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Sepsis-Induced Coagulopathy: A Comprehensive Narrative Review of Pathophysiology, Clinical Presentation, Diagnosis, and Management Strategies

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Physiological hemostasis is a balance between pro- and anticoagulant pathways, and in sepsis, this equilibrium is disturbed, resulting in systemic thrombin generation, impaired anticoagulant activity, and suppression of fibrinolysis, a condition termed sepsis-induced coagulopathy (SIC). SIC is a common complication, being present in 24% of patients with sepsis and 66% of patients with septic shock, and is often associated with poor clinical outcomes and high mortality.[1,2] Recent preclinical and clinical studies have generated new insights into the molecular pathogenesis of SIC. In this article, we analyze the complex pathophysiology of SIC with a focus on the role of procoagulant innate immune signaling in hemostatic activation—tissue factor production, thrombin generation, endotheliopathy, and impaired antithrombotic functions. We also review clinical presentations of SIC, the diagnostic scoring system and laboratory tests, the current standard of care, and clinical trials evaluating the efficacies of anticoagulant therapies. (Anesth Analg 2024;138:696–711)

KEY POINTS

What Is Known:

1. Sepsis-induced coagulopathy (SIC) is a common finding in critically ill septic patients and is characterized by systemic inflammation with concomitant coagulation activation.
2. Increased procoagulant tissue factor expression via activated circulating monocytes, neutrophil extracellular trap (NET) formation that promotes thrombin generation, marked vascular inflammation with endothelial injury, and impaired anticoagulant mechanisms are the central events in SIC pathophysiology.

What Is Still Being Learned:

3. Inflammation and coagulation are intricately linked, and how persistent innate immune activation leads to dysregulated coagulation in sepsis is still being elucidated.
4. In SIC, there is early systemic coagulation activation with progressive dysfunction and increasing coagulation abnormalities that will continue to deteriorate if left unchecked. Ongoing research is aimed at identifying nuances of SIC to improve diagnostic accuracy for earlier identification.

Future Research Direction:

5. Targeting the inflammatory molecules that directly mediate platelet activation, tissue factor production, and thrombin generation to modulate coagulopathy and thrombosis in SIC, without increased risk of bleeding, is the focus of ongoing research.
6. Future clinical research is aimed at improving the diagnostic techniques to optimize stratification of patients with specific coagulation phenotypes for systemic anticoagulant/antithrombotic therapies.

Sepsis-induced coagulopathy (SIC) is a major complication in sepsis. SIC is present in 24% of patients with sepsis and is associated with a 2-fold increase in mortality.[1,2] SIC is characterized by systemic inflammation and coagulation activation leading to microvascular thrombi, impaired

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organ perfusion, and subsequent organ dysfunction. SIC is often used synonymously with disseminated intravascular coagulation (DIC), but in DIC, there is an overt or gross consumptive intravascular coagulopathy, meaning significant reductions in platelets, fibrinogen, and clotting factors with clinical evidence of thrombotic and/or bleeding diathesis. In comparison, SIC is a type of nonovert DIC, also described by a systemic intravascular coagulation, but without gross consumption of platelets, fibrinogen, and clotting factors, and often preempts the decompensated coagulopathy of DIC.

SIC is a complex condition triggered by pathological interactions between the innate immune and the coagulation systems. However, detailed understanding of the normal and dysregulated interactions of these systems and their components—to improve diagnostic accuracy and develop targeted therapeutics—represents a significant knowledge gap in SIC and is the goal of ongoing research. This article is a critical review of the literature on SIC in the following areas: (1) the experimental evidence of pathogen- and host-derived inflammatory molecules linked to hemostatic activation in sepsis, (2) the systemic impact of dysregulated immunothrombotic responses and the resultant clinical presentations, (3) the clinical diagnostic criteria for SIC, (4) the experimental therapies targeting imbalanced coagulation in SIC, and (5) the gaps in our knowledge of the pathophysiology, presentation, and management of SIC.

PATHOPHYSIOLOGY OF SIC

In Vivo Thrombin Generation

Thrombin or factor (F) IIa is a serine protease, converter of fibrinogen to insoluble fibrin, potent mediator of platelet activation, and strong potentiator of systemic coagulation via a series of positive feedback reactions[3,4] that serve to maintain its own production (Figure 1). The process of in vivo thrombin generation occurs through 3 phases: initiation, amplification, and propagation.[5] The initiation phase starts on tissue factor (TF)–expressing cells such as monocytes, endothelial cells (EC), or platelets.[6–8] TF, a procoagulant glycoprotein, binds to and converts FVII to activated FVII (FVIIa). TF and FVII are essential coagulation proteins as their complete deficiency results in fatal perinatal bleeding.[9,10] The extrinsic tenase complex (TF + FVIIa) then activates FX and FV to form the prothrombinase complex (FXa + FVa), which proteolytically cleaves prothrombin to thrombin. In the amplification phase, thrombin strongly induces platelet activation, which creates more surface area for further clotting reactions. Thrombin also cleaves circulating FVIII from its carrier, von Willebrand factor (vWF), and converts it to its active form (FVIIIa). Extrinsic tenase and activated FXI will activate FIX to FIXa, which complexes with FVIIIa on activated platelets to form the intrinsic tenase (FIXa + FVIIIa) and further generate FXa and amplify thrombin generation. In the final phase of propagation, persistent amounts of thrombin are generated on activated platelets for continued coagulation.

The plasma contact system, consisting of kallikrein-kinin, high-molecular-weight kininogen (HMWK), and FXII, further propagates thrombin generation.[11] FXII is the primary initiator of this system and plays a role in pathological thrombus formation.[12,13] FXII circulates as a free zymogen capable of autoactivation to FXIIa after contact with negatively charged surfaces.[14] After activation, FXIIa proteolytically cleaves prekallikrein to kallikrein, which can further activate FXII to FXIIa in a positive feedback reaction. FXIIa, as a serine protease, can subsequently mediate additional cleavage of FIX to FIXa,[15] and further propagate thrombin generation.

Monocytes and Neutrophils Promote Thrombin Generation in Sepsis

Elevated plasma levels of TF and TF-bearing microparticles have been demonstrated in animal and human sepsis[16–18] and are recognized as drivers of intravascular thrombin generation. In sepsis, monocytes are considered a primary source of endogenous TF.[19] In mice, genetic deletion of myeloid cell–specific TF (but not that of ECs or platelets) markedly reduced plasma thrombin levels after stimulation with endotoxin (also known as lipopolysaccharide [LPS]).[20] Moreover, in vitro small interfering (si) RNA-mediated genetic knockdown of TF in human blood monocytes resulted in a 5-fold reduction in TF activity, while knockdown of TF in granulocytes demonstrated no reduction in TF activity in whole blood treated with LPS,[21] thus confirming the primacy of monocytes in generating plasma TF in response to endotoxemia. Subsequently, thrombin can interact with monocytes via protease-activated receptors (PARs) to further enhance expression of TF,[22] creating a positive feedback loop of leukocyte activation, TF expression, and thrombin generation (Figure 1).

In response to inflammatory signaling, neutrophils undergo a rearrangement of cellular architecture that causes the release of web-like structures known as neutrophil extracellular traps (NETs), which consist of DNA, histones, myeloperoxidase, and other antimicrobial proteins.[23] During sepsis, NETs provide polyanionic surfaces that facilitate FXII autoactivation[23,24] and contact-mediated coagulation (Figure 1). NETs also serve as an additional framework for platelet adhesion and aggregation, providing increased surface area for procoagulant activity and thrombin generation.[25] Considerable animal evidence supports the importance of NETs in thrombin activation. For instance, mice

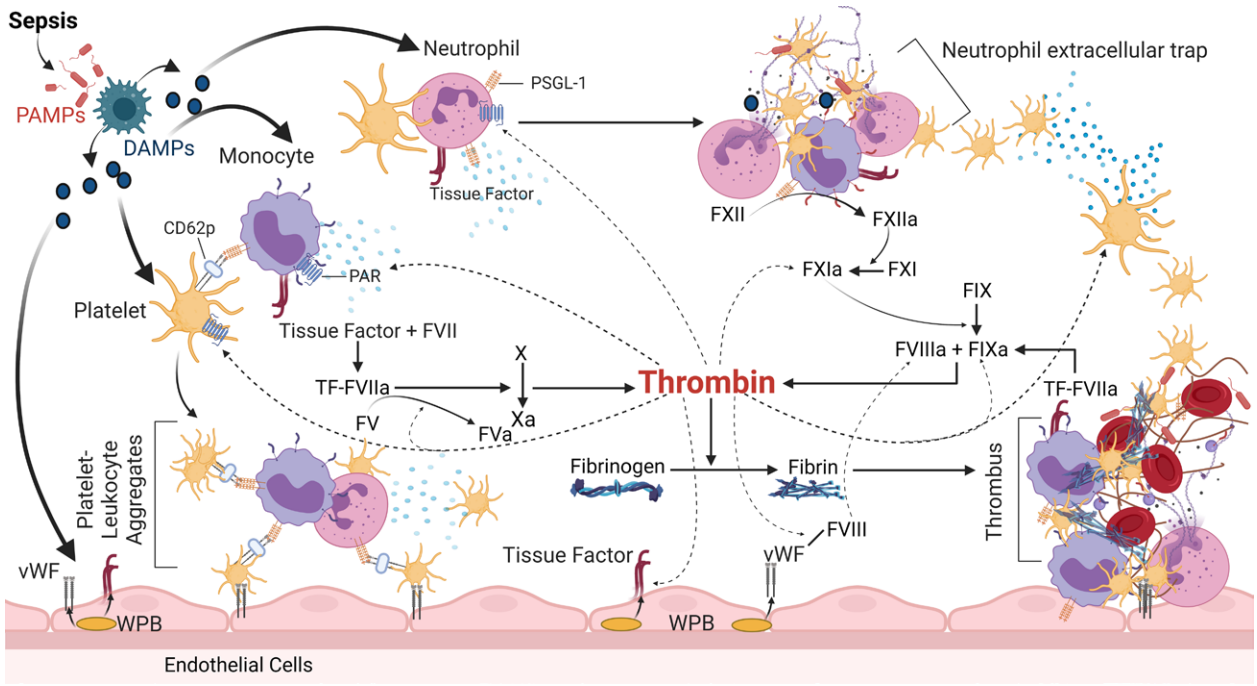

Figure 1. Thrombin generation and propagation during sepsis. Thrombin is a powerful positive feedback signaler for its own propagation. Sepsis results in the release of PAMPs from microbial sources, or DAMPs from injured host cells, both of which lead to immune cell activation and TF expression from monocytes, endothelial cells, and neutrophils with subsequent thrombin generation. Moreover, activated NETs serve as polyanionic surface for further thrombin generation. Platelet degranulation, leukocyte TF expression, NET formation, and PLA formation propagate (dotted lines) thrombin generation leading to fibrin production and platelet consumption resulting in microvascular thrombosis. DAMPs indicates danger-associated molecular patterns; NETs, neutrophil extracellular traps; PAMPs, pathogen-associated molecular patterns; PLA, platelet-leukocyte aggregate; PSGL-1, p-selection (CD62p) glycoprotein ligand-1; TF, tissue factor; vWF, von Willebrand factor; WPB, Weibel Palade body. Created with BioRender.com.

administered intraperitoneal *Escherichia coli* or endotoxin demonstrate increase colocalization of thrombin protein with NETs within the liver microvasculature.[26] Further, mice with genetic deletion of peptidylarginine deiminase 4 (PAD4), an enzyme essential for NET formation, experience not only premature NET breakdown but also lower intravascular thrombin activity.[27] During sepsis, NET formation is thus strongly linked with procoagulant signaling and thrombin generation.

Role of Pathogen-Associated Molecular Patterns in Procoagulant Signaling

Pathogen-associated molecular patterns (PAMPs) play a key role in SIC. PAMPs are molecular fragments of glycoproteins, membrane components, and nucleic acids of pathogens. Patterns of these molecules are recognized by host receptors, including toll-like receptors (TLRs),[28] and trigger activation of both cellular and noncellular components of the innate immune system.[29] Bacterial cell membrane components are well-recognized PAMPs, and several have been linked directly to procoagulant activity as highlighted in Table 1.

PAMP-TLR signaling can trigger NET formation and TF expression on monocytes to promote thrombin generation and fibrin deposition.[30,31] Mice injected with bacterial lipoprotein Pam3CysK or *E. coli*–derived peptidoglycan-associated lipoprotein (PAL) exhibit a 16-fold increase in cell adhesion molecule p-selectin and significant lung fibrin deposition in a TLR2-dependent manner.[32] LPS, another PAMP found in the cell walls of Gram-negative bacteria, promotes coagulation in both TLR-dependent and -independent manners. In mice, LPS induced fibrin deposition in liver microvasculature in a TLR4-dependent manner.[33] Independent of TLR4, LPS and *E. coli*–derived type III secretion system (T3SS) proteins can interact with cytosolic proinflammatory caspase 11 to activate a class of pore-forming proteins called gasdermins, which create large gasdermin D (GSDMD) pores in cell membranes. GSDMD pores allow an influx of Ca^{2+}, which leads to enhanced TF activity, and are believed to play a role in pyroptosis.[33–36] The relevance of GSDMD in TF activity is supported by in vitro experiment findings that macrophages treated with LPS generate only modest amounts of TF, but when LPS is delivered to the cytosol in macrophages, they demonstrate increased phosphatidylserine (PS), TF, and thrombin activity in a caspase 11/GSDMD–dependent manner.[33] Further, GSDMD-deficient mice demonstrate considerably less thrombin generation and microvascular fibrin deposition when injected with *E. coli* T3SS protein compared to normal controls.[36] These studies suggest

Table 1. Procoagulant PAMPs/DAMPs in SIC and Roles in Coagulation Activation

	Receptor	Impact on coagulation
PAMPs		
PAL/Pam3CysK	TLR2	Increases expression of p-selectin, a cell adhesion molecule involved in platelet leukocyte aggregate formation and in vivo injection results in lung fibrin deposition.[32]
LPS	TLR4	Induces platelet aggregation and fibrin deposition in vivo, and in vitro it leads to platelet aggregation in presence of thrombin, suggesting synergistic endogenous signaling with thrombin.[33,79]
Cytosolic LPS	Caspase 1/11	Increases expression of phosphatidylserine on peripheral leukocytes enhancing TF procoagulant activity.[33]
T3SS inner rod protein	Caspase 1/11	Increases TF expression on macrophages and plasma thrombin generation in vivo.[36]
DAMPs		
Histones	TLR2/4	Thrombin generation via platelet-dependent mechanisms.[76] Upregulation of TF and downregulated thrombomodulin in endothelial cells.[38,46]
HMGB1	TLR2/4	Upregulation of TF on monocytes and downregulation of TM-thrombin activation of the protein C pathway and resultant excessive microvascular thrombosis in rats.[148]
cfDNA	TLR9	cfDNA is a major component of NETs and triggers thrombin generation via FXII and FXI.[53,54] TLR9 recognizes unmethylated CpG DNA, a microbial product. Human mtDNA with reportedly hypomethylated CpG content, similar to bacterial DNA, can induce inflammation in a TLR9-dependent manner,[149] but studies on direct human mtDNA-TLR9 inducing coagulation activation are lacking.
exRNA	TLR3 (ds) TLR7 (ss)	exRNA is a cofactor for FXII and FVII, found to be procoagulant via contact pathway activation.[150] ex-miRNA induces TF expression in macrophages via TLR7.[16]

Abbreviations: cfDNA, cell-free DNA; CpG, cytosine-guanine; DAMP, danger-associated molecular patterns; ds, double-stranded; ex-miRNA, extracellular microRNA; exRNA, extracellular RNA; F, factor; HMGB1, high mobility group box-1 protein; LPS, lipopolysaccharide; mt, mitochondrial; PAL, peptidoglycan-associated lipoprotein; PAMP, pathogen-associated molecular patterns; SIC, sepsis-induced coagulopathy; ss, single-stranded; T3SS, type 3 secretion system; TF, tissue factor; TLR, toll-like receptor; TM, thrombomodulin.

a mechanism linking PAMPs to SIC wherein bacterial components, LPS/T3SS, result in GSDMD-mediated Ca^{2+} influx into cells, and PS translocation to the outer membrane, enhancing TF activity and substrate binding, and increasing thrombin generation.

Role of Danger-Associated Molecular Patterns in Procoagulant Signaling

Danger-associated molecular patterns (DAMPs) are endogenous biomolecules that are released from host cells under stress conditions and can trigger innate immune responses. DAMPs have been recognized as mediators of immune dysregulation[11,23] and procoagulant signaling[37] in sepsis (Table 1). They include nuclear binding proteins such as histones[38] and high mobility group box-1 (HMGB-1),[39] and nucleic acids such as cell-free DNA (cfDNA)[40] and extracellular RNA (ex-RNA),[41–43] which may signal via TLR-dependent (Figure 2) or independent pathways, and will be further discussed in detail below.

Histones are intranuclear chromosomal support proteins that are undetectable in the plasma of healthy humans,[44] but are significantly higher in septic patients with coagulation abnormalities (range, 2.2–120 ng/mL).[45] Further, histones induce TF expression in human ECs via a mechanism partially dependent on TLR2/4 signaling.[46] Human ECs stimulated with 10 to 100 µg/mL histones demonstrated a dose-dependent increase in TF expression and triggered thrombin generation, and the latter was attenuated in the presence of antihuman TF antibody.[38] To test the in vivo toxicity of histones, a sublethal dose within the pathological range reported in septic patients was injected intravenously into mice and led to cytotoxicity of the endothelium with the appearance of alveolar platelet-fibrin aggregates and microvascular thrombi similar to septic animals.[47] The administration of an antihistone antibody decreased mortality in septic animals, indicating a role for histones in driving SIC pathology. Although these translational studies suggest a role for histones in aggravating TF and thrombin production, clinical research demonstrating a direct impact of histones on coagulation activation and hemostatic abnormalities in SIC patients remains to be seen.

Similar to histones, HMGB-1 protein is below detection limits in healthy patients, moderately elevated in septic patients (4.54 ± 8.18 ng/mL), but 3-fold higher (14.05 ± 12.56 ng/mL) in patients with coagulation abnormalities.[48] In a cohort of 201 septic humans, HMGB-1 protein levels correlate with progressively worse coagulopathy ($r = 0.586$, $P < .001$) and organ failure scores ($r = 0.572$, $P < .001$).[48] Further, in vitro cell studies demonstrate HMGB-1 is sufficient to induce TF and PS expression in ECs and macrophages in a partial TLR2/4-dependent manner,[49] but others show TF responses only at doses approximately 100× greater than reported human plasma levels (1 µg/mL),[50] thereby questioning whether this DAMP alone is sufficient to drive intravascular coagulation. HMGB-1 protein does demonstrate synergy with LPS, as it can bind and facilitate its translocation into peripheral blood monocytes,[51] allowing LPS to induce formation of GSDMD pores, Ca^{2+}-mediated externalization of PS, and TF procoagulant activity. LPS-induced coagulopathy in mice was associated with increased HMGB-1 plasma levels, and thrombin and platelet deposition in liver microvasculature,

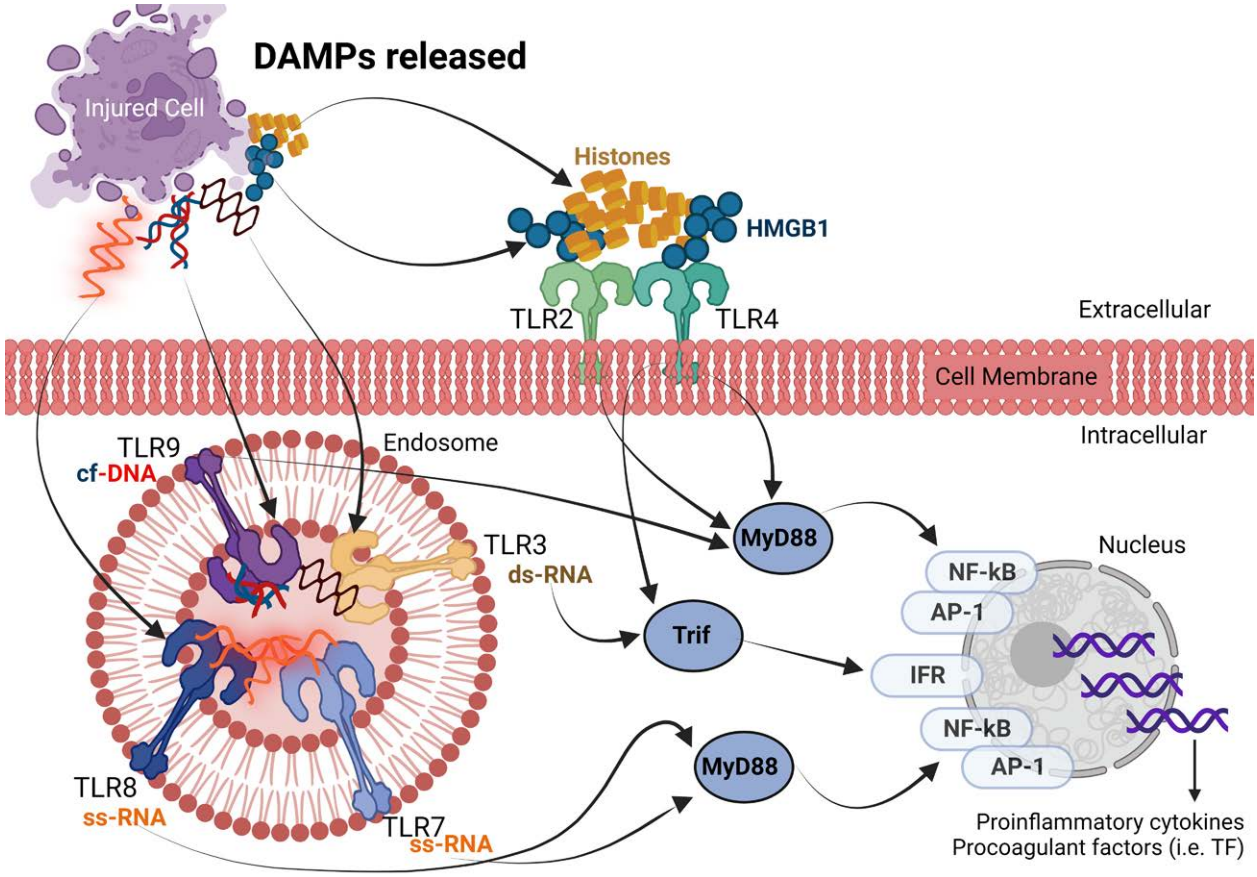

Figure 2. Toll-like receptors and procoagulant DAMPs. Sepsis results in widespread cell injury with the release of host-associated danger molecules or DAMPs. DAMPs signal via specific TLRs to induce proinflammatory or procoagulatory responses in sepsis independent of initial infection. Histones and HMGB-1 signal via TLR2/4 on the cell surface, while cfDNA, ssRNA, and dsRNA signal via TLR9, TLR7/8, and TLR3, respectively, in the endosomes. Activation of these receptors results in nuclear translocation of transcription factors NF-kB and AP-1 via MyD88 except for TLR3 signaling, which induces Trif signaling and translocation of IRF. These signaling pathways result in induction of proinflammatory cytokines and TF expression in immune cells furthering procoagulant signaling. AP-1 indicates activator protein 1; DAMPs, danger-associated molecular patterns; dsRNA, double-stranded RNA; HMGB-1, high mobility group box-1; IRF, interferon regulatory factor; MyD88, myeloid differentiation primary response 88; NF-kB, nuclear factor kappa B; ssRNA, single-stranded RNA; TF, tissue factor; TLR, toll-like receptor; TRIF, TIR-domain-containing adapter inducing IFN-β. Created with BioRender.com.

which was significantly attenuated in the presence of anti–HMGB-1 monoclonal antibodies or with selective hepatocyte HMGB-1 deletion,[50] thereby suggesting selective blockade/deficiency of HMGB-1 can influence in vivo coagulation in the context of endotoxemia (LPS). However, whether manipulation of HMGB-1 influences coagulopathy in the context of polymicrobial sepsis, and whether these animal studies may be translated to future human clinical research in SIC, remains a point of investigation.

In a 2006 observational study of septic patients, levels of cfDNA, another potential DAMP, were increased and predicted intensive care unit (ICU) mortality with a sensitivity and specificity of 92% and 80%, respectively.[52] Reported cfDNA plasma levels vary widely across studies, likely due to different approaches for quantification, including spectrophotometry, which does not discriminate among mitochondrial, nuclear, or microbial DNA and is subject to potential overestimation of eukaryotic cfDNA.[40] In comparison, real-time quantitative polymerase chain reaction (PCR) provides only relative changes in gene expression, but which quantity can then be inferred based off a standard curve using human genomic DNA.[52] In septic human plasma, thrombin generation, based off fluorescent intensity after cleavage of a fluorogenic substrate, correlated with cfDNA levels (<5 μg/mL or >15 μg/mL).[53] Further, accumulated evidence from in vitro studies suggests that activated neutrophils/NETs exert their procoagulant activity in part via the release of cfDNA. Stimulated human neutrophils, or cfDNA, isolated from human septic plasma similarly enhanced thrombin generation in naive plasma, but significantly less so in the presence of deoxyribonuclease (DNase).[53,54] This suggests that procoagulant activity was partly mediated by cfDNA content. When FXII-deficient plasma was utilized, the response was abolished,[54] indicating that the negatively charged cfDNA from septic plasma can mediate the autoactivation of FXII and promote in vitro thrombin generation.

Finally, ex-miRNAs, a newly discovered DAMP, are the dominant biotype of plasma RNA, accounting for 70% to 80% of circulating ex-RNA, and are differentially expressed in septic patients compared with healthy controls.[55] Existing data suggest that some mature single-stranded miRNAs, such as miR-146a-5p, not only show a strong correlation between plasma copy number and international normalized ratio (INR) and partial thromboplastin time in septic patients,[55] but also are capable of activating macrophages to produce cytokines[56,57] and TF[16] via TLR7, the sensor for single-stranded RNA including ex-miRNAs.[58,59] Moreover, TLR7-deficient mice are partially protected against SIC with reduced plasma TF levels.[16] Plasma ex-miRNAs are carried by various macromolecular complexes that are thought to protect them from RNase digestion in the circulation, including extracellular vesicles (EVs).[57] In addition to miRNA cargo, EVs express various proteins unique to the cell of origin, its activation state, and systemic pathology. For instance, human septic plasma EVs of endothelial origin were rich in membrane-bound TF and associated with worsening coagulopathy, suggesting a potential role in mediating coagulation activation in SIC.[60,61] In support of this, PS-positive plasma EVs from septic humans shortened clotting time significantly in recalcified control plasma, and fluorescently labeled FXa and thrombin demonstrated greater colocalization with these septic-derived EVs, indicating the presence of an active biological surface for binding of coagulation factors and amplification of thrombin generation.[62] Beyond changes in 1 or 2 proteins, genomic and proteomics data have further revealed dynamic molecular changes in RNA and protein content of septic EVs with pathway analysis revealing significant associations among TLR signaling, clotting cascade, integrin and platelet signaling, and upregulated EV proteins.[63] Taken together, these studies advocate for new exploration into the dynamic changes of EV content in SIC, and the various mechanisms (eg, miRNA, protein) by which septic EV cargo may mediate coagulation and platelet activation and drive SIC.

For each of the DAMPs highlighted above, studies consistently demonstrate that plasma levels change with disease course or severity, thereby offering potential as clinical biomarkers. However, whether these DAMPS are the passive result of cellular injury and release or, when released, actively mediate systemic coagulation and thrombin generation, and impact development of coagulopathy in translational and human studies, remains a significant point of interest in understanding the pathogenesis of SIC.

Platelet Activation in SIC

Platelets are anucleate, highly reactive cells that have physiological roles in hemostasis and inflammation.[64] Thrombocytopenia has been associated with worse prognosis and survival in sepsis.[65–67] In SIC, platelets adhere to activated monocytes/neutrophils, or attach to injured/activated ECs via exposed adhesion proteins (eg, von Willebrand factor [vWF]), leading to endothelial and microvasculature sequestration and early reductions in platelet counts.[68] In particular, vWF, a multimeric glycoprotein stored in ECs, mediates platelet adhesion at sites of activated and damaged endothelium.[69] ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is a protease that cleaves ultralarge (>20,000 kDa) vWF multimers, reducing their size and thus their vWF platelet binding and activating capacity.[70,71] In patients diagnosed with SIC, 49% of subjects had severely reduced activity levels of ADAMTS-13 (<20%).[72] Due to the decline of ADAMTS-13 activity in sepsis, endothelial injury exposes more ultralarge vWF multimers to plasma, contributing to enhanced platelet adhesion, activation, and sequestration in SIC.[73] The association between low ADAMTS-13 activity and severity of coagulopathy in the critically ill[74] highlights the impact of persistent ultralarge vWF multimers in mediating SIC.

It is further hypothesized that excessive TLR-based signaling by PAMPs/DAMPs contributes to platelet activation (Figure 1) and thrombocytopenia in sepsis. TLR subtypes, however, play diverse roles in platelet activation and regulation in disease. In human platelet-rich plasma, the TLR2 agonist Pam_3CSK4 (10 μg/mL) induced platelet aggregation comparable to thrombin,[75] and in purified human platelets, histones induce dose-dependent (5–80 μg/mL) platelet aggregation and a 5-fold increase in expression of p-selectin that was lost in the presence of TLR2 neutralizing antibodies.[76] Accordingly, TLR2-deficient septic mice had preserved platelet counts and better clot strength on viscoelastic testing thought to be due to reduced TLR2-mediated platelet activation and subsequent clearance.[16] Similarly, TLR7-deficient septic mice demonstrated improved platelet numbers[16] and attenuated increases in circulating activated platelet-leukocyte aggregates (PLA)[77] compared to controls. Moreover, plasma from septic mice induced in vitro platelet activation, and this response was attenuated in TLR7-deficient mouse platelets,[77] indicating a circulating mediator in septic plasma that signals via platelet TLR7, and further supporting a role for platelet-TLR7 signaling in SIC pathology.

The impact of TLR4 signaling on platelet activation is more complex due to whether an endotoxemia or polymicrobial sepsis model is utilized. LPS/endotoxin treatment induced in vitro platelet activation,[78] and potentiated platelet aggregation,[79] while in vivo, significant thrombocytopenia in mice developed within 1 hour of LPS administration,[80] and both

responses were attenuated with blockade/deficiency of TLR4. In the endotoxemia model, LPS is the single toxin that signals through TLR4; there is less platelet activation and loss because there is no platelet TLR4 for LPS to bind and modulate immune and coagulation responses. In comparison, with polymicrobial sepsis, TLR4-deficient mice had significant reductions in platelet counts and evidence of more severe coagulopathy compared to controls.[16] In polymicrobial sepsis (eg, cecal ligation and puncture model), there is extensive host barrier disruption and presence of multiple microorganisms, and TLR4 is essential to phagocytosis and bacterial clearance in this context.[81,82] Therefore, TLR4 deficiency becomes a double-edged sword, as polymicrobial septic animals succumb to overwhelming infection because of inefficient immune responses.

Taken together, these data suggest that TLR subtypes have differing effects on thrombocytopenia in translational animal studies depending on the model used, with TLR2 and 7 deficiency being protective in polymicrobial sepsis, and TLR4 deficiency being protective in endotoxemia.

Endotheliopathy and Impaired Antithrombotic Mechanisms in SIC

The vascular endothelium is responsible for vascular integrity, homeostasis, and maintenance of an antithrombotic environment. The anticoagulant properties of the intact endothelium include release of TF pathway inhibitor (TFPI), nitric oxide, and prostaglandins, and an intact EC glycocalyx consisting of heparan sulfate proteoglycans (HSPs), glycosaminoglycans, and thrombomodulin (TM).[83] In sepsis, pathogen components (eg, LPS) and inflammatory cytokines (eg, tumor necrosis factor alpha [TNFα], interleukin [IL]–6) trigger vascular EC activation.[84,85] Increased vascular permeability reduces intravascular volume, leading to hypoperfusion and tissue hypoxia with release of reactive oxygen species and oxidative-induced EC damage.[86] Ongoing inflammation triggers intracellular pathways in ECs mediated by nuclear factor-κB (NF-κB), which further drives cytokine production and perpetuates systemic inflammation and endotheliopathy.[87] This endotheliopathy impairs 2 endogenous anticoagulant proteins in sepsis, TM and antithrombin III (ATIII).[3]

TM is expressed on the endothelium, scavenges thrombin, and prevents its binding to fibrinogen and platelets. TM is a cofactor necessary for thrombin-mediated cleavage of protein C to activated protein C (APC). APC inhibits FVa and FXa activity and is anti-inflammatory.[88] Sustained increase in plasma levels of soluble TM have been observed in patients with DIC, suggesting loss of TM from the endothelium and impaired antithrombotic mechanisms.[89] TM is further degraded by increase circulating neutrophil elastases in sepsis leading to additional protein loss.[88] After in vitro treatment with specific PAMP/DAMP, LPS, and histones, ECs displayed increased TF and PS expression and thrombin generation, but reduced TM expression.[90] The anticoagulant properties of ECs were restored with supplemental TM after LPS treatment, thereby attenuating thrombin generation in a dose-dependent manner.[90]

ATIII is a serine protease produced by the liver and inhibitor of intravascular thrombin and FXa. ATIII can anchor to the endothelium via HSPs to facilitate its inhibitory activity against thrombin.[91] During sepsis, ATIII activity levels are significantly reduced to 40% to 60% in patients with overt DIC[92] (normal, 80%–120%) secondary to increased thrombin generation and consumption, and through inactivation by increased circulating levels of neutrophil elastases.[93] ATIII binding to the endothelium decreased by 40% after in vitro treatment with proinflammatory cytokines such as IL-1β and TNFα.[94] Inflammatory cytokines and endotoxins trigger release of angiopoietin-2, an antiangiogenic factor, from ECs, inducing degradation of endothelial heparan sulfates via an increase in heparanases enzymatic action.[95] Loss of heparan sulfates from the vascular endothelium partly accounts for reduced ATIII presence due to loss of its primary binding site, resulting in dysregulated procoagulant activity that is pathognomonic in SIC.

CLINICAL FEATURES OF SIC

The term coagulopathy is a general term for systemic coagulation disturbances, but depending on the balance between procoagulant, anticoagulant, and fibrinolytic pathways, variable phenotypes may manifest. SIC presents clinically as a nonovert DIC in sepsis (Figure 3), in which there is evidence of systemic thrombin generation with microvascular thrombi formation and organ dysfunction, hypothesized to be mediated by circulating PAMPs/DAMPs, but excessive or overt clotting factor, fibrinogen, and platelet consumption is not present. Typically with septic coagulopathy, laboratory analysis reveals increased procoagulant signaling (eg, TF)[18] and markers of thrombin generation (eg, thrombin-antithrombin [TAT] complexes)[96] with moderate decreases in antithrombotic proteins (eg, ATIII).[97] Fibrinogen levels in SIC are normal or elevated (250–500 mg/dL) at the time of ICU admission, while platelets decrease early in the disease course.[98] Another clinical feature of SIC is impaired fibrinolysis attributed to elevated plasma levels of plasminogen activator inhibitor-1 (PAI-1) released by activated ECs (Figure 3). PAI-1 expression is induced in the presence of cytokines, such as TNFα, and with the DAMP, HMGB-1.[99] Increasing plasma levels of PAI-1 and fibrinolytic shutdown in

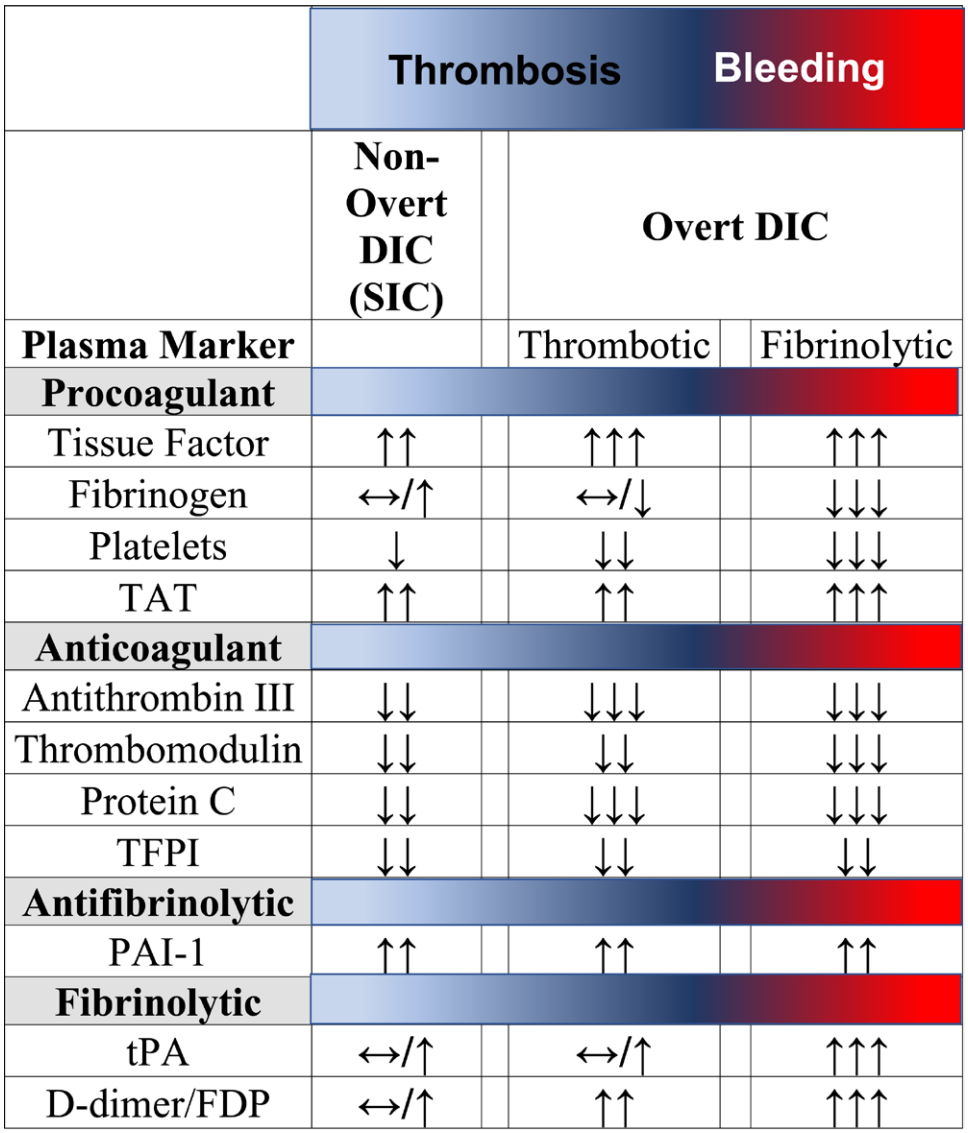

Figure 3. Clinical laboratory features and trends in SIC. Sepsis-induced coagulopathy is a form of nonovert DIC in septic patients in which intravascular coagulation driven by inflammatory-mediated TF expression results in TAT and mild-to-moderate consumption of platelets and endogenous anticoagulants (ATIII). Further, PAI-1 is significantly elevated, resulting in early suppression of fibrinolysis. The coagulopathy in SIC can progress to overt DIC of a thrombotic phenotype with overactive clotting and worsening consumption of clotting factors and platelets. Finally, elevated tPA antigen and markers of fibrinolysis (d-dimer) characterize overt DIC of a predominant fibrinolytic phenotype. ↔ = no change, ↑ = mild changes, ↑↑ = moderate changes, and ↑↑↑ = severe changes. ATIII indicates antithrombin III; DIC, disseminated intravascular coagulation; FDP fibrin degradation products; PAI-1, plasminogen activator inhibitor-1; SIC, sepsis-induced coagulopathy; TAT, Thrombin-antithrombin complex; TF, tissue factor; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator. Created with BioRender.com.

sepsis have been linked to disease severity.[100] At the onset of sepsis, PAI-1 levels increase (Figure 3), may remain elevated for up to 7 days, and correlate with impaired lysis on thromboelastometry.[97]

If dysregulated immune-thrombotic responses continue, SIC can progress to overt DIC with gross consumption of fibrinogen, platelets, and antithrombotic proteins, and manifests as a thrombotic, fibrinolytic, or mixed coagulopathy (Figure 3).[101] In DIC with thrombosis, there is overactive clotting and consumption of platelets and fibrinogen with suppressed or balanced fibrinolysis.[101] In DIC with fibrinolysis, there are still significantly reduced platelet and fibrinogen levels, but with pronounced fibrin breakdown, and elevations in plasma fibrinolytic markers (eg, d-dimer), resulting in excessive bleeding.[102] The presence of severe thrombocytopenia (platelets $<50 \times 10^9$/L) is independently associated with lower survival, and higher plasma levels of cytokines and EC injury markers,[65] and patients with significant reductions in plasma fibrinogen levels <200 mg/dL also showed increased mortality.[103] In 1 retrospective study, 30% of patients diagnosed with septic shock progressed to overt DIC 3 days after admission, and had lower platelet counts and higher 28-day mortality compared to the SIC (nonovert DIC in sepsis) group.[104] These studies highlight the critical need to identify and prevent progression of SIC to the point of hemostatic deterioration and excessive mortality associated with DIC.

Although we have focused on bacterial sepsis and coagulopathy, we must also mention the unique clinical features associated with respiratory viruses. Viral-mediated coagulopathy may be secondary to direct cellular effect, generation of autoimmune antibodies against platelets, or increase in procoagulant mediators such as TF and vWF.[105] During the 2009 H1N1 influenza pandemic, several case reports and case series demonstrate occurrence of thrombotic events including deep

vein thrombosis, pulmonary emboli, acute myocardial infarctions, and thrombotic microangiopathy in infected individuals.[106,107] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease-2019 [COVID-19]) infection is also associated with increased risk of thromboembolic (TE) events[108–110] and mortality.[111] In this population, d-dimer is significantly increased compared to patients without a TE phenomenon, and was a risk factor for mortality with levels >1 µg/mL, and a predictor of mortality with levels >2 µg/mL.[112,113] Further, approximately 1.4% of patients diagnosed with SARS-CoV-2 experienced cerebrovascular accidents, with most cases (87%) being ischemic stroke secondary to embolic events.[114,115] Pulmonary ECs express surface angiotensin-converting enzyme 2 receptors in which the COVID-19 virus can gain entry to the host. COVID-19 coagulopathy involves formation of intra-alveolar and intravascular thrombin/fibrin deposition and rapid viral replication resulting in substantial EC apoptosis and widespread endotheliopathy.[116,117] Patients with SARS-CoV-2 complicated by TE events also demonstrate elevated fibrinogen levels and mild decreases in platelet and ATIII levels, giving it a predominantly prothrombotic phenotype without evidence of excessive consumption.[117] This was further supported by a recent study that identified increased plasma markers of EC activation including sCD40L and soluble TM in critically ill COVID-19 patients, but with preserved endogenous anticoagulant activity[118] indicating a coagulopathy driven primarily by endotheliopathy as opposed to a consumptive process as in DIC.

CLINICAL DIAGNOSIS OF SIC

Diagnostic Scoring Systems

Multiple scoring systems exist to diagnose coagulopathy during sepsis. As detailed in Table 2, most use a point system to weigh the impact of changes in plasma coagulation parameters such as prothrombin time (PT), fibrinogen, fibrinogen degradation products (FDP), and platelet count. The Japanese Association for Acute Medicine (JAAM) guidelines are similar to the International Society on Thrombosis and Haemostasis (ISTH) DIC score but omit fibrinogen levels and include an additional point for the presence of systemic inflammatory response syndrome.[119] The JAAM score has a high sensitivity for DIC in patients with infection, while the ISTH-DIC criteria demonstrate greater specificity.[120] Sepsis and its associated dynamic coagulation abnormalities, however, spawned modifications in both the JAAM[121] and ISTH (mISTH) scores to aid in earlier identification of patients with SIC. The mISTH score, for instance, removes fibrinogen from the measurement, as fibrinogen levels do not aid in SIC diagnosis and do not affect early outcome prediction.[119,122]

The ISTH further adopted an additional screening tool, the SIC score (Table 2), which demonstrates a strong predictive value for 28-day mortality in patients with SIC.[123] Because early sepsis is characterized by high PAI-1 levels and suppression of fibrinolysis with normal fibrinogen, the SIC score is targeted at nonovert DIC and does not include fibrinogen and FDP/d-dimer levels.[100] In a retrospective review of septic patients in 2017, fibrinogen/FDP levels did not differ between SIC survivors and nonsurvivors and therefore may not be relevant for early discrimination.[123] Both the mISTH and SIC scores are independently associated with disease severity and ICU mortality, but the mISTH score better predicts ICU mortality compared to the SIC score (mISTH, area under the curve [AUC], 0.684 vs SIC, 0.658).[124] SIC score has a higher sensitivity (74.3%) compared to mISTH (49.5%), but lacks specificity[124,125] in part because the SIC score includes 3

Table 2. Diagnostic Scoring Systems Used in Diagnosis of Coagulopathy in Sepsis

Scoring System	ISTH-DIC	mISTH-DIC	ISTH-SIC	JAAM-DIC
Criteria				
SOFA score			1: 1 point ≥2: 2 points	≥3: 1 point
Platelet count (×10⁹/L)	≤100: 1 point ≤50: 2 points	≤100: 1 point ≤50: 2 points	<150: 1 point <100: 2 points	<120: 1 point <80: 3 points
FDP (µg/mL)				≥10: 1 point ≥25: 3 points
d-dimer (µg/mL)	≥1: 2 points >2: 3 points	≥1: 2 points ≥2: 3 points		
Fibrinogen (mg/dL)	≤100: 1 point			
PT prolongation (s)[a]	≥3: 1 point ≥6: 2 points	≥3: 1 point ≥6: 2 points		
PT ratio (patient/normal)				≥1.2: 1 point
PT/INR ratio			>1.2: 1 point >1.4: 2 points	
DIC/SIC diagnosis	≥5 points	≥5 points	≥4 points	≥4 points

Abbreviations: DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; INR, international normalized ratio; ISTH, International Society of Thrombosis and Hemostasis; JAAM, Japanese Association for Acute Medicine; mDIC, modified disseminated intravascular coagulation; mISTH, modified International Society of Thrombosis and Haemostasis; PT, prothrombin time; SIC, sepsis-induced coagulopathy; SOFA, sequential organ failure assessment.
[a]PT prolongation above upper limit of normal.

parameters, 1 of which is the sequential organ failure assessment (SOFA) value, which is elevated given the current Sepsis-3 diagnostic guidelines.

The SIC score was designed for earlier identification of patients with coagulopathy who have an elevated risk of deterioration from nonovert to overt DIC, which explains its high sensitivity. Given that diagnosis of SIC using the SIC score preceded a diagnosis of overt DIC, once this patient subset is identified, they may be followed using the ISTH overt DIC score, which carries a higher specificity.[125] A combination of the SIC score with the ISTH DIC score may allow for earlier detection of SIC and institution of therapy before progression to overt DIC.

Coagulation Testing in SIC

Diagnostic criteria for SIC do not include evaluation of endogenous anticoagulants, the fibrinolytic-antifibrinolytic system, inflammation, or endothelial activation. Recent work has identified new metrics for SIC, including markers of inflammation (eg, vascular endothelial growth factor and IL-6:IL-10 ratio), infection (eg, procalcitonin), endothelial function (eg, endocan), and platelet activation (eg, platelet factor-4), which have strong predictive ability for mortality (AUC, 0.87).[126] An experimental scoring system including plasma levels of EC-derived microparticles, platelet count, and PT demonstrated a negative predictive value for DIC of 93% at admission, allowing early stratification of coagulopathy risk development in septic patients.[127] Such markers may provide more precise characterization, but have not been widely validated to distinguish SIC from other forms of DIC, nor are they readily available for routine testing. Therefore, no recommendations currently exist for routine measurements beyond standard coagulation testing.[128]

Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) may be useful as a diagnostic screen in SIC; however, a majority of studies focus on capturing overt DIC.[129] Patients with overt DIC had reduced maximum clot firmness (MCF) on ROTEM compared to those without DIC, and MCF demonstrated a high sensitivity for DIC diagnosis.[130] A 2021 meta-analysis evaluated 11 observational studies using TEG or ROTEM, and found that a hypocoaguable profile (reduced MCF) was a valid parameter associated with mortality in septic patients.[131] MCF is strongly dependent on platelets and fibrinogen, and reduced MCF suggests reductions in both secondary to ongoing activation and consumption. In a cohort of 295 patients with SIC, 30% progressed to DIC within 3 days of admission, and an initial MCF value on TEG <64 mm was proven to be an independent risk factor for DIC development.[104] However, the range of reported MCF values in patients that developed DIC was 52.2 to 67.6 mm (vs 60.2–73.4 mm in non-DIC, $P < .001$),[104] showing that although reduced, TEG/ROTEM values often remain within established reference ranges.[132] Whether TEG/ROTEM is sensitive enough to detect early changes in coagulation characteristic of SIC is unclear, and this highlights the need for additional clinical research into determining viscoelastic reference ranges for SIC across multiple time points to capture dynamic changes in coagulation and establish appropriate reference ranges.

MANAGEMENT AND TREATMENT

Symptomatic Treatment and Supportive Therapy for SIC

In 2016, the Surviving Sepsis guidelines were published that emphasize a mortality benefit with early and goal-directed therapy of antibiotics for treatment of underlying infection, intravenous fluids, and vasoactive medications to maintain perfusion pressure for patients diagnosed with sepsis.[133] There are limited specific recommendations for management of SIC. For SIC progressing to overt DIC and a bleeding phenotype, recommendations include replacement of red cells (strong recommendation) in cases of anemia, plasma (weak recommendation) with active bleeding/invasive procedures, and platelets (weak recommendation) with counts $<50 \times 10^9$/L.[133] Few clinical trials have evaluated plasma use in SIC, but a clinical study registered in October 2020 with recruitment completed in January 2023 may shed light on the impact of plasma therapy.[134] In cases of SIC progressing to overt DIC and a thrombotic phenotype, the only recommendation is prophylactic or therapeutic anticoagulation (eg, heparin).[135]

Restoration of Anticoagulants

Direct options for treatment of septic coagulopathy include replacement of endogenous anticoagulants (eg, APC [or drotrecogin alpha activated], TFPI, ATIII, and TM), but none have consistently shown a mortality benefit in sepsis (Table 3), and therefore, therapeutic interventions specifically targeting SIC to prevent coagulopathy progression are unfortunately lacking.

In a trial of 1754 septic patients, TFPI failed to show a mortality benefit and actually caused in an increased risk of bleeding, and therefore was not approved for use in sepsis or sepsis-associated complications.[136] The 2001 Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial of APC included 1690 patients and demonstrated a 19.4% reduction in relative risk of death compared to placebo, and a nonsignificant increased risk of bleeding.[137] Subsequently, 2 large RCTs, including 2167 adult and pediatric septic patients, demonstrated no mortality benefit with APC in patients with severe sepsis.[138,139] The 2012 Protein C Worldwide Evaluation in Severe Sepsis and Shock (PROWESS-SHOCK) trial likewise found no significant reduction

Table 3. Clinical Trials Assessing Efficacy of Targeted AC Therapies Aimed at Repletion of Endogenous Coagulation Inhibitors in Patients With Sepsis and/or DIC

Clinical Trial	AC vs	28-d Mortality		Bleeding		DIC Resolution[a]		Subgroup Analysis	28-d Mortality	
		AC (%)	vs (%)	AC (%)	vs (%)	AC (%)	vs (%)		AC (%)	vs (%)
Warren et al[143] (KyberSept) 2001 Sepsis N = 2314	ATIII (3000 IU) vs placebo	37.8	43.6	22	12.8			Kienast et al[144] Sepsis + DIC w/o heparin 2006 N = 563	25.4	40
Iba et al[151] 2012 Sepsis + DIC N = 729	ATIII (3000 IU) vs ATIII (1500 IU)	25.3	34.8	4.2	1.4	69.6	55.4			
Bernard et al[137] (PROWESS) 2001 Sepsis N = 1690	DAA (24 μg/kg) vs placebo	24.7	30.8	3.5	2			Dhainaut et al[152] Sepsis + overt DIC 2004 N = 454	30.5	43
Bernard et al[153] (ENHANCE) 2004 Sepsis N = 273	DAA (24 μg/kg) vs placebo	26.4	32.9	5.5	3.7					
Abraham et al[139] 2005 Sepsis N = 2613	DAA (24 μg/kg) vs placebo	18.5	17	3.9	2.2					
Ranieri et al[140] (PROWESS-SHOCK) 2012 Sepsis N = 1697	DAA (24 μg/kg) vs placebo	26.4	24.2	1.2	0.96					
Abraham et al[136] 2003 Sepsis N = 1754[b]	TFPI (0.025 mg/kg) vs placebo	34.2 12	33.9 22.9	6.5 6	4.8 3.3					
Saito et al[145] (ART-123) 2006 Infection N = 102[c]	rh-soluble TM (0.06 mg/kg) vs heparin (8 units/kg)	28	34.6	43.1	56.5	66.7	54.9	Aikawa et al[154] Sepsis + DIC 2011 N = 80	21.4	31.6
Vincent et al[155] 2013 Sepsis + DIC N = 741	rh-soluble TM (0.06 mg/kg) vs placebo	17.8	21.6			28.9	18.9			
Vincent et al[141] (SCARLET) 2019 SIC N = 800	rh-soluble TM (0.06 mg/kg/d) vs placebo	26.8	29.4	5.8	4					

Abbreviations: AC, anticoagulant; ATIII, antithrombin III; DAA, drotrecogin alpha; DIC, disseminated intravascular coagulation; ENHANCE, Extended Evaluation of Recombinant Human Activated Protein C; INR, international normalized ratio; PROWESS, Protein C Worldwide Evaluation in Severe Sepsis; rh, recombinant human; SCARLET, Sepsis Coagulopathy Asahi Recombinant LE Thrombomodulin; SIC, sepsis-induced coagulopathy; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin.

[a]DIC resolution was defined as a score of less than the thresholds of DIC criteria used in each study.

[b]Results shown are 28-d mortality and incidence of bleeding, for high INR (>1.2)—top row, and low INR (<1.2)—bottom row.

[c]Study included DIC secondary to both malignancy and infection. Mortality and DIC resolution results for the infection cohort only are presented, while bleeding complications are a composite of both groups.

in mortality in the APC group (26.4% vs 24.2%, P = .31),[140] and APC was withdrawn from the market.

Evidence supporting recombinant human soluble TM (rhTM or ART-123) and ATIII supplementation is also mixed. In a 2019 randomized clinical trial, rhTM demonstrated no significant reduction in 28-day mortality in patients diagnosed with coagulopathy.[141] However, approximately 20% of patients in this trial no longer exhibited coagulopathy at the time of intervention. In 1998, a placebo-controlled randomized trial of ATIII supplementation in 42 septic patients found a 39% reduction in 30-day mortality,[142] but the larger (n = 2314) multicenter phase 3 KyberSept trial in 2001 failed to show any significant reduction in 28-day mortality, and found an increased bleeding risk with concomitant prophylactic heparin administration.[143] A subgroup analysis of the KyberSept trial in 2006 (Table 3) examined the effects of ATIII in septic patients and no heparin usage, and found improved mortality in patients with DIC compared to placebo treatment but not in patients without DIC.[144] However, as a result of inconsistent mortality benefit in primary trials, neither rhTM nor ATIII is currently approved for use in sepsis or SIC in the United States.

In other clinical studies evaluating anticoagulant therapies for SIC and/or DIC, authors report in vivo evidence of reduced thrombin generation and improvement in coagulation parameters,[119,136,145] suggesting potential therapeutic benefit specifically to septic patients with coagulopathy. A 2016 meta-analysis including 24 RCTs and 14,767 septic patients found less mortality with anticoagulant therapy in septic patients with DIC (relative risk, 0.72; 95% confidence interval [CI], 0.62–0.85; P < .01), but not without (relative risk, 0.97; 95% CI, 0.92–1.02; P = .25), and specifically when DIC was confirmed by one of the major diagnostic scoring systems.[146] In addition, a 2021 study found a 17.8% risk reduction in 28-day mortality with rhTM treatment in septic patients with coagulopathy, defined by severely low platelet counts and fibrinogen with prolonged PT-INR, and high D-dimer levels, an effect not seen in septic

patients with mild-to-moderate changes in the above tests.[147] Although evidence is mixed regarding anticoagulant therapy and mortality benefit in the sepsis population, secondary analysis studies (Table 3) and other systematic reviews/meta-analyses demonstrate improvement in coagulation parameters and mortality in patients with a certain degree of coagulopathy. This suggests the existence of an optimal coagulopathic phenotype in septic patients that might benefit from replacement of endogenous anticoagulants.

As a consequence of mixed data regarding the clinical benefit of anticoagulant therapy in septic patients, the Surviving Sepsis Campaign does not recommend targeted antithrombotic treatments.[133] However, different criteria for diagnosis of coagulopathy and/or broad inclusion of all septic patients regardless of coagulation status may have contributed to the inconsistent clinical trial results. Improved outcomes from anticoagulant therapy may only be demonstrated in a subset of septic patients as therapeutic efficacy is dependent on specific patient factors, and type and degree of coagulopathy.

SUMMARY

SIC is a complication of sepsis involving dysregulated coagulation that is mechanistically linked to innate immune activation and contributes to organ injury and high mortality. While immune-mediated thrombin generation, platelet activation, endotheliopathy, and impaired antithrombotic mechanism are separate mechanistic pathways, they interact in a coordinated fashion in the pathogenesis of SIC. The current therapeutic approaches in treating SIC have focused on reintroducing exogenous regulators of these systems, but their effectiveness appears to lie in accurate and timely diagnostics. Clarification of underlying mechanisms in SIC has continued, but efforts to develop targeted therapeutics have stalled. New focus and insight into pathological mechanisms underlying coagulopathy will help advance translational approaches to rapid diagnosis and prognosis of SIC to identify patients who would benefit most from therapies.

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