Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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REVIEW

Recent Advances in Pathogenesis and Anticoagulation Treatment of Sepsis-Induced Coagulopathy

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Abstract: Coagulopathy in sepsis is common and is associated with high mortality. Although immunothrombosis is necessary for infection control, excessive thrombus formation can trigger a systemic thrombo-inflammatory response. Immunothrombosis plays a core role in sepsis-induced coagulopathy, and research has revealed a complex interplay between inflammation and coagulation. Different mechanisms underlying sepsis-related coagulopathy are discussed, including factors contributing to the imbalance of pro- and anticoagulation relevant to endothelial cells. The potential therapeutic implications of anticoagulants on these mechanisms are discussed. This review contributes to our understanding of the pathogenesis of coagulopathy in patients with sepsis. Recent studies suggest that endothelial cells play an important role in immunoregulation and hemostasis. Meanwhile, the non-anticoagulation effects of anticoagulants, especially heparin, which act in the pathogenesis of coagulopathy in septic patients, have been partially revealed. We believe that further insights into the pathogenesis of sepsis-induced coagulopathy will help physicians evaluate patient conditions effectively, leading to advanced early recognition and better decision-making in the treatment of sepsis.

Keywords: sepsis, coagulopathy, endotheliopathy, immunothrombosis, thromboinflammation, anticoagulant

Introduction

Coagulopathy, which commonly develops during sepsis, is a complex process involving simultaneous intravascular inflammation, thrombocytopathy, and endotheliopathy.[1] These distinct but interrelated responses to external pathogen invasion can be devastating and even enhance lethality. Patients with sepsis who develop coagulopathy usually have a high mortality rate.[2] Immunothrombosis and thromboinflammation are intricately linked in the pathogenesis of sepsis.[3] Terms such as septic coagulopathy, sepsis-related coagulopathy, sepsis-induced coagulopathy, sepsis-associated coagulopathy, and sepsis-induced disseminated intravascular coagulation have been introduced because coagulopathy management has become a major concern in septic patients, mainly due to intravascular environment changes that are not fully explained by currently known mechanisms.

Although diagnostic criteria for overt disseminated intravascular coagulation (DIC) have been proposed by the International Society on Thrombosis and Haemostasis (ISTH), the clinical presentations of DIC are variable and present in different forms. Manifestations of coagulopathy in the early phase of sepsis may not be able to alarm the potential amplification of coagulopathy, which often results in overt DIC. Therefore, a new category termed "sepsis-induced coagulopathy" (SIC) has been proposed, which aims to provide timely assessments, recognitions, and interventions in patients with sepsis.[4] Laboratory features that differ from true DIC molecular dysfunction suggest the actual entity of sepsis-induced coagulopathy, which is now considered endotheliopathy-associated vascular microthrombotic disease (EA-VMTD).[5]

Received: 8 September 2024
Accepted: 31 December 2024
Published: 18 January 2025

Delineating the mechanisms underlying SIC is essential in sepsis management. In this review, we have attempted to clearly illustrate the recent interpretation of coagulopathy in sepsis (Figure 1). Furthermore, we briefly discuss current SIC management.

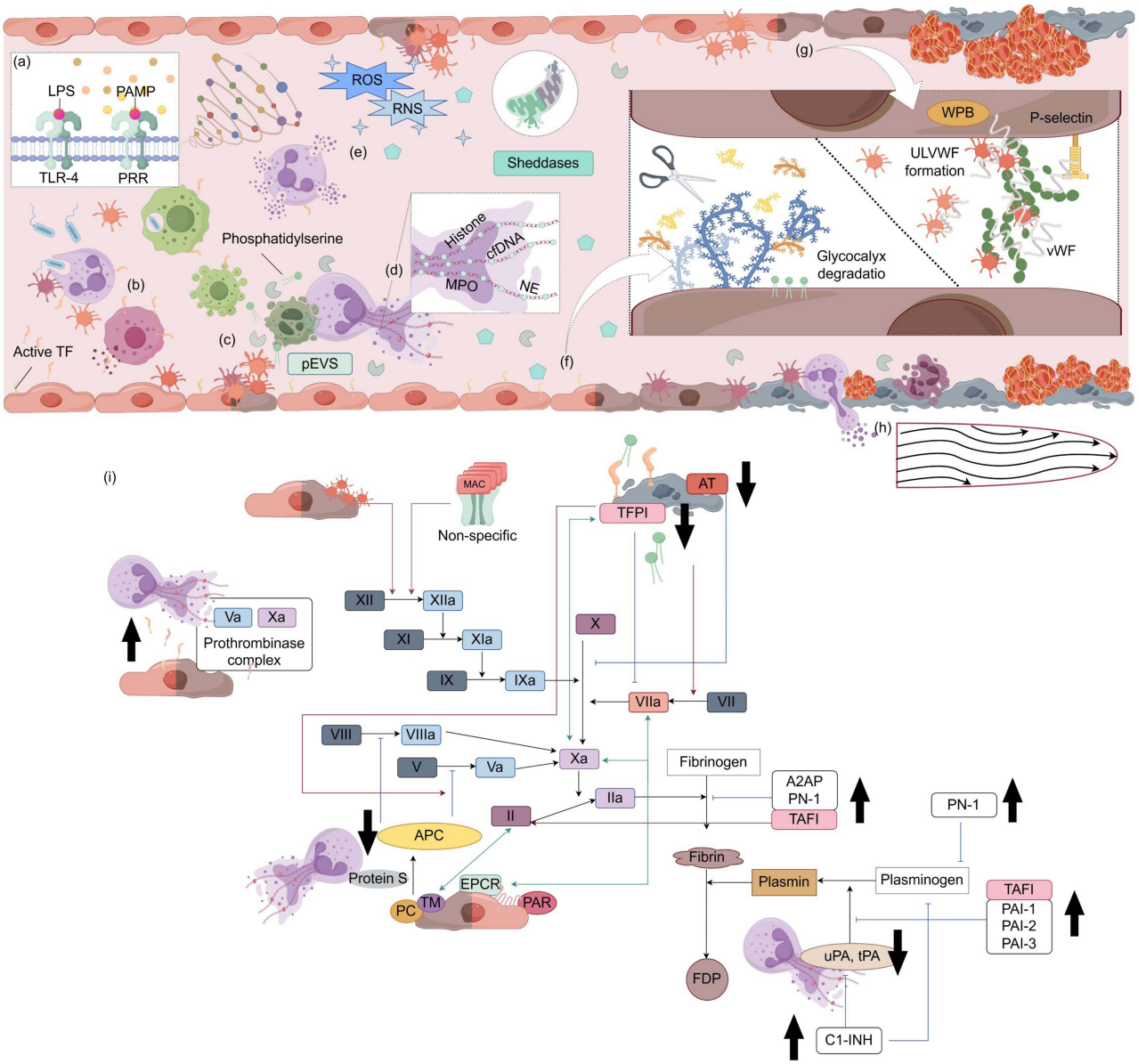

Figure 1 Pathogenesis of Sepsis-induced Coagulation. (**a**) External pathogen invasion induces intravascular hypercytokinemia through PAMP-PRR recognition. (**b**) Pathogen clearance is initiated by pan-cellular activation, involving neutrophils, monocytes-macrophages, megakaryocytes-platelets, and endothelial cells. Immune and non-immune cells synergistically regulate immunomodulation and coagulation. (**c**) Activated immune cells release a series of pro-coagulant factors that further initiate the coagulation cascade while causing endothelial cell damage. (**d**) Neutrophils play a crucial role in innate immune defense. NETosis, aimed at pathogen elimination, ultimately leads to intravascular coagulation due to increased circulatory and cytotoxic components. (**e**) Oxidative stress generated during pan-cellular activation is closely associated with immunomodulation, endotheliopathy, and mitochondrial dysfunction. (**f** and **g**) Intact endothelium with a well-preserved endothelial glycocalyx is essential for the expression of endothelial antithrombotic and anticoagulant factors. Under systemic inflammatory conditions, the endothelial glycocalyx is degraded by heparinase, and ULVWF formation occurs due to secondary ADAMTS13 deficiency. (**h**) Increased shear stress exacerbates endothelial damage. (**i**) The regulation of immunothrombosis and thromboinflammation by endothelial cells along the coagulation cascade is highly complex. By Figdraw.

Abbreviations: LPS, lipopolysaccharide; PAMP, pathogen-associated molecular pattern; TLR-4, toll-like receptor 4; PRR, pattern recognition receptor; TF, tissue factor; pEVs, platelet-derived extracellular vesicles; ROS, reactive oxygen species; RNS, reactive nitrogen species; MPO, myeloperoxidase; NE, neutrophil elastase; cfDNA, cell-free DNA; WPB, Weibel–Palade body; ULVWF, ultra-large von Willebrand factor; vWF, von Willebrand factor; MAC, membrane attack complex; TFPI, tissue factor pathway inhibitor; AT, antithrombin; APC, activated protein C; PC, protein C; TM, thrombomodulin; EPCR, endothelial protein C receptor; PAR, protease-activated receptor; FDP, fibrin degradation products; A2AP, alpha-2 antiplasmin; PN-1, protease nexin-1; TAFI, thrombin-activatable fibrinolysis inhibitor; PAI, plasminogen activator inhibitor; uPA, urokinase-type plasminogen activator; tPA, tissue-type plasminogen activator; C1-INH, C1 esterase inhibitor.

Methods

We performed a search of PubMed, Web of Science, Google Scholar, and the China National Knowledge Infrastructure (CNKI). With the use of MeSH and keywords, such as "sepsis", "immunothrombosis", "thromboinflammation", "inflammation", "coagulopathy", "endothelial", and "anticoagulant". We identified studies and reviews that are relevant to EA-VMTD that can lead to coagulopathy in septic patients. Based on the included articles and reviews, a general pathophysiology and anticoagulant strategy for coagulopathy in sepsis was provided.

Results

Pathogenesis

Uncontrolled Inflammation: Activation of Coagulation Cascade

Sepsis and sepsis-related deaths commonly result from major infections that mediate endotoxemia induction.[6] Over the past decade, research has revealed a complex interplay between immunothrombosis and thromboinflammation in sepsis. Immunothrombosis is a process driven by an altered innate immune system that aims for pathogen clearance through a series of activations of immune cells, including neutrophils, monocytes-macrophages, and megakaryocytes-platelets,[7] usually initiated once the external pathogens are recognized by a series of molecular patterns. Lipopolysaccharide (LPS) is a prevalent pathogen-associated molecular pattern (PAMPs) that enables rapid distinction and response to pathogens through counterpart pattern recognition receptors (PRRs) interactions.[8] Toll-like receptor 4 (TLR4) in macrophages and neutrophils serves as a pathogen sensor.[9,10] Sepsis induces auto-amplification of cytokines after LPS-TLR4 recognition.[11,12] The aberrant expression of pro-inflammatory and anti-inflammatory factors, such as tumor necrosis factor-α (TNF-α), interferons (IFNs), and interleukins (ILs), including IL-6, IL-2, IL-12, IL-4, IL-10, and transforming growth factor-β (TGF-β) are known to be involved in the development of coagulopathy.[13,14]

Upon hypercytokinemia, apart from its role in immunomodulation, monocyte-macrophage transitions into a procoagulant status due to surface tissue factor (TF) expression.[15,16] The released TF-positive extracellular vesicles initiate clot formation, leading to macrophage pyroptosis via caspase-11 activation, which is induced by type I IFN signaling.[17] During pyroptosis, cells undergo membrane shrinkage and blebbing, and surface phosphatidylserine exposure recruits macrophages and stimulates coagulation.[18]

Infection-induced endotoxemia activates macrophages and neutrophils for phagocytosis.[19,20] Neutrophils serve as powerful host innate immune defense.[9] Activated live neutrophils release antimicrobial enzymes (eg, neutrophil elastase and myeloperoxidase) while forming neutrophil extracellular traps (NETs), which are web-like structures composed of tangled decondensed DNA, histones (mainly H1 and H3), and other granules.[21,22] Proper NETosis is beneficial for pathogen clearance. However, under sepsis conditions, massive NETs ejection disrupts the intravascular microenvironmental homeostasis.[23,24] During NET degradation, NETs debris includes pathogens, cell-free DNA (cfDNA), and cell-free histones (CFHs), which can enter circulation and act as precursors of clot formation and complement activation. Extensive circulating NETs debris induces the release of TF and upregulates TF expression on monocytes, which are harmful to the host by cytotoxic disruption of the endothelial barrier and increase the release of TF on endothelial cells (ECs). Moreover, CFHs can indirectly contribute to the formation of the prothrombinase complex and directly interact with prothrombin, resulting in thrombin generation.[16,17,20,25]

Damage-associated molecular patterns (DAMPs) derived from NETs and their degraded debris trigger leukocyte activation and adhesion, and generate more NETs through platelet activation, either directly or indirectly.[26,27] During sepsis, changes in the transcriptome of megakaryocytes and platelets result in intravascular platelet rolling, aggregation, and activation. Activated platelets interact with neutrophils and ECs to initiate immunothrombosis.[28,29] During pancellular activation, platelets undergo degranulation and release polyphosphate to activate intrinsic coagulation.[5,15] The simultaneous release of platelet-derived extracellular vesicles (pEVs) consist of platelet factor 4 (PF4), soluble PF4, high-mobility group box 1 (HMGB1), and histones, is able to interact with histone-decorated NETs and further promotes intercellular binding and clot modifications.[30]

C-system activation during sepsis induces the generation of a non-specific membrane attack complex (MAC) to facilitate pathogen clearance.[31] However, while the coagulation and complement systems are intricately linked and

mutually regulated to ensure optimal host protection, MAC is destructive.[5,26] The complement/TF/neutrophil axis, known as the TF-dependent procoagulant activity, can lead to coagulation activation.[30,32] Activation of C3 and C5 can be activated by coagulation enzymes such as thrombin, factor Xa, and FXIIa. C5a and C5b-9 alternatively induce platelet surface expression of phosphatidylserine and facilitate assembly of the prothrombinase complex.[31,33]

It is worth paying attention to cytotoxic histones, which are now assumed to be major mediators of sepsis-related death, because they induce microcirculation dysfunction without obvious hemodynamic changes.[34] Cytotoxic histones are a key factor in dysregulated immune responses by releasing IL-8 and myeloperoxidase (MPO), resulting in oxidative stress (OS), neutrophil activation and degranulation, and the release of inflammatory factors and adhesion molecules.[18] OS is required for both the NETosis process and neutrophil respiratory bursts.[35]

Unavoidable Endotheliopathy: Dysregulated Intravascular Microenvironment

ECs are non-immune cells that respond to external pathogens, circulating endotoxins, and subsequent cytokine storms via various phenotypic and functional modifications. Endothelial cell dysregulation represents an adaptive but harmful characteristic that intensifies inflammation and coagulopathy, disrupts vascular permeability, and results in vascular leakage and microcirculatory disturbances through immunothrombosis, particularly in the early phase of sepsis.[36]

A well-preserved endothelial glycocalyx is critical for vascular hemostatic regulation through the release of various antithrombotic substances and the expression of anticoagulant factors.[27,37] Intact endothelium regulates plasma anticoagulant protein levels, including antithrombin (AT), tissue factor pathway inhibitor (TFPI), and protein C.[38,39] Intact ECs are essential for coping with shear stress and accommodating blood supply, as they prevent inappropriate adhesion and activation of various functional cells under hemodynamic instability.[40]

With tissue damage, ECs' natural anticoagulant properties are compromised due to the massive release of TF and complement system activation.[17,26] TF induces the transition of the ECs phenotype into pro-inflammatory and prothrombotic states by degrading the surface endothelial glycocalyx through the action of endothelial heparinase.[20,41,42] Heparinase exposes the glycocalyx-covered phosphatidylserine that contains coagulation factors (FII, FVII, FIX, and FX) toward the lumen and induces intravascular coagulation.[38,43] Injured ECs exocytose the Weibel-Palade body, which increases circulating levels of adhesion molecules such as vWF and P-selectin, promoting platelets and leukocytes activation, adhesion, aggregation, and endothelial phenotype transition.[43] Importantly, ultra-large von Willebrand factor (ULVWF) formation during endothelial exocytosis is considered to be the major initiator of microthrombogenesis.[5,44] Under systemic inflammatory conditions, such as sepsis, rapid proteolysis of ULVWF multimers by ADAMTS13 is limited because of secondary ADAMTS13 deficiency under conditions of heightened consumption, diminished synthesis, proteolytic clearance, and the presence of inhibitors targeting the metalloprotease.[45]

During sepsis, disruption of redox homeostasis leads to a pro-oxidant intravascular environment. ROS, RNS, and inflammatory cytokines provoke the transition of pro-inflammatory microcirculation dysfunction through tissue damage and have a significant impact on endothelial function, such as activating sheddases, including metalloproteinases, heparanase, and hyaluronidase, which induce the enzymatic degradation of cytotoxic histones and further increase OS to injure ECs.[46] Sepsis-mediated OS upregulates endothelial transient receptor potential melastatin 7 (TRPM7) expression to alter calcium and magnesium permeability. TRPM7 upregulation results in endothelial injury due to endothelial adhesion to neutrophils and platelets, and mediates the increased expression of vWF, P-selectin, and intercellular adhesion molecule 1 (ICAM 1) and the release of free radicals.[47,48] The lack of equivalence in eliminating OS by non-enzymatic and enzymatic antioxidant systems contributes to the procoagulant state during microcirculatory dysfunction.[49,50] OS is also highly related to the structural integrity and functional stability of mitochondria to maintain certain levels of organ function.[46,51]

Natural Anticoagulants Defect: Functional ECs are Essential

Acquired anticoagulant deficiency frequently occurs in patients with sepsis.[52] The functional endothelium is central to providing a favorable environment for natural anticoagulants to achieve efficient anticoagulation and anti-inflammation mechanisms, including antithrombin (AT), protein C and tissue factor pathway inhibitor (TFPI).[38,53]

AT, considered the most important and abundant natural anticoagulant, is significantly reduced during sepsis.[52,54] Optimization of antithrombin activity (at least 70% and ideally 80%) is highly associated with disease severity and survival rate.[55–57] AT is an endothelium-related marker that is essential for endothelium stabilization, possibly by preventing the shedding of endothelial glycocalyx. Intact endothelium prevents AT decline and exerts anti-inflammatory effects.[58,59] In the early stage of sepsis, endogenous AT production decreases significantly and is rapidly depleted due to proteolysis by NE and massive TAT complex formation.[60] AT expression is inversely proportional to the plasma levels of cytokines and cytotoxic debris, and the remaining AT is proteolyzed and catalyzed.[61] Notably, endothelial glycosaminoglycan heparan sulphate (HS), known as endogenous heparin, can be destroyed after sheddase activation during sepsis.[43,62]

The protein C system is a vital component of the natural anticoagulant mechanisms in the body. Protein C, protein S, thrombomodulin (TM), and activated protein C (APC) serve as cytoprotective factors that help counteract inflammation-related dysregulation of the internal environment via various mechanisms such as stimulation of the protease activated receptor (PAR) on ECs and cleavage of cytotoxic histone.[63,64] Functional protein C systems provide endothelial barrier protective effects by playing a role in the activation of PAR-1 and endothelial protein C receptor (EPCR), as well as through other potential mechanisms that are not yet fully understood. EPCR binds to FVIIa and FXa, resulting in physiologically relevant anticoagulant effects. During sepsis, protein C and TM are downregulated.[15,54,65] Extracellular CFHs also affect protein C activation and TM-thrombin complex formation.[15,66]

Isolated TFPI synthesized by ECs has an indispensable impact on the anticoagulant system compared to the other anticoagulant mechanisms, especially during AT deficiency. TFPI inhibits the FVIIa-TF complex by inhibiting the FVII-activating protease and factor Xa via Xa-TFPI complex formation.[67] TFPI can synergistically inhibit the prothrombinase complex with greater anticoagulant activity together with APC and Protein S and facilitate APC-mediated inactivation of FVa.[68] TFPI is a strong fibrinolysis promoter due to its efficient inhibition of plasmin inhibitors.[69] During the early stage of sepsis, cleavage and inactivation of TFPI can be mediated by the excessive generation of plasmin.[70] Imbalanced production of TFPI fails to deactivate the coagulation cascade triggered by massive TF expression in activated immune cells and ECs. TFPI can be oxidized by FXa, thrombin, NE, and MPO released from the activated neutrophils.[71,72]

Fibrinolytic Dysfunction: Disrupted Coagulation/Fibrinolysis Balance

Hypo-fibrinolysis can be observed in patients with sepsis due to the abnormally increased expression of the superfamily of serine protease inhibitors (SERPINs), resulting in enhanced thrombotic events due to the co-existence of fibrin deposition and impaired removal. SERPINs are a group of plasminogen activation inhibitors that regulate the fibrinolytic, inflammatory, and complement systems in the hemostasis pathway.[73]

With an increase in circulating inflammatory factors, the serum Plg level can decrease significantly in patients with severe sepsis. LPS induces the active transition of Plg to Pla during inflammation and is accompanied by increased fibrin/fibrinogen degradation products, D-dimer, and the plasmin-A2AP complex (PAP).[74] Notably, while these fibrin/fibrinogen degradation products and D-dimer were significantly enriched in patients with organ dysfunction, they show a marked decline in sepsis-induced DIC.[75–77] α2-antiplasmin (A2AP) serves as a principal inhibitor of Pla in vivo and generally synthesizes PAP in a 1:1 ratio.[78,79] Under conditions of increased shear stress, the crosslinking of A2AP into the fibrin meshwork becomes more efficient. Consequently, the presence of ultra-large von Willebrand factor (ULVWF) on the endothelial surface serves as a relatively protective factor.[80]

The serum level of plasminogen activator inhibitor-1 (PAI-1) positively correlates with the level of circulating IL-6 in septic patients, particularly in patients who develop organ failure and DIC.[71,81,82] During immune-inflammatory activation, PAI-1 is expressed by platelets and ECs, and is driven by TNF-α.[83] The DNA-histone complex release during NETosis prolongs fibrinolysis by interacting with tissue-type plasminogen activator (t-PA) and unknown interactions with urokinase-type plasminogen activator (uPA).[84] Studies have suggested that NETs serve as an internal medium to increase the heterogeneity of clots by forming thicker fibrin fibers through fibrin skeletal support enhancement. Therefore, NETosis debris inhibits fibrinolysis in the microcirculation,[37,84] rendering microthrombi more resistant to anticoagulants during sepsis.[15,23] In contrast, while the role of plasminogen activator inhibitor-2 (PAI-2) during sepsis is

not fully understood, it is known to have a complex interplay with PAI-1 and to share functions with PAI-1 in response to inflammatory stimuli.[85–87]

C1-INH is the most abundant protease inhibitor, which targets the fibrinolytic system during sepsis by inhibiting Pla, tPA, and uPA.[88,89] Abnormally increased expression of C1-INH leads to insufficient fibrinolysis. C1-INH acts effectively on the C system by neutralizing factors Xa, FXIIa, kallikrein, and the C1 component.[90] The increased expression of C1-INH during sepsis enables effective anti-inflammatory action and helps preserve the endothelium through interactions with endotoxins, bacteria, neutrophils, macrophages, ECs, and extracellular matrix components. These effects are achieved independently of its role in protease inhibition. These interactions result in suppression of inflammatory factors and enhanced phagocytosis, as well as modulation of leukocyte rolling and migration.[31,91,92]

Protease nexin (PN) is a member of the SERPIN superfamily and is closely associated with PAI-1.[93,94] PN-1 mitigates plasmin generation and activity of plasmin.[95]

Nevertheless, endothelium thrombomodulin-thrombin complex formation increases thrombin-activatable fibrinolysis inhibitor (TAFI) activity, which contributes to pronounced hypofibrinolysis and anti-inflammatory activity, while AT decreases contribute to natural anticoagulant defects in patients with sepsis.[96,97] TAFI activation reflects both thrombin generation and clot stability, and generally leads to fibrinolytic resistance in platelet-rich clots.[98]

Vicious Circle: Immunothrombosis and Thromboinflammation

The optimal event after pathogen invasion and recognition at the infectious site is localized immunothrombosis, a process of intravascular thrombus formation that facilitates pathogen elimination without causing diffuse activation of the innate immune response.[99,100] However, uncontrolled systemic immunothrombosis was triggered. Immunothrombosis in sepsis is initiated by a series of activations of the inflammation and complementary system, and the release of these massive and varied cytokines leads to an alteration of the surface protein expression on immune and non-immune cells, which in turn results in feedback and feedforward effects on inflammatory events, a phenomenon known as thromboinflammation.[101,102] Immunothrombosis and thromboinflammation contribute to intravascular injury and global systemic damage during sepsis.[3,4,51,100,103]

As discussed before, ECs in the vasculature are considered to be the major contributors to thromboinflammation due to their antithrombotic and anti-inflammatory roles.[53] During immunothrombosis, with the activation of coagulation, studies have suggested that some coagulation factors and products also promote or trigger an inflammatory response.

Thrombin, also known as Factor IIa, plays a crucial role in the various pathways associated with inflammation and coagulation. In the common pathway, thrombin plays a key role in promoting fibrin formation and results in barrier disruption after PARs activation, including PAR-1, −3, and −4, inducing M1 macrophage polarization and directly activating ECs. These actions contribute to the activation of the NF-κB pathway.[104–106] Thrombin upregulates IL-1, IL-6, IL-8, TNF-α, TGF-β, ICAM-1, VCAM-1, and P-selectin in ECs, smooth muscle cells, fibroblasts, epithelial cells, and monocytes.[107–109] Thrombin induces the release of MCP-1, VEGF, metalloproteinases, and PDGF, further promoting inflammation.[110–114] Thrombin generation is also induced by the TF-factor VIIa complex and factor Xa via PAR-1, and PAR-2 activation.[104] FXIIa can directly activate the kallikrein-kinin and complement systems as well as activating the intrinsic pathway of the coagulation cascade. Bradykinin leads to thrombus stabilization, kinin formation, cytokine production, cell growth, and cell migration.[115]

The accompaniment of fibrin deposition is important for isolating and limiting the spread of pathogens.[116] Fibrin exerts multiple effects by serving as a ligand for various cell surface receptors on leukocytes, ECs, platelets, fibroblasts, and smooth muscle cells, which induces inflammation in ECs and promotes leukocyte transmigration.[117,118]

Treatment

The comprehensive management of sepsis includes a series of supportive treatments, including fluid resuscitation, vasopressors, and mechanical ventilation.[119] The recommended fundamental strategies are antimicrobial use and source control. Recently, some recognized anticoagulants have been shown to contribute to the regulation of coagulopathy and inflammatory host response in critically ill patients, and to deliver both therapeutic anticoagulant and non-anticoagulant effects in sepsis management.[84,120]

Anticoagulants

Heparin

Heparin, including UFH and LMWH, is a widely used anticoagulant and antithrombotic drug that plays a major role in sepsis management. Heparin has interdependent and interacting biological features associated with anti-inflammatory, immunomodulatory, and anti-complementary activities, in addition to its anticoagulant effects. Regulatory effects are more predominant in UFH than in LMWH; however, inconsistencies remain in their therapeutic efficiency.[3,24,54,121,122]

Heparin plays a crucial role beyond anticoagulation in the management of sepsis.[123] Heparin is a heterogeneous, linear, highly sulfated, anionic glycosaminoglycan with a high anion charge density. During sepsis, heparin selectively binds to key modulators of cell adhesion, migration, proliferation, and differentiation, and alters the pathological progression of thromboinflammation, which further improves systemic microcirculation.[124] Heparin neutralizes cytokines and chemoattractants, reduces NETs, and inhibits the feedback loop that amplifies pro-inflammatory factors.[54,125] Heparin has a high affinity for proteins with a positive charge and can selectively interact with the central effectors during immunothrombosis, especially heparan sulfate-binding proteins.[30,84] Circulating extracellular histones mediate cytotoxicity and procoagulant activity associated with death in patients with sepsis.[122,126] Due to its structural similarity to heparan sulfate (HS), heparin can neutralize the debris released from the shedding of the endothelial glycocalyx.[120,127,128] When endothelial glycocalyx shedding and NETosis occur, heparin with heparin fragments >1.7 kDa produces a neutralizing effect on histones and interrupts the direct interaction between cfDNA and vWF.[44,129,130] Early administration of heparin (within 6 h of hospitalization) decreases the circulating levels of NET-related markers such as cfDNA, NE, and the MPO-DNA complex.[121] Moreover, heparin-functionalized adsorbents showed a similar efficacy in reducing thrombotic complications by removing the core effect factors of immune thrombosis, acting independently of AT and its interaction with heparin's antithrombin-binding pentasaccharide.[30,130,131] Some in vitro animal experiments have shown that purified heparin with eliminated anticoagulant effect but other independent mechanisms relieve thromboinflammation and SIC progression while reducing the risk of bleeding.[122,130] Therefore, heparin holds great promise for the treatment of sepsis and sepsis-associated coagulopathy through its anticoagulant and non-anticoagulant effects.

Heparin and heparin-like compounds have been introduced as possible adjunctive therapies for patients with sepsis.[132] A meta-analysis including 3482 patients from nine trials showed that heparin reduced 28-day mortality in patients with severe sepsis [odds ratio = 0.656, 95% confidence interval (CI) = 0.562–0.765, $P < 0.0001$] without increasing the incidence of bleeding events.[133] However, another meta-analysis enrolling 2637 patients from nine trials showed that while heparin decreased mortality in patients with sepsis, septic shock, and DIC associated with infection, a small trial reported a significantly increased risk of major bleeding.[134] Therefore, uncertainty regarding heparin safety and efficacy remains.

Activated Protein C, APC

APC is a natural mediator protein that regulates various pathological conditions through cleavage of cytotoxic histone H3 and alleviation of sepsis-induced interactions between platelets, neutrophils, and ECs.[135] Recombinant human activated protein C (rhAPC), known as drotrecogin alfa (activated) (DAA), was the first APC variant applied in septic patients with high mortality and was approved by the US Food and Drug Administration (FDA) in 2001.[136–138] In vitro studies showed that mono-drug application of rhAPC significantly reduced sepsis-induced platelet-neutrophil aggregates in plasma and decreased neutrophil aggregation and adhesion to damaged endothelial cells, suppressing excessive thrombus formation.[135,139] However, the clinical benefit-to-risk ratio of rhAPC did not support its administration due to rising concerns regarding its proven efficacy in anticoagulant and anti-inflammatory effects in a PAR-1 targeted, but EPCR-independent manner.[140,141] Especially in septic patients, because their coagulation system has been extensively disturbed, further multi-organ complications, commonly hemorrhage-related adverse events, can be easily triggered.[136,138,142,143] In patients with severe sepsis and a low risk of death (APACHE II score <25 or single organ involvement), intravenous infusion (24 μg/kg/h) of rhAPC for 96 h showed no clinical benefit, but significantly increased risk of the bleeding events.[144] Therefore, rhAPc was withdrawn from the anticoagulant market in 2011 because of its variable clinical benefits and perhaps increased bleeding risk between septic sub-phenotypes.[137,142,145,146]

Table 1 Chinese Herbal Medicines and Their Use in the Treatment of Sepsis

Options	Mechanism of Action	Effect	Research Progress	Ref.
Xuebijing injection	Anti-inflammatory, anticoagulation, immune regulation, vascular endothelial protection, anti-oxidative stress	Improve the 28-day mortality and other indexes, such as the APACHE II score, body temperature, and white blood cell count	Clinical trials, animal or cellular experiments	[158,159]
Nano-curcumin	Anti-inflammatory, vascular endothelial protection, anti-oxidative stress	Significant decrease the SOFA score and the duration of mechanical ventilation	Clinical trials, animal experiment	[160,161]
Shenfu injection	Anti-inflammatory, anti-apoptosis	Significantly improved the 7-day survival rate, significantly increased cardiac function	Animal experiment	[162]
Shenhuangdan decoction	Anti-inflammatory, prevent pyroptosis, immune regulation	Reduce mortality and alleviate lung pathological damage	Animal experiment	[163]
QiShenYiQi pills	Anti-inflammatory, vascular endothelial protection, prevent ferroptosis, anti-oxidative stress	Mitigate sepsis-induced acute lung injury	Animal experiment	[164]
Stachydrine	Suppressed platelet activation, decreased platelet-neutrophil interactions	Alleviative sepsis-induced multiorgan damage	Animal experiment	[165]

To minimize the risks of complications and take advantage of APC properties. Several APC variants have been designed with enhanced neutralizing abilities of extracellular histone H3 and permanently diminished anticoagulant abilities, unlike wild-type APC. For example, the variants 3D2D-APC and 3D2D2A-APC. These rationally designed and produced novel APC variants are potential therapeutic agents for histone-associated diseases, including cancer and inflammatory diseases.[126] Site-directed mutagenesis was used to modify the cytoprotective and antiapoptotic activities of APC while eliminating its anticoagulant activity, such as 229/230-APC and 3K3AAPC, also present similar therapeutic effects while greatly reducing the anticoagulant activity (<10%) through corresponding surface loop amino acid mutations.[142,147]

Antiplatelet Drugs

Thrombocytopenia is associated with poor outcomes in sepsis. Antiplatelet strategies aim to slow the progression of coagulopathy by decreasing platelet reactivity, which acts as a functional mediator between immunothrombosis and thromboinflammation. These strategies aim to prevent extensive microthrombus formation and progression to DIC.[148–150]

Antiplatelet drugs can reduce inflammatory biomarkers, such as CRP and P-selectin, and suppress leukocyte-platelet aggregates.[1,151,152] Recently, the application of aspirin (ASA) in patients with sepsis has been suggested to have anti-inflammatory activity and bacterial control effects. A meta-analysis involving 689,897 patients with sepsis has shown that ASA effectively reduces mortality and improves prognosis.[153,154] While ASA has a stronger effect in reducing mortality when managing patients with sepsis without established cardiovascular problems,[155,156] septic patients with cardiovascular disease who receive chronic pre-sepsis ASA treatment before hospital admission also have reduced 90-day mortality.[157]

Chinese Herbal Medicine

Some traditional Chinese herbal medicines have the potential to be effective in treating sepsis and sepsis-mediated multi-organ injuries (Table 1).

Conclusion

In conclusion, this review underscores the critical interplay between coagulation and inflammation in sepsis and emphasizes the pivotal role of endothelial cells in these processes. By elucidating the mechanisms behind sepsis-

related coagulopathy and evaluating the therapeutic potential of anticoagulants, we offer insights that could transform the clinical approaches for managing sepsis. Our findings highlight the importance of early recognition and targeted intervention strategies that are vital for improving patient outcomes in this challenging condition. Ongoing research is essential to further refine these strategies and optimize the effectiveness of sepsis treatment protocols.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Project of Shanghai Science and Technology Commission (22Y11900300) to Li Ma, the Project of China Primary Health Care Foundation (MTP2022A0132) to Li Ma and the Project of Shanghai Administration of Traditional Chinese Medicine (ZXXT-202213) to En-Qiang Mao and Li Ma.

Disclosure

The authors declare that they have no competing interests in this work.

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