



HAL
open science

Description of an outbreak of hemorrhagic fever with renal syndrome in the southern Jura Mountains, France, in 2021

A Brun, M Greusard, Jm Reynes, M Grenier, J Bamoulid, Patrick Giraudoux, Q Lepiller, C Chirouze, K Bouiller, B Bailly

► To cite this version:

A Brun, M Greusard, Jm Reynes, M Grenier, J Bamoulid, et al.. Description of an outbreak of hemorrhagic fever with renal syndrome in the southern Jura Mountains, France, in 2021. *Infectious Diseases Now*, 2023, 53 (4), pp.104639. 10.1016/j.idnow.2022.12.004 . hal-04082359

HAL Id: hal-04082359

<https://hal.science/hal-04082359v1>

Submitted on 23 Feb 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Description of an outbreak of hemorrhagic fever with renal syndrome in the southern Jura Mountains, France, in 2021

A Brun¹, M Greusard², JM Reynes³, M Grenier⁴, J Bamoulid⁵, P Giraudoux⁶, Q Lepiller⁷, C Chirouze^{8,9}, K Bouillier^{8,9}, B Bailly^{1,9}

¹ Department of infectious disease, Hospital of Lons Le Saunier, F-39000 Lons Le Saunier, France

² Department of general medicine, Hospital of Besancon, F-25000, France

³ Institut Pasteur, Université Paris Cité, Unité Environnement et Risques Infectieux, Centre National de Référence des Hantavirus, Paris, France

⁴ Department of medical laboratory, Hospital of Lons Le Saunier, F-39000 Lons Le Saunier, France

⁵ Department of nephrology, University Hospital of Besancon, F-25000 Besançon, France

⁶ Chrono-environment, University of Bourgogne Franche-Comté/CNRS, F-25000 Besançon, France

ORCID: 0000-0003-2376-0136

⁷ Department of Virology, University Hospital of Besancon F-25000, France

⁸ UMR-CNRS 6249 Chrono-environnement, Université Bourgogne Franche-Comté, F-25000 Besançon, France

⁹ Department of infectious disease, University Hospital of Besancon F-25000, France

CORRESPONDING AUTHOR

Dr BAILLY Benoît, MD.

Department of infectious disease, University Hospital of Besançon, F-25000 Besançon, France.

Department of infectious disease, hospital of Lons Le Saunier, F-39000 Lons Le Saunier, France

Phone: +33 6 73 69 21 12 (Lons Le Saunier)

Email: benoit.bailly@hopitaux-jura.fr

KEYWORDS: Hantavirus; Puumala virus; hemorrhagic fever

Introduction

Hemorrhagic fever with renal syndrome (HFRS) is a zoonotic disease caused by various species of hantaviruses. *Puumala orthohantavirus* (PUUV) is the most common species detected in France, transmitted by the rodent *Myodes glareolus* (bank vole) [1]. Clinical presentation is often benign, although half of cases require hospitalization [2]. An epidemic of HFRS occurred in the southern Jura Mountains (France) in 2021. The aim of our study was to accurately describe this outbreak.

Method

We included all laboratory-confirmed HFRS cases reported during the epidemic period from April to September 2021 in the three hospitals with emergency services located in the cities of Lons-le-Saunier, Pontarlier, and Saint Claude.

Laboratory-confirmed HFRS cases were suspected HFRS cases firstly tested positive using the rapid tests Reascan and Reagent POC Puumala IgM (Reagent, Finland; performed at the hospital), and secondarily tested positive for both IgM and IgG using enzyme-linked immunosorbent assays (ELISA) and immunofluorescence assay (IF), and/or tested positive using real-time RT-PCR detecting PUUV (performed at the French National Reference Center for Hantavirus - Hantavirus NRC, Institut Pasteur, Paris).

Patients were interviewed by telephone. Clinical and biological information were retrospectively collected from the medical record. We assessed the differences between hospitalized and non-hospitalized patient using Fisher's exact test for qualitative variables and Mann-Whitney test for continuous variables, as appropriate. All patients gave informed consent before participation. Parental consent was requested for minor patients. The study was approved by the Ethics Committee of Bourgogne Franche-Comté university (CERUBFC-2021-034).

Results

During the epidemic period, 112 patients had a positive or equivocal rapid test (performed in hospital laboratories), of which 110 were secondarily confirmed by the French NRC. Among these patients, 75 were hospitalized (hospitalization rate: 68.2%). Two hospitalized cases and 18 cases among the 35 non-hospitalized cases were excluded due to non-consent. Lastly, 90 patients were enrolled in the study: 73 hospitalized and 17 non-hospitalized patients. Exposure factors to rodent excreta reported by patients were activities in uninhabited premises (barns, cottages, attics) for 35 patients (38.9%), activity in the forest for 31 patients (34.4%), and rodent contact for 11 patients (12.2%).

Median age of the 90 patients was 43.5 years, ranging from 3 to 89 years, and 68.9% were males. Symptoms were fever for 77 patients (85.6%), myalgia for 63 patients (70%), headaches for 49 patients (54.4%), abdominal pain for 43 patients (47.8%), and transient myopia for 18 patients (20%). Forty-one (45.6%) patients had a combination of fever, elevated serum creatinine value ($>100 \mu\text{mol/L}$), and thrombocytopenia (platelet count $<150 \text{ G/L}$) at the time of hantavirus serology testing.

The detailed clinical and laboratory characteristics of hospitalized and non-hospitalized patients are shown in Table 1. Hospitalized patients were older than non-hospitalized patients (median age of 47.0 [35.0; 64.0] years vs. 36.0 [31.0; 41.0] years, respectively, $p=0.046$), and more frequently had at least one pre-existing comorbidity (31.5% vs. 11.8%, $p=0.14$). Transient myopia was only reported in hospitalized patients (20% vs. 0%, $p=0.02$).

The mean duration of hospitalization was 6.48 days (range 1-23). Indications for hospitalization were acute renal failure whether or not combined with fever for 46 patients (63.0%), isolated fever without diagnosis for 20 patients (27.4%), abdominal pain or headache refractory to analgesics for five patients (6.8%), and symptomatic bradycardia for two patients (2.7%). Some patients had multiple indications for hospitalization.

Forty (44.4%) patients underwent medical imaging before hantavirus diagnosis. An abdominal computed tomography (CT) scan or abdominal ultrasound was performed for kidney injury or/and abdominal pain for 25 and 17 patients, respectively. Cerebral CT scan and cerebral magnetic resonance imaging were also carried out for severe headache in 10 and 3 patients, respectively. Moreover, lumbar puncture was performed for febrile

headache in three patients. Finally, CT scan, abdominal ultrasound, cerebral magnetic resonance imaging, and lumbar puncture showed no abnormality related to the symptoms.

Analgesic treatment, parenteral hydration, and biological monitoring were the only treatments performed in 69 (94.5%) of the hospitalized patients. During hospitalization, 21 patients (28.8%) presented a severe acute kidney injury (AKI) (plasma creatinine >353.6 $\mu\text{mol/L}$), but no patient developed severe hyperkalemia (serum potassium level ≥ 6.0 mmol/L) or severe metabolic acidosis (arterial blood pH ≤ 7.20). The median of the maximum plasma creatinine among patients with severe AKI was 549 (interquartile range: 397-621 $\mu\text{mol/L}$). Only one patient was dialyzed for two days. He had severe AKI with plasma creatinine at 550 $\mu\text{mol/L}$, but no major metabolic disorder or congestive heart failure.

Among hospitalized patient with thrombocytopenia the median platelet count was 77 G/L (interquartile range: 62-106). Three patients had severe thrombocytopenia (platelet count <30 G/L), and two of them received platelet transfusions for bleeding prevention. Among them, a 78-year-old patient with a history of congestive heart disease and atrial fibrillation treated with direct anticoagulation presented sudden death after 3 days of hospitalization. Another 78-year-old patient presented lipothymia caused by atrioventricular blocks. Cardiovascular implantable electronic device was implanted before diagnosis of HFRS. In total, 23 patients had a severe form of HFRS or presented complications: 21 patients had severe AKI, one patient was hospitalized in the cardiologic intensive care unit for bradycardia, and one patient died. Of note, 11 of the 25 hospitalized patients (44%) with a Hentzien score ≥ 20 at admission developed a severe disease and 33 of the 45 hospitalized patients (73%) with a Hentzien score <20 developed a benign disease [3]. At the end of the epidemic period, our infectious diseases team proposed an algorithm, which has yet to be validated in a prospective study, to assist the ambulatory management of patients with HFRS for the next epidemic (Figure 1).

Discussion

The hantavirus epidemic in the Jura Mountains led to a high number of hospitalizations. The clinical presentation and the clinical course of our patients were comparable to those of other studies: the prominent clinical findings were the combination of fever with widespread

pain (abdominal pain, myalgia, headaches) [3–5]. Transient myopia was present in 20% of patients and was only present in hospitalized patients. Myopia has already been reported as a risk factor for a severe form of HFRS probably because it reflected higher tissue permeability [3,6,7]. In our study, 23% of all patients presented severe AKI but only one patient was dialyzed. No patient presented severe metabolic disorder. In literature, the fatality rate of HFRS caused by PUUV is relatively low (<1%) and 4-6% of hospitalized patients needed transient dialysis treatment [8,9]

In France, the national health insurance does not cover hantavirus laboratory diagnosis. Moreover, the wide clinical spectrum of HFRS make diagnosis challenging. In our cohort, the triad of fever, elevation of creatinine, and thrombocytopenia was present in less than half of the cases at the time of the first consultation in hospital. This might explain the CT scan, abdominal ultrasound, and lumbar puncture performed before diagnosis. Performing CT scans with injection of contrast media may promote the development of severe AKI in this context [3]. During an epidemic period and in high-risk areas, rapid tests detecting Puumala IgM could be performed in patients presenting fever associated with abdominal disorder or headache in the absence of other diagnoses. Excellent performances have been reported for these tests, with analytical sensitivity and specificity reaching 100% and 99%, respectively [10] . Performing this rapid test could avoid unnecessary radiological and biological investigations.

Hentzien *et al.* reported a score to identify patients at high risk of severe HFRS at hospital admission [3]. In this study, nephrotoxic drug exposure, visual disorders, microscopic or macroscopic hematuria, leukocyte count >10 G /L and thrombocytopenia <90 G/L were predictive factors of severe HFRS. In hospitalized patients, the use of the bioclinical score to predict severe acute kidney injury could be useful in reducing the length of hospitalization. In our study, the positive predictive value of this score seemed low. However, the retrospective nature of our study and the sample size do not enable us to assess this score.

In our cohort, most hospitalized patients only received parenteral hydration and analgesic treatments. Most of these patients could have benefited from ambulatory monitoring alone. Ambulatory medical management could include analgesic treatment, oral hydration,

discontinuation of nephrotoxic and anticoagulant treatments. Ambulatory laboratory monitoring could include bi-weekly platelet count, plasma creatinine level and a daily diuresis. As specific treatments are lacking, hospitalization could be limited to severe HFRS or to patients with severe comorbidities such as patients on diuretics, anticoagulant treatments, and/or bradycardia treatment.

Cleaning activities in uninhabited places, activities in forest, and contact with rodents were the main sources of exposure identified in our cohort, as described in the literature [11,12]. To date, available data on bank vole population dynamics are insufficient to explain the time pattern of epidemic peaks [13–15]. As a consequence, for lack of well-designed wildlife observatories, there is currently no possibility of anticipating epidemics in France, which makes it difficult to implement strong preventive actions.

Conclusion

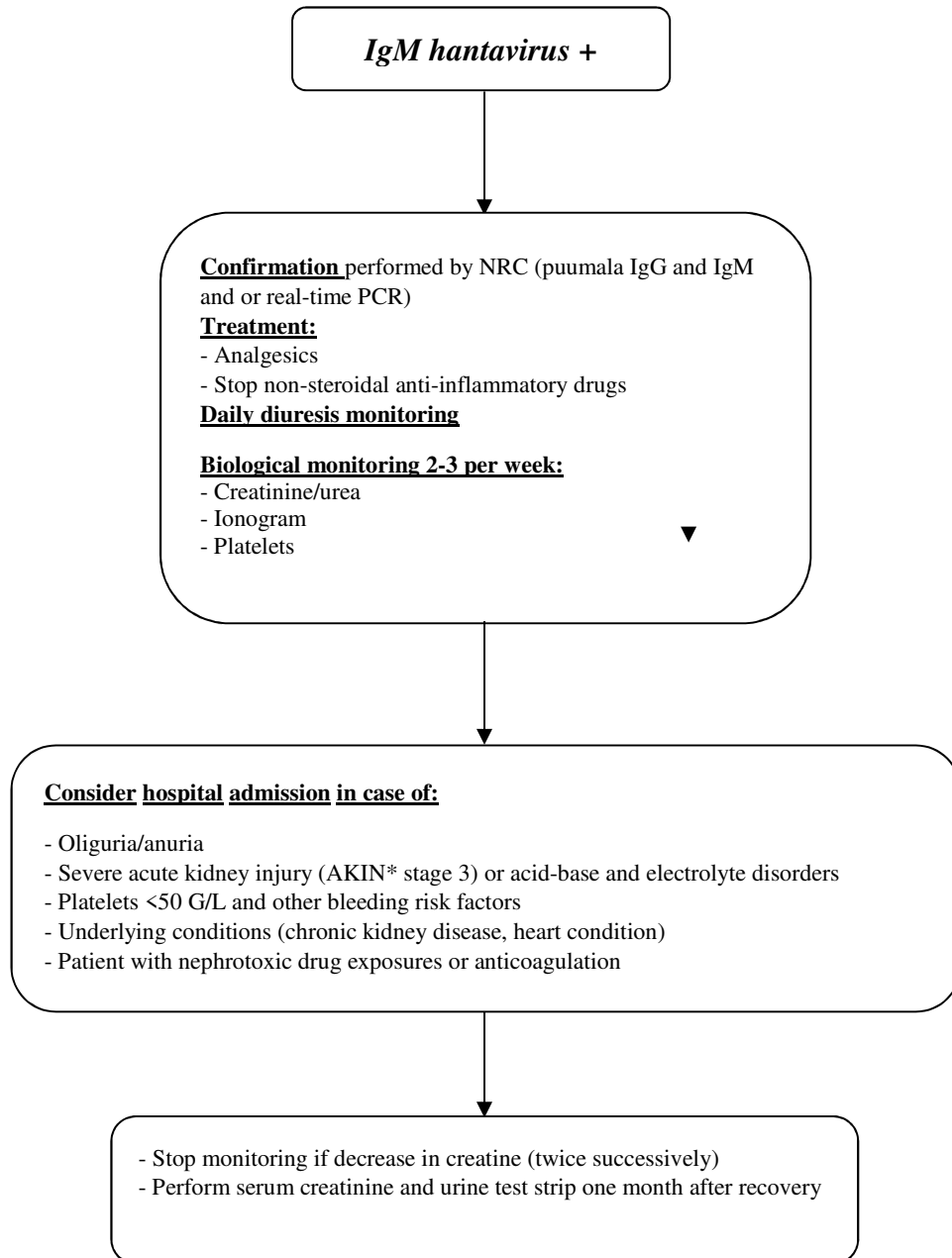
The hantavirus epidemic in the Jura Mountains led to numerous hospitalizations, one dialysis treatment, and one death. Early diagnosis by rapid test could avoid unnecessary radiological and biological investigations.

References

1. Jean Marc Reynes, Carli D, Renaudin B, Fizet A, Bour jean B, Brodard V, et al. SURVEILLANCE OF HUMAN HANTAVIRUS INFECTIONS IN METROPOLITAN FRANCE, 2012-2016. *Bull Epidemiol Hebd.* 23^e éd. 24 oct 2017;492-9.
2. Makary P, Kanerva M, Ollgren J, Virtanen MJ, Vapalahti O, Lyytikäinen O. Disease burden of Puumala virus infections, 1995-2008. *Epidemiol Infect.* oct 2010;138(10):1484-92.
3. Hentzien M, Mestrallet S, Halin P, Pannet LA, Lebrun D, Dramé M, et al. Bioclinical Test to Predict Nephropathia Epidemica Severity at Hospital Admission. *Emerg Infect Dis.* juin 2018;24(6):1045-54.
4. Latus J, Schwab M, Tacconelli E, Pieper FM, Wegener D, Dippon J, et al. Clinical Course and Long-Term Outcome of Hantavirus-Associated Nephropathia Epidemica, Germany. *Emerg Infect Dis.* janv 2015;21(1):76-83.
5. Bermejo M, Mestrallet S, Servettaz A, Pannet LA, Lebrun D, N'Guyen Y, et al. Eosinophilia during Hantavirus infection: a cohort study. *Infect Dis Lond Engl.* avr 2022;54(4):277-82.
6. Hautala T, Mähönen SM, Sironen T, Hautala N, Pääkkö E, Karttunen A, et al. Central nervous system-related symptoms and findings are common in acute Puumala hantavirus infection. *Ann Med.* juill 2010;42(5):344-51.
7. Hautala N, Kauma H, Vapalahti O, Mähönen SM, Vainio O, Vaheri A, et al. Prospective study on ocular findings in acute Puumala hantavirus infection in hospitalised patients. *Br J Ophthalmol.* avr 2011;95(4):559-62.
8. Settergren B. Clinical aspects of nephropathia epidemica (Puumala virus infection) in Europe: a review. *Scand J Infect Dis.* 2000;32(2):125-32.
9. Mustonen J, Outinen T, Laine O, Pörsti I, Vaheri A, Mäkelä S. Kidney disease in Puumala hantavirus infection. *Infect Dis Lond Engl.* may 2017;49(5):321-32.
10. Hujakka H, Koistinen V, Eerikäinen P, Kuronen I, Mononen I, Parviainen M, et al. New immunochromatographic rapid test for diagnosis of acute Puumala virus infection. *J Clin Microbiol.* juin 2001;39(6):2146-50.
11. Crowcroft NS, Infuso A, Ilf D, Le Guenno B, Desenclos JC, Van Loock F, et al. Risk factors for human hantavirus infection: Franco-Belgian collaborative case-control study during 1995-6 epidemic. *BMJ.* 26 juin 1999;318(7200):1737-8.
12. Van Loock F, Thomas I, Clement J, Ghooos S, Colson P. A case-control study after a hantavirus infection outbreak in the south of Belgium: who is at risk? *Clin Infect Dis Off Publ Infect Dis Soc Am.* avr 1999;28(4):834-9.
13. Reil D, Imholt C, Drewes S, Ulrich RG, Eccard JA, Jacob J. Environmental conditions in favour of a hantavirus outbreak in 2015 in Germany? *Zoonoses Public Health.* mars 2016;63(2):83-8.

14. Khalil H, Ecke F, Evander M, Bucht G, Hörnfeldt B. Population Dynamics of Bank Voles Predicts Human Puumala Hantavirus Risk. *EcoHealth*. sept 2019;16(3):545-57.
15. Giraudoux P. Pics épidémiques de fièvre hémorragique à syndrome rénal et stabilité historique des foyers : les connaissances écologiques sont encore insuffisantes pour les comprendre. 2021;(34):131-42.

Figure 1. Clinical management proposition for non-hospitalized adult HFSR patients.



*AKIN: acute kidney injury Network

Stage 3 : increase in serum creatinine to more than 300% from baseline or serum creatinine >354 µmol/L with an increase of at least 44 µmol/L

NRC: national reference center

Table 1. Clinical characteristics and laboratory results for 90 patients with acute hantavirus infection, South Jura Mountains, France, 2021

	All patients (n=90)	Hospitalized patients (n=73)	Non hospitalized patients (n=17)	p value
Age - median [IQR]	44 [33 ; 60]	47 [35 ; 64]	36 [31 ; 41]	p=0.046
Male - n (%)	62 (68.9)	48 (65.8)	14 (82.4)	p=0.25
Comorbidity - n (%)				
At least 1 comorbidity	25 (27.8)	23 (31.5)	2 (11.8)	p=0.14
Hypertension	11 (12.2)	11 (15.1)	0	p=0.12
Chronic renal insufficiency	4 (4.4)	4 (5.5)	0	p=1
Chronic cardiac insufficiency	3 (3.3)	3 (4.1)	0	p=1
Diabetes mellitus	2 (2.2)	2 (2.7)	0	p=1
Coronary artery disease	1 (1.1)	1 (1.4)	0	p=1
Cancer	1 (1.1)	0	1 (5.9)	p=0.2
Stroke	1 (1.1)	0	1 (5.9)	p=0.2
Dementia	1 (1.1)	1 (1.4)	0	p=1
Nephrotoxic drugs*	25 (27.8)	24 (32.9)	1 (5.9)	p=0.03
Clinical signs and symptoms				
Duration of symptoms - median [IQR] days	9 [7 ; 12]	9 [6 ; 10]	9 [7 ; 12]	p=0.39
Fever— n (%)	77 (85.6)	62 (84.9)	15 (88.2)	p=1
Headache— n (%)	49 (54.4)	40 (54.8)	9 (53)	p=1
Intestinal disorder— n (%)	43 (47.8)	37 (50.7)	6 (35.3)	p=0.29
Myalgia —n (%)	63 (70)	52 (71.2)	11 (84.6)	p=0.57
Transient myopia—n (%)	18 (20)	18 (24.7)	0	p=0.02
Laboratory test				
Highest C-reactive protein (mg/L) - median [IQR]	52 [25 ; 83]	60 [37 ; 89] 205 [105 ; 334]	25 [16 ; 45] 88 [78 ; 101]	p<0.001 p<0.001
Highest creatinine - median [IQR]	156 [92 ; 316]	94 [68 ; 125]	96 [87 ; 100]	p=0.84
Lowest platelet count (G/L)- median [IQR]	316	21 (28.8)	0	p=0.009
Plasma creatinine >353.6 µmol/L —n (%)	95 [68 ; 124]	11 (15.1)	0	p=0.12
Platelet count <50 G/L —n (%)	124	44/70 (63)	3/16 (19)	p=0.001
Hematuria — n (%) **	21 (23.3) 11 (12.2) 47/86 (54.6)			
Triad of fever, low platelet <150 G/L and creatinine >100 µmol/L — n (%)	39 (43.3)	37 (50.6)	2 (11.8)	p=0.005

* We considered the following nephrotoxic drug exposures: non-steroidal anti-inflammatory drugs, iodinated contrast media, diuretics, renin angiotensin aldosterone system inhibitors, and nephrotoxic antimicrobial drugs (aminoglycosides, glycopeptides).

** Missing data for four patients