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Heparin-Based Anticoagulation Strategies in Sepsis-Associated Coagulopathy: A Systematic Review

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ABSTRACT

Background: Sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) are core drivers of organ failure and death in sepsis, and heparins occupy a distinctive therapeutic niche by combining antithrombin-potentiated anticoagulation with antithrombin-independent anti-inflammatory and glycocalyx-protective actions. Objective: To systematically synthesize the clinical evidence for unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in sepsis-associated coagulopathy and to compare this evidence against the natural-anticoagulant replacement trials (antithrombin, tissue factor pathway inhibitor, and thrombomodulin) tested in severe sepsis. Methods: A narrative systematic review was conducted of randomized controlled trials, meta-analyses, and coagulopathy-stratified cohort studies of heparin therapy in adult sepsis and sepsis-associated DIC, with all sources independently verified against original publications. Findings: The largest unselected randomized trial of unfractionated heparin (HETRASE, n=305) found no significant 28-day mortality benefit, whereas coagulopathy-enriched propensity-matched cohorts and observational studies restricted to patients with sepsis-induced coagulopathy scores consistently reported reduced mortality, particularly with early initiation and moderate cumulative dosing. Five meta-analyses of randomized trials pooling low molecular weight and unfractionated heparin reported mortality risk or odds ratios ranging from 0.52 to 0.86, generally favoring heparin, although the associated bleeding-risk signal varied from significantly increased to significantly decreased across analyses. In contrast, three large phase III trials of single-target natural-anticoagulant replacement (antithrombin, tissue factor pathway inhibitor, and recombinant thrombomodulin) in unselected or coagulopathy-enriched severe sepsis populations each failed to demonstrate a significant mortality benefit, though coagulopathy-severity-stratified subgroup analyses of these same trials revealed benefit signals analogous to those seen with heparin. Conclusions: Heparin-based anticoagulation shows a mechanistically coherent and increasingly consistent, though not yet definitively proven, mortality benefit in sepsis-associated coagulopathy, particularly when restricted to coagulopathy-enriched populations, and this coagulopathy-stratified approach should guide the design of future confirmatory randomized trials.

Keywords: *sepsis-induced coagulopathy; disseminated intravascular coagulation; unfractionated heparin; low molecular weight heparin; anticoagulant therapy in sepsis*

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Introduction

Sepsis is defined, under the current consensus framework, as a life-threatening organ dysfunction caused by a dysregulated host response to infection, with septic shock representing the subset in which profound circulatory, cellular, and metabolic derangements markedly increase mortality [1,2]. A substantial proportion of patients who meet these criteria also develop a coagulation disturbance that ranges from subclinical activation of thrombin generation to fulminant disseminated intravascular coagulation (DIC), a syndrome in which widespread microvascular fibrin deposition consumes platelets and clotting factors, produces simultaneous thrombotic and hemorrhagic tendencies, and independently worsens organ failure and death [3]. This coagulation disturbance is not an incidental laboratory abnormality but a core pathophysiological feature of sepsis: endotoxin- and cytokine-driven tissue factor expression on monocytes and endothelium triggers unchecked extrinsic-pathway thrombin generation, while simultaneous suppression of the natural anticoagulant pathways (antithrombin, protein C, and tissue factor pathway inhibitor) and impaired fibrinolysis allow that thrombin generation to

proceed without the brakes that operate in health, producing the self-amplifying prothrombotic-inflammatory loop that defines sepsis-induced coagulopathy (SIC) [4,3].

Because this loop links coagulation activation directly to the inflammatory cascade that drives organ failure, anticoagulant therapy has long been proposed not merely as a means of correcting a laboratory abnormality but as a disease-modifying intervention in sepsis. Heparins occupy a distinctive position among the anticoagulants that have been tested for this purpose. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) both potentiate antithrombin-mediated inhibition of thrombin and factor Xa, but they additionally exert antithrombin-independent, anti-inflammatory actions, including neutralization of circulating histones and high-mobility group box-1 protein, inhibition of leukocyte adhesion and heparanase-mediated glycocalyx degradation, and restoration of the endothelial surface layer's barrier and anticoagulant functions, actions that in principle address the inflammatory and endothelial dimensions of sepsis-induced coagulopathy rather than its thrombin-generation dimension alone [4,3]. This dual mechanistic profile distinguishes heparins from the more selective natural-anticoagulant replacement strategies, such as antithrombin concentrate, recombinant tissue factor pathway inhibitor, and recombinant soluble thrombomodulin, each of which was pursued as a single-target intervention in large phase III trials during the 1990s and 2000s and each of which ultimately failed to demonstrate a mortality benefit in unselected severe sepsis populations [5,6,7].

The recurring failure of single-target anticoagulant replacement in unselected sepsis cohorts, contrasted with a smaller but more consistent body of heparin-specific evidence suggesting benefit in coagulopathy-enriched populations, has renewed clinical and academic interest in heparin as a therapeutic rather than purely prophylactic agent in sepsis, prompting a wave of randomized trials, propensity-matched cohort studies, and meta-analyses over the past two decades. This systematic review synthesizes that literature across five themes: the pathophysiological rationale for heparin therapy in sepsis-associated coagulopathy; the randomized and quasi-randomized trial evidence for unfractionated heparin; the meta-analytic and observational evidence for low molecular weight heparin; the comparative lessons drawn from the failed natural-anticoagulant replacement trials; and the unresolved questions of patient selection, dosing, and timing that continue to limit heparin's translation into standard sepsis care.

Pathophysiological Rationale for Heparin in Sepsis-Induced Coagulopathy

The pathophysiological case for heparin therapy in sepsis begins with the observation that sepsis-induced coagulopathy is fundamentally a tissue factor-driven process. Pathogen-associated molecular patterns and damage-associated molecular patterns released during infection activate monocytes and endothelial cells to express tissue factor, which complexes with circulating factor VIIa to initiate thrombin generation at a rate that overwhelms the capacity of the physiological anticoagulant systems, namely the antithrombin, protein C, and tissue factor pathway inhibitor pathways, all three of which are simultaneously downregulated or consumed during sepsis [3,4]. Excess thrombin generation deposits fibrin in the microvasculature, consumes platelets and coagulation factors, and, once consumption outpaces hepatic synthetic replacement, produces the combined thrombotic-hemorrhagic phenotype that the International Society on Thrombosis and Haemostasis (ISTH) formalized into an overt DIC scoring system based on platelet count, fibrin-related marker elevation, prothrombin time prolongation, and fibrinogen level, a framework still used to stage and enroll patients in most heparin trials discussed below [8]. The subsequent introduction of the sepsis-induced coagulopathy (SIC) score, incorporating platelet count, international normalized ratio, and Sequential Organ Failure Assessment (SOFA) subscore, was explicitly designed to identify patients earlier in this continuum, before they meet criteria for overt DIC, precisely because anticoagulant intervention is mechanistically most plausible before consumptive coagulopathy and hemorrhagic risk have become established [4].

Heparin's candidacy as a therapeutic intervention in this cascade rests on a broader mechanistic base than its canonical antithrombin-potentiating anticoagulant action alone. Circulating histones released from neutrophil extracellular traps and damaged cells during sepsis are directly cytotoxic to endothelium and independently activate platelets and complement, and heparin binds and neutralizes these histones, an action demonstrated to attenuate organ injury in preclinical sepsis models independent of its effect on thrombin generation [4]. Heparin similarly binds and neutralizes high-mobility group box-1 protein, a late inflammatory mediator implicated in sustained sepsis-associated organ dysfunction, and inhibits leukocyte rolling and adhesion to activated endothelium by interfering with selectin-mediated interactions, actions that collectively position heparin as an agent capable of interrupting the inflammation-coagulation crosstalk at multiple nodes rather than only at the point of thrombin generation [3,4]. A further, increasingly emphasized mechanism is heparin's capacity to preserve the endothelial glycocalyx: because heparin competitively inhibits heparanase, the principal enzyme responsible for pathological shedding of glycocalyx heparan sulfate during sepsis, heparin administration limits the exposure of adhesion molecules and procoagulant surface that follows glycocalyx degradation, providing a further mechanistic bridge between heparin therapy and preservation of microvascular perfusion in sepsis [3].

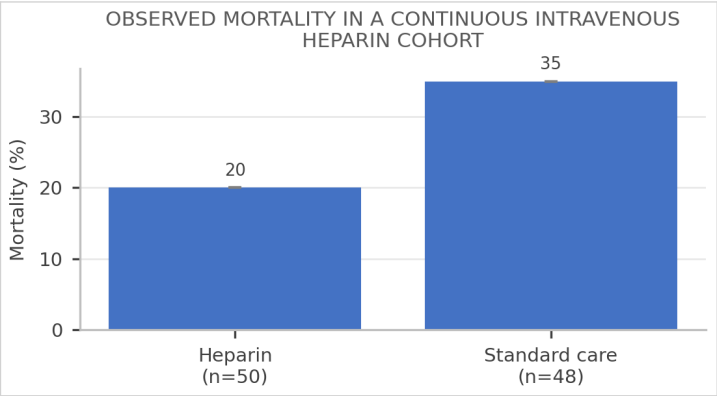
These pleiotropic actions have been demonstrated experimentally in a canine model of septic shock, in which unfractionated heparin administration was shown to directly improve intestinal microcirculatory perfusion, measured by laser Doppler and microvascular imaging, independent of systemic hemodynamic parameters, providing translational plausibility for the hypothesis that heparin's benefit, where observed clinically, may operate substantially through microcirculatory and endothelial protection rather than through correction of macroscopic coagulation parameters alone [9]. Taken together, this mechanistic literature establishes a biologically coherent, multi-pronged rationale for heparin therapy in sepsis-induced coagulopathy that extends well beyond simple anticoagulation, and it is against this rationale that the clinical trial evidence reviewed in the following sections must be interpreted.

Unfractionated Heparin: Randomized Trial and Cohort Evidence

The largest dedicated randomized trial of unfractionated heparin in sepsis, the HETRASE study, randomized 305 patients with sepsis of any severity to receive intravenous unfractionated heparin (500 IU/hour for seven days) or usual care and found no

significant difference in 28-day mortality between groups, nor in secondary outcomes including organ dysfunction scores, although the trial was criticized for enrolling a broad sepsis population not enriched for coagulopathy and for using a fixed, unmonitored heparin dose rather than one titrated to activated partial thromboplastin time or coagulopathy severity [10]. This null result, from the only large trial to randomize an unselected sepsis population to a fixed heparin regimen, has been a persistent reference point tempering enthusiasm for unfractionated heparin as a blanket therapy, and it illustrates a theme that recurs throughout this literature: trials and cohorts that enroll broadly across sepsis severity, rather than specifically among patients with document coagulopathy, have tended to show weaker or null heparin effects than those enriched for coagulopathic patients.

In-hospital mortality by treatment arm in a continuous intravenous unfractionated heparin cohort in sepsis, alongside significantly improved platelet counts, DIC scores, and SOFA scores in the heparin arm without a significant increase in bleeding events (Sun et al., 2025).



Observational cohort evidence has partially reframed this picture by focusing on coagulopathy-enriched populations and by examining dose and timing more granularly. Zarychanski and colleagues, in a retrospective propensity-matched cohort of patients with septic shock, found that early intravenous unfractionated heparin administration (within the first day of shock onset) was associated with a substantial reduction in adjusted mortality compared with no early heparin, an association that held after adjustment for illness severity and that motivated subsequent prospective evaluation of the early-administration hypothesis [11]. This early-timing hypothesis was tested most directly by Huang and colleagues in a large propensity-matched analysis of 3,377 patients meeting SIC criteria, of whom 815 received unfractionated heparin; early heparin therapy was associated with reduced intensive care unit mortality (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.52-0.92) as well as reductions in mortality at seven, fourteen, and twenty-eight days and at hospital discharge, with the benefit most pronounced among patients with the most severe coagulopathy (SIC score of 4) and among those receiving a moderate cumulative daily dose of 6,250 to 13,750 IU per day, a dose-response observation suggesting that both patient selection by coagulopathy severity and heparin dosing intensity modulate the observed benefit [12].

More recent observational data specifically targeting patients with moderate, rather than mild or severe, sepsis-induced coagulopathy have extended this coagulopathy-severity-dependent pattern: Ushio and colleagues, studying a cohort restricted to patients with SIC scores in the moderate range, found that unfractionated heparin administration was associated with improved outcomes relative to no anticoagulation in this specific severity band, reinforcing the concept that the population most likely to benefit from heparin therapy is neither the mildest nor the most advanced coagulopathy stratum but an intermediate window in which thrombin generation remains modifiable without the platelet and factor depletion that raises bleeding risk in overt DIC [13]. Consistent with this, a geriatric-specific retrospective cohort study found that heparin therapy was associated with reduced intensive care unit mortality among older septic patients, a population in whom baseline coagulopathy risk and competing bleeding risk are both elevated, again supporting a coagulopathy-severity-stratified rather than uniform approach to heparin use [14]. Finally, a recent single-center study examining continuous intravenous heparin infusion in sepsis reported a numerically lower mortality in the heparin group (20%, 10 of 50 patients) compared with standard care (35%, 17 of 48 patients), a difference that did not reach statistical significance (P = .088) in this modestly powered cohort but that was accompanied by significantly higher platelet counts from treatment day three onward, significantly lower DIC scores from day four onward, and significantly reduced SOFA scores between days five and seven, without a significant increase in bleeding events [15]. Considered together, these unfractionated heparin studies depict a therapy whose apparent benefit strengthens as trial populations are increasingly restricted to patients with documented, moderate-to-severe coagulopathy and as heparin administration is initiated earlier and dosed within an intermediate intensity range, a pattern the single large unselected trial was not designed to detect [10,11,12,13,14,15].

Low Molecular Weight Heparin: Meta-Analytic Evidence

Low molecular weight heparin has been evaluated primarily through meta-analyses pooling multiple smaller randomized trials rather than through a single large definitive trial, and this meta-analytic literature has, on balance, reported more consistent mortality benefit than the unfractionated heparin literature, albeit with important caveats regarding bleeding risk and trial quality. Wang and colleagues, pooling nine studies encompassing 3,482 adult patients with severe sepsis, found that heparin therapy (predominantly low molecular weight formulations) was associated with significantly reduced 28-day mortality (odds ratio 0.656, 95% CI 0.562-0.765) without a significant increase in bleeding complications, an early and influential meta-analysis that helped establish heparin therapy as a plausible adjunct in severe sepsis specifically, as distinct from sepsis of any severity [16]. Fan and colleagues subsequently focused specifically on low molecular weight heparin and found a comparable mortality reduction (risk ratio [RR] 0.72, 95% CI 0.57-0.91) alongside significant improvements in APACHE II score, prothrombin time, and platelet count and significant reductions in interleukin-6 and tumor necrosis factor-α, indicating a concurrent anti-inflammatory signal; however, this same analysis found a significantly increased risk of bleeding complications with LMWH (RR 3.82, 95% CI 1.81-8.08), including a higher rate of gastrointestinal hemorrhage (4.26% versus 0.75% in controls), a safety signal that stands in contrast to the neutral bleeding findings reported for unfractionated heparin in several of the cohort studies above [17].

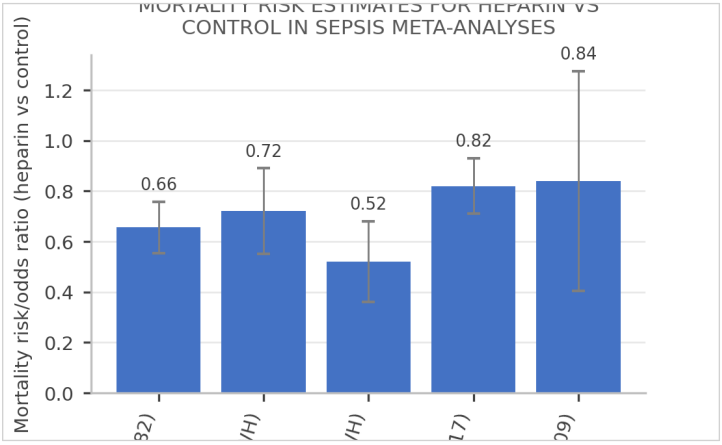
This apparent discordance in bleeding risk across meta-analyses was substantially reconciled by Li and colleagues, whose meta-analysis of low molecular weight heparin in adult sepsis reported a mortality benefit of similar magnitude to Wang's (RR 0.52, 95% CI 0.38-0.70) together with significant improvements in

prothrombin time, D-dimer, platelet count, APACHE II score, and multiple organ dysfunction syndrome incidence (RR 0.54, 95% CI 0.36-0.80), but, unlike Fan and colleagues, found no significant increase in bleeding events with LMWH (RR 1.29, 95% CI 0.76-2.17), a discrepancy the authors attributed to differences in the specific trials pooled and in bleeding definitions used across the included studies [18]. Complementing these sepsis-specific pooled analyses, Fu and colleagues performed a broader systematic review and meta-analysis of unfractionated heparin across fifteen randomized controlled trials totaling 2,617 patients and similarly reported a significant 28-day mortality reduction (RR 0.82, 95% CI 0.72-0.94), with greater benefit among patients with higher baseline APACHE II scores (RR 0.83 in the subgroup with APACHE II greater than 15), improved platelet counts and activated partial thromboplastin time, reduced multiple organ dysfunction incidence, shorter ICU stay and ventilation duration, and no significant increase in bleeding events (RR 1.10, 95% CI 0.54-2.23), a result that, unlike the LMWH-specific analyses of Fan and colleagues, aligned with a more favorable bleeding profile for unfractionated formulations pooled across a larger trial base [19]. The most recent and most methodologically conservative synthesis, by Totoki and colleagues, restricted its meta-analysis to three randomized controlled trials specifically enrolling patients with sepsis-associated DIC (109 patients) and separately analyzed 426 patients with sepsis overall, and in both analyses found no statistically significant mortality benefit for heparin (risk ratio 0.84 in the DIC subgroup and 0.86 overall), while nonetheless identifying a significant reduction in bleeding risk with heparin therapy (risk ratio 0.49, 95% CI 0.24-0.99, P = .047), a finding that inverts the safety concern raised by earlier LMWH-focused work and underscores how sensitive pooled conclusions remain to the specific trials included and the DIC-versus-sepsis framing of the analysis [20].

Summary of meta-analyses pooling randomized controlled trials of heparin therapy in adult sepsis and sepsis-associated DIC.

Study	Formulation	Trials / patients pooled	Mortality effect estimate	Bleeding risk
Wang et al. 2014	Heparin (mixed)	9 studies / 3482 patients	OR 0.656 (95% CI 0.562-0.765)	No significant increase
Fan et al. 2016	LMWH	RCTs pooled	RR 0.72 (95% CI 0.57-0.91)	RR 3.82 (95% CI 1.81-8.08), increased
Li et al. 2021	LMWH	RCTs pooled	RR 0.52 (95% CI 0.38-0.70)	RR 1.29 (95% CI 0.76-2.17), not significant
Fu et al. 2022	Unfractionated heparin	15 RCTs / 2617 patients	RR 0.82 (95% CI 0.72-0.94)	RR 1.10 (95% CI 0.54-2.23), not significant
Totoki et al. 2024	Heparin (DIC subgroup)	3 RCTs / 109 patients (DIC)	RR 0.84 (95% CI 0.51-1.38), not significant	RR 0.49 (95% CI 0.24-0.99), decreased

Twenty-eight-day mortality risk estimates for heparin versus control across five meta-analyses of randomized controlled trials in adult sepsis and sepsis-associated disseminated intravascular coagulation (Wang et al., 2014; Fan et al., 2016; Li et al., 2021; Fu et al., 2022; Totoki et al., 2024), illustrating a consistent direction of effect favoring heparin despite variable statistical significance.



Across this body of five meta-analyses spanning a decade, mortality point estimates consistently favor heparin therapy, with risk or odds ratios ranging from approximately 0.52 to 0.86, yet statistical significance and the direction of the bleeding-risk signal vary appreciably depending on which trials, which coagulation phenotype, and which heparin formulation are included [16,17,18,19,20]. This heterogeneity, rather than undermining the case for heparin therapy outright, points toward the same conclusion suggested by the unfractionated heparin cohort literature: that heparin's benefit in sepsis is most reliably observed, and most safely delivered, in patients with defined coagulopathy rather than in unselected sepsis populations, a hypothesis now being tested prospectively.

Lessons from Failed Natural-Anticoagulant Replacement Trials

The heparin literature cannot be interpreted in isolation from the larger, and largely disappointing, history of natural-anticoagulant replacement trials in severe sepsis, against which heparin's more selective, coagulopathy-enriched signal stands in instructive contrast. The KyberSept trial randomized 2,314 patients with severe sepsis to high-dose antithrombin III concentrate or placebo and found no significant difference in 28-day all-cause mortality between groups, despite antithrombin's central role in the coagulation cascade that heparin itself potentiates; a post hoc subgroup analysis suggested possible benefit among patients not receiving concomitant heparin, an observation that inadvertently highlighted a pharmacodynamic interaction between antithrombin replacement and heparin coadministration that has informed subsequent trial design in this field [5]. The OPTIMIST trial similarly randomized patients with severe sepsis to recombinant tissue factor pathway inhibitor (tifacogin) or placebo and found no significant reduction in 28-day mortality, with a post hoc analysis again suggesting that concomitant heparin use was associated with increased bleeding and attenuated efficacy in the tifacogin arm, reinforcing the theme that natural-anticoagulant replacement strategies tested in broad, unselected severe sepsis populations have failed to translate mechanistic plausibility into clinical benefit [6].

The most recent and most rigorously designed of these trials, SCARLET, randomized 800 patients with sepsis-associated coagulopathy, defined by a composite of coagulation and

organ-dysfunction criteria intended to enrich for a coagulopathic phenotype more precisely than earlier trials, to recombinant human soluble thrombomodulin (ART-123) or placebo, and found a 28-day all-cause mortality of 26.8% in the thrombomodulin group versus 29.4% in the placebo group, a difference that did not reach statistical significance despite the trial's coagulopathy-enrichment design [7]. An accompanying editorial characterized SCARLET as another negative sepsis trial and questioned whether any single-target anticoagulant agent, however mechanistically plausible and however carefully the enrolled population is enriched for coagulopathy, can be expected to alter mortality in a syndrome as biologically heterogeneous as sepsis [21]. A subsequent updated meta-analysis pooling SCARLET with an earlier phase IIb trial of the same agent found a statistically significant mortality benefit for thrombomodulin specifically among the subset of patients with the most severe coagulopathy, suggesting that even within a single failed phase III trial, coagulopathy-stratified subgroup analysis can reveal a benefit signal obscured in the overall trial population, a pattern directly analogous to the coagulopathy-severity gradient observed across the heparin literature reviewed above [22].

Major randomized controlled trials of anticoagulant replacement strategies in severe sepsis and sepsis-associated coagulopathy, illustrating the contrast between single-target natural-anticoagulant replacement and heparin-based approaches.

Trial	Agent	Population (n)	Primary outcome result
KyberSept (Warren et al., 2001)	High-dose antithrombin III	Severe sepsis (n=2314)	No significant 28-day mortality difference vs placebo
OPTIMIST (Abraham et al., 2003)	Tifacogin (recombinant TFPI)	Severe sepsis (n=1754)	No significant 28-day mortality difference vs placebo
SCARLET (Vincent et al., 2019)	Recombinant soluble thrombomodulin (ART-123)	Sepsis-associated coagulopathy (n=800)	28-day mortality 26.8% vs 29.4%, not significant
HETRASE (Jaimes et al., 2009)	Unfractionated heparin	Sepsis, unselected severity (n=305)	No significant 28-day mortality difference vs usual care

This convergence of the antithrombin, tissue factor pathway inhibitor, and thrombomodulin trial experiences delivers two lessons directly relevant to interpreting the heparin literature. First, single-target replacement of one natural anticoagulant, delivered to an unselected severe sepsis population, has now failed in three large, well-conducted phase III trials spanning three distinct anticoagulant pathways, a consistency across mechanistically diverse agents that argues the failure mode is more likely related to population heterogeneity and trial design than to the specific pathway targeted [5,6,7]. Second, and more encouragingly for heparin, subgroup and updated analyses of these same trials repeatedly locate a benefit signal specifically among patients with more severe, better-characterized coagulopathy, precisely the enrichment strategy that the more positive unfractionated and low molecular weight heparin studies have increasingly adopted, whether by restricting enrollment to SIC-positive patients, by analyzing outcomes stratified by SIC or DIC score, or by focusing specifically on early treatment initiation [22,12,13]. Heparin's pleiotropic, multi-target mechanism, discussed above, may also make it more robust to the biological heterogeneity that undermined the single-target replacement agents, since heparin's histone-neutralizing, anti-adhesive, and glycocalyx-protective actions operate through pathways largely independent of the specific natural-anticoagulant pathway that happens to be depleted in an individual patient [4,3].

Patient Selection, Dosing, and Future Directions

The cumulative evidence reviewed above converges on a consistent, if still incompletely proven, hypothesis: heparin therapy, whether unfractionated or low molecular weight, is most likely to benefit septic patients who have been identified as coagulopathic by an explicit scoring system, and is least likely to benefit, and most likely to appear falsely neutral in trials, when applied unselected across the full severity spectrum of sepsis. The HETRASE trial's null result in an unselected sepsis population, set against the more consistent positive signal in the SIC-score-stratified and coagulopathy-enriched cohorts of Huang, Ushio, and Ren and colleagues, together with the coagulopathy-severity-dependent subgroup benefit uncovered in the thrombomodulin meta-analysis, collectively support enrichment by a validated coagulopathy score, most practically the ISTH overt DIC score or the SIC score, as a prerequisite for future heparin trials rather than an optional refinement [10,12,13,14,22,8,4].

Dosing and timing likewise emerge as variables that the existing literature has only begun to resolve systematically. The observation that a moderate cumulative unfractionated heparin dose (6,250 to 13,750 IU per day) was specifically associated with reduced mortality in the Huang cohort, while HETRASE's fixed 500 IU per hour (12,000 IU per day) regimen in an unselected population showed no benefit, hints that dose-response relationships in this setting may not be monotonic and may interact with coagulopathy severity and bleeding risk in ways that a single fixed-dose randomized protocol cannot capture [12,10]. Similarly, the mortality benefit associated specifically with early heparin initiation in the Zarychanski cohort, contrasted with the absence of a timing-based intervention in the older fixed-duration trials, suggests that a therapeutic window analogous to that established for early antimicrobial therapy and early hemodynamic resuscitation in sepsis may exist for anticoagulant therapy as well, though this remains a hypothesis generated from observational rather than randomized timing comparisons and is therefore subject to residual confounding by indication [11].

Recognizing these unresolved questions, the ongoing HepSIC trial has been designed explicitly to test heparin's efficacy in a population restricted to patients with sepsis-induced DIC, using a multicenter randomized design intended to overcome the enrollment heterogeneity that has limited interpretation of the prior literature, and its results, when available, are positioned to be the most directly informative prospective evidence on this question since HETRASE [23]. Beyond trial design, several practical gaps remain unaddressed by the current evidence base: no trial has directly compared unfractionated heparin against low molecular weight heparin head-to-head in a coagulopathy-enriched sepsis population, so the apparent difference in bleeding risk between formulations observed across separate meta-analyses cannot be attributed with confidence to the drug class itself rather than to differences in included trial populations; renal dose adjustment of LMWH, a standard consideration in other indications, has not been systematically evaluated in the sepsis-associated acute kidney injury population

in which it would be most relevant; and no study has yet integrated heparin dosing decisions with real-time biomarkers of ongoing thrombin generation or glycocalyx injury, such as D-dimer trajectory or circulating syndecan-1, to individualize therapy rather than relying on a single baseline coagulopathy score [17,18,3]. Addressing these gaps through adequately powered, coagulopathy-stratified, dose-titrated randomized trials represents the most direct path toward converting heparin's currently promising but heterogeneous evidence base into a defensible clinical recommendation.

Conclusion

This systematic review of the heparin-based anticoagulation literature in sepsis-associated coagulopathy finds a body of evidence that is mechanistically coherent and increasingly, though not uniformly, favorable, in contrast to the consistently null results of single-target natural-anticoagulant replacement strategies tested in unselected severe sepsis populations [5,6,7]. Unfractionated heparin's largest dedicated randomized trial in unselected sepsis was neutral, but cohort studies restricting analysis to patients with defined sepsis-induced coagulopathy, and particularly those initiating heparin early and at moderate cumulative doses, have repeatedly found reduced mortality [10,11,12,13,14,15]. Meta-analyses of low molecular weight and unfractionated heparin across randomized trials consistently estimate mortality risk or odds ratios below 1.0, generally in the range of 0.52 to 0.86, though the associated bleeding-risk signal varies from significantly increased to significantly decreased depending on the specific trials and populations pooled [16,17,18,19,20]. The pleiotropic, multi-target mechanism by which heparin neutralizes histones and high-mobility group box-1 protein, inhibits leukocyte-endothelial adhesion, and preserves the endothelial glycocalyx via heparanase inhibition provides biological plausibility for why heparin's benefit may prove more robust to the biological heterogeneity of sepsis than the single-pathway replacement strategies embodied by antithrombin, tissue factor pathway inhibitor, and thrombomodulin [4,3,9]. What the field now requires, and what the ongoing HepSIC trial and future coagulopathy-stratified studies are positioned to provide, is prospective, adequately powered confirmation that heparin therapy, selectively applied to patients identified by a validated coagulopathy score and dosed and timed according to the patterns suggested by the observational literature, improves survival in sepsis-associated coagulopathy without an unacceptable increase in bleeding risk [23]. Until that confirmation is available, heparin-based anticoagulation should be regarded as a biologically well-justified and increasingly evidence-supported, but not yet definitively proven, therapeutic strategy in sepsis-associated coagulopathy, best reserved for patients with objectively documented coagulopathy rather than applied uniformly across the sepsis spectrum.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Kask K conceived the review, conducted the literature search, and drafted the manuscript. Chevalier C contributed to the literature screening and hematological framing and critically revised the manuscript for important intellectual content. Pichler C contributed additional clinical pharmacology context and approved the final version for submission.

Ethics Statement

Not applicable. This is a systematic review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

References

1. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M (2016) Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 315(8):775-787, DOI:10.1001/jama.2016.0289.

2. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC (2016) Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 315(8):762-774, DOI:10.1001/jama.2016.0288.

3. Levi M, van der Poll T (2017) Coagulation and sepsis. Thrombosis Research, 149:38-44, DOI:10.1016/j.thromres.2016.11.007.

4. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M (2019) Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. Journal of Thrombosis and Haemostasis, 17(11):1989-1994, DOI:10.1111/jth.14578.

5. Warren BL, Eid A, Singer P, Pillay SS, Carl P, Novak I, Chalupa P, Atherstone A, Penzes I, Kubler A, Knaub S, Keinecke HO, Heinrichs H, Schindel F, Juers M, Bone RC, Opal SM (2001) High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA, 286(15):1869-1878, DOI:10.1001/jama.286.15.1869.

6. Abraham E, Reinhart K, Opal S, Demeyer I, Doig C, Lopez Rodriguez A, Beale R, Svoboda P, Laterre PF, Simon S, Light B, Spapen H, Stone J, Seibert A, Peckelsen C, De Deyne C, Postier R, Pettila V, Sprung CL, Artigas A, Percell SR, Shu V, Zwingelstein C, Tobias J, Poole L, Stolzenbach JC, Creasey AA (2003) Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. JAMA, 290(2):238-247, DOI:10.1001/jama.290.2.238.

7. Vincent JL, Francois B, Zabolotskikh I, Daga MK, Lascarrou JB, Kirov MY, Pettila V, Wittebole X, Meziani F, Mercier E, Lobo SM, Barie PS, Crowther M, Esmon CT, Fareed J, Gando S, Gorelick KJ, Levi M, Mira JP, Opal SM, Parrillo J, Russell JA, Saito H, Tsuruta K, Sakai T, Fineberg D (2019) Effect of a recombinant human soluble thrombomodulin on mortality in patients with sepsis-associated coagulopathy: the SCARLET randomized clinical trial. JAMA, 321(20):1993-2002, DOI:10.1001/jama.2019.5358.

8. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M (2001) Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thrombosis and Haemostasis, 86(5):1327-1330.

9. Zhang H, Sun Y, An X, Ma X (2021) Unfractionated heparin improves the intestinal microcirculation in a canine septic shock model. Mediators of Inflammation, 2021:9985397, DOI:10.1155/2021/9985397.

10. Jaimes F, De La Rosa G, Morales C, Fortich F, Arango C, Aguirre D, Munoz A (2009) Unfractioned heparin for treatment of sepsis: a randomized clinical trial (the HETRASE Study). Critical Care Medicine, 37(4):1185-1196, DOI:10.1097/CCM.0b013e31819c06bc.

11. Zarychanski R, Doucette S, Fergusson D, Roberts D, Houston DS, Sharma S, Gulati H, Kumar A (2008) Early intravenous unfractionated heparin and mortality in septic shock. Critical Care Medicine, 36(11):2973-2979, DOI:10.1097/CCM.0b013e31818b8c6b.

12. Huang JJ, Zou ZY, Zhou ZP, Liu Y, Yang ZJ, Zhang JJ, Luan YY, Yao YM, Wu M (2023) Effectiveness of early heparin therapy on outcomes in critically ill patients with sepsis-induced coagulopathy. Frontiers in Pharmacology, 14:1173893, DOI:10.3389/fphar.2023.1173893.

13. Ushio N, Yamakawa K, Mochizuki K, Hisamune R, Umemura Y, Takasu A (2024) Efficacy of unfractionated heparin in patients with moderate sepsis-induced coagulopathy: an observational study. Thrombosis Research, 241:109095, DOI:10.1016/j.thromres.2024.109095.

14. Ren ZF, Huang JJ, Xin K, Yang ZJ, Li DZ, Chen YH, Guan YH, Liu ZF, Wu M (2025) Heparin therapy was associated with the reduction of ICU mortality in geriatric patients with sepsis: a retrospective cohort study. Clinical and Applied Thrombosis/Hemostasis, 31:10760296251386049, DOI:10.1177/10760296251386049.

15. Sun Q, Wang S, Ding X, Sun T, Wang B, Shao T, Yu Z, Han Y (2025) The impact of continuous intravenous administration of heparin on coagulation dysfunction and organ failure in patients with sepsis. Scientific Reports, 15:38781, DOI:10.1038/s41598-025-22773-x.

16. Wang C, Chi C, Guo L, Wang X, Guo L, Sun J, Sun B, Liu S, Chang X, Li E (2014) Heparin therapy reduces 28-day mortality in adult severe sepsis patients: a systematic review and meta-analysis. Critical Care, 18:563, DOI:10.1186/s13054-014-0563-4.

17. Fan Y, Jiang M, Gong D, Zou C (2016) Efficacy and safety of low-molecular-weight heparin in patients with sepsis: a meta-analysis of randomized controlled trials. Scientific Reports, 6:25984, DOI:10.1038/srep25984.

18. Li X, Liu Z, Luo M, Xi Y, Li C, Wang S, Yang R (2021) Therapeutic effect of low-molecular-weight heparin on adult sepsis: a meta-analysis. Annals of Palliative Medicine, 10(3):3115-3127, DOI:10.21037/apm-21-169.

19. Fu S, Yu S, Wang L, Ma X, Li X (2022) Unfractionated heparin improves the clinical efficacy in adult sepsis patients: a systematic review and meta-analysis. BMC Anesthesiology, 22:28, DOI:10.1186/s12871-021-01545-w.

20. Totoki T, Koami H, Makino Y, Wada T, Ito T, Yamakawa K, Iba T (2024) Heparin therapy in sepsis and sepsis-associated disseminated intravascular coagulation: a systematic review and meta-analysis. Thrombosis Journal, 22:84, DOI:10.1186/s12959-024-00653-0.

21. van der Poll T (2019) Recombinant human soluble thrombomodulin in patients with sepsis-associated coagulopathy: another negative sepsis trial? JAMA, 321(20):1978-1980, DOI:10.1001/jama.2019.5792.

22. Yamakawa K, Levy JH, Iba T (2019) Recombinant human soluble thrombomodulin in patients with sepsis-associated coagulopathy (SCARLET): an updated meta-analysis. Critical Care, 23:302, DOI:10.1186/s13054-019-2587-2.

23. Sun Y, Ding R, Sun H, Liang Y, Ma X (2024) Efficacy and safety of heparin for sepsis-induced disseminated intravascular coagulation (HepSIC): study protocol for a multicenter randomized controlled trial. Trials, 25:4, DOI:10.1186/s13063-023-07853-5.