Mini Review

Pro-inflammatory Cytokine Storm in Puumala Virus Infection: Immunopathogenesis and Therapeutic Implications

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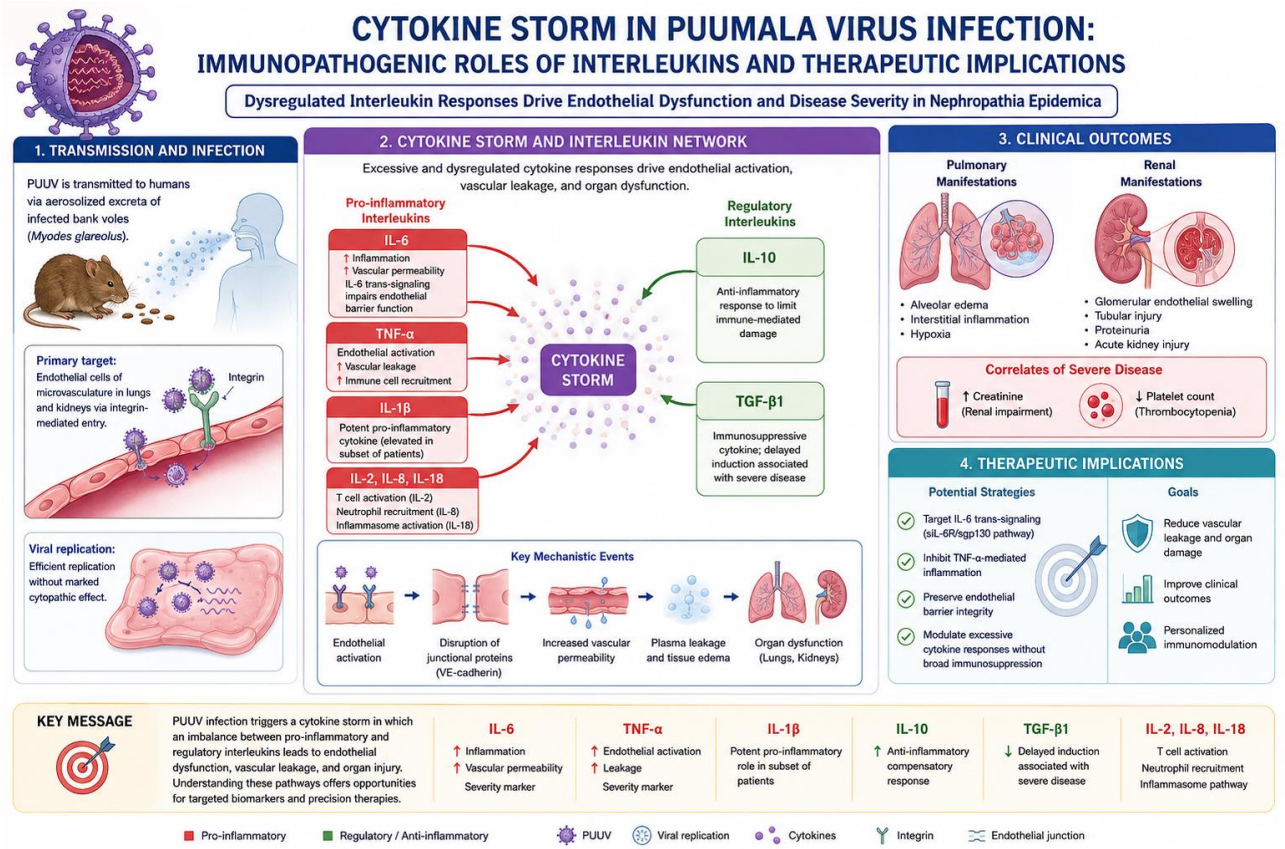
Abstract:

Puumala orthohantavirus (PUUV) is the principal cause of hemorrhagic fever with renal syndrome in Europe, where it manifests as nephropathia epidemica. Although clinical features of PUUV infection are well described, disease severity is increasingly recognized to result from dysregulated host immune responses rather than direct viral cytopathicity. This review synthesizes current evidence on the immunopathogenic roles of interleukins in PUUV infection, with a particular focus on cytokine-mediated endothelial dysfunction and its translational implications. Acute PUUV infection is characterized by a pronounced systemic inflammatory response, often described as a cytokine storm, involving elevated levels of both pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, IL-2, IL-8) and regulatory mediators (IL-10, TGF-β1). Among these, IL-6 and TNF-α are consistently associated with disease severity, renal impairment, and thrombocytopenia, and contribute to endothelial activation and increased vascular permeability. IL-6 trans-signaling has emerged as a key mechanism in endothelial barrier disruption, while TNF-α promotes vascular leakage and immune cell recruitment. In contrast, IL-10 and TGF-β1 appear to function as compensatory anti-inflammatory mediators whose delayed or insufficient responses may contribute to uncontrolled inflammation and tissue injury. Additional interleukins, including IL-2, IL-8, and IL-18, further contribute to T-cell activation, neutrophil recruitment, and inflammasome-associated inflammation, highlighting the complexity of cytokine networks in PUUV pathogenesis. Collectively, these pathways converge on endothelial dysfunction, which represents the central event driving vascular leakage and organ damage. Understanding interleukin dynamics in PUUV infection provides important mechanistic insight and identifies potential biomarkers for disease severity. Moreover, selective targeting of cytokine pathways, particularly IL-6 trans-signaling and TNF-α activity, offers promising therapeutic opportunities. However, given the dual protective and pathogenic roles of cytokines, precise immunomodulation rather than broad suppression is required. Overall, PUUV infection serves as a model of immune-mediated vascular disease, where cytokine-driven endothelial dysfunction determines clinical outcome and therapeutic strategies.

Keywords: Puumala Orthohantavirus, Cytokine Storm and Interleukins, Endothelial Dysfunction, Hemorrhagic Fever with Renal Syndrome, Immunopathogenesis.



Graphical Abstract: Hantavirus Pathogenesis: Immune-Mediated Endothelial Dysfunction and Vascular Leakage. This graphical abstract summarizes the key mechanisms of hantavirus disease, emphasizing immune-mediated endothelial dysfunction as the central driver of pathology. Following infection via aerosolized rodent excreta, hantaviruses target endothelial cells in the pulmonary and renal microvasculature. Despite minimal direct cytopathic effects, infection triggers strong innate and adaptive immune responses, including macrophage activation, cytotoxic T-cell infiltration, and excessive production of pro-inflammatory cytokines such as TNF-α and IL-6. These mediators, together with activation of VEGF-, bradykinin-, and RhoA/ROCK-associated pathways, disrupt endothelial junction integrity and increase vascular permeability. The resulting capillary leakage leads to tissue edema, hypoxia, and organ dysfunction, particularly in the lungs and kidneys. Overall, the figure highlights that disease severity is primarily driven by dysregulated host immune responses and endothelial barrier failure, supporting endothelial stabilization and targeted immunomodulation as key therapeutic strategies.

Introduction

Puumala orthohantavirus is the predominant etiological agent of hemorrhagic fever with renal syndrome (HFRS) in Europe, where it is referred to as nephropathia epidemica (NE) (1). The PUUV is transmitted to humans via aerosolized excreta of its natural reservoir host, the bank vole (Myodes glareolus). PUUV infection usually presents as an acute febrile illness ranging from mild flu-like symptoms to severe disease with acute kidney injury, thrombocytopenia, and increased vascular permeability (1, 2). The pathogenesis of NE is not mediated by direct viral cytopathology but by an overactive and dysregulated host immune response. Consequently, research has increasingly focused on the complex network of cytokines and inflammatory mediators that contribute to the clinical manifestations of the disease.

This immune-mediated pathophysiology is driven by a complex network of cytokines and inflammatory mediators. Following PUUV infection, a robust inflammatory response is initiated, resulting in the release of numerous soluble mediators (2-5). Clinical studies have

consistently documented that the acute phase of the disease is characterized by significantly elevated serum levels of both pro-inflammatory and regulatory cytokines such as IL-6, TNF-α, IL-2, IL-8, IL-10 and interferon-gamma (IFN-γ) (2, 6).

An important feature of Hantavirus infections, which are characterized by acute inflammation and vascular leakage, is the massive and simultaneous release of cytokines, which is frequently called a "cytokine storm" (2, 7). The complex balance between these inflammatory and regulatory substances ultimately defines the severity and duration of the disease. The therapeutic relevance of these cytokine responses is revealed by their strong association with disease severity (6, 8, 9). These observations underscore the importance of cytokine profiling in understanding disease progression and highlight the potential of interleukin networks as both prognostic biomarkers and therapeutic targets in hantavirus infection (10). Increased levels of pro-inflammatory cytokines IL-6 and TNF-α were substantially linked with markers of severe disease such as increased creatinine levels (indicating renal impairment) and reduced platelet counts (6). In contrast, low levels of the immunosuppressive cytokine transforming growth factor-beta 1 (TGF-β1) during the early phase of disease are associated with a more severe outcome, indicating that inadequate suppression of the initial inflammatory response is deleterious (11). One such mechanism is IL-6 trans-signaling, which contributes to endothelial barrier dysfunction and correlates with disease severity in PUUV-infected patients (9). Overall, recent mechanistic frameworks of hantavirus pathogenesis further support the concept that endothelial dysfunction and cytokine-mediated immune dysregulation, rather than direct viral cytopathicity, represent the central drivers of disease severity and vascular leakage (12). These findings have shown that several interleukins are markers of disease progression and potential targets for therapy. Therefore, knowledge of the specific roles of individual interleukins, from the pro-inflammatory IL-1β, IL-6 and TNF-α to the regulatory IL-10 and TGF-β1, is essential in understanding the immunopathogenesis of PUUV infection and in the development of novel therapeutic approaches for this important zoonotic disease (6, 8, 9, 11). Interleukin-1β (IL-1β) is a potent pro-inflammatory cytokine that has a complex and somewhat changeable role in Puumala virus infection. Unlike IL-6 and TNF-α that are elevated in the majority of patients, IL-1β is increased only in a minority of PUUV-infected individuals (2, 8, 13). In vitro investigations have demonstrated that PUUV infection upregulates IL-1β gene expression in infected cells, and plasma levels of IL-1β as well as IL-6, IL-1Ra and TNF-α are considerably increased after acute PUUV infection (8, 13, 14). Genetic studies have shown associations between IL-1β gene polymorphisms and susceptibility to PUUV infection or disease severity, suggesting that host genetic variations in IL-1β signaling pathways may influence clinical outcomes. The polymorphism of IL-1β (-511) allele 2 has been known as a potential genetic determinant for the disease manifestation. Unlike the more broadly upregulated cytokines IL-6 and TNF-α (6), IL-1β levels are not always increased in all PUUV patients, despite the pro-inflammatory features of IL-1β (13, 15). The present study provides an overview of current evidence regarding immunoinflammatory biomarkers associated with disease severity in PUUV infection, with particular emphasis on the role of IL-1β in the immunopathogenesis of the disease.

IL-6

Interleukin-6 (IL-6), a key regulator of the inflammatory response, is among the most markedly elevated cytokines in PUUV infection (6). A study of 64 hospitalized patients with acute PUUV infection found significantly elevated IL-6 levels both in the early and late phase of the disease compared to healthy controls. Importantly, IL-6 levels declined significantly between the early and convalescent phases of disease (about 6 to 12 days after the onset of symptoms), suggesting that IL-6 production is most prominent during the acute phase of infection. Greater disease severity, reflected by higher creatinine levels and lower platelet counts, was associated with elevated pro-inflammatory IL-

6 levels, supporting the role of IL-6 as both a biomarker and a pathogenic mediator of severe disease (6).

In addition to promoting inflammation, IL-6 signaling pathways play a significant role in PUUV pathogenesis. Recent research has emphasized the importance of IL-6 trans-signaling, by which IL-6 binds to soluble IL-6 receptor (sIL-6R) to activate cells that do not express the membrane-bound receptor. In vitro studies reveal that treatment of PUUV-infected endothelial cells with sIL-6R enhances IL-6 and CCL2 production, upregulates ICAM-1 expression and disrupts VE-cadherin-mediated cell barrier integrity, leading to enhanced vascular permeability. Patients with HFRS exhibited altered plasma concentrations of sIL-6R and soluble gp130 (sgp130), resulting in an increased sIL-6R/sgp130 ratio, a marker of enhanced IL-6 trans-signaling activity. In patients on oxygen therapy the sIL-6R/sgp130 ratio was increased relative to those not on oxygen therapy, correlating IL-6 trans-signaling to more severe clinical outcomes (9). IL-6 was substantially associated with renal involvement in PUUV infection. Increased plasma IL-6 and urine IL-6 levels were positively associated with PUUV-induced acute kidney injury (AKI) (16). The urinary excretion of IL-6 is correlated with proteinuria in acute Puumala hantavirus-induced nephritis suggesting that local IL-6 synthesis in the kidneys is involved in renal disease (17). IL-6 concentrations consistently correlate with disease severity and have therefore been proposed as a valuable prognostic biomarker in HFRS (14). Indeed, the complexity of IL-6 signaling, with classical signaling generally leading to protective responses and trans-signaling possibly inducing pathogenic effects, highlights the need for targeted therapeutic strategies aimed at selectively inhibiting the pathogenic trans-signaling pathway while preserving the protective functions of classical IL-6 signaling (9).

TNF-α

Tumor necrosis factor-alpha is an important pro-inflammatory cytokine that remains elevated throughout PUUV infection and is implicated in disease progression. In the group of 64 hospitalized PUUV patients, TNF-α levels were significantly greater in the early and late stages of infection compared to healthy controls, and showed a significant reduction from early to late stages of disease (6). IL-6 levels were increased and TNF-α levels were increased with disease severity (6, 18). Serum samples from HFRS patients, regardless of the causative hantavirus, showed increased levels of TNF-α in all but one case, suggesting that TNF-α is a common component of the host response to hantavirus infection (18).

TNF-α participates in PUUV pathophysiology in many ways, e.g. by increasing endothelial cell activation and inducing vascular leakage. The virus is not cytopathic and it is assumed that the immune responses to it, notably TNF-α production, are important in the genesis of the illness. TNF-α may induce vascular hyperpermeability, a key feature of HFRS. Cynomolgus macaques in non-human primate models of PUUV infection demonstrated classic signs of HFRS, including lethargy, anorexia, and proteinuria, with elevated TNF-α levels, as well as IL-6 and IL-10 responses. Immunized monkeys displaying no symptoms likewise had absence of elevated TNF-α levels, providing strong evidence that TNF-α elevation is closely connected with symptomatic sickness (19). The biological properties of TNF-a during PUUV infection are consistent with its role as an early inflammatory mediator. The observed decrease in TNF-α from early to late phase implies that the most intense TNF-α-mediated inflammation occurs during the first response to infection (6). In PUUV-infected patients, the levels of IFN-γ were negatively correlated with time, and the concentrations of IL-10, TNF-α and IFN-γ were greater in all samples (18). Elevated TNF-α has been correlated with disease severity, and data from animal models indicate that increased TNF-α corresponds with symptomatic disease, thereby establishing TNF-α as a critical pathogenic mediator and potential therapeutic target in PUUV infection (6, 18, 19).

IL-10

Interleukin-10 is an anti-inflammatory cytokine which interestingly is raised during the acute PUUV infection, reflecting the host attempt to counteract the strong pro-inflammatory response. In the German cohort study, IL-10 levels were measured alongside other cytokines and showed a significant decline from the early to the late phase of illness, similar to IL-6 and TNF-α (6). Increased IL-10 levels have been seen in nearly all blood samples from HFRS patients irrespective of the Hantavirus involved. Increased elevated levels of IL-10, IFN-γ, and TNF-α were detected in almost all serum samples studied (18). In non-human primates, PUUV infection induced increased IL-10 levels along with IL-6 and TNF-α responses. In contrast, vaccinated asymptomatic monkeys did not exhibit elevated IL-10 levels (19, 20).

The up-regulation of IL-10 during PUUV infection is a classic example of an immunoregulatory feedback loop. IL-10 is produced by monocytes and other immune cells to inhibit cytokine synthesis and has an auto-regulatory role. A similar pattern was observed at the protein level following PUUV infection, characterized by a significant upregulation of IL-10 expression. The simultaneous rise of pro-inflammatory cytokines (IL-6, TNF-α) and the anti-inflammatory cytokine IL-10 highlights the complicated balance between inflammatory tissue damage and regulatory control (5, 6). The significant decrease of IL-10 from early to late disease implies that immunoregulation becomes less necessary as the acute inflammatory response wanes (6).

The predictive value of IL-10 in PUUV infection is less evident than that of pro-inflammatory cytokines. High levels of IL-6 and TNF-α are linked with severe disease, whereas elevated IL-10 may be a reflection of the magnitude of the inflammatory response that it strives to moderate (6, 21). A similar pattern was observed at the protein level following PUUV infection, characterized by a significant upregulation of IL-10 expression. This indicates that the kinetics of IL-10 and other cytokines may differ depending on the specific hantavirus species (18). The correlation of IL-10 levels with disease severity is more likely to reflect the intensity of the underlying pro-inflammatory response rather than a direct pathogenic role for IL-10, thereby defining IL-10 as a marker of immunological activation rather than a significant driver of disease (6, 21).

Other Interleukins in PUUV Infection

Beyond the regulatory and pro-inflammatory cytokines described above, several other interleukins are involved in PUUV infection. In a German cohort study, interleukin-2 (IL-2) levels were significantly elevated in both the early and late phases of acute infection compared with healthy controls. At the same time, IL-2 expression in peripheral blood mononuclear cells was reduced, whereas IL-10 expression was markedly increased, supporting a complex immune regulatory response. Overall, patients with PUUV infection exhibit a robust cytokine response, characterized by elevated plasma levels of IL-2, IL-6, IL-8, IL-10, TNF-α, TGF-β, IFN-γ, and VEGF (6).

Interleukin-8 (IL-8), a potent neutrophil chemoattractant, is strongly upregulated during acute PUUV-HFRS. Both plasma and urinary IL-8 levels are increased in acute infection and correlate positively with renal impairment. Notably, the highest urinary IL-8 concentrations are associated with severe acute kidney injury induced by PUUV. In addition, circulating neutrophil activation markers are markedly elevated in acute PUUV-HFRS and correlate with renal dysfunction, in parallel with IL-8 levels (16, 22). Interleukin-18 (IL-18) levels are also significantly higher in patients with severe thrombocytopenia compared with those with higher platelet counts (23).

Furthermore, IFN-γ remains consistently elevated during PUUV infection (18). CD8+ T cell responses to PUUV are characterized by IFN-γ production, and IFN-γ ELISPOT assays have been used to detect PUUV-specific memory T cell responses (24, 25). In addition, type I interferons induced during PUUV infection contribute to the activation of innate lymphoid cells and early antiviral responses (5).

Transforming growth factor-beta 1 (TGF-β1) is an immunosuppressive cytokine that is significantly elevated during the early to late phases of PUUV

infection. Reduced levels of TGF-β1 have been associated with greater disease severity, as indicated by higher creatinine levels and lower platelet counts. Delayed production of TGF-β1 may contribute to the pathogenesis of hantavirus disease in humans by failing to adequately downregulate the early robust pro-inflammatory response (6). Furthermore, patients with hantavirus pulmonary syndrome have been reported to exhibit decreased serum TGF-β1 levels, whereas asymptomatic convalescent individuals show higher levels of this cytokine (26). Finally, although interleukin-12 (IL-12) concentrations in patients with HFRS are generally within the normal range, higher levels have been observed in PUUV-infected patients compared with those infected with other hantavirus species (27).

Conclusion

Infection with Puumala orthohantavirus represents a model of immune-mediated viral disease in which clinical outcomes are primarily determined by the host inflammatory response rather than direct viral cytopathicity. The evidence reviewed here indicates that the acute phase of nephropathia epidemica is characterized by a pronounced and dysregulated cytokine response involving both pro-inflammatory mediators, such as IL-6, TNF-α, IL-1β, IL-2, and IL-8, and regulatory cytokines, including IL-10 and TGF-β1. Sustained elevations of IL-6 and TNF-α, together with their association with renal dysfunction and thrombocytopenia, support their central role as key mediators of disease severity. Recent insights into IL-6 trans-signaling have further clarified its contribution to endothelial barrier dysfunction, suggesting that selective inhibition of this pathway may offer therapeutic benefit while preserving the protective effects of classical IL-6 signaling. In contrast, the increased IL-10 levels observed during the acute phase likely reflect a compensatory anti-inflammatory response that is insufficient to counterbalance excessive inflammation. Delayed TGF-β1 induction may further contribute to disease pathogenesis by failing to adequately suppress the early inflammatory response. The involvement of additional interleukins, particularly IL-2 and IL-8, underscores the complexity of the immune response, suggesting roles for T cell activation and neutrophil recruitment in vascular leakage and renal injury. Collectively, these findings indicate that the magnitude and timing of cytokine responses, shaped by both viral and host factors, determine whether infection resolves with mild disease or progresses to severe HFRS. Overall, the growing understanding of the interleukin network in PUUV infection has advanced knowledge of hantavirus immunopathogenesis and highlighted potential avenues for therapeutic intervention. Distinct cytokine signatures may serve as useful biomarkers for disease stratification and prognosis. Future work should focus on translating these findings into targeted therapies, particularly those modulating IL-6 trans-signaling or TNF-α activity in relevant preclinical models. Further studies exploring host genetic susceptibility and long-term clinical outcomes will also be essential for a more comprehensive understanding of disease progression and sequelae. Ultimately, improved mechanistic insight into cytokine-mediated immune dysregulation may facilitate the development of effective adjunctive therapies aimed at reducing morbidity and improving outcomes in hantavirus infections.

Mechanistic and Translational Relevance

Puumala orthohantavirus infection provides a clear example of immune-mediated pathogenesis in which clinical manifestations are driven predominantly by dysregulated host immune responses rather than direct viral cytopathic effects. At the mechanistic level, disease severity appears to be determined by the magnitude, timing, and balance of cytokine responses. Excessive production of pro-inflammatory mediators such as IL-6 and TNF-α contributes to endothelial activation, increased vascular permeability, and subsequent renal dysfunction and thrombocytopenia. In parallel, anti-inflammatory mediators including IL-10 and TGF-β1 represent compensatory regulatory mechanisms that are often insufficient or delayed, thereby failing to adequately

restrain early inflammatory injury. Emerging evidence further highlights pathway-specific mechanisms, particularly IL-6 trans-signaling, as a critical driver of endothelial barrier disruption. This suggests that not all cytokine signaling exerts uniform biological effects, and that selective modulation of pathogenic signaling pathways may be more effective than broad immunosuppression. Similarly, the involvement of IL-2, IL-8, and IL-18 underscores the contribution of T cell activation, neutrophil recruitment, and inflammasome-related pathways in the development of vascular leakage and acute kidney injury. From a translational perspective, distinct cytokine profiles observed in PUUV infection offer potential utility as biomarkers for early risk stratification and prognosis. Elevated IL-6 and TNF-α levels, together with altered regulatory cytokine responses, may help identify patients at increased risk of severe disease. Importantly, these mechanistic insights provide a rationale for targeted therapeutic strategies aimed at modulating specific inflammatory pathways rather than globally suppressing immune function. In particular, selective inhibition of IL-6 trans-signaling or TNF-α-mediated pathways represents a promising avenue for intervention. However, translation into clinical practice requires careful consideration of the dual protective and pathogenic roles of cytokines in antiviral immunity. Future studies integrating mechanistic immunology with clinical cohorts and experimental models will be essential to validate therapeutic targets and define optimal timing of intervention. Ultimately, a deeper understanding of cytokine network dynamics in hantavirus infection may facilitate the development of precision-based immunomodulatory therapies that reduce disease severity while preserving antiviral host defense.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interests

The author declares that there is no conflict of interest.

Author Contributions

Both authors contributed equally to the conception and design of the study, literature search, data interpretation, drafting of the manuscript, and critical revision of the article. Both authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics Statement

All ethical considerations, including plagiarism, data fabrication, and duplicate publication, have been fully observed by the authors.

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