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Review

Cardiopulmonary Failure in Hantavirus Disease: Mechanisms, Recognition, and ECMO-Based Management

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Abstract

Background: Hantavirus pulmonary syndrome (HPS), also designated hantavirus cardiopulmonary syndrome, is caused by New World hantaviruses, principally Sin Nombre virus in North America and Andes virus in South America. The syndrome is characterized by rapidly progressive noncardiogenic pulmonary edema and myocardial depression, with case fatality rates of 30% to 50%. **Methods:** This review synthesizes peer-reviewed literature on the virological, pathophysiological, clinical, and therapeutic aspects of HPS, with emphasis on cardiopulmonary mechanisms. Sources were identified through PubMed, prioritizing original research, clinical series, and controlled trials published through 2025. **Results:** Pathogenic hantaviruses enter endothelial cells and platelets via $\alpha v\beta 3$ integrins, disrupting the VEGF-VEGFR2 signaling axis and rendering endothelial cells hypersensitive to physiological VEGF concentrations. Expansion of CD8+ T cells and activated macrophages releases TNF-alpha, IFN-gamma, and nitric oxide, amplifying microvascular permeability and contributing to myocardial depression. Autopsy studies demonstrate direct hantaviral myocarditis with viral antigen in cardiac endothelium and interstitial macrophages. Transpulmonary thermodilution confirms simultaneous hypovolemia, reduced global ejection fraction, and elevated extravascular lung water. VA-ECMO initiated at the first signs of cardiopulmonary decompensation has reported survival rates approaching 80% in selected experienced centers. No antiviral has demonstrated efficacy in controlled trials during the cardiopulmonary phase. **Conclusions:** HPS produces a mixed shock state through increased microvascular permeability, T cell-mediated immunopathology, and direct myocarditis. Management follows a stepwise algorithm: suspected HPS triggers immediate complete blood count with peripheral blood smear and hantavirus IgM serology or RT-PCR, followed by ICU admission, conservative fluid resuscitation guided by transpulmonary thermodilution, and early contact with an ECMO-capable center at the first sign of rising lactate, falling cardiac index, refractory shock, arrhythmia, or rapid oxygenation failure.

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1. Introduction

In May 1993, a cluster of previously healthy young adults in the Four Corners region of the United States presented with acute respiratory failure from an unrecognized cause. Retrospective surveillance identified 24 cases since December 1992, with a case fatality rate of 50% [1]. The clinical series of the first 17 confirmed patients, published in the *New England Journal of Medicine* in 1994, reported a 76% case fatality rate within that cohort [2]. The causative agent was identified as Sin Nombre virus (SNV), an enveloped, negative-sense, tripartite RNA virus of the genus

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Orthohantavirus, family Hantaviridae [3]. In South America, Andes virus (ANDV) produces an identical syndrome and is the only hantavirus with documented person-to-person transmission [4]. The United States has reported 890 confirmed cases from 1993 through 2023, averaging fewer than 30 per year, with the highest burden in New Mexico, Colorado, and Arizona [5]. In South America, more than 100 cases occur annually; Argentina consistently reports the highest regional case counts [6]. Across eight countries in the Americas in 2025, 229 cases and 59 deaths were recorded (case fatality rate 25.7%) [6]. Transmission is via inhalation of aerosolized viral particles from the excreta, urine, or saliva of infected rodents. *Peromyscus sonoriensis* (western deer mouse) is the primary reservoir for SNV in North America; *Oligoryzomys longicaudatus* (long-tailed pygmy rice rat) is the primary reservoir for ANDV in southern South America [7,8].

Hantavirus pulmonary syndrome (HPS), as known as hantavirus cardiopulmonary syndrome (HCPS) is distinguished from other viral pneumonias by the combination of increased microvascular permeability without direct endothelial cytopathic injury, superimposed immunopathology, hemostatic dysregulation, and myocardial depression. No antiviral has proven effective and management remains supportive. This review synthesizes the mechanisms of cardiopulmonary failure in HPS and translates these into clinical practice.

2. Virology and Viral Entry

Hantaviruses have a trisegmented, single-stranded, negative-sense RNA genome. The small (S), medium (M), and large (L) segments encode the nucleocapsid protein, the glycoprotein precursor (cleaved into surface glycoproteins Gn and Gc), and the RNA-dependent RNA polymerase, respectively [3]. Hantaviruses are not arthropod-borne; human infection requires direct exposure to aerosolized rodent excreta.

Pathogenic New World hantaviruses (SNV, ANDV, New York-1 virus) enter endothelial cells, platelets, and macrophages via $\alpha v\beta 3$ integrins; the nonpathogenic Prospect Hill virus uses $\beta 1$ integrins instead [9]. Pathogenic Old World hantaviruses causing hemorrhagic fever with renal syndrome (Hantaan, Seoul, Puumala viruses) also use $\beta 3$ integrins [10]. This receptor specificity has direct pathogenic consequences: $\beta 3$ integrins regulate vascular permeability and platelet activation, and their occupation by pathogenic hantaviruses disrupts both functions [9,10]. Hantaviruses replicate extensively in pulmonary endothelial cells without inducing recognizable cytopathic changes; infected endothelial monolayers remain intact in vitro, and endothelial necrosis is absent at autopsy [11].

3. Pathophysiology of Cardiopulmonary Failure

3.1. Increased Microvascular Permeability and Pulmonary Edema

Following inhalation, SNV is taken up by alveolar macrophages, disseminates hematogenously, and replicates in pulmonary capillary endothelial cells without producing direct endothelial injury [11,12]. Increased permeability requires the combination of $\beta 3$ integrin dysregulation and available VEGF. Pathogenic hantaviruses inhibit $\alpha v\beta 3$ integrin function two to three days after infection, disrupting the $\alpha v\beta 3$-VEGFR2 receptor complex that normally restrains VEGF-directed permeabilizing signaling [13]. In vitro studies with Hantaan, ANDV, and New York-1 viruses demonstrate markedly enhanced endothelial permeability in response to VEGF following infection, an effect absent with the nonpathogenic Prospect Hill and Tula viruses [13]. Angiopoietin-1 and sphingosine 1-phosphate suppress this hantavirus-directed permeability at physiological concentrations, as do antibodies to VEGFR2, identifying potential therapeutic targets [13].

Extravasation of protein-rich fluid into the pulmonary interstitium and alveoli produces the noncardiogenic pulmonary edema that defines HPS. Transpulmonary thermodilution in mechanically ventilated HCPS patients demonstrates markedly elevated extravascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI), confirming a permeability rather than hydrostatic mechanism [14]. EVLWI correlates inversely with global ejection fraction ($r = -0.36$)

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and mean arterial pressure (r = −0.27), indicating that pulmonary flooding directly tracks hemodynamic deterioration [14]. The resulting intravascular volume depletion independently contributes to the shock state.

The contribution of the pulmonary epithelium to increased alveolar permeability has been underexplored. A 2023 cross-sectional study measured plasma soluble receptor for advanced glycation end-products (sRAGE), a marker of type I alveolar epithelial cell injury, in critically ill HCPS patients and found substantially higher concentrations in severe compared with mild disease [15]. Whether this reflects a primary pathological event or a downstream consequence of severe hypoxia requires prospective study in larger cohorts.

3.2. Immunopathogenesis

Upon recognition of hantaviral RNA by pattern recognition receptors, infected macrophages and dendritic cells secrete type I and III interferons, IL-1β, TNF-α, IL-6, IL-15, and chemokines including CCL5 and CXCL10 [16]. Unlike many hemorrhagic fever viruses that impair dendritic cell maturation, hantavirus-infected dendritic cells mature normally and prime robust T cell responses, amplifying the adaptive immune response [17]. A sustained elevation of proinflammatory cytokines and plasminogen activation system components has been documented throughout the clinical course of SNV-associated HCPS [18].

CD8+ cytotoxic T lymphocytes reach peak expansion at the time of maximum clinical severity [17]. HLA typing studies support their pathogenic role: HLA-B35 is associated with increased disease severity and enhanced susceptibility to apoptosis, while HLA-B27 is associated with milder outcomes [19]. Virus-specific CD8+ T lymphocytes directed against SNV nucleocapsid protein epitopes have been isolated from acutely ill patients, producing IFN-γ and demonstrating cytolytic activity ex vivo [20]. The proposed mechanism of endothelial injury is cytotoxin and cytokine release in proximity to infected endothelial cells, impairing endothelial integrity through paracrine signaling.

A 2024 study demonstrated that activated inflammatory monocytes and macrophages are the immune subset most strongly correlated with disease severity in human HFRS and rodent models, driving a TNF-α-centered cytokine storm [21]. Plasminogen activator inhibitor-1 (PAI-1) rises 30- to 100-fold in plasma of terminal-stage SNV-infected patients, representing profound fibrinolysis inhibition and contributing to microvascular obstruction [22]. TNF-α, IFN-γ, and nitric oxide released by these immune effectors increase capillary endothelial permeability and are proposed mediators of myocardial depression [17].

Hantavirus-specific IgM antibodies are detectable at symptom onset in the majority of patients, reflecting an early plasmablast expansion [16,23]. IgG responses emerge concurrently and persist lifelong. This seroconversion underlies the utility of IgM serology as a diagnostic tool.

3.3. Hantaviral Myocarditis

Myocardial depression in HPS was originally attributed to cytokine-mediated contractile suppression. A histopathological study of 14 fatal HPS cases revised this interpretation: hantaviral antigen and viral particles were identified in cardiac endothelium and interstitial macrophages in all 14 cases, accompanied by discrete foci of myofiber necrosis, interstitial edema, and an inflammatory infiltrate of macrophages and memory T lymphocytes [24]. TNF-α expression was significantly greater in cardiac macrophages and cardiomyocytes in HPS patients than in controls dying of other causes with acute lung injury [24]. These findings establish hantavirus as a cause of myocarditis, though the relative contributions of direct viral injury and cytokine-mediated suppression to the clinical hemodynamic picture have not been quantified.

Transpulmonary thermodilution studies confirm reduced stroke volume index, reduced global ejection fraction, and reduced preload-related parameters alongside elevated EVLWI and PVPI [14]. Volume depletion from capillary leak reduces preload, and myocarditis with cytokine-mediated suppression reduces contractility, producing the mixed cardiogenic-distributive shock that defines

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advanced HPS. Lactic acidosis from the low cardiac output is among the strongest predictors of fatal outcome [25].

Thrombocytopenia occurs in 98% of patients, with platelet counts below 150 $\times 10^9$/L at presentation. Mechanisms include direct binding of pathogenic hantaviruses to platelet αIIbβ3 integrins, immune-mediated platelet destruction, and microvascular consumption [9,10]. Despite profound thrombocytopenia, fibrinogen levels are typically normal, distinguishing HPS coagulopathy from disseminated intravascular coagulation [12].

4. Clinical Presentation and Disease Phases

HPS advances through four phases: incubation, prodrome, cardiopulmonary, and diuretic-convalescent (Table 1). The incubation period averages 14 to 17 days, with a range of one to five weeks [26]. The prodromal phase lasts 3 to 10 days with fever, chills, myalgia, and gastrointestinal symptoms. Physical examination yields no specific findings, and the presentation is indistinguishable from nonspecific viral illness [25]. ANDV infection additionally produces facial flushing, fine petechiae, and conjunctival injection, features not typical of SNV disease [27].

The cardiopulmonary phase begins abruptly, typically within 12 to 48 hours of prodromal onset. The interval from onset of dyspnea to need for mechanical ventilation is 1 to 6 hours in some reported series [17]. Most patients develop hypotension within 24 hours. Chest radiographs progress from peribronchial haze and Kerley B lines to diffuse bilateral alveolar infiltrates [14]. Fatal infections are marked by progressive myocardial depression evolving to sinus bradycardia, electromechanical dissociation, ventricular tachycardia, or fibrillation [25]. In survivors, the diuretic phase begins 2 to 4 days after peak illness, with polyuria and rapid resolution of pulmonary edema. Convalescence may take weeks to months.

Table 1. Clinical phases of hantavirus pulmonary syndrome.

Phase	Duration	Key Clinical Features	Key Laboratory Findings
Incubation	1–5 weeks (mean 14–17 days)	Asymptomatic	None
Prodrome	3–10 days	Fever, myalgia, headache, nausea, vomiting, diarrhea. ANDV: facial flushing, conjunctival injection, fine petechiae.	Early thrombocytopenia; circulating immunoblasts; mild transaminitis; normal or mildly elevated leukocyte count
Cardiopulmonary	Hours to 2–3 days; most deaths occur within 24–48 h of onset	Cough, dyspnea, hypoxia, bilateral alveolar infiltrates, pleural effusions, hypotension, tachycardia, cardiogenic shock, arrhythmia	Thrombocytopenia (<150 $\times 10^9$/L in 98%); left-shift leukocytosis; hemoconcentration; immunoblasts >10%; elevated lactate; cardiac index <2.2 L/min/m^2
Diuretic / Recovery	2–4 days diuresis; convalescence weeks to months	Polyuria, resolution of pulmonary edema, normalizing hemodynamics	Normalizing platelet count, resolving hemoconcentration

Abbreviations: ANDV, Andes virus; CI, cardiac index.

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5. Diagnosis

5.1. Clinical Recognition and Peripheral Blood Smear

Clinical recognition depends on epidemiological context (rural setting, rodent exposure, endemic region) combined with hematological findings [2]. A five-criterion peripheral blood smear triage protocol was established at the University of New Mexico Health Sciences Center: thrombocytopenia, hemoconcentration, granulocytic left shift, absence of toxic granulation, and immunoblasts exceeding 10% of lymphoid cells [28]. Retrospective validation over ten years (188 smear results compared with serology) confirmed that a four-of-five threshold yields sensitivity of 89% and specificity of 93% for serologically confirmed HCPS [29]. Meeting this threshold triggers preparation for critical care transfer and VA-ECMO. Because cytopenias may be absent during the prodrome, the complete blood count and smear should be repeated every 8 to 12 hours in suspected cases.

5.2. Serological and Molecular Confirmation

ELISA for hantavirus-specific IgM is the preferred method for acute diagnosis. IgM is present at symptom onset in most patients and detectable at hospital admission in the majority of confirmed cases [23,30]. IgG antibodies are detectable concurrently and persist lifelong. RT-PCR for viral RNA is most sensitive during the prodromal phase, when viremia is highest; sensitivity declines during the cardiopulmonary phase as antibody titers rise [31]. Immunofluorescence and immunoblot assays are alternative confirmatory platforms [32].

5.3. Hemodynamic Thresholds

Plasma lactate above 4.0 mmol/L and cardiac index below 2.2 L/min/m^2 at admission are independent predictors of fatal outcome [25]. Both parameters should be assessed at presentation and serially, as they define thresholds for VA-ECMO escalation. Hematocrit above 50% in men or 48% in women reflects severe intravascular depletion and is present in approximately 50% of cases [12]. Diagnostic and prognostic parameters are summarized in Table 2.

Table 2. Diagnostic and prognostic parameters in hantavirus pulmonary syndrome.

Parameter	Threshold / Finding	Pathophysiological Basis	Clinical Significance
Platelet count	<150 ×10^9/L (98% of cases); rapid progressive decline	Platelet αIIbβ3 integrin binding; immune-mediated destruction; microvascular consumption	Progressive thrombocytopenia marks transition to cardiopulmonary phase; serial monitoring required
Hematocrit	>50% (men); >48% (women); present in ~50% of cases	Massive capillary leak and intravascular fluid loss	Marker of severe capillary leak; correlates with disease severity
Plasma lactate	>4.0 mmol/L	Tissue hypoperfusion from low cardiac output	Independent predictor of fatal outcome; threshold for VA-ECMO consideration
Cardiac index	<2.2 L/min/m^2	Cytokine-mediated myocardial depression	Independent predictor of fatal outcome;

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		and direct hantaviral myocarditis	threshold for VA-ECMO consideration
EVLWI and PVPI	Elevated; EVLWI inversely correlated with GEF (r = −0.36) and MAP (r = −0.27)	Permeability pulmonary edema from increased microvascular permeability	Guides fluid management and VA-ECMO timing; obtained by transpulmonary thermodilution
Peripheral smear immunoblasts	>10% of lymphoid series; sensitivity 89%, specificity 93% in validated series	CD8+ T cell and plasmablast expansion at peak immune activation	Part of validated five-criterion triage protocol; triggers VA-ECMO preparation
PAI-1	30–100-fold elevation in terminal-stage patients	Inhibition of fibrinolysis; hemostatic imbalance	Elevated in severe HCPS; fibrinogen typically normal, distinguishing from DIC
sRAGE	Elevated in severe vs. mild HCPS	Type I alveolar epithelial cell injury	Emerging biomarker of alveolar epithelial injury; requires prospective validation

Abbreviations: DIC, disseminated intravascular coagulation; EVLWI, extravascular lung water index; GEF, global ejection fraction; MAP, mean arterial pressure; PAI-1, plasminogen activator inhibitor-1; PVPI, pulmonary vascular permeability index; sRAGE, soluble receptor for advanced glycation end-products; VA-ECMO, venoarterial-extracorporeal membrane oxygenation.

6. Management

6.1. Fluid and Hemodynamic Management

The central hemodynamic challenge in HPS is simultaneous intravascular volume depletion and permeability pulmonary edema. Fluid administration corrects hypovolemia but directly worsens pulmonary edema. Transpulmonary thermodilution data support conservative fluid strategies guided by EVLWI and PVPI [14]. No vasopressor or inotropic regimen has been validated in controlled trials of HPS, and cardiotonic agents are used to support depressed cardiac output [33].

High-volume hemofiltration (HVHF) has been reported in isolated cases as a strategy to remove accumulated extracellular fluid before refractory shock develops [34,35]. The evidence consists of case reports and small series; HVHF is a rational option in patients with progressive fluid overload who have not yet entered refractory cardiogenic shock, but cannot be considered standard of care.

6.2. Mechanical Ventilation

Mechanical ventilation is required in most patients presenting in the cardiopulmonary phase. Lung-protective ventilation (tidal volume 6 mL/kg predicted body weight; plateau pressure ≤30 cmH^2O) is applied by analogy with ARDS management, as no HPS-specific ventilatory trials exist [36]. Prone positioning has been used as bridge therapy to improve oxygenation during interhospital transfer to ECMO-capable centers [37].

6.3. Venoarterial ECMO

VA-ECMO supports both cardiac output and pulmonary gas exchange, bridging patients through the critical 24- to 72-hour period of maximum capillary leak and myocardial depression. The CDC reports that VA-ECMO initiated at the earliest sign of cardiopulmonary decompensation is

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associated with an 80% survival rate [25]. An observational study of 47 HCPS patients in Chile (2015–2022) found overall cohort mortality of 33.6%, rising above 60% in patients meeting critical illness criteria who did not receive timely ECMO [38]. A 2024 review of Chilean HCPS experience reports that 25% of cases diagnosed in 2023 required VA-ECMO, with mortality of 43% to 76% in patients requiring mechanical ventilation and hemodynamic support before ECMO escalation [33].

Established criteria for VA-ECMO initiation are cardiac index below 2.2 L/min/m^2, plasma lactate above 4.0 mmol/L, progressive lactic acidosis unresponsive to conventional support, or hemodynamically significant arrhythmia [25,33]. Interhospital transfer to an ECMO-capable center should be arranged before refractory shock develops.

6.4. Antiviral and Immunomodulatory Therapy

No antiviral agent has demonstrated efficacy in controlled trials for HPS. Intravenous ribavirin was evaluated in two clinical trials and showed no benefit in either; most HPS deaths occur within 24 to 48 hours of hospital admission [39,40].

Favipiravir inhibits SNV and ANDV in vitro at a 90% effective concentration at or below 5 μg/mL, and significantly improves survival in the lethal ANDV Syrian hamster model when administered before viremia peaks [41]. Treatment initiated after viremia onset loses protective efficacy in this model. A 2021 in vitro study found comparable potency between ribavirin and favipiravir against Hantaan virus individually, with enhanced efficacy at reduced individual doses when combined [42].

High-dose intravenous methylprednisolone was evaluated in a double-blind, placebo-controlled randomized trial of 66 ANDV-associated HCPS patients in Chile. The composite primary endpoint was reached by 15 of 30 placebo-treated and 11 of 30 methylprednisolone-treated patients ($P = 0.43$); no significant survival benefit was demonstrated [43]. Methylprednisolone is not recommended for HCPS.

Recombinant human monoclonal antibodies targeting the ANDV Gn glycoprotein demonstrate potent neutralizing activity and protect against lethal ANDV challenge in the Syrian hamster model, providing a basis for future clinical evaluation [44].

7. Prognosis

The overall case fatality rate of HPS ranges from 30% to 50%. SNV-associated HPS carries a case fatality rate of approximately 36% in United States surveillance data spanning 1993 to 2023 [5]. ANDV-associated disease carries a 35% case fatality rate in the Vial et al. randomized trial cohort [44]. Plasma lactate above 4.0 mmol/L and cardiac index below 2.2 L/min/m^2 at presentation are the most reliable bedside predictors of death [25]. Multiorgan dysfunction is uncommon despite the severity of cardiopulmonary failure, which distinguishes HPS from other forms of viral septic shock. Survivors of the cardiopulmonary phase recover without permanent hepatic, renal, or neurological sequelae, though pulmonary function abnormalities have been documented in a minority [25].

8. Conclusions

HPS results from three converging mechanisms: increased microvascular permeability from $\alpha v\beta 3$ integrin dysregulation and VEGF hypersensitivity; immunopathology from CD8+ T cells and macrophages releasing cytokines that amplify vascular leak, cause PAI-1-mediated coagulopathy, and suppress myocardial contractility; and direct hantaviral myocarditis causing structural cardiac injury. These processes generate a cardiogenic-distributive shock refractory to conventional resuscitation alone.

A practical management algorithm follows from the pathophysiology. When HPS is suspected on clinical and epidemiological grounds, a complete blood count with peripheral blood smear and hantavirus IgM serology with concurrent RT-PCR should be obtained immediately. A four-of-five smear criterion score or a positive IgM result warrants ICU admission regardless of initial

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hemodynamic status. In the ICU, fluid resuscitation should be conservative, guided by EVLWI and PVPI on transpulmonary thermodilution, targeting correction of hypovolemia without worsening pulmonary edema. Serial plasma lactate and cardiac index should be measured at admission and every four to six hours thereafter. Contact with an ECMO-capable center should be initiated at the first appearance of any of the following: plasma lactate above 4.0 mmol/L, cardiac index below 2.2 L/min/m^2, refractory hypotension, hemodynamically significant arrhythmia, or rapid oxygenation failure. Transfer should not await cardiac arrest; VA-ECMO initiated before circulatory collapse is associated with substantially better survival [25,39].

Clinical management rests on three pillars: early recognition during the prodromal phase using the peripheral blood smear triage protocol; hemodynamic monitoring by transpulmonary thermodilution to guide fluid balance; and early VA-ECMO at first hemodynamic decompensation. No antiviral has been proven effective in the cardiopulmonary phase. Methylprednisolone was shown to be ineffective in a randomized controlled trial. Research priorities include antiviral treatment during the prodromal phase before viremia peaks, VEGF-VEGFR2-targeted permeability interventions, and expansion of VA-ECMO infrastructure in endemic regions.

Conflicts of Interest Statement: All authors declare no conflict of interest.

Data Availability Statement: No new data were generated or analyzed in support of this research.

References

1. MacNeil, A., Ksiazek, T. G., & Rollin, P. E. (2011). Hantavirus pulmonary syndrome, United States, 1993–2009. Emerging infectious diseases, 17(7), 1195. https://doi.org/10.3201/eid1707.101306
2. Duchin, J. S., Koster, F. T., Peters, C. J., Simpson, G. L., Tempest, B., Zaki, S. R., ... & Hantavirus Study Group. (1994). Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. New England Journal of Medicine, 330(14), 949-955. https://doi.org/10.1056/NEJM199404073301401
3. Jonsson, C. B., Figueiredo, L. T. M., & Vapalahti, O. (2010). A global perspective on hantavirus ecology, epidemiology, and disease. Clinical microbiology reviews, 23(2), 412-441. https://doi.org/10.1128/CMR.00062-09
4. Padula, P. J., Edelstein, A., Miguel, S. D. L., Lopez, N. M., Rossi, C. M., & Rabinovich, R. D. (1998). Hantavirus pulmonary syndrome outbreak in Argentina: molecular evidence for person-to-person transmission of Andes virus. Virology, 241(2), 323-330. https://doi.org/10.1006/viro.1997.8976
5. CDC. (2024, June 26). Reported Cases of Hantavirus Disease. Hantavirus. https://www.cdc.gov/hantavirus/data-research/cases/index.html
6. Epidemiological Alert Hantavirus Pulmonary Syndrome in Americas Region - 19 December 2025. (2025, December 19). Paho.org. https://www.paho.org/en/documents/epidemiological-alert-hantavirus-pulmonary-syndrome-americas-region-19-december-2025
7. Figueiredo, L. T. M., de Souza, W. M., Ferrés, M., & Enria, D. A. (2014). Hantaviruses and cardiopulmonary syndrome in South America. Virus research, 187, 43-54. https://doi.org/10.1016/j.virusres.2014.01.015
8. Goodfellow, S. M., Nofchissey, R. A., Ye, C., Banther-McConnell, J. K., Suriyamongkol, T., Cook, J. A., ... & Bradfute, S. B. (2025). A human pathogenic hantavirus circulates and is shed in taxonomically diverse rodent reservoirs. PLoS Pathogens, 21(1), e1012849. https://doi.org/10.1371/journal.ppat.1012849
9. Gavrilovskaya, I. N., Shepley, M., Shaw, R., Ginsberg, M. H., & Mackow, E. R. (1998). β3 integrins mediate the cellular entry of hantaviruses that cause respiratory failure. Proceedings of the National Academy of Sciences, 95(12), 7074-7079. https://doi.org/10.1073/pnas.95.12.7074
10. Gavrilovskaya, I. N., Brown, E. J., Ginsberg, M. H., & Mackow, E. R. (1999). Cellular entry of hantaviruses which cause hemorrhagic fever with renal syndrome is mediated by β3 integrins. Journal of virology, 73(5), 3951-3959. https://doi.org/10.1128/jvi.73.5.3951-3959.1999
11. Zaki, S. R., w Greer, P., Coffield, L. M., Goldsmith, C. S., Nolte, K. B., Foucar, K., ... & Peters, C. J. (1995). Hantavirus pulmonary syndrome: pathogenesis of an emerging infectious disease. The American journal of pathology, 146(3), 552.

 doi:10.20944/preprints202605.0912.v1

12. Nolte, K. B., Feddersen, R. M., Foucar, K., Zaki, S. R., Koster, F. T., Madar, D., ... & Zumwalt, R. E. (1995). Hantavirus pulmonary syndrome in the United States: a pathological description of a disease caused by a new agent. Human Pathology, 26(1), 110-120. https://doi.org/10.1016/0046-8177(95)90123-X
13. Gavrilovskaya, I. N., Gorbunova, E. E., Mackow, N. A., & Mackow, E. R. (2008). Hantaviruses direct endothelial cell permeability by sensitizing cells to the vascular permeability factor VEGF, while angiopoietin 1 and sphingosine 1-phosphate inhibit hantavirus-directed permeability. Journal of virology, 82(12), 5797-5806. https://doi.org/10.1128/jvi.02397-07
14. López, R., Pérez-Araos, R., Salazar, Á., Ulloa, A. L., Vial, C., Vial, P. A., & Graf, J. (2019). Hemodynamic and pulmonary permeability characterization of hantavirus cardiopulmonary syndrome by transpulmonary thermodilution. Viruses, 11(10), 900. https://doi.org/10.3390/v11100900
15. Meza-Fuentes, G., López, R., Vial, C., Cortes, L. J., Retamal, M. A., Delgado, I., & Vial, P. (2023). Assessing Pulmonary Epithelial Damage in Hantavirus Cardiopulmonary Syndrome: Challenging the Predominant Role of Vascular Endothelium through sRAGE as a Potential Biomarker. Viruses, 15(10), 1995. https://doi.org/10.3390/v15101995
16. Saavedra, F., Díaz, F. E., Retamal-Díaz, A., Covián, C., González, P. A., & Kalergis, A. M. (2021). Immune response during hantavirus diseases: implications for immunotherapies and vaccine design. Immunology, 163(3), 262-277. https://doi.org/10.1111/imm.13322
17. Hallin, G. W., Simpson, S. Q., Crowell, R. E., James, D. S., Koster, F. T., Mertz, G. J., & Levy, H. (1996). Cardiopulmonary manifestations of hantavirus pulmonary syndrome. Critical care medicine, 24(2), 252-258. https://doi.org/10.1097/00003246-199602000-00012
18. Simons, P., Guo, Y., Bondu, V., Tigert, S. L., Harkins, M., Goodfellow, S., ... & Buranda, T. (2021). Longitudinal assessment of cytokine expression and plasminogen activation in hantavirus cardiopulmonary syndrome reveals immune regulatory dysfunction in end-stage disease. Viruses, 13(8), 1597. https://doi.org/10.3390/v13081597
19. Terajima, M., Hayasaka, D., Maeda, K., & Ennis, F. A. (2007). Immunopathogenesis of hantavirus pulmonary syndrome and hemorrhagic fever with renal syndrome: Do CD8+ T cells trigger capillary leakage in viral hemorrhagic fevers?. Immunology letters, 113(2), 117-120. https://doi.org/10.1016/j.imlet.2007.08.003
20. Ennis, F. A., Cruz, J., Spiropoulou, C. F., Waite, D., Peters, C. J., Nichol, S. T., ... & Koster, F. T. (1997). Hantavirus pulmonary syndrome: CD8+ and CD4+ cytotoxic T lymphocytes to epitopes on Sin Nombre virus nucleocapsid protein isolated during acute illness. Virology, 238(2), 380-390. https://doi.org/10.1006/viro.1997.8827
21. Ma, H., Yang, Y., Nie, T., Yan, R., Si, Y., Wei, J., ... & Zhang, F. (2024). Disparate macrophage responses are linked to infection outcome of Hantan virus in humans or rodents. Nature Communications, 15(1), 438. https://doi.org/10.1038/s41467-024-44687-4
22. ondu, V., Bitting, C., Poland, V. L., Hanson, J. A., Harkins, M. S., Lathrop, S., ... & Buranda, T. (2018). Upregulation of P2Y2R, active uPA, and PAI-1 are essential components of hantavirus cardiopulmonary syndrome. Frontiers in cellular and infection microbiology, 8, 169. https://doi.org/10.3389/fcimb.2018.00169
23. Vapalahti, O., Mustonen, J., Lundkvist, Å., Henttonen, H., Plyusnin, A., & Vaheri, A. (2003). Hantavirus infections in Europe. The Lancet infectious diseases, 3(10), 653-661. https://doi.org/10.1016/S1473-3099(03)00774-6
24. Saggioro, F. P., Rossi, M. A., Duarte, M. I. S., Martin, C. C. S., Alves, V. A., Moreli, M. L., ... & Neder, L. (2007). Hantavirus infection induces a typical myocarditis that may be responsible for myocardial depression and shock in hantavirus pulmonary syndrome. The Journal of infectious diseases, 195(10), 1541-1549. https://doi.org/10.1086/513874
25. CDC. (2024, May 31). Clinician Brief: Hantavirus Pulmonary Syndrome (HPS). Hantavirus. https://www.cdc.gov/hantavirus/hcp/clinical-overview/hps.html
26. Young, J. C., Hansen, G. R., Graves, T. K., Deasy, M. P., Humphreys, J. G., Fritz, C. L., ... & Peters, C. J. (2000). The incubation period of hantavirus pulmonary syndrome. The American journal of tropical medicine and hygiene, 62(6), 714-717. https://doi.org/10.4269/ajtmh.2000.62.714

 doi:10.20944/preprints202605.0912.v1

27. Toro, J., Vega, J. D., Khan, A. S., Mills, J. N., Padula, P., Terry, W., ... & Ksiazek, T. G. (1998). An outbreak of hantavirus pulmonary syndrome, Chile, 1997. Emerging Infectious Diseases, 4(4), 687. https://doi.org/10.3201/eid0404.980425
28. Koster, F., Foucar, K., Hjelle, B., Scott, A., Chong, Y. Y., Larson, R., & McCabe, M. (2001). Rapid presumptive diagnosis of hantavirus cardiopulmonary syndrome by peripheral blood smear review. American journal of clinical pathology, 116(5), 665-672. https://doi.org/10.1309/CNWF-DC72-QYMR-M8DA
29. Dvorscak, L., & Czuchlewski, D. R. (2014). Successful triage of suspected Hantavirus cardiopulmonary syndrome by peripheral blood smear review. American Journal of Clinical Pathology, 142(2), 196-201. https://doi.org/10.1309/AJCPNFVWG46NUHED
30. Hjelle, B., Jenison, S., Torrez-Martinez, N., Herring, B., Quan, S., Polito, A., ... & Dinello, R. (1997). Rapid and specific detection of Sin Nombre virus antibodies in patients with hantavirus pulmonary syndrome by a strip immunoblot assay suitable for field diagnosis. Journal of clinical microbiology, 35(3), 600-608. https://doi.org/10.1128/jcm.35.3.600-608.1997
31. Hjelle, B., Jenison, S., Torrez-Martinez, N., Yamada, T., Nolte, K., Zumwalt, R., ... & Myers, G. (1994). A novel hantavirus associated with an outbreak of fatal respiratory disease in the southwestern United States: evolutionary relationships to known hantaviruses. Journal of Virology, 68(2), 592-596. https://doi.org/10.1128/jvi.68.2.592-596.1994
32. Feldmann, H., Sanchez, A., Morzunov, S., Spiropoulou, C. F., Rollin, P. E., Ksiazek, T. G., ... & Nichol, S. T. (1993). Utilization of autopsy RNA for the synthesis of the nucleocapsid antigen of a newly recognized virus associated with hantavirus pulmonary syndrome. Virus Research, 30(3), 351-367. https://doi.org/10.1016/0168-1702(93)90101-R
33. Ulloa-Morrison, R., Pavez, N., Parra, E., Lopez, R., Mondaca, R., Fernandez, P., ... & Kattan, E. (2024). Critical care management of hantavirus cardiopulmonary syndrome. A narrative review. Journal of critical care, 84, 154867. https://doi.org/10.1016/j.jcrc.2024.154867
34. López, R., Pérez-Araos, R., Salazar, Á., Espinoza, M., Vial, C., Cuiza, A., ... & Graf, J. (2021). Targeted high volume hemofiltration could avoid extracorporeal membrane oxygenation in some patients with severe Hantavirus cardiopulmonary syndrome. Journal of medical virology, 93(8), 4738-4747. https://doi.org/10.1002/jmv.26930
35. Bugedo, G., Florez, J., Ferres, M., Roessler, E., & Bruhn, A. (2016). Hantavirus cardiopulmonary syndrome successfully treated with high-volume hemofiltration. Revista Brasileira de Terapia Intensiva, 28, 190-194. https://doi.org/10.5935/0103-507X.20160032
36. Acute Respiratory Distress Syndrome Network. (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. New England Journal of Medicine, 342(18), 1301-1308. https://doi.org/10.1056/NEJM200005043421801
37. Cornejo, R., Ugalde, D., Llanos, O., Bisbal, P., De la Barrera, L., Romero, C., ... & Gajardo, J. (2013). Prone position ventilation used during a transfer as a bridge to ecmo therapy in hantavirus-Induced severe cardiopulmonary syndrome. Case Reports in Critical Care, 2013(1), 415851. https://doi.org/10.1155/2013/415851
38. Hernandez, F. A., Fritz, R., Sepúlveda, C., Gavilán, J., Espinoza, C., Ossandon, E., ... & Iturra, S. (2022). Impact of early ECMO support on survival of patients with Hantavirus cardiopulmonary syndrome in Chile. https://doi.org/10.1183/13993003.congress-2022.122
39. Mertz, G. J., Miedzinski, L., Goade, D., Pavia, A. T., Hjelle, B., Hansbarger, C. O., ... & Collaborative Antiviral Study Group. (2004). Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. Clinical infectious diseases, 39(9), 1307-1313. https://doi.org/10.1086/425007
40. Chapman, L. E., Mertz, G. J., Peters, C. J., Jolson, H. M., Khan, A. S., Ksiazek, T. G., ... & Ribavirin Study Group. (1999). Intravenous ribavirin for hantavirus pulmonary syndrome: safety and tolerance during 1 year of open-label experience. Antiviral therapy, 4(4), 211-219. https://doi.org/10.1177/135965359900400404
41. Safronetz, D., Falzarano, D., Scott, D. P., Furuta, Y., Feldmann, H., & Gowen, B. B. (2013). Antiviral efficacy of favipiravir against two prominent etiological agents of hantavirus pulmonary syndrome. Antimicrobial agents and chemotherapy, 57(10), 4673-4680. https://doi.org/10.1128/AAC.00886-13

 doi:10.20944/preprints202605.0912.v1

42. Mayor, J., Engler, O., & Rothenberger, S. (2021). Antiviral efficacy of ribavirin and favipiravir against hantaan virus. Microorganisms, 9(6), 1306. https://doi.org/10.3390/microorganisms9061306
43. Vial, P. A., Valdivieso, F., Ferres, M., Riquelme, R., Rioseco, M. L., Calvo, M., ... & Bedrick, E. (2013). High-dose intravenous methylprednisolone for hantavirus cardiopulmonary syndrome in Chile: a double-blind, randomized controlled clinical trial. Clinical infectious diseases, 57(7), 943-951. https://doi.org/10.1093/cid/cit394
44. Garrido, J. L., Prescott, J., Calvo, M., Bravo, F., Alvarez, R., Salas, A., ... & Barria, M. I. (2018). Two recombinant human monoclonal antibodies that protect against lethal Andes hantavirus infection in vivo. Science translational medicine, 10(468), eaat6420. https://doi.org/10.1126/scitranslmed.aat6420