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Review article

Hantavirus infection: A narrative review focusing on epidemiology, diagnosis, infection control and treatment in the era of globalisation

Infección por Hantavirus: una revisión narrativa centrada en epidemiología, diagnóstico, control de infecciones y tratamiento en la era de la globalización

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ABSTRACT

Hantavirus infection remains a major challenge in intensive care medicine because of its rapid progression, high mortality, and limited therapeutic options. This narrative review summarizes current evidence regarding the epidemiology, diagnosis, infection control, and critical care management of hantavirus cardiopulmonary syndrome (HCPS), with particular focus on Andes virus (ANDV) infection in South America. Hantaviruses are zoonotic RNA viruses transmitted mainly through inhalation of aerosolized rodent excreta. Unlike other hantaviruses, ANDV has demonstrated sustained person-to-person transmission, particularly in Argentina and Chile, creating important implications for infection prevention and hospital isolation measures.

HCPS is characterized by a prodromal febrile phase followed by abrupt cardiopulmonary deterioration with non-cardiogenic pulmonary edema, shock, and respiratory failure. Early recognition is essential and relies on epidemiological exposure combined with laboratory findings such as thrombocytopenia, hemoconcentration, neutrophilia, immunoblasts in peripheral blood, and elevated lactate dehydrogenase. Confirmatory diagnosis is based on serology and RT-qPCR.

Management remains primarily supportive. Careful fluid administration, vasopressor support, invasive mechanical ventilation with lung-protective strategies, and early transfer to experienced intensive care units are critical. Venous-arterial extracorporeal membrane oxygenation (VA-ECMO) has emerged as a potentially lifesaving therapy in refractory cases, with encouraging survival outcomes in specialized centers. Current evidence does not support routine corticosteroid use, although they may be considered in selected patients with acute respiratory distress syndrome. Ribavirin has not demonstrated benefit during the cardiopulmonary phase, whereas convalescent plasma remains a promising but still investigational therapy. Prevention, rapid diagnosis, strict infection control, and timely organ support remain the cornerstones of HCPS management.

RESUMEN

La infección por hantavirus sigue siendo un gran desafío en la medicina intensiva debido a su rápida progresión, alta mortalidad y opciones terapéuticas limitadas. Esta revisión narrativa resume la evidencia actual sobre la epidemiología, diagnóstico, control de infecciones y manejo de cuidados críticos del síndrome cardiopulmonar por hantavirus (HCPS), con especial atención a la infección por el virus de los Andes (ANDV) en Sudamérica. Los hantavirus son virus de ARN zoonóticos transmitidos principalmente por inhalación de excrementos aerosolizados de roedores. A diferencia de otros hantavirus, ANDV ha demostrado una transmisión de persona a persona,

especialmente en Argentina y Chile, lo que genera importantes implicaciones para la prevención de infecciones y las medidas de aislamiento hospitalario.

El HCPS se caracteriza por una fase febril prodrómica seguida de un deterioro cardiopulmonar abrupto con edema pulmonar no cardiogénico, shock e insuficiencia respiratoria. El reconocimiento temprano es esencial y depende de la exposición epidemiológica combinada con hallazgos de laboratorio como trombocitopenia, hemoconcentración, neutrofilia, inmunoblastos en la sangre periférica y elevación de lactato deshidrogenasa. El diagnóstico confirmatorio se basa en la serología y la RT-qPCR.

El tratamiento sigue siendo principalmente de apoyo. La administración cuidadosa de líquidos, el soporte vasopresor, la ventilación mecánica invasiva con estrategias de protección pulmonar y el traslado temprano a unidades de cuidados intensivos experimentadas son fundamentales. La oxigenación veneoarterial por membrana extracorpórea (VA-ECMO) ha surgido como una terapia potencialmente salvavidas en casos refractarios, con resultados de supervivencia alentadores en centros especializados. La evidencia actual no respalda el uso rutinario de corticoides, aunque pueden considerarse en pacientes seleccionados con síndrome agudo de dificultad respiratoria. La ribavirina no ha demostrado beneficio durante la fase cardiopulmonar, mientras que el plasma convaleciente sigue siendo una terapia prometedora pero aún en proceso de investigación. La prevención, el diagnóstico rápido, el control estricto de infecciones y el apoyo puntual de los órganos siguen siendo las bases del manejo del HCPS.

Epidemiology

Hantaviruses belong to the family *Hantaviridae*, order *Bunyvirales*, and represent a globally distributed group of zoonotic RNA viruses with rodents as their natural reservoir. In the Americas (New World hantaviruses), the predominant clinical syndrome is Hantavirus cardiopulmonary syndrome (HCPS), which carries a significantly higher case fatality rate than haemorrhagic fever with renal syndrome (HFRS), the form endemic (Old World hantaviruses) to Europe and Asia.^{1,2} Transmission to humans occurs primarily through inhalation of aerosol particles contaminated with the urine, saliva, or faeces of infected rodents, with additional routes including mucous membrane contact and ingestion of contaminated foodstuffs.³

The predominant causative agent of HCPS in South America is Andes virus (ANDV) and closely related genotypes. ANDV is unique among hantaviruses globally in demonstrating this capacity for sustained interhuman transmission, documented repeatedly in both Argentina and Chile through epidemiological and virological evidence.^{4–6} Despite this evidence, a systematic review has proposed that most studies are subject to bias, mainly due to coexisting environmental exposure. The affected population is predominantly young adult males, reflecting occupational exposures.⁷ Risk groups include construction workers, agricultural labourers, and tourists visiting endemic areas, with no demonstrable seasonal predominance in ICU-admitted patients, though winter months showed a relative reduction in incidence.⁷ Additionally, close contacts of primary cases show an increased risk of developing the disease.⁸

The health crisis associated with hantavirus that we are experiencing has, once again, highlighted the risk of the global emergence of infectious diseases and the need to strengthen epidemiological surveillance systems, translational research, and international cooperation in public health. In particular, within the field of intensive care medicine, hantavirus infection represents a growing challenge due to the high mortality associated with hantavirus cardiopulmonary syndrome and its rapid clinical progression.

Diagnosis

The incubation period varies from 7 to 49 days, with most cases presenting after 2–4 weeks following exposure. The clinical course of HCPS evolves through four phases: a prodromal febrile phase lasting a median of 6 days (range 3–15), followed by the cardiopulmonary, diuretic, and convalescent phases.⁷ The absence of upper respiratory tract symptoms during the prodrome, combined with rapid haemodynamic deterioration, distinguishes HCPS from community-acquired pneumonia and other atypical pneumonic illnesses.³

Laboratory findings are central to early presumptive diagnosis, particularly in resource-limited settings where serological confirmation

may be delayed. The combination of thrombocytopenia, neutrophilia, haemoconcentration, the presence of immunoblasts (>10% of total leucocytes) on peripheral blood, and absence of toxic granulation in the myeloid series achieves a sensitivity of 96% and specificity of 99% for HCPS.³ Elevated lactate dehydrogenase (LDH) is the most consistently abnormal parameter⁷ and hypoalbuminaemia (<3.5 g/dL) was present in 90.9% of patients, reflecting endothelial permeability and systemic inflammation.⁷ A platelet count below 40,000 cells/mm³ at ICU admission has been associated with a significantly higher risk of progression to severe HCPS and death.⁷ The presence of proteinuria in urine test is associated to a worst prognosis too.⁹

Confirmatory diagnosis is based on the detection of specific IgM antibodies against hantavirus in acute-phase serum using an enzyme-linked immunosorbent assay (ELISA), or on an increase in IgG titres. IgG titres can persist for years, and their absence in the context of fulminant disease may be an indicator of a poor prognosis.³ RT-qPCR in serum or clotted blood samples can yield positive results up to 7–10 days after the onset of symptoms and is particularly valuable for early confirmation during the prodromal phase.³

Prevention and isolation precautions

Environmental exposure avoidance remains the cornerstone of primary prevention, given the absence of a licensed vaccine. Rodent population control, airtight food storage, adequate ventilation of premises in endemic areas, and the use of personal protective equipment (PPE) during high-risk activities (cleaning rodent-infested spaces, agricultural work) and providing information or advisories to tourists in endemic areas constitute the principal public health recommendations^{1,3} (Fig. 1).

The unique capacity of ANDV and Buenos Aires/Hu39694 genotypes to transmit between persons has profound implications for infection control in healthcare settings, and this represents one of the most contentious areas in current practice.³ The US Centers for Disease Control and Prevention recommends standard precautions for hantavirus infections in North America, where person-to-person transmission has not been documented. However, this approach is insufficient for clinical settings in central and southern Argentina, where ANDV-South and Buenos Aires/Hu39694 circulate.³

For patients with suspected or confirmed ANDV or Buenos Aires/Hu39694 infection, current Argentine and Chile expert guidance recommends airborne/respiratory isolation in a single-occupancy room, preferably with negative pressure and a minimum of 12 air changes per hour, or with portable HEPA filtration units.³ Healthcare workers should enter the patient's room wearing an FFP2/N95 respirator; when contact with body fluids is anticipated, full barrier precautions (gown, eye protection, gloves, disposable medical cap and disposable shoe covers) are additionally required. For patients receiving invasive mechanical



Fig. 1. Key recommendations on hantavirus isolation, prevention and treatment.

ventilation, 99.9% filtration on the expiratory limb and closed-suction systems are recommended to minimise aerosol generation.³ Visitor access should be restricted to one person at a time, each wearing a continuous N95 respirator. Clinical experience in Chile (unpublished data) during the early nineties, when diagnosis was not known in the country, did not demonstrate transmission to health-care workers with standard precautions.¹⁰ Afterwards, when person to person transmission was recognized, most intensive care units implemented droplet precautions or airborne precautions for at least one week. Nosocomial transmission was demonstrated in standard facilities of a low-complexity hospital.⁶

For patients infected with hantavirus from northern Argentina and Chile to North America and European Union, specifically in regions where human-to-human transmission has not been demonstrated, standard precautions combined with droplet precautions (guided by the clinical differential diagnosis, e.g., influenza) are considered appropriate until a specific hantavirus diagnosis is confirmed.³ The Epuéyén outbreak demonstrated conclusively that prompt isolation of index cases and quarantine of contacts, when implemented within a defined transmission chain, substantially reduces the effective reproductive number and curtails further spread.⁴

The potential for vertical and breast milk transmission of ANDV represents an emerging concern. A Chilean case report documented RT-qPCR-positive breast milk and subsequent neonatal death attributed to ANDV acquired via breastfeeding; experts have recommended deferral of breastfeeding until ANDV RNA is undetectable in both blood and breast milk in the southern region, though robust evidence to guide a definitive universal recommendation remains absent.³

Treatment and organ support

There is no licensed antiviral therapy for HCPS, and the management of all patients admitted to the ICU is currently supportive.^{1,3,7} The hemodynamic phenotype of HCPS differs from both cardiogenic and septic shock, and is characterized by a combination of hypovolaemia, systolic dysfunction and increased capillary permeability, leading to non-cardiogenic pulmonary oedema. Therefore, careful fluid management is essential to avoid volume overload¹; nonetheless, the optimal parameters to guide fluid management remain undefined. Almost half of patients require vasoactive support, and all patients who died require both mechanical ventilation and vasopressors, compared with only 34.6% of survivors.⁷

With regard to corticosteroids, the only randomised controlled trial comparing high-dose intravenous methylprednisolone with a placebo in acute multiple organ failure syndrome (HCPS), conducted in Chile, showed a non-significant reduction in mortality in the treatment group, with an acceptable safety profile; however, corticosteroids were only administered for 72 h.³ Current consensus does not support routine corticosteroid use in HCPS; however, they may be considered in patients fulfilling criteria for ARDS (PaO₂/FiO₂ ≤300), and should be administered early and in the context of concurrent clinical monitoring.³

Convalescent plasma enriched with neutralising antibodies represents the most promising disease-specific therapeutic approach currently available. The largest published open-label multicentre trial from Chile, enrolling 29 HCPS patients who received neutralising antibody units at 5000 IU/kg, demonstrated 30-day mortality of 14% compared with 32% in untreated historical controls, with borderline statistical significance (p = 0.049).³ Chilean health guidelines recommend convalescent plasma for all confirmed or suspected HCPS cases, with doubling of the dose in patients requiring veno-arterial extracorporeal membrane oxygenation (VA-ECMO).³

Ribavirin, an antiviral nucleoside analogue with demonstrated efficacy against Old World hantaviruses (Hantaan, Puumala) in haemorrhagic fever with renal syndrome when administered before day 6 of illness, has not shown benefit in the cardiopulmonary phase of HCPS.³ At present, ribavirin may only be indicated during the prodromal phase of the disease and in research studies.

VA-ECMO has emerged as a potentially life-saving salvage therapy for refractory HCPS. An evaluation of 51 patients with predicted 100% mortality who received ECMO demonstrated survival in 34 (67%), with complete recovery.¹ Timely escalation to ECMO (ideally at a centre with established expertise) must be anticipated early in the clinical course, as deterioration can occur within hours.⁷ In Chile, similarly, an observational study including 47 patients transferred to a hospital in Santiago where ECMO was available, including 17 patients connected to early VA-ECMO support showed a global hospital survival of 89.4%.¹¹

Conclusion

Hantavirus infection, and in particular HCPS, remains one of the most serious viral infections encountered in the ICU. The illness is marked by a rapid clinical deterioration, high mortality rates and the absence of an established antiviral treatment. Recent advances have led to a better understanding of the specific epidemiology of the Andes virus, particularly its capacity for person-to-person transmission, whilst improvements in intensive care management and ECMO support have contributed to increased survival rates in specialist centres. However, significant controversies remain regarding optimal infection control measures, the role of corticosteroids and antiviral treatment, and the potential utility of immunomodulatory strategies such as convalescent plasma. Early recognition, immediate transfer to the ICU, meticulous organ support and rigorous public health surveillance remain the cornerstones of current treatment.

Declaration of Generative AI and AI-assisted technologies in the writing process

Artificial intelligence was used solely for the linguistic and spelling revision of the manuscript and for the creation of the figure included therein.

Declaration of competing interest

None of the authors of this manuscript has any conflict of interest related to the subject addressed herein.

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