Clinical Management on Hantavirus Infection

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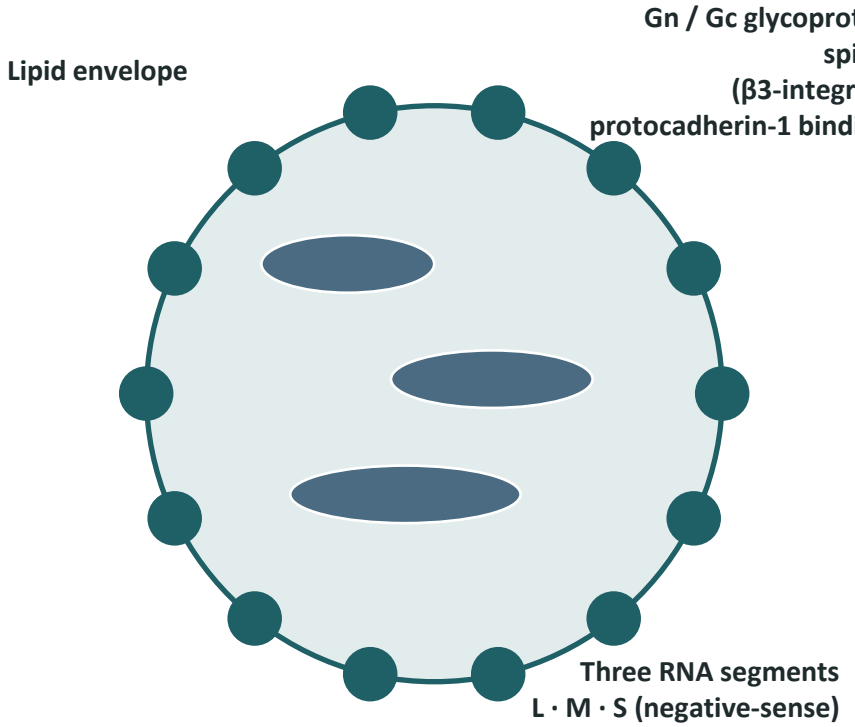
Hantavirus virion — schematic structure



Genome segments

Seg	Encodes	Function
L	RNA-dep RNA polymerase	Replication, transcription
M	Gn / Gc glycoproteins	Cell entry; neutralising-antibody target
S	Nucleocapsid (N) protein	RNA encapsidation; main serology antigen

Hantaviruses at a glance

Family

Hantaviridae, genus Orthohantavirus, order Bunyavirales. ≥40 species; ~22 pathogenic to humans.

Entry receptors

β3-integrins on endothelium and platelets (pathogenic strains); protocadherin-1 for New-World HCPS viruses, directing lung tropism.

Two syndromes

HFRS (Old World — Eurasia) and HCPS / HPS (New World — Americas). Same family, distinct clinical phenotype.

Haemorrhagic fever with renal syndrome (HFRS)
Hantavirus cardiopulmonary syndrome (HCPS)
Hantavirus pulmonary syndrome (HPS)

Pathogenesis: Viral Entry Mechanism

Endothelial Tropism: The virus primarily targets vascular endothelial cells.

The Endothelial Target & Integrity

Unlike many hemorrhagic viruses (e.g., Ebola), hantaviruses are NOT cytopathic.

There is no necrosis or direct viral destruction of the infected endothelial cells.

Vascular structures remain anatomically intact.

Functional Disruption:

- Infection causes down-regulation of VE-cadherin, weakening cell-to-cell tight junctions.
- Results in a profound, reversible increase in vascular permeability (pure capillary leak).

The Capillary Leak Syndrome

The hallmark of severe hantavirus disease is dramatic fluid extravasation.

Starling Forces Alteration:

- High-protein fluid leaks from the intravascular space into the interstitium and alveoli.
- Creates a devastating mismatch: Intravascular hypovolemia combined with tissue fluid overload.

Clinical Manifestations:

- Hemoconcentration (Hematocrit > 50%).
- Hypoalbuminemia, generalized edema, and profound distributive shock.

Pathogen and syndrome mapping

Old-World hantaviruses

mainly HFRS — Eurasia

Hantaan virus (HTNV)

Striped field mouse · Apodemus agrarius

CFR 5–15%

Dobrava–Belgrade

Yellow-necked mouse · Apodemus flavicollis

CFR up to 12%

Seoul virus (SEOV)

Brown rat · Rattus norvegicus — urban worldwide

CFR 1–2%

Puumala virus

Bank vole · Myodes glareolus

CFR <1%

New-World hantaviruses

mainly HCPS — Americas

Sin Nombre virus (SNV)

North American deer mouse · Peromyscus

CFR ~30-50%

Andes virus (ANDV)

Long-tailed pygmy rice rat · Oligoryzomys longicaudatus

CFR 30-50%; person-to-person

Laguna Negra

Vesper mouse · Calomys laucha

HCPS · CFR variable

Choclo, Maripa, Juquitiba…

Multiple cricetid reservoirs

HCPS; variable CFR

Hantaviruses are geographically restricted by their specific rodent reservoir hosts.

Reservoirs and global distribution

Region	Virus	Reservoir	Syndrome
East Asia (China, Korea)	Hantaan; Seoul	*Apodemus agrarius; Rattus norvegicus*	HFRS
Russia / Balkans / N. Europe	Dobrava–Belgrade; Puumala	*Apodemus flavicollis; Myodes glareolus*	HFRS
Worldwide (urban rats)	**Seoul**	***Rattus norvegicus***	**HFRS (often milder)**
North America	Sin Nombre; Bayou; New York	*Peromyscus spp.; Oryzomys palustris*	HCPS
South America (Andes region)	Andes virus	*Oligoryzomys longicaudatus*	HCPS · person-to-person
Brazil / Bolivia / Paraguay	Juquitiba; Laguna Negra; Castelo de Sonhos	*Multiple cricetids*	HCPS

Transmission — rodent excreta and the Andes-virus exception

Inhalation of aerosolised excreta

Urine, faeces, saliva in enclosed spaces — cabins, sheds, barns, ship cabins.

Direct mucous-membrane contact

Touching excreta or contaminated objects, then face/eyes/mouth.

Bite or scratch (rare)

Documented in pest-control and laboratory workers.

Contaminated food / water

Less common; described in some HFRS outbreaks.

Andes virus — person-to-person

- Only hantavirus with documented person-to-person spread.
- Close, prolonged contact — household, intimate, shared transport.

Incubation Period

HFRS: typically, 7–14 days (range up to 8 weeks).

HCPS: 1–8 weeks, median approximately 2–3 weeks.

For Andes virus specifically: 1-6 weeks (with longer incubation reported rarely), most commonly reported between 2-4 weeks (median 18 days), according to WHO specific guideline.

Case definition and notification of Andes virus infection

- Definition of suspected cases
  - Compatible symptoms (including fever and/or myalgia, headache, fatigue, GI distress, or respiratory symptoms) AND
  - Relevant exposure history within the last 42 days (=6 weeks), including either:
    - (i) travel on the cruise ship 'MV Hondius' since April 1, 2026; or
    - (ii) close contact with symptomatic passengers/crew members from this ship; or
    - (iii) contact with a confirmed Andes hantavirus patient

- Notify via NDORS, inform MCO/CHP (9260 7090) & ICT

Clinical Manifestation

- Clinical presentation ranges from asymptomatic or mild febrile illness to severe, life- threatening disease. Most infections begin with fever, headache, myalgia and gastrointestinal symptoms; subsequent organ involvement differentiates HFRS from HCPS

HFRS Phase 1: Febrile Phase

Timeline: Days 3 to 7

Presentation: Abrupt onset of high fever, chills, severe retro-orbital headache.

Pathognomonic Signs: Severe lower back pain (renal capsule stretching) and intense facial flushing/conjunctival injection.

Lab Derangements:

- Rapid drop in platelet count.
- Appearance of petechiae on the soft palate and axillae.

The initial cytokine cascade is underway, setting up the impending capillary leak.

HFRS Phase 2: Hypotensive Phase

Timeline: Lasts a few hours to 3 days.

Pathophysiology: Maximum onset of vascular permeability.

Clinical Findings:

- Tachycardia, falling blood pressure, and progression to frank shock.
- Marked hemoconcentration and rising hematocrit.
- One-third of HFRS fatalities occur here due to irreversible cardiovascular collapse.

Management: Requires highly cautious fluid resuscitation and early vasopressors.

HFRS Phase 3: Oliguric Phase

Timeline: Days 3 to 7

Renal Pathology: Acute tubulointerstitial nephritis and renal medullary hemorrhage.

Clinical Findings:

- Urine output drops dramatically (< 400 mL/day).
- BUN and Creatinine spike.
- Severe risk of hyperkalemia, metabolic acidosis, and fluid overload.

Fatal Pitfall: Over-resuscitation during the hypotensive phase leads to acute pulmonary edema during this oliguric phase.

Renal Replacement Therapy (RRT)

Crucial intervention during the Oliguric phase of HFRS.

Indications for Early RRT:

- Refractory fluid overload (especially if pulmonary edema develops).
- Severe hyperkalemia or intractable metabolic acidosis.
- Uremic encephalopathy or pericarditis.

Modality: Continuous Renal Replacement Therapy (CRRT) is strongly preferred over intermittent hemodialysis due to profound hemodynamic instability.

HFRS Phase 4: Polyuric Phase

Timeline: days to weeks.

Pathophysiology: Renal tubular regeneration begins, but tubules cannot yet concentrate urine.

Clinical Findings:

- Massive diuresis ensues (urine output 3 to 6 Liters per day).
- Edema resolves, but patient is at extremely high risk for hypovolemic shock.
- Life-threatening electrolyte shifts (profound hypokalemia and hyponatremia).

Management: Rigorous matching of urinary output with IV fluid and electrolyte replacement.

HFRS Phase 5: Convalescent Phase

Timeline: Lasts several weeks to months.

Clinical Findings:

- Gradual return of normal urine concentrating ability and resolution of anemia.
- Prolonged asthenia (weakness) and fatigue are common.

Long-Term Sequelae:

- While most recover completely, severe cases (esp. Dobrava virus) carry a long-term risk of Chronic Kidney Disease (CKD).
- Persistent hypertension is reported in a subset of survivors.

HFRS: Diagnostic Laboratory Profile

Hematology:

- Profound thrombocytopenia (<50k is common).
- Leukocytosis with a prominent left shift and atypical lymphocytes.
- Elevated Hematocrit due to plasma leak.

Renal & Chemistry:

- Rapidly rising Cr/BUN, hyponatremia.
- Mild to moderate AST/ALT elevations.

Urinalysis:

- Massive proteinuria (often nephrotic range early on).
- Microscopic hematuria is nearly universal.

HCPS/HPS: Disease Overview

Case Fatality Rate: Historically >50%, currently 30-40% with advanced ICU/ECMO care.

Leading Cause of Death: Intractable cardiogenic shock and pulseless electrical activity (PEA), NOT simply refractory hypoxemia.

Disease course is frighteningly rapid, progressing from mild symptoms to death in 24-48 hours.

HCPS: The Prodromal Phase

Timeline: Lasts 2 to 8 days.

Symptoms: Highly non-specific, mimicking a severe flu-like illness.

- Fever, severe myalgias (especially large muscle groups like back/thighs).
- Gastrointestinal symptoms (nausea, vomiting, diarrhea) occur in ~50% of patients.

Critical Distinctions:

- Coryza, sore throat, and productive cough are typically ABSENT initially.
- Early labs show thrombocytopenia, which should prompt immediate suspicion in endemic areas.

HCPS: Cardiopulmonary Decompensation

Timeline: Onset is extremely rapid (hours).

Clinical Findings:

- Abrupt onset of dry cough, dyspnea, and tachypnea.
- Rapid development of massive non-cardiogenic pulmonary edema.
- Copious frothy airway secretions (high protein content).

Radiography:

- Initially interstitial edema (Kerley B lines) rapidly progressing to dense bilateral alveolar infiltrates.
- Pleural effusions are common; cardiomegaly is typically absent.

Imaging for HCPS — pulmonary oedema, ARDS pattern

Chest radiograph

- Diffuse bilateral interstitial or alveolar infiltrates
- Kerley B lines; perihilar bat-wing pattern
- Small pleural effusions common
- Heart size usually normal (noncardiogenic oedema)

HRCT

- Ground-glass opacities
- Smooth interlobular septal thickening
- Areas of consolidation in severe disease

Echocardiography

- Global LV hypokinesis common in severe HCPS
- Reduced ejection fraction
- Pulmonary capillary wedge pressure normal or low
- **Cardiac index often <2.5 L/min/m² — ECMO trigger**

Specific complications of HCPS

Pulmonary: ARDS, respiratory failure.
Cardiovascular: shock, arrhythmias.
Renal: AKI requiring dialysis.
Ocular: retinal haemorrhage, optic neuritis.
Neurologic: encephalopathy, seizures (especially ANDV).
ENT: sensorineural hearing loss.
Coagulation: DIC (especially ANDV).

Laboratory profile for HCPS — the “five-criteria” smear

Peripheral smear (Mertz et al.)

In patients with pulmonary oedema, ≥4 of 5 had 96% sensitivity and 99% specificity for HCPS.

1. Thrombocytopenia
2. Left-shifted myeloid lineage
3. Lack of neutrophil toxic granulation
4. >10% immunoblasts among lymphoid cells
5. Haemoconcentration (elevated haematocrit)

Supporting laboratory clues

- Elevated LDH (often early)
- Mild–moderate transaminase rise
- Hypoalbuminaemia, hyponatraemia
- Rising serum lactate
- Elevated creatinine, proteinuria, haematuria (if renal involvement)
- Coagulopathy (especially ANDV)

Specimen and confirmatory testing of Hantavirus Infection

Test	Sample	Timing	What it does
IgM-capture ELISA	Serum (acute + convalescent)	Often positive by day 3–5 of illness	First-line confirmatory test; high specificity with N antigen
IgG ELISA	Paired sera	Four-fold rise in convalescent sample	Supports diagnosis; useful for retrospective cases
RT-PCR (S segment)	EDTA blood / buffy coat; tissue	Prodrome through early convalescence	Detects RNA; enables typing (ANDV vs SNV vs Hantaan)
Immunohistochemistry	Autopsy; lung / kidney	Post-mortem	Demonstrates N antigen in capillary endothelium

Blood x RT-PCR: most useful early as viremia typical clears within 7-10 days

Diagnostic Triage & Clinical Triggers

Do NOT wait for serologic confirmation to initiate life-saving ICU care.

Triage Triggers for Immediate ICU Transfer:

- Rising respiratory rate or new oxygen requirement.
- Dropping platelet count or rising hematocrit on serial labs.
- Hypotension or rising serum lactate.
- Oliguria.

Action: Admit to ICU, secure central access, prepare for intubation, and consult ECMO early.

The Fluid Paradox in Hantavirus

The most challenging aspect of hantavirus critical care is fluid management.

The Paradox: Patients present with hypotension and intravascular depletion, yet have massive total-body fluid overload (leaking into lungs).

The 'Dry' Strategy:

- Aggressive crystalloid boluses (e.g., 30cc/kg sepsis bundles) are highly lethal and rapidly worsen pulmonary edema.
- Administer only small, cautious fluid aliquots (250 mL).
- Assess fluid responsiveness strictly via dynamic measures (POCUS, SVV, pulse pressure variation).

Vasoactive and Inotropic Support

Because fluids must be restricted, vasoactive support must be initiated early.

First-Line Vasopressor: Norepinephrine.

- Supports vascular tone and maintains MAP without excessive tachycardia.

Inotropic Support: Dobutamine.

- Indicated for patients with low cardiac index / cardiogenic shock.
- Helps overcome the elevated SVR and depressed myocardium.

Mechanical Ventilation Strategies

Intubate early before catastrophic hypoxia and cardiac arrest occur.

Lung-Protective Ventilation (ARDSnet Protocols):

- Low Tidal Volume: 6 mL/kg of Ideal Body Weight.
- Plateau Pressure Goal: Keep < 30 cmH2O to prevent barotrauma.
- PEEP Optimization: Titrate PEEP to maintain oxygenation, but monitor for worsened hypotension due to decreased venous return.
- Permissive hypercapnia is acceptable to protect the lungs.

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is the ultimate rescue therapy for severe HCPS.

Rationale: Temporizes the patient, providing complete cardiac and respiratory support while waiting for the capillary leak to spontaneously resolve (usually 3-5 days).

Modality: Veno-Arterial (VA) ECMO is required for severe HCPS with cardiac dysfunction.

- Veno-Venous (VV) ECMO provides oxygenation but NO cardiac support.
- Because HCPS involves cardiogenic shock, VA ECMO is mandatory to maintain systemic perfusion.

ECMO: Patient Selection & Timing

Timing is everything. Delayed cannulation guarantees mortality.

Triggers for ECMO Cannulation:

- Cardiac Index < 2.2 L/min/m^2 despite inotropes.
- Rising serum lactate (> 4.0 mmol/L).
- Refractory hypoxemia (PaO2/FiO2 ratio < 80).
- Escalating doses of multiple vasopressors.

Action: Contact regional ECMO centers as soon as HCPS is suspected. Do not wait for shock to deepen.

Antivirals and adjunctive therapies for HFRS and HCPS

Therapy	Evidence	Practical stance
Ribavirin (HFRS)	RCT — 7-fold mortality reduction vs placebo (Hantaan virus)	Recommended for severe Hantaan HFRS, especially early
Ribavirin (HCPS)	Underpowered open-label & RCT; no clear 28-day survival benefit	Not recommended
Methylprednisolone (HCPS)	Chilean double-blind RCT — no mortality reduction	Not recommended
Convalescent plasma (ANDV)	Non-randomised Chilean study — CFR 14% vs 32% (OR 0.35)	Promising; access limited; bias and small numbers
Monoclonal antibodies Broadly neutralising mAbs targeting Gn/Gc	Preclinical efficacy; phase-I anti-Hantaan trial	No approved product as of May 2026

Current vaccine status for HFRS and HCPS

No licensed vaccine for HCPS-causing viruses (ANDV, SNV) as of May 2026.

HFRS vaccines in use: Hantavax (Korea, formalin-inactivated Hantaan) for military; bivalent Hantaan/Seoul (China) for endemic provinces.

DNA vaccines for Hantaan and Puumala have completed phase I trials; phase II ongoing.

No hantavirus vaccine is approved in Europe, the US, or Hong Kong.