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MINIREVIEWS

Current approach to disseminated intravascular coagulation related to sepsis - organ failure type

Jose J Zaragoza, Missael V Espinoza-Villafuerte

Jose J Zaragoza, Missael V Espinoza-Villafuerte, Intensive Care Unit, Hospital Español, Mexico City 11520, Mexico

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Correspondence to: Jose J Zaragoza, MD, Intensive Care Unit, Hospital Español, Ejercito Nacional 613 Piso 9, Granada, Mexico City 11520, Mexico. zaragozagalvan@hotmail.com
Telephone: +52-55-52559600

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Abstract

Disseminated intravascular coagulation (DIC) is a syndrome characterized by the systemic activation of blood clotting, which generates large amount of intravascular thrombin and fibrin. Various diseases may cause acceleration of the clotting cascade, inactivate the endogenous anticoagulants and modify fibrinolysis, having thus the formation of micro thrombi in the systemic circulation. The abnormalities in the hemostatic system in patients with DIC result from the sum of pathways that generate both hypercoagulability and augmented fibrinolysis. When the hypercoagulability state prevails, the main manifestation is organic failure. This subtype of DIC is often referred as "organ impairment" type, frequently seen in patients suffering from severe sepsis. To identify the underlying infection, early initiation of culture-based antimicrobial treatment, and to resolve any infection source promptly are keystone actions of DIC related to sepsis prevention and treatment. These should be combined with specific treatment related to each DIC subtype. In the context of septic shock, DIC is associated to increased severity, greater number and seriousness of organ failures, more frequent side-effects from treatment itself, and worse outcomes. Therefore, we ought to review the information available in the literature about approach and management of DIC in severe sepsis.

Key words: Septic shock; Disseminated intravascular coagulation; Coagulation impairment; Organ failure; Antithrombin; Sepsis

Core tip: Disseminated intravascular coagulation (DIC) is a syndrome characterized by the systemic activation of blood clotting, which generates large amount of intravascular thrombin and fibrin. In the context of severe sepsis and septic shock, DIC is related to increased severity, greater number and seriousness of organ failures, more frequent side-effects from treatment itself, and worse outcomes. We ought to review the most important and updated information available in the literature about DIC in severe sepsis and septic shock.

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INTRODUCTION

Disseminated intravascular coagulation (DIC) is a syndrome characterized by the systemic activation of blood clotting that generates a large amount of intravascular thrombin and fibrin. This process results in small and medium vessel thrombosis and, eventually, organ failure and severe hemorrhage[1,2]. DIC could be the consequence of infections, hematologic malignancy, obstetric complications, trauma, aneurisms or hepatopathy. Each etiology signifies individual hazards related to the underlying disorder. Therefore, the diagnosis and treatment should be dictated by the disease[3,4].

In the context of septic shock, DIC is related to increased severity, number and seriousness of organ failures, more frequent side-effects from treatment itself, and worse outcomes, including death[5,6]. Therefore, we ought to review the most important and updated information available in the literature about DIC in severe sepsis and septic shock setting.

NORMAL HEMOSTASIS

Hemostasis is an organized process that aids to maintain vascular integrity. In the presence of endovascular damage, thrombin generation with simultaneous negative feedbacks and coordination of fibrinolysis occur, to avoid massive hemorrhage or excessive thrombosis. The first step in hemostasis is the formation of a platelet plug over the damaged zone[7]. On the surface of platelets, Integrins interact with each other and with endothelial cells surface through the von Willebrand factor and fibrinogen. Nevertheless, the formation of a platelet plug is not enough to achieve stable hemostasis, given that the contribution of a fibrin mesh to stabilize the structure of the clot is needed.

Clotting cascade

Physiologic clotting initiates with tissue factor (TF) and activated Factor Ⅶ (FⅦ) complexes that cleave Factor Ⅹ (FⅩ) into activated FX. This initial step has a short duration, due to quick inhibition of TF-aFVⅦ complexes by the tissue factor inhibitor. The second pathway starts with Factor Ⅸ (FⅨ) that cracks into activated FⅨand joins activated FⅧ to transform FⅩ into activated FⅩ. Activated FⅩ forms a complex with activated Factor Ⅴ (FⅤ), with both phospholipids on platelet surface and calcium to turn prothrombin into thrombin[8]. Subsequently, thrombin turns fibrinogen into fibrin. At that time, activated Factor ⅩⅢ (FⅩⅢ) forms crossbred fibrin connections inside the clot, which serve as an additional support. Finally, fibrin clots are degraded by a protease called plasmin (Figure 1)[8].

DIC PATHOPHYSIOLOGY

Any alteration in hemostasis balance could generate hemorrhage or thrombosis[8]. In critically ill patients, this alteration is usually associated with sepsis, malignancy, and multiple trauma. These diseases usually accelerate the clotting cascade, inactivate endogenous anticoagulants, and modify fibrinolysis, resulting in micro thrombi formation in the systemic circulation[3].

The abnormalities in the hemostatic system in patients with DIC result from either hypercoagulability or hyperfibrinolysis[8] (Figure 2). When hypercoagulability prevails, the main clinical manifestation is organ failure. This type of DIC is referred as organ impairment type (both hypercoagulability and/or hypo-fibrinolysis exist)[9]. Organ impairment or organ failure DIC subtype is often seen in patients with severe sepsis. The activation of the coagulation cascade is an important part of the defense mechanisms to prevent infection dissemination. The increase in serum plasminogen activator inhibitor type 1 (PAI-1) caused by high levels of cytokines and lipopolysaccharides (LPS) in the blood of septic patients has been identified as one of the causes of hypofibrinolysis. Moreover, activated neutrophils in patients with sepsis liberate histones, neutrophil elastase and Catepsin G as a defense mechanism against pathogens[10]. Histones promote endothelial cell apoptosis, and platelet aggregation; meanwhile, neutrophil elastase inhibit Antithrombin (AT) and the Catepsin G decrease levels of the tissue factor pathway inhibitor (TFPI) promoting thrombus formation[10,11].

Cytokines

Endotoxin LPS are a component of the external membrane of gram negative bacteria, responsible of many of the cases of sepsis[12]. The entrance of endotoxin into systemic circulation causes the production of pro inflammatory cytokines. The consequent tissue damage is aggravated through free radicals generated by activated leucocytes. This causes an imbalance in normal hemostasis with the ulterior formation of thrombi in small and medium blood vessels that promote loss of vascular tone. All of this mechanisms contribute to the development of multiple organ failure[11-13].

Tumor necrosis factor: Tumor necrosis factor alpha (TNF-α) is synthesized in macrophages, and it is amongst the first cytokines to appear when endotoxin reaches blood circulation. It grasps it maximum concentration at 90 min from stimuli; then, it gradually disappears despite if the toxic stimulus remains. TNF-α has an important role initiating the inflammatory cytokine cascade and tissue damage. It has effects over monocytes, neutrophils, and vascular endothelium causing the production of other pro inflammatory interleukins (1b, 6 or 8). Furthermore, it stimulates the production of adhesion molecules such as

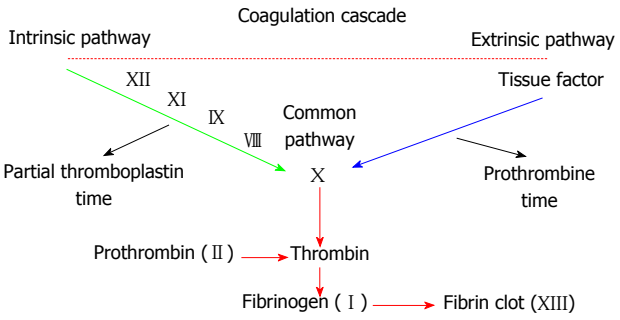

Figure 1 Schematic drawing of the coagulation cascade.

Intercellular Adhesion Molecule-1, vascular cell adhesion molecule-1 or E-Selectin.

Interleukin 1b: When the LPS enter the bloodstream, one can detect interleukin 1b (IL-1b) in plasma, and its presence serves as a severity marker. Patients with septic shock have high levels of IL-1b. It has been shown that the administration of this protein in primates induces a reduced fibrinolytic response equivalent to the one obtained with LPS or TNF-α. This suggests that IL-1b contributes to hypo-fibrinolysis mediated by PAI-1 in the presence of endo-toxemia[14,15].

IL-6: Endothelial cells synthesize IL-6 in presence of LPS. It also appears in the general circulation just after TNA-α shows up. IL-6 has a pathophysiologic role during sepsis as a clotting activator, and its concentration correlates with the disease severity[14,15].

Other cytokines: Other molecules participate in the inflammatory process in presence of the LPS: IL-12, IL-8, and interferon-γ. Nevertheless, their role in DIC is not yet well defined[15].

DIC DIAGNOSIS

At the bedside, is necessary to consider the clinical conditions that could alter the commonly used laboratory tests to diagnose DIC. Ergo, the diagnosis requires clinical expertise along biochemical workshop. The recurrently used test that might be affected include platelet count, prothrombin time (PT), fibrinogen, and fibrin degradation products (FDP), among others. Some clinical guidelines issued recommendations regarding this aspect[1,16,17]. In 2013 the International Society of Thrombosis and Hemostasis published recommendations for diagnosis and treatment of disseminated intravascular coagulation[18]. This guidance was based on a previous consensus by the British Committee for Standards in Hematology, the Japanese Society of Thrombosis and Hemostasis, and the Italian Society for Hemostasis and Thrombosis (Società Italiana per lo Studio dell'Emostasi e della Trombosi - SISET). They stated that in sepsis related DIC the major variation is either hyper-coagulation or hypo-fibrinolysis. As mentioned above, the main clinical manifestation

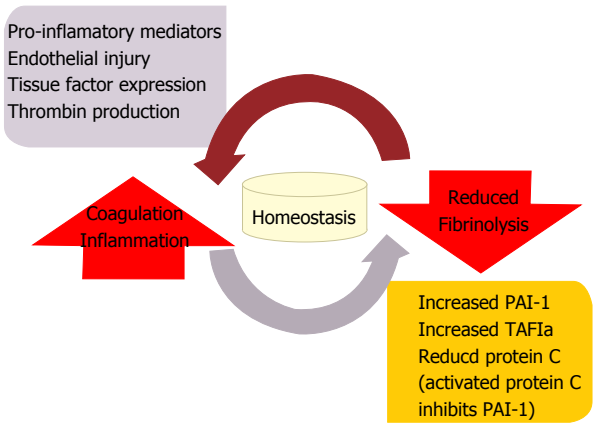

Figure 2 Mechanisms associated with hypercoagulability and/or hypofibrinolysis observed in sepsis related disseminated intravascular coagulation. PAI-1: Plasminogen activator inhibitor type 1; TAFIa: Thrombin activatable fibrinolysis inhibitor.

is organ failure, so several validated score systems to recognize DIC have been distributed using platelet count, prothrombin time, and anti-thrombin. The Japanese Association of Acute Medicine (JAAM) published a score system to detect sepsis related DIC, with a sensitivity and specificity of 100% and 65.0% respectively[5,19,20] (Table 1). Recently, Iba *et al*[21] proposed a modified version of the JAAM-DIC diagnostic criteria. They suggest to replace Systemic Inflammatory Response Syndrome (SIRS) by antithrombin activity, since SIRS is no longer used for the diagnosis of Sepsis. The new criteria could diagnose the same number of patients with comparable severity (mortality, 34.6% *vs* 34.8%). Also, mortality increased as the baseline antithrombin activity decreased (patients with a baseline antithrombin activity ⩾ 70% had a mortality of 26.5% *vs* 35.5% for those with an antithrombin activity < 70%). Despite this promising results, future studies to examine the worth of the modified scoring system in different populations are warranted[21].

Laboratory findings

A complete coagulation examination, including prothrombin time and platelet count is essential[4]. In some types of DIC (bleeding, massive hemorrhage, and asymptomatic) identifying the elevation of fibrin-associated biomarkers (D dimer, FDP, and soluble Fibrin) is useful to establish diagnosis[9]. Table 2 highlights the laboratory tests useful to diagnose DIC in a septic patient. It is important to consider that a coagulation disorder has around 35%-40% chance to be related to any other cause beside sepsis. A positive result does not guarantee the diagnosis. Delabranche *et al*[22] in 2016 published a multicenter, prospective observational study completed in 4 intensive care units in France. They used de JAAM score, sequential organ failure assessment score, and the acute physiology and chronic health evaluation Ⅱ to identify patients with DIC at early stage. They concluded that a combination of PT, endothelium-derived

Table 1 Score for disseminated intravascular coagulation diagnosis established by the Japanese Association of Acute Medicine

Parameter	Points
SIRS criteria	
3 or more	1
2-0	0
Platelet count (× 10^3/μL)	
< 80 or a reduction of > 50% in 24 h	3
80-120 or a reduction of > 30% in 24 h	1
> 120	0
Prothrombin time	
1.2 times over control or higher	1
< 1.2 times over control	0
Fibrin degradation products/fibrinogen (mg/L)	
25 or more	3
10 to 24	1
< 10	0
Diagnosis DIC: 4 or more points	

SIRS: Systemic inflammatory response syndrome; DIC: Disseminated intravascular coagulopathy.

Table 2 Laboratory findings in sepsis-related disseminated intravascular coagulation

Test	Alteration	Other causes
Platelet count	Reduction	Bone marrow abnormalities
Anti-thrombin/C protein	Reduction	Hepatic failure, capillary leakage syndrome
Prothrombin time	Extended	Hepatic failure, vitamin K deficiency
Soluble fibrin/thrombin	Increased	VTD, surgery
vWF-PP/PAI-1	Increased	Organic failure
aPTT	Bifasic wave	Infection
ADAMTS-13	Reduction	Hepatic failure, thrombotic microangiopathy
FDP/DD	Increased	VTD, surgery

VTD: Venous thromboembolic disease; vWF-PP: Von Willebrand factor pro-peptide; PAI-1: Type 1 plasminogen activator inhibitor; ADAMTS-13: A desintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; FDP: Fibrin degradation products; DD: D-dimer; aPTT: Activated partial thromboplastin time.

CD105$^+$-microparticles, and platelet count at admission could predict the absence of disseminated intravascular coagulation[22].

Liu *et al*[23] found four thrombin derived biomarkers that were triggered before PT, activated partial thromboplastin time (aPTT), or platelet count became altered. These markers include fibrinopeptide type A, soluble fibrin monomer complex, prothrombin fragment 1 + 2 (F1 + 2), and the thrombin-antithrombin complex. The F1 + 2 represents the total amount of fibrin produced, while the other three markers only show it partially. F1 + 2 is considered the most sensitive marker of thrombin production.

In the last few years the identification of endothelial damage markers and inflammatory cascade activators have made possible to find coincidences between the inflammation trigger mechanisms and coagulation. This extend the possibilities for future treatment targets[11].

Table 3 Treatment recommendations amongst different types of disseminated intravascular coagulation

Dysfunction	Recommended treatment
Pre-DIC	Treat cause and UFH 70 IU/kg per day or LWMH anti-Xa target: 0.8-1.2
Multiple organ failure	Treat cause and AT 30 IU/kg per day of 3 d
Hemorrhagic	Treat cause and Hemo-transfusion Anti-fibrinolytics Protease synthetic inhibitor
Massive hemorrhage	Treat cause and Hemo-transfusion Anti-fibrinolytics Protease synthetic inhibitor

DIC: Disseminated intravascular coagulopathy; UFH: Unfractionated heparin; LWMH: Low molecular weight heparin; Xa: Activated X factor; AT: Anti-thrombin.

DIC TREATMENT

To identify the underlying infection, early initiation of culture-based antimicrobial treatment, and to resolve any infection source promptly are keystone actions of DIC related to sepsis prevention and treatment. Table 3 lists key recommendations for the treatment of different types of CID.

The Surviving Sepsis Campaign guidelines[24], do not recommend treatment of any associated coagulopathy as for the lack of evidence to support it. Recently, Umemura *et al*[25] reported a meta-analysis of anticoagulation therapy in three different types of patients: (1) septic patients without coagulopathy; (2) patients with sepsis induced coagulopathy; and (3) patients with induced sepsis DIC. They identified that only septic induced DIC patients had a reduced mortality with no difference in the prevalence of hemorrhagic complications[25]. In septic patients, biomarkers of the homeostasis loss, such as histones (H3, H4), the TFPI, and the neutrophil extracellular traps are useful to determine whether to start treatment[26].

Antithrombin

AT has proven to be effective to revert sepsis induced DIC. As mentioned above, when germs disseminate throughout the organism, a diffuse coagulopathy that results in massive thrombi formation in small and medium blood vessels occur[13]. The KybertSept trial[27] was the first to evaluate the effectiveness of AT substitution in patients with severe sepsis and septic shock. The results showed an increase in the incidence of bleeding complications related to AT use. It is important to reflect that some of their patients used heparin as deep vein thrombosis prophylaxis. A sub-analysis of patients without heparin prophylaxis showed a reduction of adverse effects in AT group[27]. Later on, Gando *et al*[28] showed that in patients

with activated-AT levels of 50%-80%, the administration of AT at a dose of 30 UI/kg perday during 3 d improved platelet counts, and reduced the score punctuation for sepsis associated DIC without increasing bleeding events[28].

Heparin use

Antithrombin-Ⅲ (AT-Ⅲ) inactivates thrombin and other proteases, including FXa[29]. Heparin attaches to a AT-Ⅲ producing a conformational change that increases AT-Ⅲ activity. The unfractionated heparin (UFH) dose in Pre-DIC is 70 UI/kg per hour in continuous infusion for 5-7 d[23]. There are few randomized controlled trials evaluating the utility of heparin in DIC. Liu *et al*[23] shown that low molecular weight heparin was superior to UFH due to a higher inhibition of FXa[29]. The utility of other compounds like Fondaparinux and Danaparoid sodium is restricted to asymptomatic DIC for risk reduction of thrombotic events[9].

Blood components administration

Because of coagulation factors (specially fibrinogen) and platelet consumption, most clinical guidelines[1,16,17] recommend blood components administration only in hemorrhagic and massive hemorrhage DIC. The recommended platelet goal count has been established at 50 × 10^3/μL if active bleeding or 20 × 10^3/μL along high risk of hemorrhage. If PT or aPTT are 1.5 times over the standard, or fibrinogen is below 1.5 g/dL, fresh frozen plasma (15 mL/kg) is indicated. If volume restriction is intended, a concentrate of prothrombin complex, cryoprecipitates, or purify fibrinogen concentrates are preferred[1,16,17].

Human recombinant thrombomodulin

Thrombomodulin may reduce massive thrombotic events caused by the expression of extracellular histones observed in sepsis DIC[26]. In the double blind controlled study, Vincent *et al*[30] administered human recombinant thrombomodulin to patients with sepsis induced DIC that developed one or more organ failures and an international normalized ratio > 1.4. The dose of 0.06 mg/kg per day for 6 d along with conventional treatment reduced the severity of hematologic failure and reduced DIC incidence. Further trials are needed to safely recommend the therapy.

CONCLUSION

In critically ill patients, the early diagnosis of coagulopathy is essential to reduce morbidity and mortality. Identification of sepsis related DIC is difficult, especially when precise laboratory tests are not available. Clinicians should suspect the diagnosis in every severe sepsis or septic shock patient, and use whatever tools accessible to investigate it. It is important to treat promptly even subtle changes linked to coagulopathy, to diminish the extent of DIC.

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