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SEPSIS IN THE ICU (J LIPMAN, SECTION EDITOR)

Septic Coagulopathy: Pathophysiology, Diagnosis, and Therapeutic Strategies

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Abstract

Purpose of Review Septic coagulopathy is a complex disorder linked with multiple organ dysfunction and increased mortality, and definitive treatments are still lacking. This review summarizes the current understanding of septic coagulopathy, covering its pathophysiology, diagnosis, and debatable treatment approaches. Additionally, it provides a thorough overview of recent research and emerging trends in this area.

Recent Findings Recent studies have highlighted the interplay between coagulation mechanisms in sepsis and inflammatory response. Diagnostic tools include the newly published scoring system for sepsis-induced coagulopathy and the existing scoring systems for disseminated intravascular coagulation, enhancing early detection and treatment. Several drugs targeting abnormal clotting have been investigated in septic coagulopathy or wider septic groups, including heparin, antithrombin, activated protein C, and human-soluble thrombomodulin. However, they have not yielded clear survival benefits. Nonetheless, recent studies indicate that some of those therapies may benefit specific groups with septic coagulopathy, emphasizing the growing interest in emerging biomarkers and precision medicine to enhance patient outcomes.

Summary Despite recent advancements, no pharmaceutical intervention is currently endorsed for septic coagulopathy. However, a noted association exists between disseminated intravascular coagulation and unfavorable prognosis. Future research is imperative, especially in devising individualized treatment strategies tailored to each patient's condition.

Keywords Immunothrombosis · Endothelial damage · Disseminated intravascular coagulation · Sepsis-induced coagulopathy · Biomarkers · Precision medicine

Introduction

Septic coagulopathy is a prominent complication in patients with sepsis. This condition is marked by an abnormality in the coagulation system, leading to serious clotting disorders and bleeding complications [1]. Disordered coagulation is one of the characteristic features of sepsis, and almost every patient suffering from sepsis experiences increased coagulation activation, reduced anticoagulation, and impaired fibrinolysis [2]. The incidence of coagulopathy in septic patients ranges from 50 to 70%, depending on the specific definition used [3]. Furthermore, its correlation with increased mortality rates underscores the significance of this condition. In a post hoc analysis of two large randomized controlled trials (RCTs) on sepsis, it was associated with significantly higher 90-day mortality (13.9% vs. 26.8%) and morbidity in patients diagnosed with septic coagulopathy based on the latest diagnostic criteria [4].

The pathophysiology of septic coagulopathy is highly complex, involving the intricate interplay of coagulation mechanisms, anticoagulant pathways, and fibrinolysis, all intertwined with the systemic inflammatory response [5, 6]. These changes serve as both detrimental effects and defensive reactions to the invasion of pathogens [7]. Such intricacy poses significant challenges to effective management,

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as therapeutic strategies must adapt to their variable course and strive to strike a balance between controlling coagulation and minimizing the risk of bleeding [8]. Notably, there is no pharmaceutical treatment for septic coagulopathy with clinically solid evidence backing its recommendation. These aspects stress the necessity for a comprehensive understanding of septic coagulopathy, from its initial triggers to its ultimate manifestations, to optimize the management of sepsis.

Given these considerations, this review aims to consolidate the current knowledge on septic coagulopathy, detailing its pathophysiology, diagnostic tools, and debatable treatment options. Additionally, we seek to spotlight ongoing research initiatives, offering a strategic roadmap for future explorations in septic coagulopathy.

Methods

We conducted a comprehensive search on PubMed for relevant articles addressing septic coagulopathy published by June 22, 2023. The search strategy is shown in the Supplementary Information. To ensure consistent language throughout our review, we only included literature described in English. Additionally, we incorporated relevant articles obtained from a review of the references in the identified manuscripts.

Systemic Inflammatory Response and Coagulation in Sepsis: Immunothrombosis and Septic Coagulopathy

The essential mechanism of sepsis is an exaggerated systemic inflammatory response, leading to hypercoagulability. This response involves a complex interplay of immune cells, cytokines, and other mediators, collectively contributing to a pro-coagulant state. This state is characterized by the activation of coagulation pathways, inhibition of anticoagulant pathways, and impairment of fibrinolysis, culminating in the widespread formation of microvascular thrombi [9, 10].

In sepsis, the onset of the inflammatory response is driven by the detection of pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs) on immune cells [11]. This recognition triggers the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which subsequently activate the coagulation system. The activated coagulation system can further amplify the inflammatory response, creating a vicious cycle of inflammation and coagulation [11, 12].

A significant player in sepsis is immunothrombosis, a process that intertwines the immune response and coagulation (Fig. 1). Neutrophil extracellular traps (NETs), web-like structures released by neutrophils, are vital contributors to this process. NETs can trap and kill pathogens and provide a scaffold for platelets and coagulation factors, promoting thrombus formation [13]. This interaction between the immune system and coagulation can contribute to the pathogenesis of sepsis. NETs are formed by a unique NETosis process, a cell death distinct from apoptosis and necrosis [14, 15]. During NETosis, the nuclear membrane of the neutrophil ruptures, and the chromatin, mixed with granular proteins, is expelled into the extracellular space [16]. These NETs can trap and neutralize pathogens, preventing their dissemination. However, the exposed chromatin and granular proteins can activate platelets and coagulation, forming thrombi [7].

While essential for the body's defense mechanism, the coagulation cascade can also harm septic patients. The widespread formation of microvascular thrombi can lead to organ dysfunction due to impaired perfusion [12]. Moreover, clot formation causes consumptive coagulopathy, resulting from the consumption of coagulation factors and platelets, and an increased fibrinolytic system, which increases the risk of bleeding. [17–19]. Therefore, patients with septic coagulopathy are at risk for both thrombotic and hemorrhagic complications due to immunothrombosis. The adverse effects of the coagulation cascade in sepsis extend beyond thrombosis and bleeding. The activation of coagulation can also lead to the generation of thrombin, which can have pro-inflammatory effects and cause endothelial dysfunction [20, 21, 22•]. Thrombin can induce the expression of adhesion molecules on endothelial cells, promoting the recruitment and adhesion of leukocytes. It can also cause the release of pro-inflammatory cytokines, further amplifying the inflammatory response and endothelial damage [23].

The systemic inflammatory response and coagulation in sepsis are closely intertwined, amplifying the other. This interplay can lead to a dysregulated coagulation, resulting in widespread thrombosis, consumptive coagulopathy, and organ dysfunction. The intricate balance between inflammation and coagulation and the role of NETs in sepsis remains to be explored and understood.

Definition and Diagnostic Criteria of Septic Coagulopathy: An Exploration of Terminology and Conceptual Framework

"Septic coagulopathy" is a term used to describe a multifactorial composite state that reflects the complex pathophysiology of sepsis, involving altered coagulation, immune response, and inflammatory pathways. Within this broad spectrum, two specific entities disseminated intravascular coagulation (DIC) and sepsis-induced coagulopathy (SIC), have been defined and distinguished but have commonalities between the two (Fig. 2). These scores are designed to identify the most severely ill population in terms of

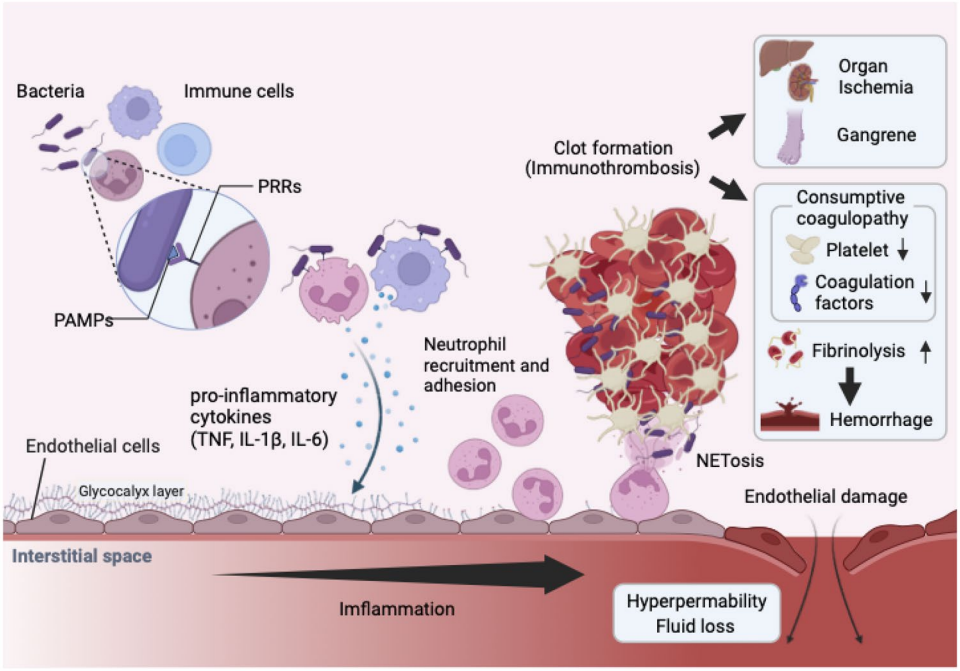

Fig. 1 Pathogenesis of septic coagulopathy: immune activation and thrombotic response. In the initial process of septic coagulopathy, immune cells recognize pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs). This recognition triggers the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1β (IL-1β), and interleukin-6 (IL-6). The ensuing inflammation destroys the glycocalyx that covers the surface of vascular endothelial cells. Subsequently, the inflammatory cytokines promote the induction of neutrophils, which then adhere to the exposed vascular endothelial cells. Once activated, the neutrophils release neutrophil extracellular traps (NETs), networks of fibers primarily composed of deoxyribonucleic acid (DNA) from neutrophils, which serve to trap, localize, neutralize, and kill bacteria. These NETs also have the effect of activating platelets and promoting thrombosis. Excessively formed clots cause organ ischemia and gangrene. Platelets and coagulation factors are consumed, and fibrinolysis is activated, resulting in an increased risk of bleeding. Finally, the inflammation-injured vascular endothelium becomes hyperpermeable, leading to fluid loss

coagulation, and in this respect, they serve more as prognostic criteria to identify patients at high risk of death, rather than as diagnostic criteria. Due to their validated prognostic performance, these scores have been used in many clinical trials to select populations for therapeutic intervention.

Disseminated Intravascular Coagulation

DIC is a complex and severe pathological condition encountered in critical illnesses, characterized by a simultaneous occurrence of hypercoagulability and fibrinolysis, resulting in widespread microvascular thrombosis and paradoxical bleeding [10, 24]. These manifestations impact multiple organ systems, leading to significant morbidity and mortality. Among conditions leading to DIC, sepsis is notable for its immune response to infection. This response causes a complex interplay between the inflammatory and coagulation systems, ultimately leading to DIC. The study of sepsis-associated DIC has been extensive, with research focusing on understanding the underlying mechanisms, identifying diagnostic markers, and developing targeted therapeutic strategies [25–27].

Two predominant scoring systems have been developed to facilitate the diagnosis of DIC: the International Society on Thrombosis and Hemostasis (ISTH) DIC diagnostic scoring

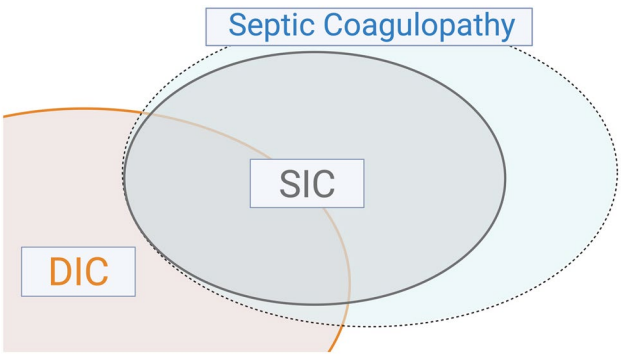

Fig. 2 Conceptual Venn diagram of septic coagulopathy, disseminated intravascular coagulation, and sepsis-induced coagulopathy. Septic coagulopathy is a conceptual term that refers to various degrees of coagulopathy occurring in patients with sepsis. Disseminated intravascular coagulation (DIC) is a condition of severe coagulopathy resulting from a variety of conditions, including sepsis, and is defined by criteria. Sepsis-induced coagulopathy (SIC) is defined by criteria specifically established for sepsis to identify severely ill patients, which broadly encompasses DIC due to sepsis

system and the Japanese Association for Acute Medicine (JAAM) DIC diagnostic scoring system [28, 29].

The DIC Diagnostic Criteria by ISTH

The ISTH has formulated a concept of DIC and a scoring system to enhance patient outcomes [28]. The ISTH DIC scoring system is structured to be applied in the presence of an underlying disorder associated with DIC. This scoring system incorporates the results of routine laboratory tests, which are generally available daily in most hospitals. Depending on the type of test used, cutoff values for a "strongly" or "moderately" elevated result of the test for fibrin-related markers, including soluble fibrin monomers, D-dimer, or fibrin degradation products (FDP), are established. A score equal to or more than five is compatible with overt-DIC, whereas a score of less than five may be indicative (but not affirmative) for non-overt DIC (Table 1). A systematic review reported a consistent association between the presence of DIC, as determined by the ISTH DIC scoring system, and mortality [30]. Furthermore, the act of conducting ISTH overt-DIC screening itself on the day of intensive care unit admission was associated with a lower mortality rate, and this association became even stronger when the screening was repeated 2 days later [31]. These findings suggest that early and repeated screening using the ISTH DIC scoring system may decrease the mortality of patients afflicted with DIC.

The primary objective of developing ISTH DIC criteria was identifying patients who would benefit from specific treatments [32]. The ISTH DIC criteria have been used to select participants in clinical trials, underlining the practical utility of the criteria in both clinical practice and research settings [33].

The DIC Diagnostic Criteria by JAAM

The JAAM issued a distinct set of scoring systems for diagnosing DIC in 2005 [29]. This diagnostic criteria set was developed and validated based on data from sepsis and trauma populations [29, 34]. The criteria are designed with an emphasis on early detection and treatment. The distinguishing feature of the JAAM DIC criteria is its focus on systemic inflammatory response and organ dysfunction. They incorporate both clinical and laboratory factors that mirror inflammation and organ failure, including platelet count, fibrin/FDP, prothrombin time (PT) ratio, and the systemic inflammatory response syndrome (SIRS) score (Table 1).

The JAAM DIC diagnostic criteria have been used for patient selection and as endpoints in numerous clinical trials on DIC [35–40]. However, with the introduction of the updated Sepsis-3 definition [41] that eliminated the SIRS criterion for sepsis diagnosis, the JAAM DIC criteria became obsolete [42•]. In a study by Iba et al., analyzing data from 819 septic patients treated with recombinant human-soluble thrombomodulin (rhTM), they found a correlation between 28-day mortality and baseline coagulation parameters. They suggested that replacing the SIRS criteria with antithrombin activity in the JAAM DIC diagnostic

Table 1 Scoring systems for disseminated intravascular coagulation and sepsis-induced coagulopathy

Parameters	Score	ISTH overt DIC	JAAM DIC	SIC
Platelet count ($\times 10^9$/L)	3	-	< 80 or ≥ 50% decrease within 24 h	-
	2	< 50	-	< 100
	1	≥ 50, < 100	≥ 80, < 120	≥ 100, < 150
Prothrombin time	2	≥ 6 s	-	> 1.4
	1	≥ 3 s, < 6 s	≥ 1.2 (test result of the patient/normal value)	> 1.2, ≤ 1.4 (INR)
FDP	3	Strong increase	≥ 25 μg/mL	-
	2	Moderate increase	-	-
	1	-	≥ 10, < 25 μg/mL	-
Fibrinogen (g/mL)	1	< 100	-	-
SIRS score	1	-	> 3	-
SOFA score	2	-	-	≥ 2
	1	-	-	1
The diagnostic thresholds for DIC or SIC	-	≥ 5	≥ 4	≥ 4

DIC disseminated intravascular coagulation, *FDP* fibrinogen degradation products, *INR* international normalized ratio, *ISTH* International Society on Thrombosis and Haemostasis, *JAAM* Japanese Society on Acute Medicine, *SIRS* systemic inflammatory response syndrome, *SOFA* sequential organ failure assessment, *PT* prothrombin time, *SIC* sepsis-induced coagulopathy

criteria might be a feasible alternative [43]. However, the pertinent authorities have not formally approved the proposal.

Sepsis-Induced Coagulopathy

The SIC Diagnostic Criteria by ISTH

Following the introduction of the Sepsis-3 definition, the ISTH presented the SIC criteria, a scoring system specifically tailored for coagulation disturbances in sepsis [41, 44]. The SIC scoring system comprises three parameters: the platelet count, the PT international normalized ratio, and the Sequential Organ Failure Assessment (SOFA) score [45]. A SIC score of 4 points or higher is considered positive, indicating an elevated risk of mortality [44, 46]. This system seeks to pinpoint a consistent group of patients with analogous pathophysiology and clinical attributes, enhancing the prospects of improved outcomes through targeted treatment interventions [44].

Distinctively, the SIC score introduces features that differentiate it from both the JAAM and other ISTH diagnostic criteria. The SIC criteria utilize the SOFA score, a pivotal component of the Sepsis-3 diagnostic criteria, contrasting the JAAM DIC criteria [41, 47] that employ the SIRS score (Table 1) [41, 47]. Significantly, the SIC criteria deviate from the traditional ISTH DIC diagnostic approach by omitting the FDP criterion. Studies show a strong correlation between the SIC score and overt-DIC as delineated by the ISTH criteria, and DIC as described by JAAM [48, 49]. Additionally, the SIC score showcases predictive efficacy for mortality and is instrumental in discerning ideal candidates for anticoagulant treatments [49–51].

Furthermore, the ISTH's Scientific Standardization Committee has proposed a two-stage sequential scoring strategy. This initiates with the SIC score for preliminary screening, succeeded by the calculation of the overt DIC score when the SIC criteria thresholds are met [52]. Such a bifurcated approach stands to bolster early detection and identification, thus optimizing the treatment trajectory for septic coagulopathy, paving the way for innovative therapeutic interventions.

Management of Septic Coagulopathy

Treating Septic Coagulopathy: A Therapeutic Target or a Risky Endeavor?

The decision to treat septic coagulopathy remains contentious, primarily due to the delicate equilibrium between potential therapeutic advantages and inherent intervention risks [42•, 53–56]. The interplay between coagulation and inflammation in sepsis provides a compelling argument for treatment [57–59]. Coagulation activation paired with fibrinolysis suppression in sepsis can amplify the inflammatory response, perpetuating a detrimental cycle that exacerbates disease progression [60]. Consequently, targeting coagulopathy might temper the sepsis inflammatory response, presenting a hopeful strategy for enhancing patient outcomes.

However, the decision to treat is not straightforward. The complexity of the coagulation system, coupled with the delicate equilibrium of coagulation, anticoagulation, and fibrinolysis, introduces a significant risk of bleeding complications due to intervention [60, 61]. These challenges emphasize the inherent dangers involved in treating septic coagulopathy and raise questions about the feasibility and safety of such an approach. In clinical practice, prevailing evidence does not advocate specific therapies targeting coagulation to enhance sepsis prognosis. Clinicians are encouraged to follow established research and guidelines for holistic sepsis management rather than isolating coagulopathy as a singular therapeutic focus.

In the following sections, we will examine various treatments for septic coagulopathy, including anticoagulant or anti-thrombotic therapies in general sepsis populations, providing a detailed insight into the current research landscape in this field.

Role of Antithrombotic Agents

Heparin

Heparin, known to amplify antithrombin activity and thereby inhibit thrombin formation, has been rigorously researched for its potential in treating septic coagulopathy. Both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have been evaluated for their efficacy in sepsis management.

The HETRASE RCT evaluated heparin's efficacy in septic patients. Involving a cohort of 319 participants, the study compared mortality outcomes between those treated with heparin and a placebo group [62]. Nonetheless, no significant mortality difference was observed: 14% in the heparin group versus 16% in the placebo (odds ratio, 0.87; 95% confidence interval [CI], 0.44 to 1.69) [62]. A subsequent meta-analysis of nine studies hinted at a potential advantage of administering UFH or LMWH, indicating a decrease in mortality rates (risk ratio [RR], 0.88; 95% CI, 0.77 to 1.00) [63]. A recent systematic review focused solely on UFH's impact on sepsis reported reduced 28-day mortality in the UFH group (RR, 0.82; 95% CI, 0.72 to 0.94) [64]. While these results indirectly suggest a promising role for heparin in treating coagulopathy, it is crucial to recognize that these reviews encompass general sepsis populations and not specifically those with septic coagulopathy.

These analyses were limited by underreported safety outcomes in the included studies, masking the potential risk of significant bleeding—a notable adverse effect of heparin. Addressing these ambiguities, subsequent clinical investigation, including a large-scale RCT evaluating UFH's effectiveness in septic shock (ClinicalTrials.gov number, NCT03378466), was initiated. However, the study's recruitment was prematurely halted due to the coronavirus disease 2019 pandemic.

Antithrombin

Antithrombin (AT), a serine protease inhibitor family (serpins) member, has been the focus of extensive research to explore its potential efficacy in managing septic coagulopathy. AT, recognized for its ability to inhibit thrombin and factor Xa, and to a lesser extent, factors IXa and XIa, initially emerged as a promising candidate for sepsis treatment due to its inherent anticoagulative properties.

The KyberSept trial, the most extensive study evaluating AT in sepsis, involved 1157 patients with severe sepsis. It aimed to determine whether AT therapy offered a survival advantage over placebo. However, the results showed no significant survival benefit with AT therapy (RR, 1.01; 95% CI, 0.91 to 1.11) [65]. Further, a meta-analysis of 30 RCTs, encompassing the KyberSept trial, also found no survival advantage for patients with severe sepsis complicated by DIC (RR, 0.95; 95% CI, 0.88 to 1.03) [66]. Importantly, this meta-analysis highlighted a significantly elevated risk of bleeding associated with AT use (RR, 1.58; 95% CI, 1.35 to 1.84), underscoring critical safety concerns.

Activated Protein C

The journey of recombinant human-activated protein C (rhAPC) in sepsis treatment is a significant chapter in clinical therapeutics. Defined by its antithrombotic and anti-inflammatory qualities, achieved through the inhibition of thrombin formation, rhAPC was once heralded as a promising remedy for sepsis. This enthusiasm was primarily fueled by the PROWESS trial, an RCT of 1690 severe sepsis patients, which reported a marked 28-day mortality reduction with rhAPC treatment to 24.7%, compared to 30.8% in the placebo group (RR, 0.80; 95% CI, 0.69 to 0.94) [67].

However, a pre-specified subgroup analysis suggested that rhAPC's effectiveness was mainly in patients with an APACHE II score ≥ 25. Consequently, the Food and Drug Administration mandated a further RCT for septic patients with an APACHE II score < 25. The ensuing ADRESS trial of 2613 patients was prematurely halted due to its inconclusive nature, revealing no significant 28-day mortality difference between rhAPC and placebo groups (RR, 1.08; 95% CI, 0.92 to 1.28) [68]. Moreover, the PROWESS trial faced criticism for potential methodological lapses, particularly a mid-study protocol shift that questioned its initial findings' credibility. In 2007, the European Medicines Agency sought another definitive RCT to validate rhAPC's risk-benefit in sepsis. However, the subsequent PROWESS-SHOCK trial with 1697 participants did not indicate a survival advantage for rhAPC (RR, 1.09; 95% CI, 0.92 to 1.28) [61].

Given these trial setbacks and methodological concerns, rhAPC was withdrawn from the market. This sequence of events underscores the importance of consistent and transparent research when appraising potential treatments for intricate ailments like septic coagulopathy.

Thrombomodulin

Recombinant human-soluble thrombomodulin (rhTM), a co-factor for thrombin-activated protein C that inhibits thrombin generation, has garnered interest as a potential intervention in septic coagulopathy. An initial Japanese RCT that focused on patients with DIC from hematological malignancies or sepsis presented encouraging findings, demonstrating improved DIC scores with rhTM [69]. However, subsequent studies brought this optimism into question. The SCARLET trial, a comprehensive international RCT of 816 septic coagulopathy patients, found no discernible survival benefit with rhTM (28-day mortality, 26.8% in the rhTM group vs. 29.4% in the placebo group, with an absolute risk reduction of 2.55%; 95% CI, −3.68 to 8.77%) [70]. A meta-analysis covering five trials with 1762 patients echoed these findings [71].

Although the broad applicability of rhTM effectiveness in sepsis or septic coagulopathy has been largely discredited, recent analyses suggest its effectiveness might be tailored to specific patient characteristics. A post hoc review of the SCARLET trial indicated reduced mortality in patients exhibiting elevated baseline coagulation markers, specifically prothrombin fragment $1+2$ and thrombin-antithrombin complex, when treated with rhTM [72]. Adding complexity, a review by Valeriani et al. posited that rhTM lowered 28-day mortality in sepsis patients with coagulopathy but not in those without [73]. These diverse outcomes suggest that the efficacy of rhTM may be contingent upon the severity of the coagulopathy. Therefore, future studies should explore whether rhTM's effectiveness correlates with specific patient indicators, including distinct coagulopathy states denoted by select biomarkers.

Tissue Factor Pathway Inhibitor

Recombinant tissue factor pathway inhibitor (TFPI) has been investigated as a potential therapeutic agent for septic coagulopathy. Naturally synthesized by endothelial cells,

TFPI is a crucial serine protease inhibitor that neutralizes factor Xa and the factor VIIa/tissue factor complex [74, 75]. The recombinant variant of TFPI may mitigate excessive coagulation, particularly in cases of sepsis, possibly protecting the microvascular endothelium from coagulation-related damage [76, 77].

Clinical trials focused on TFPI, including the OPTIMIST trial, took place in the early 2000s [76, 78, 79]. The OPTIMIST trial, a major RCT on sepsis involving TFPI, evaluated the safety and effectiveness of tifacogin, a recombinant TFPI, in patients with severe sepsis [76]. Although tifacogin was well-tolerated and maintained consistent endogenous TFPI levels, it failed to reduce the 28-day mortality rate compared to the placebo significantly. Consequently, tifacogin has not gained acceptance for clinical application in the treatment of septic coagulopathy.

Antiplatelet Agents

Platelets play a pivotal role in the inflammatory response associated with sepsis, contributing to the initiation and propagation of the inflammatory cascade [80•]. Therefore, antiplatelet agents have been hypothesized to mitigate the severity of sepsis through their anti-inflammatory effects. This theoretical benefit is grounded in the fundamental understanding of the inflammatory response and the role of platelets in this process [81].

Aspirin, a nonsteroidal anti-inflammatory drug, has been investigated in sepsis management due to its ability to inhibit cyclooxygenase enzymes, thereby exerting anti-inflammatory and anti-platelet effects [82]. The ANTISEPSIS trial, involving over 16,000 participants aged 70 years and older, examined the effect of aspirin on sepsis-associated deaths [83]. The participants were followed up for a median of 4.6 years, with approximately half receiving aspirin and the other half a placebo. The study found 203 deaths associated with sepsis, but univariate analysis showed similar death rates in both the aspirin and placebo groups (hazard ratio for aspirin vs. placebo 1.08; 95% CI, 0.82 to 1.43) [83]. These findings suggest that aspirin may not translate into a survival benefit in sepsis.

Other antiplatelet agents, such as P2Y12 inhibitors (clopidogrel, prasugrel, and ticagrelor) and glycoprotein (GP) IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban), have also been evaluated in the context of sepsis. A study on the effect of antiplatelet therapy on the systemic inflammatory response in human endotoxemia found that aspirin did not significantly affect circulating cytokines, except for a slight attenuation of the aspirin-induced increase in TNFα by ticagrelor [84]. However, the literature on using P2Y12 inhibitors in sepsis is sparse, and the role of the GP IIb/IIIa inhibitors has not yet been well-studied [85, 86]. Thus, further studies are needed to investigate these antiplatelet agents' potential benefits and risks in managing sepsis.

Transfusion Strategy in the Management of Septic Coagulopathy

Platelets

Thrombocytopenia is frequently observed in septic coagulopathy. Thrombocytopenia in the ICU often signals a more unfavorable prognosis [87]. The underlying mechanisms for this phenomenon are multifaceted, encompassing platelet consumption in the coagulation process, impaired platelet production, and platelet sequestration within the spleen [88]. "Septic thrombocytopenia" commonly refers to platelet count < 150,000/μL in septic patients but is not clearly defined; instead, it is included as an element in the definition of coagulation disorders such as DIC and SIC [89•]. Similarly, treatment strategies for septic thrombocytopenia have not been well-studied. The clinical guidelines advocate for platelet transfusion in sepsis patients who exhibit a platelet count of less than 50,000/μL and are either actively bleeding or at a high risk of bleeding, such as those scheduled for invasive procedures [90]. Without significant bleeding, platelet transfusions have not demonstrated notable benefits, and maintaining a platelet count of 20,000–30,000/μL is typically considered adequate [91].

Fresh-Frozen Plasma and Coagulation Factor Concentrates When considering the transfusion of fresh frozen plasma (FFP) and coagulation factor concentrates, including prothrombin complex and fibrinogen products, the guidelines advise that decisions should not be made solely based on laboratory results. Instead, these interventions should be contemplated for patients who are actively bleeding or those who are due to undergo an invasive procedure [90]. In situations where FFP transfusion is not an option due to the risk of fluid overload, using factor concentrates may be an alternative. However, they may only partially rectify the defect as they contain a limited selection of factors. In contrast, DIC presents with a comprehensive deficiency of coagulation factors. In cases of severe hypofibrinogenemia that persist despite FFP replacement, fibrinogen concentrate or cryoprecipitate may be administered [90].

Therapeutic Plasma Exchange

Therapeutic plasma exchange (TPE) is a procedure wherein plasma is separated from blood cells using a specialized device. Once separated, the patient's plasma—which may contain harmful or excess substances—is discarded and replaced with fresh plasma or a plasma substitute. This process allows for the removal of pathological factors from the blood. Some research indicates that the properties of human plasma and albumin may help stabilize or even restore glycocalyx components [92]. Additionally, TPE might play a role in modulating levels of heparanases, enzymes vital for maintaining the glycocalyx, thereby supporting endothelial

integrity. Weng et al. recently suggested that TPE might be a promising treatment for sepsis [93]. Their findings reveal TPE's superiority over heparin precipitation in enhancing platelet counts, bettering coagulation, increasing 28-day survival rates, and positively impacting biomarkers of endothelial injury [93]. Echoing this, a review by Lee et al. associated TPE with reduced mortality in severe sepsis and shock patients when using fresh frozen plasma (FFP) as the sole replacement fluid [94]. However, due to the small sample sizes in most RCTs and the predominance of patients in observational studies, considerable biases cannot be ignored in incorporating the results into clinical practice [94]. Further research is needed to understand these mechanisms and their implications for patient outcomes fully.

Current Research and Future Directions

Use of Viscoelastic Testing

Rotational thromboelastometry (ROTEM) and thromboelastography (TEG) are diagnostic techniques that serve as point-of-care tests that evaluate whole-blood coagulation. These tests can measure clots' formation, stabilization, and breakdown, capturing the roles of both plasma and cellular elements [95]. These tests offer insightful data into sepsis-related coagulation disorders. The complexity and variability in coagulation disorders in septic patients have been reported, with hypocoagulable states observed more frequently in septic shock patients and those with overt-DIC than patients without these conditions [96, 97]. TEG parameters have shown good diagnostic value for diagnosing SIC [98].

The TEG profile can detect signs of hypocoagulability, even when the usual measurements, such as PT and activated partial thromboplastin time, may appear normal, indicating a higher sensitivity in detecting septic coagulopathy [99]. The lysis index of ROTEM has also shown superior accuracy in identifying patients with severe sepsis compared to biomarkers such as procalcitonin, IL-6, and C-reactive protein [100].

The relationship between viscoelastic tests and mortality in sepsis has been the subject of intensive research. Several studies and a meta-analysis have demonstrated that specific alterations in TEG and other viscoelastic parameters, such as prolonged clotting times and reduced clot firmness, are associated with an increased mortality risk [101–103]. Whole-blood hypocoagulable profiles also correlate with a greater risk of death within 28 days in severe sepsis patients [104]. The observation of acute fibrinolysis shutdown early in septic shock is another finding associated with increased morbidity and mortality [103].

Viscoelastic tests have been examined in attempts to predict DIC in septic patients. TEG values, except lysis after 30 min, have demonstrated significant differences between the DIC and non-DIC groups [105]. Future insights into the viscoelasticity assay in predictive and diagnostic contexts open new perspectives in the management of septic coagulopathy, including the targeted identification and treatment of at-risk patients.

Emerging Biomarkers to Detect Coagulation Abnormalities

Recent advancements in the study of septic coagulopathy have unveiled a range of innovative biomarkers associated with inflammation and coagulation, providing deeper insights into the complex nature of this condition. These biomarkers are currently under investigation for their potential to improve patient outcomes in sepsis, recognizing the crucial role of early and accurate diagnosis for effective intervention. These biomarkers are associated with DIC and heightened mortality rates, particularly when evaluated alongside traditional assays [106, 107]. These biomarker categories encompass indicators related to thrombin generation, fibrinolysis, endothelial dysfunction, and cellular responses. In recent years, microRNAs and other measurable genetic markers, including non-coding RNAs, have gained significant prominence in the pathways governing inflammation, coagulation, and vascular endothelial impairment [108•, 109, 110]. For a comprehensive understanding, a detailed compilation of these emerging biomarkers, along with their distinctive attributes and implications, is provided in Table 2. Introducing and utilizing these markers can reshape the landscape of septic coagulopathy diagnosis and management, ushering in a new era of personalized medical approaches and precision-targeted therapeutic strategies.

Role of Precision Medicine in Septic Coagulopathy

Precision medicine is increasingly recognized as a promising approach to managing sepsis. This approach, which tailors treatment to individual patient characteristics, can improve outcomes by addressing the heterogeneity of sepsis. Recent research has identified distinct clinical phenotypes of sepsis that correlate with host-response patterns and clinical outcomes [139]. These phenotypes may help understand the variability of treatment effects in sepsis, paving the way for more personalized therapeutic strategies.

Precision medicine has been applied to identify specific phenotypes with varying coagulation features in septic coagulopathy. For instance, one phenotype was notably impacted using rhTM. Specifically, patients exhibiting severe coagulopathy, characterized by low platelet counts, extremely high levels of FDP and D-dimer, and severe organ dysfunction, were found to have decreased in-hospital mortality when treated with rhTM [140]. Further developments in machine learning have resulted in a model capable

Table 2 Emerging biomarkers being studied in septic coagulopathy

Name	Profile	Theoretical background	Clinical data	References
Biomarkers of coagulation and fibrinolysis				
TAT	A protein complex of thrombin and antithrombin	Elevation indicates increased thrombin levels due to coagulation response.	- Peak levels were observed on the first day of ICU admission, and this initial value was associated with the subsequent development of overt DIC. - Higher levels were associated with increased mortality among patients with sepsis.	[106]
PAI-1	A serine protease inhibitor that regulates fibrinolysis by inhibiting plasminogen activators and plasmin	Elevation indicates the suppression of fibrinolysis, which occurs in hypercoagulable states of sepsis.	- Patients with sepsis and PAI-1 levels ≥ 83 ng/mL were at higher risk of coagulopathy, organ failure, and mortality. - Potential therapeutic target of embelin, natural benzoquinone, which inhibits PAI-1	[111, 112]
PF 1 + 2	Fragments of peptide are produced when prothrombin is converted to thrombin	Elevation indicates increased thrombin generation.	In the post hoc analysis of the SCARLET trial, patients with higher baseline PF 1 + 2 and TAT levels treated with rhTM experienced lower mortality.	[72]
Soluble fibrin	Product of fibrinolysis	Presence in plasma indicates intravascular fibrin formation unaffected by extravascular fibrin creation.	Levels on ICU day 2 exhibited good predictive value for 28-day mortality after adjustment for the APACHE II score.	[106]
Protein C	Serine protease activated to inhibit thrombin formation	Depletion indicates the consumption of physiologic anticoagulants.	Higher levels were observed in sepsis survivors than non-survivors and sepsis patients without DIC.	[113]
Antithrombin	Serine protease inhibitor that acts to inhibit thrombin and FXa	Deficiency indicates decreased anticoagulant activity and further thrombus formation.	Antithrombin levels significantly differed between survivors and non-survivors among pediatric patients with sepsis.	[114]
TFPI	Kunitz-type protease inhibitor that acts to inhibit TF in the extrinsic coagulation pathway	Level of TFPI changes in response to tissue factor pathway activity.	- Total and free TFPI levels were higher than the values found in healthy controls throughout sepsis. - Free TFPI was higher in patients with septic shock than those with sepsis without shock.	[115]
sCLEC-2	A receptor activated by platelets and expressed on the surface of platelet membranes	Elevation indicates platelet activation and may signal inflammation and thrombotic microangiopathy.	A consistent increase in sCLEC-2/platelet count ratio effectively predicted the progression to sepsis-induced DIC.	[116]
ADAMTS-13	Metalloproteinase that regulates blood clotting by cleaving VWF	Deficiency may lead to pathological platelet-vessel wall interactions and thrombotic microangiopathy.	The predictive value of decreased ADAMTS13 level for mortality was equivalent to APACHE II scores.	[117, 118]
Endothelial/glycocalyx components				
sTM	A soluble form of thrombomodulin, an endothelial anticoagulant cofactor that promotes activation of protein C	- Elevation indicates endothelial injury. - Depletion may be a result of consumption by excessive coagulation process.	Elevation in the initial 24 h of sepsis diagnosis was linked to increased disease severity and the requirement for renal replacement therapy.	[119]
Syndecan-1	Proteoglycan found in the endothelial glycocalyx	Elevation indicates endothelial glycocalyx degradation.	Elevated levels on the initial day of ICU admission were correlated with organ failure, thrombocytopenia, DIC, and fatal outcomes in patients suspected of having sepsis.	[120, 121]

Table 2 (continued)

Name	Profile	Theoretical background	Clinical data	References
Hyaluronan	Polysaccharide found in the extracellular matrix	Elevation indicates endothelial damage.	- Elevated hyaluronan was observed in patients with sepsis-induced DIC. - Correlation with APTT, PT, and platelet counts.	[122]
EPCR	Transmembrane receptor protein involved in activating protein C, which mediates cytoprotective activities	Elevation indicates endothelial injury.	Elevation in the early phase of sepsis was associated with higher 28-day mortality.	[123]
VEGFR2	Receptor for vascular endothelial growth factors	Imbalance indicates endothelial damage and an increase in vascular permeability.	VEGFR2 exhibited better predictive performance than the traditional test items for subsequent deterioration in patients in the emergency department.	[124]
uPAR	Receptor for urokinase-type plasminogen activator	Elevation indicates activated immune systems and inflammatory response	uPAR exhibited good predictive performance for subsequent deterioration when combined with VEGFR2.	[124]
Immunological biomarkers				
Complement C3	- Protein in the complement system - Direct activator of platelets	Indicator of complement activation associated with thrombocytopenia and subsequent coagulopathy	- Reduced levels are observed in septic patients with DIC than those without DIC. - Depletion of C3-Alpha was associated with mortality in patients with septic shock.	[125, 126]
Presepsin	N-terminal fragment of CD14 involved in immune response	Elevation reflects the early immune response of sepsis.	Predictive of the severity of sepsis-induced DIC when combined with protein C	[127, 128]
Nuclear materials				
HMGB-1	Chromosomal protein released from damaged cell	Indicating cell death	- Elevation was observed in patients with sepsis and DIC - Association with increased organ dysfunction and mortality	[129]
Nucleosome	Complex of DNA and histone proteins	Indicating cell death	Elevated levels were observed in septic patients with overt-DIC.	[130]
Histone	Protein involved in DNA packaging	Indicating cell death	- Elevation was correlated to an increase in thrombin generation. - Higher levels were observed in sepsis patients with DIC than healthy volunteers. - rhTM neutralizes the prothrombotic action of histone.	[131, 132]
Cell-free DNA	Fragments of DNA released from dead cells	Indicating cell death	- Higher levels upon ICU admission were observed in patients with sepsis than in healthy controls. - Levels were correlated to ICU mortality.	[133]
microRNAs				
miR-122	Noncoding small RNA that enhances inflammation and coagulation through the complement pathway	Reflecting active inflammation and coagulation	- Higher expression was observed in sepsis patients with abnormal coagulation and correlated to APTT, fibrinogen, and AT III levels. - Lower expression was observed in survivors than non-survivors in sepsis patients.	[110, 134]

Table 2 (continued)

Name	Profile	Theoretical background	Clinical data	References
miR-92a	Noncoding small RNA associated with angiogenesis and endothelial function	- miR-92a causes reduced VWF expression, leading to FVIII instability and extended APTT. - Elevated expression indicates endothelial dysfunction and increased vascular permeability.	Higher expression was observed in patients with SIC than those with non-SIC sepsis.	[135]
miR-19a	Noncoding small RNA associated with inflammation and coagulation process by regulating TF through the NF-κB/IκB pathway	miR-19a inhibits the coagulation pathway by TF regulation.	- miR-19a-3p was downregulated, and TF was upregulated in neonates with sepsis-induced DIC. - Potential therapeutic option targeting TF	[136]
miR-125b	Noncoding small RNA is associated with immune response and promotes coagulation through regulating FIX mini-gene.	Elevated expression reflects enhanced immune response, inflammation, and coagulation.	- miR-125b elevated in sepsis patients, correlating with APACHE II, SOFA scores, and inflammation markers. - Expression was lower in survivors than non-survivors and independently associated with a higher mortality risk in sepsis.	[137, 138]

APACHE II Acute Physiology and Chronic Health Evaluation II, *APTT* activated partial thromboplastin time, *AT III* antithrombin III, *CD14* Cluster of differentiation 14, *DIC* disseminated intravascular coagulation, *DNA* deoxyribonucleic acid, *EPCR* endothelial protein C receptor, *FVIII* factor VIII, *FIX* factor IX, *FXa* factor Xa, *HMGB-1* High-mobility box chromosomal protein 1, *ICU* intensive care unit, *IκB* inhibitor of kappa B, *NF-κB* nuclear factor-kappa B, *PF 1 + 2* prothrombin fragment 1 + 2, *rhTM* recombinant human-soluble thrombomodulin, *RNA* ribonucleic acid, *SCARLET trial* Sepsis Coagulopathy Asahi Recombinant LE Thrombomodulin trial, *sCLEC-2* soluble type C lectin-like receptor 2, *SIC* sepsis-induced coagulopathy, *SOFA* sequential organ failure assessment, *sTM* soluble thrombomodulin, *TAT* thrombin-antithrombin complex, *TF* tissue factor, *TFPI* tissue factor pathway inhibitor, *uPAR* urokinase-type plasminogen activator receptor, *VEGFR2* vascular endothelial growth factor receptors 2, *VWF* Von Willebrand factor

of predicting the rhTM-responsive phenotype in septic patients. This model demonstrated high-performance metrics, boasting a C statistic of 0.996, sensitivity of 0.991, and specificity of 0.967, and was effective in predicting patients likely to have less severe coagulopathy [141].

Additionally, recent studies have identified three distinct subphenotypes of SIC, each demonstrating unique clinical and laboratory features. Interestingly, these subphenotypes responded differently to various anticoagulant treatments [142].

These findings highlight the potential of precision medicine in customizing treatments to individual patient phenotypes, leading to more favorable outcomes for those suffering from septic coagulopathy.

Conclusion

Septic coagulopathy presents a formidable challenge, distinguished by its intricate and multifaceted pathophysiology, linked to an elevated fatality risk. Despite dedicated investigations, the underlying mechanisms remain not fully elucidated. As of now, approved pharmacological interventions for septic coagulopathy remain limited. The intrinsic diversity and complexity of this condition defy one-size-fits-all solutions. Instead, the pursuit of tailored therapeutic approaches guided by biomarkers and scoring systems emerges as an immediate research priority, potentially revolutionizing the current landscape of septic coagulopathy management.

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