HANTAVIRUS – A SPECIAL PATHOGEN

Course # DL-001

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HANTAVIRUS – A SPECIAL PATHOGEN

Course # DL-001
2.0 CE
Level of difficulty: Intermediate

Lucy Treagan, Ph.D.
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OBJECTIVES
After completing this course the participant will be able to:
1. Discuss hantaviruses and their role in human disease.
2. Describe the natural reservoir of hantavirus infection.
3. Outline geographic distribution of hantaviruses.
4. Summarize prevalence of hantavirus infection in different geographic areas.
5. Discuss classification of hantaviruses and their principal characteristics.
6. Outline transmission of hantaviruses within the animal reservoir and from natural host to human host.
7. Discuss diseases caused by hantaviruses.
8. Describe methods used in laboratory diagnosis of hantavirus infections.

I. INTRODUCTION
Newly recognized viral diseases continue to be discovered throughout the world. Some of these diseases are severe and life-threatening and are caused by viruses that are highly infectious. Although symptoms may vary, many newly recognized viruses cause hemorrhagic fevers with high case-fatality rates. Identification and control of this group of viruses had been relegated to the Centers for Disease Control and Prevention (CDC) Special Pathogens Branch Laboratory. The laboratory is a Biosafety Level 4 facility with the ability to safely handle highly infectious agents. Viruses investigated at the Special Pathogens Branch Laboratory include agents of Ebola hemorrhagic fever, Marburg hemorrhagic fever, Lassa fever, Rift Valley fever, Crimean-Congo hemorrhagic fever, hantaviruses, and arenaviruses. Hantaviruses have been categorized by the National Institute of Allergy and Infectious Diseases (NIAID) as high priority pathogens that pose a risk to national security because of easy transmission and high case-fatality rate. CDC has assigned hantaviruses to the category of agents that can be engineered for mass dissemination.

All of the agents studied at the Special Pathogens Branch Laboratory are RNA viruses (the viral genetic information is RNA-coded). These viruses are encased in a lipid envelope and show some degree of aerosol infectivity in the laboratory. Additionally, all of these agents are either vector-borne or are zoonotic (human infection is acquired from an animal host).

The mission of the CDC Special Branch Laboratory is to develop diagnostic methods, collect information on epidemiology of special viral pathogens, respond to
disease outbreaks, and offer assistance in detection, control, and prevention of these highly infectious diseases.

II. HISTORICAL BACKGROUND

Hantavirus disease is not new. More than a thousand years ago Chinese physicians had reported a disease now known as hemorrhagic fever with renal syndrome. This disease, as described in ancient records, was characterized by fever, hemorrhages, and renal impairment. Additional records available from various wars such as the U.S. Civil War, World Wars I and II, Sino-Japanese War, and the Korean Conflict describe the occurrence of hemorrhagic fevers among troops.

A different manifestation of hantavirus infection – the hantavirus pulmonary syndrome (HPS) – is not a new disease as well. Symptoms typical of hantavirus pulmonary syndrome have long been recognized by Navajo Indians and have been described in their traditional records.

The first major impact of hantavirus infection on the Western world was during the Korean Conflict when over 3,000 United Nations troops developed hemorrhagic fever with renal syndrome. The illness was accompanied by high mortality rate. The nature of the causative agent was not known at the time the outbreak took place. A breakthrough in identification of the disease agent came in 1978 when Ho-Wang Lee and his South Korea co-workers isolated a viral agent in Korean striped field mice.

In the spring of 1993 an outbreak of an unexplained pulmonary disease took place in the southwestern United States. This outbreak occurred in an area bordered by Arizona, New Mexico, Colorado, and Utah, known as the “Four Corners.” A young Navajo man developed severe pulmonary symptoms and died quite suddenly. The young man’s fiancée who had similar symptoms had died a few days previously. An investigation of the Four Corners area uncovered 5 additional cases in previously healthy young men, all of whom developed severe pulmonary symptoms followed by death. In November 1993, a viral agent that caused the Four Corners outbreak was isolated by the CDC Special Pathogens Laboratory and identified as a hantavirus. The new disease was named the hantavirus pulmonary syndrome and the virus isolated from cases in the Four Corners area was named the Sin Nombre (“no name”) virus.

The most recent outbreak of hantavirus pulmonary syndrome (HPS) took place in Summer 2012 (June – August) in California at Yosemite National Park. Ten cases of HPS were documented, with three deaths. Nine of the cases were visitors to the Park who stayed in upgraded, well-insulated tent cabins at Curry Village. Unfortunately, the insulation in these cabins proved attractive to deer mice. The large summer rodent population and the fact that 20% of the deer mice in Yosemite were found to be infected with hantavirus contributed to the outbreak. Park visitors who stayed in rodent-infested cabins were exposed to large quantities of infected mouse droppings, urine, and saliva.

III. CLASSIFICATION OF HANTAVIRUSES AND THEIR PRINCIPAL CHARACTERISTICS

A. Classification

Hantaviruses are members of the Bunyaviridae family. Over 300 viruses are included in this family. Many of these viruses have a very wide host range, infecting
animals, humans, and arthropods. Four of the genera included in the *Bunyaviridae* family represent important human and veterinary pathogens and are of major public health importance. The fifth genus in the *Bunyaviridae* family, the *Tospovirus*, represents a group of plant-pathogenic viruses.

The five genera of the *Bunyaviridae* family are unified by many common characteristics, such as genome structure, virion composition and organization, and cytoplasmic site of replication. There are, however, major differences in replication strategy and in biological behavior of these viruses. The various genera also differ in their antigenic and molecular characteristics.

Viruses in family *Bunyaviridae* are typically transmitted by arthropod vectors with the notable exception of hantaviruses, which don’t infect arthropods and do not require a vector for transmission of infection.

The five genera included in the family *Bunyaviridae* are:

- Genus *Orthobunyavirus*
- Genus *Phlebovirus*
- Genus *Nairovirus*
- Genus *Tospovirus*
- Genus *Hantavirus*

Genus *Orthobunyavirus* comprises over 170 viruses and includes a number of important human and veterinary pathogens. The viruses in this group affect primarily the central nervous system of the infected host. The infection is transmitted by mosquitoes.

Genus *Phlebovirus* represents emerging pathogens in many countries of the world. One of the phleboviruses, the Rift Valley fever virus, has long been known for zoonotic infections in Africa. More recently Rift Valley fever has spread to several countries in the Mediterranean region. The virus is an important veterinary pathogen that also infects humans. The infection is transmitted by phlebotomous flies.

Genus *Nairovirus* is carried by ticks. Viruses in this genus infect humans, causing hemorrhagic fever.

Genus *Tospovirus* represents plant pathogens. The infection is transmitted by thrips. *Tospovirus* host range includes many important agricultural and horticultural crops, as well as ornamental plants. *Tospovirus* has a world-wide distribution and is counted among the top ten viruses of major economic importance. *Tospovirus* infections of plants are responsible for over a billion dollars in annual crop losses.

Genus *Hantavirus* is widely distributed and has been identified in many countries in Europe, in North and South America, and in Asia. Viruses in this genus are carried by rodents, such as rats and mice. These viruses have also been isolated from insectivores (shrews and moles). Hantaviruses infect humans causing two types of diseases: hemorrhagic fever with renal syndrome and the hantavirus cardiopulmonary syndrome. These illnesses are associated with high mortality rate. A milder form of hemorrhagic fever with renal syndrome is known as nephropathia epidemica. This form of hantavirus infection is found primarily in Scandinavian countries.

### B. Virus structure and organization

Hantavirus virions are spherical particles with an average diameter of 80 to 120 nanometers (nm). Ultrastructural studies show a grid-like pattern on the surface of the virion. This pattern is quite distinct from the surface structure of other *Bunyaviridae*.
The grid-like pattern of hantavirus outer surface reflects the arrangement of viral glycoproteins. Some of the glycoprotein subunits extend approximately 12 nm from the lipid bilayer that envelopes the viral particle.

Viral genome

Hantaviruses have a segmented RNA genome: there are three single-stranded, negative-sense RNA segments. The genome size ranges from 11,845 to 12,317 nucleotides. Since the genome is “negative-sense,” it cannot perform the functions of messenger RNA (mRNA). The three genome segments are known as L (large), M (medium), and S (small). These RNA segments provide genetic information for 4 viral proteins.

Viral proteins

The L segment encodes the RNA-dependent RNA polymerase. This enzyme is involved in transcription of the viral genome into mRNA, generating S, M, and L mRNAs. The polymerase also functions in the replication of the S, M, and L genomic RNA.

The M genomic RNA segment encodes envelope glycoproteins. Initially a glycoprotein precursor is generated, which is subsequently cleaved into Gn and Gc glycoproteins. These proteins are associated with the outer surface of the viral particle.

The S genomic RNA segment encodes the nucleocapsid protein N (the capsid is a protein shell made of identical subunits that protects the viral genome). N protein complexes with viral RNA segments, packaging the viral genome. The N protein has a number of other functions including one in replication of the viral genome.

Surface envelope

The bilayer lipid envelope that surrounds the viral particle is derived from the host cell membranes.

C. Viral replication

Viruses require living cells for replication. Hantaviruses are able to infect a number of cell types including macrophages, lymphocytes, dendritic cells, endothelial cells, and epithelial cells. The viral replication cycle is relatively complex and consists of several steps. The first step involves contact between the virus particle and a susceptible host cell followed by entry of virus into the host cell.

Attachment of virion to host cell

The large glycoprotein Gn protrudes from the viral surface and serves as the viral receptor for host cells. Cellular receptors for hantaviruses are still being identified. Cell surface proteins, known as integrins, may act as hantavirus receptors. The function of integrins is to act as cell receptors for adhesion molecules and to promote stable interactions between cells. Beta 3 integrins have been identified as receptors for pathogenic hantaviruses, while non-pathogenic hantaviruses had been observed to use beta 1 integrin receptors. Hantaviruses are also able to infect cells that lack these receptors, indicating the existence of other cellular receptors that have not yet been characterized.

Virus entry into host cell

After attachment of virus particle to cell surface, the entry of the virion into host cell takes place through receptor-mediated endocytosis.

Uncoating and release of viral genomes
The uncoating of virus particle follows immediately after endocytosis. The process of uncoating takes place within endolysosomal compartments and results in release of viral genome segments into cell cytoplasm.

**Transcription of viral genome and translation of viral proteins**

Viral genome is transcribed into complimentary RNA (cRNA) by the viral RNA-dependent RNA polymerase using host-derived primers. Newly generated cRNA acts as mRNA. The L, M, and S mRNAs are translated into viral proteins using host cell machinery. Translation of the M segment mRNA takes place on membrane-bound ribosomes while translation of the S and L mRNA transcripts occurs on free ribosomes.

**Genome replication and viral assembly**

Viral RNA-dependent RNA polymerase switches from transcription to replication of the S, M, and L genomic RNA segments. The newly synthesized viral RNAs are encapsidated by N protein forming nucleoprotein particles. These are transported to the cell’s Golgi apparatus. The bilayer lipid membrane is acquired by immature virion through the process of budding into the Golgi cisternae. Some hantaviruses may assemble and mature at the cell plasma membrane rather than in the Golgi complex.

**Release of virus from host cell**

Virions are transported to the cell surface by exocytosis. The Golgi vesicle harboring mature virions fuses with plasma membrane, releasing virus particles from the host cell. (1)

**IV. EPIDEMIOLOGY OF HANTAVIRUS INFECTION**

**A. Animal Reservoir**

Hantaviruses are unique in the family *Bunyaviridae* because an arthropod vector is not required for their transmission. Hantaviruses are maintained in nature within an animal reservoir and are transmitted to humans from the infected natural host. Each hantavirus strain is adapted to a specific host. This specificity is historical as each hantavirus strain has apparently evolved along with its primary natural host (the single virus/single host rule of natural reservoirs). Examples of major rodent reservoirs in North America and other parts of the world and hantavirus strains associated with these rodents are the:

- deer mouse and Sin Nombre virus
- white-footed mouse and New York virus
- western harvest mouse and El Moro Canyon virus
- hispid cotton rat and Black Creek Canal virus
- Norway rat and Seoul virus
- rice rat and Andes virus.

Other mammals may become infected by hantaviruses. Antibody to hantaviruses has been demonstrated in chipmunks, cats, dogs, voles, hares, deer, shrews, and other animals (2).

In the United States rodents carrying virus strains that cause hantavirus pulmonary syndrome include the deer mouse, the cotton rat, the rice rat, and the white-footed mouse.
• The deer mouse is an attractive animal with a body that is 2 to 3 inches long. Its fur varies from gray to reddish-brown with a white underbelly. The deer mouse can be found almost everywhere in the United States. It prefers woodlands but may be found in the desert and near human dwellings. Abandoned or rarely-used sheds may harbor deer mice. Surveys of antibody to hantavirus in deer mice show that approximately 10% of mice are infected. Prevalence of rodent infection varies with seasonal fluctuations in rodent population.

• The cotton rat is found in the southeastern United States as well as in Central and South America. The cotton rat prefers areas with overgrown shrubs and tall grasses.

• The rice rat is slightly smaller than the cotton rat (5 to 6 inches long) and has a very long tail. This rat likes marshy areas and is semi-aquatic. The rice rat is found in the southeastern United States and in Central America.

• The white-footed mouse resembles the deer mouse. It is found throughout southern New England, the Mid-Atlantic and Southern states, the Midwestern and Western states, and Mexico. It prefers wooded and brushy areas but can be found in areas that lack vegetation.

Factors that affect prevalence of hantavirus in rodent population

Hantavirus prevalence is affected by seasonal fluctuations in rodent population. A number of factors have an effect on population size, including weather conditions, plant growth and maturation, types of plants in the area, soil conditions, availability of alternative food sources, destruction of the natural environment due to disastrous events, physiological state of the rodent population, host age and sex, and other factors. Generally, adult male rodents are more likely to become infected with hantavirus.

Transmission of hantavirus in rodent population

Transmission of infection among rodents generally occurs during the times of year when vegetation is abundant and reproductive activities are high. Infected rodents shed the virus in saliva, urine, and feces. Transmission of virus may take place by aerosol, by wounding, or by social contact. The size of the rodent population and the extent of reproductive activities affect the degree of contact between rodents and play a role in spread of hantavirus infection within rodent populations. There is no vertical transmission of virus from mother to fetus.

Effect of infection on the rodent host

Rodents infected with a specific hantavirus strain remain persistently infected. Typically there are no symptoms of disease, although the Seoul hantavirus strain is reportedly pathogenic for very young rats infected during the first week of life. When spillover infection from the natural host to other non-human mammals takes place, the infection is nonproductive and does not result in clinical symptoms.

Infected rodents develop a vigorous immune response to hantavirus. Circulating antibody appears early in infection but does not eliminate the virus. Apparently a specific cellular immune response is essential in order to eliminate infection. Infected rodents develop a persistent infection with hantavirus, continue to shed virus in saliva, urine, and feces but do not exhibit symptoms of disease. Antibody to hantavirus can be demonstrated throughout the course of infection. The reasons for persistence of hantavirus infection are not known. It has been suggested that viral evasion of the
immune response may take place, or viral suppression of some essential aspects of host immunity such as inhibition of interferon induction (3).

Circulating antibody to hantavirus can be found in newborn rats born to infected mothers. The antibody from the mother rat persists in newborn rats for approximately eight weeks and protects them from infection.

B. Transmission of hantavirus infection to humans

Human disease occurs when people come in contact with excrement or secretions from infected animals. Transmission of virus takes place when dried materials contaminated by rodent excreta are disturbed. Hantavirus is highly infectious – persons visiting laboratories where infected rodents are kept can become infected after only a few minutes of exposure to the air in the laboratory. The most common route of transmission is inhalation of dried materials contaminated by rodent excreta. Infection can also occur if particles contaminated with virus are introduced into broken skin or conjunctiva. In addition, hantavirus infection can be acquired through the bite of an infected rodent and, possibly, by ingestion of contaminated food or water. Person-to-person transmission has not been associated with hantavirus infections, with the exception of the Andes virus. An outbreak of hantavirus pulmonary syndrome (HPS) in Argentina involved person-to-person transmission of the Andes strain of hantavirus, causing infection in members of the medical staff. An HPS outbreak in Chile caused by Andes virus was also associated with person-to-person transmission.

Risk factors for human infection

- Increase in rodent population
- Presence of rodents in and around human dwellings
- Cleaning unused or seldom used dwellings infested by rodents
- Presence of inflammation in the airways (smoking may facilitate acquisition of hantavirus infection)
- Proximity to forests
- Occupational exposure such as farming, construction, forestry, woodcutting, field work, outdoor work, or work in confined spaces without adequate ventilation
- Failure to reduce aerosol content of the work area
- Living or working in a space infested with rodents.

C. Geographic distribution of hantavirus

Hantaviruses have a wide geographic distribution. Presence of hantaviruses in a specific geographic location is linked to the presence of their natural rodent host. Hantaviruses have been found in many countries in Europe as well as in China, Korea, North America, Mexico, Honduras, Panama, Costa Rica, Venezuela, Argentina, Chile, Paraguay, Bolivia, Peru, and Brazil. Not all hantavirus strains reported in these countries are associated with human disease.

Hantaviruses found in Europe and in Asia are commonly referred to as Old World hantaviruses. These viral strains typically cause hemorrhagic fever with renal syndrome (HFRS) in humans. The natural hosts for Old World hantaviruses include the yellow-necked forest mouse, Korean field mouse, Norway rat, Asian house rat, bandicoot rat, and bank vole.
Hantavirus strains on the American continent are called New World hantaviruses. These viruses are responsible for the hantavirus pulmonary syndrome (HPS). Occasional cases of hantavirus hemorrhagic disease may also occur in the United States. Although Old World and New World hantaviruses are responsible for different illnesses and differ in their geographic locations, they share high homology in their genetic organization and have similar life cycles.

D. Prevalence of hantavirus infection in different geographic areas

Many hantavirus infections are misdiagnosed or unreported especially when they occur in rural areas or in countries where infectious diseases are common, such as Africa and India. Because of these factors it is difficult to give a precise estimate of the prevalence of hantavirus infection in different geographic locations.

Europe: infections with Old World hantaviruses

In Europe there is considerable variation in the prevalence of HFRS among different countries as well as among specific population groups within one country. Sweden and Finland report the presence of antibody to hantavirus in 5% of population, indicating prior exposure to hantavirus. A survey of certain rural communities in these countries has demonstrated antibody to hantavirus in over 50% of elderly males. Over two thousand cases per year have been reported in certain years in Sweden and in Finland.

In other countries, such as Germany, France, and Belgium there is a lower prevalence of hantavirus infection; no HFRS cases have been reported from Great Britain. Russia, on the other hand, had 89,162 HFRS cases in the 10 year period between 1996 and 2006.

Hantavirus infections in Asia

HFRS is relatively common in China. During the past few years 12,000 to 20,000 cases of HFRS have been reported in that country. A much higher number of cases has been reported previously, with a peak of 115,985 cases in 1986. The drop in HFRS cases may be due to current use of formalin-inactivated hantavirus vaccines in China. These vaccines induce a good circulating antibody response and appear to be quite effective in preventing hantavirus infections.

The Hantavax vaccine is used in South Korea. Between the years 2001 and 2008 approximately 300 to 450 HFRS cases per year were reported in Korea.

New World hantaviruses: infections in South and Central America

Disease associated with hantaviruses was not recognized on the American continent until May 1993 when a number of cases of severe pulmonary illness occurred in southwestern United States and the causative agent was identified as a hantavirus. Approximately 2 years later a cluster of hantavirus pulmonary syndrome cases was reported in Paraguay. The hantavirus strain involved in this outbreak was the Laguna Negra strain carried by its natural host, the small vespertine mouse. Since the first outbreak in Paraguay there have been over 125 cases of HPS in that country. It is quite probable that many additional cases of HPS in rural areas remain undetected since there is no formal case recording system. The reported cases of HPS in Paraguay had a mortality rate of approximately 15%, which is lower than the 40% mortality rate reported for Chile and Argentina.

The first HPS outbreak in Argentina was reported in 1996. This outbreak differed from all previous outbreaks of HPS because of person-to-person transmission:
the three doctors who treated patients with HPS contacted the disease. The Andes strain of hantavirus carried by the long-tailed pigmy rice rat was the causative agent involved in the HPS outbreak. Person-to-person transmission has not been reported for other hantavirus strains. A number of additional HPS cases have been reported from Argentina in which hantavirus strains other then the Andes strain were involved.

Shortly after the outbreak of HPS in Argentina, 25 cases of HPS were reported in Chile. Through 2006, 485 cases of HPS have been reported in different areas of Chile with a 37% mortality rate. The first isolation of Andes virus from a human patient occurred in Chile. The patient was a 10-year-old Chilean boy who had no symptoms at the time a blood sample was drawn for virus isolation, but who died 6 days later.

The first outbreak of HPS in Panama occurred in 1999-2000. The outbreak involved 12 cases with a 25% case fatality rate. The Choclo strain of hantavirus carried by the Northern pigmy rice rat was the causative agent of the outbreak.

Between the 1990s and the year 2009 1145 cases of HPS were reported in Brazil. Five strains of hantavirus appear to be involved in HPS cases in that country. The case fatality rate is close to 40%.

New World hantaviruses: infections in the United States and Canada
Hantavirus strains in the United States are divided into two groups: Eastern and Western hantaviruses. This division is based on the geographical distribution of viral strains and is supported by information yielded by nucleotide sequencing of portions of viral genomes. Western hantaviruses include the Sin Nombre and related viruses, and Convict Creek 107 virus. Eastern hantaviruses are New York virus, Black Creek Canal virus, and Bayou virus.

Since the 1993 outbreak of HPS in the Four Corners area of New Mexico and up to the present time, 690 cases of HPS have been reported in the United States. Although the total number of cases is not large, the fatality rate of 36% is very high. Many cases of HPS are in the southwestern United States with a scattering of cases throughout other parts of the country. A total of 32 states have reported HPS cases. New Mexico, Arizona, and Colorado have the largest number of HPS cases, followed by California and Washington. A number of states report a single case of HPS. Most HPS cases have occurred among residents of rural areas with 63% male and 37% female patients.

In the southwestern states the Sin Nombre strain of hantavirus is the principal causative agent of HPS. The deer mouse is the natural host for this hantavirus strain. At least 10% of deer mice are infected with hantavirus, according to a California survey. The rate of infection varies with specific geographic location within the state: deer mice found at higher elevation tend to have a higher rate of hantavirus infection. Other factors besides elevation are involved in infection of deer mice. Evidence of infection with hantavirus has been found in other species of rodents in California but deer mice remain the primary reservoir of infection for Sin Nombre virus in southwestern United States.

Hantavirus infections in Canada
The earliest reported case of HPS in Canada occurred in Alberta in 1989. Since that time 70 cases have been reported. Most of these cases were contracted in Western Canada.
V. CLINICAL SYMPTOMS OF HANTAVIRUS INFECTIONS

Symptoms of hantavirus infections in humans range from inapparent infections to serious pulmonary disease and hemorrhagic fevers. Severity of disease is associated with the specific hantavirus strain. The existence of inapparent infections is indicated by large numbers of persons in South America with antibody to hantavirus but without any history of hantavirus infection. Among Old World hantaviruses that cause hemorrhagic fever with renal syndrome (HFRS) the Hantaan virus and the Dobrava virus cause a severe form of HFRS. Mortality rate for Hantaan virus infections is approximately 15% while for Dobrava virus the mortality rate ranges from 5% to 15%. The Seoul virus, found throughout Europe and Asia, causes a milder form of HFRS with a mortality rate of less than 1%. Infections with hantavirus Seoul strain have been reported in the United States. The mildest form of HFRS is caused by the Puumala strain of hantavirus. The mortality rate for Puumala hantavirus infections is less than 0.1%. This strain is prevalent in Scandinavian countries.

Clinical presentation of Hantavirus Pulmonary Syndrome (HPS) caused by New World hantaviruses and the case mortality rate also depend on the strain of infecting hantavirus. As noted above, some of these infections are inapparent.

At the present time 21 hantavirus strains have been identified as pathogenic for humans. Many additional hantavirus strains exist whose pathogenicity had not been demonstrated.

A. Hantavirus Fever with Renal Syndrome – Clinical Presentation

Incubation period: the incubation period for HFRS ranges from one to six weeks, with an average of two to three weeks.

Course of disease: the clinical course of HFRS is divided into 5 phases.

1. Febrile phase: the initial febrile phase begins with high fever, chills, back and abdominal pain, muscle pain, and general malaise. The febrile phase of illness lasts 3 to 4 days. By the third to fifth day petechiae (minute red spots under skin surface caused by intradermal hemorrhage) appear on the palate. There may also be conjunctival bleeding. During this stage of illness 11% to 40% of patients may develop hypotension (drop in blood pressure).

2. Hypotensive phase: this stage of illness begins 3 to 6 days after onset of fever. Hypotension is accompanied by restlessness, thirst, nausea, vomiting, and abdominal pain. Approximately one third of patients may develop mental confusion and shock. The patient’s vision may be affected. Abdominal pain and hypotension are believed to be indications of increased capillary permeability and vascular leaks. The patient experiences a drop in the number of platelets and an increase in circulating white blood cells.

3. Oliguric phase (diminished urine production and excretion): this stage of illness begins approximately on the eighth day after onset of fever and affects from 40% to 60% of patients with HFRS. Gastrointestinal, cerebral, and conjunctival hemorrhages may occur. Moderate or severe renal failure requiring dialysis may develop. Renal insufficiency, hemorrhaging, and shock may result in patient’s death. Approximately half of all deaths due to HFRS occur during the oliguric stage of disease.
4. Diuretic phase: this occurs from 12 to 14 days after onset of fever and suggests an improvement in the patient’s condition.

5. Convalescent phase: this stage of illness may last several months.

B. Nephropathia Epidemica

A much milder form of HFRS is caused by the Puumala hantavirus strain that is prevalent in Scandinavian countries. This illness is characterized by a sudden onset of high fever, headache, and back and abdominal pain. Some patients experience seizures. There is bleeding in the conjunctiva, hematuria (blood in urine), and petechiae on the trunk within 3 to 4 days of onset of symptoms. Convalescence usually takes 2 to 4 weeks. The mortality rate from this condition is 0.1% or less.

Occasionally Puumala virus infections are quite severe. The severity of infection has been linked to the genetic make-up of the patient; genes that code cytokines are implicated.

C. Hantavirus Pulmonary Syndrome – Clinical Presentation

Hantavirus Pulmonary Syndrome is a severe acute disease accompanied by respiratory failure, cardiogenic shock, and high mortality rate. HPS resembles HRFS, except that lungs are targeted instead of the kidneys, although occasionally some kidney involvement has been recognized. The clinical symptoms of HPS and the fatality rate depend on the specific strain of the infecting hantavirus.

Incubation period: the incubation period ranges from 9 to 33 days, with an average of 14 to 17 days.

Course of disease: the clinical course of HPS is divided into 3 phases.

1. Initial phase of illness: the first signs of illness are non-specific and resemble many other viral infections. The only guide to the nature of the patient’s illness is the blood picture: there is a decrease in numbers of platelets, presence of immature, large, atypical lymphocytes, and an increase in neutrophils accompanied by immature cells. Typical symptoms are fever, fatigue, muscle ache, headache, dizziness, chills, nausea, vomiting, abdominal pain, and diarrhea. These initial symptoms last no longer than 5 days and are followed by respiratory symptoms which include shortness of breath and cough.

2. Cardiopulmonary phase: patients develop pulmonary edema. Hypotension develops in approximately 45% of patients, 33% suffer shock, and renal failure may occur in a large percentage of patients. A fatal outcome may take place 4 to 7 days after onset of disease.

3. Convalescent phase: the course of disease in surviving patients may extend to three weeks. (4)

Case Presentations:

HPS is infrequent in children and in the elderly. The cases presented below are unusual because they involve a 70-year-old man and a six-year-old boy.

Case #1: on July 12, 2009, a boy aged 6 years went to a Colorado emergency department with a 5-day history of fever (103°F), erythematous facial rash, and muscle pains. On admission, the boy had shortness of breath with coarse breath sounds and wheezes. A blood sample was sent to the laboratory. His white blood cell count was elevated while the platelet count was below normal. A chest X-ray revealed pulmonary infiltrates. The boy was treated with intravenous fluids, ceftriaxone, and azithromycin. Serum antibody test (ELISA) was positive for immunoglobulin M (IgM) antibody to
Sin Nombre strain of hantavirus. The boy was hospitalized for 8 days and discharged on July 20. Family members reported that approximately 10 days before hospitalization the boy was bitten on the finger by a mouse. An environmental assessment of the house did not reveal any rodents but evidence of rodent infestation was observed in outbuildings and in abandoned vehicles.

Case #2: on April 25, 2011, the Maine Center for Disease Control and Prevention was notified of a suspected case of hantavirus pulmonary syndrome. Until that date there were no reported cases of hantavirus infections in this state. A 70-year-old male Maine resident went to a community hospital with symptoms of fatigue, decreased appetite, weakness, chills, myalgia, and progressive shortness of breath. The patient was admitted to the hospital. Laboratory findings included evidence of acute renal insufficiency, an elevated white blood cell count, and a low platelet count. The patient developed a pulmonary infiltrate and 2 days later was treated for respiratory failure and increasing renal insufficiency. Laboratory tests demonstrated serum antibody (IgM and IgG) to hantavirus and hantaviral RNA was detected in the patient’s blood. The patient was discharged to a skilled nursing facility one month after admission and recovered with extensive rehabilitation.

An investigation revealed that the patient was exposed to rodent droppings on his farm. The patient reported that he climbed a ladder in his grain storage shed in order to place a rodenticide on the upper level of the shed. The upper area of the shed had insulation contaminated with rodent droppings.

VI. PATHOGENESIS OF INFECTION

Hantaviral infection begins with an interaction of viral Gn and Gc surface glycoproteins with beta 3 integrin receptors on the surface of susceptible cells. Hantavirus binds to endothelial cells, macrophages, and platelets. Cell-bound virus directs the adherence of platelets to the surface of endothelial cells. Vascular endothelial cells normally perform a barrier function to maintain vascular integrity and infection of endothelial cells by hantavirus alters normal fluid barrier function of these cells. Infected endothelial cells become hyper-responsive to the vascular endothelial growth factor resulting in enhanced cellular permeability.

Viral replication takes place in endothelial cells and macrophages, allowing spread of virus to other cells throughout the body of the infected host. Viral dissemination involves a broad range of tissues. Antigens of HPS-associated hantaviruses have been detected in circulating monocytes, B cells, T cells, tissue macrophages, dendritic cells, and vascular endothelial cells (especially in the lungs). Replication of hantavirus in these cells does not result in cell destruction. The presence of HFRS-associated hantaviruses had been demonstrated in kidneys, spleen, and liver of experimental animals (cynomolgus monkeys).

Viral multiplication and dissemination activate the immune system of infected hosts. Pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin-1 (IL-1), and IL-6 are secreted by activated macrophages. An array of cytokines is produced by activated hantavirus-specific T cells. The cytokine interleukin-6 has an important role in inhibiting cardiac function and inducing a drop in blood pressure (hypotension). High levels of IL-6 have been demonstrated in a number of fatal HPS cases. Increased levels of tumor necrosis factor-beta are correlated with hypotension as
well as with hemoconcentration, and a positive correlation has been found between the 
presence of IL-12 and hemoconcentration.

A mixed pattern of cytokines has been demonstrated for both HPS and HFRS 
patients. Different levels of cytokines produced in these infections may indicate 
selective inhibition or dysregulation of the immune response (including cellular 
interferon production). Either as a consequence of dysregulation or in an attempt to 
compensate for a large viral load, the host produces a massive inflammatory response. 
Inflammation is accompanied by the presence of mononuclear infiltrates in various 
organs such as heart and lungs and an increased production of pro-inflammatory 
cytokines. The intense immune activation coupled with changes in vascular 
permeability results in symptoms of disease. Patients with HPS may experience 
pulmonary edema followed by respiratory failure, hypotension, and cardiogenic shock 
(failure of heart function due to inadequate blood circulation).

VII. LABORATORY DIAGNOSIS

Hantavirus infection may be diagnosed by serological tests that demonstrate the 
presence of antibody to hantavirus in the patient’s serum, by direct detection of 
hantavirus antigen in tissues using immunochemical methods, and by molecular 
methods that detect hantaviral RNA in clinical specimens.

Almost all patients with acute HFRS or HPS have antibody to hantavirus N 
protein. The antibody may be IgM or IgG, depending of the phase of illness. Generally, 
serological tests for hantavirus antibody in the patient’s serum are the most common 
methods used in diagnosis HFRS and HPS. Hantavirus N protein is the most abundant 
viral protein and it induces a strong humoral response in humans and rodents. An 
important characteristic of N protein is the presence of antigenic determinants that are 
shared by different hantaviral strains.

One of the first serological tests available for diagnosis of hantaviral infections 
in Asia and in Europe was the indirect immunofluorescent test. This assay used 
hantavirus-infected cells as antigen. Infection of cell cultures with hantavirus requires 
BSL-3 laboratories and this method of antigen preparation is seldom used at the present 
time. Most hantavirus antigens currently used in serological tests are derived by 
recombinant DNA methods. The antigens are predominantly N proteins, but Gn and Gc 
proteins are also used. A number of recombinant expression systems has been used for 
N protein expression and purification. These systems include bacteria, \textit{Saccharomyces} 
species, baculovirus, insect, plant, and mammalian cell systems. The recombinant N 
protein derived from a specific hantavirus strain may be used as antigen in serological 
tests for detection of antibody to unrelated hantavirus strains. For example, 
recombinant N protein derived from the Araraquara virus (Brazil) had been used to test 
for antibody to the Andes virus (Argentina). The recombinant N protein derived from 
Puumala virus (Scandinavian countries) had been successfully used in patients from 
Chile for diagnosis of HPS (5).

Serological tests:

The highest titers of antibody to hantavirus can be detected from 1 to 4 weeks 
after onset of symptoms. The most common serological tests for hantavirus are 
enzyme-linked-immunosorbent assays (ELISA). These assays include the indirect IgG 
and IgM ELISAs and IgM capture ELISA.
The rapid IgM capture ELISA assay was developed by the U.S. Army Medical Research Institute of Infectious Diseases and by CDC for detection of antibody that appears early after infection. In this assay the test tray is coated with antibody to human IgM prior to addition of serum samples being tested. A recombinant hantavirus antigen is used in the assay. Rapid IgM capture ELISA test takes between 4 to 6 hours and is suitable for use in diagnosis of both HFRS and HPS. An IgG test is used in conjunction with the IgM-capture test. Acute- and convalescent-phase sera should demonstrate a four-fold rise in IgG antibody or the IgM assay must be positive for antibody to be diagnostic for hantaviral disease. IgG antibody is long-lasting and sera of patients may retain antibody for many years.

In addition to ELISA assays other tests may be used for detection of antibody to hantavirus. These tests include the following:

- Rapid immunoblot strip assay (RIBA) in which recombinant antigens are coated on nitrocellulose strips before addition of test sera. This assay can be used for typing of suspected hantavirus strains.
- Western blot assay procedure that has been adapted for identification of IgM and IgG antibody.
- Indirect immunofluorescent test in which a recombinant hantavirus antigen is used.
- Immunochromatographic assay that has been developed and is being tested. This assay uses recombinant N protein from Puumala virus.
- Neutralizing plaque assay (plaque reduction neutralization test). This test is the most definitive method for identification and differentiation of hantaviruses. Plaque reduction neutralization test is a specific test that allows serotypic classification of hantavirus infection. The assay, however, is time-consuming and requires the use of BSL-3 laboratories.

Tests for direct identification of hantavirus antigen:

- Direct fluorescent antibody test: antibody against a specific hantavirus conjugated with fluorescent dye may be used for detecting virus in lung tissue or in other clinical specimens.
- Immunohistochemistry testing of formalin-fixed clinical samples with specific monoclonal and polyclonal antibodies can be used for detection of hantavirus antigens; this test has proven to be a sensitive method for confirmation of hantavirus infections.
- Electron microscopy can be used to detect viral antigen in tissues.

Diagnostic assays for detection of viral nucleic acid:

- In situ hybridization assays detect viral nucleic acid in cells infected with hantavirus.
- Molecular diagnostic tests have been developed for detection of hantavirus genome. Hantavirus RNA can be rapidly detected from the first day after onset of illness in clinical samples such as blood, serum, or organ fragments by reverse transcription-polymerase chain reaction (RT-PCR). Low levels of viral RNA present in clinical samples may require the use of a modified RT-PCR assay known as nested PCR. This
procedure increases the specificity of nucleic acid amplification by reducing background caused by non-specific nucleic acid amplification.

**Virus isolation:**

- Hantaviruses can be cultured on Vero cells but isolation of virus from clinical specimens is difficult, requires the use of BSL-3 laboratories, and is not considered for diagnostic purposes.

- Diagnostic tests for hantavirus should preferably be performed in reference laboratories such as local or state public health laboratories. The CDC Special Pathogens laboratory will accept clinical specimens for diagnosis of hantavirus infections. Guidelines for submitting specimens to the Special Pathogens Branch include the following regulations:

  - Clinical specimens for diagnosis of hantavirus infections may be submitted to the Special Pathogens Branch at CDC by state and local health departments. Physicians who wish to submit a specimen for diagnosis are requested to contact their state health department. A prior consultation with CDC is required before specimen submission. If serology is requested, the following types of specimens may be submitted: serum drawn at specific intervals after onset of illness (1 to 2.5ml) and post-mortem heart blood. Specimens should be shipped in plastic tubes on dry ice. Tissue specimens for immunochemistry may be formalin-fixed or paraffin-embedded. There are specific packaging requirements for shipping. Specimens for PCR or virus isolation may be biopsy material of the lung, bone marrow aspirate, or blood clot. These must be packaged according to CDC specifications. A specimen submission form and a case report must accompany the specimen. Detailed information for specimen submission and the required forms are available at [www.cdc.gov/hantavirus/health-care-workers/specimen-submission/protocol.html](http://www.cdc.gov/hantavirus/health-care-workers/specimen-submission/protocol.html).

**VIII. IMMUNE RESPONSE**

Hantavirus infection induces a vigorous immune response in infected persons. Innate immunity is stimulated initially followed by a specific immune response to hantavirus. Antibody production (IgM) begins at the onset of infection and is detectable in the serum approximately a week after symptoms appear.

- The Th1 subclass of T lymphocytes is stimulated early in the course of disease. An elevated Th1 cellular activity is correlated with a high virus load and an increased severity of illness, as shown in studies of infections with Puumala hantavirus strain.

- Natural killer cells, macrophages, and other cytokine-producing cells are recruited to the site of infection. Serum concentration of pro-inflammatory cytokines such as tumor necrosis factor, interleukin-1, and interleukin-6 are elevated. Expression of anti-viral proteins (interferon-beta and interferon-gamma) is increased.

- During the later phase of illness antibody production switches to the IgG class. Specific antibody to hantavirus can be detected throughout the course of illness and after recovery of the patient. During this phase of illness the Th2 subclass of T lymphocytes is stimulated; this is accompanied by production of cytokines associated with Th2 cells.

- It has been suggested that cytokines released during hantavirus infection such as the various interleukins, lymphotoxin, tumor necrosis factor, and interferon-alpha may contribute towards pathology seen in HPS.
IX. PREVENTION AND THERAPY

At the present time, there are no vaccines or drugs approved by the U.S. Food and Drug Administration for prevention or treatment of HFRS or HPS. Studies of HFRS cases in China indicate that ribavirin improves prognosis of HFRS when given early in the course of illness. When ribavirin is administered before the end of the first week of illness there is a 7-fold reduction in the risk of death. Ribavirin has no affect on the course of illness in HPS.

Since patients remain viremic during the acute phase of disease, possible use of immunotherapy has been investigated. Studies in animals indicate that passive transfer of neutralizing monoclonal or polyclonal antibody can protect animals from hantavirus infection.

An inactivated hantavirus vaccine was approved in Korea in 1990. This vaccine has been widely used in Korea and China. A decrease in the number of HFRS cases has been observed after introduction of vaccination. Clinical trials of the vaccine, however, demonstrated equivocal results. Other types of vaccines are being developed, including recombinant and DNA-based vaccines. None of the hantavirus vaccines is licensed for use in the United States at the present time.

The prevention of diseases caused by hantaviruses is based on controlling the rodent population. Control measures include reduction of rodent shelter and food sources in and around the home, elimination of rodents inside the home, use of specific precautions when cleaning rodent-infested areas, and use of preventive measures by campers and hikers and by persons who have occupational exposure to rodents. Cleaning rodent-infested areas with a disinfectant (1.5 cups of household bleach in a gallon of water) is an important preventive measure to use because sweeping or vacuuming rodent dropping stirs up dust and spreads infection. A detailed set of instructions for prevention of rodent infestation and for clean-up procedures are available online from CDC:

X. SUMMARY

Hantaviruses are highly infectious viruses that infect humans and cause diseases with high fatality rates. These agents are special pathogens that are considered a risk to national security and that require handling in laboratories with Biosafety levels 3 or 4. Studies of these agents are relegated to CDC Special Pathogens Branch Laboratory.

Hantaviruses are members of *Bunyaviridae* family. Genus *Hantavirus* is the only genus in the *Bunyaviridae* family that does not require an arthropod vector for viral transmission. Hantaviruses are maintained in an animal reservoir and are transmitted to humans directly from the natural host.

Hantaviruses are single-stranded enveloped RNA viruses, 80 to 120 nanometers in diameter. They replicate in the cytoplasm of susceptible cells and exit host cells by exocytosis without cell lysis.

Many rodent species serve as natural hosts for hantaviruses. Each hantavirus strain is adapted to a specific host. Hantavirus infection is maintained within rodent population without symptoms of illness. Infected rodents develop a vigorous immune response and shed virus in saliva, urine, and feces. New hosts are infected through
contact with materials contaminated by rodent excreta. Humans are most commonly infected by inhalation of dried materials contaminated by secretions from infected rodents. Transmission of hantavirus may also occur through the bite of infected rodent or by contact of broken skin or conjunctiva with contaminated material. Person-to-person transmission of hantavirus infection has been shown only for one hantavirus strain – the Andes virus. The most important risk factor for human infection with hantavirus is contact with rodents through occupational exposure or through rodent infestation of human dwellings. In the United States rodents that carry pathogenic hantavirus strains include the deer mouse, the cotton rat, the rice rat, and the white-footed mouse.

Hantaviruses have a wide geographic distribution. Hantavirus strains in Europe and Asia are known as Old World hantaviruses. These viruses typically cause Hemorrhagic Fever with Renal Syndrome (HFRS). Hantavirus strains in the New World: United States, Canada, Central America, and South America, cause the Hantavirus Pulmonary Syndrome (HPS). HFRS and HPS are serious illnesses with high fatality rates. The severity of disease varies with the infecting strain of hantavirus. HFRS fatality rate ranges from less than 1% to 15%. The mildest form of HFRS is caused by the Puumala strain of hantavirus. Fatality rates for HPS may reach 40% or higher.

Hantavirus infection begins with virus entry into susceptible cells and subsequent spread of virus throughout the body of the host. Infection of vascular endothelial cells by hantavirus affects the vascular integrity of these cells and increases cellular permeability. Hantavirus infection stimulates a strong immune response accompanied by inflammation and production of cytokines. The intense immune activation coupled with changes in vascular permeability result in symptoms of disease. Hantavirus infection can be diagnosed by serological tests, by detection of hantavirus antigens in tissues, and by molecular methods that detect viral RNA in clinical specimens.

At the present time, there are no vaccines or drugs approved by US Food and Drug Administration for prevention or treatment of HFRS or HPS. Prevention of hantavirus disease is currently based on controlling the rodent population. Instructions for controlling rodent infestation and for clean-up procedures are available from CDC.

REFERENCES
REVIEW QUESTIONS
Course #DL-001
Choose the one best answer

1. All but which one of the following is a reason hantaviruses are considered a threat to national security?
   a. can be transmitted by aerosols
   b. have a high fatality rate
   c. can be engineered for mass dissemination
   d. can be added to the water supply

2. Natural hosts for hantaviruses are
   a. rodents
   b. deer
   c. rabbits
   d. chipmunks

3. Records indicate that hantavirus-caused disease occurred during
   a. the Korean conflict
   b. World War I
   c. The Sino-Japanese War
   d. The Philippine Insurrection

4. Hantavirus genome has
   a. double-stranded RNA
   b. double-stranded DNA
   c. single-stranded RNA
   d. single-stranded DNA

5. Hantavirus genome
   a. has 3 segments
   b. has 10 segments
   c. is non-segmented
   d. has 100 segments

6. Hantavirus L segment codes for
   a. envelope glycoproteins
   b. RNA-dependent RNA polymerase
   c. viral membrane
   d. N protein

7. Replication of hantaviruses
   a. takes place in the nucleus of infected cells
   b. takes place in the cytoplasm of infected cells
c. takes place on the outside surface of infected cells
d. does not require presence of living cells

8. Infection of deer mice with hantavirus results in
   a. sudden death
   b. prolonged illness
   c. persistent infection
   d. none of the above

9. Hantavirus infection is transmitted to humans by
   a. inhalation of dried materials contaminated with rodent excreta
   b. tick bite
   c. flea bite
   d. mosquitoes

10. Person-to-person transmission of HPS has been demonstrated for
    a. Sin Nombre virus
    b. Andes virus
    c. New York virus
    d. Black Creek Canal virus

11. Risk factors for human infection with hantavirus include:
    a. presence of rodents in and around human dwellings
    b. mosquito breeding grounds near human dwelling
    c. presence of deer near human dwellings
    d. presence of rabbits near human dwellings

12. Old World hantaviruses:
    a. are not pathogenic
    b. cause hemorrhagic fever with renal syndrome
    c. infect only persons over 70 years of age
    d. cause hantavirus pulmonary syndrome

13. New World hantaviruses
    a. cause HFRS
    b. are found in Korea
    c. have evidently caused many inapparent infections in South America
    d. have a lower fatality rate than Old World hantaviruses

14. The first recorded outbreak of HPS in the U.S. occurred in
    a. California
    b. New York
    c. Maine
    d. Four Corners area of the U.S.

15. Sin Nombre virus is a member of
16. A patient is brought to an emergency room with hypotension, abdominal pain, and decreased urine output. If hantavirus is suspected, which of the following is an anomaly in the clues to the type of hantavirus causing the disease?
   a. the patient was from New Mexico
   b. petechiae on the palate
   c. mental confusion
   d. conjunctival hemorrhages

17. Nephropathia epidemica is a:
   a. mild form of HPS
   b. disease with about 1% mortality rate
   c. mild form of HFRS
   d. is found Southern Europe

18. One of the common diagnostic tests for HPS is:
   a. throat culture
   b. culture for fungi on Sabouraud agar
   c. IgM-capture ELISA assay
   d. stool culture

19. Which of the following is not a serological test commonly used in diagnosis of HPS?
   a. complement fixation test
   b. immunoblot strip assay
   c. ELISA assay
   d. neutralizing plaque assay

20. Hantavirus infections can be successfully treated with:
   a. sulfa drugs
   b. penicillin
   c. tetracycline
   d. none of the above