



Fatal cases of hemorrhagic fever with renal syndrome in Udmurtia, Russia, 2010 to 2019

Oleg V. Malinin¹ · Nikolay A. Kiryanov²

Received: 12 January 2022 / Accepted: 31 May 2022 / Published online: 6 June 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract

Hemorrhagic fever with renal syndrome (HFRS) continues to be a cause of death in Europe. Our aim was to describe the clinical and histopathological features of fatal HFRS in the Udmurt Republic (Udmurtia), located in the European part of Russia. This retrospective observational study included all fatal cases of HFRS that occurred in Udmurtia from January 2010 through December 2019. The most relevant clinical and autopsy data of these cases were recorded through a review of the patients' medical records and autopsy reports. During 2010–2019, Udmurtia had 41 fatal cases of HFRS of a total of 10,312 confirmed cases (case-fatality rate of 0.4%). Twenty-seven patients died in hypotensive and oliguric phases of HFRS due to refractory septic shock and acute respiratory distress syndrome. Fourteen patients died in the polyuric phase of the disease from complications of acute kidney injury or because of hospital-acquired bacterial infections. Multiorgan involvement was noted in all autopsies with variable degrees of generalized venous congestion, interstitial edema, capillary wall thickening, perivascular deposition of plasma proteins, microthrombosis formation, and perivascular hemorrhage. The more prominent histopathological features were seen in kidneys, lungs, and hypophysis.

Keywords Hemorrhagic fever with renal syndrome · Puumala virus · Case-fatality rate · Autopsy

Introduction

Hantaviruses are a large group of viruses with a worldwide distribution that circulate asymptotically in rodents, insectivores, and bats but sometimes cause illnesses in humans. The classification of human infections refers to geographical distribution: hantaviruses in Asia and Europe primarily cause hemorrhagic fever with renal syndrome (HFRS), whereas hantaviruses in the Americas cause hantavirus pulmonary (or cardiopulmonary) syndrome (HPS). Infections comprise renal and pulmonary illnesses ranging from subclinical, mild, and severe courses to a fatal outcome. In clinical practice, syndromes are not always as clear-cut as their names suggest, and pulmonary and renal complications can also occur in HFRS and HPS, respectively.

HFRS continues to be a risk in Europe, where three known hotspots of infection are Germany, with around 1000 cases annually on average, Finland, with an average of 1500 cases annually, and Russia, with around 7500 cases annually on average [1, 2]. At least five hantaviruses, Puumala (PUUV), Dobrava (DOBV), Tula (TULV), Saaremaa (SAAV) and Seoul virus (SEOV), circulate in Europe. The most prominent and most widely occurring hantavirus in Europe is PUUV, transmitted by the bank vole.

The highest incidence rate of HFRS in Russia is registered in the Udmurt Republic (Udmurtia), located in the European part of the Ural region [3]. Reported cases of HFRS in Udmurtia are caused only by PUUV [3, 4]. PUUV usually causes a relatively mild form of HFRS, called nephropathia epidemica, but all clinical presentations exist, and sometimes PUUV infection can lead to critical disease. In fact, PUUV infection remains a cause of death in endemic regions, with the case-fatality rate up to 1% [5].

To date, there are few published data concerning clinical and autopsy characteristics of 9 fatal cases of HFRS caused by PUUV [6–9]. In this paper, we present the clinical and autopsy findings recorded in 41 cases of fatal HFRS that occurred in the area endemic to PUUV.

✉ Oleg V. Malinin
oleg.v.malinin@gmail.com

¹ Department of Infectious Diseases and Epidemiology, Izhevsk State Medical Academy, Izhevsk, Russia

² Department of Pathology, Izhevsk State Medical Academy, Izhevsk, Russia

Methods

In accordance with the procedures established in Russia, patients with a laboratory-confirmed diagnosis of HFRS are notifiable and undergo 2 years of follow-up. The guidelines of the Ministry of Health stipulate that a review of clinical and autopsy data is required for each fatal event due to HFRS.

This retrospective observational study included all fatal cases of HFRS that occurred in Udmurtia from January 2010 through December 2019 and that were confirmed serologically by indirect immunofluorescence assay (“Diagnosticum HFRS”; Federal Scientific Center for Research and Development of Immune and Biological Products of the Russian Academy of Sciences, <http://chumakovs.ru>) or enzyme-linked immunosorbent assay (“Enzyme immunoassay kit for the detection of IgM and IgG against hantavirus”; AO Vector-Best, <https://vector-best.ru>).

The most relevant clinical and autopsy data of these cases were recorded through a review of the patients’ medical records and autopsy reports. Clinical data were assessed by using the Sequential Organ Failure Assessment (SOFA) [10]. HFRS-related complications, such as septic shock, acute respiratory distress syndrome (ARDS), and acute kidney injury (AKI), were defined according to current criteria [11–13]. Results of conventional autopsy were interpreted according to commonly accepted criteria. Histopathological changes of kidneys, lungs, heart, liver, spleen, lymph nodes, brain, hypophysis, adrenal glands, pancreas, and gastrointestinal wall were assessed by examination of hematoxylin and eosin-stained tissue sections under light microscopy. Immunohistochemical stainings for vascular endothelial growth factor (VEGF), markers of T cells (CD8) and macrophages (CD68) in kidney and

lung tissues were performed in single patients using the EnVision FLEX system (Dako).

Descriptive statistics are reported as percentages for categorical data and medians with interquartile range (IQR) or range for numerical data. Categorical variables were compared with the two-tailed Fisher’s exact test. Numerical variables were compared by use of the Mann–Whitney/Wilcoxon two-sample test (Kruskal–Wallis test for two groups). All analyses were done with Epi Info (version 7).

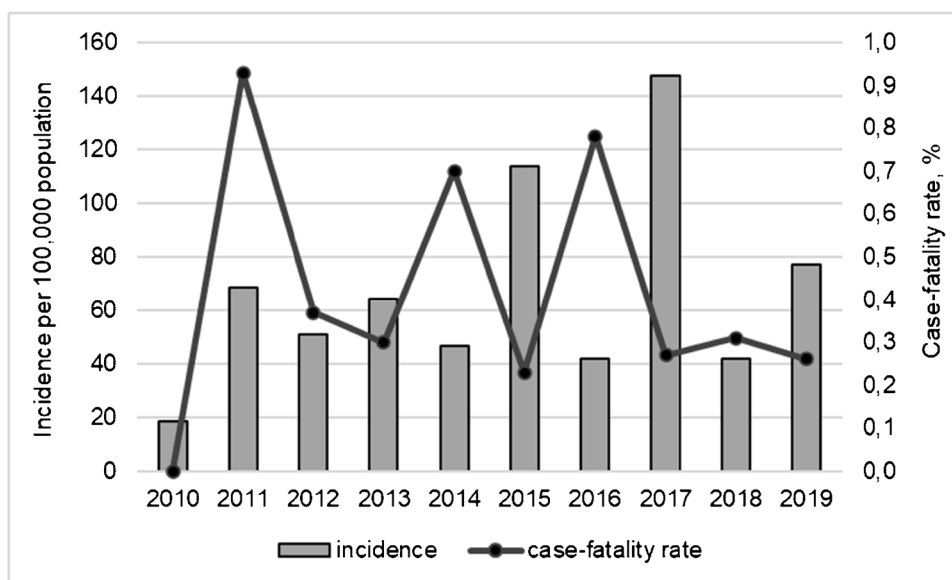
Results

During 2010–2019, Udmurtia had 41 fatal cases of HFRS of a total of 10,312 confirmed cases (case-fatality rate of 0.4%). The annually reported incidence and case-fatality rates ranged from 18.4 to 147.7 cases per 100,000 population and from 0 to 0.9%, respectively (Fig. 1).

All patients with fatal HFRS were residents of Udmurtia and did not have a history of travel during the incubation period of the disease. Males comprised 34 (83%) of the deaths and the median age was 46 years (range, 18–81 years). Comorbidities existed in 13 (32%) deaths; with cardiovascular diseases in 5, hypertension in 4, chronic hepatitis C in 2, and 1 each with a post-stroke syndrome, renal cancer, and chronic kidney disease. One patient with chronic hepatitis C had been on therapy with ribavirin and interferon-alfa for 3 months before he died on day 3 of HFRS. The other patients had no significant drug therapies before the disease.

The median duration from disease onset to hospital admission was 3 days (range, 2–10 days). Admission diagnoses recorded in the medical notes in emergency department were HFRS in 36 (88%) cases and pneumonia in 5 (12%)

Fig. 1 Incidence and case-fatality rates of HFRS in Udmurtia, Russia, 2010 to 2019



cases. All patients were admitted to intensive care units (ICU), 26 (63%) of whom directly from emergency department. For the entire cohort vasopressor support was needed in 35 cases, mechanical ventilation 31, and renal replacement therapy (RRT) 20. The median duration from disease onset to death was 7 days (range, 3–38 days). HFRS was stated as the primary cause of death in all cases. Autopsy was performed in 38 cases.

The deaths occurred more often in early phases of the disease (Fig. 2). There were 27 (66%) fatal cases in overlapping hypotensive and oliguric phases of HFRS, and 14 (34%) fatal cases in polyuric phase.

Clinical characteristics and autopsy findings were compared between patients who died in hypotensive and oliguric phases of HFRS (group 1, fatal cases before the 9th day of the disease) and patients who died in polyuric phase (group 2, fatal cases after the 10th day of the disease) (Table 1).

In group 1 (27 patients), the main clinical features were hypotension and respiratory failure. Respiratory failure preceded hypotension in 5 (19%) patients. The other patients initially developed hypotension. Twenty-six (96%) patients met the diagnostic criteria for septic shock. Twenty-three (85%) patients met the criteria for ARDS (8 patients had mild ARDS, 9 moderate ARDS, and 6 severe ARDS). On admission, all patients in this group had marked hemoconcentration with high hematocrit values (median (IQR) of 57 (54–60)%), probably as a result of the capillary leak and hypo- or isotonic dehydration (median (IQR) serum sodium level at the time of admission was 132 (130–137) mmol/l). Due to clinical signs of ARDS-associated pulmonary edema, continuous veno-venous hemodiafiltration (CVVHDF) was performed on the day of death in 7 patients. In 3 patients, CVVHDF was stopped because of

rapid clinical deterioration. Of note, there were no indications for RRT due to AKI in this group of patients. The peak levels (median (IQR)) of serum creatinine and potassium was 253.5 (160–441) $\mu\text{mol/l}$ and 4.8 (4.2–5.2) mmol/l, respectively. Hemorrhagic signs, such as petechiae, conjunctival hemorrhage, and injection site ecchymosis, were seen in 9 (33%) patients. One patient, a young man, developed ischemic stroke due to arterial thrombosis. All patients were afebrile but had a history of high fever prior to admission.

In group 2 (14 patients), 7 (50%) patients experienced septic shock early in disease, but none of them had ARDS. It was noticeable that group 2 patients had significantly lower hematocrit values on admission (median (IQR) of 45 (40–50)%) compared with group 1 patients ($p=0.0001$). The severity of their disease was mostly related to AKI. Although duration of oliguria was not more than 5 days, restoration of diuresis was accompanied by the progression of azotemia and electrolyte disorders such as hyperkalemia and hyponatremia. The peak levels (median (IQR)) of serum creatinine, potassium and sodium were 755.5 (617–915) $\mu\text{mol/l}$, 6.95 (6.4–8.0) mmol/l, and 124 (120–127) mmol/l, respectively. The main clinical features in polyuric phase were renal failure, encephalopathy, hemorrhagic manifestations, and hospital-acquired infections. Brain computed tomography revealed signs of intracranial hypertension in 9 (64%) patients. Because of hyperkalemia and encephalopathy, intermittent or continuous RRT was performed in 13 (93%) patients. Group 2 patients had more prominent thrombocytopenia on admission, but they had no spontaneous hemorrhages. Progressive deterioration of hemorrhagic manifestations, such as ecchymosis and mucosal bleeding, was noticed in 11 (79%) patients during or shortly after RRT. Severe

Fig. 2 Distribution of deaths according to days from disease onset

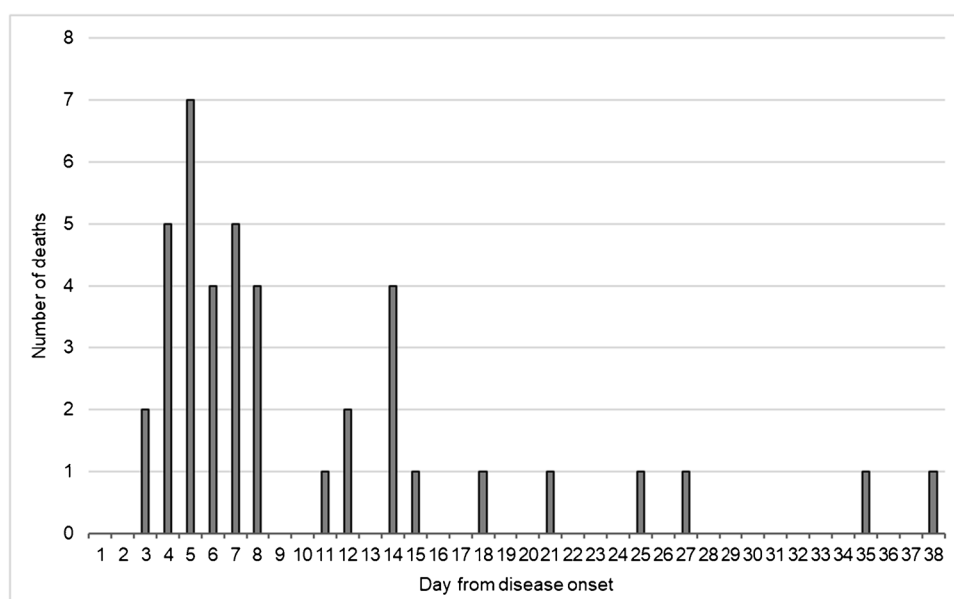


Table 1 Clinical and autopsy features of fatal HFRS (deaths in hypotensive and oliguric phases vs. deaths in polyuric phase)

	Group 1, fatal cases in hypotensive and oliguric phases of HFRS (<i>n</i> = 27)	Group 2, fatal cases in polyuric phase of HFRS (<i>n</i> = 14)	<i>p</i> -value
Demographic and disease-related characteristics, median (IQR) ^a			
Females, <i>n</i> (%)	5 (19%)	2 (14%)	1.000
Age, years	45 (32–52)	51 (43–61)	0.108
Patients with co-morbidities (%)	9 (33%)	4 (29%)	1.000
Day of hospital admission ^b	3 (2–4)	4 (3–6)	0.008
Day of ICU admission ^b	4 (3–5)	4 (4–6)	0.029
SOFA scores on day of hospital admission, median (IQR)			
Total	6 (3–8)	7.5 (5–9)	0.058
Respiratory	1 (1–2)	1 (0–1)	0.025
Coagulation	1 (0–1)	3 (2–4)	<0.0001
Liver	0 (0–0)	0 (0–0)	-
Cardiovascular	1 (0–3)	1.5 (1–3)	0.464
Neurologic	0 (0–0)	0 (0–1)	0.029
Renal ^c	0 (0–2)	2 (0–3)	0.045
SOFA scores on day of death ^d , median (IQR)			
Total	13 (10–14)	11 (10–13)	0.143
Respiratory	3 (2–3)	3 (1–3)	0.360
Coagulation	3 (2–4)	2 (1–3)	0.013
Liver	0 (0–0)	0 (0–0)	0.226
Cardiovascular	4 (3–4)	0 (0–0)	<0.0001
Neurologic ^e	1 (1–2)	2 (1–3)	0.044
Renal ^c	2 (1–3)	4 (4–4)	<0.0001
Autopsy findings, <i>n</i> (% of autopsies)			
Number of autopsies	26	12	
Acute tubular necrosis	24 (92%)	10 (83%)	0.577
Alveolar edema	26 (100%)	5 (42%)	<0.0001
Alveolar hyaline membranes	4 (15%)	0	0.287
Bilateral pleural effusion	13 (50%)	4 (33%)	0.486
Bacterial bronchopneumonia	0	9 (75%)	<0.0001
Pituitary hemorrhage	18 (69%)	8 (67%)	1.000
Adrenal hemorrhage	16 (62%)	4 (33%)	0.164
Borderline myocarditis	8 (31%)	2 (17%)	0.453
Brain edema with tonsillar herniation	8 (31%)	9 (75%)	0.016

^aIf not indicated otherwise. ^bFrom disease onset. ^cBy serum creatinine. ^dFrom 6 to 12 h before death. ^eBefore patients were intubated in cases of mechanical ventilation

RRT-associated complications were registered in 2 (14%) patients. One patient developed a spontaneous left kidney rupture and retroperitoneal bleeding during the hemodialysis procedure. The other patient had a massive hemothorax associated with vascular access placement, which resulted in thoracotomy. Hospital-acquired bacterial infections were diagnosed in 9 (64%) patients with pneumonia in 9 (including ventilator-associated pneumonia in 2) and soft-tissue infection in 1. Recurrence of fever was the initial manifestation of secondary infections in all cases.

Multiorgan involvement was noted in all 38 autopsies with variable degrees of generalized venous congestion,

interstitial edema, capillary wall thickening, perivascular deposition of plasma proteins, microthrombosis formation, and perivascular hemorrhage; however, the more prominent histopathological features were seen in kidneys, lungs, and hypophysis.

In both groups, the most common autopsy finding was kidney injury. The median (IQR) weight of kidneys was 350 (320–380) g each. The macroscopic findings of pale cortex, accentuation of corticomedullary junction, dark red pyramids and punctate hemorrhages in renal pelvic mucosa, as well as histologic signs of acute tubular necrosis, were almost uniformly seen, except for cases of deaths on days

3, 35, and 38 from disease onset. Slight focal interstitial mononuclear cell infiltration was observed in the kidneys of 7 patients who died after the 6th day of disease. Immunohistochemical stainings of kidney tissue were performed in two patients. Early in disease, the examination revealed intensive expression of VEGF on vascular endothelium and intravascular deposits, as well as mild to moderate expression of CD8 and CD68 (Supplementary Fig. S1b, S2b, and S3b). Later in the disease, there were mild to moderate expressions of these markers (Supplementary Fig. S1c, S2c, and S3c).

Postmortem lung examination revealed alveolar edema in all patients of group 1. All these cases showed alveolar wall thickening with slight infiltration of mononuclear cells, as well as serous exudate, mononuclear cells, erythrocytes, and epithelial cells in the alveolar spaces. Immunohistochemical analysis of lung tissue sections was performed in one patient who died on day 5 after onset of the disease. The expression of VEGF in lung tissue was increased, as it was in kidney tissue of the same patient (Supplementary Fig. S1a). The examination also revealed intensive expression of CD68 (Supplementary Fig. S3a). The expression of CD8 in lung tissue was mild (Supplementary Fig. S2a). Bronchopneumonia was the most common pulmonary finding in patients of group 2. Formation of multiple pulmonary microabscesses was noted in 5 patients with bronchopneumonia. Pleural effusion was seen in 17 patients, and it was more prominent in early phases of disease. The total volume of bilateral pleural effusion ranged from 300 to 3500 mL in patients of group 1, and from 200 to 650 mL in patients of group 2. The pleural fluid was clear yellowish in all cases. The patients with hydrothorax had no significant pericardial or peritoneal effusions.

The autopsy findings in the pituitary gland ranged from slightly congestion (12 cases) to total hemorrhagic necrosis (7 cases), with the similar frequency in both groups of patients (Supplementary Fig. S4a and S4b). Hemosiderosis in the hypophysis was noted in 4 patients with subtotal pituitary hemorrhage who died on days 12, 14, 18, and 21 of the disease. Focal bilateral adrenal hemorrhages located between cortex and medulla were seen in 19 patients with pituitary hemorrhage (Supplementary Fig. S4c). Total hemorrhagic necrosis of adrenal glands and hypophysis was noted in one patient who died on day 3 of the disease.

Discussion

This retrospective observational study provides some insights into fatal HFRS in the area endemic to PUUV. The case-fatality rate of HFRS in Udmurtia (0.4%) was much higher than that reported in another European hotspot of HFRS, where Germany and Finland had case-fatality rates of 0.05 and 0.08%, respectively [2, 14]. This difference may be attributed

to three reasons. First, it can be explained by the known genetic diversity of PUUV [4, 15]. Second, since only hospitalized patients are tested for HFRS in Russia, the real case-fatality rate is probably lower because of an unknown number of milder cases. Third, unfortunately, national clinical guidelines for the management of HFRS have some disagreements with international standards of care for the management of septic shock, ARDS, and acute kidney injury [16]. In fact, examples of noncompliance with evidence-based guidelines were often registered in fatal cases.

Between 2010 and 2019, there was temporal variation in case-fatality rate, with some tendency for decreased fatalities during years of high incidence. One of the explanations for this variation could be related to more awareness of medical staff regarding the management of critically ill patients with HFRS in high incidence settings.

The clinical and autopsy findings were consistent with the pathophysiology of the disease, which involves immune-mediated systemic microvascular endothelial dysfunction with capillary leakage (including, probably due to VEGF-induced endothelial hyperpermeability) and thrombohemorrhagic complications, eventually leading to septic shock, ARDS, and AKI. There were two distinct clinical patterns of fatal cases. Most patients died early in their disease due to refractory septic shock and/or ARDS as a result of microcirculatory dysfunction with increased vascular permeability. None of these patients had signs of severe AKI. Later in the disease, patients died from complications of AKI, including hemorrhagic complications of RRT or because of hospital-acquired bacterial infections. However, these patients showed no clinical signs of severe capillary leakage at the time of death.

To conclude, the most common causes of death in patients with HFRS in the area endemic to PUUV were related to septic shock and ARDS, which occurred early in the disease. It should not be expected that any current antiviral therapy would be effective in the prevention of fatal complications on the first days of the disease. A more reasonable assumption is that the reduction of the case-fatality rate of HFRS can be achieved by developing evidence-based protocols for supportive management of severe forms of the disease.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10096-022-04463-y>.

Author contribution Both authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Oleg V. Malinin and Nikolay A. Kiryanov. The first draft of the manuscript was written by Oleg V. Malinin, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The datasets analyzed during the current study are not publicly available due to individual privacy but are available from the corresponding author on reasonable request.

Declarations

Ethics approval The study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Izhevsk State Medical Academy (protocol number 685).

Consent to participate Informed consent was obtained from patients' close relatives.

Consent for publication Informed consent for publication was obtained from patients' close relatives.

Competing interests The authors declare no competing interests.

References

- Heyman P, Ceianu CS, Christova I, Tordo N, Beersma M, João Alves M et al (2011) A five-year perspective on the situation of haemorrhagic fever with renal syndrome and status of the hantavirus reservoirs in Europe, 2005–2010. *Euro Surveill* 16(36):19961. <https://doi.org/10.2807/ese.16.36.19961-en>
- Faber M, Krüger DH, Auste B, Stark K, Hofmann J, Weiss S (2019) Molecular and epidemiological characteristics of human Puumala and Dobrava-Belgrade hantavirus infections, Germany, 2001 to 2017. *Euro Surveill* 24(32):1800675. <https://doi.org/10.2807/1560-7917.ES.2019.24.32.1800675>
- Tkachenko EA, Ishmukhametov AA, Dzagurova TK, Bernshtein AD, Morozov VG, Siniugina AA et al (2019) Hemorrhagic fever with renal syndrome. *Russia Emerg Infect Dis* 25(12):2325–2328. <https://doi.org/10.3201/eid2512.181649>
- Garanina SB, Platonov AE, Zhuravlev VI, Murashkina AN, Yakimenko VV, Korneev AG et al (2009) Genetic diversity and geographic distribution of hantaviruses in Russia. *Zoonoses Public Health* 56(6–7):297–309. <https://doi.org/10.1111/j.1863-2378.2008.01210.x>
- Hjertqvist M, Klein SL, Ahlm C, Klingstrom J (2010) Mortality rate patterns for hemorrhagic fever with renal syndrome caused by Puumala virus. *Emerg Infect Dis* 16(10):1584–1586. <https://doi.org/10.3201/eid1610.100242>
- Linderholm M, Settergren B, Ahlm C, Burman LA, Träff S, Bäcklund U et al (1991) A Swedish fatal case of nephropathia epidemica. *Scand J Infect Dis* 23(4):501–502. <https://doi.org/10.3109/00365549109075100>
- Valtonen M, Kauppila M, Kotilainen P, Lähdevirta J, Svartbäck CM, Kosunen O et al (1995) Four fatal cases of nephropathia epidemica. *Scand J Infect Dis* 27(5):515–517. <https://doi.org/10.3109/00365549509047057>
- Hautala T, Sironen T, Vapalahti O, Pääkkö E, Särkioja T, Salmela PI et al (2002) Hypophyseal hemorrhage and panhypopituitarism during Puumala Virus Infection: magnetic resonance imaging and detection of viral antigen in the hypophysis. *Clin Infect Dis* 35(1):96–101. <https://doi.org/10.1086/340859>
- Sironen T, Sane J, Lokki ML, Meri S, Andersson LC, Hautala T et al (2017) Fatal Puumala hantavirus disease: involvement of complement activation and vascular leakage in the pathobiology. *Open Forum Infect Dis*. 4(4):229. <https://doi.org/10.1093/ofid/ofx229>
- Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H et al (1996) The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 22(7):707–710. <https://doi.org/10.1007/bf01709751>
- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M et al (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 315(8):801–810. <https://doi.org/10.1001/jama.2016.0287>
- ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E et al (2012) Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 307(23):2526–2533. <https://doi.org/10.1001/jama.2012.5669>
- Clinical practice guidelines for acute kidney injury 2012. <https://kdigo.org/guidelines/acute-kidney-injury/>. Accessed 11 January 2022
- Makary P, Kanerva M, Ollgren J, Virtanen MJ, Vapalahti O, Lyytikäinen O (2010) Disease burden of Puumala virus infections, 1995–2008. *Epidemiol Infect* 138(10):1484–1492. <https://doi.org/10.1017/S0950268810000087>
- Castel G, Chevenet F, Razzauti M, Murri S, Marianneau P, Cosson JF et al (2019) Phylogeography of Puumala orthohantavirus in Europe. *Viruses* 11(8):679. <https://doi.org/10.3390/v111080679>
- Национальное Научное Общество Инфекционистов; 2014. Геморрагическая лихорадка с почечным синдромом у взрослых: клинические рекомендации [National Scientific Society of Infectious Diseases Specialists; 2014. Haemorrhagic fever with renal syndrome in adults: clinical guidelines]. Russian. <http://nnoi.ru/uploads/files/protokoly/GLPS.pdf>. Accessed 11 January 2022

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.