Review Article

The Endotheliopathy of Sepsis: Vascular Dysfunction as a Therapeutic Target

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Abstract

Background- Sepsis is responsible for nearly one in five deaths worldwide, yet no targeted therapy has improved survival. Increasing evidence identifies the vascular endothelium as the organising principle of sepsis pathophysiology, integrating inflammation, coagulation, and metabolic failure into a single cascade of glycocalyx shedding, junctional disruption, coagulation imbalance, and immunothrombosis. Methods- These lesions underpin haemodynamic incoherence, acute respiratory distress syndrome, acute kidney injury, disseminated intravascular coagulation, and the long-term sequelae of post-sepsis syndrome. Circulating and urinary biomarkers—including syndecan-1, angiopoietin-2, soluble thrombomodulin, and glycosaminoglycans—mirror the extent of endothelial injury and provide translational anchors, yet remain underused in clinical classification and trial design. **Result-** Most vascular-targeted therapies, such as albumin, antithrombin, recombinant thrombomodulin, vitamin C, and statins, have failed to improve outcomes, largely due to unselected enrolment, delayed intervention, and reliance on crude mortality endpoints. Emerging strategies, including Tie2 agonists, angiopoietin-2 antagonists, and glycocalyx protectants, show promise but require biomarker-guided, adaptive evaluation. Reframing sepsis as endothelial failure offers a unifying paradigm for risk stratification, trial enrichment, and therapeutic innovation. **Conclusion**- To reduce the global burden, future strategies must be endotype-specific, mechanistically informed, and feasible across both high- and low-resource health systems.

Keywords: tip pain,laparoscopic

Introduction

One in five deaths worldwide is due to sepsis, accounting for nearly 11 million fatalities each year [1]. Despite decades of investment in antimicrobials and critical care, survival has scarcely improved, and many survivors face long-term physical and cardiovascular disability. The burden is greatest in low- and middle-income countries, where delayed recognition and limited access to intensive care amplify mortality [2].

For decades, sepsis was framed as a disorder of immune dysregulation: an early cytokine surge followed by immune exhaustion. This immune-centric model has dominated but delivered neither predictive biomarkers nor effective therapies. Mounting evidence now identifies the vascular endothelium as the nexus where inflammation, coagulation, and metabolism converge [3]. Far from a passive lining, the endothelium orchestrates vascular tone, barrier integrity, and haemostasis. In sepsis, this regulatory hub collapses—glycocalyx shedding, endothelial activation, and microvascular thrombosis transform the vasculature from protector to perpetrator [4,5].

Circulating biomarkers such as soluble thrombomodulin, syndecan-1, and angiopoietin-2 directly reflect endothelial injury and consistently predict severity and mortality, confirming endotheliopathy as a defining feature of the syndrome [6,7]. Crucially, endothelial injury is not secondary but central to the clinical trajectory. Recognising vascular dysfunction alongside immune dysregulation reframes sepsis biology and highlights opportunities for biomarker-guided risk stratification and vascular-targeted therapy.Placing the endothelium at the heart of sepsis research is not a semantic shift but a therapeutic imperative. This reconceptualisation offers a unifying explanation for circulatory collapse, coagulopathy, and long-term vascular sequelae, while setting the stage for precision strategies—biomarker-enriched trials, endotype-based stratification, and real-time monitoring of microvascular function—that could finally alter outcomes where the burden is highest.

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Endothelial Biology in Health and Sepsis

The vascular endothelium, the body's largest endocrine organ, orchestrates vascular tone, barrier integrity, and haemostasis [8]. Once regarded as a passive lining, it is now recognised as the key determinant of organ-specific vulnerability in sepsis. Endothelial heterogeneity—tight junctions in the brain, fenestrated sinusoids in the liver, and fluid–gas balancing in the lung—helps explain why injury manifests as encephalopathy, cholestasis, or acute respiratory distress syndrome [8].In health, permeability is tightly controlled: basal exchange occurs through capillaries, and inducible leak during inflammation is confined to post-capillary venules, regulated by caveolae and vesiculo–vacuolar organelles [8]. In sepsis, this control collapses. Glycocalyx degradation, reflected by circulating fragments such as syndecan-1 and heparan sulfate, correlates with organ failure and coagulopathy [9–11]. Loss of this protective layer exposes adhesion molecules, promotes leukocyte–platelet interactions, and disrupts mechanotransduction, producing oedema and maldistributed flow [9,10].Endothelial activation amplifies the lesion. Adhesion molecule upregulation (ICAM-1, VCAM-1, E-selectin) accelerates leukocyte recruitment and vascular injury [12]. Anticoagulant balance is lost: tissue factor expression rises, thrombomodulin activity falls, and neutrophil extracellular traps fuel immunothrombosis [13].

Clinically, this creates the paradox of concurrent microvascular thrombosis and systemic hypocoagulability. Observational studies suggest that every 100 ng/mL rise in syndecan-1 delays clot initiation and reduces clot strength, while also suppressing fibrinolysis [14]. Although consistent, these findings remain associative, and causal pathways are unproven.

Upstream drivers include cytokines, DAMPs, and surges of endogenous catecholamines during shock—a phenomenon termed *shock-induced endotheliopathy*. These destabilise the glycocalyx and junctional complexes. Angiopoietin-2, a Tie2 antagonist, destabilises intercellular junctions and is consistently higher in non-survivors (median 24.9 ng/mL vs 13.5 ng/mL), correlating with IL-6 and severity [15]. Soluble thrombomodulin reflects loss of anticoagulant surface integrity, while urinary glycosaminoglycans—particularly heparan sulfate and hyaluronic acid—identify patients at risk of acute kidney injury and death, with discriminative power exceeding conventional haemodynamics (AUC ≈0.86) [6,10,14].

Taken together, sepsis endotheliopathy is not a single lesion but a cascade—glycocalyx shedding, barrier leak, activation, and immunothrombosis—that transforms the vasculature from protector to perpetrator. Yet most data are observational, cross-sectional, and derived from small cohorts. Whether interventions that restore glycocalyx integrity, stabilise junctions, or modulate Tie2 signalling can alter outcomes remains untested in prospective interventional studies [6,14]. Emerging single-cell and multi-omics approaches may further clarify how organ-specific endothelial phenotypes shape these responses. The challenge is to translate mechanistic plausibility into therapies that are standardised, scalable, and feasible across diverse health systems.

Pathophysiological Mechanisms of Endotheliopathy in Sepsis

The vascular endothelium is both target and amplifier of sepsis pathology. Endothelial dysfunction links inflammation, coagulation, barrier disruption, tone dysregulation, and cell death into a single cascade that drives haemodynamic incoherence and multiorgan failure [16–18].

Inflammation–coagulation cross-talk

Cytokines such as TNF, IL-1β, and IL-6 activate NF-κB/MAPK signalling, inducing tissue factor and suppressing anticoagulant pathways. Weibel–Palade body release of von Willebrand factor (vWF) and P-selectin, together with reduced ADAMTS13 activity, shifts haemostasis towards thrombosis. The vWF–ADAMTS13 imbalance is a reproducible marker of endothelial injury, although causality in human sepsis remains unproven [16,17]. Complement activation and neutrophil extracellular traps (NETs) reinforce microthrombosis, but dismantling NETs with DNase has so far shown benefit only in preclinical models, highlighting the translational gap [18,19].

Microvascular leak and tissue hypoperfusion

Barrier failure reflects both glycocalyx degradation and junctional disruption. Heparanase, elastase, and metalloproteinases shed syndecan-1 and heparan sulfate, while RhoA–ROCK activation destabilises VE-cadherin complexes [20–22]. The result is paracellular leak, interstitial oedema, and heterogeneous flow, visible on bedside videomicroscopy even when systemic haemodynamics appear normal [18]. Soluble VE-cadherin has emerged as a marker of this junctional injury [21]. These lesions explain why patients may deteriorate despite apparently "adequate" resuscitation.

Loss of vascular tone regulation

Nitric oxide (NO) biology is disrupted in opposing directions: inducible NOS overproduction drives vasoplegia and catecholamine resistance, whereas endothelial NOS uncoupling depletes protective NO [16,18]. Dysregulated prostacyclin, endothelin-1, and RAAS signalling further amplify hypotension. Attempts to restore NO balance, whether by inhaled NO or systemic donors, have not improved microvascular function. Vitamin C and other adjuncts likewise show neutral or harmful results in meta-analyses [23]. Mitochondrial dysfunction compounds tone dysregulation, producing "cytopathic hypoxia": impaired bioenergetics despite intact oxygen delivery [24].

Endothelial cell death and prognostic signals

Apoptosis, pyroptosis, and ferroptosis accelerate endothelial injury [17,24]. Circulating biomarkers reflect these processes: angiopoietin-2 rises with severity and predicts mortality [25]; syndecan-1 associates with coagulopathy [20]; soluble thrombomodulin correlates with poor outcome, though recombinant thrombomodulin therapy has failed to improve survival in unselected sepsis [26,27]. The vWF/ADAMTS13 ratio is a consistent predictor but represents a marker of stress rather than a mechanistic driver [16,17].

Together, these mechanisms show how endothelial injury evolves from early glycocalyx shedding to barrier leak, thrombosis, tone collapse, and cell death. Most evidence remains observational or preclinical, underlining the urgent need for prospective interventional studies. Bridging this gap will require phenotype-specific enrichment and mechanistic validation across diverse health systems, particularly where the burden of sepsis is greatest.

Clinical Consequences of Endotheliopathy

Endothelial dysfunction is not an epiphenomenon but the organising principle of sepsis pathophysiology. It explains the rapid transition from infection to shock, the paradox of simultaneous microvascular thrombosis and bleeding, and the long-term vascular sequelae that persist after apparent recovery [28–30].

Shock and haemodynamic incoherence

Barrier failure, glycocalyx loss, and vasoplegia disrupt the normal relation between macrocirculation and microcirculation. Patients may remain hypotensive and poorly perfused despite apparently "adequate" fluid resuscitation and normal global haemodynamics [28]. Videomicroscopy confirms heterogeneous perfusion and capillary dropout even in well-oxygenated patients, highlighting why conventional resuscitation strategies fail to reverse tissue hypoxia.

Acute respiratory distress syndrome (ARDS)

Pulmonary endothelial injury increases permeability, promotes alveolar flooding, and recruits neutrophils through ICAM-1 and VCAM-1 upregulation. Angiopoietin-2 levels are consistently higher in patients with ARDS, correlating with oxygenation defect

and mortality [29]. Yet trials of Ang-2 modulation remain absent, underscoring the translational gap.

Acute kidney injury (AKI)

Renal microvascular dysfunction reflects both glycocalyx degradation and microthrombosis. Urinary glycosaminoglycans, notably heparan sulfate and hyaluronic acid, identify patients at risk of AKI with discriminative power exceeding serum creatinine (AUC ≈0.86) [30]. These markers position the renal microvasculature as a sentinel of systemic endothelial failure.

Disseminated intravascular coagulation (DIC)

Loss of thrombomodulin activity, NET-driven tissue factor expression, and vWF–ADAMTS13 imbalance create a paradox of clotting and bleeding. Elevated soluble thrombomodulin identifies patients at risk of overt DIC and death, but recombinant thrombomodulin failed to improve survival in unselected sepsis cohorts [26,27]. This disconnect between biomarker association and therapeutic efficacy highlights the need for endotype-guided trials.

Long-term sequelae

Survivors of sepsis face persistent vascular dysfunction, manifesting as premature cardiovascular events, neurocognitive decline, and impaired physical recovery. Endothelial senescence and microvascular rarefaction are emerging as biological explanations for the "post-sepsis syndrome," but prospective data remain scarce [31]. Together, these clinical manifestations form a recognisable syndrome of endothelial failure. They unify acute features—shock, ARDS, AKI, DIC—with chronic sequelae, and they explain why supportive strategies alone cannot alter sepsis mortality. The challenge is to embed endothelial dysfunction into sepsis classification, prognosis, and trial design in both high- and low-resource settings.

Emerging Diagnostics and Biomarkers

Although endothelial biomarkers are firmly established as correlates of sepsis severity, their translation into clinical decision-making has been uneven. The challenge is not their ability to rise in acute illness, but whether they provide **independent, actionable information** and can be standardised across diverse settings.

Syndecan-1 and **soluble thrombomodulin (sTM)** illustrate this tension. Both increase during sepsis, reflecting glycocalyx shedding and endothelial detachment. Yet their prognostic weights diverge: in adjusted analyses, sTM was a stronger predictor of mortality, whereas syndecan-1 correlated more closely with **hypocoagulability on thromboelastography**, suggesting it is more a marker of endothelial–coagulation cross-talk than a stand-alone prognosticator [6, 7]. Translation into therapy has been challenging. Despite strong prognostic associations, the phase 3 **SCARLET** trial of recombinant thrombomodulin was neutral for 28-day mortality (26·8% vs 29·4%; p=0·32) and signalled increased bleeding risk (5·8% vs 4·0%) [26], underscoring that **prognostic value does not imply therapeutic efficacy**.

For the **angiopoietin/Tie2 axis**, **angiopoietin-2 (Ang-2)**, a context-dependent Tie2 antagonist, rises within **4–6 h** after endotoxin challenge and remains persistently elevated in non-survivors [38]. A recent meta-analysis of 33 studies including more than 4700 patients reported a pooled AUC of 0·76 for predicting 28-day mortality [25]. Although such early kinetics make Ang-2 attractive for triage, its predictive performance is inconsistent under **Sepsis-3 definitions** and across geographic settings, arguing against universal cut-offs without local validation and recalibration.

The imbalance between **von Willebrand factor (vWF) and ADAMTS13** is another consistent finding. High vWF release and relative ADAMTS13 deficiency are associated with poor outcomes, but contemporary analyses suggest this imbalance is primarily a **biomarker of inflammatory stress and endothelial injury** rather than a proven mechanistic driver of thrombosis in sepsis [17]. Assay variability and non-standardised thresholds further constrain its clinical applicability.

Microvascular imaging offers a direct functional readout. Sublingual videomicroscopy and incident dark-field imaging quantify **proportion of perfused small vessels (PPV)**, capillary density, and flow heterogeneity. In severe sepsis, PPV discriminates survivors from non-survivors with an AUC of **0·82**, outperforming global haemodynamics [39], and early improvements in microvascular flow during resuscitation predict reduced organ failure [40]. Yet clinical use is limited by operator dependence, pressure and motion artefacts, and **non-interchangeability between devices**. The 2018 ESICM consensus formalised these caveats and introduced the concept of **loss of hemodynamic coherence**, highlighting the need for standardised acquisition and analysis before bedside adoption [41].

Finally, **multi-marker panels** are being investigated to overcome the limitations of single analytes. Combining syndecan-1 (glycocalyx), sTM (anticoagulant surface), and Ang-2 (permeability/vasoplegia) yields additive prognostic value, and their **divergent temporal trajectories** suggest that dynamic panels may capture evolving endothelial phenotypes more faithfully than static thresholds [38]. However, collinearity, limited external validation, and the absence of prospective impact studies—such as net reclassification or decision-curve analyses—remain major obstacles.

Moving forward, several gaps must be addressed. **Assay and operational standardisation** is essential, including harmonised thresholds, strict pre-analytical handling (timing relative to fluid load, anticoagulant choice, freeze–thaw stability), and inter-assay reproducibility. **Clinical utility** must be established in prospective trials that test whether biomarker- or microcirculation-guided strategies improve outcomes, ideally using **enrichment designs** that stratify by endothelial phenotype and incorporate microvascular endpoints. Finally, **equity and feasibility** must be central: biomarker panels and bedside imaging remain costly and technically demanding, and their validation in **low- and middle-income countries** is critical to ensure global applicability.

Therapeutic Interventions Targeting the Endothelium

Established and Repurposed Approaches

Glycocalyx degradation and coagulopathy are central features of sepsis endotheliopathy, and several conventional agents have been tested with the aim of stabilising these pathways. **Albumin** has been evaluated as a glycocalyx-preserving resuscitant. In the ALBIOS trial (n=1818), daily albumin administration did not reduce 28-day mortality overall (31.8% vs 32.0%), although patients with septic shock showed higher mean arterial pressures and a possible survival signal [42]. These findings remain hypothesis-generating and require confirmatory trials. **Anticoagulants** have yielded mixed results. High-dose antithrombin III in the KyberSept trial (n=2314) did not reduce mortality (38.9% vs 38.7%) and increased bleeding (22.0% vs 12.8%) [43]. Activated protein C initially reduced mortality in the PROWESS trial (n=1690) [44], but this benefit was not reproduced in PROWESS-SHOCK, leading to withdrawal. Heparins and low-molecular-weight heparins may still offer benefit in patients with overt disseminated intravascular coagulation (DIC), but robust evidence is lacking [30]. **Vitamin C and hydrocortisone**, proposed as endothelial-protective agents, have also failed to show consistent benefit. The VITAMINS trial (n=216) found no improvement in vasopressor-free days [45], while the larger

LOVIT trial (n=872) reported increased risk of death or persistent organ dysfunction with vitamin C (44.5% vs 38.5%; relative risk 1.21, 95% CI 1.04–1.40) [46]. These data argue against indiscriminate use.

Investigational and Novel Strategies

Targeted endothelial stabilisation is the focus of several investigational approaches.**Tie2 pathway modulation** has shown striking efficacy in preclinical models. The synthetic Tie2 agonist vasculotide reduced vascular leakage and mortality in murine sepsis [47], while the angiopoietin-2–binding antibody ABTAA converted Ang-2 into a Tie2 agonist and rescued mice from endotoxin shock [48]. Human studies are awaited. **Sphingosine-1-phosphate receptor agonists** reinforce adherens junctions and stabilise the endothelial cytoskeleton. In murine endotoxin models, S1P reduced vascular leak, lung injury, and mortality [49]. However, adverse cardiovascular and immunosuppressive effects of first-generation drugs limit their immediate clinical potential. **Recombinant thrombomodulin (rhTM)** has been extensively studied. Circulating soluble thrombomodulin is a strong prognostic marker of severity, yet therapeutic administration has been disappointing: in the SCARLET trial (n=800), 28-day mortality was 26.8% with rhTM versus 29.4% with placebo (p=0.32), and major bleeding was more common (5.8% vs 4.0%) [26]. Subgroup analyses suggest possible benefit in patients with overt DIC, highlighting the need for enrichment strategies in future studies. **Extracorporeal therapies** such as plasma exchange and haemoadsorption aim to clear injurious mediators including syndecan-1 and histones. A pilot cohort (n=20) showed feasibility and haemodynamic improvement, but mortality remained 65% [50]. Randomised haemoadsorption trials demonstrate cytokine clearance without consistent survival benefit [51]. These approaches remain experimental.

Future Directions

The repeated failure of broad-spectrum endothelial therapies highlights a central lesson: promising biomarkers or mechanistic plausibility do not guarantee clinical benefit. Neutral or harmful results with albumin, anticoagulants, recombinant thrombomodulin, and vitamin C illustrate that **unselected populations and fixed trial designs are ill-suited to complex vascular biology.** Future work must therefore embrace precision, timing, and adaptivity.

Biomarker-guided selection will be pivotal. Endothelial injury markers such as angiopoietin-2, soluble thrombomodulin, and syndecan-1 have proven prognostic value, but their real utility lies in enriching trials for patients most likely to respond. Moving beyond correlation, prospective studies must test whether stratifying by endothelial activation or coagulopathy phenotypes alters therapeutic efficacy [52]. Integration with **sepsis endotypes** offers a complementary approach. Transcriptomic and proteomic studies have delineated reproducible biological clusters within sepsis, including an “endothelial-predominant” subgroup characterised by vascular leak, coagulopathy, and glycocalyx degradation [53]. Linking endothelial biomarker panels to endotype classifiers could transform sepsis management from syndromic diagnosis to biologically defined therapy. Closing the translational gap will also require **real-time vascular monitoring at the bedside**. Sublingual videomicroscopy and related microcirculatory imaging methods provide proof of concept but require automation, quality control, and multi-centre validation before clinical deployment [54]. Surrogate assays of glycocalyx integrity or point-of-care multiplex biomarker platforms could enable clinicians to titrate interventions to dynamic changes in vascular health rather than static systemic parameters. Finally, **innovative clinical trial design** is essential. Adaptive platform trials, enriched by biomarker profiles and incorporating microvascular endpoints, offer a framework to evaluate multiple endothelial-targeted strategies while refining enrolment criteria in real time [55]. This flexibility is particularly important in sepsis, where timing and patient heterogeneity confound fixed designs. Ensuring **global equity** will be equally crucial. Most of the sepsis burden falls in low- and middle-income countries, yet biomarker assays and bedside imaging remain expensive and technically demanding. Without validation and scalable implementation in diverse health systems, endothelial therapeutics risk widening rather than narrowing disparities in care.

Taken together, the next phase of research must move beyond descriptive biomarkers and neutral trials. The path forward lies in **precision-aligned, globally applicable, and adaptively tested strategies** that recognise endotheliopathy as both a driver of acute organ failure and a targetable lesion in long-term sepsis survivorship. Redefining sepsis as an endothelial disease and testing therapies within that frame should be considered a research priority.

Conclusion

Endothelial dysfunction is not a secondary consequence of sepsis but a central driver of its pathophysiology. Glycocalyx degradation, junctional disruption, and dysregulated coagulation converge to transform the vascular surface from a protective interface into a propagator of shock, organ failure, and long-term cardiovascular disease. Recognition of this endotheliopathy reframes sepsis from a purely immunological disorder to one of coupled vascular–immune injury. Therapeutic strategies targeting the glycocalyx, barrier integrity, and anticoagulant balance represent the next frontier in sepsis management. The lessons of past neutral trials—albumin, anticoagulants, recombinant thrombomodulin, and vitamin C—demonstrate that broad, unselected interventions are insufficient. The future lies in precision medicine: biomarker-guided enrichment, endotype-based stratification, and dynamic monitoring of microvascular function to deliver therapies at the right time, to the right patients, in the right context. Framing sepsis as a vascular disease has broad implications. It positions endothelial protection and repair as unifying goals, spanning early resuscitation to long-term survivorship. Ensuring that endothelial-targeted strategies are validated and accessible in low- and middle-income countries, where sepsis burden is greatest, will be essential for global impact. Redefining sepsis as an endothelial disease and testing therapies within that frame should now be considered a research and policy priorty

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