Journal of Microbiology and Infectious Diseases / JMID
2014; Special Issue 1: S41-S49
doi: 10.5799/ahinjs.02.2014.S1.0140

REVIEW ARTICLE

Hemorrhagic fever with renal syndrome (Hantaviruses)

Hande Berk, Nefise Öztoprak

Antalya Education and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Antalya/ Turkey

ABSTRACT

Hantaviruses are enveloped RNA viruses belonging to the genus Hantavirus, family Bunyaviridae. These agents are usual parasites of wild rodents and insectivores. Many species worldwide are infected with these viruses and each Hantavirus type is carried by its own type specific rodent species. Human transmission occurs accidentally by inhalation of aerosolized virus containing particles, contact with urine, feces or secretions of infected rodents. Hantavirus leads to two type of zoonotic infections; Hemorrhagic fever with renal syndrome (HFRS) and Hantavirus pulmonary syndrome (HPS). Ecological and environmental changes, alterations in rodent population size, viral durability in nature, and changes in human life style that augment rodent exposure are the main causes that may affect the incidence of HFRS infection. The hallmarks of HFRS infection are fever, hypotension, hemorrhage and acute renal failure with acute interstitial nephritis. Clinical course of the disease varies between HFRS virus types. PUUV infection that is mostly seen in Europe has the mildest course and up to 90% of the cases are asymptomatic. Serological tests, molecular tests and virologic cell culture are used for HFRS diagnosis. There is no specific antiviral drug, immunotherapy or vaccine approved by Food and Drug Administration (FDA). Although ribavirin seems to decrease mortality in animal models; there are few data in the literature considering the effect of ribavirin on HFRS infections. Control and management of the symptoms with supportive care is the main modality for HFRS treatment. Reduction of the frequency and intensity of rodent exposure is very important for the prevention. *J Microbiol Infect Dis 2014; Special Issue 1: S41-S49*

Key words: Hantavirus, hemorrhagic fever with renal syndrome, viral hemorrhagic fever, Turkey

Hemorajik ateşle seyreden renal sendrom (Hantaviruslar)

ÖZET

Hantaviruslar Bunyaviridae ailesinin Hantavirus cinsinde yer alan zarflı RNA viruslarıdır. Bu etkenler vahşi kemirgen ve böcekçigillerin bilinen parazitlerindendir. Dünya genelinde birçok tür bu viruslarla enfektedir. Her Hantavirus tipi kendine özgül kemirgen türü ile taşınır. İnsan bulaşı virus içeren aerosolleşmiş partiküllerin inhalasyonu veya enfekte kemirgenin idrar, dışkı veya sekresyonları ile direkt temas sonucu gerçekleşir. Hantaviruslar iki tip zoonotik enfeksiyona neden olur; Hemorajik ateşle seyreden renal sendrom (HFRS) ve Hantavirus pulmoner sendrom (HPS). Ekolojik ve çevresel değişimler, kemirici populasyonundaki değişiklikler, virusun dış ortama dayanıklığı ve kemirici maruziyetini artıran insan yaşam tarzındaki değişimler HFRS insidansını artıran en önemli nedenlerdendir. HFRS enfeksiyonlarının en belirgin özelliği ateş, hipotansiyon, kanama ve akut tübülointerstisiyal nefritle seyreden akut böbrek yetmezliğidir. Hastalığın kliniği HFRS virus tiplerine göre değişir. Avrupada sık görülen PUUV enfeksiyonu en hafif seyirli tiptir ve olguların 90% kadarı asemptomatiktir. HFRS tanısında serolojik testler, moleküler testler ve virolojik hücre kültürü kullanılmaktadır. HFRS için Food and Drug Administration (FDA) tarafından onaylanmış antiviral ilaç, immünolojik tedavi veya aşı yoktur. Ribavirin hayvan modellerinde mortaliteyi azaltıyor gibi görülse de HFRS enfeksiyonlarında deneyim azdır. HFRS tedavisinde destek tedavisi temel yaklaşımdır. Korunmada kemirgenlerle maruziyetin sıklığı ve şiddetini azaltıcı yöntemler çok önemlidir.

Anahtar kelimeler: Hantavirus, hemorajik ateşle seyreden renal sendrom, viral hemorajik ateş, Türkiye

INTRODUCTION

Hantaviruses are enveloped RNA viruses belonging to the genus Hantavirus, family Bunyaviridae.[1] These agents are usual parasites of wild rodents and insectivores.[2] Many species worldwide are infected with these viruses and each Hantavirus type is carried by its own type specific rodent or insectivore species.[2] These species are persistently and usually asymptomatically infected by the viruses.

Correspondence: Hande Berk, Antalya Education and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Antalya/ Turkey Email: handeberk@hotmail.com
Received: 28 April 2014, Accepted: 02 September 2014

The virus is excreted by urine, feces or saliva for weeks and months.[2] Human transmission occurs accidentally by inhalation of these aerosolized virus containing particles, or contact with urine, secretions, or feces of infected rodents.[3] Hantavirus leads to two type of zoonotic infections; Hemorrhagic fever with renal syndrome (HFRS) and Hantavirus pulmonary syndrome (HPS).

VIROLOGY

Hantaviruses are 90-160 nm sized, negative sense single-stranded RNA viruses with lipid envelope.[4] Viral nucleic acid is composed of three segments. S segment codes for nucleocapsid protein, M segment codes for envelope glycoprotein precursors and L segment codes for L protein that serves as viral transcriptase/replicase.[4] Hantaviruses adhere host cells via β3-integrin receptors and infect endothelial, epithelial, macrophage, follicular dendritic, and lymphocyte cells.[4] There are over 40 Hantavirus species currently known and 22 of them are considered pathogenic for human.[1,2]

HISTORY

In the past century, some outbreaks occurred that lead to the discovery of Hantaviruses. Between 1900 and 1950, diseases named as trench nephritis, hemorrhagic nephrosonephritis and nephropathia epidemica (NE) were reported from China, Korea and Scandinavian region. Also in Korean War, between 1950 and 1953, more than 3000 American troops were affected by a disease causing fever, shock and renal failure. The triad was called as “Korean fever” and was thought to be of rodent origin but could not be confirmed methodogically. Hantavirus only first was isolated in 1978 by Lee et al. from the field mouse Apodemus agrarius who named it Hantaan virus.[5] Later, the disease formerly described as NE in Sweden in the 1930s, was shown to be due to Puumala virus (PUUV) infection.[6,7] In the subsequent years many Hantavirus types are reported from Asian and European countries and in 1983 World Health Organization named the disease as HFRS.8,9 In 1993 in the south-western United States, Four Corners region, a new outbreak with a high fatality rate (60%) and characterized by respiratory failure and shock was reported. Initially it was named as Four Corners disease but subsequently the etiological agent Sin Nombre virus (SNV) and the natural reservoir, Peromyscus maniculatus, the deer mouse were identified respectively.[10,11] The disease was named as Hantavirus cardiopulmonary syndrome (HCPS) or HPS and many new Hantavirus types were isolated from rodent species in America thereafter.

Epidemiology and transmission

HFRS is found throughout the world. The viruses that lead to HFRS include Hantaan (HTNV), Puumala (PUUV), Dobrava-Belgrade (DOBV), Seoul (SEOV), Saaremaa (SAAV) and Amur (AMRV). HTNV is widely distributed in eastern Asia, especially in China, Russia, and Korea. PUUV is found primarily in Scandinavia, Western Europe, and European Russia. DOBV-Belgrade is found in the Balkans and European Russia. SEOV is found worldwide, SAAV is found in central Europe and Scandinavia, and AMRV is found in far eastern Russia.[12] Each of these virus types are strictly associated with a unique rodent host. The rodents that are known to be the reservoirs for HFRS are the striped field mouse (Apodemus agrarius), which carries both the SAAV and HTNV; the brown or Norway rat (Rattus norvegicus), the carrier of SEOV; the bank vole (Myodes glareolus), the carieer of PUUV; Korean field mouse (Apodemus peninsulae), the carrier for AMRV; and the yellow-necked field mouse (Apodemus flavicollis), the carrier of DOBV (Table1).[12]

Currently it is estimated that 150-200 thousand cases of HFRS occur each year with the majority of cases (70%-90%) seen in China, Korea and Russia.[13,14] A retrospective surveillance conducted in European Union countries reported that 33 587 Hantavirus cases occurred between 1990- 2006 and approximately 90% of cases were seen in Scandinavian countries. Finland was the most endemic region (n=24672) followed by Sweden (n=3516) and Norway (n=1084). In the study, countries with more than 1000 cases were Belgium (n=1859), France (n=1536) and Germany (n=1320) whereas countries with lesser cases include Balkan countries like Bosnia and Herzegovina (n=555), Croatia (n=552), Bulgaria (n=399) and Greece (n=210). The countries Denmark, Spain, Italy and Cyprus did not report any cases.[1] In Russian Federation between 1996 and 2006, European region was also reported to be most endemic region with almost 95% of cases.[1]

In Turkey, during Korean War, HFRS like infections were reported in Turkish brigade but the disease could not be confirmed serologically. In February 2009, an outbreak with 23 cases emerged in Zonguldak-Bartın province and Celebi et al confirmed the first HFRS infection in Turkey. PUUV was the most common HFRS type in the majority of cases.[15] The outbreak lead to an important public awareness and National Hantavirus Study Group was generated. The study group found 5.2% seropositivity for Hantavirus antibodies amongst the healthy but at risk population in one of the affected provinces.[16] In a cross sectional another seroprevalance study conducted in the same region by Gozalan et al, 626 human samples are screened by ELISA and Hantavirus IgG was positive in 65 (10.4%) of samples. In the study, only 20 of the 65 ELISA-positive samples could be confirmed by an immunobloting assay, and the overall seroprevalence was reported as 3.2% (20/626). PUUV, DOBV and SAAV were the detected HFRS virus types.[17] A comprehensive preventive and survelliance strategy against Hantavirus infection was conducted after the outbreak and sporadic reports of HFRS infections from nearby provinces like Giresun, Ordu, Istanbul, Bursa, and Ankara were stated between 2009 and 2012.[18-22]

Table 1. Hantaviruses Known to Cause Disease in Humans, Natural Hosts and Geographic Distribution.[12]

Virus	Natural Host	Disease	Geographic Distribution
Hantaan	*Apodemus agrarius*	HFRS	China, Korea, Russia
Dobrava-Belgrade	*Apodemus flavicollis*	HFRS	Balkans, European Russia, Turkey
Puumala	*Myodes glareolus*	HFRS	Europe, European Russia, Turkey
Seoul	*Rattus norvegicus*	HFRS	Asia, USA,Turkey
Saaremaa	*Apodemus agrarius*	HFRS	Central and Northern Europe, Turkey
Amur	*Apodemus peninsulae*	HFRS	Far Eastern Russia
Sin Nombre	*Peromyscus maniculatus*	HPS	Canada, USA
Andes	*Oligoryzomys longicaudatus*	HPS	Southwestern Argentina, Chile
Bayou	*Oryzomys palustris*	HPS	Southeastern USA
Black Creek Canal	*Sigmodon hispidus*	HPS	Southeastern USA
New York	*Peromyscus leucopus*	HPS	Northeastern USA
Choclo	*Oligoryzomys fulvescens*	HPS	Panama
Anajatuba	*Oligoryzomys fornesi*	HPS	Northern Brazil
Araraquara	*Bolomys lasiurus*	HPS	Southern Brazil
Araucária	*(not known)*	HPS	Southern Brazil
Bermejo	*Oligoryzomys flavescens*	HPS	Northern Argentina, southern Bolivia
Castelo dos Sonhos	(not known)	HPS	Central Brazil
Central Plata	*Oligoryzomys flavescens*	HPS	Uruguay
Hu39694	(not known)	HPS	Argentina
Juquitiba	*Oligoryzomys nigripes*	HPS	Southeastern Brazil
Laguna Negra	*Calomys laucha*	HPS	Paraguay
Lechiguanas	*Oligoryzomys flavescens*	HPS	Central Argentina
Orán	*Oligoryzomys chacoensis*	HPS	Northwestern Argentina

HFRS: Hemorrhagic fever with renal syndrome; HPS: Hantavirus pulmonary syndrome; Table is modified from the reference number 12.

The worldwide rodent carriers of Hantavirus, M. glaerolus, A. flavicollis, A.agrarius and R.norvegicus, are present in Turkey. Therefore, PUUV, DOBV, SAAV and SEOV infections may well be expected.[15]

Initially it is believed that HFRS was a rural disease and rural inhabitants such farmers are the victims of the disease. As the surveillances progress it was found that HFRS can occur in urbinized cities and many countries.[2,12,14] Hantavirus exposure can occur when humans enter rodent's natural habitat such as farmers as well as hunters, forestry workers, camping tourists, soldiers and conversely when rodents invade human housing for feeding needs.[2,14] Recently, infections of SEOV derived from United Kingdom domestic pet rats of R.norvegicus species are reported which may further extend the risk of exposure to people who did not come across to rodent's natural habitat.[23-25] In the future pet rat safety before sale may be of concern to diminish such cases.

Studies show that two major factors affect incidence of human Hantavirus infection. First factor is the climate and ecological changes. These changes may increase rodent population size which leads to higher amount of environmental Hantavirus contamination followed by an increase in human infections.[26] For instance, in western Europe, HFRS epidemics are seen in especially warm and rainy years in which there is an increase in broad leaf tree (i.e. valonia oak, beech) seeds and concomitant rodent population size.[27] Similarly other studies suggested that HFRS incidence is correlated with the yearly rain and cumulative temperature increase, wooden forest and fruit garden existence.[28-33] The second factor that increase human Hantavirus infection is the outdoor activities in the contaminated surroundings. An example is the incidence of infection in China which peaks in spring and fall when cropping and harvesting occur.[3,34]

Human Hantavirus infection occurs when viral particles scattered form urine, feces or saliva of the infected rodent are inhaled or contaminate the mucosa. Bite of the infected animal might also be a possible route for transmission.[14,35-36] As much as environmental contamination, virus survival outside the rodent is another important factor for transmission. Under optimal conditions the virus may remain in the environment for weeks but the virus is susceptible to temperature, ultraviolet light, humidity, the organic content of the contaminated fluid, detergents and disinfectants such as sodium hypochlorite.[14,37]

In conclusion, the ecological and environmental changes, increases in rodent population size, viral durability in nature, and the changes in human life style that increase rodent exposure are the main causes that may affect incidence of HFRS infection.

Pathogenesis

Endothelial cells of capillaries of various organs, primarily kidneys are the target organs of HFRS infection. Other organs such as heart, lymphoid organs and cells such as epithelial cells, macrophages, follicular dendritic cells, lymphocytes, neutrophiles and platelets are also involved in the disease.[14] β3-integrin receptors on the endothelial cell surface are the main receptors that play role on adherence of Hantavirus. These receptors are also located on macrophage and platelet cellular membrane surface. After the cellular infection, impairment of the barrier function of endothelial cells with fluid extravasations occur and subsequent organ failure follows. The mechanisms for the vascular leak are largely unknown. Studies show that Hantavirus is not cytopathic in vitro and in vivo but the viral infection causes a strong immune reaction through macrophage and cytotoxic CD8+ T cell activation. Activated macrophages secrete proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6).[2,14] Other than this cytokine storm, marked bradykinin production, complement pathway activation, and increased levels of circulating immune complexes occur. All these components increase vascular permeability and fluid extravasation occurs followed by hypotension and shock.[14,15]

During the very early course of the disease, T-cell activation occur. This leads to an abrupt rise in neutrophile, monocyte, B cell and cytotoxic CD8+ T cell count. Helper CD4+ T cells does not increase so the ratio of CD4+/CD8+ T cells decrease. Cytotoxic CD8+ T cells are responsible for the degradation of infected cells followed by subsequent tissue damage. Cases with high viremia and higher organ involvement have worsened course.[15]

HFRS leads to renal edema and retroperitoneal leakage of fluid. Acute tubulointerstitial nephritis with mononuclear cells and CD8+cell infiltration is the most prominent finding in the renal histopathology.[39] Congestion and dilatation of the medullar vessels, perirenal and medullary hemorrhage, interstitial edema and tubular degeneration are the other histopathological findings.[39-41]

In the very beginning of the disease IgM, IgG and IgA type antibodies are secreted. Neutralizing antibodies (NA's) against viral N protein are produced in the acute phase whereas NA's against GN and Gc proteins are produced in the later disease.[42] These antibodies decrease viral dissemination and cytotoxic tissue damage and it was shown that the patients having earlier and relatively higher amount of NA's have milder disease. NA's sustain in the patient sera for years and maintain protection from reinfection of the same virus type.[42]

Clinical features

The hallmarks of HFRS infection are fever, hypotension, hemorrhage and acute renal failure with acute interstitial nephritis. However, the disease severity can be extremely variable and some individuals may have asymptomatic disease. The severity of the clinical course differs based upon the HFRS virus type. HTNV and DOBV infections have a more drastic course with a case fatality rate of 5-10%. Infections with SEOV have a case fatality rate of 2% whereas PUUV infection which is more relevantly found in Europe has a milder course with a lower fatality rate of approximately 0.1%.[2,34,43-44]

The incubation period varies between 5-42 days with approximately 2 weeks.[45] The course of the illness have 5 phases: febrile phase, hypotensive phase, oliguric phase, polyuric phase, and convalescence phase.[3,12] In mild disease, these phases may not be prominent. Febrile phase presents with high fever, malaise, headache, abdominal and lower back pain, nausea, vomiting, conjunctival injection and blurred vision.[46-49] On trunk and face an erythematous eruption that blenches on pressure is seen. Leukocyte levels may be normal but are more likely elevated with left shift. In the peripheral blood examination atypical lymphocytes may be seen. Other abnormal laboratory findings are trombocytopenia, slightly elevated liver function tests and elevated lactate dehydrogenase levels.[45-50] Febrile phase lasts about 4 to 7 days and 11-40% of patients enter the hypotensive phase. In this phase, up to one third of patients experience severe clinical shock and mental confusion which may lead to death.[2,3,51] Those who survive, suffer from acute oliguria (%40-60) which lasts for approximately 1-6 days. In the oliguric phase, renal insufficiency leads to elevation in serum creatinin; microscopic hematuria, proteinuria, and electrolyte and acid base imbalances may occur requiring dialysis. Renal involvement with possible related kinin and cytokine release may also lead to disseminated intravascular coagulation (DIC) and mucosal bleeding diathesis. Hypertension and pulmonary edema may be seen in the course of the disease and abnormal electrocardiographic and echocardiographic findings are common.[3,45] More than half of the patients in the oliguric phase die due to the renal failure and bleeding disorders. Patients who survive enter the polyuric phase which lasts for days to several weeks. Fluid and electrolyte imbalances occur in this phase. Convalescent phase starts after the polyuric phase and if the patient survives, renal functions generally return to normal in several months.[45] However, there are some case reports showing decreased GFR and possible subsequent hypertension after the disease.[3,52-53]

Clinical course of the disease varies between HFRS virus types. PUUV infection mostly seen in Europe has the mildest course and up to 90% of cases are asymptomatic.[45] Bleeding disorders are rare in PUUV but many cases of pituitary insufficiency due to intraputitary gland hemorrhage were reported.[1] Eye involvement with transient vision loss, blurred vision and diplopia is seen in %20 of PUUV infections. Although encephalitis is rare in HFRS, PUUV RNA has been shown in cerebrospinal fluid (CSF) of patients which may reflect central nervous system invasion and may explain confusion and headache in these patients.[2] Renal involvement is also less severe in PUUV infections and only 5-7% of patients require dialysis.[15] Clinical picture with DOBV infections have a similar course with PUUV but renal involvement is much more severe and 30-40% of patients may require dialysis.

On the contrary, HFRS due to Asian strains are more severe. Up to 80% of patients are hypotensive, almost two thirds develop oliguria and 30-40% of cases require dialysis. Also DIC is a more prominent finding and one third of patients may have a bleeding disorder like gastrointestinal, conjunctival and intracranial hemorrhage.[2,3] Visual symptoms are much more frequent in HTNV infection (60%) than PUUV infection.

PUUV was the most common virus type in 2009 HFRS outbreak in Zonguldak, Turkey. Fever 83%, chills 91%, fatigue 96%, headache 74%, nausea 74%, vomiting 54%, myalgia 52%, cough %48 and abdominal pain 44% was the most prominent symptoms. Renal failure was seen in the approximately 30% of patients but dialysis is required only 20% of patients (unpublished data). The fatality rate among hospitalized patients were 8%.[16]

Other than HFRS virus type, factors that affect disease severity are basal Hantavirus RNA level, patient's immunity, age and some genetic factors. Patients who have high levels of viral RNA at the beginning of the disease have a bad prognosis and HTNV and DOBV infections usually cause higher viremia than PUUV infections. Individual immunity also seems to play a role. For some individuals interestingly HTNV infections may cause milder infections whereas PUUV infections may be somewhat fatal.[15] Age is another factor for the disease severity. Although HFRS is rarely reported in children, the disease has a milder course.[1] Renal involvement may be affected by human genetics. As an example, patients infected with PUUV and having HLA-B27 have milder renal disease, whereas adults having HLA-B8 and DR3 develop much more severe disease requiring dialysis.[3,54-56] Studies also show that people who have HLA-B8, DRB1*0301, C4A*Q0, and DQ2 genes might be at increased risk for HFRS.[4,57-58]

DIAGNOSIS

Patients with acute high fever, thrombocytopenia and acute renal failure should be questioned for about epidemiological exposure and HFRS should be included in differential diagnosis.

Serological tests, molecular tests and virologic cell culture are used for HFRS diagnosis. Serological tests are the most widely used tests in the diagnosis of HFRS whereas virologic cell culture is more laborious and can be made only in reference laboratories with a Biosafety level of 3 (BSL-3).[15]

a- Serological tests

Serological tests are preferred in most laboratories for the diagnosis of acute or remote infections. Early in the disease as the symptoms become evident, IgM and IgG antibodies against viral nucleocapsid or N protein of Hantavirus can be detected in the patient's sera.[34] Almost 100% of patients have IgM and IgG antibodies in the acute phase when vascular leak begins. But in 2-4% of PUUV infections, occurrence of these antibodies may be delayed up to 5th day of the disease.[2]

Indirect immunoflorescent assay (IFA), enzyme-linked immunosorbent assay (ELISA), immunoblotting and immunochromatographic methods are used for antibody detection. ELISA is the most widely used serological test. IgM antibody detection in the acute phase and fourfold rise in the IgG titers between acute and convalescent phase are used for the diagnosis of HFRS infection. Due to cross reactivity, serological tests like ELISA and IFA may not differ between Hantavirus types. For this purpose viral neutralization tests may be used. This test is the golden standard for serotyping of HFRS infections but needs reference laboratories with BSL-3.[15]

b- Molecular tests

Detection of viral genom by reverse transcriptase polymerase reaction (RT-PCR) may be used for early detection of HFRS. Hantavirus can be detected by RT-PCR at the beginning of the symptoms even before IgM is negative, from clinical specimens like serum, urine and tissue biopsies.[59] There are also some reports of PUUV RNA detection in CSF, saliva and breast milk.[29,60] RT-PCR amplification followed by molecular sequence analysis also helps detection of genotyping variations for epidemiological purposes. Besides diagnosis, detection of viral load level may help predicting disease prognosis as high viral load at the beginning of the disease has a poorer outcome.[1-2,59-60] An important disadvantage of RT-PCR over serological tests is its lower sensivity in the acute phase which is affected by the viremia as viral RNA may become negative in a few days by the occurrence of neutralizing antibodies. Moreover viral load in HFRS infections are not as high as other Bunyaviridae family member diseases like Crimean Congo Hemorrhagic Disease (CCHD). Therefore, negative PCR results should be interpreted cautiously.

c- Viral cell culture

Vero E6 cell culture (green monkey renal cell) is mostly used for cell culture. But it is both time consuming and laborious. Besides, for safety regulations, cell culture should only be conducted in a laboratory with BSL-3. Therefore, a reference laboratory with experienced personnel is needed.[61]

d- Differential diagnosis

Any disease presenting with fever, acute renal failure and hemorraghe should be included in the differential diagnosis. Diseases like leptospirosis, other viral hemorrhagic fevers like CCHD, bacterial sepsis with organ failure, murine or louse-borne typhus, malaria, poststreptococcal glomerulonephritis, blood dyscrasias, glaucoma, and acute abdominal emergencies should be kept in mind for differential diagnosis. Also noninfectious causes of acute interstitial nephritis such as nonsteroidal antiinflammatory drugs should be excluded.[3,15,34]

TREATMENT

For HFRS, there is no specific antiviral drug, immunotherapy or vaccine approved by Food and Drug Administration (FDA). Control and management of the symptoms with supportive care is the main modality.[15]

a- Supportive Care

Organ and tissue perfusion should be maintained with adequate fluid replacement and if needed, vasopressors may be used. In patients with oliguric acute renal failure and vascular leak, overt fluid resuscitation may lead to pulmonary edema and extravasation of fluid. Close monitoring should be done for renal functions, fluid and electrolyte imbalances and respiratory insufficiency. Acute renal failure may require dialysis and bleeding diathesis which is a fatal complication may be controlled with platelet and blood cell transfusions.[3]

b- Antiviral treatment

Although ribavirin seems to decrease mortality in animal models; there are few data in the literature considering the affect of ribavirin on HFRS infections.[2] In a prospective, randomized, double blind, placebo controlled clinical trial conducted in China, between 1985 and 1987, intravenous (IV) ribavirin (loading dose of 33 mg/kg, 16 mg/kg every 6 h for 4 days, and 8mg/kg every 3 days) and placebo were experienced in 242 serologically confirmed HFRS patients. The study stated that if antiviral therapy is started within seven days, reduction in mortality, decreased frequency of entering oliguric phase and less hemorrhage were observed with statistical significance.[62] In another cohort study conducted in Korea, 33 HFRS cases who received IV ribavirin therapy is compared with retrospectively evaluated HFRS control cases who did not receive the therapy. In the records of the retrospective patients 39-69% were oliguric and 40% required dialysis whereas those 33 patients receiving ribavirin therapy had no dialysis requirement and only 3% had oliguria. The authors suggested that IV ribavirin therapy may decrease occurrence of oliguria and severity of renal failure.[63]

c- Immunotherapy

Regarding HCPS infections, there are some studies showing that, high titers of NA's early in the disease is related to good prognosis and suggesting that passive transfer of these antibodies may be helpful in Hantavirus infections.[64-66] Although there are no controlled clinical trials showing effectiveness of passive transfer of these antibodies in HCPS and HFRS infections; animal studies with HTNV, PUUV and Andes virus infection, supporting the benefit has been shown. According to these studies, passive immunization with NA's may protect form infection, help cure and protect against lethal challenge.[2,66-68] Further data are needed for experience in humans.

Disease prevention and control

Reduction of the frequency and intensity of rodent exposure is the main approach for the prevention of Hantavirus infections. As the disease is usually seen in forestry or rural areas; rodent control in the nearby housing and living places are very important. These places and barns should be prevented from becoming rodent shelter, rodent entrance and contamination. Penthouse, basement and storerooms are the most risky places with increased likelihood of rodent existence. Therefore, cleaning and dusting should be carried cautiously by wearing mask and gown; surfaces with possible rodent contamination should be decontaminated with chlorine based solutions and hand hygiene should be maintained.[15]

Mucosal or percutaneous exposure of secretions of patients with Hantavirus infection may lead to occupational transmission. While handling and studying these materials, laboratory staff should take standart (eg, gloves, hand hygiene) and maximum barrier (N95 mask, gown, glass) precautions if there is a risk of aerosolization or spillage. Diagnostic tests should be performed in biosafety cabinets. In case of spillage of infected material to surroundings, decontamination with 5000 ppm chlorine solution should be done.[15]

Vaccine

There are two types of Hantavirus vaccines, conventional and molecular vaccines. In conventional methods rodent brain and cell-culture derived vaccines are used and tested in humans. Rodent brain derived vaccines are not preferred in western countries and have no FDA approval as there are concerns about possibility of autoimmune encephalitis.[69]

Inactivated vaccines have been developed in Korea and China for protection against HFRS. In Korea, a suckling mouse brain derived inactive HTNV vaccine is used for more than 10 years with no serious side effects but as a vaccine response NA's have been detected only in half of the patients. In China, inactive HTNV and SEOV vaccines derived from rodent renal cells are used. Three doses of SEOV vaccine achieved NA's in 80% of cases whereas three doses of HTNV vaccines achieved NA's only in 50% of cases.[70] Another inactivated bivalent vaccine composed of HTNV and SEOV was experienced in more than thousand cases in China and after three doses of two week intervals, the vaccine developed NA's to HTNV and SEOV in 93% and 92% of cases respectively.[71] In European countries and United States these inactive HFRS vaccines are not used as the efficacy and safety have not been proved.

There are also molecular vaccines developed. One molecular vaccine is a recombinant virus vectored vaccine (VACV) that expresses the S and M genomic segments of HTNV. In a phase one, dose escalation VACV study conducted in 16 volunteers, although no adverse effects are observed; only those receiving the highest dose developed protective NA's but levels dropped to baseline in a few months.[72-73] Other studies showed similar unfavorable results and this vaccine has not been pursued.

Another molecular Hantavirus vaccine is plasmid DNA delivered by gun. In animal studies, this DNA vaccine showed cross-protection among HTNV, SEOV and DOBV but not PUUV. Full protection from HFRS necessitates for a vaccine having all the Hantavirus components (HTNV, SEOV, DOBV, PUUV). Through these perspective, a molecular vaccine has been developed in USA which was found successful in animal studies and further studies on volunteers are being conducted.[69,74-75]

REFERENCES

1. Heyman P, Vaheri A, Lundkvist A, Avsic-Zupanc T. Hantavirus infections in Europe: from virus carriers to a major public-health problem. Expert Rev Anti Infect Ther 2009;7:205-217.
2. Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on Hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev 2010;23:412-41.
3. Appel GB, Mustonen J. Renal involvement with Hantavirus infection (hemorrhagic fever with renal syndrome). UpToDate. Available from: http://www.uptodate.com/online/content/topic.do?topicKey=renlfail/9308&selectedTitle=2%7E20&source=search_result.
4. Korukluoglu G. Hantavirus. Türk Hij Den Biyol Derg 2011;68 (Suppl. 1):29-33.
5. Lee HW, Lee PW, Johnson KM. Isolation of the etiologic agent of Korean Hemorrhagic fever. J Infect Dis 1978;137:298–308.
6. Smadel JE. Epidemic hemorrhagic fever. Am J Public Health Nations Health 1953;43:1327–1330.
7. Schmaljohn C, Hjelle B. Hantaviruses: a global disease problem. Emerg Infect Dis 1997;3:95–104.
8. Simpson SQ, Spikes L, Patel S, Faruqi I. Hantavirus pulmonary syndrome. Infect Dis Clin North Am 2010;24:159-173.
9. Hjelle B. Hantavirus cardiopulmonary syndrome. UpToDate. Available from: "http://www.uptodate.com/contents/Hantavirus-cardiopulmonary-syndrome?source=related_link.
10. Nichol ST, Spiropoulou CF, Morzunov S, et al. Genetic identification of a Hantavirus associated with an outbreak of acute respiratory illness. Science 1993;262:914–917.
11. Ksiazek TG, Peters CJ, Rollin PE, et al. Identification of a new North American Hantavirus that causes acute pulmonary insufficiency. Am J Trop Med Hyg 1995;52:117–123.
12. Fulhorst CF, Koster FT, Enría DA, Peters CJ. Hantavirus Infections. In: Guerrant LG, Walker DH, Weller PF. Tropical Infectious Diseases: Principles, Pathogens and Practice, Third Edition. 2011:470-480.
13. Kariwa H, Yoshimatsu K, Arikawa J. Hantavirus infection in East Asia. Comp Immunol Microbiol Infect Dis 2007;30:341-356.
14. Manigold T, Vial P. Human Hantavirus infections: epidemiology, clinical features, pathogenesis and immunology. Swiss Med Wkly 2014;144:w13937.
15. Çelebi G. Hantavirus Infections. Klimik Journal 2011;24:139-149.
16. Ertek M, Buzgan T. An outbreak caused by Hantavirus in the Black Sea region of Turkey, January-May 2009. Eurosurveillance 14,20.
17. Gozalan A, Kalaycioğlu H, Uyar Y, et al. Human Puumala and Dobrava Hantavirus Infections in the Black Sea Region of Turkey: A Cross-Sectional Study. Vector-Borne Zoon. Dis 2013;13:111-118.
18. Kaya S, Yılmaz G, Erensoy S, et al. Hantavirus Infection: Two Case reports from a province in the eastern blacksea region, Turkey. Mikrobiyol Bul 2010;44:479-487.
19. Kebapcı N, Mıstık R, Heper Y, et al. Renal sendromla seyreden bir hantavirus infeksiyonu olgusu. In: Akhan S. ed. 15. Türk Mikrobiyoloji ve Infeksiyon Hastalıkları Kongresi (23-27 Mart 2011, Antalya) Kongre Kitabı. Istanbul: Türk Klinik Mikrobiyoloji ve Infeksiyon Hastalıkları Dernegi, 2011:322-323. (Congress book, in Turkish).
20. Oncul O, Atalay Y, Onem Y, et al. Hantavirus infection in Istanbul,Turkey [Letter] Emerg Infect Dis 2011;17:303-304.
21. Sunbul M, Yılmaz H, Cetinkaya H, et al. Two cases of Hantavirus infection in Crimean-Congo Haemorrhagic Fever endemic region. J Microbiol Infect Dis 2012;2:117-120.
22. Ulu Kılıc A, Caglayık Yagcı D, Dede G, et al. A Hantavirus infection case report from rural area of Kazan district, Ankara. Turk Hij Den Biyol Derg 2013;70:27-32.
23. Jameson LJ, Taori SK, Atkinson B, et al. Pet rats as a source of Hantavirus in England and Wales, 2013. Euro Surveill; 2013;18:8–10.
24. Taori SK, Jameson LJ, Campbell A, et al. UK Hantavirus, renal failure, and pet rats. Lancet 2013;381(9871):1070.
25. Lundkvist A, Verner-Carlsson J, Plyusnina A, et al. Pet rat harbouring Seoul Hantavirus in Sweden, June 2013. Euro Surveill 2013;18:20521.
26. Olsson GE, Dalerum F, Hörnfeldt B, et al. Human Hantavirus infections, Sweden. Emerg Infect Dis 2003;9:1395-1401.
27. Heyman P, Vaheri A; ENIVD Members. Situation of Hantavirus infections and haemorrhagic fever with renal syndrome in European countries as of December 2006. Euro Surveill 2008;13:18925.
28. Palo RT. Time series analysis performed on nephropathia epidemica in humans of northern Sweden in relation to bank vole population dynamic and the NAO index. Zoonoses Public Health 2009;56:150-156.
29. Pettersson L, Boman J, Juto P, et al. Outbreak of Puumala virus infection, Sweden. Emerg Infect Dis 2008;14:808-810.
30. Dearing MD, Dizney L. Ecology of Hantavirus in a changing world. Ann NY Acad Sci 2010;1195:99-112.
31. Evander M, Ahlm C. Milder winters in northern Scandinavia may contribute to larger outbreaks of haemorrhagic fever virus. Glob Health Action 2009;2:16.
32. Klempa B. Hantaviruses and climate change. Clin Microbiol Infect 2009;15:518-523.
33. Yan L, Fang LQ, Huang HG, et al. Landscape elements and Hantaan virus-related hemorrhagic fever with renal syndrome, People's Republic of China. Emerg Infect Dis 2007;13:1301-1306.
34. Hjelle B. Epidemiology and diagnosis of Hantavirus infections. UpToDate. Available from: http://www.uptodate.com/contents/epidemiology-and-diagnosis-of-Hantavirus-infections?source=related_link.
35. Torres-Pérez F, Wilson L, Collinge SK, et al. Sin Nombre Virus Infection in Field Workers, Colorado, USA. Emerg Infect Dis 2010;16:308-310.

36. Merino C, Arias A, Castillo C. First Case of Hantavirus Cardiopulmonary Syndrome Occurring after a Rodent Bite. Rev Chil Enf Respir 2002;18:199-205.
37. Bi Z, Formenty PB, Roth CE. Hantavirus infection: a review and global update. J Infect Dev Ctries 2008;2:3-23.
38. Bhimma R. Hemorrhagic Fever With Renal Failure Syndrome. Medscape Available from: http://emedicine.medscape.com/article/982142-overview
39. Mustonen J, Helin H, Pietila K, et al. Renal biopsy findings and clinicopathologic correlations in nephropathia epidemica. Clin Nephrol 1994;41:121.
40. Collan Y, Mihatsch MJ, Lähdevirta J, et al. Nephropathia epidemica: mild variant of hemorrhagic fever with renal syndrome. Kidney Int Suppl 1991;35:S62.
41. Heiske A, Anheier B, Pilaski J, et al. Polymerase chain reaction detection of Puumala virus RNA in formaldehyde-fixed biopsy material. Kidney Int 1999;55:2062.
42. Schonrich G, Rang A, Lutteke N, et al. Hantavirus-induced immunity in rodent reservoirs and humans. Immunol Rev 2008;225:163-189.
43. Nichol ST. Bunyaviruses. In: Knipe DM, Howley PM, eds. Field's Virology Vol 2, 4th ed. Philadelphia, Pa Lippincott Williams Wilkins 2001:1603–1633.
44. Vaheri A, Strandin T, Hepojoki J, et al. Uncovering the mysteries of Hantavirus infections. Nat Rev Microbiol 2013;11:539-550.
45. Peters CJ. California Encephalitis, Hantavirus Pulmonary Syndrome, and Bunyavirid Hemorrhagic Fevers In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th ed. 2009:2289-2293.
46. Al Hazmi M, Ayoola EA, Abdurahman M, et al: Epidemic Rift Valley fever in Saudi Arabia: a clinical study of severe illness in humans. Clin Infect Dis 2003;36:245-252.
47. Burt FJ, Swanepoel R, Shieh W-J, et al. Immunohistochemical and in situ localization of Crimean-Congo hemorrhagic fever virus in human tissues and pathogenic implications. Arch Pathol Lab Med 1997;121:839.
48. Deyde VM, Khristova ML, Rollin PE, et al. Crimean-Congo hemorrhagic fever virus genomics and global diversity. J Virol 2006;80:8834-8842.
49. Lee JS, Cho BY, Lee MC, et al. Clinical features of serologically proven Korean hemorrhagic fever patients. Seoul J Med 1980;21:163.
50. Laine O et al. Enhanced thrombin formation and fibrinolysis during acute Puumala Hantavirus infection. Thromb Res 2010;126:154.
51. Peters CJ, Simpson G, Levy H, et al. Spectrum of Hantavirus infection: hemorrhagic fever with renal syndrome and Hantavirus pulmonary syndrome. Annu Rev Med 1999;50:531-545.
52. Kleinknecht D, Rollin PE. Hypertension after hemorrhagic fever with renal syndrome. Nephron 1992;61:121.
53. Novo R, Gagnadoux MF, Le Guenno Y, et al. Chronic renal failure after Puumala virus infection. Pediatr Nephrol 1999;13:934.
54. Mäkelä S, et al. Human leukocyte antigen-B8-DR3 is a more important risk factor for severe Puumala Hantavirus infection than the tumor necrosis factor-alpha(-308) G/A polymorphism. J Infect Dis 2002;186:843.
55. Mustonen J, Partanen J, Kanerva M, et al. Genetic susceptibility to severe course of nephropathia epidemica caused by Puumala Hantavirus. Kidney Int 1996;49:217-221.
56. Mustonen J, Partanen J, Kanerva M, et al. Association of HLA B27 with benign clinical course of nephropathia epidemica caused by Puumala Hantavirus. Scand J Immunol. 1998;47:277-279.
57. Geimonen E, LaMonica R, Springer K, et al. Hantavirus pulmonary syndrome-associated Hantaviruses contain conserved and functional ITAM signaling elements. J Virol 2003;77:1638-1643.
58. Plyusnin A, Horling J, Kanerva M, et al. Puumala Hantavirus genome inpatients with nephropathia epidemica: Correlation of PCR positivity with HLA haplotype and link to viral sequences in local rodents. J Clin Microbiol 1997;35:1090-1096.
59. Evander M, Eriksson I, Pettersson L. et al. Puumala Hantavirus viremia diagnosed by real-time reverse transcriptase PCR using samples from patients with hemorrhagic fever and renal syndrome. J Clin Microbiol 2007;45:2491-2497.
60. Vaheri A, Vapalahti O, Plyusnin A. How to diagnose Hantavirus infections and detect them in rodents and insectivores. Rev Med Virol 2008;18:277-288.
61. Machado AM, de Figueiredo GG, dos Santos Jr GS, Moraes Figueiredo LT. Laboratory diagnosis of human Hantavirus infection: novel insights and future potential. Future Virol 2009;4:383-389.
62. Huggins JW, Hsiang CM, Cosgriff TM, et al. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. J Infect Dis 1991;164:1119-1127.
63. Rusnak JM, Byrne WR, Chung KN, et al. Experience with intravenous ribavirin in the treatment of hemorrhagic fever with renal syndrome in Korea. Antiviral Res 2009; 81: 68-76.
64. Bharadwaj M, Nofchissey R, Goade D, et al. Humoral immune responses in the Hantavirus cardiopulmonary syndrome. J Infect Dis 2000;182:43-48.
65. Ye C, Prescott J, Nofchissey R, et al. Neutralizing Antibodies and Sin Nombre Virus RNA after Recovery from Hantavirus Cardiopulmonary Syndrome. Emerg Infect Dis 2004;10:478-482.
66. Kariwa H, Arikawa J, Takashima I, Hashimoto N. Development and application of protein G antibody assay for the detection of antibody to Hantavirus. J Virol Methods 1992;37:345–354.
67. Schmaljohn CS, Chu YK, Schmaljohn AL, Dalrymple JM. Antigenic subunits of Hantaan virus expressed by baculovirus and vaccinia virus recombinants. J Virol 1990;64:3162–3170.
68. Klingstrom J, Stoltz M, Hardestam J, et al. Passive immunization protects cynomolgus macaques against Puumala Hantavirus challenge. Antivir Ther 2008;13:125–133.
69. Schmaljohn C. Vaccines for Hantaviruses. Vaccine, 2009;27 (Suppl 4):61-64.
70. Hooper JW, Li D: Vaccines against Hantaviruses. Curr Top Microbiol Immunol 2001;256:171-191.
71. Dong GM, Han L, An Q, et al. Immunization effect of purified bivalent vaccine to haemorrhagic fever with renal syndrome manufactured from primary cultured hamster kidney cells. Chin Med J (Engl) 2005;118:766-768.
72. Schmaljohn C, Hasty SE, Dalrymple JM, et al: Preparation of candidate vaccinia-vectored vaccines for haemorrhagic fever with renal syndrome. Vaccine 1992;10:10-13.
73. McClain DJ, Summers PL, Harrison SA, et al: Clinical evaluation of a vaccinia-vectored Hantaan virus vaccine. J Med Virol 2000;60:77-85.
74. Chu YK, Jennings GB, Schmaljohn CS, et al. A vaccinia virus-vectored Hantaan virus vaccine protects hamsters from challenge with Hantaan and Seoul viruses but not Puumala virus. J Virol 1995;69:6417-6423.
75. Hooper JW, Custer DM, Thompson E, et al. DNA vaccination with the Hantaan virus M gene protects Hamsters against three of four HFRS Hantaviruses and elicits a high-titer neutralizing antibody response in Rhesus monkeys. J Virol 2001;75:8469-8477.