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Review

Clinical Features, Mechanisms, and Renal Outcomes of Hantavirus-Associated Kidney Injury: A Narrative Review

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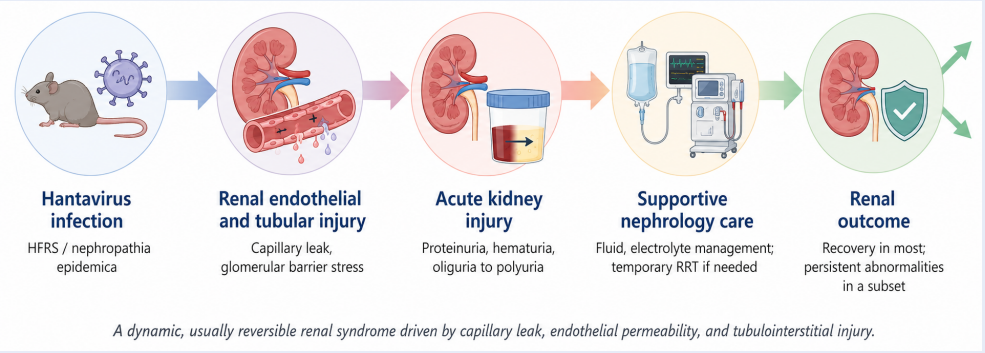
ABSTRACT

Hantavirus infection is an underrecognized infectious etiology of acute kidney injury (AKI), with hemorrhagic fever with renal syndrome (HFRS) defining its dominant renal phenotype. Kidney involvement spans from transient urinary abnormalities to severe AKI with oliguria, electrolyte and acid-base disturbances, and a requirement for temporary renal replacement therapy in selected cases. Available clinicopathologic and translational evidence supports an integrated model in which tubulointerstitial injury, microvascular inflammation, tubular epithelial stress, glomerular barrier disruption, and hemodynamic vulnerability interact dynamically to produce an acute, albeit typically reversible, form of kidney injury. Clinical management remains supportive but requires structured vigilance: meticulous assessment of volume status, urine output, electrolytes, acid-base balance, blood pressure, bleeding risk, and the evolving phase of illness is essential for optimal nephrology care. Complete functional renal recovery is common—particularly in nephropathia epidemica and other survivable forms of HFRS—yet normalization of serum creatinine does not consistently equate to full physiologic recovery. Persistent proteinuria, hematuria, hypertension, or subtle tubular dysfunction may occur in subsets of patients, although large long-term cohorts indicate that progressive chronic kidney disease is not the typical outcome. A robust clinicopathologic framework integrating urinary sediment findings, AKI severity staging, renal histopathology, phase-oriented supportive care, and risk-stratified post-discharge follow-up can significantly enhance the clinical recognition and management of hantavirus-associated kidney injury in daily practice.

GRAPHICAL ABSTRACT



A dynamic, usually reversible renal syndrome driven by capillary leak, endothelial permeability, and tubulointerstitial injury.

Key words: Hantavirus, acute kidney injury, hemorrhagic fever with renal syndrome, nephropathia epidemica, proteinuria, tubulointerstitial nephritis, renal replacement therapy

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INTRODUCTION

Hantavirus infection occupies a distinctive position in clinical nephrology. Whereas acute kidney injury (AKI) in most viral diseases occurs as a downstream consequence of sepsis, systemic hemodynamic compromise, or nephrotoxin exposure, in hemorrhagic fever with renal syndrome (HFRS)—and in nephropathia epidemica (NE), its milder European expression—kidney injury constitutes a defining, central feature of the pathogenesis [1,2]. Patients typically present with abrupt onset of fever, flank or abdominal pain, thrombocytopenia, capillary leak, urinary abnormalities, and rapidly deteriorating kidney function. Globally, hantavirus causes an estimated 150,000–200,000 cases of HFRS annually. China and Korea account for the largest documented burden, driven predominantly by Hantaan and Seoul viruses, whereas Puumala virus is respon-

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sible for NE across Northern and Central Europe, and Dobrava-Belgrade virus drives more severe disease in the Balkans [3–5].

Viral species, geographical distribution, and host factors collectively dictate clinical severity. Hantaan and Dobrava-Belgrade viruses are associated with severe HFRS; Puumala virus with NE; and Seoul virus with a globally distributed, generally milder renal syndrome [2,4,6]. For the consulting nephrologist, the diagnosis of HFRS must be translated into phase-specific risk stratification: oliguria, dialysis necessity, bleeding diathesis, electrolyte derangement, and recovery trajectory (Table 1). The differential diagnosis of febrile AKI accompanied by thrombocytopenia and hematuria is broad, encompassing sepsis-associated AKI, leptospirosis, severe fever with thrombocytopenia syndrome, thrombotic microangiopathy, acute glomerulonephritis, systemic vasculitis, and drug-induced acute interstitial nephritis [1,2]. Hantavirus infection should be prioritized when a compatible exposure history is present, proteinuria is disproportionate to the initial serum creatinine elevation, thrombocytopenia occurs in the absence of overt disseminated intravascular coagulation, and the clinical course transitions characteristically from oliguria toward polyuria [7]. Hantavirus-associated nephropathy is increasingly recognized in core nephrology curricula as a unique infectious cause of AKI requiring tailored diagnostic and management considerations [8].

A foundational nephrology-focused framework was established by Koehler et al. [1]. The present narrative review expands upon that work by synthesizing literature published through May 2026, with focused emphasis on integrin receptor tropism, endothelial glycocalyx degradation, interleukin-6 (IL-6) trans-signaling, immune checkpoint dynamics, coagulation monitoring, structured biomarker risk stratification, and long-term renal sequelae. Our primary objective is to provide a comprehensive clinicopathologic model to guide bedside nephrology assessment, renal replacement therapy (RRT) decision-making, and long-term post-discharge follow-up.

Relevant literature was identified through systematic searches of PubMed, Scopus, and Google Scholar utilizing search terms including *hantavirus*, *hemorrhagic fever with renal syndrome*, *nephropathia epidemica*, *acute kidney injury*, *proteinuria*, and *renal outcomes*. Priority was given to clinical cohort studies, renal pathology reports, mechanistic translational studies, and long-term renal outcome evaluations; review articles were cited selectively for context and synthesis. All primary human studies cited were conducted in accordance with the Declaration of Helsinki and received appropriate institutional ethical approvals.

CLINICAL SPECTRUM OF KIDNEY INJURY

The renal presentation in hantavirus infection is often abrupt. In European Puumala virus cohorts, elevated serum creatinine and Kidney Disease: Improving Global Outcomes (KDIGO) stage 2–3 AKI are frequent among hospitalized patients, though mortality and irreversible kidney failure are rare when supportive care is accessible [9–12]. Long-term cohort evaluations reveal a nuanced clinical picture: although most patients achieve complete normalization of serum creatinine, a distinct subset exhibits persistent microscopic hematuria, proteinuria, hypertension, or tubular proteinuria years after the acute illness [13–15]. Dobrava-Belgrade virus infection induces a significantly more severe AKI phenotype than Puumala virus, characterized by higher rates of anuria and RRT in comparative studies [16,17]. In East Asian HFRS caused by Hantaan virus genetic variants, severe AKI develops in approximately one in seven hospitalized cases, accompanied by universal thrombocytopenia and prominent hepatic transaminase elevations that can complicate initial diagnostic triage [18]. Seoul virus continues to cause sporadic renal disease via contact with pet or laboratory rats in urban settings, with recent cases from Korea and Germany illustrating the expanding geographic reach of Seoul virus-associated AKI [7,19].

The clinical distinction between Puumala-driven NE and Hantaan-driven HFRS carries direct bedside relevance (Figure 1). European NE cohorts document dialysis requirements ranging from 1% to 15% among hospitalized patients, minimal case fatality (<1%), and near-universal creatinine recovery [9–12]. In contrast, hospitalized patients with Hantaan virus HFRS exhibit a markedly higher risk profile: shock, anuria, severe coagulopathy, and multiorgan failure are substantially more common; RRT is required in approximately 20–40% of severe East Asian cases [4,18]; and historical case fatality reached 5–15% in resource-limited settings [4,6]. Dobrava-Belgrade virus occupies an intermediate-to-high severity tier in European comparative cohorts, causing more frequent anuria and dialysis dependency than Puumala virus within the same geographic regions [16]. These species-specific gradients should directly inform clinical triage: a patient returning from a Hantaan-endemic region in East Asia

Table 1: Major Hantavirus species associated with renal disease and typical severity

Virus species	Main geographic distribution	Main clinical syndrome	Typical renal involvement	Mortality pattern
Puumala virus (PUUV)	Scandinavia, Russia, Central Europe	Nephropathia epidemica (mild HFRS)	Mild-to-moderate AKI; proteinuria appears early and is common; KDIGO stage 3 reported in approximately 34% of hospitalized patients in the Tampere PUUV cohort	Low case fatality (<1% in most published series)
Hantaan virus (HTNV)	China, Korea, Far East Russia	Severe HFRS	Severe AKI with prominent oliguria; high rates of KDIGO stage 3 disease	Higher than PUUV; historical hospitalized estimates approximately 1-5%
Dobrava-Belgrade virus (DOBV)	Balkans, Central and Eastern Europe	HFRS (severity varies by viral lineage)	Moderate-to-severe AKI; lineage-dependent (Dobrava lineage > Kurkino lineage)	Intermediate-to-high (Dobrava lineage); Kurkino lineage typically milder
Seoul virus (SEOV)	Worldwide via Rattus norvegicus	Mild-to-moderate HFRS	Variable; generally milder than HTNV; AKI may occur	Low case fatality
Sin Nombre / Andes virus	Americas (North and South)	Hantavirus cardiopulmonary syndrome (HCPS/HPS)	Renal involvement mild and secondary to cardiopulmonary failure	High case fatality (HCPS; historical estimates approximately 35–40%)

Abbreviations: AKI, acute kidney injury; HFRS, hemorrhagic fever with renal syndrome; HCPS, hantavirus cardiopulmonary syndrome; KDIGO, Kidney Disease: Improving Global Outcomes. Mortality figures reflect historical hospitalized cohort data and should be interpreted cautiously given variability across eras, healthcare settings, and case ascertainment methods.

or the Balkans with febrile AKI and thrombocytopenia has a substantially higher a priori risk of severe oliguria and dialysis than a patient presenting similarly in a Puumala-endemic European setting. Nevertheless, viral species should serve as a prior probability guide rather than a substitute for individualized bedside assessment, given the broad clinical variability within each viral phenotype.

Serum creatinine elevation alone inadequately captures the full spectrum of the syndrome. Staging of AKI must be integrated with serial monitoring of urine output, fluid balance, body weight, blood pressure, oxygenation requirements, and urine chemistry. A patient with a stable serum creatinine plateau but escalating pulmonary edema presents greater immediate clinical risk than one with a rising creatinine whose urine output is recovering[20,21].

Proteinuria warrants meticulous clinical appraisal due to its characteristically dramatic yet transient nature. Studies of acute Puumala virus infection describe a "flash-like" albuminuric surge that frequently precedes peak serum creatinine and rapidly resolves as the polyuric phase commences[22,23]. Microscopic hematuria and leukocyturia routinely accompany acute disease (Table 2). Identified host risk factors—including active smoking, lymphopenia, dyspnea at presentation, and an elevated neutrophil-to-lymphocyte ratio—identify patients at elevated risk for a complicated clinical course[24–27].

A frequent diagnostic pitfall is misinterpreting heavy acute proteinuria as primary nephrotic syndrome; during active hantavirus infection, proteinuria reflects reversible disruption of the glomerular and tubular filtration barriers[1]. Persistent proteinuria following the acute phase, active urine sediment that fails to clear, or a progressive decline in estimated glomerular filtration rate (eGFR) should prompt investigation for superimposed or infection-triggered glomerular pathology[9]. The clinical course is best interpreted across defined clinical phases (Figure 1), recognizing that fluid balance requirements change rapidly: an edematous, oliguric patient with severe capillary leak and thrombocytopenia requires fundamentally different management than a volume-depleted patient with un-

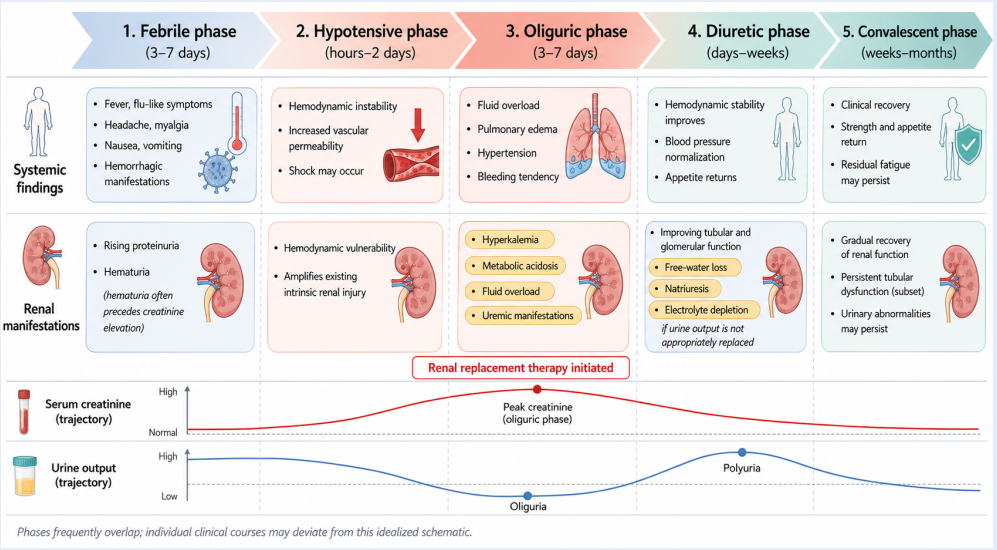

Figure 1: Schematic overview illustrating the five classic sequential clinical phases of hemorrhagic fever with renal syndrome (HFRS)—febrile, hypotensive, oliguric, diuretic, and convalescent phases—along with their approximate clinical durations and hallmark manifestations. **Upper panels:** Systemic clinical features across phases, progressing from early constitutional symptoms and headache (febrile phase) to hemodynamic instability and shock (hypotensive phase), fluid overload and pulmonary edema (oliguric phase), hemodynamic stabilization (diuretic phase), and eventual functional convalescence. **Middle panels:** Corresponding renal manifestations across phases, demonstrating that heavy proteinuria and microscopic hematuria often precede marked serum creatinine elevation. The oliguric phase carries the highest clinical risk, characterized by hyperkalemia, metabolic acidosis, fluid overload, and uremic symptoms; renal replacement therapy (RRT) is most frequently initiated during this window (red highlight). The diuretic phase brings functional tubular recovery but introduces significant risks of brisk natriuresis, solute wasting, and dehydration if urinary losses are not adequately replaced. **Lower panels:** Idealized serial clinical trajectories for serum creatinine (peaking during the oliguric-to-diuretic transition) and urine output (reaching a trough during oliguria and peaking during polyuria). Clinical phases frequently overlap, and individual patient trajectories may deviate from this idealized timeline. Abbreviations: AKI, acute kidney injury; HFRS, hemorrhagic fever with renal syndrome; RRT, renal replacement therapy.

complicated prerenal azotemia. Hyponatremia, hyperkalemia, and metabolic acidosis during the oliguric phase frequently give way to solute wasting, hypokalemia, and intravascular depletion during the polyuric recovery phase [1,9,11].

RENAL PATHOLOGY AND MECHANISTIC INTERPRETATION

The predominant histopathologic pattern in hantavirus nephropathy is tubulointerstitial injury accompanied by microvascular inflammation, rather than immune-complex glomerulonephritis. Contemporary renal pathology series describe acute tubular injury/necrosis, marked interstitial edema, medullary hemorrhage, and prominent cortical peritubular capillaritis [28]. These structural lesions account for the clinical presentation of sudden AKI, impaired tubular concentration ability, and subsequent polyuria during recovery [15,29]. In severe cases, microvascular congestion and endothelial activation exacerbate hypoxic tubular stress beyond what would occur from systemic hemodynamic instability alone [28,30].

Glomerular involvement is increasingly supported by translational research (Figure 2). Pathogenic Old World hantaviruses directly infect human glomerular endothelial cells, tubular epithelial cells, and podocytes, leading to the disassembly of intercellular tight junction and adherens junction proteins, including zonula occludens-1 (ZO-1) and vascular endothelial cadherin (VE-cadherin) [31]. Elevated urinary excretion of nephrin, immunoglobulin G (IgG), and other markers of glomerular filtration barrier breakdown are detectable during severe acute disease [32]. Furthermore, biopsy-confirmed reports demonstrating podocyte foot-process effacement in patients with massive proteinuria provide ultrastructural confirmation of a reversible viral glomerulopathy [33]. Hantaviruses replicate within human

Table 2: Renal manifestations of Hantavirus infection and their nephrologic interpretation

Manifestation	Typical clinical features	Nephrologic interpretation
Acute kidney injury	Rising creatinine, oliguria, fluid retention; severity ranges from mild to dialysis-requiring; KDIGO stage 3 in roughly one-third of hospitalized PUUV patients	Intrinsic AKI; tubulointerstitial injury with microvascular component, not pure prerenal disease
Proteinuria	Often appears early; dipstick ≥2+ may precede peak creatinine; mixed glomerular and tubular components; nephrin and IgG correlate with severity	Marker of renal parenchymal involvement; glomerular proteinuria correlates with AKI severity in PUUV
Hematuria	Microscopic hematuria common during acute phase; persists in 25% at 7–35 months and 6% at long-term follow-up	Reinforces parenchymal injury; persistence after recovery warrants reassessment
Tubular dysfunction	Impaired urinary concentration, polyuria, electrolyte disturbance, raised urinary α1-microglobulin and KIM-1	Reflects tubular injury; may lag behind creatinine recovery; explains diuretic-phase risks
Oliguria-polyuria transition	Oliguria during acute phase, often followed by brisk polyuria during recovery	Dynamic injury–repair pattern; both phases carry distinct risks (overload vs depletion)
Glomerular barrier stress	Urinary nephrin elevation, foot-process effacement, increased serum suPAR; in vitro disruption of ZO-1 and VE-cadherin	Self-limiting glomerulopathy; supports barrier dysfunction without classic primary glomerulonephritis
Hypertension	May appear or worsen during the acute episode; reported in subsets at follow-up; high prevalence in long-term cohorts	Causality with prior infection uncertain; reflects vascular and volume changes plus baseline risk

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HFRS, hemorrhagic fever with renal syndrome; IgG, immunoglobulin G; KDIGO, Kidney Disease: Improving Global Outcomes; KIM-1, kidney injury molecule-1; NE, nephropathia epidemica; PUUV, Puumala virus; SC5b-9, terminal complement complex; suPAR, soluble urokinase plasminogen activator receptor; VE-cadherin, vascular endothelial cadherin; ZO-1, zonula occludens-1.

mesangial cells without inducing immediate cytolysis, reinforcing the concept that functional filtration barrier failure—rather than direct parenchymal cell death—drives the proteinuric phenotype[34]. Glycocalyx shedding, tight-junction disassembly, cytokine exposure, and complement activation collectively impair vascular and podocyte permeability in a self-limiting manner that aligns with the rapid onset and clearance of albuminuria seen clinically[35–38].

A critical molecular determinant of pathogenic hantaviruses is their selective utilization of β3 integrins for cell entry. Pathogenic Old World and New World strains enter endothelial cells and platelets via αvβ3 and αIIbβ3 integrins, whereas non-pathogenic strains (such as Prospect Hill and Tula viruses) utilize β1 integrins (α5β1)[39]. This receptor preference is mechanistically crucial: endothelial β3 integrins modulate vascular permeability downstream of vascular endothelial growth factor (VEGF) signaling. Co-option of β3 integrins by pathogenic hantaviruses hyper-sensitizes endothelial cells to VEGF-mediated capillary leak—an effect absent in cells infected by β1 integrin-binding non-pathogenic strains[40]. Pathogenic hantaviruses selectively dysregulate β3 integrin-dependent endothelial barrier function without altering β1 integrin pathways, directly linking viral entry receptor choice to the systemic vascular permeability phenotypes of both HFRS and hantavirus cardiopulmonary syndrome[39,40]. Furthermore, because αIIbβ3 is the primary fibrinogen receptor on platelets, this integrin tropism links vascular hyperpermeability directly to the thrombocytopenia and platelet dysfunction characteristic of severe HFRS.

Endothelial pathology extends beyond integrin signaling. Elevated levels of urinary heparanase and matrix metalloproteinase-9 (MMP-9)—key enzymes responsible for endothelial glycocalyx degradation—are measurable in HFRS patients and correlate directly with disease severity[35,36]. IL-6 trans-signaling mediates proinflammatory cytokine secretion and endothelial barrier breakdown in infected tissues, independently predicting AKI severity and protein-

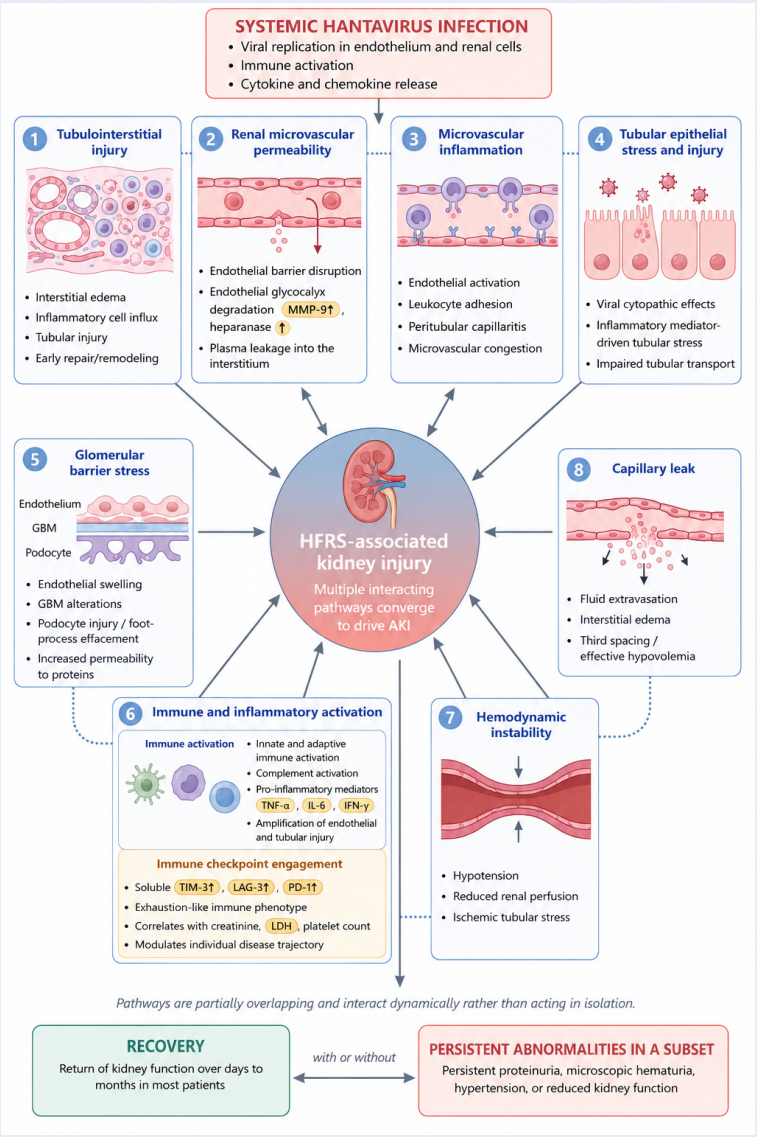

Figure 2: Comprehensive mechanistic diagram detailing the eight major interacting cellular and molecular pathways triggered by systemic hantavirus infection that converge to drive HFRS-associated acute kidney injury (AKI): **(1) Tubulointerstitial injury:** Interstitial edema, inflammatory cell infiltration, tubular necrosis, and early tissue remodeling. **(2) Renal microvascular hyperpermeability:** Endothelial barrier disruption, MMP-9 and heparanase degradation of the endothelial glycocalyx, and plasma extravasation. **(3) Microvascular inflammation:** Microvascular endothelial activation, leukocyte adhesion, cortical peritubular capillaritis, and vascular congestion. **(4) Tubular epithelial stress and injury:** Viral cytopathy, inflammatory cytokine-driven tubular stress, and impaired solute transport. **(5) Glomerular barrier stress:** Glomerular endothelial swelling, basement membrane alterations, podocyte foot-process effacement, ZO-1/VE-cadherin disassembly, and heavy proteinuria. **(6) Immune and inflammatory activation:** Innate/adaptive immune activation, cytokine storm (TNF-α, IL-6, IFN-γ), complement cascade activation (SC5b-9), and immune checkpoint upregulation (soluble TIM-3, LAG-3, PD-1) reflecting T-cell exhaustion dynamics. **(7) Hemodynamic instability:** Systemic hypotension, reduced renal blood flow, and ischemic tubular injury. **(8) Capillary leak syndrome:** Widespread vascular leakage, fluid extravasation, third-spacing, and effective intravascular hypovolemia. These pathways interact dynamically rather than in isolation. Following the acute phase, most patients achieve complete functional renal recovery, whereas a subset exhibits persistent proteinuria, microscopic hematuria, hypertension, or subtle tubular dysfunction. Abbreviations: AKI, acute kidney injury; GBM, glomerular basement membrane; HFRS, hemorrhagic fever with renal syndrome; IFN-γ, interferon-gamma; IL-6, interleukin-6; LAG-3, lymphocyte-activation gene 3; LDH, lactate dehydrogenase; MMP-9, matrix metalloproteinase-9; PD-1, programmed cell death protein 1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TNF-α, tumor necrosis factor-alpha.

uria magnitude in clinical cohorts[37,41,42]. Complement system activation, evidenced by elevated terminal complement complex (SC5b-9) and reduced C3 levels, correlates strongly with disease severity metrics during acute Puumala virus infection[38]. Neutrophil activation triggered by infected microvascular endothelial cells—with elevated plasma myeloperoxidase, elastase, and IL-8—amplifies inflammatory tissue damage without requiring widespread viral cytolysis[30]. Furthermore, elevated serum concentrations of soluble immune checkpoint molecules (TIM-3, LAG-3, and PD-1) indicate that an exhaustion-like immune state coexists with systemic inflammation, potentially modulating individual clinical trajectories[43].

Biomarkers of hantavirus nephropathy can be stratified into two clinical tiers based on diagnostic readiness. At the established tier, serum/plasma cystatin C and urinary α1-microglobulin reliably detect tubular and filtration impairment prior to peak serum creatinine, while plasma or urinary IL-6 correlates strongly with AKI severity[41,42,44]. At the investigational tier, urinary nephrin[27,32], soluble urokinase plasminogen activator receptor (suPAR)[45], plasma thrombomodulin[46,47], coagulation indices (such as fibrinogen and prothrombin time)[48], and soluble immune checkpoint proteins[43] offer mechanistic insight and cohort-level prognostic value, though external validation is required before routine clinical implementation.

MANAGEMENT FROM A NEPHROLOGY PERSPECTIVE

Management of hantavirus-associated AKI remains primarily supportive, but supportive care must be proactive and highly structured (Table 3). Initial clinical evaluation should document exposure history, day of illness, blood pressure trends, body weight changes, urine output, urinalysis with microscopy, serum creatinine trajectory, serum potassium, bicarbonate, sodium, albumin, platelet count, coagulation profile, and evidence of cardiopulmonary involvement. Standard AKI principles—avoidance of nephrotoxic medications, maintenance of renal perfusion, and timely application of RRT—are paramount. However, HFRS introduces two unique management challenges: systemic capillary leak renders intravascular volume status difficult to assess using single static parameters, and profound thrombocytopenia increases the risk of vascular access procedures[20,21].

Early nephrology consultation is most effective prior to crossing the dialysis threshold to determine whether AKI represents an isolated renal insult or part of a systemic capillary leak syndrome, verify that urinary findings align with hantavirus nephropathy, and establish an appropriate monitoring plan[1,2]. In healthcare facilities lacking on-site hemodialysis capabilities, patient transfer should be arranged before severe hyperkalemia, refractory pulmonary edema, or progressive coagulopathy render transport hazardous.

A structured monitoring protocol updated at each phase transition should incorporate: urine output recorded hourly in critically ill patients or per shift in stable ward patients; daily serum creatinine, electrolytes (potassium, sodium, bicarbonate, phosphate), and fluid balance; serial blood pressure and body weight measurements; complete blood count and coagulation profile; and serial pulse oximetry accompanied by careful pulmonary examination[20,21]. Indications for clinical escalation include KDIGO stage 2 or higher AKI, oliguria (<0.5 mL/kg/h for >6 hours), serum potassium >5.5 mmol/L, serum bicarbonate <18 mmol/L with clinical deterioration, or new pulmonary infiltrates in a fluid-overloaded oliguric patient[20,21].

Fluid administration represents the most delicate bedside decision. Judicious crystalloid resuscitation may be required during the early vascular leak phase to maintain systemic organ perfusion; however, aggressive fluid boluses accelerate pulmonary edema once oliguria and capillary leak predominate[1,2]. Dynamic monitoring—including serial oxygenation requirements, chest imaging or point-of-care lung ultrasound, hematocrit trends, and small fluid challenge responsiveness—is substantially more reliable than static volume assessments.

Initiation of RRT should follow standard clinical indications: refractory hyperkalemia, severe metabolic acidosis, medically refractory volume overload/pulmonary edema, uremic complications, or progressive oligoanuria with severe biochemical derangement[20,21]. RRT requirement is almost universally temporary among survivors[9,10,12]. Coagulopathy and thrombocytopenia necessitate individualized anticoagulation strategies: intermittent hemodialysis without systemic anticoagulation is suitable for hemodynamically stable patients, whereas continuous renal replacement therapy (CRRT) is preferred when shock, severe fluid overload, or high bleeding risk complicates management[1,20,21]. Coagulation abnormalities require

Table 3: Supportive nephrology care in hantavirus-associated acute kidney injury

Phase / problem	Key monitoring and intervention	Pitfalls to avoid
Capillary leak / early hypovolemia	Cautious volume resuscitation; serial blood pressure, urine output, lactate; track hemoconcentration and platelets	Persistent aggressive fluids after physiology shifts toward retention
Oliguric AKI	Daily creatinine, potassium, bicarbonate, fluid balance; early correction of hyperkalemia and acidosis; consider RRT per KDIGO indications	Forced diuresis as a substitute for assessment; delaying RRT when conventional indications are present
Renal replacement therapy	Modality choice driven by hemodynamic tolerance, bleeding risk, and local expertise; standard AKI thresholds apply; favorable outcome despite KDIGO stage 3	Treating the etiologic diagnosis as an indication or contraindication in itself
Diuretic phase	Replace ongoing losses; monitor sodium, potassium, magnesium; avoid abrupt volume contraction	Assuming polyuria equals full recovery
Bleeding risk	Platelet count and bleeding tendency considered before vascular access and during anticoagulation	Routine systemic anticoagulation without weighing thrombocytopenia and active bleeding
Antiviral / immunomodulatory therapy	Supportive care remains the foundation; ribavirin reduced mortality and oliguria in a Chinese HFRS RCT but not generalizable to all syndromes	Treating case-report agents (e.g., icatibant) as standard therapy
Early biomarker risk stratification	Plasma cystatin C and urinary α1-microglobulin rise earlier than creatinine and predict severe AKI; high IL-6 identifies severe NE	Relying solely on creatinine in the first 24-48 h
Post-discharge follow-up	Reassess creatinine/eGFR, urinalysis, quantified proteinuria, and blood pressure, especially after dialysis-requiring or persistent abnormalities; apply ADQI acute kidney disease framework	Equating a normalized creatinine with full physiologic recovery

Abbreviations: ADQI, Acute Disease Quality Initiative; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HFRS, hemorrhagic fever with renal syndrome; IL-6, interleukin-6; KDIGO, Kidney Disease: Improving Global Outcomes; NE, nephropathia epidemica; PUUV, Puumala virus; RCT, randomized controlled trial; RRT, renal replacement therapy.

vigilant parallel monitoring: in a retrospective cohort of 395 HFRS patients, disseminated intravascular coagulation (DIC) was documented in 27.3% of cases, and prolonged prothrombin time, reduced fibrinogen, and elevated serum bilirubin were independent predictors of in-hospital mortality[48]. Consequently, coagulation parameters should be routinely integrated into monitoring bundles alongside renal and hematologic tests, particularly in Hantaan or Dobrava-Belgrade virus cases with stage 3 AKI.

Evidence regarding specific antiviral therapy remains limited and species-dependent. A double-blind, placebo-controlled randomized trial of intravenous ribavirin in 242 Chinese patients with Hantaan virus-associated HFRS demonstrated significant reductions in mortality and risk of oliguria when treatment was initiated within seven days of fever onset[49]. Conversely, a subsequent randomized trial involving 73 patients with Puumala virus HFRS in Russia showed no significant effect on viral load kinetics, alongside higher rates of adverse events including hemolysis, hyperbilirubinemia, and bradycardia in the ribavirin arm[50]. This discrepancy highlights key biological differences: Hantaan virus replicates to significantly higher viremic titers during the early febrile phase than Puumala virus, creating a broader therapeutic window for a nucleoside analogue; differences in patient acuity, sample size, and timing of intervention further preclude direct comparison. Therefore, ribavirin efficacy in Hantaan virus HFRS cannot be extrapolated to Puumala-dominated NE. Currently, no specific antiviral agent is approved for hantavirus treatment by major regulatory authorities[51].

From a pathophysiological standpoint, complement activation in HFRS provides a rationale for complement-targeted therapies (such as eculizumab), familiar to nephrologists from atypical hemolytic uremic syndrome[38]; however, clinical trial data in HFRS are lacking. Endothelial barrier-

stabilizing agents, including the fibrin-derived peptide FX06 (which preserves VE-cadherin integrity via Fyn kinase-mediated RhoA inhibition), have shown promise in reducing capillary leak in animal models of dengue hemorrhagic fever and endotoxemia[52], but remain unstudied in human HFRS. Bradykinin receptor blockade with icatibant remains speculative based on isolated case reports[53]. This review focuses on supportive nephrology management; detailed appraisals of experimental antiviral and immunomodulatory agents are available in specialized infectious disease literature[2,51].

RENAL OUTCOMES AND FOLLOW-UP

The short-term renal prognosis of hantavirus-associated AKI is highly favorable among patients who survive the acute phase. Serum creatinine typically recovers over days to weeks, proteinuria resolves during the polyuric phase, and RRT can almost always be successfully discontinued. The Acute Disease Quality Initiative (ADQI) framework distinguishes acute kidney disease (AKD) from complete recovery, emphasizing the necessity of structured post-episode monitoring[21]. In the 556-patient Tampere Puumala virus cohort, KDIGO stage 3 AKI was associated with higher serum creatinine at one month, but no significant difference in median creatinine was observed at one year; after five years, all but one patient had returned to baseline renal function[10].

Long-term outcome studies present a more nuanced perspective. Progression to end-stage kidney disease following a single episode of Puumala virus infection is rare[11,12]. However, elevated blood pressure[14], persistent urinary sediment abnormalities[15], subtle tubular protein wasting[17], and circulating endothelial dysfunction markers detectable up to 14 years post-infection have been reported in survivor subsets[54]. In a 20-year follow-up cohort of 156 NE survivors, chronic kidney disease (CKD) was identified in 8%, persistent hematuria in 6%, and hypertension in 78%; however, the authors concluded that these rates did not support an increased risk of incident CKD attributable to prior hantavirus infection[12]. These observations suggest that prior hantavirus AKI represents a renal risk state warranting structured long-term health surveillance, rather than a cause of progressive nephropathy[21].

Post-AKI follow-up should be risk-stratified. Patients with a history of severe AKI, RRT requirement, prolonged oliguria, persistent proteinuria or hematuria, uncontrolled hypertension, advanced age, diabetes mellitus, pre-existing CKD, or infection with Hantaan or Dobrava-Belgrade viruses should undergo structured nephrology follow-up[11]. A practical follow-up schedule includes evaluation at 4–12 weeks post-discharge, followed by repeat assessment at 6–12 months if abnormalities persist. Evaluation should include blood pressure measurement, serum creatinine/eGFR, urine albumin-to-creatinine ratio (UACR), and urine sediment microscopy, with formal nephrology referral indicated for unresolving proteinuria, hematuria accompanied by declining eGFR, or persistent tubular dysfunction[11,15,21]. Survivors of New World hantavirus infections who experience documented AKI or proteinuria during their acute illness should also be included in renal follow-up programs, regardless of their primary cardiopulmonary presentation[55].

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Significant knowledge gaps remain in hantavirus nephropathy. The field lacks prospective, biopsy-correlated longitudinal cohorts that simultaneously evaluate viral species, urine sediment kinetics, novel glomerular and tubular biomarkers, endothelial shed markers, and long-term renal outcomes[28,29]. Most mechanistic studies to date are limited by small sample sizes and single-center designs. The most immediate priority is the establishment of integrated nephrology registries to determine whether early measurement of proteinuria[22,23], cystatin C and α1-microglobulin[44], urinary nephrin[27,32], suPAR[45], thrombomodulin[46,47], or IL-6 trans-signaling markers[37,41] improves prediction of RRT requirement and non-recovery beyond standard clinical variables.

Comparative research spanning the full geographic and viral spectrum—including East Asian Hantaan and Seoul viruses, Balkan Dobrava-Belgrade strains, and American New World hantaviruses—is essential. Standardized renal phenotyping across endemic regions will help differentiate universal pathophysiological mechanisms from species-specific features and health-system variables, establishing a necessary foundation for validating novel prognostic biomarkers and targeted therapeutic interventions[1,2].

CONCLUSIONS

Hantavirus-associated kidney injury is a complex, dynamic renal syndrome resulting from the interplay of systemic capillary leak, integrin-mediated

endothelial permeability signaling, tubulointerstitial inflammation, tubular epithelial stress, glomerular barrier breakdown, and cytokine-mediated inflammatory amplification. Its clinical signature comprises febrile AKI, severe thrombocytopenia, marked transient proteinuria, hematuria, an oliguric-to-polyuric transition, and generally favorable—though occasionally incomplete—long-term functional recovery. A dedicated nephrology-focused management approach optimizes diagnostic accuracy, ensures safe fluid and electrolyte management, guides RRT timing, and structures long-term post-discharge surveillance. Future clinical research must advance from descriptive biomarker studies toward validated renal risk-prediction models and mechanism-targeted therapeutic trials.

DECLARATIONS

Abbreviations

ADQI — Acute Disease Quality Initiative; **AKI** — acute kidney injury; **CKD** — chronic kidney disease; **CRRT** — continuous renal replacement therapy; **DIC** — disseminated intravascular coagulation; **DOBV** — Dobrava-Belgrade virus; **eGFR** — estimated glomerular filtration rate; **HCPS** — hantavirus cardiopulmonary syndrome; **HFRS** — hemorrhagic fever with renal syndrome; **HTNV** — Hantaan virus; **IgG** — immunoglobulin G; **IL-6** — interleukin-6; **KDIGO** — Kidney Disease: Improving Global Outcomes; **KIM-1** — kidney injury molecule-1; **MMP-9** — matrix metalloproteinase-9; **NE** — nephropathia epidemica; **PD-1** — programmed cell death protein 1; **PUUV** — Puumala virus; **RRT** — renal replacement therapy; **SC5b-9** — terminal complement complex; **SEOV** — Seoul virus; **suPAR** — soluble urokinase plasminogen activator receptor; **TIM-3** — T-cell immunoglobulin and mucin-domain containing-3; **VE-cadherin** — vascular endothelial cadherin; **VEGF** — vascular endothelial growth factor; **ZO-1** — zonula occludens-1

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Competing interests

The authors declare that they have no competing interests.

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