Sepsis-induced Coagulopathy and Disseminated Intravascular Coagulation

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Patients with sepsis commonly require invasive procedures and frequently have an associated coagulopathy.[1] In a recent observational survey conducted in Japan, among 1,895 patients with sepsis treated in intensive care units, 29% were diagnosed with sepsis-induced coagulopathy, a term that is synonymous with disseminated intravascular coagulation (DIC) as defined by laboratory criteria.[2] In patients with sepsis, the imbalance in clot generation (coagulation) and clot breakdown (fibrinolysis) is a pivotal response that occurs due to host defense mechanisms but is associated with the development of organ dysfunction.[3,4] In a prior Anesthesiology editorial, Gropper suggested that "all of these conditions (in sepsis) likely share a common pathway for the development of multiple system organ failure: diffuse activation of endothelium by proinflammatory cytokines, leukocytes, and other proteins. Activated endothelium becomes prothrombotic in these conditions, leading to the formation of microvascular thrombosis. In addition, fibrinolysis is inhibited, resulting in the buildup of fibrin thrombus, which itself is proinflammatory."[5] This description is also consistent with our understanding of the coagulopathy that occurs in sepsis, which is more commonly described as DIC. Although sepsis is a common cause of DIC, other pathophysiologic states including trauma, cardiogenic shock, or acute ischemic injury can also cause DIC, a pathologic diagnosis and clinical sequelae due to another underlying disease process. Inflammatory responses after surgery, in particular after cardiopulmonary bypass, can produce a systemic inflammatory response syndrome and coagulopathy.

Pathophysiology of Sepsis-induced Coagulopathy and DIC

The major pathways that lead to sepsis-induced coagulopathy and DIC include activation of coagulation, platelets, and other inflammatory cells (*e.g.*, neutrophils, lymphocytes) and vascular endothelial injury.[6] Classically, tissue factor, a critical component of the extrinsic coagulation pathway, expressed on macrophages and monocytes, was thought to play a central role coagulation initiation.[7] Tissue factor is expressed on extracellular vesicles, and phosphatidylserine residue, an initiator of the contact pathway, expressed on the cell membranes is known to initiate hemostasis and clot formation.[8] In sepsis, neutrophils are activated, releasing extracellular traps for limiting infection that consist of DNA, histones (the binding protein for DNA structural integrity), and other neutrophil granule proteins, all of which are highly prothrombotic as shown in figure 1.[9] In addition, the release of damage-associated molecular patterns from injured host cells further increase prothrombotic activity. Upon cellular damage and hematopoietic cell activation, cell-free DNA and nuclear proteins are released into the circulation, such as histones, which possess strong procoagulant activity as shown in figure 1.[10] To balance this prothrombotic effect, circulating plasma proteins including antithrombin and protein C/S provide important anticoagulant effects.[11] The antithrombotic contribution of the vascular endothelium is also important in sepsis but under physiologic conditions to prevent clot formation, maintain vascular integrity, and regulate vascular tone. Vascular endothelial cells release nitric oxide and prostacyclin, thereby contributing to physiologic antithrombotic effects, whereas it promotes prothrombotic effects under septic conditions by expressing tissue factor and releasing von Willebrand factor.

Endothelial dysfunction and derangement of anticoagulation are the hallmarks of sepsis-induced coagulopathy. The vascular endothelial surface is lined by membrane-binding proteoglycans and glycosaminoglycan side chains that provide critical antithrombotic effects by binding to antithrombin.[12] Endothelial cells also balance fibrinolysis by producing tissue-type plasminogen activator and plasminogen activator inhibitor-1, and this balance shifts to inhibit fibrinolysis during sepsis.[13] Derangement of the coagulation/fibrinolytic system is another hallmark of sepsis-induced coagulopathy.

Definitions and Diagnoses of Sepsis-induced Coagulopathy and DIC

DIC was first described as a unique condition in which thrombosis and bleeding coexist. In patients with septic shock, coagulation is activated, and consumption of clotting factors occurs, which is the hallmark of DIC.[14] The International Society on Thrombosis and Haemostasis scientific standardization subcommittee has defined DIC as

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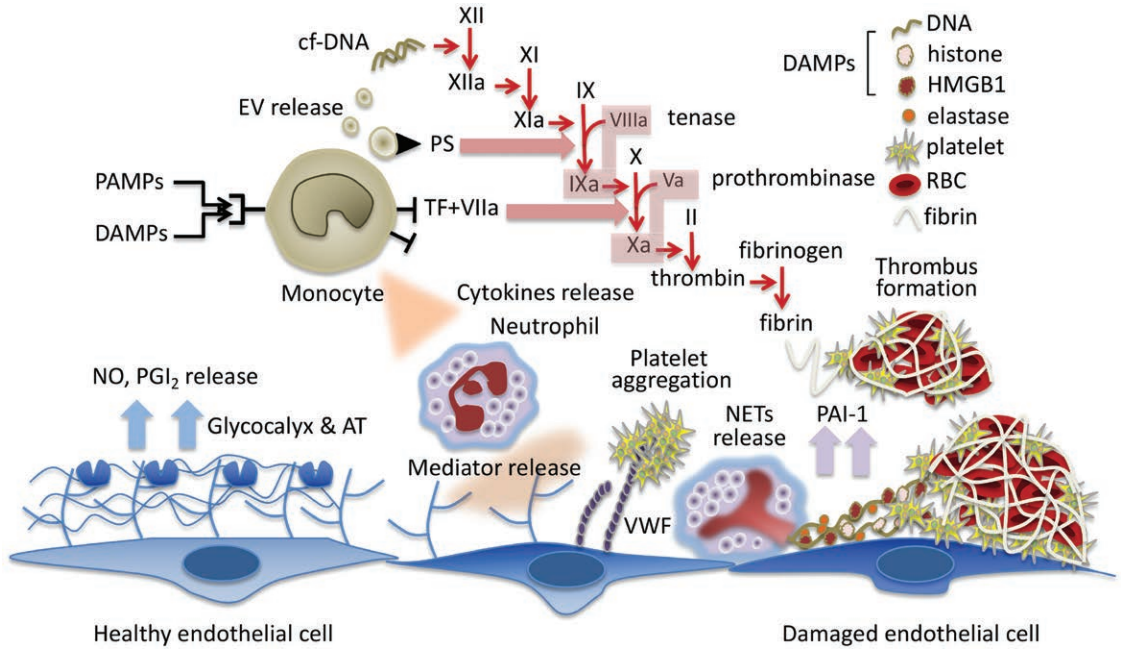

Fig. 1. Mechanisms of inflammatory thrombus formation in sepsis. Both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) can stimulate monocytes through specific pattern-recognizing receptors expressed on the cell surface. Activated monocytes release cytokines and chemokines that activate platelets, neutrophils, and endothelial cells. Monocytes and other cells release extracellular vesicles (EVs) that express procoagulant tissue factor (TF) and phosphatidylserine (PS) on their surfaces. Healthy endothelial cells maintain their antithrombogenicity by producing nitric oxide (NO) and prostacyclin (PGI_2) and expressing glycocalyx and its binding protein antithrombin (AT). Damaged endothelial cells change their properties to procoagulant after disruption of the glycocalyx, with expression of ultra-large von Willebrand factor (VWF). Neutrophils play pivotal roles in the activation of coagulation by expressing tissue factor and releasing granule proteins and chemical mediators. Neutrophils also activate coagulation by expelling neutrophil extracellular traps (NETosis). NETs are composed of procoagulant DNA, histones, and other DAMPs. cf-DNA, cell-free deoxyribonucleic acid; HMGB1, high-mobility group box; RBC, erythrocyte (red blood cell); PAI-1, plasminogen activator inhibitor-1.

"an acquired syndrome characterized by intravascular activation of coagulation with loss of localization arising from different causes that can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction" in 2001.[15] The four laboratory tests used to make the diagnosis of DIC as shown in table 1 include elevated levels of fibrin-related markers such as fibrin/fibrinogen degradation products or D-dimers, decreased platelet counts, prolonged prothrombin time, and decreased fibrinogen levels.[15]

Additional diagnostic criteria were established to categorize an advanced decompensated stage of hemostatic function termed overt DIC to emphasize "systemic intravascular coagulation" and "consumptive coagulopathy" and defined by the scoring system as shown in table 1. If the total DIC score is 5 or more, patients are diagnosed as having overt DIC to represent an advanced, "full-blown coagulopathic state." Other organizations have used similar scoring systems based on other combinations of coagulation biomarkers; however, because DIC is a conceptual laboratory-based clinical entity, the relevance of these criteria is debatable. The International Society on Thrombosis and Haemostasis overt-DIC criteria have been adopted as the gold standard for the diagnosis of DIC worldwide.[16] Overt-DIC scoring should ideally be used to identify patients already at an advanced and possibly irreversible stage of coagulopathy, thereby late from a therapeutic perspective. Thus, identifying patients earlier in the course of their hemostatic dysfunction would be important for potential management, especially in the intensive care unit.[17]

Coagulopathy in patients with sepsis continues from an initial compensatory phase to the decompensated stage of DIC. Although there is still debate regarding the definition of coagulopathy, it is generally suggested as "a condition in which the ability of the blood to clot is impaired,"[18] and conventionally, the term coagulopathy predominantly had represented a hemorrhagic state. However, the term coagulopathy is now used to represent a disordered condition that includes both the hemorrhagic and thrombotic states.[19] In regard to managing sepsis-induced coagulopathy, recent studies have suggested that any delay in intervention can be detrimental,[20] and the early detection of a coagulation disorder using criteria has currently been recommended by the International Society on Thrombosis and Haemostasis

Table 1. Sepsis-induced Coagulopathy and International Society on Thrombosis and Haemostasis Overt-DIC Scoring Systems

	Points	SIC	Overt DIC
Platelet count ($\times 10^9$ l^{-1})	2	< 100	< 50
	1	≧ 100, < 150	≧ 50, < 100
FDP or D-dimer	3	–	Strong increase
	2	–	Moderate increase
	1	–	–
Prothrombin time–INR	2	> 1.4	≧ 6 s
	1	> 1.2, ≦ 1.4	≧ 3, < 6 s
Fibrinogen (g/l)	1	–	< 1
Total SOFA score	≧ 2	2	–
	1	1	–

The total SIC score is 4 or more with the sum of the SOFA score and coagulation criteria exceeding 2. The total SOFA score is the sum of four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA). The overt-DIC total score is 5 or more.

DIC, disseminated intravascular coagulation; FDP, fibrinogen/fibrin degradation products; INR, international normalization ratio; SIC, sepsis-induced coagulopathy; SOFA, sequential organ failure assessment.

DIC subcommittee.[21] Criteria for diagnosing sepsis-induced coagulopathy include thrombocytopenia, prolonged prothrombin time and organ dysfunction as assessed by the Sequential Organ Failure Assessment score (table 1). A comparison of the scoring system for sepsis-induced coagulopathy with that of overt DIC revealed that the sensitivity was approximately twice as much as that of overt DIC, and patients met sepsis-induced coagulopathy criteria earlier than overt International Society on Thrombosis and Haemostasis criteria.[22] Another validation study reported that the diagnosis of sepsis-induced coagulopathy may be valuable for identifying appropriate therapeutic approaches for anticoagulant therapy in sepsis, similar to the once-used therapeutic approach of activated protein C.[23]

Differential Diagnoses

The development of thrombocytopenia is often the clue to recognize coagulopathy in sepsis-induced coagulopathy. However, different causes of thrombocytopenia should be considered in critically ill patients because specific management differs depending upon the underlying cause. Important prothrombotic states that may occur in a perioperative presentation include thrombotic microangiopathy and heparin-induced thrombocytopenia.

In patients with thrombotic microangiopathy, extensive thrombus forms within the microcirculation that causes thrombocytopenia and hemolytic anemia and includes thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. There are two types of thrombotic thrombocytopenic purpura: congenital and acquired. Acquired thrombotic thrombocytopenic purpura is an autoimmune disease caused by depletion or inhibition of a cleaving enzyme called ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) that cleaves von Willebrand factor into multimeric units to prevent hypercoagulability. ADAMTS13 depletion is often triggered by infection[24] and requires daily therapeutic plasma exchanges to reduce morbidity and mortality.[25] Two types of hemolytic uremic syndromes are recognized. The Shiga toxin–producing *Escherichia coli*–induced type occurs in children, is common in developing countries, and is characterized by severe hemorrhagic colitis, microangiopathic hemolytic anemia, and renal failure with a high mortality.[26] The less common form is the atypical hemolytic uremic syndrome, which presents similarly but is caused by complement activation, and therapy is complement inhibition with eculizumab.[27] Although the clinical presentations are similar, the differential diagnosis as shown in figure 2 may be helpful.[28]

One important thrombotic microangiopathy that perioperative clinicians need to be aware of is heparin-induced thrombocytopenia, an autoimmune disease caused by platelet-activating antibodies that recognize the multimolecular complexes of platelet factor 4 bound to heparin. This interesting disease state is when a commonly used anticoagulant (heparin) produces a prothrombotic effect caused by platelet activation. The clinical probability of heparin-induced thrombocytopenia can be evaluated using the clinical "4 Ts" scoring system (thrombocytopenia, timing of onset, thrombosis, and other causes of thrombocytopenia).[29] Diagnosis of heparin-induced thrombocytopenia is supported by a positive platelet factor 4–dependent immunoassay.[30,31] In clinical practice, heparin-induced thrombocytopenia can be easily confused with sepsis-associated coagulopathy, especially when it occurs in association with organ dysfunction such as shock liver, adrenal hemorrhage, and skin/limb necrosis.[32] Therapy includes stopping heparin and initiating a non-heparin anticoagulant therapy when appropriate, usually a direct thrombin inhibitor; either argatroban or bivalirudin. Other conditions also mimic DIC, and practical guidelines for the diagnosis and management of these conditions have been recently reported.[33]

Biomarkers and Other Tests

DIC is diagnosed based on laboratory testing that can be performed in most local hospitals as routine tests, and so-called global hemostatic tests have been adopted as diagnostic criteria, although additional biomarkers are needed.[34] Other molecular markers, such as the thrombin–antithrombin complex, soluble fibrin, and prothrombin fragment 1.2, have been adopted in a proposed Japanese Society on Thrombosis and Hemostasis criteria.[35] One of the unique features of sepsis-associated coagulopathy is the suppression of fibrinolysis caused by increased plasminogen activator inhibitor-1 production, and its circulating levels have been reported to be useful markers of the severity in sepsis.[36] Suppression of fibrinolysis could also be evaluated by measuring the thrombin–antithrombin/plasmin–plasmin inhibitor complex ratio, and this ratio has been reported to be significantly higher in patients with severe sepsis.[37]

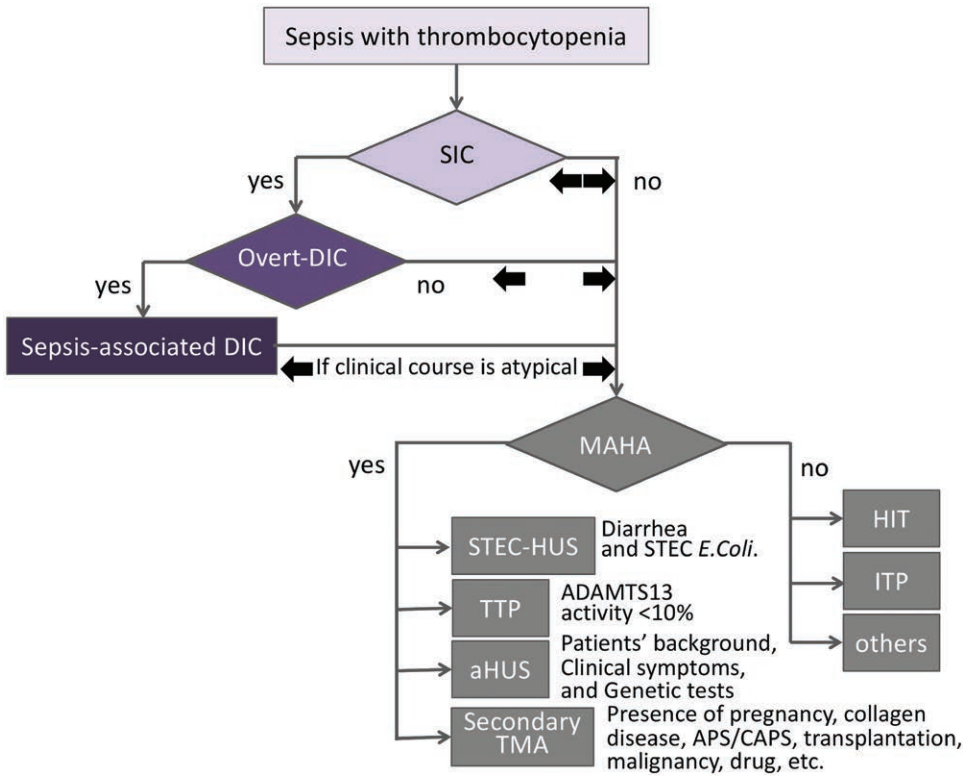

Fig. 2. The diagnostic algorithm for sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC). The presence of SIC or DIC needs to be carefully evaluated in patients with sepsis who develop thrombocytopenia. As the first step, the presence of SIC is checked by using the scoring system for SIC (table 1), and if it is determined to be present, the presence of overt DIC should be confirmed (table 1) in the second step. When neither SIC nor DIC is found to be present, thrombotic microangiopathy (TMA) and other conditions should be considered as the cause of the thrombocytopenia. As a first step, the presence of microangiopathic hemolytic anemia (MAHA: erythrocyte fragmentation, elevated lactate dehydrogenase, elevated bilirubin, decreased hemoglobin [less than 10 g/dl], and depleted haptoglobin) is examined, and if it is found to be present, the presence of thrombotic thrombocytopenic purpura (TTP), Shiga toxin-producing *Escherichia coli* (STEC)–induced hemolytic uremic syndrome (HUS), atypical HUS (aHUS), and secondary TMA should be considered. If MAHA is excluded, other conditions such as heparin-induced thrombocytopenia (HIT) and immune thrombocytopenia (ITP) should be considered. APS, antiphospholipid syndrome; CAPS, catastrophic APS.

One of the hallmarks of sepsis-induced coagulopathy is consumption of physiologic anticoagulants such as antithrombin and protein C, circulating anticoagulants that are thought to be important in the pathogenesis, and plasma levels have been reported to correlate with the disease severity.[38] The mechanisms underlying the decreases in the levels of these anticoagulants are multifactorial and include increased consumption, decreased production, and excess extravasation caused by increased vascular permeability.

Monitoring of the dynamic changes of coagulation and fibrinolysis provides information to determine the stage of the coagulation disorder, and viscoelastic testing is frequently used as a point-of-care device.[39] Thromboelastography and rotational thromboelastometry are used in managing patients with trauma-associated coagulopathy to detect fibrinolysis. In sepsis, early inhibition of plasmin activity leads to acute shutdown of fibrinolysis, and its association with increased morbidity and mortality in sepsis patients has been reported.[40] However, the usefulness of these tests remains to be established.[41] Rotational thromboelastometry correlates well with DIC scoring, and the diagnostic ability increases when combined with other biomarkers that conclude protein C levels or antithrombin.[42]

In patients with sepsis, components of the glycocalyx are shed from the vascular endothelium into the circulation. Measuring their levels in plasma has been proposed as a method for measuring endothelial damage.[43] However, the reliability of this test has not been established yet, and further work is needed.

Extracellular vesicles are other potential novel biomarkers, and leukocyte-derived extracellular vesicle count has been reported as an early and relevant biomarker of sepsis-associated coagulopathy.[44] However, the clinical relevance of such tests is hampered by the lack of standardized assay procedures.

Other important coagulation biomarkers in sepsis, including circulating damage–associated molecular patterns such as cell-free DNA and histones, have been demonstrated to influence hemostasis by promoting coagulation activation, platelet aggregation, and inhibition of fibrinolysis.[10] However, their usefulness remains to be examined.

Treatment

Critical to the management of sepsis-induced coagulopathy is the rapid and timely treatment of the underlying infection. Other strategies that have been extensively studied are directed at suppressing the prothrombotic effects. Heparin and heparinoids are the most popularly used anticoagulants for a variety of thromboembolic diseases; however, their effectiveness for treating sepsis-induced coagulopathy or DIC still are debated and generally limited to the prevention of deep vein thrombosis.

There is no globally approved therapeutic agent at present for the specific treatment of sepsis-induced coagulopathy. The effectiveness of natural anticoagulants, such as antithrombin, activated protein C, and tissue factor pathway inhibitors, have been studied in large-scale controlled trials in the early 21st century. Unfortunately, the primary goal could not be achieved in any of these trials, although it must be remembered that all of these trials targeted sepsis and not sepsis-associated coagulopathy and DIC. In contrast, *post hoc* analyses performed to examine the effects in the DIC patient subgroup showed favorable effects of antithrombin and recombinant activated protein C.[45,46] Although recombinant activated protein C has been withdrawn from the world market, the efficacy of antithrombin for septic DIC has been extensively studied in Japan, and nationwide-database studies have repeatedly demonstrated a potential survival benefit of supplemental doses of antithrombin supplementation.[47] In addition, a meta-analysis demonstrated a trend toward better survival associated with antithrombin use in septic patients with DIC.[48] However, the use of antithrombin has not been recommended in the international sepsis guidelines.[49] The important lesson to learn from these studies is that anticoagulant therapy may be expected to be beneficial for sepsis patients who developed coagulopathy but not in those without a coagulation disorder.

Although the role of fresh frozen plasma as a therapeutic approach in patients with sepsis-induced DIC may have potential theoretical benefits, there are no data supporting its application unless there is a specific therapy to treat including bleeding or factor depletion beyond antithrombin. Based on this consideration, the effect of recombinant thrombomodulin was recently examined in a multinational, randomized controlled phase III trial in sepsis patients with coagulopathy (with a platelet count less than 150 × 10^9/l and a prothrombin time ratio of more than 1.4). The 28-day mortality improved by 2.6% in a total of 800 sepsis patients, although this result was not found to reach statistical significance. It was also reported that more than 20% of the patients recovered even before the initiation of the treatment, and a subgroup analysis performed in the patients who fulfilled the entry criteria at baseline (approximately 600 cases) revealed a reduction of the 28-day all-cause mortality by 5.4%.[50] In summary, the effectiveness of natural anticoagulants has not yet been proven, and continued research is warranted.

Finally, we admit that there are some unanswered questions in this review. First, coagulopathy in sepsis is a dynamic phenomenon, with heterogeneous presentations, and we still do not have an ideal tool to assess this dynamic change in sepsis. Second, we do not have an established therapy worldwide for sepsis-induced coagulopathy at present. The above important issues should be addressed in the future.

Conclusions

Coagulopathy is an important and common complication in patients with sepsis and contributes to the development of organ dysfunction. Sepsis is a common cause of vascular injury and thrombocytopenia and can progress to DIC, which is synonymous with sepsis-induced coagulopathy. DIC is a laboratory-based diagnosis representing the decompensated status of coagulopathy that can also arise from other causes, including traumatic injury, cardiogenic shock, and multiorgan injury. Diagnosing coagulopathy in sepsis is often not established early or correctly, and there are different classifications for DIC. Recently, a two-step approach for the rapid diagnosis of DIC has been reported (table 1).[21] Other conditions in critically ill patients such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome can also occur in patients with sepsis, conditions that should be differentiated for therapy. Although the diagnosis of sepsis-induced coagulopathy is made based on the combination of hemostatic biomarkers, new candidates that would allow simpler diagnosis could emerge in the future. Continued efforts to develop new therapeutics to treat these complicated disorders and a more target-specific approach are needed. Until new therapies are developed, a multimodal approach is needed that includes timely antibiotic therapy of the underlying infection, cardiopulmonary resuscitation, and appropriate management of the underlying coagulopathy if bleeding or thrombotic sequela have occurred.

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Competing Interests

Dr. Levy serves on research steering committee data safety monitoring boards or advisory boards for CSL Behring (King of Prussia, Pennsylvania), Instrumentation Laboratories (Bedford, Massachusetts), Octapharma (Lachen, Switzerland), Leading Biosciences (Carlsbad, California), and Merck (Kenilworth, New Jersey). The other author declares no competing interests.

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References

1. Kinasewitz GT, Yan SB, Basson B, Comp P, Russell JA, Cariou A, Um SL, Utterback B, Laterre PF, Dhainaut JF; PROWESS Sepsis Study Group: Universal changes in biomarkers of coagulation and inflammation occur in patients with severe sepsis, regardless of causative micro-organism. Crit Care 2004; 8:R82–90
2. Saito S, Uchino S, Hayakawa M, Yamakawa K, Kudo D, Iizuka Y, Sanui M, Takimoto K, Mayumi T, Sasabuchi Y; Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study group: Epidemiology of disseminated intravascular coagulation in sepsis and validation of scoring systems. J Crit Care 2019; 50:23–30
3. Gando S: Role of fibrinolysis in sepsis. Semin Thromb Hemost 2013; 39:392–9
4. Delabranche X, Helms J, Meziani F: Immunohaemostasis: A new view on haemostasis during sepsis. Ann Intensive Care 2017; 7:117
5. Gropper MA: Multisystem organ failure: Predicting the future. ANESTHESIOLOGY 2007; 107:6–7
6. Iba T, Levy JH: Inflammation and thrombosis: Roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J Thromb Haemost 2018; 16:231–41
7. Østerud B, Bjørklid E: The tissue factor pathway in disseminated intravascular coagulation. Semin Thromb Hemost 2001: 27:605–17
8. Iba T, Ogura H: Role of extracellular vesicles in the development of sepsis-induced coagulopathy. J Intensive Care 2018; 6:68
9. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y, Zychlinsky A: Neutrophil extracellular traps kill bacteria. Science 2004; 303:1532–5
10. Liaw PC, Ito T, Iba T, Thachil J, Zeerleder S: DAMP and DIC: The role of extracellular DNA and DNA-binding proteins in the pathogenesis of DIC. Blood Rev 2016; 30:257–61
11. Levy JH, Sniecinski RM, Welsby IJ, Levi M: Antithrombin: Anti-inflammatory properties and clinical applications. Thromb Haemost 2016; 115:712–28
12. Iba T, Levy JH: Derangement of the endothelial glycocalyx in sepsis. J Thromb Haemost 2019; 17:283–94
13. Muth H, Maus U, Wygrecka M, Lohmeyer J, Grimminger F, Seeger W, Günther A: Pro- and antifibrinolytic properties of human pulmonary microvascular *versus* artery endothelial cells: Impact of endotoxin and tumor necrosis factor-α. Crit Care Med 2004; 32:217–26
14. Gando S, Levi M, Toh CH: Disseminated intravascular coagulation. Nat Rev Dis Primers 2016; 2:16037
15. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH): Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001; 86:1327–30
16. Iba T, Umemura Y, Watanabe E, Wada T, Hayashida K, Kushimoto S; Japanese Surviving Sepsis Campaign Guideline Working Group for disseminated intravascular coagulation: Diagnosis of sepsis-induced disseminated intravascular coagulation and coagulopathy. Acute Med Surg 2019; 6:223–32
17. Scully M, Levi M: How we manage haemostasis during sepsis. Br J Haematol 2019; 185:209–18
18. Hunt BJ: Bleeding and coagulopathies in critical care. N Engl J Med 2014; 370:2153
19. Iba T, Levy JH, Thachil J, Wada H, Levi M; Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis: The progression from coagulopathy to disseminated intravascular coagulation in representative underlying diseases. Thromb Res 2019; 179:11–4
20. Iba T, Gando S, Thachil J: Anticoagulant therapy for sepsis-associated disseminated intravascular coagulation: The view from Japan. J Thromb Haemost 2014; 12:1010–9
21. Iba T, Levy JH, Yamakawa K, Thachil J, Warkentin TE, Levi M: Proposal of a two-step process for the diagnosis of sepsis-induced disseminated intravascular coagulation. J Thromb Haemost 2019; 17:1265–8
22. Iba T, Arakawa M, Di Nisio M, Gando S, Anan H, Sato K, Ueki Y, Levy JH, Thachil J: Newly proposed sepsis-induced coagulopathy precedes international society on thrombosis and haemostasis overt-disseminated intravascular coagulation and predicts high mortality. J Intensive Care Med 2018; 1:885066618773679
23. Yamakawa K, Yoshimura J, Ito T, Hayakawa M, Hamasaki T, Fujimi S: External validation of the two

newly proposed criteria for assessing coagulopathy in sepsis. Thromb Haemost 2019; 119:203–12
24. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, Cheung B, Machin SJ; British Committee for Standards in Haematology: Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol 2012; 158:323–35
25. Saha M, McDaniel JK, Zheng XL: Thrombotic thrombocytopenic purpura: Pathogenesis, diagnosis and potential novel therapeutics. J Thromb Haemost 2017; 15:1889–900
26. Talarico V, Aloe M, Monzani A, Miniero R, Bona G: Hemolytic uremic syndrome in children. Minerva Pediatr 2016; 68:441–55
27. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, Bingham C, Cohen DJ, Delmas Y, Douglas K, Eitner F, Feldkamp T, Fouque D, Furman RR, Gaber O, Herthelius M, Hourmant M, Karpman D, Lebranchu Y, Mariat C, Menne J, Moulin B, Nürnberger J, Ogawa M, Remuzzi G, Richard T, Sberro-Soussan R, Severino B, Sheerin NS, Trivelli A, Zimmerhackl LB, Goodship T, Loirat C: Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med 2013; 368:2169–81
28. Noris M, Mescia F, Remuzzi G: STEC-HUS, atypical HUS and TTP are all diseases of complement activation. Nat Rev Nephrol 2012; 8:622–33
29. Warkentin TE: Clinical picture of heparin-induced thrombocytopenia (HIT) and its differentiation from non-HIT thrombocytopenia. Thromb Haemost 2016; 116:813–22
30. Warkentin TE, Greinacher A, Gruel Y, Aster RH, Chong BH; Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis: Laboratory testing for heparin-induced thrombocytopenia: A conceptual framework and implications for diagnosis. J Thromb Haemost 2011; 9:2498–500
31. Greinacher A, Selleng K, Warkentin TE: Autoimmune heparin-induced thrombocytopenia. J Thromb Haemost 2017; 15:2099–114
32. Warkentin TE: Ischemic limb gangrene with pulses. N Engl J Med 2015; 373:642–55
33. Iba T, Levy JH, Wada H, Thachil J, Warkentin TE, Levi M; Subcommittee on Disseminated Intravascular Coagulation: Differential diagnoses for sepsis-induced disseminated intravascular coagulation: Communication from the SSC of the ISTH. J Thromb Haemost 2019; 17:415–9
34. Iba T, Ito T, Maruyama I, Jilma B, Brenner T, Müller MC, Juffermans NP, Thachil J: Potential diagnostic markers for disseminated intravascular coagulation of sepsis. Blood Rev 2016; 30:149–55
35. Asakura H, Takahashi H, Uchiyama T, Eguchi Y, Okamoto K, Kawasugi K, Madoiwa S, Wada H; DIC Subcommittee of the Japanese Society on Thrombosis and Hemostasis: Proposal for new diagnostic criteria for DIC from the Japanese Society on Thrombosis and Hemostasis. Thromb J 2016; 14:42
36. Gando S, Kameue T, Nanzaki S, Nakanishi Y: Disseminated intravascular coagulation is a frequent complication of systemic inflammatory response syndrome. Thromb Haemost 1996; 75:224–8
37. Kidokoro A, Iba T, Fukunaga M, Yagi Y: Alterations in coagulation and fibrinolysis during sepsis. Shock 1996; 5:223–8
38. Fourrier F, Chopin C, Goudemand J, Hendrycx S, Caron C, Rime A, Marey A, Lestavel P: Septic shock, multiple organ failure, and disseminated intravascular coagulation: Compared patterns of antithrombin III, protein C, and protein S deficiencies. Chest 1992; 101:816–23
39. Lancé MD: A general review of major global coagulation assays: Thrombelastography, thrombin generation test and clot waveform analysis. Thromb J 2015; 13:1
40. Schmitt FCF, Manolov V, Morgenstern J, Fleming T, Heitmeier S, Uhle F, Al-Saeedi M, Hackert T, Bruckner T, Schöchl H, Weigand MA, Hofer S, Brenner T: Acute fibrinolysis shutdown occurs early in septic shock and is associated with increased morbidity and mortality: Results of an observational pilot study. Ann Intensive Care 2019; 9:19
41. Drumheller BC, Stein DM, Moore LJ, Rizoli SB, Cohen MJ: Thromboelastography and rotational thromboelastometry for the surgical intensivist: A narrative review. J Trauma Acute Care Surg 2019; 86:710–21
42. Favaloro EJ: Laboratory testing in disseminated intravascular coagulation. Semin Thromb Hemost 2010; 36:458–67
43. Schmidt EP, Overdier KH, Sun X, Lin L, Liu X, Yang Y, Ammons LA, Hiller TD, Suflita MA, Yu Y, Chen Y, Zhang F, Cothren Burlew C, Edelstein CL, Douglas IS, Linhardt RJ: Urinary glycosaminoglycans predict outcomes in septic shock and acute respiratory distress syndrome. Am J Respir Crit Care Med 2016; 194:439–49
44. Delabranche X, Quenot JP, Lavigne T, Mercier E, François B, Severac F, Grunebaum L, Mehdi M, Zobairi F, Toti F, Meziani F, Boisramé-Helms J; on behalf to the Clinical Research in Intensive Care and Sepsis Network: Early detection of disseminated intravascular coagulation during septic shock: A multicenter prospective study. Crit Care Med 2016; 44:e930–9
45. Dhainaut JF, Yan SB, Joyce DE, Pettilä V, Basson B, Brandt JT, Sundin DP, Levi M: Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. J Thromb Haemost 2004; 2:1924–33
46. Kienast J, Juers M, Wiedermann CJ, Hoffmann JN, Ostermann H, Strauss R, Keinecke HO, Warren BL,

Opal SM; KyberSept investigators: Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. J Thromb Haemost 2006; 4:90–7

47. Tagami T, Matsui H, Horiguchi H, Fushimi K, Yasunaga H: Antithrombin and mortality in severe pneumonia patients with sepsis-associated disseminated intravascular coagulation: An observational nationwide study. J Thromb Haemost 2014; 12:1470–9
48. Wiedermann CJ: Antithrombin concentrate use in disseminated intravascular coagulation of sepsis: Meta-analyses revisited. J Thromb Haemost 2018; 16:455–7
49. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP: Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017; 43:304–77
50. Vincent JL, Francois B, Zabolotskikh I, Daga MK, Lascarrou JB, Kirov MY, Pettilä V, Wittebole X, Meziani F, Mercier E, Lobo SM, Barie PS, Crowther M, Esmon CT, Fareed J, Gando S, Gorelick KJ, Levi M, Mira JP, Opal SM, Parrillo J, Russell JA, Saito H, Tsuruta K, Sakai T, Fineberg D: Effect of a recombinant human soluble thrombomodulin on mortality in patients with sepsis-associated coagulopathy: The SCARLET randomized clinical trial. JAMA 2019; 321:1993–2002