition des infections à hantavirus. Les mesures prophylactiques dans les zones endémiques reposent essentiellement sur les campagnes d’information et sur la lutte contre les rongeurs.

Mots-clés

Infecciones por hantavirus

S. Escutenaire & P.-P. Pastoret

Resumen
Los hantavirus son agentes etiológicos de las zoonosis conocidas como fiebre hemorrágica con síndrome renal (FHSR) en Europa y Asia y como síndrome pulmonar por hantavirus (SPH) en el continente americano. Los roedores silvestres constituyen el reservorio natural de esos patógenos, que se transmiten principalmente por partículas de aerosoles. En los animales huéspedes, la infección es crónica y en apariencia asintomática. Los agentes causales de la FHSR son los hantavirus Hantaan, Seoul, Dobrava y Puuma. El SPH, por su parte, aparece asociado a virus afines al virus Sin Nombre. Entre los signos clínicos comunes a ambas enfermedades se cuentan: fiebre, mialgia, trombocitopenia, leucocitosis y un síndrome de pérdida capilar asociado, en los casos más graves, a estados de shock. Los brotes de FHSR y SPH se observan generalmente en años en que las poblaciones de roedores, gozando de condiciones ambientales y climáticas favorables, proliferan y se densifican. Actividades humanas como la colocación de cepos para roedores, la actividad agropecuaria, la limpieza de zonas infestadas de roedores, las obras de construcción, la acampada o la caza también están ligadas a la aparición de la enfermedad por hantavirus. Las medidas de profilaxis adoptadas en zonas endémicas consisten esencialmente en campañas de información y en el control de las poblaciones de roedores.

Palabras clave
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