DIC cause, molecular mechanism, diagnosis and therapy

Journal:	*MedComm*
Manuscript ID	MCO2-2024-1967
Wiley - Manuscript type:	Review
Date Submitted by the Author:	30-Aug-2024
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Category:	DIC
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Abstract

Disseminated Intravascular Coagulation (DIC) is a complex and serious condition characterized by widespread activation of the coagulation cascade, leading to both thrombosis and bleeding. This review provides a comprehensive overview of DIC, covering its etiology, molecular mechanisms, diagnostic approaches, and treatment options. The primary causes of DIC include severe infections, trauma, malignancies, and obstetric complications, which trigger an overactive coagulation response. Molecularly, DIC involves the excessive generation of thrombin, which activates platelets and fibrinogen, while simultaneously depleting clotting factors and platelets, resulting in a paradoxical bleeding tendency. Diagnosis of DIC is challenging and typically relies on a combination of clinical features and laboratory tests. Treatment strategies focus on addressing the underlying cause and may include

supportive care, anticoagulation therapy, and supportive treatment. Advances in understanding the pathophysiology of DIC are paving the way for more targeted therapeutic approaches. This review highlights the need for ongoing research to improve diagnostic accuracy and treatment efficacy for DIC.

Keywords: DIC; Coagulation; inflammation; platelet

Introduction

Disseminated intravascular coagulation (DIC) is an acquired syndrome characterized by widespread microvascular thrombosis and simultaneously consumption of platelet and coagulative factors, causing multiple organ dysfunction and uncontrolled life-threatening hemorrhage [1]. Imbalance of coagulative system, anti-coagulant activity, and end-stage consumption of coagulant factors constitute the main process of DIC course, closely relevant to clinical presentation [2] (Figure 1). Activation of coagulative disorder is secondary to many clinical conditions, could cause disease progression and increase mortality if DIC is not diagnosed and treated timely. Underscore the pathophysiology of different underlying disease is essential for the identification of DIC course. The treatments of DIC vary greatly concerning different underlying causative diseases. Currently, it is still a big challenge for clinicians to better understand the importance of DIC, especially the early identification of the hypercoagulable state in DIC and prompt treatment. This review gives a comprehensive description of the pathophysiology and molecular mechanism of DIC, diagnosis criteria for DIC, and faces the challenges of current treatment for DIC, providing a guidance on clinical management.

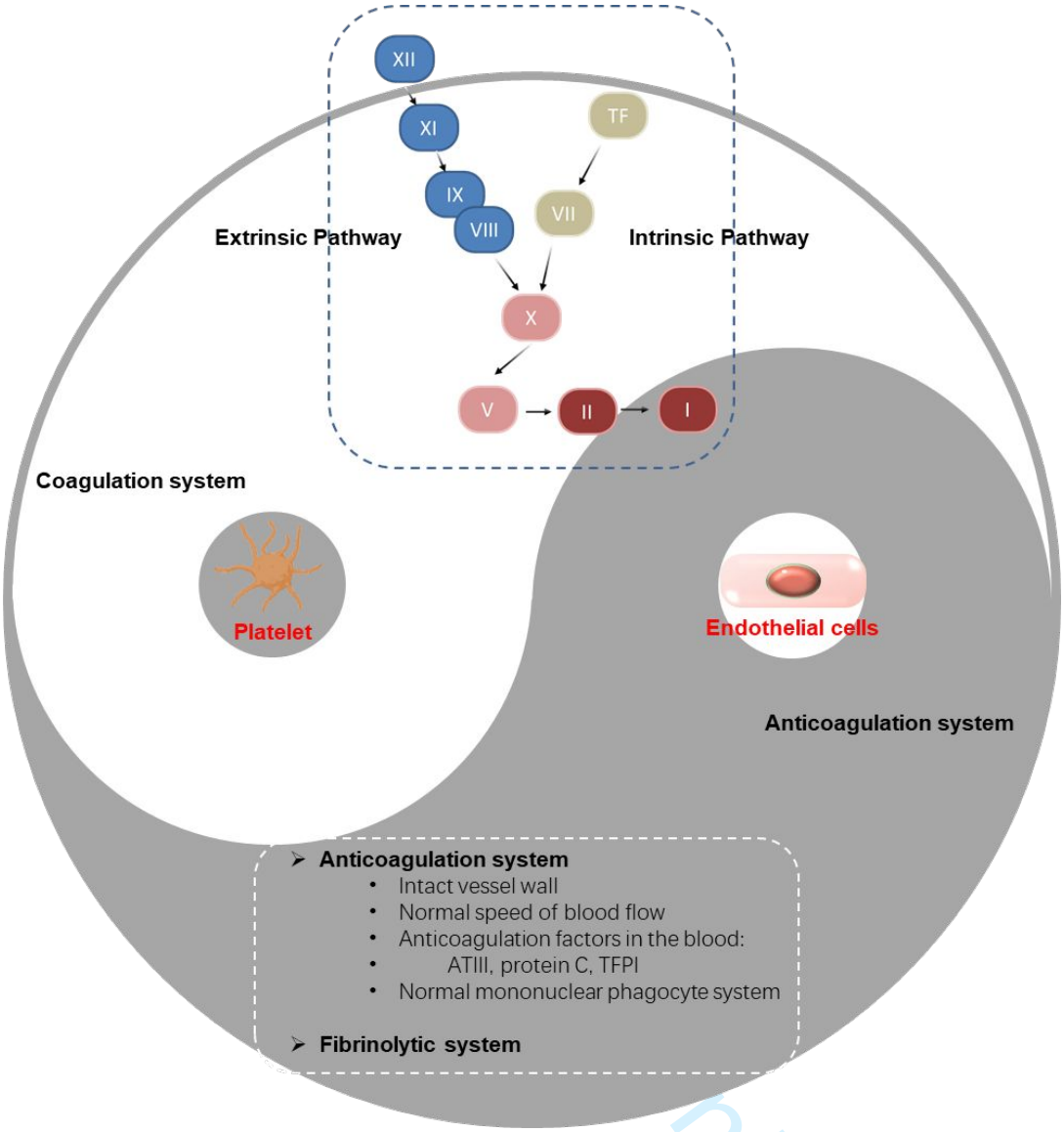

Figure1. DIC course: imbalance of coagulative system, anti-coagulant activity and end-stage consumption of coagulant factors. The coagulation cascade is shown with the intrinsic and extrinsic pathways converging on the activation of Factor X, which ultimately leads to the conversion of prothrombin (Factor II) to thrombin and fibrinogen (Factor I) to fibrin, facilitating clot formation. Platelets play a crucial role in the coagulation system. The anticoagulation system, involving endothelial cells and various factors (e.g., antithrombin III, protein C, and tissue factor pathway inhibitor [TFPI]), functions to maintain the integrity of the vessel wall, regulate blood flow, and prevent excessive clot formation. The balance between these systems is essential for maintaining vascular health.

Epidemiology

Elucidating the epidemiology should not ignore the heterology of DIC. Statistics on the incidence and outcome of DIC varied because patients with this condition often have underlying diseases and additional causes, leading to diagnostic delay and inaccuracy [3]. Besides, different DIC score has been established, this may lead to statistical differences in the disease across different countries and hospitals, depending on the score system that has been employed. The incidence of DIC ranges from 8.5% to 34% in intensive care unit (ICU) patients, depending on the diagnostic methods used [4]. The 28-day mortality rate for DIC is about 20%-50%. Sepsis and septic shock can lead to the occurrence of DIC due to factors such as the cytokine storm and endothelial injury, while the progression of DIC can further exacerbate organ dysfunction. Sepsis is the most common cause of DIC. The incidence of DIC in patients with sepsis is high as 46.8% based on JAAM DIC [5]. Trauma, particularly severe injury associated with substantial tissue damage and shock, can account for a considerable percentage of DIC cases. Patients with head trauma could have incidence of DIC amount to 30-40% [6, 7]. Approximately 7% of individuals with solid malignancies exhibit DIC, a figure that escalates with the progression of the disease and in those considered at risk for thrombotic events [8]. Furthermore, DIC is identified in a considerable proportion of patients afflicted with hematological malignancies, with a heightened incidence in cases of acute leukemia (15–17%) [9]. Complications such as abruptio placentae, amniotic fluid embolism, and eclampsia are significant causes of DIC in pregnant women. Other causes of DIC are associated with vascular abnormalities, liver diseases, immune reactions, toxins, and transfusion reactions, all having their instinct pathophysiology.

Table 1 DIC causes

Etiology Category	Causes	Estimated Incidence	Prognosis
Infectious Diseases	Sepsis, bacterial pneumonia	30-50%	Mortality rate 40%; timely antibiotic treatment and supportive care are crucial
Trauma	Severe injury, traffic accidents	10-50% head trauma 36-41%	Mortality rate 25-34%; Related to the severity of trauma and timely medical intervention; may progress to multiple organ failure
Solid tumors [8]	Pancreatic, gastric, lung cancer	5-15%	Related to cancer type, stage, and treatment. Compared to patients without DIC, those with early and late-stage malignant tumors who developed DIC had lower survival rates.
Hematological cancers [10-12]	ALL	15-20%	
	APL	70-80%	Mortality rate 20% (30 days)
	AML	20%	Mortality rate 42.5% (30 days)
Obstetric Complications [13]	Abruptio placentae, severe preeclampsia	1% 0.2%	Mortality rate 1%, Emergency situations requiring rapid diagnosis and management; prognosis is related to maternal and fetal conditions
Heat Stroke [14-16]	Heat stroke due to high temperatures	9.6-28.4%	Mortality rate 26%
Snake Bite [17, 18]	Snake Bite	36-50%, geographically dependent	
out-of-hospital cardiac arrest [16]		10–30%	Mortality rate 83%

Vascular Abnormality		a small percentage	
Immune-Mediated Diseases	Systemic lupus erythematosus, antiphospholipid syndrome	Small proportion	Related to disease control and immunosuppressive therapy; may affect long-term prognosis

Pathophysiology and molecular mechanism

Coagulative disorders and modulation

DIC is characterized by a disruption in the balance between coagulation and bleeding within the body (Figure 2). During the initiation phase of the coagulation pathway, various factors such as endothelial injury or inflammatory stimuli lead to the exposure of tissue factor (TF), triggering extrinsic coagulative pathway activation [19]. TF activates circulating factor VII, forming FVIIa, which combines with TF to create a TF-FVIIa complex that further activates factor X to FXa, ultimately resulting in the conversion of prothrombin to thrombin, thereby triggering coagulation and clot formation. TF is extensively expressed on monocytes, endothelial cells, platelets, lymphocytes, and malignant cells [19-23]. During acute inflammation/sepsis, pattern recognition receptors (PRRs) bind to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) induced TF expression primarily on monocytes, initiating procoagulant responses [24, 25]. Activated vascular endothelial cells, platelets, and extracellular vesicles released from related cells exaggerate TF responses, accelerating procoagulant state [26]. DAMP-induced inflammasome activation also triggers TF releases through pyroptosis [27]. TF neutralization has been reported to prevent thrombosis in sepsis model [28, 29], however, due to the significant physiological role of TF, it is challenging to conduct clinical research on systemic TF inhibitors.

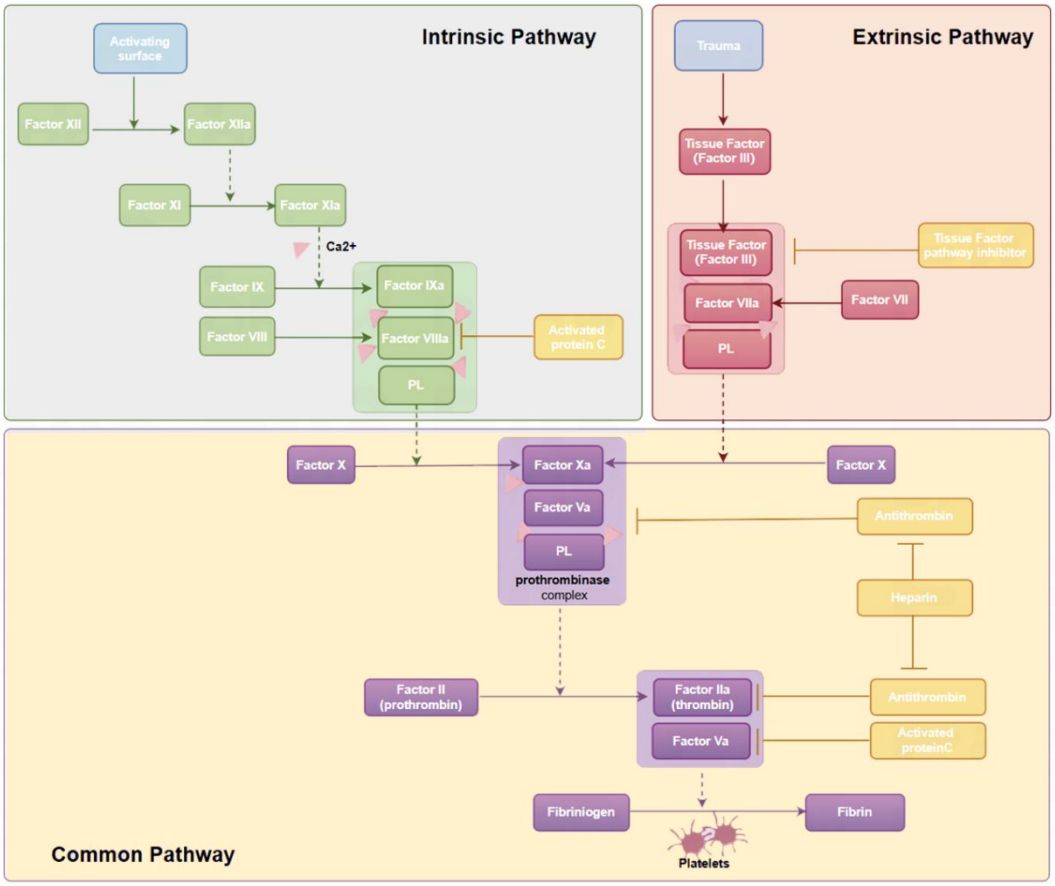

Figure 2. The Coagulation Cascade Pathways. The intrinsic pathway is initiated by Factor XII activation, leading to a cascade involving Factors XI, IX, and VIII, and converges at Factor X activation. The extrinsic pathway is triggered by tissue factor (Factor III) interacting with Factor VII, also leading to Factor X activation. The common pathway begins with the activation of Factor X, resulting in the conversion of prothrombin (Factor II) to thrombin (Factor IIa), which then converts fibrinogen to fibrin, culminating in clot formation. Regulatory factors such as antithrombin, heparin, and activated protein C are highlighted, emphasizing their roles in inhibiting various steps of the cascade.

As the coagulation pathway progresses, the formation of thrombin emerges as the central event in the entire process. Thrombin not only converts fibrinogen into fibrin, forming a blood clot, but also positively feeds back to activate factors

V, VII, VIII, X, and XI, as well as itself, generating more thrombin [30]. Additionally, thrombin promotes platelet aggregation and the release of granules, stimulating the contraction of the clot. In adults, 1 milliliter of plasma contains approximately 300 units of prothrombin. If all the prothrombin in 10 ml of plasma is activated to thrombin, it can lead to the coagulation of the entire blood volume. Beyond its role in clot formation, thrombin is also involved in inflammation, immune response, cell adhesion, and platelet activation [30]. Thrombin interacts with protease-activated receptors (PAR-1) on endothelial cells, activating inflammatory signaling pathways that lead to the release of von Willebrand factor (vWF), angiopoietin-2 (Ang2), and P-Selectin, thereby amplifying the inflammatory response and inducing microthrombus formation [31]. Targeting thrombin using antithrombin (AT) administration has clinical implications in underlying DIC causes such as sepsis, trauma, burns and complicated pregnancy, worthy of further attention.

Platelet activation and aggregation play essential roles in the development of clot formation during DIC. Platelets are on the first line to respond to damaged blood vessels. Underlying DIC causes such as endothelial damage, pathogen contact, or inflammatory factors trigger platelet aggregation [32]. Cell-free DNA and histones, bacterial lipopolysaccharides and neutrophil extracellular traps in sepsis could directly activate platelet. The activation of the coagulation cascade by TF and the subsequent production of thrombin not only promotes fibrin formation but also strongly activates platelets [33]. Activated platelets can further promote monocyte TF expression and fibrin formation by expressing P-selectin and facilitate the adhesion of platelets to leukocytes and the vascular wall. Additionally, the large amounts of vWF released due to inflammation-induced endothelial damage are another key factor contributing to increased platelet-vessel wall interactions in DIC. vWF is an acute-phase factor that is upregulated and released during systemic inflammation. It enhances platelet adhesion and aggregation in the microcirculation during DIC

[34]. Patients with DIC had higher platelet activation than patients without DIC [35]. Platelet count has been considered a criterion in DIC diagnosis, however, examining platelet function is also important for identifying patients at high risk of developing DIC.

Crosstalk between inflammation and DIC

The interplay between the inflammatory response and DIC is intricate and involves numerous molecular mechanisms (Figure 3). The immune system, upon encountering stimuli such as infections or trauma, initiates a cascade that leads to the activation of the coagulation pathways. The inflammatory response initiated by PAMPs can induce the expression of TF on the surface of various cells, including monocytes, endothelial cells, and even some cancer cells, triggering activation of the coagulation cascade [36]. Activated monocytes releases extracellular vesicles expressing procoagulant tissue factor and phosphatidylserine on their surfaces, activate the intrinsic and extrinsic coagulation pathways [37]. As a systemic inflammatory response, there is an increase in inflammatory mediators in patients with sepsis. Proinflammatory cytokines like tumor necrosis factor (TNF), interleukin-1β (IL-1β), and IL-6 not only acts as a procoagulant, but also damages endothelial cells and initiates clotting. In addition, the release of DAMPs, including extracellular DNA and high mobility group box 1 protein (HMGB1), can directly influence the coagulation process [16]. Moreover, NETs released from activated neutrophils, composed of DNA, histones, and granular proteins, can mediate inflammatory responses but also lead to microvascular thrombosis and tissue ischemia. NETs can carry neutrophil derived TF into the extracellular space as well as activate factor XII, enhancing thrombin generation by intrinsic and extrinsic coagulation pathway. The interaction between immune cells and coagulation activation has been termed "immunothrombosis", which denotes the innate intravascular immune response that triggers thrombin production and microthrombi formation. Immunothrombosis initially creates an intravascular scaffold that helps

pathogen recognition and eradication, improving endothelial integrity. However, when immunothrombosis is uncontrolled, it causes tissue damage and contribute to organ dysfunction.

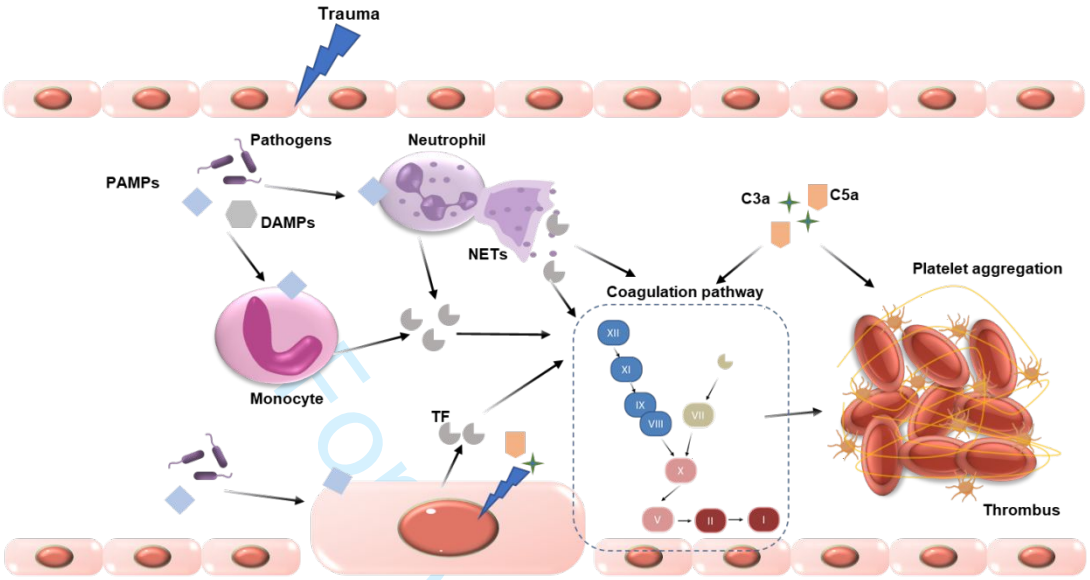

Figure 3. Crosstalk between inflammation and DIC. Schematic representation of the interplay between trauma, pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), immune response, and coagulation pathways leading to thrombus formation. Trauma and pathogens trigger neutrophil activation, resulting in the release of neutrophil extracellular traps (NETs) and monocyte activation. The activated monocytes express tissue factor (TF), further amplifying the coagulation cascade. Complement components C3a and C5a also contribute to platelet aggregation, which together with the coagulation cascade, leads to thrombus formation.

The complement system interacts closely with coagulation pathways, amplifying both inflammatory and thrombotic responses. Components such as C3a and C5a produced during complement activation can stimulate the assembly of prothrombinase, leading to thrombin generation [38]. Complement activation can also lead to the upregulation of adhesion molecules on endothelial cells, promoting the attachment and activation of leukocytes, which can further contribute to the procoagulant state. In addition, complement

activation products can interact with platelets, promoting their activation and aggregation, contributing to the formation of thrombi. The interaction of these elements with the coagulation system can result in a hypercoagulable state and impaired fibrinolysis, exacerbating the clinical manifestations of DIC. As a result, PAMPs, DAMPs, neutrophil extracellular traps, activated immune cells, endothelial cells, and damaged host cells propagate prothrombotic and proinflammatory responses and coagulopathies. Therefore, there must be many regulatory mechanisms in normal human tissues that control this central aspect of the coagulation response.

Altered anticoagulant activity and fibrinolytic system

Natural anticoagulant mechanisms were suppressed during procoagulant state of DIC [39]. Antithrombin (AT) is the primary endogenous coagulant inhibitor. AT is a 58-kDa plasma glycoprotein synthesized by the liver and endothelial cells, belongs to the serine protease inhibitor family. AT inhibits IIa, Xa, and IXa, and also has a mild inhibitory effect on factors XIa and VIIa. Platelet aggregation and attachment can be suppressed by AT. AT also has anti-inflammatory property. AT reduces the production of cytokines by neutrophils and endothelium, prevents neutrophil rolling and adhesion, decreasing the interaction between neutrophils and endothelium. AT deficiency is common in DIC. In sepsis-related DIC, decreased AT levels were associated with poor prognosis. AT can guide anticoagulation in sepsis; if a sepsis patient has insufficient antithrombin III levels, the effectiveness of heparin may be poor.

Thrombomodulin is a key endothelial cell surface glycoprotein that plays a significant role in the regulation of the coagulation system. It forms a complex with thrombin, which is a central enzyme in the coagulation cascade, thereby inhibiting thrombin's pro-coagulant activity and promoting the activation of protein C, an important natural anticoagulant. The complex of thrombomodulin and thrombin accelerates the conversion of protein C to its activated form APC,

which has anticoagulant, anti-inflammatory, and profibrinolytic properties [40, 41].

Activated protein C (APC) and protein S (PS) are essential anti-coagulant molecules. Plasma protein C (PC) is a double-chain glycoprotein synthesized by liver megakaryocytes and endothelial cells and is a vitamin K-dependent factor. PC can bind to the endothelial protein C receptor (EPCR) on endothelial cells, while thrombin also binds to the thrombin receptor (TM). PC forms a 1:1 complex with thrombin, which leads to the cleavage and activation of PC into APC. On phospholipid surfaces, APC inhibits the coagulation pathway by specifically cleaving the peptide bonds of factors VIIIa and Va with its cofactor, protein S (PS), achieving an anticoagulant effect. The primary function of PS is to act as a cofactor for PC, enhancing its inactivation effects. In plasma, there are two forms of PS: 40% exists in a free form, exerting cofactor activity, while 60% is bound to C4b in plasma, lacking cofactor function. Protein C can also lead to a decrease in levels of plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI), promoting fibrinolysis. A substantial reduction in the protein C system can severely disrupt the proper regulation of activated coagulation. This dysfunction arises from impaired protein synthesis, down-regulation of endothelial thrombomodulin due to cytokines, and a decrease in the free fraction of protein S (a crucial cofactor for protein C). In addition to its anticoagulant functions, APC can also mediate anti-inflammatory effects and increase endothelial barrier function. Clinical trials, such as the PROWESS trial, have demonstrated the benefits of APC in treating sepsis by leveraging both its anticoagulant and anti-inflammatory properties, although the use has been refined over time to target specific patient populations based on ongoing research and clinical experience.

Tissue Factor Pathway Inhibitor (TFPI), is a plasma serine protease inhibitor synthesized by endothelial cells and is an important anticoagulant substance. TFPI primarily functions through two pathways: the main pathway involves

inhibiting the TF-VIIa complex formation, preventing its activity and thus blocking the initiation of the extrinsic coagulation pathway. Additionally, TFPI can bind to Xa, forming an Xa complex, which then combines with the TF-VIIa complex to form a quaternary complex, exerting its anticoagulant effect. Administering recombinant Tissue Factor Pathway Inhibitor (rTFPI) to hinders the formation of blood clots and fibrin accumulation, alleviates fatality rates from septic shock, and guards against the onset of DIC. Studies have detected high levels of TFPI in individuals with sepsis-induced DIC, which coincide with high levels of Tissue Factor (TF), indicating an insufficiency of TFPI to counteract the TF-triggered coagulation process.

Fibrinolytic system also plays pivotal roles in the pathogenesis of DIC. The fibrinolytic system is primarily composed of plasmin, plasminogen activators, and plasminogen activator inhibitors. Plasminogen is a zymogen synthesized by the liver and circulates in plasma. Upon activation by tissue-type plasminogen activator (tPA) or urokinase-type plasminogen activator (uPA), plasminogen is converted into plasmin, which degrades the fibrin mesh structure and forms soluble fibrin degradation products (FDPs), thereby dissolving blood clots. While regulating thrombus formation, the fibrinolytic system itself is also controlled by various inhibitors. PAI-1 can regulate fibrinolysis by inhibiting the activity of tPA and uPA, while α2-antiplasmin can prevent excessive fibrinolysis by directly inhibiting the activity of plasmin. Following major trauma, there are alterations in the coagulation and fibrinolytic systems. Endothelial cells release tPA to initiate the fibrinolytic while PAI-1 remain unchanged. Imbalances of tPA and PAI-1 induces hyper-fibrinolytic phenotype of trauma patients in the initial few hours. This phase of enhanced fibrinolysis is short-lived, typically ends a few hours after PAI-1 secretion by endothelial cells and, in some instances, platelets. This swift transition is referred to as "fibrinolytic shutdown". In acute promyelocytic leukemia (APL), reduced expression of PAI-1 promote the hyper-fibrinolytic state.

Clinical manifestations of DIC

Patients could experience bleeding and thrombosis independently or simultaneously, depending on the DIC course that they are going through. The widespread activation of the coagulation system in DIC can lead to consumptive coagulopathy, manifested by bleeding at multiple sites, such as dermatologic bleeding, encephalorrhagia, gastrointestinal bleeding, airway bleeding, genitourinary tract bleeding, and bleeding of surgical sites, resulting in persistent hypotension, shock and organ dysfunction. Thrombosis may be less obvious and subclinical. Pulmonary thrombosis leads to impaired gas exchange and damage to the alveolar-capillary barrier, resulting in hypoxemia and acute respiratory distress syndrome. Similarly, microthrombi in the glomeruli and renal tubules can cause decreased perfusion, leading to acute kidney injury. Distinguishing whether organ failure stems from the underlying condition or clot formation in microvasculature can be difficult, complicate diagnosis and lead to delays. Clinical features of DIC is also related to different causes. Sepsis as a primary cause of DIC, commonly present a thrombotic type of DIC and organ dysfunction. Trauma-related DIC, meanwhile, is characterized by early fibrinolytic phenotype and subsequent thrombotic response. This disparity underscores the need for vigilant monitoring and management in different patient populations.

Diagnosis

There is no single clinical test or examination index that can be used for the definitive diagnosis of DIC. The International Society on Thrombosis and Haemostasis (ISTH) defines overt DIC with several criteria in 2001. These include thrombocytopenia (low platelet count), significant prolongation of prothrombin time (PT), moderate to high levels of fibrin-related markers (such as fibrin degradation products), and reduced fibrinogen levels. These markers reflect severe, widespread activation of the coagulation system leading to both clot formation and breakdown. Overt DIC typically manifests in patients with

severe underlying conditions like sepsis or trauma. Non-overt DIC, or subclinical DIC, is identified through sensitive molecular markers rather than classical indicators in 2006 by ISTH. These include decreased levels of antithrombin, protein C, and increased thrombin-antithrombin (TAT) complexes. However, the molecular markers used for diagnosing non-overt DIC are not widely implemented due to their complexity and cost. This restricts their use in everyday clinical practice, making it difficult to identify and manage early DIC cases. The JAAM criteria were introduced in 2006 to provide a practical and clinically applicable approach for diagnosing DIC, particularly in patients with acute conditions such as sepsis. The JAAM criteria use a scoring system that integrates these parameters to assess the presence and severity of DIC. The total score helps to categorize the degree of coagulation dysfunction and determine the appropriate clinical management. However, The JAAM DIC criteria have been critiqued for becoming outdated, particularly after the update of the sepsis definition to Sepsis-3.

In response to the limitations of existing criteria, particularly for early detection and specific contexts like sepsis, the Sepsis-Induced Coagulopathy (SIC) criteria were introduced in 2017. SIC is designed to diagnose early DIC in patients with sepsis. The SIC criteria are based on readily available and routine clinical tests, making them practical for rapid assessment. SOFA score assesses the degree of organ failure, while PT-INR and platelet count reflect the coagulation status. This approach aims to facilitate early intervention and appropriate management in sepsis-related DIC.

Both the overt DIC criteria and SIC criteria have limitations in terms of sensitivity and specificity. For instance, routine tests like PT-INR and platelet count may not detect early or non-overt stages of DIC effectively. Current diagnostic tools may not sufficiently capture the progression of DIC from early to overt stages. Understanding the diagnostic approaches and limitations of current standards is crucial for effective management and treatment. Monitoring requires a

combination of tests and longitudinal assessments, which can be resource-intensive and challenging to implement in real-time clinical scenarios. Establishing criteria tailored to specific underlying conditions such as hematologic disorders and cancer-induced DIC is also necessary.

Diagnostic criteria for DIC

measurement	**score**	**ISTH overt**	**JAAM**	**SIC**
Platelet (10^9/L）	0	> 100	≥ 120	> 150
	1	≤ 100	≥ 80，< 120	< 150
	2	< 50		< 100
	3		< 80	
PT (s)	0	< 3	< 1.2 (PT ratio)	
	1	≥ 3, < 6	≥ 1.2	1.2 > INR 1.4
	2	≥ 6		INR > 1.4
FDPs (mg/L)	0	DDI < 1	FDP < 10	
	1		10 ≤ FDP < 25	
	2	1 ≤ DDI < 5		
	3	DDI ≥ 5	≥ 25	
Fg (g/L)	0	> 1.0	> 3.5	
	1	≤ 1.0	≤ 3.5	
SIRS score	0-2		0	
	≥ 3		1	

organ dysfunction	1			SOFA = 1
	2			SOFA ≥ 2
DIC score		DIC ≥ 5	DIC ≥ 5	≥ 4

Differential diagnosis of DIC and thrombotic microangiopathy

Thrombotic microangiopathy (TMA), manifests as a clinical syndrome characterized by microangiopathic hemolytic anemia (MAHA), is increasingly gaining the attention of clinicians. TMA encompasses hemolytic anemia, thrombocytopenia, and organ dysfunction, particularly affecting the kidneys and central nervous system, as well as other organs. Thrombocytopenia and potential organ dysfunction are common clinical features of DIC and TMA, thus differential diagnosis between DIC and TMA is important. The core pathogenesis of TMA lies in the abnormal activation of platelets and endothelial cell dysfunction, while coagulation and fibrinolytic system were not activated in most circumstances. Microvascular thrombosis in TMA results from the platelets and endothelial cells activation while it is predominantly driven by the coagulation system's activation in DIC. Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS) are used to be considered as the primary causes of TMA syndromes. TMA is more commonly associated with concurrent conditions such as infections, pregnancy, autoimmune diseases, or malignant hypertension. Unlike DIC that has no specific markers, TMA has some diagnostic markers. TTP requires a markedly decreased ADAMTS13 level, that of STEC-HUS requires the detection of a STEC infection. aHUS involves identifying abnormalities in the complement system. Concerning treatment, platelet transfusion is contraindicated for TMA, whereas is advised for DIC with thrombocytopenia and major bleeding. Anti-fibrinolytic therapy is suggested for DIC patients with hyperfibrinolysis. Plasma exchange is recommended for certain TMA cases like TTP but not for DIC. Antithrombin concentrate and

recombinant thrombomodulin are commonly used for DIC, while eculizumab is effective for complement-mediated TMA, such as aHUS, and rituximab is beneficial for TTP in patients with high ADAMTS13 inhibitor titers.

Treatment

Considering the complex pathophysiology of DIC, treatment of DIC is a multifaceted endeavor that requires a tailored approach based on the clinical context and underlying cause. During non-overt DIC, treatment targeting the underlying causes is essential. In fact, when the cause of DIC is effectively addressed, the coagulopathy could resolves on its own. As DIC progresses, effective anticoagulation therapy during the hypercoagulable phase is necessary, although the timing of initiating anticoagulation and the potential risk such as bleeding remain current challenges in research. Use of blood products and clotting factor concentrates should be considered to manage bleeding due to platelet and coagulative factors consumption. Overall, restoration of the pathological coagulopathy to a physiological hemostatic may be a potential solution and is currently widely studied.

Antithrombin Treatment

As is mentioned above, AT is a serine protease inhibitor that plays a pivotal role in the natural anticoagulation system by neutralizing thrombin and other coagulation factors [42]. In the setting of DIC, where there is an overwhelming activation of coagulation pathways, the levels of AT can be significantly depleted, contributing to a hypercoagulable state [43]. In sepsis where AT activity is strongly suppressed, the use of AT concentrate has been extensively studied. Significant reduction in 28-day mortality was observed in patients with sepsis-associated DIC treated with AT. The benefits were particularly pronounced when AT was not co-administered with heparin [44, 45]. However, meta-analysis did not find a significant reduction in overall mortality with AT treatment across all critically ill patients, subgroup analyses also suggested no

potential benefits in patients with DIC and sepsis [46]. In addition, AT treatment seems to increase bleeding risk based on a Cochrane review that included 30 RCTs, although the adjuvant heparin use should be considered as a risk [47] The Japanese sepsis guidelines recommend the use of AT for sepsis-associated DIC, supported by a propensity score-matched analysis showing improved survival rates [48, 49]. The rationale for this recommendation is based on the understanding that severe insults leading to systemic thrombin generation can overwhelm the body's natural anticoagulant mechanisms, including AT. Restoring these pathways with AT concentrate is thought to mitigate the hypercoagulable state and reduce the associated mortality. Recent evidence on the efficacy and safety of AT has become more favorable in sepsis and sepsis-associated DIC, although optimal dosing and patient selection for AT therapy remain contentious issues that require further research [50, 51]. AT administration could also be considered in acquired AT deficiency such as DIC associated trauma, burns, complicated pregnancy, although further clinical study is needed [52, 53].

Heparin Treatment

The interaction between heparin and antithrombin is an important pathway for the action of antithrombin. Endogenous heparin is a naturally occurring anticoagulant substance, primarily secreted by mast cells and basophils . When antithrombin binds to heparin, its conformation changes, resulting in a 4000-fold increase in its ability to inhibit coagulation factors [54]. In cases of DIC where thrombosis is the primary clinical feature, the use of unfractionated heparin or low-molecular-weight heparin (LMWH) is recommended by ISTH. However, there have been no randomized controlled trials demonstrating a clinically relevant outcome for patients with DIC [55]. A meta-analysis suggested potential benefits of unfractionated heparin in reducing mortality in sepsis, particularly in patients with high severity [56]. However, this study did not specifically focus on patients with DIC. The use of heparin in the treatment

of sepsis-associated DIC is complicated by the fact that it may not only affect the coagulation pathways but also interact with inflammatory processes, which are central to the pathophysiology of sepsis [57-59]. In a randomized controlled study aiming at evaluating effect of LMWH in COVID-19 patients at risk of thrombosis (plasma D-dimer level greater than 4 times the upper limit or SIC score ≥4), therapeutic doses of LMWH reduced major thromboembolism and death compared with institutional standard heparin thromboprophylaxis, while the treatment effect was not observed in critically ill patients [60]. Heparins may be most effective when administered early in the disease course to prevent both macrovessel and microvascular thrombosis in this condition. Still the prophylactic use of heparin or LMWH is advocated in critically ill, non-bleeding patients with DIC to prevent venous thromboembolism, although more clinical trials are needed to evaluate the effect.

Use of heparin should be particularly cautious or suspended in DIC patients with bleeding, high bleeding risk, or when platelet counts fall below 20 × 10^9/L [61]. For DIC patients with APL, careful consideration of heparin use is required, platelet counts should above 20 × 10^9/L and bleeding risk should be considered. In obstetric DIC, which primarily presents with bleeding, the use of UFH or LMWH is uncertain and should be limited to situations where thrombosis is a more pressing concern.

Heparin-induced thrombocytopenia (HIT), characterized by a drop in platelet count and an increased risk of venous or arterial thrombosis, is a serious complication arising from heparin therapy [62]. HIT is caused by synthesis of antibodies targeting platelet factor 4 (PF4) modified by heparin [63]. Upon suspicion of HIT, heparin therapy should be immediately discontinued, a Doppler ultrasound of the lower limbs should be conducted, and an alternative anticoagulant, such as danaparoid sodium or argatroban, should be prescribed [64].

Other anticoagulant therapy

Thrombomodulin (TM)

In the context of DIC, where the balance between coagulation and anticoagulation is disrupted, the use of thrombomodulin has shown promise. Recombinant human soluble thrombomodulin (rTM) has been studied in clinical trials, particularly in Japan, where it has demonstrated potential benefits in patients with DIC due to hematologic malignancy or severe infection [65]. A meta-analysis including 1409 patients from 3 RCTs and 9 observational studies found a reduction of death risk sepsis-induced DIC patients, indicating a better outcome of rTM treatment [66]. However, the SCARLET study, a RCT investigated the effect of rTM on 28-day mortality in patients with SIC showed no risk reduction in the intervention group compared to the placebo group, while the risk of major bleeding is increasing [67]. A post-hoc analysis of the SCARLET study indicated that the mortality risk reduction was most pronounced in subgroups of patients with increased levels of thrombin-antithrombin complex (TAT) and prothrombin fragment suggesting that rTM may be particularly effective in patients with higher disease severity [68]. A following updated meta-analysis did not found statistically significant difference in mortality risk reduction in SIC, although a trend favoring significant enhancement in coagulation parameters was observed. Ongoing research aims to clarify the ideal role of rTM in treating DIC and DIC associated causes.

Activated Protein C (APC)

Recombinant activated protein C (rAPC) was the first natural anticoagulant to be approved for the treatment of sepsis, following the results of the PROWESS trial, which showed a beneficial effect in patients with severe sepsis. A subgroup analysis of the PROWESS trial indicated an even more beneficial effect on survival in patients with overt DIC . However, subsequent trials failed to demonstrate a consistent benefit of rAPC, and it was associated with an increased risk of bleeding, leading to its withdrawal from the market. The withdrawal of rAPC from the market highlights the complexity and challenges

in treating DIC. While rAPC showed promise in certain patient populations, its broader application was limited due to safety concerns. This underscores the need for a nuanced approach to the use of anticoagulants in DIC, where the risk of bleeding must be carefully balanced against the potential benefits of treatment.

Tissue Factor Pathway Inhibitor (TFPI):

TFPI is an endogenous inhibitor of the coagulation system that directly inhibits factor Xa and the tissue factor/factor VIIa complex. Given its role in inhibiting the initiation of the coagulation cascade, TFPI theoretically represents a promising target for the treatment of DIC. Early studies, including animal models and trials in healthy individuals, suggested that recombinant TFPI (rTFPI) could be a viable treatment option [69]. However, the transition from theoretical promise to clinical efficacy has been challenging. A phase II trial of rTFPI in patients with severe sepsis reported a non-significant reduction in 28-day mortality [70]. The subsequent phase 3 trial, known as the OPTIMIST trial, failed to show a survival benefit for patients with severe sepsis receiving rTFPI compared to placebo [71]. These results highlight the gap between the theoretical mechanisms of action and the clinical outcomes in complex conditions such as DIC.

In conclusion, while thrombomodulin, activated protein C, and tissue factor pathway inhibitor have shown theoretical promise in the treatment of DIC, their clinical efficacy has been variable. Thrombomodulin, particularly in its recombinant form, has demonstrated the most consistent potential benefit, especially in patients with more severe disease manifestations. The challenges faced by rAPC and rTFPI in clinical trials emphasize the need for a more tailored approach to treatment, taking into account the specific characteristics and severity of DIC in individual patients. Ongoing research and clinical trials are essential to refine our understanding of these treatments and to identify the patient populations most likely to benefit from them.

Anti-fibrinolysis Treatment

In DIC, the system that regulates fibrinolysis can become overwhelmed or suppressed, depending on the pathophysiology of underlying diseases. In sepsis, fibrinolysis system is commonly impaired, anti-fibrinolysis treatment is not recommended. In the setting of trauma, initial activation of fibrinolysis induced extensive tissue injury and massive bleeding are common, anti-fibrinolytic agents such as tranexamic acid (TXA) play a crucial role. The CRASH-2 trial demonstrated that early administration of TXA within 3 hours of injury reduced mortality in bleeding trauma patients [46]. In APL, a condition where both DIC and hyperfibrinolysis coexist, antifibrinolytic therapy may be appropriate. The use of TXA in these scenarios is supported by clinical data, emphasizing the importance of timely intervention.

Substitution Therapy in Bleeding and Overt DIC

Substitution therapy is a critical component in the management of DIC, particularly in patients with active bleeding or at high risk of bleeding complications (Figure 4). This therapy involves the transfusion of platelets, fresh frozen plasma (FFP), and the use of coagulation factor concentrates. The ISTH provides guidance on treatment thresholds for these therapies. Platelet concentrates are recommended for DIC patients experiencing significant bleeding, with a threshold set at 50 × 10^9/L. For DIC patients with minimal or no bleeding, a lower threshold of 20 × 10^9/L is generally accepted. Substitution with coagulation factors is advised for patients with major bleeding and significantly prolonged aPTT or PT. Fresh frozen plasma (FFP) is the preferred initial treatment. Prothrombin complex concentrate (PCC) is also an alternative, containing vitamin K-dependent factors but lacking some crucial ones. PCC can be used with caution in actively bleeding patients, but the risk of thromboembolism must be monitored. Vitamin K can help with deficiencies in vitamin K-dependent factors but takes over 6 hours to be effective. For low fibrinogen levels, fibrinogen concentrate or cryoprecipitate is used, aiming to

maintain levels above 1.5 g/L, or above 2.0 g/L for postpartum hemorrhage. The role of recombinant human activated factor VII (rhFVIIa) in severe bleeding DIC has also being explored, with no proven effectiveness and potential risks. However, it should be noted that for now no clinical trials has been established to prove the efficacy of such treatment. During the hypercoagulable phase, blood transfusions should be avoided. In the consumption coagulopathy and overwhelmed fibrinolysis induced bleeding, transfusion therapy could be implemented. Correctly assessing the pathological process of DIC before initiating replacement therapy is crucial, during substitution treatment, coagulation indicators should be monitored dynamically to avoid potential risks, such as thrombosis.

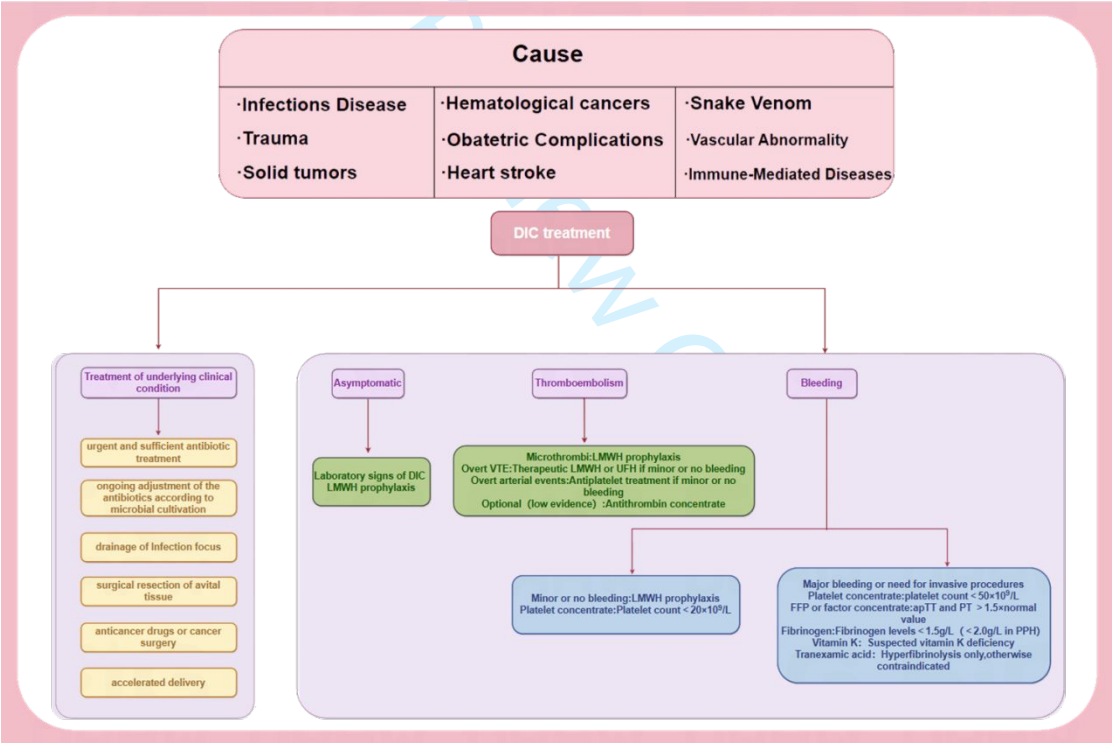

Figure 4. The causes and treatments of DIC. Treatment is divided into addressing the underlying condition and specific management for asymptomatic patients, thromboembolism, and bleeding, with recommendations for LMWH prophylaxis, antithrombin, platelet concentrates, and other supportive therapies based on clinical presentation.

Overall, the management of DIC necessitates a delicate balance between treating the coagulopathy and avoiding exacerbation of the underlying condition. Ongoing research and clinical trials are essential to further refine these treatment strategies and improve patient outcomes. The future of DIC treatment lies in the continued exploration of these and other novel therapies, with a focus on individualized patient care and the integration of emerging evidence into clinical practice.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors have declared that no competing interest exists.

Funding

This work was supported by National Natural Science Foundation of China (82300100, 82270087, 82372203), Program for Outstanding Medical Academic, Shanghai Shenkang Hospital Development Center of China (grant numbers SHDC2020CR1028B, SHDC22021304), Shanghai Municipal Committee of Science and Technology (23DZ2305400), Shanghai Natural Science Foundation Project (22ZR1439400), Shanghai Municipal Health Commission (202340068), and Physician-Scientist Project of Shanghai Jiaotong University (20240804).

Authors' contributions

F. Gong, X. Zheng, and S. Zhao contributed equally to this work. F. Gong, X. Zheng, and S. Zhao were responsible for the conception and design of the review. H. Liu performed the literature search and data analysis. E. Chen and R. Xie contributed to the interpretation of the findings and critically revised the manuscript. R. Li and Y. Chen provided overall guidance and supervision, and also contributed to the final revision of the manuscript. All authors have read and approved the final version of the manuscript.

Acknowledgements

Not applicable

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