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REVIEW

The Mechanisms of Sepsis Induced Coagulation Dysfunction and Its Treatment

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Abstract: Sepsis is a critical condition characterized by organ dysfunction due to a dysregulated response to infection that poses significant global health challenges. Coagulation dysfunction is nearly ubiquitous among sepsis patients. Its mechanisms involve platelet activation, coagulation cascade activation, inflammatory reaction imbalances, immune dysregulation, mitochondrial damage, neuroendocrine network disruptions, and endoplasmic reticulum (ER) stress. These factors not only interact but also exacerbate one another, leading to severe organ dysfunction. This review illustrates the mechanisms of sepsis-induced coagulopathy, with a focus on tissue factor activation, endothelial glycocalyx damage, and the release of neutrophil extracellular traps (NETs), all of which are potential targets for therapeutic interventions.

Keywords: sepsis, coagulation dysfunction, thrombosis

Introduction

The prevalence and mortality rates of sepsis remain extremely high, particularly in economically undeveloped regions such as Africa, South Asia, and Latin America.[1,2] In China, One-fifth of ICU patients suffer from sepsis, with a 90-day mortality rate of 35.5%. A shortage of ICU beds exacerbates the situation, hindering optimal management and accurate data collection, thereby emphasizing the need for comprehensive research into its prevalence and mortality.[3] In 2016, the third international consensus on sepsis redefined it as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[4] The coagulation dysfunction leading to microthrombosis caused by sepsis is a very serious disease, eventually leading to disseminated intravascular coagulation (DIC) and organ dysfunction. Thus, it has a high mortality rate.[5]

Currently, the mechanisms underlying coagulopathy in sepsis are focused on the imbalance of immune system and inflammatory response, activation of platelets and coagulation factors, endothelial cell injury, and disruption of the coagulation-fibrinolysis balance.[6] Sepsis is typically caused by bacterial or other pathogenic microbial infections, leading to systemic inflammatory response.[4] The infection initially triggers immune response, in which immune cells recognize the pathogen and release a large number of inflammatory cytokines. These cytokines not only provoke local inflammatory responses but also activate the coagulation system throughout the body.[7,8] They further damage endothelial cells (ECs), exposing more tissue factor (TF) and simultaneously decreasing the synthesis of anticoagulant and antifibrinolytic factors,[9] thus promoting the activation of the coagulation cascade and accelerating blood clotting.[10,11] The activation of platelets and coagulation factors results in sepsis-induced coagulopathy (SIC), leading to microthrombi formation. As these elements are depleted, the balance between coagulation and fibrinolysis is disrupted, resulting in DIC.[12,13] In addition, mitochondrial damage, neuroendocrine dysregulation, and endoplasmic reticulum (ER) stress may also contribute to coagulation dysfunction. However, current research has predominantly focused on the common mechanisms discussed above, without offering a systematic and comprehensive analysis.

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Historically, the lack of a single diagnostic criterion and the high costs of coagulation tests have limited their use.[14] The International Society on Thrombosis and Haemostasis (ISTH) established a clear definition and scoring system for SIC, an early phase of DIC, that includes the platelet count and international normalized ratio (INR) in 2017. The SOFA score can be used to diagnose DIC to meet the SIC criteria at the initial assessment.[15,16] I Iba et al reported that the SIC scoring system was highly sensitive, as an effective screening tool for DIC, providing insights into mortality risk and guiding the initiation of heparin anticoagualtion therapy in 2019.[17,18] Recently, advances in technology have facilitated the development of an increasing number of targeted therapies for sepsis-induced coagulopathy, providing new prospects for patient outcomes.

Mechanisms of Coagulation Dysfunction Induced by Sepsis

Coagulopathy, ranging from mild thrombocytopenia to severe conditions such as DIC, is a key determinant of mortality in sepsis patients. Most patients with sepsis undergo significant hemostatic alterations.[19] The pathogenesis of sepsis involves various mechanisms, including inflammatory imbalances, immune dysregulation, disturbance of coagulation, mitochondrial damage, neuroendocrine disruption, and ER stress, all of which ultimately lead to organ dysfunction.[20]

Activation of Platelets and Coagulation Cascades

The physiological coagulation cascade is a highly regulated process that includes vascular constriction, platelet plug formation, and coagulation (Figure 1). These phases are sequential yet overlapping, each reinforcing the others.[21] When damage occurs, vascular ECs are susceptible to various factors and pathogenic stimuli. Platelets attach to exposed collagen and von Willebrand factor in the subendothelial layer via their surface glycoprotein Ib-IX-V Complex (GPIb-IX -V), initiating activation.[22] The subsequent release of adenosine diphosphate (ADP), thromboxane A_2 (TXA_2), and platelet factor 4 (PF4) further activates and aggregates platelets, leading to thrombus formation.[23,24] Endothelial damage and trauma also trigger both intrinsic and extrinsic coagulation pathways. Foreign substances activate factor XII (FXII),

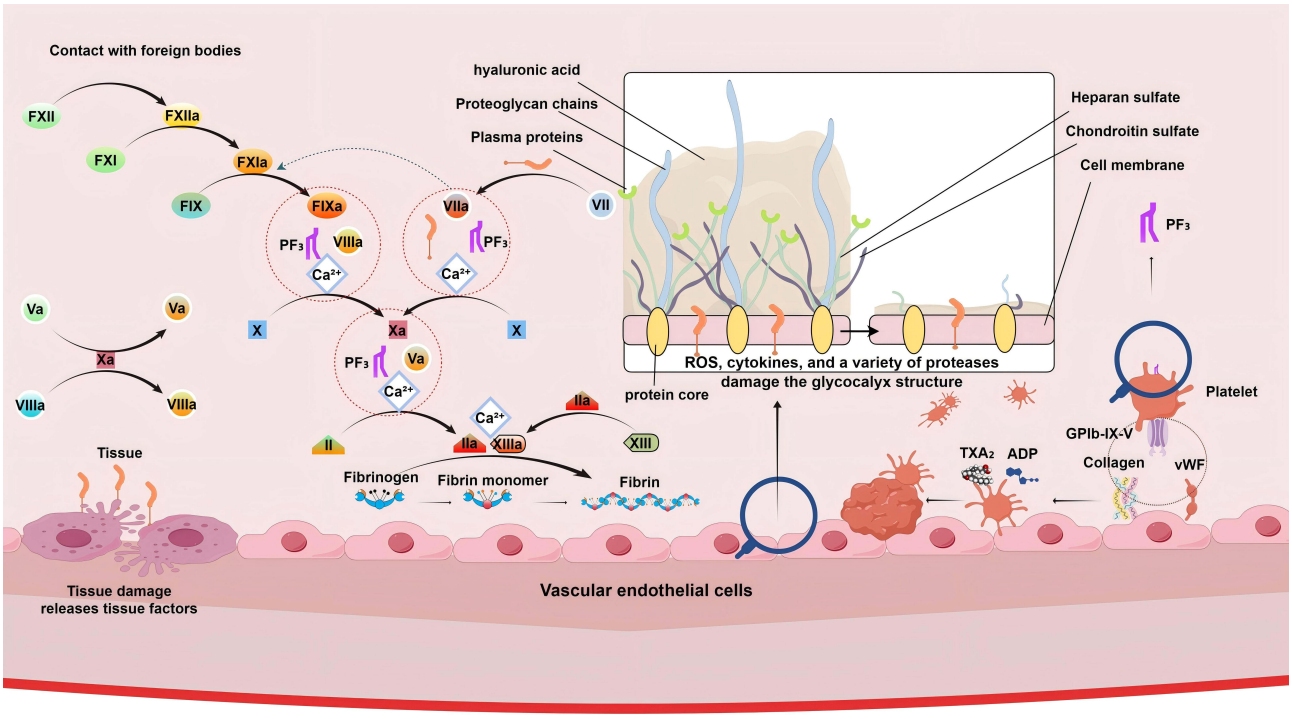

Figure 1 Activation of Platelets, Coagulation Cascade, and Endothelial Glycocalyx Damage. The figure on the left shows the activation of the coagulation cascade, with multiple coagulation factors contributing to the synthesis of fibrin; the middle figure depicts damage to the endothelial glycocalyx, which becomes thinner and sparser, leading to increased exposure of TF; and the right figure side illustrates the activation and aggregation of platelets.

sequentially activating activate factor XI (FXI), factor X (FX), factor IX (FIX), and factor VIII (FVIII), forming the intrinsic Xase complex in the presence of calcium, thereby converting FX to factor Xa (FXa).[25,26] When combined with factor VIIa (FVIIa) and calcium, TF forms the TF-FVIIa complex, activating FX to FXa. The resulting FXa, along with factor Va (FVa) and calcium from both pathways, forms the prothrombin complex on phospholipid membranes, which then converts prothrombin to thrombin, transforming fibrinogen into fibrin and finalizing the coagulation process.[27–30]

Activation of TF

TF is a glycoprotein receptor on cell membranes that is expressed primarily on ECs (Figure 2). Upon tissue injury, TF is exposed to the bloodstream, initiating the extrinsic coagulation pathway.[31] Pattern recognition receptors (PRRs) detect damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), activating the innate immune system.[28] During sepsis, lipopolysaccharide (LPS) enters the bloodstream and binds to CD14 receptors on the surfaces of monocytes/macrophages and ECs, activating Toll-like receptor 4 (TLR4). This activation initiates signaling through Myeloid Differentiation Primary Response Gene 88 (MyD88) and Toll/Interleukin-1 Receptor (TIR) Domain-Containing Adapter Inducing IFN-β (TRIF) dependent pathways, leading to the activation of the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Interferon Regulatory Factor 3 (IRF3) signaling cascades. This process promotes the production of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) and upregulates TF gene expression, thereby triggering the coagulation cascade.[32,33] Hepatocytes detect PAMPs in the circulation and release high mobility group box 1 protein (HMGB1), a key protein in the processes of proinflammatory responses and pyroptosis. HMGB1 binds to TLR4 receptors on the cell surface, promoting TF gene expression through the MyD88/NF-κB pathway. Additionally, HMGB1 can interact with the Receptor for Advanced Glycation End Products (RAGE), activating NF-κB via the Mitogen-Activated Protein Kinase

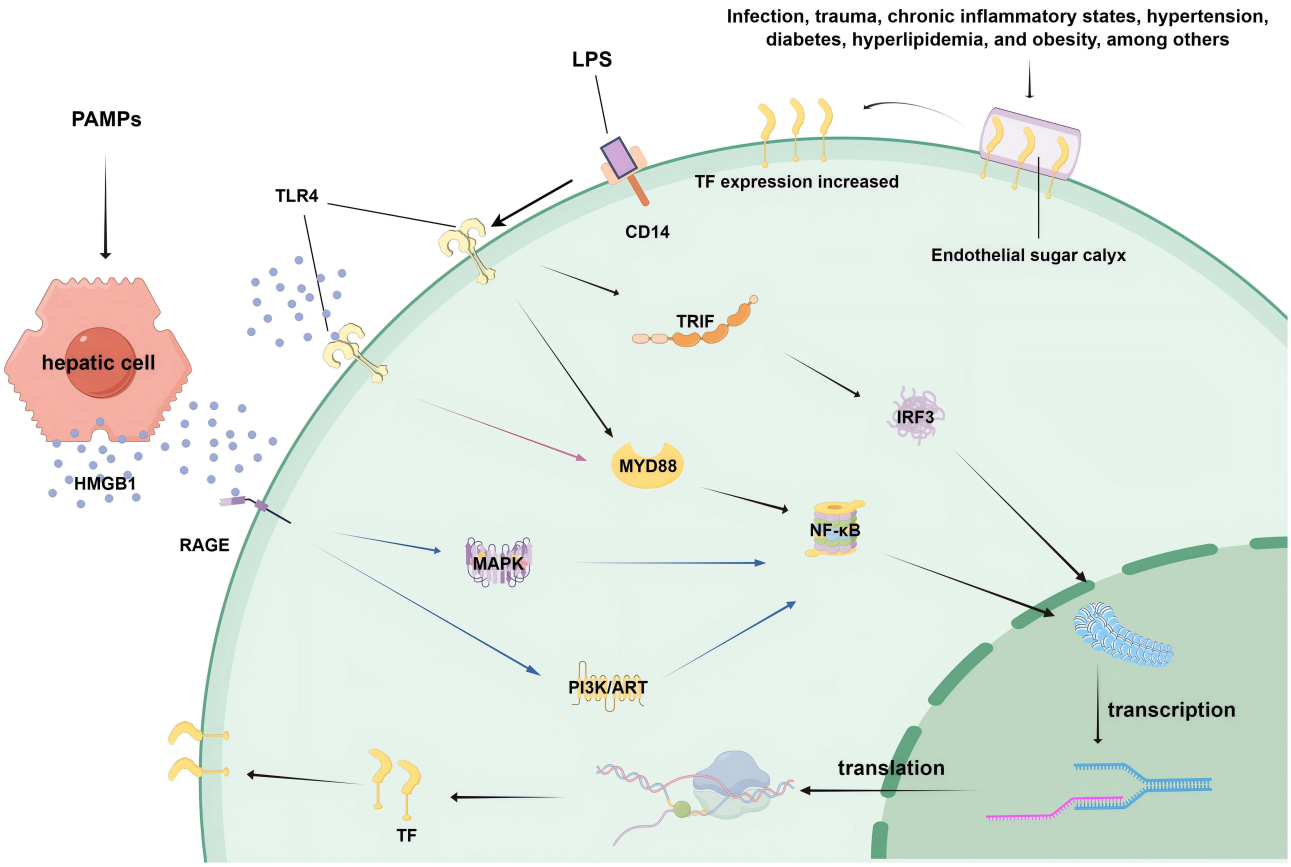

Figure 2 Expression of TF. The process by which endothelial glycocalyx damage leads to increased exposure of TF. In response to stimuli such as infection, trauma, and chronic inflammation, monocytes/macrophages and endothelial cells activate signaling pathways via HMGB1 and PAMP receptors (eg, TLR4 and RAGE), resulting in increased expression of transcription factors.

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(MAPK) pathways, including Extracellular Signal-Regulated Kinase 1/2 (ERK1/2), c-Jun N-terminal Kinase (JNK), and p38 Mitogen-Activated Protein Kinase (p38), as well as the Phosphoinositide 3-Kinase (PI3K)/Protein Kinase B (Akt) pathways. This activation, in turn, upregulates TF gene expression. Research by Deng indicated that HMGB1, upon binding to LPS, can enter lysosomes via the RAGE pathway. HMGB1 disrupts the lysosomal membrane structure, allowing LPS to enter the cytoplasm and activate caspase-11.[32,34] Activated caspase-11 triggers the formation of gasdermin D (GSDMD) pores and phosphatidylserine exposure, thereby activating pathways such as the NF-κB and MAPK pathways to promote the expression of TF. Furthermore, GSDMD promotes the maturation of IL-1 by inducing the activation of inflammasomes.[35] Inflammasomes, exemplified by NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3), not only mediate the maturation and secretion of IL-1 but also induce monocytes/macrophages to release TF.[36] As proinflammatory factors, the expression of TF is continuously upregulated, and inflammation and coagulation are further activated.[37]

Antithrombin (AT) and Activated Protein C (APC)

AT is a crucial natural anticoagulant that regulates the coagulation process by interacting with key coagulation factors. Synthesized in the liver, AT circulates in the bloodstream, playing a vital role in maintaining hemostasis. Its primary targets are FIIa and FXa.[38] The reactive peptide region of AT binds to the catalytic triad of thrombin, which includes serine (Ser195), histidine (His57), and aspartic acid (Asp102), thus inducing a conformational change in thrombin that accelerates its inactivation, followed by clearance in the liver.[39] Heparin enhances the anticoagulant activity of AT by binding to it, inducing a conformational change that increases its affinity for thrombin, thus further accelerating thrombin inactivation and improving AT's anticoagulant effect.[40,41] Sepsis triggers a systemic inflammatory response that activates the coagulation cascade, leading to the activation of multiple coagulation factors. These activated factors require inhibition by AT, contributing to its rapid consumption. In addition, inflammatory mediators such as TNF-α and IL-6 suppress AT synthesis and promote its accelerated degradation. Simultaneously, the functionality of AT is compromised, primarily due to a decreased affinity for coagulation factors, which impairs its ability to effectively inhibit the coagulation process.[42]

APC is another important natural anticoagulant in the body, primarily regulating coagulation and inflammation through multiple mechanisms.[43] Initially, the zymogen protein C is activated by thrombin in the presence of thrombomodulin (TM), a receptor on ECs, which converts it into active APC. Once activated, APC, in conjunction with its cofactor Protein S, cleaves coagulation FVa and FVIIIa, thereby inhibiting the amplification of the coagulation cascade.[44] Specifically, APC cleaves distinct peptide bonds in FVa and FVIIIa,[45] which reduces their ability to activate FXa and FIXa, ultimately inhibiting thrombin generation.[43,46] Furthermore, APC promotes the release of nitric oxide (NO) from ECs, leading to vasodilation, improving blood flow, and a reduction in thrombus formation.[47] In addition to its anticoagulant function, APC exerts anti-inflammatory effects by binding to Proteinase-Activated Receptor-1 (PAR-1), thereby inhibiting the activation of endothelial and immune cells.[48] This interaction reduces the release of pro-inflammatory cytokines, such as TNF-α and IL-6, mitigating systemic inflammation.[43] During sepsis, although thrombin activates protein C via the endothelial receptor TM, the generation of APC are significantly reduced due to suppression of protein C synthesis[49] by elevated inflammatory cytokines (eg, TNF-α, IL-6).[50] Sepsis-induced endothelial damage further impairs TM function, diminishing APC activation. The excessive activation of coagulation factors in sepsis leads to consumption of APC, depleting its levels. Similar to AT, inflammatory cytokines in sepsis can alter the conformation of APC, reducing its affinity for coagulation factors and impairing its ability to degrade FVa and FVIIIa,[45] thereby exacerbating coagulation.[51] Additionally, high concentrations of pro-inflammatory cytokines in sepsis inhibit APC binding to PAR-1,[48] further diminishing its anti-inflammatory effects.

Inflammatory Imbalance Induces Coagulation Dysfunction

Systemic inflammatory response syndrome (SIRS) refers to the complex pathophysiologic response to an insult, such as infection, trauma, burns, pancreatitis, or a variety of other injuries, and comes from the Sepsis Definitions Consensus Conference held in Chicago, Interleukin-8 (IL-8), in August 1991.[52] The clinical definition of sepsis that emerged from the consensus conference sponsored by the American College of Chest Physicians and the Society of

Critical Care Medicine was met with mixed reactions.[53,54] The focus of sepsis has shifted toward organ dysfunction following the 2017 international consensus.[4] In sepsis, the immune system's balance is disrupted, resulting in both excessive inflammation and immune suppression, with inflammatory responses potentially activating the coagulation cascade.[36,55] PRRs recognize DAMPs and PAMPs, triggering inflammatory pathways that release cytokines, chemokines, and growth factors, such as TNF-α and IL-6, which activate coagulation factors VII and XII. Platelet-activating factor (PAF) and PF4 promote platelet aggregation.[56] DAMPs and PAMPs also activate the complement cascade through the classical, alternative, and lectin pathways,[57] generating Complement Component 3a (C3a) and Complement Component 5a (C5a), and forming the membrane attack complex (MAC), which promotes inflammation and damages cells.[58,59] In 2013, it was reported that platelets could promote P-selectin expression to form complexes with P-selectin glycoprotein ligand 1 (PSGL-1) on leukocytes at inflammatory sites, enhancing the inflammatory response.[60,61]

Endothelial Damage

ECs play a critical role in regulating coagulation by both pro-coagulant and anti-coagulant mechanisms.[27] During vascular injury or inflammation, ECs release pro-coagulant factors such as von Willebrand factor (vWF) and TF. vWF facilitates platelet adhesion to the damaged vascular wall, while TF activates the extrinsic coagulation pathway, leading to the activation of FX and the subsequent formation of thrombus. These mechanisms enable ECs to promote thrombosis, which is essential for preventing excessive bleeding. However, uncontrolled activation of this process can result in thrombotic disorders.[62,63] Conversely, ECs regulate coagulation through negative feedback mechanisms to maintain blood flow stability and prevent unnecessary clotting.[64] Under normal physiological conditions, ECs secrete anti-coagulant substances, such as NO and prostacyclin (PGI2), which dilate blood vessels and inhibit platelet activation, ensuring smooth blood flow.[65] NO activates soluble guanylate cyclase (sGC), increasing intracellular cyclic Guanosine Monophosphate (cGMP) levels, which in turn inhibits platelet aggregation.[66] ECs also express TM on their surface, which binds to thrombin and promotes the activation of protein C, resulting in the formation of APC.[67] APC then degrades coagulation FVa and FVIIIa, thereby inhibiting the coagulation cascade.[68] In addition, ECs secrete tissue-type plasminogen activator (tPA),[69] further inhibiting coagulation factor activation and promoting fibrinolysis, thus preventing coagulation abnormalities.[70] ECs prevent excessive coagulation under normal physiological conditions by these mechanisms, ensuring the stability of blood flow.

In sepsis, LPS stimulates ECs, exposing TF expression and triggering coagulation.[71] The reduction in nitric oxide synthesis and promotion of endothelin-1 expression further contribute to the formation of thrombosis.[72] The endothelial glycocalyx plays a crucial role in these processes,[73] acting as a barrier against vascular permeability and allowing adhesion molecules to protect against oxidative stress (Figure 1).[74,75] Damage to the glycocalyx during sepsis leads to increased vascular permeability and edema and facilitates the adhesion of leukocytes and platelets, promoting immune and coagulation responses.[76,77] Glycocalyx injury is progressive, illustrating the worsening of microcirculatory dysfunction in DIC,[9] even after fluid resuscitation and hemodynamic stabilization. There is variability in endothelial glycocalyx thickness across different vascular locations and conditions. The limitations of current technology in measuring its thickness make directly assessing glycocalyx damage challenging. Hypothetically, assessing glycocalyx degradation through circulating component levels could offer diagnostic and prognostic insights, although the reliability of this approach requires further validation.[76,78]

Coagulation Dysfunction Caused by Immune Disorders

The immune system activates the NF-κB and MAPK pathways via PRRs and DAMPs to detect pathogens and initiate the release of inflammatory cytokines such as IL-1, IL-6, and TNF-α, recruiting immune cells such as neutrophils and macrophages and triggering innate immunity.[79] Neutrophils, as the primary defense cells involved in innate immunity, are recruited by activated ECs during infection and inflammation. However, in the dynamic context of blood flow, neutrophils release neutrophil extracellular traps (NETs) to increase pathogen capture.[80] The systemic inflammatory response in sepsis can lead to hyperactivation of neutrophils, prolonging their lifespan and inhibiting their migration.

Confined within the vasculature, neutrophils can release NETs, which not only activate ECs but also directly damage the endothelial glycocalyx, exacerbating vascular inflammation and thrombosis.[81,82]

Formation of NETs

NETs formation involves multiple processes (Figure 3). Upon stimulation by inflammation or pathogens, the Nncotinamide ndenine dinucleotide phosphate hydrogen (NADPH) oxidase within neutrophils is activated, leading to the generation of reactive oxygen species (ROS). These ROS can activate signaling pathways such as protein kinase C (PKC), which amplifies the signal and further activates MAPK pathways, including p38 and ERK, to mediate chromatin decondensation. Myeloperoxidase (MPO), neutrophil elastase, and cathepsins can facilitate nuclear membrane degradation. Once chromatin decondensation and nuclear membrane rupture occur, neutrophils release their DNA and associated proteins. NETs are formed in the cytoplasm through vesicular transport, without the occurrence of membrane rupture.[83,84] Furthermore, depending on the type of pathogen component present, various Toll-like receptors on neutrophil surfaces can be activated, leading to the activation of the NF-κB and MAPK signaling pathways. This process initiates neutrophil activation and culminates in NETs formation. For example, Toll-Like Receptor 2 (TLR2) recognizes bacterial lipoproteins and peptidoglycans. TLR4 is the primary receptor for detecting LPS, and Toll-Like Receptor 9 (TLR9) can detect cytosine-phosphate-guanine motifs (CpG motifs) within bacterial and viral DNA.[84–86] NETs not only participate in the body's immune response but also interact with the coagulation system. MPO and histones within NETs can activate G protein-coupled receptors (GPCRs) on the surfaces of platelets, leading to the release of platelet factor 4

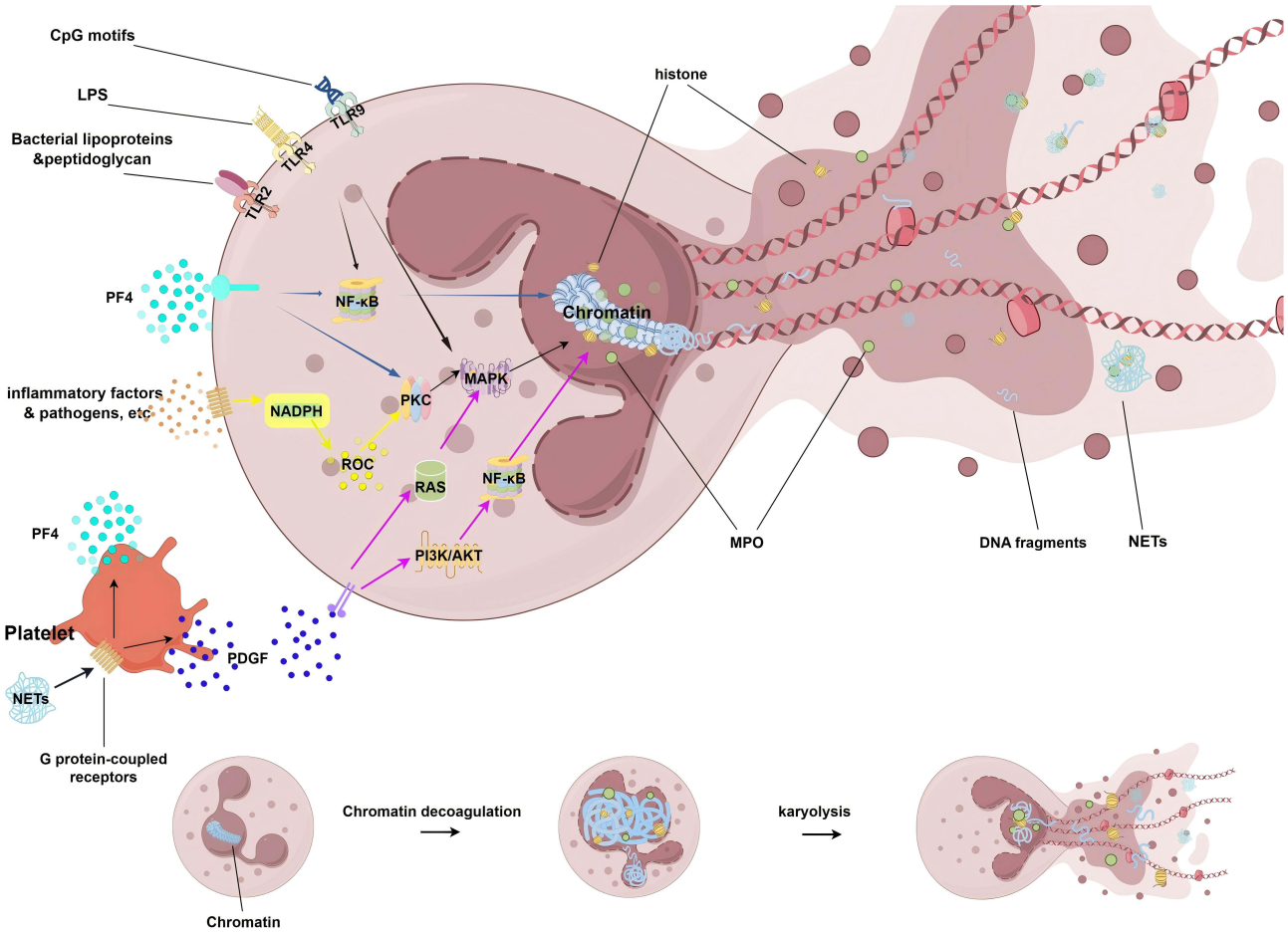

Figure 3 The formation of the NETs. Signaling pathways and cellular processes involved in the formation and release of NETs during the immune response. This highlights the role of TLRs in recognizing bacterial components, the NF–κB pathway triggered by TLR signaling, and the PKC/MAPK pathway involved in chromatin remodeling. The NADPH oxidase complex contributes to ROS formation, whereas the PI3K/AKT pathway contributes to chromatin decondensation. MPO and histone DNA fragments are also involved in this process, leading to the formation of NETs. PF4 and PDGF interact with neutrophils, and inflammatory factors and pathogens act as stimuli for NETs.

(PF4) and platelet-derived growth factor (PDGF), thereby promoting platelet aggregation and thrombosis. Moreover, platelets are also significant inducers of NETs formation. PF4 and PDGF released by activated platelets can bind to receptors on the surface of neutrophils, activating the MAPK and NF-κB signaling pathways via the PKC, Rat Sarcoma (Ras), and PI3K/Akt pathways, respectively, ultimately contributing to the formation of NETs.[77,83,87,88] During the formation of NETs and through the catalytic action of MPO, a significant amount of ROS are produced. These ROS can affect the stability of coagulation factors (such as FV, FVII, and FVIII) through oxidative modifications, thereby influencing the coagulation process.[89,90] Research by Silva and Wanderley suggested that the caspase-11/GSDMD pathway can induce NETs formation in sepsis patients. The inhibitor disulfiram may reduce NETs release, potentially mitigating organ damage. However, owing to contradictions involving immunopathology, further research is necessary.[91] Mesenchymal stem cells with apoptotic vesicles can promote NETs formation, increasing survival rates in septic mice.[92] Inhibitors of TLR4/Triggering Receptor Expressed on Myeloid Cells 1 (TREM1) signaling can alleviate NETs formation and mitigate its deleterious effects.[93] Monocytes and macrophages secrete cytokines such as Interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). The anti-inflammatory molecule indoleamine 2.3-dioxygenase (IDO) can regulate immunity and prevent excessive inflammation. The expression of TF and various proinflammatory factors is involved in the activation of the extrinsic coagulation pathway and thrombin generation.[94]

In adaptive immunity, lymphocytes enhance inflammation and coagulation by producing cytokines. B lymphocytes form immune complexes with antigens produced by pathogens, activating the complement system to promote coagulation by expressing FVII and FVIII, which directly participate in the coagulation cascade. PDGF released by T lymphocytes enhances platelet function, whereas interferon-γ (IFN-γ) produced by T cells inhibits TF expression on ECs, promoting anticoagulation.[94]

During sepsis, destruction of immune homeostasis leads to immune cell dysfunction characterized by excessive inflammation and immune suppression.[8,55] Immune cell exhaustion, dysregulation of anti-inflammatory mechanisms, and a reduction in human leukocyte antigen-DR (HLA-DR) expression and that of other factors can induce immune suppression.[95] Within this context, immune cells can protect or eliminate pathogens via "suicidal" methods such as apoptosis, pyroptosis, autophagy, and release.[96] The release of substances such as histones, nucleosomes, proteases, and tissue factors from many dead immune cells significantly promotes inflammation and endothelial damage and facilitates coagulation.[97]

Mitochondrial Damage Induces Coagulation Abnormalities

Mitochondria are essential for maintaining cellular homeostasis and function. As the primary energy producers of the cell, they generate adenosine triphosphate (ATP) through oxidative phosphorylation, supporting cellular metabolism. Additionally, mitochondria regulate intracellular calcium levels, which are critical for various cellular processes, particularly blood coagulation. Calcium ions play a central role in converting prothrombin to thrombin, a key step in the coagulation cascade. Furthermore, mitochondria produce ROS under normal physiological conditions, which act as key signaling molecules involved in these processes such as cell growth, differentiation, and stress responses.[36,98]

In sepsis, however, the inflammatory response leads to the release of pro-inflammatory cytokines, which exacerbate oxidative stress and increase ROS production. These ROS cause damage to mitochondrial membrane and protein, impairing the mitochondrial electron transport chain (ETC), and reduce ATP production, compromising cellular energy.[99] The accumulation of ROS also results in elevated intracellular calcium levels, further activating coagulation. Excessive calcium ions enhance the activity of prothrombinase complexes and platelets, and increase the activity of coagulation FV and FVIII, which intensify coagulation.[100] Moreover, mitochondrial damage alters cellular metabolism, particularly by upregulating glycolysis, which leads to lactate accumulation and decrease blood pH. The resulting acidic environment further activates coagulation factors and enhances platelet aggregation, exacerbating coagulation abnormalities.[101] Research by Zou in 2022 further revealed that DNA-dependent protein kinase catalytic subunit (DNA-PKcs) signaling exacerbates liver dysfunction by inducing mitochondrial impairment, consequently affecting the production of coagulation factors.[102]

Neuroendocrine Network Disorders Induce Coagulation Abnormalities

The neuroendocrine system regulates various physiological functions, through the interaction of hormones, neurotransmitters, and their receptors. Neuroendocrine factors, particularly norepinephrine (NE), cortisol, and adrenaline, play a pivotal role in stress response.[103] Norepinephrine activates platelets and promotes platelet aggregation by binding to β-adrenergic receptors.[104] Cortisol further enhances coagulation by upregulating the synthesis of coagulation FVII and fibrinogen, thereby promoting thrombus formation. Adrenaline indirectly exacerbates the coagulation response through vasoconstriction and increased blood flow velocity.[105,106] Additionally, neuroendocrine hormones can activate NF-κB and MAPK signaling pathways in ECs, triggering the release of pro-coagulant factors and inflammatory cytokines. These cytokines not only drive the coagulation cascade but also amplify coagulation by altering vascular permeability and platelet activity.[107]

In sepsis, neuroendocrine dysregulation exacerbates coagulation by activating the sympathetic nervous system, resulting in vasoconstriction and altered blood flow velocity, which further aggravates coagulation.[108] On the other hand, infection-or injury-associated molecules transmit signals through the vagus nerve, stimulating T cells to release acetylcholine. Acetylcholine binds to α7-nicotinic acetylcholine receptors (α7nAChR) on immune cells, thereby suppressing cytokine release from macrophages.[109] Simultaneously, inflammatory mediators and damage-associated molecules interact with the central nervous system (CNS), altering the function of the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB), which triggers sterile neuroinflammation.[110,111] Activation of glial cells leads to neuronal injury and suppression of the vagus nerve, further intensifying the inflammatory response in sepsis. Stimulation of the vagus nerve and activation of the cholinergic anti-inflammatory pathway can mitigate the release of pro-inflammatory factors, thereby reducing thrombus formation.[112,113]

ER Stress Induces Coagulation Abnormalities

ER is integral to the modification and transport of proteins and regulates numerous cellular pathways and physiological activities, including protein synthesis, protein quality control, and lipid synthesis. When the function of one or more ERs is dysregulated and saturated, the ER enters a state of stress, which in turn activates the highly conserved unfolded protein response (UPR). The UPR triggers pathways to restore ER homeostasis by sensing the accumulation of unfolded proteins or lipid bilayer stress on the ER. If stress remains unresolved, it ultimately induces apoptosis.[114] During apoptosis, substances such as phosphatidylserine (PS) are released and serve as substrates for the coagulation reaction, promoting the generation of thrombin and the formation of thrombi.[115]

The UPR involves three main ER membrane protein sensors: inositol-requiring enzyme 1 (IRE1), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6). These sensors are activated when unfolded or misfolded proteins accumulate, thereby initiating a series of intracellular signaling events. During sepsis, ER stress activates the UPR. If stress exceeds the compensatory capacity of the UPR, it accelerates calcium ion release, activates the caspase cascade, and eventually leads to apoptosis or necrosis. Additionally, the activation of the UPR is involved in inflammation and angiogenesis.[114,116] Professor Zhang reported that transmembrane protein 173 (TMEM173) is an ER-associated membrane protein that mediates ER stress and can participate in the release of TF, a key initiator of the coagulation cascade, thereby activating coagulation.[117]

Microthrombus Formation in Sepsis

In sepsis, the activation of coagulation mechanisms results in the formation of microthrombi (Figure 4), which impair blood flow within the microcirculation, obstructing the supply to vital organs such as the brain, kidneys, and lungs. This disruption contributes to significant hemodynamic changes, typically marked by reducing cardiac output and blood pressure, which often progress to shock.[118,119]

During the initial stage of septic shock, inflammatory mediators in the circulation can lead to damage to vascular ECs, activation of coagulation, and increased capillary permeability, resulting in the leakage of fluid and proteins. The stimulation of inflammatory mediators also causes the dilation of both precapillary and postcapillary sphincters, which reduces the resistance of the capillary bed. The sympathetic–adrenal axis is activated, and catecholamines cause systemic

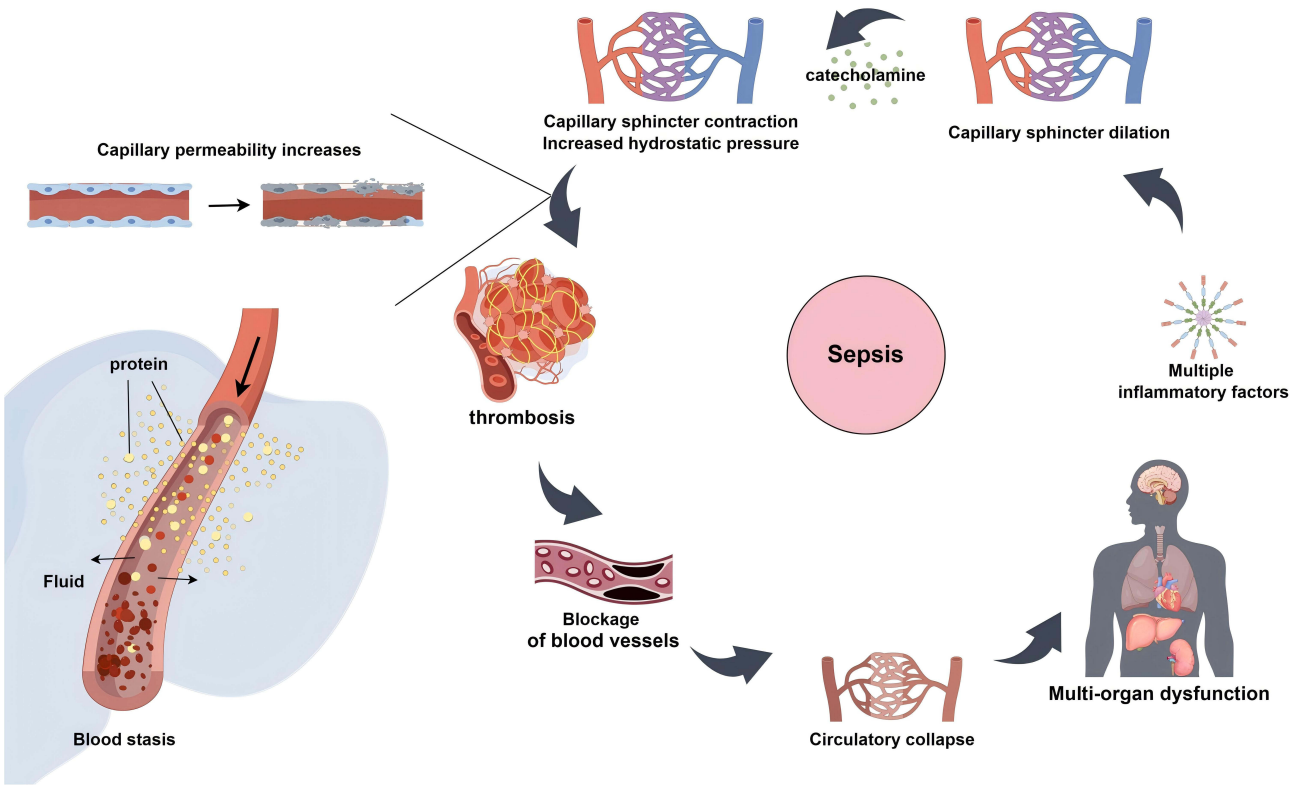

Figure 4 Progression of thrombosis in the context of sepsis. Sepsis induces the release of multiple inflammatory mediators, which damage vascular endothelial cells, ultimately causing microvascular constriction, increased capillary permeability, and elevated hydrostatic pressure. This cascade leads to the leakage of fluid and proteins, blood stasis within the microcirculation, and consequently, the formation of thrombi. This sequence can culminate in microcirculatory dysfunction and multiorgan failure.

vasoconstriction, especially in the skin, kidneys, and gastrointestinal tract, to ensure blood supply to vital organs. At this point, tissues can still receive sufficient perfusion; therefore, hemodynamic changes are not significant.[120–122]

As the condition worsens, the release of numerous inflammatory mediators results in the impairment and potential death of vascular ECs, significantly increasing capillary permeability and leading to the leakage of fluid and proteins, which in turn causes severe tissue edema. The reduction in blood volume within the microcirculation, coupled with hyperactivation of the sympathetic–adrenal axis, leads to the release of substantial amounts of catecholamine hormones. These hormones cause capillaries, particularly precapillary sphincters, to contract strongly, resulting in blood retention within the microcirculation. This exacerbates capillary hydrostatic pressure and permeability, facilitating the formation of numerous microthrombi and ultimately causing a continuous decline in effective blood flow.[123–125]

In the irreversible microcirculatory failure phase, persistent hypoxia and inflammation contribute to the death of a significant number of ECs, causing the microcirculation to lose its ability to self-regulate. Changes in intracellular calcium concentrations may exacerbate the constriction of both the precapillary and postcapillary sphincters. At this critical juncture, the microcirculatory blood volume is severely depleted, leading to critically inadequate tissue perfusion. Following the sustained activation of the sympathetic–adrenal axis, the vascular responsiveness to catecholamines diminishes, resulting in a further drop in blood pressure. Blood flow becomes extensively trapped within the microcirculation, the coagulation system becomes hyperactive, fibrinolysis is inhibited, and DIC occurs, ultimately resulting in severe tissue hypoxia and organ failure.[10,126–129]

Treatment of Coagulation Dysfunction Caused by Sepsis

Early and accurate diagnosis of SIC is crucial. Initially, patients exhibit elevated thrombin levels and paradoxical reductions in platelet counts due to activation and aggregation, presenting a procoagulant state that leads to microvascular thrombosis and subsequent tissue ischemia. During this period, the balance between the production and consumption of

coagulation factors and platelets is maintained. Clinical symptoms may not be evident, making laboratory results challenging and potentially leading to overdiagnoses. Combining SIC with thrombin-related marker testing may improve diagnostic accuracy[12] but requires distinguishing it from noninfectious conditions, a common challenge with other DIC diagnostic methods.[18]

As the disease progresses, the consumption of coagulation factors and platelets surpasses their production. Low coagulation activity, such as bleeding symptoms, can occur. When coagulation factors and platelets are depleted and fibrinolysis becomes excessive, significant bleeding or even shock may occur. Therefore, patients with severe infection, thrombotic and/or bleeding symptoms, and laboratory test abnormalities indicate coagulopathy, and any organ dysfunction should be suspected of suffering DIC.[130]

TF Pathway Inhibitor (TFPI)

Currently, no drugs have been identified that can directly inhibit TF activation. However, TFPI is the primary inhibitor of the tissue factor-mediated extrinsic coagulation pathway and is the most critical and specific endogenous anticoagulant protein.[131,132] It belongs to the Kunitz-type serine protease inhibitor family and possesses three consecutive functional domains: K1, K2, and K3. Primarily secreted by vascular ECs, TFPI can directly bind to FXa to inhibit its activity. The FXa-TFPI complex, through its K1 domain, binds to the active site of FVIIa within the FVIIa-TF complex, thereby inhibiting the FVIIa-TF complex[133] and fundamentally preventing the activation of the extrinsic coagulation pathway.[134] Furthermore, TFPI-related medications have concluded clinical trials in recent years and obtained regulatory approval for market release in 2024.

Endothelial Biomarkers and Endothelial Pathways

Therapeutic strategies targeting endothelial biomarkers and pathways focus on microRNAs (miRs), microparticles (MPs), and pharmacological interventions.[9] miRs such as miR-146,[135,136] miR-181,[137] and miR-155[138] could reduce endothelial activation and inflammation by inhibiting the NF-κB and MAPK pathways and by regulating adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and endothelial-leukocyte adhesion molecule 1 (E-selectin).[139] miRs like miR-150[135] and miR-147b could help maintain endothelial barrier function by modulating Angiopoietin-2 (Ang2) and A Disintegrin And Metalloproteinase Domain 15 (ADAM15). Additionally, miRs such as miR-30b and miR-181b[137] regulate PAI-1 levels, thereby reducing endothelial injury during sepsis. MPs derived from ECs serve as biomarkers of damage and are involved in coagulation and inflammation during sepsis and DIC.[9] Complement inhibitors such as eculizumab show promise in diseases characterized by complement activation. Pharmacological treatments, including statins, vitamin C, and anticoagulants, protect the endothelium by reducing oxidative stress, while agents like APC, recombinant TM, and Ang-1 have shown potential in restoring endothelial function in animal models.[10,140] These strategies offer hope for treating sepsis and related diseases.

Inhibitors of NETs

In the treatment of coagulopathy caused by sepsis, intervention strategies targeting NETs have become an important area of research. Protein arginine deiminase 4 (PAD4) is a calcium-dependent enzyme that mediates the citrullination of histones. This chemical modification weakens the binding between histones and DNA, leading to chromatin loosening and decondensation, which could lead to NETs release. PAD4 inhibitors effectively suppress NETs formation through multiple mechanisms.[141,142] First, they block histone citrullination, preventing chromatin decondensation and thus inhibiting NETs release. Secondly, PAD4 inhibitors indirectly reduce ROS production, attenuating oxidative stress-mediated activation of neutrophils, further suppressing NETs formation. Moreover, by restricting chromatin decondensation, PAD4 inhibitors reduce the space required for degranulation, leading to decreased release of enzymes such as elastase and myeloperoxidase, which in turn inhibits NETs formation.[143,144]

Another therapeutic strategy involves Toll-like receptor (TLR) inhibitors. These compounds block the signaling pathways that induce NETs formation, thereby reducing NETs release and suppressing inflammatory responses and procoagulant activities.[10]

Furthermore, vitamin D (Vit D) exerts inhibitory effects on NETs formation through several mechanisms. By binding to the vit D receptor (VDR) on neutrophils, Vit D inhibits their activation. It also downregulates the expression of ROS-producing enzymes such as NADPH oxidase, thereby inhibiting ROS-dependent formation of NETs.[145] Additionally, Vit D suppresses the activity of the NF-κB signaling pathway, reducing the expression of pro-inflammatory cytokines[146] while upregulating anti-inflammatory cytokines (such as IL-10). It also modulates the antioxidant enzyme system, enhancing cellular defense against oxidative stress, and further suppressing NET formation.[147,148]

Conventional Treatment

Aggressive treatment of the underlying condition and prompt administration of antibiotics and anticoagulants are pivotal in managing DIC. Although heparin has been traditionally used in DIC treatment, clinical trials have shown inconsistent results regarding its efficacy. In addition, its mechanism remains somewhat unclear.[149,150] Antiplatelet drugs such as aspirin, clopidogrel, and ticagrelor may also reduce mortality events, but similar to heparin, their clinical efficacy needs further study.[151] Additionally, research on fibrinolytic activator preparations has shown some potential.[152]

When DIC patients present with bleeding, supplementation of platelets and coagulation factors, along with adequate anticoagulation, is necessary. Fibrinolytic inhibitors, which can impede the resolution of microthrombi and may lead to irreversible kidney damage, should be used with caution. Antagonists targeting the aforementioned mechanisms could theoretically mitigate the induction and progression of DIC to a certain extent, but their effectiveness remains to be confirmed.[20] Maintaining a perioperative oxygen partial pressure (PaO_2) between 97–339 mmHg, a PaO_2/ Fraction of inspiration O2 (FiO_2) between 189–619, and a Pulse Oximeter Oxygen Saturation (SpO_2) ≥ 93% can effectively prevent the occurrence of sepsis-related brain injury.[153]

The optimal strategy for treating DIC involves early diagnosis, timely intervention, and dynamic continuous management. Clinicians should assess patients' disease progression accurately and initiate antibiotic and anticoagulant treatment as early as possible. It is prudent to select medications that have a relatively minor impact on coagulation function to avoid exacerbating the patient's coagulopathy. Employing crystalloids, component transfusions, and vasoactive drugs to maintain stable vital signs in patients can minimize the risk of thrombus detachment due to blood pressure fluctuations.

Conclusion

Coagulopathy is a common complication of sepsis and strongly correlates with mortality. The pathogenesis of sepsis involves interconnected and interdependent events that collectively exacerbate coagulopathy. Inflammatory processes activate ECs and platelets, enhancing coagulation, while the activation of the coagulation system further promotes inflammation. The immune system also contributes to coagulation through various mechanisms, including increased inflammation, the release of NETs, and immune cell death. Moreover, mitochondrial damage, neuroendocrine network disruption, and ER stress initiate different pathways that induce coagulation. Additionally, disruption of the endothelial glycocalyx, release of NETs, and activation of TF are critical in the development of SIC. The complexities of infection, surgical stress, and shock pose significant challenges in managing sepsis-induced coagulopathy. We advocate the use of the SIC assessment system as a basis for the early diagnosis of DIC and recommend dynamic treatment strategies tailored to the various stages of DIC progression. Clinicians must be vigilant and prepared to ensure patient safety under these challenging conditions.

Abbreviations

ADAM15, A Disintegrin and Metalloproteinase Domain 15; ADP, Adenosine Diphosphate; Akt, Protein Kinase B; Ang2, Angiopoietin-2; APC, Activated Protein C; AT, Antithrombin; ATF6, Activating Transcription Factor 6; ATP, Adenosine Triphosphate; BBB, Blood-Brain Barrier; BCSFB, Blood-Cerebrospinal Fluid Barrier; C3a, Complement Component 3a; C5a, Complement Component 5a; cGMP, cyclic Guanosine Monophosphate; CNS, Central Nervous System; CpG motifs, Cytosine-Phosphate-Guanine motifs; DAMPs, Damage-Associated Molecular Patterns; DIC, Disseminated Intravascular Coagulation; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; ECs, Endothelial Cells; ER, Endoplasmic Reticulum; ERK1/2, Extracellular Signal-Regulated Kinase 1/2; E-selectin, Endothelial-leukocyte adhesion molecule 1; ETC, Electron Transport Chain; FiO_2, Fraction of inspiration O2; FIX,

Factor IX; FVa, Factor Va; FVII, Factor VII; FVIIa, Factor VIIa; FVIII, Factor VIII; FVIIIa, Factor VIII; FX, Factor X; FXa, Factor Xa; FXI, Factor XI; FXII, Factor XII; GPCRs, G protein-coupled receptors; GPIb-IX-V, Glycoprotein Ib-IX -V Complex; GSDMD, Gasdermin D; HLA-DR, Human Leukocyte Antigen-DR; HMGB1, High Mobility Group Box 1 Protein; IDO, Indoleamine 2.3-Dioxygenase; IFN-γ, Interferon-γ; IL-1, Interleukin-1; IL-10, Interleukin-10; IL-6, Interleukin-6; IL-8, Interleukin-8; INR, International Normalized Ratio; IRF3, Interferon Regulatory Factor 3; ISTH, International Society on Thrombosis and Haemostasis; JNK, C-Jun N-terminal Kinase; LPS, Lipopolysaccharide; MAC, Membrane Attack Complex; MAPK, Mitogen-Activated Protein Kinase; miRs, MmicroRNAs; MPO, Myeloperoxidase; MPs, Microparticles; MyD88, Myeloid Differentiation Primary Response Gene 88; NADPH, Nicotinamide Adenine Dinucleotide Phosphate Hydrogen; NE, Norepinephrine; NETs, Neutrophil Extracellular Traps; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; NO, Nitric Oxide; p38, p38 Mitogen-Activated Protein Kinase; PAD4, Protein arginine deiminase 4; PAF, Platelet-Activating Factor; PAMPs, Pathogen-Associated Molecular Patterns; PaO_2, Perioperative oxygen partial pressure; PAR-1, Proteinase-Activated Receptor-1; PDGF, Platelet-Derived Growth Factor; PERK, PKR-like ER kinase; PF4, Platelet Factor 4; PF4, Platelet Factor 4; PGI2, Prostacyclin; PI3K, Phosphoinositide 3-Kinase; PKC, Protein Kinase C; PRRs, Pattern Recognition Receptors; PS, Phosphatidylserine; PSGL-1, P-selectin glycoprotein ligand 1; RAGE, Receptor for Advanced Glycation End Products; Ras, Rat Sarcoma; ROS, Reactive Oxygen Species; sGC, soluble Guanylate Cyclase; SIC, Sepsis-Induced Coagulopathy; SIRS, Systemic inflammatory response syndrome; SpO_2, Pulse Oximeter Oxygen Saturation; TF, Tissue Factor; TFPI, TF Pathway Inhibitor; TGF-β, Transforming Growth Factor-β; TIR, Toll/Interleukin-1 Receptor; TLR, Toll-like receptor; TLR2, Toll-Like Receptor 2; TLR4, Toll-Like Receptor 4; TLR9, Toll-Like Receptor 9; TM, Thrombomodulin; TMEM173, Transmembrane protein 173; TNF-α, Tumor Necrosis Factor-alpha; tPA, Tissue-type Plasminogen Activator; TREM1, Triggering Receptor Expressed on Myeloid Cells 1; TRIF, TIR Domain-Containing Adapter Inducing IFN-β; TXA_2, Thromboxane A_2; UPR, Unfolded Protein Response; VCAM-1, Vascular Cell Adhesion Molecule-1; VDR, Vit D receptor; Vit D, Vitamin D; vWF, von Willebrand factor; α7nAChR, α7-nicotinic Acetylcholine receptors.

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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.

Disclosure

The authors report no conflicts of interest in this work.

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