CKJ REVIEW

The kidney in hantavirus infection—epidemiology, virology, pathophysiology, clinical presentation, diagnosis and management

Felix C. Koehler, Veronica Di Cristanziano, Martin R. Späth, K. Johanna R. Hoyer-Allo, Manuel Wanken, Roman-Ulrich Müller and Volker Burst

1Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany, 2CECAD, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany and 3Institute of Virology, University of Cologne, Faculty of Medicine and University Hospital of Cologne, Cologne, Germany

Correspondence to: Volker Burst; E-mail: volker.burst@uk-koeln.de

ABSTRACT

Hantavirus-induced diseases are emerging zoonoses with endemic appearances and frequent outbreaks in different parts of the world. In humans, hantaviral pathology is characterized by the disruption of the endothelial cell barrier followed by increased capillary permeability, thrombocytopenia due to platelet activation/depletion and an overactive immune response. Genetic vulnerability due to certain human leukocyte antigen haplotypes is associated with disease severity. Typically, two different hantavirus-caused clinical syndromes have been reported: hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). The primarily affected vascular beds differ in these two entities: renal medullary capillaries in HFRS caused by Old World hantaviruses and pulmonary capillaries in HCPS caused by New World hantaviruses. Disease severity in HFRS ranges from mild, e.g. Puumala virus-associated nephropathia epidemica, to moderate, e.g. Hantaan or Dobrava virus infections. HCPS leads to a severe acute respiratory distress syndrome with high mortality rates. Due to novel insights into organ tropism, hantavirus-associated pathophysiology and overlapping clinical features, HFRS and HCPS are believed to be interconnected syndromes frequently involving the kidneys. As there are no specific antiviral treatments or vaccines approved in Europe or the USA, only preventive measures and public awareness may minimize the risk of hantavirus infection. Treatment remains primarily supportive and, depending on disease severity, more invasive measures (e.g., renal replacement therapy, mechanical ventilation and extracorporeal membrane oxygenation) are needed.

Keywords: hantavirus cardiopulmonary syndrome, hantavirus disease, hemorrhagic fever with renal syndrome, kidney, nephropathia epidemica
INTRODUCTION

Hantavirus-associated diseases are emerging zoonoses that remain a clinical challenge with increasing incidence and multiple serious outbreak situations (Figure 1) [1–4]. Hantavirus infections were first recognized during the Korean War, when more than 3000 United Nation’s troops developed a syndrome typically comprising hemorrhagic fever and kidney failure. This clinical picture was eventually referred to as hemorrhagic fever with renal syndrome (HFRS). The causative viral pathogen, Hantaan virus (HTNV), was first discovered in its natural reservoir, the striped field mouse (Apodemus agrarius), in the late 1970s (Figure 2) [5]. Puumala virus (PUUV), causing a milder course of HFRS also named nephropathia epidemica, was identified in a different mouse strain, bank voles (Myodes glareolus), in the 1980s, although the disease had been known in Scandinavia since the 1930s [6]. Dobrava–Belgrade virus (DOBV) was first isolated from a field mouse (Apodemus flavicollis) in Slovenia in the 1990s and was recognized as a frequent hazard for soldiers during the Yugoslav wars [7–11]. Mortality due to HFRS ranges from <1% in PUUV infections to 10–15% in HTNV or DOBV infections [12–14].

Apart from HFRS, there is the hantavirus cardiopulmonary syndrome (HCPS), with a high mortality rate of up to 40% in America [3, 15]. The causative hantavirus of HCPS, Sin Nombre (SNV), was identified within months after its first outbreak in the Four Corners Region in the USA [16, 17]. Other hantaviruses causing HCPS have been found in North and South America [18–21] over the years. Based on the geographical evolution, hantaviruses are separated into Old World viruses (e.g., HTNV, DOBV, PUUV) that commonly elicit HFRS and New World viruses (e.g., SNV, Andes virus (ANDV)) that commonly elicit HCPS (Table 1).

Hantavirus infections are rare infectious diseases. However, hantavirus diseases emerge progressively, in particular in Europe, and new hantaviruses with yet unknown pathogenic impact are being discovered in different parts of the world, calling for joint efforts at the crossroads of nephrology, infectious diseases and public health [1, 2, 14, 22].

Hantavirus ecology and epidemiology

Hantaviruses are carried and transmitted to humans by persistently infected rodents, insectivore hosts and bats. The geographic distribution and ecology of hantaviruses are therefore closely connected to their hosts. Myodes, Ratus and Apodemus are the primary rodent reservoirs of Old World hantaviruses, whereas New World hantaviruses are transmitted via Sigmodontines, a rodent subfamily of New World rats and mice [1]. Hantavirus species have been discovered in Africa, Asia and Europe, as well as North America and South America (Table 1) [1, 23, 24]. The evolution and distribution of hantavirus populations and the subsequent rate of infections are associated with climate change and disturbed rodent habitats caused by excessive agriculture and deforestation [25–27]. Increases in temperature,
humidity and rainfall are directly associated with the incidence of hantaviral infections in different parts of the world [28–30]. For example, warm ambient temperature and abundant rainfall directly affect vegetation growth, boosting rodent populations [31, 32]. In Europe, rodent food availability and higher ambient temperatures in cold seasons have been reported to cause more frequent and severe outbreaks of hantavirus infections [30, 33]. Higher temperature is also correlated with increased rodent reproduction, sexual maturation and survival [34, 35]. The extent of rodent habitat growth and subsequent hantavirus distribution by long-term climate change is unclear (Table 2) [24]. Nevertheless, migration of humans due to climate change to areas less vulnerable to extreme weather events will increase rodent density and may even contribute to hantavirus disease in new regions [36]. Of note, the increase in atmospheric moisture as well as the increase in air temperature facilitates aerosolization and thus augments hantaviral infectivity [29, 37].

Hantaviruses are circulating between chronically infected host reservoirs, whose infection is usually inapparent. Transmission to humans is caused by inhalation of contaminated aerosolized rodent excreta, leading to so-called spillover infections [3]. These spillover infections to humans or other animals, such as red fox, moose or domestic cat and dog, are a concern for public health, as they facilitate the evolution of new hantavirus species by natural reassortment (Table 2) [33, 38, 39]. The risk of hantavirus infections in humans mainly depends on the closeness to and frequency of contact with rodents. Therefore
| Disease | Virus | Geographic distribution | Reservoir host | Commercial serological test | Comments |
|---------|-------|--------------------------|----------------|-----------------------------|----------|
| HFRS   | HCPS  |                           |                |                             |          |
| X      | Old World hantaviruses | SENV Worldwide | Rat (Rattus) | X                            | Metropolitan distribution |
| NE     | PUUV  | Europe, Russia, Americas | Bank vole (Myodes glareolus) | X                            | Main European virus |
| X      | DOBV  | Balkans                  | Yellow-necked mouse (Apodemus flavicollis) | X                            |          |
| X      | TULV  | Europe, Russia           | Common vole (Microtus arvalis) | X                            |          |
| X      | AMRV/SOOV | Far-East Russia China, Korea, Russia, Central Europe | Korean field mouse (Apodemus peninsulae) | X                            |          |
| X      | HTNV  | China                     | Striped field mouse (Apodemus agrarius) | X                            | Main Asian virus |
| X      | Luxi virus (LUXV) | China | Yunnan red-backed vole (Eothenomys miletus) | X                            |          |
| X      | THAV  | Southeast Asia | Greater bandicoot rat (Bandicota indica) | X                            |          |
| X      | SANGV | Africa                    | African Wood Mouse (Hylomyscus simus) | X                            | First African virus, spillover infections to bats |
|       | New World hantaviruses | North America | Marsh rice rat (Oryzomys palustris) | X                            | Main North American virus |
| X      | Bayou virus (BAYV) | North America | Hispid cotton rat (Sigmodon hispidus) | X                            |          |
| X      | Black Creek Canal virus (BCCV) | North America | White-footed mouse (Peromyscus leucopus) | X                            |          |
| X      | New York virus (NYV) | North America | Eastern deer mouse (Peromyscus maniculatus) | X                            | Main South American virus, human-to-human transmission |
| X      | SNV   | North America | Fulvous colilargo (Oligoryzomys fulvescens) | X                            |          |
| X      | Choco virus (CHOV) | Panama | Hairy-tailed bolo mouse (Bolomys lasiurus) | X                            |          |
| X      | Araraquara virus (ARQV) | Brazil | Fornes’ colilargo (Oligoryzomys fornesi) | X                            |          |
| X      | Anajatuba virus (ANJV) | South America | Brazilian colilargo (Oligoryzomys eliurus) | X                            |          |
| X      | Castelo dos Sonhos virus (CASV) | South America | Long-tailed colilargo (Oligoryzomys longicaudatus) | X                            |          |
| X      | ANDV  | Argentina, Chile | Hairy-tailed bolo mouse (Bolomys lasiurus) | X                            |          |
| X      | Bermejo virus (BMJV) | Argentina | Small vesper mouse (Calomys laucha) | X                            |          |
| X      | Laguna Negra virus (LANV) | Argentina, Bolivia, Paraguay | Flavescent colilargo (Oligoryzomys flavescens) | X                            |          |

*PUUV causes nephropathia epidemica, a mild form of HFRS. PUUV is the main European hantavirus, whereas HTNV is the main Asian hantavirus. ANDV and SNV are the major South and North American hantaviruses causing HCPS. Novel New World hantaviruses were detected recently with unknown pathogenicity. 

*aSo far only serological evidence reported.

NE: nephropathia epidemica.
people with close exposure to rodent habitats, such as farmers, forestry workers, military personnel and zoologists are subject to a greater risk [40–42]. However, many cases are observed after sporadic cleansing of environments that are a habitat for rodents, like basements or attics, without a specific professional exposure.

The epidemiology of hantavirus-associated diseases depends on their host reservoirs’ distribution. In Europe, Tula virus (TULV), DOBV and PUUV are detected most frequently in their rodent reservoirs (Figure 2). PUUV is the most widely distributed hantavirus in Northern and Central Europe and usually causes mild disease (Figure 1, Table 1) [43]. However, PUUV still poses a threat due to its increasing incidence, with recurring outbreak situations and thousands of patients in epidemic years [2, 44, 45]. In contrast, Southeastern Europe is dominated by DOBV, resulting in a moderate–severe disease form of HFRS (Figure 2) [2]. Here, the Balkan region is primarily affected by DOBV, although its host distribution is greater [3, 46, 47]. Of note, DOBV has been emerging in Central and Eastern Europe in recent years [48–51]. TULV is dominantly circulating in the Tula region in Russia and leads to a mild disease course [52]. However, patient cases are found throughout Central Europe and the Baltic states (Figure 2) [52–55].

Asia is the continent with the longest history of hantavirus infections. HTNV and the related Amur/Soochong virus (AMRV/SOOV) are found in China, Far East Russia and Korea, causing moderate forms of HFRS [1, 5, 56, 57]. China reports >10 000 cases and southern Korea ~300–500 cases/year [58]. Further species with unknown pathogenicity, such as Thailand virus (THAV), Imjin virus (MIV) and Jeju virus (JJUV) have been recognized in different parts of Asia (Table 1) [1, 2, 59, 60].

Due to the cosmopolitan distribution of rats as its natural host, Seoul virus (SEOV) is considered to circulate worldwide [1]. SEOV is primarily reported from urban China; however, patient cases have also been observed occasionally in the USA and Europe [61–63]. Surveillance studies indicate that HFRS caused by rat-borne SEOV usually occurs in metropolitan areas and current trends in urbanization may further influence SEOV epidemiology [64].

New World hantaviruses were first discovered after an outbreak of an acute respiratory disease named HCPS in the USA in 1993 and SNV was found as a first causative pathogen [15, 17]. SNV is the main pathogen circulating in North America [2]. In contrast, ANDV is the dominant hantavirus in Latin America [65]. Of note, ANDV is the only known hantavirus that can be transmitted from human to human by superspreading events, further threatening public health and making pandemics a potential scenario [18–21, 66]. Recently, novel hantaviruses with unclear taxonomic status were discovered in their natural reservoirs in America, but little is known about their pathogenicity (Table 1) [1, 22].
Africa is the continent with the most recent scientific progress in hantavirus ecology and epidemiology. Fifteen years ago the first pathogenic hantavirus in Africa, Sangassou virus (SANGV), phylogenetically related to Old World hantaviruses, was isolated in Guinea [67, 68]. Novel hantavirus species have been discovered not only in rodents, but also in shrews and bats in Africa [2, 69, 70]. In particular, the role of bats as novel hosts facilitating easier spillover infections to humans reflects an additional concern for public health (Table 2) [3].

Taken together, the ecology and epidemiology of hantaviruses and their associated diseases are mainly reflected by their host reservoirs’ distribution. Hence HFRS caused by DOBV, HTNV and PUUV dominates Eurasia, whereas SNV- and ANDV-associated HCPS is primarily found in America (Table 1).

**Hantavirus structure and life cycle**

Hantaviruses, members of the Bunyaviridae family, are enveloped, single-stranded ribonucleic acid (ssRNA) viruses [71].

The total size of the viral RNA (vRNA) ranges from 11 845 nucleotides for HTNV to 12 317 nucleotides for SNV [1]. The viral genome is separated into three segments referred to as S (small), M (medium) and L (large), which share a 3′ terminal sequence and encode the nucleocapsid (N) protein, the glycoprotein precursors (GPCs) and the RNA-dependent RNA polymerase (RdRp) [23, 72]. The vRNA itself is encapsulated by the N protein, forming circular ribonucleoproteins (RNPs) [73]. The virion’s surface consists of the two glycoproteins Gn and Gc (formerly G1 and G2, respectively) that mature from GPCs. The RdRp amplifies and transcribes vRNA and is essential for hantavirus replication (Figure 3). Hantaviruses can survive for >10 days at room temperature and for >18 days at +4°C outside cells, facilitating transmission and spillover infection [74].

Hantaviruses not only infect primarily endothelial cells, but also replicate in the epithelium—including podocytes and tubular cells in the kidney as well as alveolar cells in the lungs—macrophages, dendritic cells and lymphocytes [21, 75–79]. Figure 3 highlights the hantavirus life cycle. In vitro studies...
suggest that hantaviruses attach to integrins (αvβ3, α5β1, αMβ2 and αXβ2) on host cells through binding with their larger glycoprotein Gn [76, 80, 81]. β3- and β1-containing integrins are proposed as the major entry receptors for both virulent and avirulent Old and New World hantaviruses [80–82]. There is evidence that binding to α5β1 integrin instead of αvβ3 is associated with reduced virulence—as can be seen with the apathogenic Prospect Hill virus (PHV). On the other side, the African SANGV is the only pathogenic hantavirus known to bind to α5β1 and to cause hantavirus disease [83, 84]. Different nucleotide polymorphisms have been implicated in infection susceptibility in humans, calling for further research in hantaviral attachment (Table 2) [85, 86]. Of note, protocadherin-1 (PCDH1) was reported recently to be another critical determinant of attachment, entry and infection of New World but not Old World hantaviruses [87].

After cellular attachment, Old World hantaviruses enter host cells by clathrin-dependent endocytosis, whereas New World viruses employ different mechanisms of cell invasion simultaneously, including micropinocytosis, clathrin-independent receptor-mediated endocytosis and cholesterol- or caveolae-dependent endocytosis (Figure 3) [23, 88, 89]. After cell entry, viral particles are processed in endosomes or lysosomes, where they detach from their cellular receptors and uncoat as a consequence of decreasing pH. Afterwards, hantavirus RNPs are liberated into the cytoplasm by fusion of viral and endolysosomal membranes [88]. In the cytoplasm, vRNA is then transcribed to L, M and S messenger RNA (mRNA), enabling their translation into viral proteins that hijack the host machinery [1]. Additionally, vRNA is transcribed to complementary RNA (cRNA) using host-derived primers facilitating amplification and replication of vRNA [1]. Both transcription and replication processes of hantaviruses are performed by viral RdRP [23]. After replication of the hantavirus genome, the vRNA is encapsulated by the N protein. Then, further N proteins bind, resulting in larger RNPs [90, 91]. The different hantavirus components are finally assembled at the Golgi apparatus, or alternatively, as currently suggested for New World hantavirus, at the plasma membrane itself [92]. By fusion with the host’s cell membrane, hantaviruses finally egress [93].

### Hantavirus pathogenesis and immunopathology

Despite different causative pathogens and disease patterns, HFRS and HCPS have an overlapping pathophysiology consisting of increased vascular permeability, platelet activation and an overreacting host immune response (Figure 4, Table 3) [23, 46]. Differences in disease are reflected by the different vascular beds that are primarily infected—renal medulla or pulmonary capillaries. However, the mechanisms mediating cell tropism and organ-specific dysfunction during HFRS and HCPS remain unknown (Table 2) [94].

The pathophysiology of capillary leakage is characterized by the disruption of endothelial cell–cell contacts. Hantaviruses primarily infect and replicate in endothelial cells of capillaries; however, there are few to no direct cytopathic effects to the endothelium as detected in histological samples [23, 95]. In contrast, it is hypothesized that the breakdown of endothelial cell-to-cell contact is mainly caused by the release of vasoactive factors, including vascular endothelial growth factors (VEGF), bradykinin and cytokines, rather than endothelial cell death [96, 97]. Mechanistically, released VEGF results in a decrease of VE-cadherin, a major component of adherens junctions in endothelial cells, in vitro [98, 99]. VEGF-induced capillary hyperpermeability may additionally be a direct consequence of hantavirus-caused inactivation of αvβ3 integrins followed by a decrease of VEGFR receptor 2 (VEGFR2) on the cell surface [75, 100]. VEGFR2 and αvβ3 integrins normally form a complex affecting VEGFR2-directed permeability in response to VEGF [101]. Hantaviruses functionally block the VEGFR2/αvβ3 integrins complex that causes VEGF-orchestrated cellular permeability in vitro and in vivo [102–105]. In line with these findings, levels of VEGF and soluble VEGFR2 in serum and urine correlate with disease severity, indicated by low urine output and haemorrhages in PUUV- and DOBV-infected patients [106]. Moreover, as hypoxia additionally challenges VEGF production, elevated levels of VEGF are detected in pulmonary edema fluids of HCPS patients and correlate with HCPS disease severity [99]. Of note, vandetanib, a small-molecule antagonist of VEGFR2, leads to modest survival benefits in vivo as examined in the Syrian hamster model of ANDV-caused HCPS [107]. However, transfer of this treatment approach to the patient setting has not been successful due to the reported frequent severe adverse
life-threatening viral infections and our growing knowledge function contributes significantly to pathophysiology in many
diseases. Hence dysregulation in vascular mediators of disease and the extent of endothelial damage (including dengue virus) and filoviruses (i.e., Ebola and Marburg viruses), although endothelial receptor, entry mechanism, production of nitric oxide [117]. In particular, capillary leakage and extracellular matrix degradation are linked to certain cytokine profiles in serum samples in both HFRS and HCPS; cytokine storm is a common central component in response in hemorrhagic fevers.

Evidence reported in

| Pathogenic mechanisms in hantavirus disease | Cell culture | In vivo models | Humans | Comments | References |
|---------------------------------------------|--------------|----------------|--------|----------|------------|
| Increased vascular permeability             | X            | X              | X      | Orchestrated by a decrease in VEGF-α induced endothelial hyperpermeability | [98, 99, 105–107] |
| Bradykinin-induced capillary leakage        | X            | X              |        | Interaction of viral glycoproteins and integrin αIIβ3 on platelets | [109–111] |
| Cytokine-mediated hyperpermeability          | X            | X              |        | Release of adhesive agents, such as fibrinogen, fibronectin, extracellular vesicle tissue factor and von Willebrand factor after endothelial infection | [113–119] |
| Platelet activation                          | X            |                |        | Causes further activation | [124, 125] |
| Direct viral-caused platelet consumption    | X            |                |        | May explain interpersonal and regional differences in susceptibility and vulnerability | [126, 127, 131, 132] |
| Endothelial cell injury causing platelet activation | X            |                |        | Distinct cytokine profiles in HFRS and HCPS; cytokine storm is a common central component in response in hemorrhagic fevers | [116, 118, 119, 138, 142–145] |

Increased vascular permeability, platelet activation and an overreacting host immune response are the central pathomechanisms in human disease caused by pathogenic Old World and New World hantaviruses.

A common feature of hantavirus infection is thrombocytopenia; however, the exact pathomechanisms remain unknown [3, 23, 78]. Currently it is hypothesized that the adhesion of hantaviruses mediated by viral glycoproteins and integrin αIIβ3 on the surface of platelets contributes to platelet depletion [124, 125]. Also, hantavirus infection–derived endothelial cell injury may directly cause platelet activation through the release of adhesive agents, such as fibrinogen, fibronectin and von Willebrand factor [23, 126]. Moreover, hantaviruses promote intravascular coagulation, leading to an increase in thrombin and fibrinolysis that additionally may cause thrombocytopenia due to increased platelet consumption [127]. Of note, clinical criteria of disseminated intravascular coagulation (DIC) are fulfilled frequently in hantavirus patients, posing risks for bleeding and thromboembolic complications [128–130]. Platelet activation and elevated levels of tissue factor and extravascular tissue factor expressed by both endothelial and immune cells are reported to promote this systemic procoagulant state [131–133]. Although the clinical picture consisting of renal injury and thrombocytopenia might suggest thrombotic microangiopathy, no histological or laboratory evidence for this entity has been reported. Hemolysis as well as schistocytes are usually not present.

In human kidneys, hantaviruses primarily replicate in the endothelial cells of the renal medulla [134]. However, hantaviruses may additionally infect other cell types in the kidney, i.e. tubular cells, podocytes and the glomerular endothelium as detected in kidney biopsy specimens of infected patients [135]. Of note, the barrier function in all these cell types
can be altered due to the breakdown of cell–cell contacts, which may be an explanation for the observed proteinuria during hantavirus infection [135, 136]. The detection of viral antigen along with inflammatory cell infiltrations in the peritubular area indicates that viral replication and the host's immune response together cause tissue damage in human disease [137, 138]. The renal immunopathology is primarily characterized by an upregulation of pro-inflammatory cytokines, such as type I interferons (IFNs) and interleukin-8 (IL-8) in the distal nephron activating both innate and adaptive immune cells [139–141]. The further systemic immune response is driven by macrophages and antigen-specific cells, including CD4+ and CD8+ T cells, as well as antibody-producing B cells [1, 3, 23]. Inflammatory cytokines and chemokines, i.e. transforming growth factor (TGF)-β, tumour necrosis factor (TNF)-α, IL-6 and IL-10, play double-sided roles in human hantavirus infection. On the one hand, immunosuppressive TGF-β, acts protectively in the late phase of PUUV infection by limiting tissue damage caused by the immune system [142]. On the other hand, TNF-α, IL-1 and IL-6 are associated with fever and septic shock as well as the further induction of acute-phase proteins and increased levels of those cytokines can be detected in urine, plasma and tissue samples of severely infected patients [115, 116, 142, 143]. In line with this notion, disease severity in PUUV and DOBV infections is associated with elevated serum levels of TNF-α, IL-6 and IL-10 [115, 116, 143, 144]. Elevated urinary IL-6 levels in PUUV-induced HFRS indicate local renal production of IL-6 in addition to the systemic immune response [115]. With regard to HCPS, elevated serum IL-6 levels are directly linked to fatal outcomes in humans [145]. Interestingly, IL-6 production is an overlapping characteristic of viral hemorrhagic fevers, as high levels of IL-6 have been linked to disease severity in Ebola virus infection, dengue virus infection and Crimean–Congo hemorrhagic fever [146–148].

Another remarkable parallel can be drawn to the cytokine release syndrome (CRS), a toxic immune reaction upon cancer treatment with chimeric antigen receptor–modified T cells that leads to a systemic increase in IL-6 and IL-10 [149]. Symptoms of CRS and hantavirus disease highly overlap—in mild cases, flu-like symptoms; in severe cases, vascular leakage, coagulopathy, hypotension, acute kidney injury (AKI) and pulmonary edema—and blockage of the IL-6 receptor with tocilizumab reverses CRS [150]. This raises the question whether hantavirus-infected patients could benefit from similar treatment. However, in vivo animal and human data in hantavirus disease are lacking and the full causal roles of the highlighted mediators on local tissue damage remain largely unaddressed [145].

With regard to the adaptive immune system, hantaviruses increase the number of CD8+ T cells and reverse the CD4+:CD8+ T-cell ratio [3]. As a consequence, further pro-inflammatory cytokines are produced while regulatory cytokines are downregulated, enhancing the harmful effect of the immune system [151, 152]. Of interest, certain human leukocyte antigen (HLA) haplotypes are associated with severe disease courses in both HFRS and HCPS by triggering T-cell-mediated immune responses, especially of CD8+ T-cells [153–156]. This genetic vulnerability may explain interindividual and regional differences in disease severity of both HFRS and HCPS in endemic areas [136]. For example, HLA alleles HLA-B*08, HLA-DRB1*0301 and HLA-DRB1*15 are associated with a severe form of PUUV infection, whereas HLA-B*27 has a benign prognosis [153, 157, 158]. In HTNV-caused HFRS, individuals with HLA-B*46 and HLA-B*46-DRB1*09 or HLA-B*51-DRB1*09 haplotypes are at a greater risk, whereas HLA-DRB1*12 is protective [159, 160]. With regard to HCPS, HLA-B*3501, HLA-DRB1*1402 and HLA-B*08 are negative prognostic factors in SNV- and ANDV-infected patients, respectively [156, 161]. In contrast, HLA-DRB1*15 and HLA-B*35-restricted memory T-cell responses are reported to be protective in ANDV-caused HCPS [161, 162]. Of note, different hantaviruses may be processed differently through the same HLA molecules, leading to either a mild or severe disease course as shown for HLA-DRB1*13 and HLA-B*35 in PUUV- and DOBV-caused HFRS [160, 163].

Small animal models recapitulating human hantavirus disease are scarce, as human pathogenic hantaviruses are maintained in nature by persisting rodent infection. For example, mice, rats and hamsters infected with HTNV, DOBV and PUUV fail to develop a human HFRS phenotype, whereas new born rodents that are infected within 3 days after birth die due to neurologic complications not recapitulating any disease characteristics resembling human disease [164]. The generation of HFRS animal models reflecting human hantavirus disease remains an urgent scientific need to fully understand hantaviral pathogenesis (Table 2). In contrast, Syrian hamsters infected with ANDV and SNV mimic human disease with regard to incubation time, rapid-progressing respiratory failure and pathological lung findings, but biosafety measurements make experimental design complex [165–167].

Clinical presentation

Common early symptoms in the prodromal phase of both HFRS and HCPS include myalgia, fatigue, abdominal pain, headache, high fever and other flu-like symptoms [168]. Although similar in pathogenesis, further observed clinical differences between HFRS and HCPS are the consequence of the primarily affected organs [3].

HFRS. HFRS is a generalized infection and its clinical course and outcome are dependent on the causative (Old World) hantavirus, although disease courses vary individually from subclinical to lethal.

The incubation phase of hantavirus ranges from 2 to 6 weeks [1]. Afterwards, the disease can be divided in five distinct phases: fever, hypotension, oliguria, polyuria and convalescence (Figure 5) [1, 3]. HFRS is characterized by the sudden onset of prodromal symptoms, such as myalgia, fatigue, abdominal pain, headache, high fever, blurred vision and other flu-like symptoms lasting 3–6 days. Somnolence is reported less frequently. The beginning of the hypotensive phase is characterized by hemorrhage (i.e. conjunctival suffusion, skin and mucosal petechiae, hematemesis, epistaxis, melaena, hematuria or even intracranial bleeding) due to thrombocytopenia, as well as hypotension or shock caused by vascular leakage. Of note, approximately one-third of case fatalities are related to an irreversible and fulminant shock [3]. Hemorrhage is also facilitated by thrombocytopenia, which is usually present in this stage and is the direct consequence of hantavirus-caused activation and depletion of platelets. The nadir in platelet count ranges from ~70 × 10^9/L in PUUV to ~30 × 10^9/L in DOBV- and HTNV-caused HFRS [46, 169, 170]. Bleeding events, typically reported as gastrointestinal bleeding, hematuria or hemoptysis are reported in ~10% of HFRS cases. However, the incidence of bleeding events ranges from <5% in PUUV to 20% in DOBV and 35% in HTNV infections [171–173]. Microscopic hematuria is present in the vast majority of HFRS patients, whereas macroscopic hematuria is more frequently reported in DOBV and HTNV
infections [174]. Hematuria usually derives from medullary or interstitial hemorrhages, i.e. is of intrarenal origin [175, 176]. DIC occurs in ~30% of DOBV- or HTNV-infected patients as a consequence of an activated coagulation system and is a negative prognostic factor [127, 128, 177]. DIC is reported in ~20% of PUUV patients according to the modified scoring system of the International Society of Thrombosis and Haemostasis; however, DIC is less severe in PUUV-caused disease [128, 177]. The hypotensive stage typically lasts 1–2 days and is followed by the often rapidly progressing oliguric AKI. With hemodynamic stabilization, renal function is eventually restored over a period of 3–7 days (Figure 5). The decrease in systemic blood pressure does not fully explain AKI, as a decline in kidney function may even occur without hypotension and measured blood pressures do not correlate with disease severity [96]. Intrarenal events—especially hantaviral-caused acute interstitial nephritis with cortical and peritubular capillaritis—are currently believed to contribute to the development of AKI; however, the exact mechanisms remain elusive and call for further research (Table 2) [96, 97, 176].

Due to the intrarenal inflammatory processes, swelling of the kidneys is a hallmark of hantavirus-caused AKI, which is typically accompanied by—sometimes very severe—abdominal pain or backache. Proteinuria, sometimes in the nephrotic range, is also a typical finding in hantavirus-caused AKI and reflects the involvement of podocytes. The magnitude of proteinuria is associated with disease severity [178–180]. Renal replacement therapy (RRT) is needed in ~5% of PUUV and 30% of both DOBV and HTNV infections, and half of HFRS deaths occur in this oliguric phase [3, 181–185]. Approximately 10% of DOBV- and HTNV-infected patients require mechanical ventilation due to the development of acute respiratory distress syndrome (ARDS) caused by acute progressive noncardiac pulmonary edema, whereas mechanical ventilation is rarely needed in PUUV-caused disease [168, 172, 186–188]. With the onset of the polyuric stage, kidney function gradually improves and urinary output may be increased for several weeks (Figure 5). Finally, convalescence, which is characterized by full recovery of kidney function, is usually prolonged and takes up to 3–6 months [189]. Of note, the risk for acute myocardial infarction, stroke and venous thromboembolisms is significantly elevated in this phase as a consequence of enhanced coagulation and inflammation after hantavirus disease [129, 130]. Although kidney function is usually completely restored, chronic kidney disease (CKD) and hypertension have been reported as rare long-term sequelae—robust data on the frequency and relative risk of CKD and RRT in HFRS (especially in DOBV- and HTNV-infected patients) are missing (Table 2) [172, 190–192].

PUUV-caused nephropathia epidemica is a mild form of HFRS that is the most common hantavirus disease in Europe. The typical disease stages are often not clearly distinguishable, as most patients suffer from less severe kidney failure that rarely requires RRT and hemorrhagic manifestations are usually mild [177, 181, 182]. PUUV-caused HFRS is often misdiagnosed due to its rather uncharacteristic clinical phenotype that resembles a febrile disease with abdominal pain [3, 193]. Different from other
hantaviruses, SEOV is characterized by accompanying liver dysfunction during HFRS [194].

Children have a similar clinical presentation of HFRS as adults; however, the disease course is usually milder, with abdominal manifestations of hantavirus infection being more frequent [195, 196].

HCPS. The clinical phenotype of HCPS is characterized by ARDS, with case fatality rates of 30–50% [15, 197]. However, disease severity ranges from mild hypoxemia to fatal respiratory failure with precapillary cardiogenic shock [198].

The prodromal phase observed in HCPS is similar to HFRS and includes unspecific flu-like symptoms, including fever, chills, myalgia, nausea and vomiting. The disease course is characterized by progress to a cardiopulmonary stage with tachycardia, arrhythmia, shortness of breath and cough. Due to the vascular leakage in lung capillaries, patients rapidly develop noncardiac pulmonary edemas, oxygenation impairment and hypotension. Additionally, pulmonary infiltrates and pleural effusion may be detected. Patients with severe HCPS frequently require mechanical ventilation; often the disease course is further complicated by cardiogenic shock, lactic acidosis and hemocoagulation [3]. Therefore patients often die within hours after hospitalization when entering the fulminating cardiopulmonary phase [3]. When pulmonary edema resolves, patients develop polyuria and full recovery is achieved only after months [199].

With regard to kidney involvement in HCPS, proteinuria is frequently seen and is associated with mortality [200–202]. Moreover, AKI occurs in ~15–20% of HCPS patients and RRT is needed in ~10% of all HCPS patients [200, 203, 204]. The pathogenesis of kidney involvement in HCPS is currently unclear, as—due to the profound thrombocytopenia and DIC in the critically ill HCPS patient cohort—kidney biopsy samples are not available. A recent but small Brazilian autopsy study reported marked acute tubular necrosis. This notwithstanding, more pathological characterization of kidney phenotype in HCPS is needed [205]. Long-term kidney outcome in HCPS has been scarcely examined, mainly due to the low incidence and high mortality of the disease (Table 2). A small prospective study from the USA reported kidney sequelae after HCPS consisting of proteinuria and development of CKD in half of the reported cases [206].

Hantavirus disease—an interconnected syndrome beyond HFRS and HCPS. Renal and pulmonary diseases are often assigned to either Old World or New World hantaviruses in a dichotomous manner. However, HFRS and HCPS are defined and named after symptoms that also may be partly absent or incomplete. Recent advances in characterizing and understanding pathogenesis, organ tropism and clinical phenotype have confirmed common features of HFRS and HCPS and have therefore led to the perception of an interconnected disease [200, 207]. To this end, various reports indicate a large overlap of renal and pulmonary impairment in Old World and New World hantaviruses [168, 200, 206, 208–210]. For example, frequent development of ARDS is observed in HFRS caused by DOBV and HTNV [186–188, 211]. In PUUV infections, there are case reports that the human lung may be the primarily organ system affected, with PUUV being additionally detected in bronchoalveolar lavage (BAL) fluid [168, 208, 209, 212–215]. In HCPS-assigned SNV and ANDV, RRT is often needed for acute treatment [198, 203, 216]. In order to refine our knowledge on epidemiologic and clinical aspects of hantavirus disease and to determine disease progression beyond the dichotomous denominations of HFRS and HCPS—i.e., to define diagnostic criteria from large cohorts rather than case reports—a novel platform, the Hantavirus Registry (NCT04323904), was recently developed [217].

Diagnosis

The diagnosis of hantavirus-associated diseases is based on clinical findings, local epidemiology and laboratory methods. Hallmark laboratory findings of hantavirus infection are thrombocytopenia, leukocytosis, hemocoagulation, elevated serum creatinine levels, hematuria and proteinuria. Further laboratory markers depend on the other preferentially targeted organs [2].

Hantavirus-specific immunoglobulin M (IgM) and IgG antibodies are usually present in patients at the onset of symptoms. In contrast to IgG antibodies that persist lifelong, IgM titers are detectable in the acute phase of infection and decline over a period of 2–6 months (Figure 5) [3, 218–220]. Therefore an IgM capture test is combined with an IgG test to detect acute infection. In Europe, hantavirus-specific diagnostic strategies should at least cover DOBV and PUUV. The serodiagnosis of hantavirus infection can be performed by enzyme-linked immunosorbent assay (ELISA) or immunoblot, predominantly detecting antibodies against N proteins [3, 218, 222]. ELISA is used in most commercially available serologic tests and employs recombinant protein antigens taken from DOBV, HTNV, PUUV, SEOV, SNV and ANDV (Table 4) [223]. The sensitivity and specificity for ELISA-based serodiagnosis are both ~95% [223–225]. Also, immunoblots for DOBV, HTNV, PUUV and SEOV are commercially available and the reported sensitivity and specificity are 96% and 100%, respectively [223, 226]. Immunoﬂuorescence assays (IFAs) examine the reaction of patient serum samples to uninfected or hantavirus-infected cells. IFAs have been most widely used in Europe and facilitate the detection of DOBV/HTNV and PUUV. The reported sensitivity and specificity are 98% and 91%, respectively [227]. Of note, results obtained from ELISAs should be confirmed by independent tests and in Europe both immunoblot and IFA are used for conﬁrmation. Rapid immunochromatographic IgM antibody tests allow for point-of-care diagnosis but have not yet entered widespread use; they are also limited in sensitivity [228, 229].

The hantavirus genome can be detected by both traditional and real-time polymerase chain reaction (PCR)-based diagnostics in blood, saliva, BAL fluids and tissue samples. Of note, PCR-based diagnostics facilitate postmortem diagnosis and organ involvement. The viral load detected in blood samples at the onset of infection may even predict disease severity in both HFRS and HCPS; however, the viremic phase is limited to the very early stage of the disease (Figure 5) [230–233]. Another drawback of PCR-based diagnostics is the possibility of obtaining false-negative results in low-viremic infections often seen in, for example, PUUV or in patients tested late in disease [2]. Moreover, PCR-based diagnostics are prone to cross-contamination. Major advantages of molecular-based diagnostics are rapid test results obtained within 24 h, especially important in critically ill patients, and the ability to sequence the viral genome for phylogenetic analysis [223].
Table 4. Comparison of frequently used commercially available diagnostic approaches for hantavirus disease

| Diagnostic test | Antigen type/hantavirus detected | Sensitivity (%) | Specificity (%) | Comments | References |
|-----------------|---------------------------------|----------------|----------------|----------|------------|
| ELISA           | DOBV HTNV PUUV SEOV ANDV SNV    | 95–97          | 94–99          | Combination of IgG test and IgM capture test is recommended | [224, 225] |
| IFA             | DOBV HTNV PUUV                 | 98             | 91             | Used as a confirmation test in Europe | [227] |
| Immunoblot assay| DOBV HTNV PUUV SEOV            | 96             | 100            | Used as a confirmation test in Europe | [226] |
| Rapid immunochromatographic IgM antibody tests | DOBV HTNV PUUV SEOV SNV | 80–93 | 96 | Point-of-care test | [228, 229] |
| (Real-time)-PCR | Facilitates sequencing of the viral genome and the detection of novel hantaviruses | 92–98 | 80–98 | Time to test positivity <24 h Only useful in early viremic stage of infection | [265, 266] |

Prevention

Exposure to infected rodents is the main risk factor for hantavirus-associated diseases and, due to a lack of targeted antiviral therapy, preventive measures such as rodent control and avoiding contact with potentially infected areas are recommended to minimize risk of transmission [234–236]. A history of possible exposure to rodent excreta can be obtained in ~50% of cases. Thus, identifying typical scenarios (e.g., sweeping out areas that are likely inhabited by rodents) is helpful but can certainly not be a prerequisite for making the diagnosis. Especially in endemic areas, hantavirus diseases should be suspected based on the clinical picture and laboratory findings rather than a history of exposure [236].

Vaccinations still remain controversial: in Korea, Hantavax is in use, a vaccine derived from formalin-inactivated HTNV-infected suckling mouse brain; however, frequent booster doses are mandatory for achieving immunity [237, 238]. Several formalin-inactivated vaccines have been used in China with unknown protective efficacies [238, 239]. No vaccines are currently approved in Europe or the USA. DNA vaccines for hantaviruses that may facilitate construction of multivalent vaccines and long-lasting immunity are being tested in clinical trials [240, 241]. Based on the recent experiences in the COVID-19 pandemic, RNA vaccines may actually be a very promising strategy to extend to hantaviruses.

Therapy

Currently treatment of both HFRS and HCPS is mainly supportive, as there is no specific therapy available [242]. For close monitoring, patients with a severe disease course should be admitted to the intensive care unit to maintain euvolemia and electrolyte balance. Especially in anuric patients, the volume status should be closely monitored to avoid extensive fluid retention and pulmonary edema due to leaky capillaries. RRT is needed in 4–6% of the hospital-treated patients in PUUV, in 10–20% in DOBV and up to 40–50% in HTNV infections [170, 179, 182, 183, 193, 243–245]. In the case of severe thrombocytopenia and major bleeding events due to DIC, platelet transfusion and/or fresh frozen plasma may be necessary to improve coagulation and control the bleeding event [3, 246]. Of note, there are hints that the extent of thrombocytopenia at the onset of infection predicts AKI severity as well as the clinical course in HFRS patients [170, 247]. In HCPS patients, supportive therapy consists of oxygen supplementation, mechanical ventilation when necessary, inotropic support and maintenance of euvolemia [199]. Additionally, extracorporeal membrane oxygenation improves outcome in patients with refractory shock and ARDS [248, 249].

Currently there is no targeted antiviral therapy available in Europe or the USA. Ribavirin has shown some antiviral effects against hantaviruses in in vitro models of HTNV-caused HFRS, since it is inhibiting viral replication through targeting the RdRp [250, 251]. In humans, ribavirin has been tested in a double-blind, placebo-controlled clinical trial in China, suggesting improved outcome and reduced severity of renal insufficiency when administered within 5 days after the onset of symptoms in HTNV-caused HFRS (Table 5) [252, 253]. In contrast, a randomized, open-label Russian trial revealed that ribavirin-associated side effects such as rash, sinus bradycardia, hyperbilirubinemia and anemia were significantly increased, while showing no protective effects in PUUV-infected patients [254]. Of note, disease severity in PUUV-caused HFRS is—in contrast to HTNV—not associated with the viral load, which may be a reasonable explanation for these different outcomes (Table 5) [255–257]. Ribavirin has also been examined in HCPS patients in a prospective, double-blind, placebo-controlled trial revealing no beneficial effects. Currently there is no recommendation to use ribavirin in HFRS or HCPS [258, 259].
Table 5. Comparison of clinical trials examining ribavirin in hantavirus disease

| Characteristics                      | Huggins et al. [252] | Malinin et al. [254] | Mertz et al. [258] |
|--------------------------------------|----------------------|----------------------|---------------------|
| **Disease entity**                   | HFRS                 | HFRS                 | HCPS                |
| **Study period**                     | 1985–1987            | 2004–2005            | 1996–2001           |
| **Trial design**                     | Prospective, double-blind, placebo-controlled trial | Prospective, open-label, phase II study | Prospective, double-blind, placebo-controlled trial |
| **Number of patients**               | 293                  | 73                   | 36                  |
| **Dose of ribavirin**                | Loading dose of 33 mg/kg, followed by a dose of 16 mg/kg every 6 h for the first 4 days and 8 mg/kg every 8 h for the subsequent 3 days | Loading dose of 33 mg/kg, followed by a dose of 16 mg/kg every 6 h for the first 4 days and 8 mg/kg every 8 h for the subsequent 3 days | Loading dose of 33 mg/kg, followed by a dose of 16 mg/kg every 6 h for the first 4 days and 8 mg/kg every 8 h for the subsequent 3 days |
| **Timing of ribavirin with respect to onset of infection** | 4 days (lengthened to 6 days in 1986) after onset of symptoms | 4 days after onset of symptoms | Not specified; however, patients had to be in the prodromal or cardiopulmonary stage |
| **Hantaviruses involved**            | HTNV (confirmed in 82.6% by ELISA) | PUUV | SNV (confirmed in 63.9% by ELISA) |
| **Primary endpoint**                 | Reduction in mortality, occurrence of oliguria and hemorrhages | Change in viral load | Survival at day 28 after study entry |
| **Results for primary endpoint**     | 7-fold reduction of mortality in the ribavirin group (\(P = .01\)) | Insufficient efficacy of ribavirin | No difference in survival between the ribavirin and placebo group |
| **Adverse events**                   | Drug-related anemia in all male study subjects (males accounted for 75% of study subjects). Females showed similar trends that were less dramatic due to sex-related differences in hematocrit | Low hemoglobin levels in 95%, hyperbilirubinemia in 81%, sinus bradycardia in 43% and rash in 19% of the ribavirin-treated patients | No significant differences in the frequency of adverse events; however, there was trend toward a higher rate in anemia in the ribavirin group |
| **Inclusion criteria**               | Age ≥ 14 years<br> Fever duration ≤ 4 days (lengthened to 6 days in 1986)<br>Clinical diagnosis of HFRS including fever and proteinuria<br>History making exposure to infection likely<br>OR<br>Findings consistent with early HFRS<br>Hantaviral IgM antibodies<br>No other evidence for an alternative diagnosis | Age 18–65 years<br> Suspected diagnosis of HFRS within 4 days of onset of disease<br>SOFA score = 1 | Age ≥ 12 years<br> Suspected or serologically confirmed acute hantavirus disease in the prodromal of cardiopulmonary stage |
| **Exclusion criteria**               | Advanced renal failure manifested by oliguria or uremia<br>Pregnancy or breast feeding<br>Known intolerance to ribavirin<br>NYHA cardiac function ≥ 2<br>History of severe chronic pulmonary or kidney disease<br>History of autoimmune hepatitis<br>Serum aminotransferase levels greater than two times the upper limit of normal<br>Hemoglobin level < 12 g/dL | Known intolerance to ribavirin<br>Pregnancy or breast feeding<br>NYHA cardiac function ≥ 2<br>History of severe chronic pulmonary or kidney disease<br>History of autoimmune hepatitis<br>Serum aminotransferase levels greater than two times the upper limit of normal<br>Hemoglobin level < 12 g/dL | Pregnancy or breast-feeding<br>A likely diagnosis other than HFRS<br>Immunocompromised status<br>Receipt of systemic corticosteroids within 30 days prior to enrolment<br>A mean arterial pressure of < 60 mmHg for 2 h despite optimal medical management<br>A cardiac index < 2.1 L/min/m²<br>Arterial oxygen pressure < 65 mmHg in intubated subjects receiving 100% oxygen<br>The presence of unilateral pulmonary infiltrates that did not become bilateral within 24 h |<br>Pregnancy or breast-feeding<br>A likely diagnosis other than HFRS<br>Immunocompromised status<br>Receipt of systemic corticosteroids within 30 days prior to enrolment<br>A mean arterial pressure of < 60 mmHg for 2 h despite optimal medical management<br>A cardiac index < 2.1 L/min/m²<br>Arterial oxygen pressure < 65 mmHg in intubated subjects receiving 100% oxygen<br>The presence of unilateral pulmonary infiltrates that did not become bilateral within 24 h |
| **Comments**                         | Study showed efficacy in reducing case fatality and oliguria in HTNV-infected patients | Study revealed insufficient efficacy and safety of intravenous ribavirin in PUUV-infected patients. Severity of PUUV-caused HFRS is not associated with viral load, in contrast to HTNV, explaining the different outcomes observed [255–257] | Premature termination of the study due to the slow rate of accrual of subjects and the findings of futility analysis |

NYHA: New York Hearth Association; SOFA: Sepsis-related Organ Failure Assessment score.
Apart from ribavirin, methylprednisolone has been tested in a randomized controlled clinical trial in ADNV-infected patients, failed to provide any significant benefit to patients (Table 6) [204]. Novel potential therapeutic strategies that were tested in noncontrolled clinical trials include murine and human-derived neutralizing antibodies that block viral entry. In contrast to murine-derived neutralizing antibodies, for which efficacy is unknown, human-derived neutralizing antibodies resulted in a 50% reduction of case fatalities in ANDV infections (Table 6) [260–262]. In addition, bradykinin type 2 receptor antagonists have been tested in PUUV-infected patients and may be promising candidates [107, 111, 112, 263]. However, standardized, large-scale clinical trials examining both efficacy and safety are lacking [238].

CONCLUSION

Hantavirus-associated diseases are emerging zoonotic infections with increasing incidence rates in Europe. The distribution of hantaviruses is influenced by climate change and disturbed rodent habitats and new hantavirus species with unknown pathogenicity are encountered in these reservoirs. Recently discovered human-to-human transmission by superspreading events may further cause hantavirus spread and make a pandemic a possible scenario. Therefore further research in hantavirus pathogenesis, diagnosis antiviral and preventive measures, including vaccine development, remain mandatory.

AUTHORS’ CONTRIBUTIONS

F.C.K., R.-U.M. and V.B. wrote the manuscript. V.D.C., M.R.S., K.J.R.H.-A. and M.W. revised the manuscript.

CONFLICT OF INTEREST STATEMENT

F.C.K. has received a grant from the Maria-Pesch Stiftung, Cologne, Germany for setup and maintenance of the Hantavirus Registry. All other authors have nothing to disclose.
12. Makary P, Kanerva M, Olgren J et al. Disease burden of Puumala virus infections, 1995–2008. Epidemiol Infect 2010; 138: 1484–1492
13. Hjertqvist M, Klein SL, Ahlm C et al. Mortality rate patterns for hemorrhagic fever with renal syndrome caused by Puumala virus. Emerg Infect Dis 2010; 16: 1584–1586
14. Heyman P, Vaheri A, Lundkvist A et al. Hantavirus infections in Europe: from virus carriers to a major public-health problem. Expert Rev Anti Infect Ther 2009; 7: 205–217
15. Duchin JS, Koster FT, Peters CJ et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. The Hantavirus Study Group. N Engl J Med 1994; 330: 949–955
16. Hjelle B, Jenison S, Torrez-Martinez N et al. A novel hantavirus associated with an outbreak of fatal respiratory disease in the southwestern United States: evolutionary relationships to known hantaviruses. J Virol 1994; 68: 592–596
17. Nichol ST, Spiropoulou CF, Morznov S et al. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 1993; 262: 914–917
18. Martinez VP, Di Paola N, Alonso DO et al. “Super-spreaders” and person-to-person transmission of Andes virus in Argentina. N Engl J Med 2020; 383: 2230–2241
19. Wells RM, Sosa Estani S, Yadon ZE et al. An unusual hantavirus outbreak in southern Argentina: person-to-person transmission? Hantavirus Pulmonary Syndrome Study Group for Patagonia. Emerg Infect Dis 1997; 3: 171–174
20. Padula PJ, Edelstein A, Miguel SD et al. Hantavirus pulmonary syndrome outbreak in Argentina: molecular evidence for person-to-person transmission of Andes virus. Virology 1998; 241: 323–330
21. Pizarro E, Navarrete M, Mendez C et al. Immunocytochemical and ultrastructural evidence supporting that Andes hantavirus (ANDV) is transmitted person-to-person through the respiratory and/or salivary pathways. Front Microbiol 2019; 10: 2992
22. Schmaljohn C, Hjelle B. Hantaviruses: a global disease problem. Emerg Infect Dis 1997; 3: 95–104
23. Vaheiro A, Strandin T, Hepojoki J et al. Uncovering the mysteries of hantavirus infections. Nat Rev Microbiol 2013; 11: 539–550
24. Klempe B. Hantaviruses and climate change. Clin Microbiol Infect 2009; 15: 518–523
25. Zeimes CB, Quolfin S, Henttonen H et al. Landscape and regional environmental analysis of the spatial distribution of hantavirus human cases in Europe. Front Public Health 2015; 3: 54
26. Gutierrez A, de Lemos ERS. Hantaviruses and a neglected environmental determinant. One Health 2018; 5: 27–33
27. Koch DE, Mohler RL, Goodin DG. Stratifying land use/land cover for spatial analysis of disease ecology and risk: an example using object-based classification techniques. Geospat Health 2007; 2: 15–28
28. Hansen A, Cameron S, Liu Q et al. Transmission of haemorrhagic fever with renal syndrome in China and the role of climate factors: a review. Int J Infect Dis 2015; 33: 212–218
29. Prits FR, Uriarte M, Fernandes K et al. Climate change and sugarcane expansion increase Hantavirus infection risk. PLoS Negl Trop Dis 2017; 11: e0005705
30. Roda Gracia J, Schumann B, Seidler A. Climate variability and the occurrence of human Puumala hantavirus infections in Europe: a systematic review. Zoonoses Public Health 2015; 62: 465–478
31. Liu J, Xue FZ, Wang JZ et al. Association of haemorrhagic fever with renal syndrome and weather factors in Junan County, China: a case-crossover study. Epidemiol Infect 2013; 141: 697–705
32. Prevedelio JA, Dickman CR, Vieira MV et al. Population responses of small mammals to food supply and predators: a global meta-analysis. J Anim Ecol 2013; 82: 927–936
33. Monchatre-Leroy E, Crespin L, Boué F et al. Spatial and temporal epidemiology of nephropathia epidemica incidence and hantavirus seroprevalence in rodent hosts: identification of the main environmental factors in Europe. Transbound Emerg Dis 2017; 64: 1210–1228
34. Luís A, Douglass RJ, Mills JN et al. The effect of seasonality, density and climate on the population dynamics of Montana deer mice, important reservoir hosts for Sin Nombre hantavirus. J Anim Ecol 2010; 79: 462–470
35. Fang LQ, Wang XJ, Liang S et al. Spatiotemporal trends and climatic factors of hemorrhagic fever with renal syndrome epidemic in Shandong Province, China. PLoS Negl Trop Dis 2010; 4: e789
36. Borg MA, Bi P. The impact of climate change on kidney health. Nat Rev Nephrol 2021; 17: 294–295
37. Xiao H, Tian HY, Cazelles B et al. Atmospheric moisture variability and transmission of hemorrhagic fever with renal syndrome in Changsha City, Mainland China, 1991–2010. PLoS Negl Trop Dis 2013; 7: e2260
38. Zhou Y, Hu J, Wang ZX et al. Genetic characterization of hantaviruses isolated from Guizhou, China: evidence for spillover and reassortment in nature. J Med Virol 2008; 80: 1033–1041
39. Reusken C, Heyman P. Factors driving hantavirus emergence in Europe. Curr Opin Virol 2013; 3: 92–99
40. Clement J, Underwood P, Ward D et al. Hantavirus outbreak during military manoeuvres in Germany. Lancet 1996; 347: 336
41. Vapalahti K, Paunio M, Brummer-Korvenkontio M et al. Puumala virus infections in Finland: increased occupational risk for farmers. Am J Epidemiol 1999; 149: 1142–1151
42. Watson DC, Sargianou M, Papa A et al. Epidemiology of hantavirus infections in humans: a comprehensive, global overview. Crit Rev Microbiol 2014; 40: 261–272
43. Vapalahti O, Mustonen J, Lundkvist A et al. Hantavirus infections in Europe. Lancet Infect Dis 2003; 3: 653–661
44. Hofmann J, Meisel H, Klempe B et al. Hantavirus outbreak, Germany, 2007. Emerg Infect Dis 2008; 14: 850–852
45. Ettinger J, Hofmann J, Enders M et al. Multiple synchronous outbreaks of Puumala virus, Germany, 2010. Emerg Infect Dis 2012; 18: 1461–1464
46. Avsic-Zupanc T, Petrovec M, Furlan P et al. Hemorrhagic fever with renal syndrome in the Dolenjska region of Slovenia—a 10-year survey. Clin Infect Dis 1999; 28: 860–865
47. Antoniadias A, Stylianakis A, Papa A et al. Direct genetic detection of Dobrava virus in Greek and Albanian patients with hemorrhagic fever with renal syndrome. J Infect Dis 1996; 174: 407–410
48. Klempe B, Radosa L, Kruger DH. The broad spectrum of hantaviruses and their hosts in Central Europe. Acta Virol 2013; 57: 130–137
49. Lee SH, No JS, Kim WK et al. Molecular epidemiology and genetic diversity of orthohantaviruses in small mammals in Western Poland. Am J Trop Med Hyg 2020; 103: 193–199
50. Faber M, Krüger DH, Auste B et al. Molecular and epidemiological characteristics of human Puumala and Dobrava-
Belgrade hantavirus infections, Germany, 2001 to 2017. Euro Surveill 2019; 24: 1800675

51. Dzagurova TK, Klempa B, Tkachenko EA et al. Molecular diagnostics of hemorrhagic fever with renal syndrome during a Dobrava virus infection outbreak in the European part of Russia. J Clin Microbiol 2009; 47: 4029–4036

52. Hofmann J, Kramer S, Herrlinger KR et al. Tula virus as causative agent of hantavirus disease in immunocompetent person, Germany. Emerg Infect Dis 2021; 27: 1234–1237

53. Klempa B, Stanko M, Labuda M et al. Central European Dobrava hantavirus isolate from a striped field mouse (Apodemus agrarius). J Clin Microbiol 2005; 43: 2756–2763

54. Sjölander KB, Golovljova I, Vasilienko V et al. Serological divergence of Dobrava and Saaremaa hantaviruses: evidence for two distinct serotypes. Epidemiol Infect 2002; 128: 99–103

55. Klempa B, Meisel H, Rath S et al. Occurrence of renal and pulmonary syndrome in a region of northeast Germany where Tula hantavirus circulates. J Clin Microbiol 2003; 41: 4894–4897

56. Baek LJ, Kariwa H, Lokugamage K et al. Soochong virus: an antigenically and genetically distinct hantavirus isolated from Apodemus peninsulae in Korea. J Med Virol 2006; 78: 290–297

57. Jiang JF, Zhang WY, Wu XM et al. Soochong virus and Amur virus might be the same entities of hantavirus. J Med Virol 2007; 79: 1792–1795

58. Zhang YZ, Zou Y, Fu ZF et al. Hantavirus infections in humans and animals, China. Emerg Infect Dis 2010; 16: 1195–1203

59. Lee SH, Kim WK, Park K et al. Genetic diversity and phylogeography of Jeju orthohantavirus (Hantaviridae) in the Republic of Korea. Virology 2020; 543: 13–19

60. Lee SH, Kim WK, No JS et al. Dynamic circulation and genetic exchange of a shrew-borne hantavirus, Imjin virus, in the Republic of Korea. Sci Rep 2017; 7: 44369

61. Lee PW, Gibbs CJ Jr, Gajdusek DC et al. Identification of epidemiologic hantavirus with renal syndrome in China with Korean haemorrhagic fever. Lancet 1980; 1: 1025–1026

62. Knust B, Brown S, de St Maurice A et al. Hantavirus pulmonary syndrome in a region of northeast Germany for two distinct serotypes. Emerg Infect Dis 2002; 8: 1840

63. Reynes JM, Carli D, Bour JB et al. Human hantavirus infections in Guinea, West Africa. J Infect 2012; 79: 185–224

64. Lee HW, van der Groen G. Hemorrhagic fever with renal syndrome. Prog Med Virol 1989; 36: 62–102

65. Calderón G, Pini N, Bolpe J et al. Hantavirus reservoir hosts associated with peridomestic habitats in Argentina. Emerg Infect Dis 1999; 5: 792–797

66. Khan A, Khan M, Ullah S et al. Hantavirus: the next pandemic we are waiting for? Interdiscip Sci 2021; 13: 147–152

67. Klempa B, Fichet-Calvet E, Lecompte E et al. Hantavirus in African wood mouse, Guinea. Emerg Infect Dis 2006; 12: 838–840

68. Klempa B, Kouloumou K, Aste B et al. Seroepidemiological study reveals regional co-occurrence of Lassa- and Hantavirus antibodies in Upper Guinea, West Africa. Trop Med Int Health 2013; 18: 366–371

69. Weiss S, Witkowski PT, Aste B et al. Hantavirus in bat, Sierra Leone. Emerg Infect Dis 2012; 18: 159–161

70. Sumibcay L, Kadjo B, Gu SH et al. Divergent lineage of a novel hantavirus in the banana pipistrelle (Neoromicia nanus) in Côte d’Ivoire. Virol J 2012; 9: 34

71. Schmaljohn CS, Hasty SE, Dalrymple JM et al. Antigenic and genetic properties of viruses linked to hemorrhagic fever with renal syndrome. Science 1985; 227: 1041–1044

72. Schmaljohn CS, Dalrymple JM. Analysis of Hantaan virus RNA: evidence for a new genus of bunyaviridae. Virology 1983; 131: 482–491

73. Hewlett MJ, Pettersson RF, Baltimore D. Circular forms of Uukuniemi virus RNA: an electron microscopic study. J Virol 1977; 21: 1085–1093

74. Kallio ER, Klingstrom J, Gustafsson E et al. Prolonged survival of Puuimala hantavirus outside the host: evidence for indirect transmission via the environment. J Gen Virol 2006; 87: 2127–2134

75. Mackow ER, Gavrilovskaya IN. Hantavirus regulation of endothelial cell functions. Throm Haemost 2009; 102: 1030–1041

76. Mackow ER, Gavrilovskaya IN. Cellular receptors and hantavirus pathogenesis. Curr Top Microbiol Immunol 2001; 256: 91–115

77. Raber R, Deubel K, Kraus AA, Ulrich R et al. Hantavirus infection of dendritic cells. J Virol 2002; 76: 10724–10733

78. Zaki SR, Greer PW, Coffield LM et al. Hantavirus pulmonary syndrome. Pathogenesis of an emerging infectious disease. Am J Pathol 1995; 146: 552–579

79. Hagem S, Müller A, Nussnag C et al. Mothiness of human renal cells is disturbed by infection with pathogenic hantaviruses. BMC Infect Dis 2018; 18: 645

80. Gavrilovskaya IN, Shepley M, Shaw R et al. beta3 Integrins mediate the cellular entry of hantaviruses that cause respiratory failure. Proc Natl Acad Sci USA 1998; 95: 7074–7079

81. Gavrilovskaya IN, Brown EJ, Ginsberg MH et al. Cellular entry of hantaviruses which cause hemorrhagic fever with renal syndrome is mediated by beta3 integrins. J Virol 1999; 73: 3951–3959

82. Dieterle E, Dieterle ME, Hôlter da Riera C, Ye C et al. Genetic depletion studies inform receptor usage by virulent hantaviruses in human endothelial cells. Elife 2021; 10: e69708

83. Hittler E, Dieterle ME, Kleinfelter LM et al. Hantavirus entry: perspectives and recent advances. Adv Virus Res 2019; 104: 185–224

84. Klempa B, Koivogui L, Sylla O et al. Serological evidence of human hantavirus infections in Guinea, West Africa. J Infect Dis 2010; 201: 1031–1034

85. Martinez-Valdebenito C, Angulo J, Le Corre N et al. Single-nucleotide polymorphism of αβ3 integrin is associated with the Andes virus infection susceptibility. Viruses 2019; 11: 169

86. Chen XP, Xiong HR, Zhu N et al. Lack of association between integrins αβ3 gene polymorphisms and hemorrhagic fever with renal syndrome in Han Chinese from Hubei, China. Virology 2017; 521: 32–39

87. Jangra RK, Herbert AS, Li R et al. Protocadherin-1 is essential for cell entry by New World hantaviruses. Nature 2018; 563: 559–563

88. Jin M, Park J, Lee S et al. Hantavirus enters cells by clathrin-dependent receptor-mediated endocytosis. Virology 2002; 294: 60–69

89. Ramanathan HN, Jonsson CB. New and Old World hantaviruses differentially utilize host cytoskeletal components during their life cycles. Virology 2008; 374: 138–150

90. Hupojoki J, Strandin T, Lankinen H et al. Hantavirus structure—molecular interactions behind the scene. J Gen Virol 2012; 93: 1631–1644
associated thrombocytopenia. Blood Coagul Fibrinolysis 2011; 22: 468–472

127. Laine O, Mäkelä S, Mustonen J et al. Enhanced thrombin formation and fibrinolysis during acute Puumala hantavirus infection. Thromb Res 2010; 126: 154–158

128. Sundberg E, Hultdin J, Nilsson S et al. Evidence of disseminated intravascular coagulation in a hemorrhagic fever with renal syndrome–a self-controlled case series study. PLoS One 2011; 6: e21134

129. Connolly-Andersen AM, Whitaker H, Klingström J et al. Risk of venous thromboembolism following hemorrhagic fever with renal syndrome: a self-controlled case series study. Clin Infect Dis 2013; 66: 268–273

130. Connolly-Andersen AM, Hammargren E, Whitaker H et al. Increased risk of acute myocardial infarction and stroke during hemorrhagic fever with renal syndrome: a self-controlled case series study. Circulation 2014; 129: 1295–1302

131. Schmedes CM, Grover SP, Hisada YM et al. Circulating extracellular vesicle tissue factor activity during orthohantavirus infection is associated with intravascular coagulation. J Infect Dis 2020; 222: 1392–1399

132. Tatsumi K, Hisada Y, Connolly AF et al. Patients with severe orthohantavirus cardiopulmonary syndrome due to Sin Nombre virus infection have increased circulating extracellular vesicle tissue factor and an activated coagulation system. Thromb Res 2019; 179: 31–33

133. Connolly-Andersen AM, Sundberg E, Ahlm C et al. Increased thrombopoiesis and platelet activation in hantavirus-infected patients. J Infect Dis 2015; 212: 1061–1069

134. Kim S, Kang ET, Kim YG et al. Localization of Hantaan viral envelope glycoproteins by monoclonal antibodies in renal tissues from patients with Korean hemorrhagic fever. Am J Clin Pathol 1993; 100: 398–403

135. Krautkrämer E, Grouls S, Stein N et al. Pathogenic old world hantaviruses infect renal glomerular and tubular cells and induce disassembling of cell-to-cell contacts. J Virol 2011; 85: 9811–9823

136. Krautkrämer E, Zeier M, Płyusnin A. Hantavirus infection: an emerging infectious disease causing acute renal failure. Kidney Int 2013; 83: 23–27

137. Terajima M, Hayasaka D, Maeda K et al. Immunopathogenesis of hantavirus pulmonary syndrome and hemorrhagic fever with renal syndrome: Do CD8+ T cells trigger capillary leakage in viral hemorrhagic fevers? Immunol Lett 2007; 113: 117–120

138. Temonen M, Mustonen J, Helin H et al. Cytokines, adhesion molecules, and cellular infiltration in nephropathia epidemica kidneys: an immunohistochemical study. Clin Immunol Immunopathol 1996; 78: 47–55

139. Matthys V, Mackow ER. Hantavirus regulation of type I interferon responses. Adv Virol 2012; 2012: 524024

140. Schönrich G, Rang A, Lütteke N et al. Hantavirus-induced immunity in rodent reservoirs and humans. Immunol Rev 2006; 225: 163–189

141. Strandin T, Mäkelä S, Mustonen J et al. Neutrophil activation in acute hemorrhagic fever with renal syndrome is mediated by hantavirus–infected microvascular endothelial cells. Front Immunol 2018; 9: 2098

142. Sadeghi M, Eckerle I, Daniel V et al. Cytokine expression during early and late phase of acute Puumala hantavirus infection. BMC Immunol 2011; 12: 65

143. Ouitinen TK, Mäkelä SM, Ala-Houhala IO et al. The severity of Puumala hantavirus induced nephropathia epidemica can be better evaluated using plasma interleukin-6 than C-reactive protein determinations. BMC Infect Dis 2010; 10: 132

144. Saksida A, Wraber B, Avšič–Županc T. Serum levels of inflammatory and regulatory cytokines in patients with hemorrhagic fever with renal syndrome. BMC Infect Dis 2011; 11: 142

145. Maleki KT, García M, Iglesias A et al. Serum markers associated with severity and outcome of hantavirus pulmonary syndrome. J Infect Dis 2019; 219: 1832–1840

146. Vernet MA, Reynard S, Fizet A et al. Clinical, virological, and biological parameters associated with outcomes of Ebola virus infection in Macenta, Guinea. JCI Insight 2017; 2: e88864

147. Ergonul O, Tuncbilek S, Baykam N et al. Evaluation of serum levels of interleukin (IL)-6, IL-10, and tumor necrosis factor–alpha in patients with Crimean–Congo hemorrhagic fever. J Infect Dis 2006; 193: 941–944

148. Juffrie M, Meer GM, Hack CE et al. Inflammatory mediators in dengue virus infection in children: interleukin-6 and its relation to C–reactive protein and secretory phospholipase A2. Am J Trop Med Hyg 2001; 65: 70–75

149. Maude SL, Barrett D, Teachey DT et al. Managing cytokine release syndrome associated with novel T cell-engaging therapies. Cancer J 2014; 20: 119–122

150. Teachey DT, Lacey SF, Shaw PA et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T–cell therapy for acute lymphoblastic leukemia. Cancer Discov 2016; 6: 664–679

151. Chen LB, Yang WS. Abnormalities of T cell immunoregulation in hemorrhagic fever with renal syndrome. J Infect Dis 1990; 161: 1016–1019

152. Tuuminen T, Kekäläinen E, Mäkelä S et al. Human CD8+ T cell memory generation in Puumala hantavirus infection occurs after the acute phase and is associated with boosting of EBV–specific CD8+ memory T cells. J Immunol 2007; 179: 1988–1995

153. 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

154. Wang ML, Lai JH, Zhu Y et al. Genetic susceptibility to hemorrhagic fever with renal syndrome caused by Hantaan virus in Chinese Han population. Int J Immunogenet 2009; 36: 227–229

155. Mäkelä S, Mustonen J, Ala–Houhala I et al. Human leukocyte antigen–B8–DR3 is a more important risk factor for severe Puumala hantavirus infection than the tumor necrosis factor–α (−308) G/A polymorphism. J Infect Dis 2002; 186: 843–846

156. Kilpatrick ED, Terajima M, Koster FT et al. Role of specific CD8+ T cells in the severity of a fulminant zoonotic viral hemorrhagic fever, hantavirus pulmonary syndrome. J Immunol 2004; 172: 3297–3304

157. Płyusnin A, Hörling J, Kanerva M et al. Puumala hantavirus genome in patients 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

158. 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
Haematuria is a marker for the severity of acute kidney injury but does not associate with thrombocytopenia in acute Puumala hantavirus infection. Clin Microbiol Infect Dis 2017; 49: 840–846

Kidney biopsy findings and clinicopathologic correlations in nephropathia epidemica. Clin Nephrol 1994; 41: 121–126

Hematological effects of ratborne Seoul hantavirus disease. Acta Paediatr 1994; 41: 121–126

The kidney in hantavirus infection.
231. 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

232. Xiao R, Yang S, Koster F et al. Sin Nombre viral RNA load in patients with hantavirus cardiopulmonary syndrome. J Infect Dis 2006; 194: 1403–1409

233. Saksida A, Duh D, Korva M et al. Dobrava virus RNA load in patients who have hemorrhagic fever with renal syndrome. J Infect Dis 2008; 197: 681–685

234. Armstrong LR, Zaki SR, Goldoft MJ et al. Hantavirus pulmonary syndrome associated with entering or cleaning rarely used, rodent-infested structures. J Infect Dis 1995; 172: 1166

235. Abu Sin M, Stark K, van Treeck U et al. Risk factors for hantavirus infection in Germany, 2005. Emerg Infect Dis 2007; 13: 1364–1366

236. de St Maurice A, Ervin E, Schumacher M et al. Exposure characteristics of hantavirus pulmonary syndrome patients, United States, 1993–2015. Emerg Infect Dis 2017; 23: 733–739

237. Cho HW, Howard CR. Antibody responses in humans to an inactivated hantavirus vaccine (Hantavax). Vaccine 1999; 17: 2569–2575

238. Liu R, Ma H, Shu J et al. Vaccines and therapeutics against hantaviruses. Front Microbiol 2019; 10: 2989

239. Hooper JW, Li D. Vaccines against hantaviruses. Curr Top Microbiol Immunol 2001; 256: 171–191

240. Krüger DH, Schönrich G, Kleinpa B. Human pathogenic hantaviruses and prevention of infection. Hum Vaccin 2011; 7: 685–693

241. Hooper J, Paolino KM, Mills K et al. A phase 2a randomized, double-blind, dose-optimizing study to evaluate the immunogenicity and safety of a bivalent DNA vaccine for hemorrhagic fever with renal syndrome delivered by intra-muscular electroporation. Vaccines (Basel) 2020; 8: 377

242. Brocato RL, Hooper JW. Progress on the prevention and treatment of hantavirus disease. Viruses 2019; 11: 610

243. Outinen TK, Laine OK, Mäkelä S et al. Thrombocytopenia associates with the severity of inflammation and variables reflecting capillary leakage in Puumala hantavirus infection, an analysis of 546 Finnish patients. Infect Dis (Lond) 2016; 48: 682–687

244. Christova I, Pishmisheva M, Trifonova I et al. Clinical aspects of hantavirus infections in Bulgaria. Wien Klin Wochenschr 2017; 129: 572–578

245. Han D, Liu Z, Han Q et al. Acute kidney injury in patients with hemorrhagic fever with renal syndrome caused by Hantaan virus: comparative evaluation by RIFLE and AKIN criteria. Vector Borne Zoonotic Dis 2011; 11: 723–730

246. Linderholm M, Elgh F. Clinical characteristics of hantavirus infections in the Eurasian continent. Curr Top Microbiol Immunol 2001; 256: 135–151

247. Fan X, Liu Z, Fu S et al. Platelet distribution width at first day of hospital admission in patients with hemorrhagic fever with renal syndrome caused by Hantaan virus may predict disease severity and critical patients’ survival. Dis Markers 2018; 2018: 9701619

248. Wernly JA, Dietl CA, Tabo CE et al. Extracorporeal membrane oxygenation support improves survival of patients with hantavirus cardiopulmonary syndrome refractory to medical treatment. Eur J Cardiothorac Surg 2011; 40: 1334–1340

249. Chang B, Crowley M, Campen M et al. Hantavirus cardiopulmonary syndrome. Semin Respir Crit Care Med 2007; 28: 193–200

250. Huggins JW, Kim GR, Brand OM et al. Ribavirin therapy for Hantaan virus infection in suckling mice. J Infect Dis 1986; 153: 489–497

251. Chung DH, Västermark Å, Camp JV et al. The murine model for Hantaan virus-induced lethal disease shows two distinct paths in viral evolutionary trajectory with and without ribavirin treatment. J Virol 2013; 87: 10997–11007

252. 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

253. 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

254. Malinin OV, Platonov AE. Insufficient efficacy and safety of intravenous ribavirin in treatment of haemorrhagic fever with renal syndrome caused by Puumula virus. Infect Dis (Lond) 2017; 49: 514–520

255. Pettersson L, Thunberg T, Rockløv J et al. Viral load and humoral immune response in association with disease severity in Puumala hantavirus-infected patients—implications for treatment. Clin Microbiol Infect 2014; 20: 235–241

256. Korva M, Saksida A, Kejžar N et al. Viral load and immune response dynamics in patients with haemorrhagic fever with renal syndrome. Clin Microbiol Infect 2013; 19: E358–366

257. Yi J, Xu Z, Zhuang R et al. Hantaan virus RNA load in patients having hemorrhagic fever with renal syndrome: correlation with disease severity. J Infect Dis 2013; 207: 1457–1461

258. Mertz GJ, Miedzinski L, Goade D et al. Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. Clin Infect Dis 2004; 39: 1307–1313

259. Chapman LE, Mertz GJ, Peters CJ et al. Intravenous ribavirin for hantavirus pulmonary syndrome: safety and tolerance during 1 year of open-label experience. Ribavirin Study Group. Antivir Ther 1999; 4: 211–219

260. de Carvalho Nicacio C, Lundkvist A, Sjölander KB et al. A neutralizing recombinant human antibody Fab fragment against Puumula hantavirus. J Med Virol 2000; 60: 446–454

261. Xi R, Yang XY, Yang DF et al. Phase I evaluation of the safety and pharmacokinetics of a single-dose intravenous injection of a murine monoclonal antibody against Hantaan virus in healthy volunteers. Antimicrob Agents Chemother 2009; 53: 5055–5059

262. Garrido JL, Prescott J, Calvo M et al. Two recombinant human monoclonal antibodies that protect against lethal Andes hantavirus infection in vivo. Sci Transl Med 2018; 10: eaat6420

263. Gorbunova EE, Gavrilovskaya IN, Pepini T et al. VEGFR2 and Src kinase inhibitors suppress Andes virus-induced endothelial cell permeability. J Virol 2011; 85: 2296–2303

264. Abudurexiti A, Adkins S, Allioto D et al. Taxonomy of the order Bunyavirales: update 2019. Arch Virol 2019; 164: 1949–1965

265. Ahn C, Cho JT, Lee JG et al. Detection of Hantaan and Seoul viruses by reverse transcriptase-polymerase chain reaction (RT-PCR) and restriction fragment length polymorphism.
(RFLP) in renal syndrome patients with hemorrhagic fever. Clin Nephrol 2000; 53: 79–89

266. Aitichou M, Saleh SS, McElroy AK et al. Identification of Dobrava, Hantaan, Seoul, and Puumala viruses by one-step real-time RT-PCR. J Virol Methods 2005; 124: 21–26

267. Vial PA, Valdivieso F, Calvo M et al. A non-randomized multicentre trial of human immune plasma for treatment of hantavirus cardiopulmonary syndrome caused by Andes virus. Antivir Ther 2015; 20: 377–386