Angiopoietin-1/Tie2 Activation as a Therapeutic Hypothesis for Hantavirus-Induced Vascular Permeability

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Abstract

Severe hantavirus infection produces extensive vascular leakage, driven by a combination of endothelial dysfunction, dysregulated inflammation, VEGF-mediated hyperpermeability, angiopoietin imbalance, and degradation of the endothelial glycocalyx. This narrative review draws on the peer-reviewed literature, with particular attention to work published between 2016 and 2026, to examine how hantavirus-induced vascular permeability arises in hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS), and how Angiopoietin-1 (Ang-1)/Tie2 signaling and glycocalyx injury contribute to endothelial barrier failure. Direct hantavirus evidence shows that Ang-1 inhibits hantavirus-directed endothelial permeability in vitro and that angiopoietin dysregulation tracks with disease severity in patients; findings that Tie2 activation curbs vascular leakage in sepsis and other non-hantavirus models are mechanistically suggestive but remain inferential rather than hantavirus-specific. No hantavirus animal model or clinical trial has yet evaluated Ang-1/Tie2-directed therapy, so this review treats the approach as a testable hypothesis rather than an established or recommended treatment; confirming its therapeutic value will require dedicated hantavirus-specific animal and clinical studies.

Keywords: hantavirus, endothelial dysfunction, vascular permeability, angiopoietin; Tie2, therapeutic hypothesis

1. Introduction

Hantaviruses are negative-sense RNA viruses of the family Hantaviridae. They persist in chronically infected rodent reservoirs (and, in a few species, shrews or moles) and reach humans mainly through inhalation of aerosolized excreta. The Old World hantaviruses, among them Hantaan virus, Puumala virus, and Dobrava-Belgrade virus,

circulate across Europe and Asia and cause hemorrhagic fever with renal syndrome (HFRS). The New World hantaviruses, including Sin Nombre virus and Andes virus, circulate throughout the Americas and cause hantavirus pulmonary syndrome (HPS); Andes virus is unusual among hantaviruses in that it can also spread person-to-person.[1] Both syndromes share a core clinical picture, increased vascular permeability, thrombocytopenia, hypotension, and multiorgan dysfunction, but differ in which organs bear the brunt of disease: HFRS chiefly affects the kidneys, while HPS chiefly affects the lungs and heart, reflecting differences in which vascular beds each viral group preferentially colonizes. Hantaviruses infect endothelial cells without lysing them outright; disease severity instead tracks with disruption of endothelial barrier function.[2] When that barrier fails badly enough, the result is pulmonary edema, shock, renal failure, and death.

The two syndromes also differ sharply in how often they occur and how deadly they are. HFRS accounts for an estimated 150,000-200,000 cases annually, most of them in Asia and Europe, with case fatality ranging from under 1% to roughly 15% depending on the causative virus.[26] HPS is comparatively rare, with roughly 200 cases reported each year across the Americas, but it carries a substantially higher case fatality rate of up to 50%. Neither syndrome yet has an approved antiviral therapy or vaccine. This asymmetry (HFRS common but comparatively survivable, HPS rare but often fatal) resurfaces throughout this review, since the direct clinical evidence bearing on the Ang-1/Tie2 hypothesis is itself unevenly distributed between the two conditions.

The vascular leakage seen in hantavirus infection arises from an interplay of viral infection, inflammatory cytokines, vascular endothelial growth factor (VEGF) signaling, angiopoietin dysregulation, and glycocalyx degradation.[3] Angiopoietin-1 (Ang-1) is an endothelial-stabilizing ligand that activates the Tie2 receptor tyrosine kinase, promoting endothelial quiescence, reinforcing the barrier, and dampening inflammatory signaling.[4] Angiopoietin-2 (Ang-2) works in the opposite direction, destabilizing the vessel wall.

This paper is a narrative literature review that builds toward a therapeutic hypothesis, not an original experimental or clinical study. It traces the molecular mechanisms behind hantavirus-induced endothelial dysfunction, with emphasis on VEGF signaling, Ang-1/Tie2 pathway activity, IL-6 trans-signaling, angiopoietin imbalance, and glycocalyx degradation, while distinguishing evidence gathered directly from hantavirus systems from evidence inferred from related conditions such as sepsis and dengue. Sections 3 through 6 work through each mechanistic pathway in turn; Section 7 draws this evidence together into an explicit direct-versus-inferential summary (Table 1) and lays out

concrete next steps and candidate experimental systems; Sections 8 and 9 address the review's limitations and state its overall hypothesis. The central question is whether endothelial stabilization through Ang-1/Tie2 signaling, together with the related pathways discussed alongside it, is a biologically plausible direction for hantavirus research, while keeping hantavirus-specific evidence clearly separated from evidence borrowed from other diseases.

2. Literature Review Methodology

This review relies on a narrative approach to develop a therapeutic hypothesis. It is not a systematic review or meta-analysis; a PRISMA 2020 flow diagram was not used, since the aim was to synthesize mechanistic and clinical evidence rather than to pool results exhaustively. No original experiments, patient data, animal studies, or clinical trial data were generated for this manuscript.

Literature was identified through structured searches of three databases, PubMed/MEDLINE, Scopus, and Web of Science, conducted on July 23, 2026 and restricted to English-language, peer-reviewed sources. The following title/abstract/keyword search strings were used, combined with Boolean AND/OR operators:

1. ("hantavirus" OR "orthohantavirus" OR "Puumala virus" OR "Hantaan virus" OR "Andes virus" OR "Sin Nombre virus") AND ("vascular permeability" OR "endothelial dysfunction" OR "capillary leak")

2. ("hantavirus" OR "hemorrhagic fever with renal syndrome" OR "HFRS" OR "hantavirus pulmonary syndrome" OR "HPS") AND ("angiopoietin" OR "Tie2" OR "Ang-1" OR "Ang-2")

3. ("hantavirus") AND ("VEGF" OR "vascular endothelial growth factor" OR "VE-cadherin")

4. ("hantavirus" OR "HFRS" OR "HPS") AND ("glycocalyx" OR "syndecan" OR "heparan sulfate")

5. ("angiopoietin" OR "Tie2 agonist" OR "vasculotide") AND ("sepsis" OR "acute lung injury" OR "dengue") AND ("vascular leak" OR "endothelial permeability")

Titles and abstracts were screened for relevance to hantavirus pathogenesis, endothelial or vascular biology, and angiopoietin/Tie2/glycocalyx signaling; full texts of potentially relevant records were then examined.

Records were included if they were peer-reviewed original research or review articles addressing (a) hantavirus clinical disease or pathogenesis, (b) endothelial barrier or vascular permeability mechanisms relevant to VEGF,

angiopoietin/Tie2, or glycocalyx biology, or (c) Tie2-agonist or endothelial-stabilizing interventions in any disease model, the last of these retained specifically to support explicitly labeled inferential, non-hantavirus, mechanistic claims.

Records were excluded if they were non-peer-reviewed (news articles, general websites, blog posts), conference abstracts without an accompanying peer-reviewed publication, or of unclear or unverifiable peer-review status.

The initial exploratory search considered literature published between 1996 and 2026, but the reference base for this manuscript emphasizes peer-reviewed sources from 2016 to 2026. A small number of earlier, foundational studies are retained regardless, for example the 2008 in vitro demonstration that Ang-1 inhibits hantavirus-directed endothelial permeability,[6] the 2000 report that Ang-1 protects the adult vasculature against plasma leakage,[11] and the 2013 identification of kallikrein-kinin system activation in hantavirus-infected endothelium,[21] because they remain the primary direct evidence for specific mechanistic claims and no more recent hantavirus-specific study has superseded them. Each pre-2016 source retained on this basis is flagged as such at its first mention in the text.

The final evidence base comprises 26 references (see References). Throughout, this review distinguishes findings obtained directly in hantavirus-infected cells, animals, or patients (direct evidence) from findings obtained in non-hantavirus systems such as sepsis or dengue that are mechanistically relevant but untested in hantavirus infection (inferential evidence); this distinction is flagged at each relevant claim in Sections 3-7 and summarized in Table 1.

3. Hantavirus Pathogenesis and Endothelial Dysfunction

Hantaviruses target the vascular endothelial cells lining capillaries and small blood vessels by binding beta-3 integrins, an interaction that facilitates viral entry and reshapes intracellular signaling.[5] Beta-3 integrins normally restrain VEGFR2 signaling and so act as negative regulators of VEGF-driven permeability; pathogenic hantaviruses disable this restraint, and the resulting loss of integrin-mediated control is the proposed link between hantavirus infection and the VEGF hyperresponsiveness discussed in Section 4. Even as the virus replicates successfully inside endothelial cells, those cells remain structurally intact, so the vascular leakage that follows reflects altered endothelial function rather than direct viral cytotoxicity. This distinguishes hantavirus-induced vascular leak from

the cytolytic viral hemorrhagic fevers and supports pursuing host-response-directed therapy alongside antiviral approaches.

Capillary leakage and endothelial dysfunction underlie the clinical picture in both HFRS and HPS. As vascular permeability rises, plasma and cells escape into surrounding tissue, producing pulmonary edema, hypovolemia, hypotension, and organ dysfunction.[3] Immune activation contributes substantially to disease severity, particularly through cytokine-driven endothelial activation, discussed in detail in Section 3.1. The kallikrein-kinin system also contributes directly to hantavirus-induced permeability: infected endothelial cells show increased factor XII and kallikrein activity along with bradykinin release, and bradykinin in turn promotes vasodilation and vascular permeability in this setting.[21]

3.1 Cytokine-Driven Endothelial Activation: IL-6 Trans-Signaling

Direct hantavirus evidence ties elevated cytokines to endothelial dysfunction and disease severity. In a cohort of 64 patients hospitalized with acute Puumala virus infection, serum IL-2, IL-6, IL-8, TNF-α, and TGF-β1 were significantly elevated relative to healthy controls, both early and late in the course of acute disease.[23] IL-6 has since emerged as a biomarker of HFRS and HPS severity, though until recently the mechanism linking it to endothelial barrier failure was unclear.

A 2025 study closed that gap. IL-6 signals through two distinct routes: classical signaling, generally protective and dependent on a membrane-bound IL-6 receptor that endothelial cells largely lack, and trans-signaling, mediated by a soluble IL-6 receptor (sIL-6R) paired with the ubiquitous gp130 co-receptor, which can drive pathogenic responses even in receptor-poor cell types such as endothelium. Using primary human endothelial cells infected with Puumala virus and treated with recombinant sIL-6R, the study found that infection stimulates IL-6 secretion and that IL-6 trans-signaling, not classical signaling, drives endothelial barrier dysfunction in vitro. In plasma from 28 patients with acute PUUV-associated HFRS, IL-6 trans-signaling potential correlated with markers of clinical severity, including serum creatinine and thrombocytopenia.[22] This is, to date, the most direct mechanistic link between a hantavirus-elevated cytokine and endothelial barrier failure demonstrated in both an infected-cell system and hantavirus patients, and it identifies IL-6 trans-signaling as a fourth hantavirus-validated pathway relevant to endothelial-stabilizing therapy, alongside VEGF, Ang-1/Tie2, and glycocalyx degradation. As with the angiopoietin

data discussed in Section 5, however, this direct clinical evidence comes specifically from PUUV-associated HFRS and has not yet been established for HPS.

4. VEGF-Mediated Endothelial Hyperpermeability

Vascular endothelial growth factor is a potent regulator of endothelial permeability.[7] VEGF binds VEGFR2 on endothelial cells and activates Src-family kinases that disrupt adherens junction proteins, including vascular endothelial (VE)-cadherin.[8] Loss of VE-cadherin weakens endothelial junctions and raises paracellular permeability.

Pathogenic hantaviruses sensitize endothelial cells to VEGF-induced permeability, so that infected cells respond far more strongly to VEGF stimulation than uninfected ones.[9] VEGF-driven phosphorylation of VE-cadherin widens endothelial gaps and increases plasma leakage, and infected endothelial cells progressively downregulate VE-cadherin in response.[10]

Unlike the angiopoietin and IL-6 trans-signaling evidence discussed in Sections 5 and 3.1, direct clinical evidence for VEGF-driven permeability spans both hantavirus syndromes rather than just one. In HFRS, serum VEGF is elevated and correlates with reduced soluble VEGFR2 during the acute phase of Hantaan virus infection.[9] In HPS, VEGF is similarly elevated in pulmonary edema fluid and peripheral blood mononuclear cells from patients with acute Andes-virus-associated disease.[24] Of the four mechanisms reviewed here (VEGF, Ang-1/Tie2, glycocalyx, IL-6), VEGF is therefore the only one with direct human evidence in both HFRS and HPS, giving it broader direct support than the other pathways discussed (Table 1).

5. Angiopoietin-1/Tie2 Signaling Pathway

The angiopoietin-Tie2 pathway governs endothelial stability and vascular integrity. Ang-1 binds and activates the Tie2 receptor tyrosine kinase on endothelial cells, clustering Tie2 at cell-cell junctions and triggering downstream PI3K/Akt signaling; this cascade phosphorylates and inactivates the forkhead transcription factor FOXO1, stabilizes junctional complexes, supports endothelial survival and tight junction maintenance, sets anti-inflammatory signaling in motion, and suppresses vascular leakage.[4] Consistent with this broader vascular-protective role, Ang-1 has been shown to protect the adult vasculature against plasma leakage,[11] and, in direct hantavirus evidence from an in vitro

permeability assay, Ang-1 significantly inhibits hantavirus-directed endothelial permeability at physiologic concentrations.[6]

Ang-2 works against this system, destabilizing blood vessels and antagonizing Tie2 signaling. Endothelial cells release Ang-2 rapidly from Weibel-Palade bodies during inflammation and infection,[13] and elevated Ang-2 promotes endothelial activation and greater vascular leak. In direct clinical hantavirus evidence, a cohort of 31 patients with acute Puumala virus infection and one patient with Dobrava-Belgrade (Sochi) virus infection showed an elevated Ang-2/Ang-1 ratio relative to controls, and this imbalance correlated with markers of disease severity, including serum creatinine and thrombocyte levels.[12] An important caveat applies here: both patient groups contributing this direct clinical evidence had HFRS rather than HPS, and no comparable human angiopoietin dataset yet exists for HPS. Angiopoietin imbalance is not unique to hantavirus infection; similar Ang-2-driven vascular instability has been described across other host-response-mediated inflammatory syndromes, which lends inferential support to host-directed endothelial stabilization across inflammatory vascular leak syndromes generally, though it remains inferential rather than direct hantavirus evidence.[20]

Tie2-targeting therapeutics have shown efficacy in non-hantavirus experimental models of vascular leak. In murine sepsis, Tie2 activation reduces cytokine elevation, glycocalyx degradation, vascular leakage, and organ damage, a finding from a sepsis model, not a hantavirus one.[14] Vasculotide, a synthetic Tie2 agonist peptide, similarly reduces mortality and vascular permeability in murine sepsis models, again in a non-hantavirus system.[15] These studies make Tie2 activation a biologically plausible endothelial-stabilizing strategy, but neither vasculotide nor any other Tie2 agonist has yet been tested in a hantavirus model.

6. Glycocalyx Degradation and Endothelial Barrier Failure

The endothelial glycocalyx is a carbohydrate-rich layer coating endothelial cells, built from glycoproteins, proteoglycans, syndecans, and glycosaminoglycans such as heparan sulfate and hyaluronan.[16] It regulates vascular permeability, mechanotransduction, leukocyte adhesion, and plasma protein retention; when it is damaged, endothelial permeability rises and vascular leak syndromes worsen.

Inflammation, oxidative stress, cytokines, and angiopoietin dysregulation all induce glycocalyx shedding, largely by activating matrix metalloproteinases and heparanase, which cleave membrane-bound proteoglycans and release soluble syndecan-1, heparan sulfate, and hyaluronan fragments into the circulation. This shedding strips away the glycocalyx's normal steric and electrostatic barrier to plasma protein and fluid movement, directly increasing paracellular permeability in a manner independent of, though likely additive to, the VE-cadherin junctional changes described in Section 4. In sepsis, a non-hantavirus inflammatory condition, glycocalyx degradation is considered a major driver of endothelial dysfunction, with elevated syndecan-1 and heparan sulfate serving as circulating markers of injury.[17] In direct hantavirus evidence, HFRS patients show elevated glycocalyx degradation fragments associated with greater mortality risk.[18] Separately, atrial natriuretic peptide, released in response to the volume overload that can accompany aggressive fluid resuscitation, has been shown to worsen glycocalyx degradation by inducing shedding and increasing vascular permeability; this has direct clinical relevance for hantavirus management, since it suggests that fluid management strategy itself may influence glycocalyx integrity, even though the ANP-shedding link has not been established specifically within hantavirus infection.[19]

7. Therapeutic Implications and Future Directions

Current management of severe hantavirus infection remains supportive: careful fluid management, oxygen therapy, hemodynamic support, renal support when needed, and intensive care monitoring. Recent clinical reviews continue to emphasize supportive and critical care rather than a universally approved curative therapy for HFRS or HPS. Endothelial-stabilizing therapy for hantavirus infection remains investigational; it is not an available or recommended treatment. Table 1 summarizes, for each endothelial pathway discussed in this review, which claims rest on direct hantavirus evidence and which are inferred from non-hantavirus systems; the subsections below examine that evidence and identify experimental systems for testing the hypothesis.

Table 1. Evidence tiers for endothelial-stabilizing mechanisms in hantavirus disease.

Pathway	Direct hantavirus evidence	Inferential (non-hantavirus) evidence	Syndrome(s) with direct evidence
VEGF / VE-cadherin	VEGF elevated and VE-cadherin downregulated in HFRS patients;[9,10] VEGF elevated in HPS pulmonary edema fluid and PBMCs.[24]	VEGFR2/Src/VE-cadherin mechanism characterized primarily in non-hantavirus vascular biology.[7,8]	HFRS and HPS
Ang-1/Tie2	Ang-1 inhibits hantavirus-directed permeability in vitro;[6] Ang-1/Ang-2 deregulation correlates with severity in PUUV/DOBV-Sochi patients.[12]	Tie2 agonism and vasculotide reduce leakage and mortality in murine sepsis models, not tested in hantavirus.[14,15]	HFRS only
IL-6 / cytokines	IL-6, TNF-α elevated in PUUV patients;[23] IL-6 trans-signaling drives barrier dysfunction in PUUV-infected endothelial cells and correlates with HFRS severity.[22]	Broader host-directed anti-cytokine strategies proposed across sepsis, influenza, Ebola.[20]	HFRS only
Glycocalyx	Glycocalyx degradation fragments correlate with mortality risk in HFRS patients.[18]	Glycocalyx is a therapeutic target in sepsis; ANP-induced shedding characterized outside hantavirus infection.[17,19]	HFRS only
Kallikrein-kinin / bradykinin	Hantavirus infection activates factor XII/kallikrein and bradykinin release directly in infected endothelial cells.[21]	Bradykinin's broader contribution has been established directly in hantavirus systems; no inferential comparator was reviewed here.	HFRS and HPS viruses tested in vitro

7.1 What direct hantavirus evidence supports

Three lines of direct hantavirus evidence support further investigation of endothelial-stabilizing therapy. First, Ang-1 inhibits hantavirus-directed endothelial permeability in a validated in vitro hantavirus permeability assay.[6] Second, deregulation of the Ang-1/Ang-2 balance is measurable in patients with acute HFRS and correlates with clinical severity markers.[12] Third, IL-6 trans-signaling drives endothelial barrier dysfunction in PUUV-infected endothelial cells and correlates with severity in HFRS patients.[22] VEGF pathway evidence is strongest in terms of syndrome coverage, since elevated VEGF is documented directly in both HFRS and HPS patients.[9,24] Together, these findings suggest that the endothelial-stabilizing pathways discussed here are mechanistically active and clinically linked to hantavirus disease severity, providing a foundation for further hantavirus-specific research. As Table 1 shows, though, the Ang-1/Tie2, IL-6 trans-signaling, and glycocalyx evidence is currently confined to HFRS; VEGF is the only pathway with direct human evidence in HPS.

7.2 What is inferred from non-hantavirus models

The remainder of the therapeutic rationale comes from non-hantavirus models. Tie2 agonism and vasculotide administration reduce vascular leakage, inflammatory injury, and mortality in murine sepsis models,[14,15] and glycocalyx-protective strategies are under investigation in sepsis.[17] Dengue is a particularly useful comparator, since it too is a vascular-tropic viral infection rather than a bacterial or sterile inflammatory process, and severe cases feature a critical plasma-leakage phase driven by angiopoietin imbalance and glycocalyx shedding that closely parallels the hantavirus disease course described in Section 8. Dengue may be the closest available comparator for hantavirus vascular leak, but it remains a distinct pathogen with a different vector, viral family, and receptor biology, and Ang-1/Tie2-directed or glycocalyx-protective agents have not, to our knowledge, been tested in dengue patients either. Sepsis, dengue, and hantavirus infection thus share overlapping downstream vascular pathology: angiopoietin imbalance, glycocalyx degradation, and VEGF-driven permeability, without sharing an upstream cause, and no Tie2 agonist, recombinant Ang-1 analog, IL-6 trans-signaling blocker, or glycocalyx-protective agent has been administered in any hantavirus-infected cell, animal, or human system. This body of evidence supports hantavirus-specific testing, but it does not demonstrate efficacy in hantavirus disease.

7.3 Proposed next steps

Future work should begin with hantavirus-relevant endothelial cell models before moving to animal models of HFRS or HPS. These studies should measure endothelial permeability, VE-cadherin integrity, VEGF responsiveness, Ang-1/Ang-2 balance, IL-6 trans-signaling potential, inflammatory cytokine production, and glycocalyx injury markers such as syndecan-1, heparan sulfate, and hyaluronic acid, in response to Tie2 agonists, recombinant Ang-1 analogs, or IL-6 trans-signaling blockade. Early studies should target the HPS evidence gap identified in Table 1, specifically testing whether the angiopoietin and IL-6 trans-signaling findings established in PUUV-associated HFRS also hold for HPS-causing viruses such as Andes virus and Sin Nombre virus, rather than assuming they generalize. If preclinical evidence in hantavirus-relevant systems supports safety and efficacy, later translational studies could examine whether endothelial-stabilizing therapies affect outcomes in severe HFRS or HPS. At every stage, this pathway should be treated as an experimental candidate, not a therapy ready for clinical use.

7.4 Candidate experimental systems

Two existing hantavirus-relevant experimental platforms could support this testing without requiring new model development. The in vitro hantavirus endothelial permeability assay used to demonstrate Ang-1 and sphingosine-1-phosphate inhibition of hantavirus-directed permeability[6] offers a practical first step for screening Tie2 agonists, recombinant Ang-1 analogs, and IL-6 trans-signaling blockers directly in hantavirus-infected human endothelial cells. For in vivo testing, the Syrian hamster model of HPS, in which Andes virus infection reproduces the rapid-onset respiratory distress and cardiogenic shock characteristic of human disease, is currently the only animal model that recapitulates human HPS pathophysiology, and it has already been used to evaluate candidate therapeutics and antivirals.[25] No directly equivalent small-animal model with comparable validation currently exists for HFRS, a gap that complicates efforts to resolve the HFRS/HPS evidence asymmetry summarized in Table 1.

8. Limitations

This review has several limitations. First, it is a narrative literature review and therapeutic hypothesis rather than an original experimental study; no new laboratory experiments, animal studies, clinical observations, or patient datasets were generated, and no PRISMA-style systematic search was performed.

Second, direct clinical evidence that Ang-1, recombinant Ang-1 analogs, vasculotide, or other Tie2-targeting therapies improve outcomes in patients with HFRS or HPS does not currently exist. Much of the therapeutic rationale rests on endothelial biology, a single in vitro hantavirus permeability assay,[6] one clinical association study,[12] and preclinical vascular leak models from sepsis.[14,15] Sepsis and hantavirus infection share features such as endothelial dysfunction, angiopoietin imbalance, glycocalyx degradation, and increased vascular permeability, but they are not identical, and findings should not be assumed to transfer directly between them.

Third, hantavirus disease varies by viral species, host immune response, geographic distribution, and clinical syndrome, and, as Table 1 shows, the direct evidence base for this review is not distributed evenly across syndromes. The Ang-1/Ang-2 clinical data,[12] the IL-6 trans-signaling data,[22] and the glycocalyx mortality data[18] all come from HFRS patients, predominantly infected with Puumala virus; only the VEGF pathway currently has direct human evidence in HPS.[24] HFRS and HPS differ in dominant organ involvement, disease course, and case fatality (roughly 1-15% versus up to 50%, respectively[26]), so a therapy that looks promising based on HFRS-derived evidence should not be assumed to generalize to HPS without independent testing in HPS-relevant systems, such as the Andes-virus Syrian hamster model.[25]

Fourth, the timing, dosage, route of delivery, and safety of Tie2-directed therapy in acute viral infection remain unknown. Hantavirus disease follows a defined clinical course, an early febrile phase, a critical phase of peak vascular leakage, and, in survivors, a diuretic and convalescent phase, so any endothelial-stabilizing intervention would likely need to be timed to the critical phase to have a meaningful biological effect, and that timing has not been established in any hantavirus-relevant system. Modulating endothelial signaling too much, or at the wrong time, could also have unintended effects on inflammation, immune clearance, coagulation, vascular repair, or organ perfusion, particularly since some degree of controlled vascular permeability may be necessary for immune cell trafficking and viral clearance during acute infection. For this reason, Ang-1/Tie2-directed therapy is best described as a future investigational strategy rather than an established or recommended clinical treatment.

The available peer-reviewed literature supports endothelial stabilization as a plausible research direction, but the direct hantavirus evidence remains limited to one in vitro permeability study and one clinical association study. Additional mechanistic, preclinical, and clinical work in hantavirus-specific systems is needed before any conclusion about therapeutic efficacy can be drawn.

9. Conclusion

Hantavirus infection causes severe vascular leakage through interacting mechanisms: endothelial dysfunction, VEGF-driven hyperpermeability, angiopoietin imbalance, IL-6 trans-signaling, and glycocalyx degradation. Direct hantavirus evidence shows that Ang-1 inhibits hantavirus-directed endothelial permeability in vitro[6] and that angiopoietin dysregulation and IL-6 trans-signaling are each associated with HFRS disease severity in patients.[12,22] VEGF elevation is the one mechanism with direct clinical evidence in both HFRS and HPS.[9,24] Evidence that Tie2 activation limits vascular leakage in other conditions, sepsis in particular, extends the biological rationale for this pathway but has not been tested in hantavirus infection.[14,15]

Ang-1/Tie2 activation, together with the related IL-6 trans-signaling and glycocalyx-protective mechanisms discussed above, should be treated as a testable therapeutic hypothesis and a candidate direction for future hantavirus research, not a validated or recommended treatment. Dedicated hantavirus-specific preclinical studies, beginning with the existing in vitro hantavirus permeability assay and the Andes-virus Syrian hamster model of HPS,[6,25] followed by carefully designed translational research, are needed before the clinical relevance of endothelial-stabilizing therapy in hantavirus disease can be determined, with particular attention to the current gap between HFRS and HPS evidence.

Abbreviations

Ang-1: Angiopoietin-1

Ang-2: Angiopoietin-2

DOBV: Dobrava-Belgrade virus

gp130: Glycoprotein 130 (IL-6 co-receptor)

HFRS: Hemorrhagic fever with renal syndrome

HPS: Hantavirus pulmonary syndrome

IL-6: Interleukin-6

IFN-γ: Interferon-gamma

PBMC: Peripheral blood mononuclear cell

PUUV: Puumala virus

sIL-6R: Soluble interleukin-6 receptor

TNF-α: Tumor necrosis factor-alpha

VE-cadherin: Vascular endothelial-cadherin

VEGF: Vascular endothelial growth factor

VEGFR2: Vascular endothelial growth factor receptor 2

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This is a literature review manuscript. No original datasets were generated or analyzed. All information is drawn from the published literature cited in the References section.

AI Use Statement

The author used Grammarly and an AI-assisted academic editing tool for grammar, clarity, and style. The tool did not generate or alter the scientific evidence, numerical information, citations, or conclusions. The author reviewed all edits against the cited sources and remains responsible for the manuscript's accuracy and integrity.

References

1. Peters CJ, Simpson GL, Levy H. Spectrum of hantavirus infection: hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome. Annu Rev Med. 1999;50:531-545.

2. Hepojoki J, Vaheri A, Strandin T. The fundamental role of endothelial cells in hantavirus pathogenesis. Front Microbiol. 2014;5:727.

3. Jiang H, Du H, Wang LM, Wang PZ, Bai XF. Hemorrhagic fever with renal syndrome: pathogenesis and clinical picture. Front Cell Infect Microbiol. 2016;6:1.

4. Brindle NPJ, Saharinen P, Alitalo K. Signaling and functions of angiopoietin-1 in vascular protection. Circ Res. 2006;98(8):1014-1023.

5. Dalrymple NA, Mackow ER. Virus interactions with endothelial cell receptors: implications for viral pathogenesis. Curr Opin Virol. 2014;7:134-140.

6. Gavrilovskaya IN, Gorbunova EE, Mackow NA, Mackow ER. 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. J Virol. 2008;82(12):5797-5806.

7. Dvorak HF. Reconciling VEGF with VPF: the importance of increased vascular permeability for stroma formation in tumors, healing wounds, and chronic inflammation. Front Cell Dev Biol. 2021;9:660609.

8. Lampugnani MG, Dejana E, Giampietro C. Vascular endothelial (VE)-cadherin, endothelial adherens junctions, and vascular disease. Cold Spring Harb Perspect Biol. 2017;10(10):a029322.

9. Li Y, Wang W, Wang JP, et al. Elevated vascular endothelial growth factor levels induce hyperpermeability of endothelial cells in hantavirus infection. J Int Med Res. 2012;40(5):1812-1821.

10. Shrivastava-Ranjan P, Rollin PE, Spiropoulou CF. Andes virus disrupts the endothelial cell barrier by induction of vascular endothelial growth factor and downregulation of VE-cadherin. J Virol. 2010;84(21):11227-11234.

11. Thurston G, Rudge JS, Ioffe E, et al. Angiopoietin-1 protects the adult vasculature against plasma leakage. Nat Med. 2000;6(4):460-463.

12. Nusshag C, Osberghaus A, Baumann A, Schnitzler P, Zeier M, Krautkrämer E. Deregulation of levels of angiopoietin-1 and angiopoietin-2 is associated with severe courses of hantavirus infection. J Clin Virol. 2017;94:33-36.

13. Saharinen P, Alitalo K. The yin, the yang, and the angiopoietin-1. J Clin Invest. 2011;121(7):2544-2546.

14. Han S, Lee SJ, Kim KE, et al. Amelioration of sepsis by TIE2 activation-induced vascular protection. Sci Transl Med. 2016;8(335):335ra55.

15. Kümpers P, Gueler F, David S, et al. The synthetic Tie2 agonist peptide vasculotide protects against vascular leakage and reduces mortality in murine abdominal sepsis. Crit Care. 2011;15(5):R261.

16. Ushiyama A, Kataoka H, Iijima T. Glycocalyx and its involvement in clinical pathophysiologies. J Intensive Care. 2016;4(1):59.

17. Uchimido R, Schmidt EP, Shapiro NI. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. Crit Care. 2019;23(1):16.

18. Du J, Hu X, Li Y, et al. High levels of exfoliated fragments following glycocalyx destruction in hemorrhagic fever with renal syndrome are associated with mortality risk. Front Med. 2023;10:1182212.

19. Chappell D, Bruegger D, Potzel J, et al. Hypervolemia increases release of atrial natriuretic peptide and shedding of the endothelial glycocalyx. Crit Care. 2014;18(5):538.

20. Fedson DS. Treating the host response to emerging virus diseases: lessons learned from sepsis, pneumonia, influenza and Ebola. Ann Transl Med. 2016;4(21):421.

21. Taylor SL, Wahl-Jensen V, Copeland AM, Jahrling PB, Schmaljohn CS. Endothelial cell permeability during hantavirus infection involves factor XII-dependent increased activation of the kallikrein-kinin system. PLoS Pathog. 2013;9(7):e1003470.

22. Maleki KT, Niemetz L, Christ W, Wigren Byström J, Thunberg T, Ahlm C, Klingström J. IL-6 trans-signaling mediates cytokine secretion and barrier dysfunction in hantavirus-infected cells and correlates to severity in HFRS. PLoS Pathog. 2025;21(4):e1013042.

23. Sadeghi M, Eckerle I, Daniel V, Burkhardt U, Opelz G, Schnitzler P. Cytokine expression during early and late phase of acute Puumala hantavirus infection. BMC Immunol. 2011;12:65.

24. Gavrilovskaya I, Gorbunova E, Koster F, Mackow E. Elevated VEGF levels in pulmonary edema fluid and PBMCs from patients with acute hantavirus pulmonary syndrome. Adv Virol. 2012;2012:674360.

25. Safronetz D, Ebihara H, Feldmann H, Hooper JW. The Syrian hamster model of hantavirus pulmonary syndrome. Antiviral Res. 2012;95(3):282-292.

26. World Health Organization. Hantavirus. Published May 6, 2026. Accessed July 23, 2026. https://www.who.int/news-room/fact-sheets/detail/hantavirus.