Disseminated Intravascular Coagulation

Benjamin M. Boral, DO,[1] Dennis J. Williams, MD,[2] and Leonard I. Boral, MD, MBA[2]

From the Departments of [1]Medicine and [2]Pathology and Laboratory Medicine, University of Kentucky Medical Center, Lexington.

Key Words: Coagulopathy; DIC; Thrombi; Hemorrhage; Thrombocytopenia; Thrombin

Am J Clin Pathol December 2016;146:670-680

DOI: 10.1093/AJCP/AQW195

ABSTRACT

Objectives: *To provide a review of the definition, pathophysiology, differential diagnosis, and treatment of disseminated intravascular coagulation (DIC).*

Methods: *A case scenario and a review of the literature related to the pertinent facts concerning DIC are provided.*

Results: *DIC is a systemic pathophysiologic process and not a single disease entity, resulting from an overwhelming activation of coagulation that consumes platelets and coagulation factors and causes microvascular fibrin thrombi, which can result in multiorgan dysfunction syndrome from tissue ischemia. Some conditions associated with acute DIC include septic shock, exsanguinating trauma, burns, or acute promyelocytic leukemia.*

Conclusions: *The massive tissue factor stimulus results in excess intravascular thrombin, which overcomes the anticoagulant systems and leads to thrombosis. Because of consumption of coagulation factors and platelets, DIC also has a hemorrhagic phase. Treatment of the bleeding patient with DIC is supportive with the use of blood components.*

Case History

A 44-year-old man with a medical history of hepatitis C, cirrhosis, and chronic kidney disease sought treatment at the emergency room for altered mental status and an ammonia level over 400 μmol/L (11-51 μmol/L). The patient was given lactulose; however, his mental status worsened to a point where he required intubation. Vital signs on admission to the intensive care unit (ICU) on October 23 were as follows: blood pressure, 120/84 mm Hg; heart rate, 107 beats/min; respiratory rate, 18/min; and temperature, 97.8°F. The following laboratory results were obtained (reference range is in parentheses) on admission: WBC, 20.1 × 10^9/L (3.7-10.3 × 10^9/L); sodium, 111 mmol/L (136-145 mmol/L); potassium, 5.7 mmol/L (3.7-4.8 mmol/L); hemoglobin (Hb), 13.5 g/dL (13.7-17.5 g/dL in males); platelet count, 253 × 10^9/L (155-369 × 10^9/L); international normalized ratio (INR), 1.4 (0.9-1.2); prothrombin time (PT), 13.5 seconds (9.6-12.5 seconds); activated thromboplastin time (aPTT), 34 seconds (19-30 seconds); and creatinine, 5.8 mg/dL (0.8-1.3 mg/dL). On October 23, the patient was started on vancomycin, piperacillin/tazobactam, and fluids because of concern for sepsis associated with systemic inflammatory response syndrome and multiorgan failure, as well as laboratory values showing a high WBC count and an elevated lactate of 8 mmol/L (0.5-1.6 mmol/L). His vital signs worsened over the next 24 hours, and he became hypotensive, requiring treatment with norepinephrine and 6 L of normal saline on October 24. His renal function continued to decline, for which he received continuous renal replacement therapy on October 25. Laboratory values on October 25 were consistent with DIC, showing a significant decrease in hemoglobin, fibrinogen, and platelets and an increase in PT, aPTT, INR, and lactate dehydrogenase (LDH) **Table 1**. Petechiae were not present. A paracentesis was performed to rule out peritoneal bleeding, and red fluid (shown to be RBCs in the laboratory) was noted on the tap. It was felt that the patient had

Table 1
Summary of Patient Laboratory Data Related to Disseminated Intravascular Coagulation

Characteristic	Date							
	October 23	October 24	October 25	October 26	October 27	October 28	October 29 to November 3	November 4
Laboratory values (reference range)								
WBC count (3.7-10.3), $\times 10^9$/L	20.1	10	8	9	6	8	5-18	24.2
Hemoglobin (13.7-17.5), g/dL	13.5	7.7	6.7	7.7	7.9	8.1	7.5-9.8	5.8
Platelet count (155-369), $\times 10^9$/L	253	81	34	61	67	64	40-52	31
International normalized ratio (0.9-1.2)[a]	1.4	2	2.6	1.4	1.6	1.6	1.7-2.1	5.9
Prothrombin time (9.6-12.5), s[a]	13.5	19.4	25.9	14.2	13.9	13.9	15.8-22	36
Activated partial thromboplastin time (19-30), s	34		>160		41		42-49	>160
Fibrinogen (150-450), mg/dL			66		176			82
Lactate (0.5-1.6), mmol/L	8						2.0-2.5	12
pH (7.35-7.45)	7.18	7.02	7.32	7.42	7.48	7.5	7.4- 7.45	6.77
Lactate dehydrogenase (140-280), U/L			412	262	207			
Creatinine (0.8-1.30), mg/dL	5.8	6.4	2.5	1.7	1.16	1.1	1.1-4.0	5.24
Blood products, No.								
RBC units			3				None	0
Fresh-frozen plasma units			2			2	None	2
Apheresis platelet units			3				None	1
Cryoprecipitate units			10				None	10

[a]Note that the prothrombin time reagent contains a heparin neutralizer.

developed spontaneous multifocal hemoperitoneum secondary to his DIC, and he was given packed RBCs, fresh-frozen plasma, cryoprecipitate, platelets, and vitamin K to treat his peritoneal bleeding, which stopped by October 26. Over the next few days, he continued to require norepinephrine, but eventually his vital signs and laboratory values stabilized. During the next few days, he clinically seemed to improve, but he was found to have multiple infections, including a blood culture growing vancomycin-resistant enterococcus (VRE), a protected alveolar lavage growing *Stenotrophomonas maltophilia* and VRE, a peritoneal fluid growing *Acinetobacter*, and a urinalysis growing *Candida glabrata*. On October 29, he was started on daptomycin, linezolid, trimethoprim/sulfamethoxazole, and fluconazole to treat his current infections, and his vancomycin and piperacillin/tazobactam were discontinued. He remained hemodynamically stable, so he was taken off pressors and extubated on November 1. He was in the process of being transferred out of the ICU, but unfortunately overnight the patient became obtunded and hypotensive. The following laboratory values (reference range) were obtained shortly after midnight on November 4: INR, 2.6 (0.9-1.2); PT, 25.9 seconds (9.6-12.5 seconds); aPTT, 44 seconds (19-30 seconds); Hb, 5.8 g/dL (13.7-17.5 g/dL); platelet count, 34 $\times$ 10^9/L (155-369 $\times$ 10^9/L); D-dimer, 8.6 mg/L (<1.5 mg/L); and fibrinogen, 53 mg/dL (150-450 mg/dL). The diagnosis of DIC with a rebleed of the peritoneum was made. Fresh-frozen plasma, cryoprecipitate, platelets, and packed RBCs were ordered, but the patient went into cardiac arrest and died before all of the blood products could be given (Table 1).

Case questions:

1. How does normal hemostasis occur?
2. What is the definition of DIC?
3. How does acute DIC differ from chronic DIC?
4. What is the pathophysiology of DIC?
5. What are the conditions predisposing to DIC?
6. What is the differential diagnosis for DIC?
7. How is DIC treated?

Normal Hemostasis

To understand DIC, it is best to first review the normal physiology of clot formation. Normal hemostasis is a localized process that results in a primary platelet plug through platelet adhesion and aggregation followed by a secondary fibrin clot through the activation of the coagulation cascade, which occurs in a series of enzymatic steps that lead to the formation of thrombin. Thrombin then converts soluble fibrinogen to an insoluble clot of fibrin polymers, which forms a mesh that incorporates the previously formed platelet plug as well as RBCs, if present. Traditionally, this secondary hemostasis coagulation cascade was thought to be initiated either through tissue factor (TF) release into the bloodstream, which activates factor VII and then the extrinsic system, or through disruption of the endothelium exposing collagen and the subendothelium directly to blood. This results in platelet aggregation, which in the past was thought to activate factor XII in vivo and subsequently the rest of the intrinsic (contact) cascade **Figure 1**.

DOI: 10.1093/ajcp/aqw195

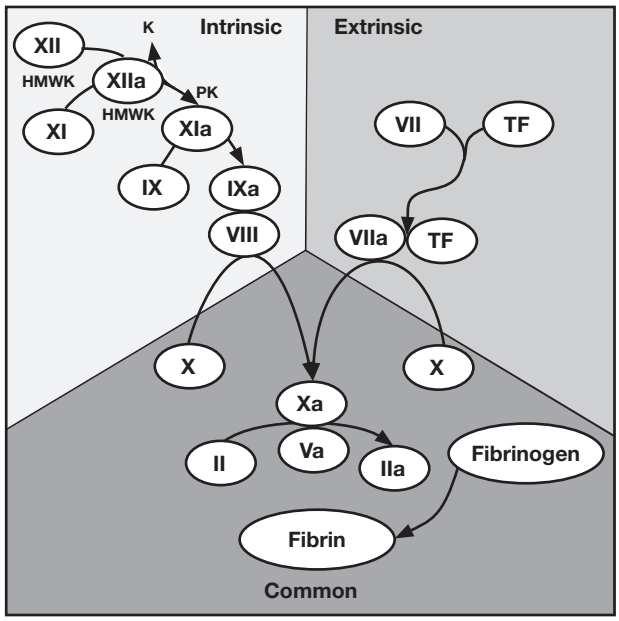

Figure 1 The coagulation cascade showing coagulation factor activation in plasma: intrinsic, extrinsic, and common pathways. a, activated factor; HMWK, high molecular weight kininogen; II, prothrombin; IIa, thrombin; K, kallikrein; PK, prekallikrein; TF, tissue factor.

Today, it is thought that in vivo secondary hemostasis takes place mainly through TF activation of the cell-based system, even where there is breakdown of the endothelium.[1] Here, TF, considered to be part of most cell membrane lipoproteins, is either released upon damage of a cell, including the endothelial cells, or secreted into the blood by platelets and/or monocytes after stimulation. Factor VII is then activated, and through a series of enzyme reactions proceeding on cell membranes involving the activation of several coagulation factors (X, IX, XI, and prothrombin), thrombin is formed and subsequently a fibrin clot. Factors V and VIII are nonenzyme catalysts in this model, and factor XII is not part of this new coagulation in vivo system. The major roles of the contact system (factor XII, high molecular weight kininogen [HMWK], and prekallikrein [PK]) are to enhance the inflammatory response by stimulating chemotaxis in neutrophils and activating C1, C3, and C5 in the complement system and to promote vascular repair. HMWK can be enzymatically altered by factor XIIa, factor XIa, and/or kallikrein to produce bradykinin, a vasoactive agent causing vascular dilation, increased vascular permeability (as seen in inflammation), and endothelial cells to release tissue plasminogen activator (TPA). Therefore, the activation of factor XII in vivo is thought to be primarily associated with inflammation and vascular repair rather than coagulation. On the other hand, in the test tube (in vitro), the plasma-based coagulation test, aPTT, will be very prolonged if there is a

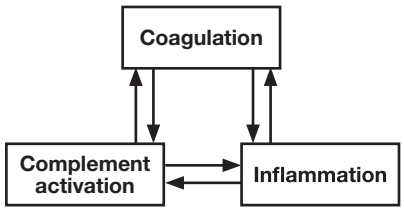

Figure 2 Generalized interrelationship between the initiation of coagulation, complement activation, and the inflammatory response.

deficiency of factor XII. Factor XII is needed in the first step (contact) of the intrinsic coagulation pathway in vitro but is thought to play a minor role, if any, in normal physiologic clot formation in vivo. However, because of prevention of pathologic thrombus formation in factor XII–deficient mice, factor XII may play a role in the pathologic propagation and stabilization of fibrin thrombi in ischemic strokes and pulmonary emboli.[2] Factor XII inhibition is under investigation as a possible anticoagulant therapy that would not increase the risk of bleeding.[3]

Once a fibrin clot is produced, it is stabilized by covalent cross-linking through the actions of factor XIII. The last step of the healing process is for blood clots to be reorganized and resorbed by fibrinolysis so that unimpeded blood flow through the originally damaged vessel can be reestablished. The plasma protein plasminogen, the inactive precursor to the active fibrinolysis agent plasmin, is bound to fibrinogen and fibrin so that it is incorporated into clots. When endothelial cells are injured, they release TPA, which causes the plasminogen in clots to convert to plasmin and digest the cross-linked fibrin clot to form soluble fibrin degradation products. Any free circulating plasmin is rapidly inactivated by plasma α2-antiplasmin, made in the liver, and plasminogen activator inhibitor 1 (PAI-1), from endothelial cells, inhibits TPA activity.[1]

There is a generalized interrelationship between the initiation of coagulation, complement activation, and the inflammatory response, so that when one is activated, the others are stimulated as well **Figure 2**. They interact through a mechanism known as "crosstalk," as shown in **Figure 3**.[4]

Essentially, primary hemostasis (platelet aggregation) stimulates secondary hemostasis (the coagulation factor cascade) through TF/factor VIIa as well as inflammation through the factor XIIa/kallikrein/bradykinin/C3a mechanism.[4] Complement can then lyse cells and/or bacteria, which release damage-associated molecular patterns (DAMPs) and/or pathogen-associated molecular patterns (PAMPs) as well as phospholipids, which all can stimulate secondary hemostasis. DAMPs are warning signals that cell damage has occurred, and DAMP receptors, when activated, cause cellular

DOI: 10.1093/ajcp/aqw195

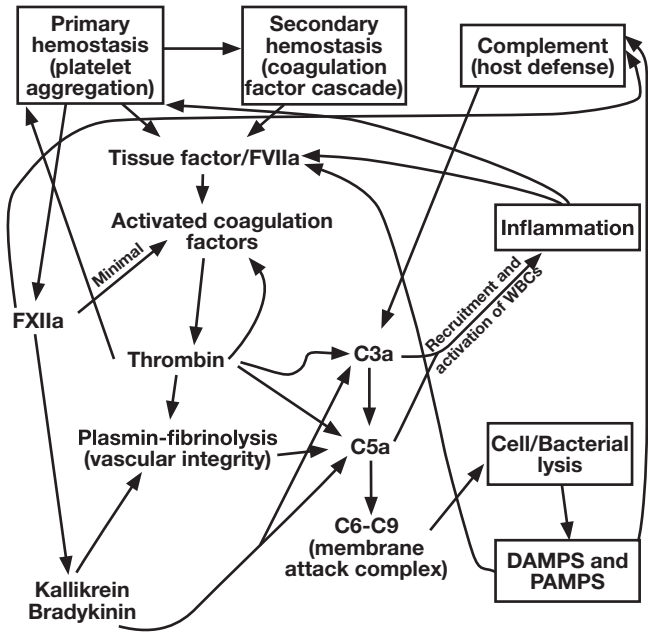

Figure 3 Crosstalk between coagulation, complement activation, and inflammation. Modified from Kurosawa S and Stearns-Kurosawa DJ.[4] a, activated factor; DAMPS, damage-associated molecular patterns; PAMPS, pathogen-associated molecular patterns.

signaling pathways to initiate physiologic actions resulting in damage containment and repair, which include inflammatory, immune, and coagulation responses. A subset of DAMPs is PAMPs consisting of microbial molecules that alert multicellular animals to the presence of invading organisms. PAMPs are detected by the immune system through Toll-like receptors, which activate signaling cellular pathways, creating both an inflammatory and an immune response. The immune response produces specific antibodies and specific T cells to destroy the intruding pathogens while the inflammatory response is more general in nature.[5] Both thrombin and plasmin can stimulate C5a to create more cell lysis.

DIC

Definition and Background

In 2001, the International Society on Thrombosis and Hemostasis (ISTH) proposed a definition of DIC that included microvascular thrombosis: "DIC is an acquired syndrome characterized by the intravascular activation of coagulation without a specific localization and arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction."[6]

In response to an injury to the blood vessel wall, clotting occurs only as a localized phenomenon, as part of normal healing, because there are many checks and balances to prevent extension of the hemostatic plug mechanism to the whole intravascular system. The pathophysiology of DIC, in simple terms, is that the underlying disease stimulates such a strong procoagulant activity that it results in an excess of thrombin, which then overcomes the anticoagulant control mechanisms of protein C (PrC), antithrombin (AT), and the tissue factor pathway inhibitor (TFPI), allowing thrombosis to freely take place throughout the vasculature.[1] In DIC, there is a battle between the excess thrombin state, which clinically manifests itself as thrombosis, embolism, and microvascular occlusion by fibrin thrombi, leading to multiorgan dysfunction syndrome (MODS) from tissue ischemia, and a hemorrhagic disorder from depletion of platelets, consumption of coagulation factors, and/or accelerated plasmin formation.[7] Both thrombosis and bleeding can be present in the same patient. DIC is a manifestation/symptom/sign of an underlying pathologic process, as is fever, and is not a specific disease entity. If the causative disease or condition is successfully treated, the DIC will disappear.

Laboratory abnormalities in this "consumption coagulopathy" include prolonged aPTT and PT/INR, a decrease in platelet count and in fibrinogen, and an increase in fibrin degradation products, including D-dimers (plasmin degradation of cross-linked fibrin).

In the older literature, DIC was also known as defibrination syndrome, acquired afibrinogenemia, consumptive coagulopathy, and thrombohemorrhagic disorder.[1]

Maladies resulting in both thrombosis and hemorrhage have been recognized for centuries, the foremost of which were the "black plague" of the Middle Ages with symptoms of gangrene of the fingers as well as generalized hemorrhage in organs. It remains controversial as to whether the cause of this plague was from *Yersinia pestis*, spread by the bites of the rat flea, or from an Ebola-like hemorrhagic virus.[8]

DIC was first experimentally induced by M. Dupuy in 1834 when he intravenously injected brain tissue into animals, resulting in clots seen throughout the vasculature. In 1873, B. Naunyn intravenously injected dissolved RBCs and observed disseminated thrombosis. A. Trousseau in 1865 described in patients with advanced malignancy, the multiple thromboses, and tendency of blood to clot. In 1961, Lasch et al introduced the concept of consumption coagulopathy as the mechanism leading to hemorrhage in DIC.[1]

DIC is relatively uncommon in the general hospitalized patient but accounts for 9% to 19% of ICU admissions and has a high mortality rate of 45% to 78%.[9]

Acute vs Chronic DIC

Acute DIC is a consumption coagulopathy state where excess thrombin is generated to such a high degree that it

DOI: 10.1093/ajcp/aqw195

overcomes the large amounts of natural anticoagulants normally present in the plasma.[10] Acute DIC is usually triggered by large amounts of tissue factor released into the intravascular space, leading to generalized deposition of fibrin thrombi in the microvasculature contributing to multiorgan dysfunction.[10,11] MODS most frequently involves the lungs and kidneys followed by brain, heart, liver, spleen, adrenals, pancreas, and the gastrointestinal (GI) tract.[10]

Thrombin has the following general procoagulant actions[12] (see Figure 1):

1. Converts fibrinogen to fibrin
2. Activates factors V, VIII, and XI to stimulate further thrombin formation
3. Activates factor XIII to stimulate fibrin cross-linking
4. Causes platelet aggregation, which induces the coagulation cascade system to generate even more thrombin

These actions of thrombin cause more activation of coagulation factors, resulting in the production of more thrombin and therefore more fibrin clot. This ultimately leads to fibrinolysis, in which fibrin thrombi are broken down by plasmin with the subsequent release of fibrin degradation products (FDPs). When intravascular, these FDPs can inhibit fibrin polymerization as well as platelet aggregation by interfering with the GPIIbIIIa fibrinogen receptor.[7] These FDPs, in concert with the consumption of platelets, fibrinogen, and coagulation factors, contribute to the most common symptom seen in acute DIC: bleeding.

Other thrombin-induced situations enhance clot formation activities in DIC. Thrombin proteolytically cleaves a class of extracellular G-protein-coupled receptors on the platelet called protease-activated receptors (PARS), which then converts the stimulus into intracellular signaling events that include release of interleukins (ILs): IL-1 and IL-6. This leads to proinflammatory activity with an increase in platelet activation and leukocyte adhesion.[13] Thrombin causes release of PAI-1 from endothelial cells and activates thrombin-activatable fibrinolysis inhibitor (TAFI) in the plasma, both of which impair plasminogen activation, thereby reducing clot dissolution from plasmin. In addition, DIC causes the consumption of AT and the downregulation of the PrC system, diminishing the ability of the body to turn thrombin off. AT production can be diminished as a consequence of hepatic MODS and can be degraded by enzymes released from neutrophils. TFPI may also be reduced in DIC.

Shock often occurs in DIC and can lead to impaired clearance of tissue factor, activated coagulation factors, and FDP by the reticuloendothelial system macrophages of the spleen and liver, thereby perpetuating the DIC.[7] Shock could be caused by the excessive stimulation of the contact system (factor XII, HMWK, and PK), resulting in large amounts of bradykinin production, which cannot be inhibited by the presence of normal concentrations of angiotensin-converting enzyme. Shock is probably responsible for the hyperfibrinolysis syndrome by endothelial cell release of TPA from and the amplification of the PrC system when there is hypoperfusion of endothelial cells. In many situations, the hyperfibrinolysis syndrome occurs in the later stages of DIC, but in acute traumatic coagulopathy, hyperfibrinolysis usually occurs in the early phase of trauma, giving rise to hypercoagulability in the later phases because of sustained increase in PAI-1.[14]

Acute DIC results in rapid consumption of platelets and coagulation factors so that at the time of diagnosis, the platelet count may be less than 50,000/μL (10%-15% of cases), the PT and aPTT may be extremely prolonged, and the D-dimers are high.[10,15] However, it is important to keep in mind that the aPTT and, less often, the PT may be minimally prolonged. The platelet-poor plasma tests, PT and aPTT, both reflect the level of factors in the common pathway of coagulation: factors X, V, and II (prothrombin) and fibrinogen (see Figure 1). This is the pathway "common" to both the extrinsic and intrinsic systems that result in the activation of thrombin and conversion of fibrinogen to fibrin. In addition, the PT reflects the level of factor VII in the extrinsic pathway. In this pathway, factor VII is activated by tissue factor, which then proceeds through the common pathway, leading to activation of thrombin and fibrin clot formation. In addition, the aPTT measures the intrinsic pathway, which includes factors XII, XI, IX, and VIII. In this pathway, factor XII is activated by collagen or polyphosphate, which eventually leads to the activation of the common pathway and fibrin clot formation. The PT and aPTT are both prolonged in DIC because they contain coagulation factors that have been consumed: factor V, factor VIII, and fibrinogen.

In acute DIC, thrombin's activity is also enhanced because of the decrease in antithrombin from (1) consumption of AT, (2) degradation of AT from the release of neutrophil elastase, and (3) decreased production of AT by the liver because of microvascular thrombosis. In addition, the PrC pathway of thrombin inactivation is diminished by downregulation of thrombomodulin by the proinflammatory cytokines tumor necrosis factor α, IL-1, and IL-6 as well as by a decrease in free protein S secondary to protein S being bound to the increased complement C4b-binding protein, an acute phase reactant.[1] The proinflammatory cytokines induce endothelial cells to release PAI-1. The capillary endothelial cell is the mediator for the bidirectional crosstalk between the coagulation and inflammatory systems.[13]

D-dimers are a specific type of fibrin degradation product consisting of polymerized fibrin monomers that have been cross-linked by activated factor XIII and subsequently cleaved by plasmin.[15] Hence, D-dimers are only produced when three enzymes are functioning: thrombin, factor XIIIa, and plasmin. D-dimers are therefore created after intravascular coagulation

DOI: 10.1093/ajcp/aqw195

and clot formation have recently occurred. D-dimers are increased in a number of conditions in which clot formation occurs, including arterial or venous thrombosis, preeclampsia, eclampsia, and DIC. However, D-dimers may also be produced during extravascular coagulation and clot formation and are commonly elevated in hospitalized patients without overt intravascular thrombosis. Such scenarios include trauma, surgery, healing, and inflammation. Elevated levels of D-dimers may also be seen in severe liver disease due to decreased clearance of the D-dimers. The absence of D-dimers is especially useful as a negative predictive tool to exclude a diagnosis of DIC. Elevated levels are useful in helping confirm an already suspected diagnosis of DIC.

Chronic DIC may develop when the body is exposed to smaller amounts of thrombin for prolonged periods (ie, malignancy, metastasis, intrauterine fetal death, vasculitis, aneurysms, hemangiomas, and large areas of healing such as a thigh or retroperitoneal hematoma).[10] While coagulation factors and platelets are consumed, it is not as brisk as that seen in acute DIC, and the body is able to partially compensate through increased production of coagulation factors, platelets, antithrombin, and antiplasmin. In addition, FDPs are still efficiently cleared by the liver. Therefore, thrombosis typically dominates bleeding in chronic DIC, and shock is often not present in this setting. In fact, there may be no symptoms, and the PT and aPTT may be only slightly prolonged or normal, making the laboratory diagnosis of DIC confusing. The platelet count is typically only mildly decreased in chronic DIC.

Acute DIC is initially a hypercoagulable state where fibrin thrombi are formed in arterioles and capillaries, often resulting in ischemia and multiorgan failure. As RBCs are pushed through these compromised tiny vessels in the microvasculature, they become fragmented to form schistocytes (broken RBCs; **Image 1**), resulting in microangiopathic hemolytic anemia (MAHA). Acute DIC is therefore a thrombotic MAHA because there is thrombocytopenia in addition to schistocyte formation. The free hemoglobin released in this hemolytic process enhances the hypercoagulable state by combining with nitric oxide (endothelial relaxing factor). The removal of intravascular nitric oxide by free hemoglobin can cause vasospasm and platelet activation. Other abnormal tests in acute DIC are related to hemolysis and include increased serum LDH and hyperbilirubinemia.

The major conditions associated with acute DIC can be seen in **Table 2**. Clinical manifestations of acute DIC can present in many ways, but the most common are petechia/purpura, altered mental status, general malaise, internal organ and/or mucosal/skin bleeding, and hypotension. The diagnosis of DIC is made through a constellation of factors, including medical history, general signs and symptoms, and laboratory tests. There is no single test to diagnose DIC. See **Table 3** for coagulation-related laboratory test results in DIC.

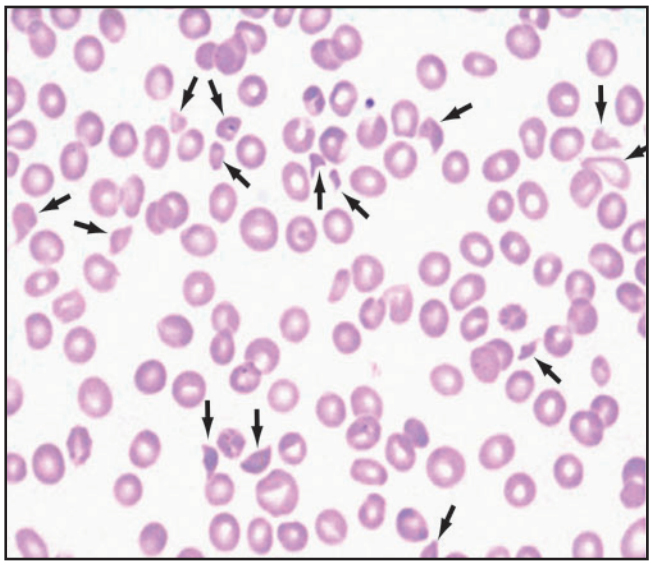

Image 1 Schistocytes on peripheral blood smear ×100. Up to three schistocytes per high-power field is normal. Arrows show more than 10 schistocytes per high-power field. Picture taken with oil emersion lens at ×100.

Table 2
Major Conditions Often Associated With Acute Disseminated Intravascular Coagulation

Condition
Infection—gram-negative septic shock, *Rickettsia* (ticks), gram-positive bacteria, fungi, viruses, malaria
ABO-incompatible transfusion reaction
Acute pancreatitis
Septic abortion, amniotic fluid embolism
Acute promyelocytic leukemia
Brain injury
Trauma and crush injury
Burns
Hypothermia/hyperthermia
Fat emboli
Vascular tumors
Snake bite venom
Transplant rejection

For those clinicians not experienced in making the diagnosis of DIC, there are two popular algorithms available to help. The ISTH has a DIC scoring system related to whether there is an underlying disorder known to cause DIC, the degree of thrombocytopenia, the level of fibrinogen, the level of PT prolongation, and whether there are elevated fibrin-related markers.[6]

The proposed acute DIC diagnostic algorithm by the Scientific Subcommittee on DIC of the ISTH is seen in **Table 4**.[6] This algorithm requires that the patient has a

DOI: 10.1093/ajcp/aqw195

Table 3
Coagulation-Related Laboratory Results in DIC[a]

Test	Results
Platelet count	Decreased—consumed
Activated partial thromboplastin time	Prolonged
Prothrombin time	Prolonged
Thrombin time	Prolonged—due to low fibrinogen and elevated D-dimer
Fibrinogen	Decreased—consumed
Coagulation factors	Decreased—consumed
Fibrin degradation products	Increased
D-dimer	Increased
Thrombin generation markers	Increased
Antithrombin	Decreased—consumed
Protein C	Decreased—consumed
Protein S	Decreased—consumed
Thrombomodulin, endothelial	Decreased by neutrophil elastase + proinflammatory cytokines
TPA trauma	Early DIC—increased Late DIC—decreased
PAI-1 trauma	Early DIC—low levels Late DIC—elevated

DIC, disseminated intravascular coagulation; PAI-1, plasminogen activator inhibitor 1; TPA, tissue plasminogen activator.
[a]Typically, the only coagulation laboratory tests routinely performed to evaluate for DIC are platelet count, prothrombin time, Activated partial thromboplastin time, fibrinogen, and D-dimer.

Table 4
Acute DIC Algorithm Proposed by the International Society on Thrombosis and Haemostasis[a]

Algorithm
1. Presence of an underlying disorder known to be associated with DIC? If yes: proceed. If no: do not use this algorithm
2. Global coagulation results:
a. Platelet count (>100,000/μL = 0, <100,000/μL = 1, <50,000/μL = 2)
b. Fibrin degradation products such as D-dimer (no increase = 0, moderate increase = 2, strong increase = 3)
c. Prolonged prothrombin time (<3 seconds = 0, >3 seconds = 1, >6 seconds = 2)
d. Fibrinogen level (>1.0 g/L = 0; <1.0 g/L = 1)

DIC, disseminated intravascular coagulation.
[a]Interpretation of algorithm: A score of 5 or higher is compatible with acute DIC. The algorithm can be repeated on occasion if acute DIC remains a consideration and the laboratory values change. Modified from Taylor et al.[6]

disease known to be associated with DIC and uses common coagulation tests. This ISTH DIC algorithm has been shown to be 93% sensitive and 97% specific for the diagnosis of overt (acute) DIC.[16]

Another acute DIC algorithm has been proposed by the Japanese Association for Acute Medicine. The scoring system is based on whether the systemic inflammatory response syndrome is present, the degree of thrombocytopenia, the amount of elevation in fibrin degradation products, and whether the INR is more than 1.2. Diseases in the differential diagnosis for acute DIC must first be excluded (see next section).[17]

Differential Diagnosis of DIC

Other Forms of Thrombotic MAHA

Besides acute DIC, the following diseases are considered to be part of the thrombotic MAHA group, which demonstrates thrombocytopenia with increased schistocytes from the formation of thrombi in the microvasculature **Table 5**.

Thrombotic Thrombocytopenic Purpura

Acquired thrombotic thrombocytopenic purpura (TTP) is a condition in which there is a decrease in the proteolytic activity of the von Willebrand factor (vWF) cleaving protease enzyme, ADAMTS13, in the plasma.[18] This is most commonly due to an autoantibody that either directly blocks its activity or accelerates its clearance. Due to the decrease in ADAMTS13 activity, when vWF is released from endothelial cells, it is not broken down to its smaller functional form. These larger vWF multimers cause platelets to aggregate throughout the vasculature, leading to diffuse platelet thrombi (not the fibrin thrombi of DIC) formation, ischemia of the affected organs, and a severely decreased platelet count, usually less than 20,000/μL at the time of diagnosis. Coagulation factors are not consumed so that the PT and PTT remain normal. It is not clear what triggers TTP, but some of the following factors may play a role:

- Pregnancy, viral illnesses, cancer, human immunodeficiency virus (HIV), lupus, and bacterial infections
- Medical procedures, such as surgery and bone marrow/stem cell transplant
- Medicines such as chemotherapy, ticlopidine, clopidogrel, cyclosporine, hormone therapy and estrogens, and quinine

ADAMTS13 activity can be measured, and activity less than 5% to 10% as well as the presence of autoantibodies can be very specific for the diagnosis. However, ADAMTS13 activity is often a send-out test and can take days to get back. Consequently, the treatment, consisting of daily plasma exchange with fresh-frozen plasma (FFP) until the platelet count rises to 150,000/μL, is often initiated before ADAMTS13 results are available. FFP plasma exchange is lifesaving in 90% of TTP cases.[18] Typically, patients with TTP can have the following findings: anemia, greater than three schistocytes per high-power field on peripheral blood smear examination, severe thrombocytopenia, elevated creatinine (acute kidney injury), fever, changing neurologic signs, increased LDH, and a severely decreased ADAMTS13 activity (<5%-10%). In a patient with symptoms suggestive of TTP, only severe thrombocytopenia and MAHA are typically required before initiating

DOI: 10.1093/ajcp/aqw195

Table 5
Laboratory Results Useful in Evaluating the Differential Diagnosis of DIC

Diagnosis	Platelet Count	PT	aPTT	Fibrinogen
DIC	↓	↑	↑	↓
TTP, HUS, aHUS	↓	N	N	N
ITP	↓	N	N	N
Cirrhosis	↓	↑	↑	N to ↓
Heparin	N	N to ↑[a]	↑	N
Coumadin	N	↑	↑	N
HIT	↓	N to ↑[a]	↑	N

aHUS, atypical hemolytic uremic syndrome; aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; HIT, heparin-induced thrombocytopenia; HUS, hemolytic uremic syndrome; ITP, immune thrombocytopenic purpura; N, normal; PT, prothrombin time; TTP, thrombotic thrombocytopenic purpura; ↓, decrease; ↑, increase.
[a]If a heparin neutralizer is present in the PT reagent, then the PT will be normal in the presence of heparin.

plasma exchange therapy. The acquired form demonstrates an antibody to ADAMTS13, but the very rare congenital form, Schulman-Upshaw syndrome, does not have an ADAMTS13 antibody. Elevations in PT and aPTT are not part of TTP.

Hemolytic Uremic Syndrome, Typical

Typical hemolytic uremic syndrome (HUS) is caused by *Escherichia coli* Shiga toxin, sometimes found in undercooked hamburger meat and originating from cow manure.[19] The toxin that is produced can cause direct cell damage to the renal microvasculature, the GI tract, and other organ systems. The hallmark of this disease is diarrhea, acute kidney injury, and severe thrombocytopenia. Typical HUS is more commonly found in children but does occur in adults. ADAMTS13 is not severely decreased in this condition, and anti-ADAMTS13 is not present. The usual treatment is only supportive in nature. Unlike acute DIC with elevations in PT and aPTT, typical HUS shows only a severe decrease in platelet count.

Atypical HUS

Another form of HUS is atypical HUS (aHUS). It is caused by a genetic predilection where a decrease in the production of complement inhibitors occurs when the patient is exposed to stressful stimuli.[19] This results in uncontrolled complement activation with direct endothelial cell damage in the kidney, GI tract, and other organ systems. Patients are usually found to have more than 11% ADAMTS13 activity and no anti-ADAMTS13. Patients with aHUS have symptoms similar to those in TTP, but GI symptoms (bloody diarrhea, vomiting, abdominal pain, and pancreatitis) and acute renal failure are more prominent than in TTP. Plasma exchange with FFP can raise the platelet count but will not prevent severe kidney failure and end-stage renal disease. The treatment of choice is eculizumab (anti-C5) because it will raise the platelet count to normal and also prevent end-stage renal disease if started early in the course of this disease. Elevations in PT and aPTT are not part of aHUS.

Patients with TTP, HUS, and aHUS will have only severe thrombocytopenia and appear ill, in contrast to those with immune thrombocytopenic purpura (ITP) who appear well. In acute DIC the patient is ill and there is not only severe thrombocytopenia but also an increase in aPTT and PT.

ITP

ITP is an acquired autoimmune process where autoantibodies are directed against the patient's own platelets, leading to their destruction. There also may be some aspect of a humoral autoimmune process involving the megakaryocyte, the platelet progenitor, which results in decreased platelet production so that the platelet count is less than 100,000/μL.[20]

There are two types of ITP. The first type is called "primary" ITP, and it is a diagnosis of exclusion that can only be made when secondary ITP has been ruled out. In primary ITP, the patient is usually healthy and has isolated thrombocytopenia with a normal peripheral blood smear. The rest of the medical workup is typically unremarkable. Secondary ITP is associated with a specific disorder or disease that causes autoantibodies to platelets. Common secondary ITP disorders/diseases include drug-induced ITP (more than 1,000 drugs that induce thrombocytopenia, including over-the-counter medications, are listed on the US Food and Drug Administration [FDA] Adverse Event Reporting System database [www.ouhsc.edu/platelets]), HIV, hepatitis C virus, *Helicobacter pylori*, vaccinations, myelodysplastic syndrome, leukemia, lymphoproliferative disorders, aplastic anemia, systemic lupus erythematosus, antiphospholipid syndrome, and common variable immune deficiency.[21] In most cases of secondary ITP, patients will appear ill and eventually develop abnormal laboratory tests.

There are multiple laboratory abnormalities in a very sick patient with acute DIC, while a patient with primary ITP would only demonstrate thrombocytopenia and appear relatively well.

Coagulopathy in Cirrhosis

Another disease process that can mimic the findings of acute DIC is the coagulopathy seen in severe chronic liver disease. Fibrosis of the liver causes loss of hepatocytes, resulting in decreased production of the vitamin K–dependent clotting factors (II, VII, IX, and X), as well as other liver-synthesized clotting and inhibitory factors, including fibrinogen; factors V, XI, and XII; proteins C and S; AT; TAFI; α2 antiplasmin, PK, kininogen, and plasminogen; plasmin inhibitor; and ADAMTS13.[13,22] This may result in prolongation of the PT and aPTT. Moderately decreased

DOI: 10.1093/ajcp/aqw195

platelet counts are also common in chronic liver disease due to decreased production of thrombopoietin, splenic sequestration of platelets from hypersplenism, autoantibody destruction of platelets, and/or bone marrow suppression of megakaryocytes.[22] The following are either produced by the endothelial cells or expressed on their surface: vWF, factor VIII, TPA, and PAI-1. These are often elevated in chronic liver disease and can result in clot dissolution, hyperfibrinolysis, and severe bleeding. Alternatively, if the procoagulant drivers (elevated factor VIII, vWF, and PAI and decreased AT, proteins C and S, and plasminogen) prevail, then hypercoagulability and thrombosis may occur.[13,22]

Common physical findings in a patient with chronic liver disease include clubbing, palmer erythema, spider nevi, gynecomastia, feminizing hair distribution, testicular atrophy, small shrunken liver, and anemia. As for laboratory findings in cirrhosis, there are no diagnostic tests other than liver biopsy that can confirm cirrhosis, but common laboratory abnormalities include thrombocytopenia, elevated aPTT and PT/INR, increased bilirubin, elevated aspartate aminotransferase/alanine aminotransferase (liver enzymes), and decreased serum albumin. A patient with normal liver enzymes who does not have the physical manifestations of liver disease would make liver involvement an unlikely cause of an elevated aPTT and PT and decreased platelet count. In addition, factor VIII (made in endothelial cells and not in the liver) may be elevated in liver disease as an acute phase reactant but consumed and therefore decreased in DIC.

Anticoagulants

Heparin

Heparin treatment to prevent deep vein thrombosis and heparin infusion to keep intravenous lines open may cause abnormalities in the PT and aPTT and is relatively common in hospitalized patients, causing prolonged aPTTs with no bleeding history. Heparin therapy might be expected to prolong a patient's PT as well as the aPTT; however, typical PT reagents today contain a heparin neutralizer to counteract the effect of any heparin present or are otherwise manufactured to be insensitive to therapeutic levels of heparin. Coagulation laboratories can rule out a heparin effect as the cause of prolonged aPTT by repeating the aPTT after adding the reagent heparinase. If the aPTT returns to normal levels in the presence of heparinase, then the prolongation of the aPTT was due to heparin.

Heparin exposure may also cause thrombocytopenia in patients who develop heparin-induced thrombocytopenia (HIT),[23] a hypercoagulable disorder and not a bleeding disorder. HIT is caused by an autoantibody that binds to platelet factor 4 in a complex with heparin. This antigen-antibody complex then activates platelets, leading to thrombocytopenia and thromboses. Thrombocytopenia from HIT typically develops 5 to 10 days after exposure with a platelet count of less than 150,000/μL or a 50% decrease from baseline. HIT is more commonly seen after exposure to unfractionated heparin but may also be seen after exposure to low molecular weight heparin.[15,23] The diagnosis is made clinically along with available laboratory tests. With high clinical suspicion, management of HIT (discontinuing or replacing heparin with another anticoagulant) should take place prior to the availability of test results.

A patient taking heparin with HIT could demonstrate not only thrombocytopenia but also an elevated PT (in a laboratory not using a PT reagent with a heparin neutralizer) and aPTT, making it difficult to differentiate from acute DIC until the patient is taken off heparin. If HIT and not DIC is present, then the PT and aPTT should return to normal.

Coumadin (Warfarin)/Vitamin K Deficiency

Warfarin is a common oral anticoagulant that works by inhibiting vitamin K reductase. This inhibition blocks the regeneration of the active form of vitamin K, which is needed for carboxylation of factors II, VII, IX, and X and proteins C and S. While the extent of anticoagulation with coumadin is measured with the PT (standardized by the INR), the aPTT is prolonged as well.

Treatment of DIC

It is not advisable to transfuse blood components prophylactically because of the risk of "fueling the fire" in acute DIC. Blood component therapy should be reserved for those who have hemorrhage, require a surgical procedure, or are at high risk for bleeding complications.

The mainstay of short-term treatment in the bleeding patient with acute DIC remains blood component therapy based on the deficit found on laboratory testing: INR more than 1.5, FFP; platelet count less than 50,000/μL, platelet concentrates; fibrinogen less than 100 mg/dL, cryoprecipitate; and hematocrit less than 21%, RBC. However, the manifestations of DIC will disappear once the underlying condition associated with this syndrome is addressed. Therefore, providing the patient with the appropriate and vigorous therapy for the underlying condition, such as antibiotics in septic shock, is most important for cessation of DIC symptoms, which may take a few days to replenish consumed factors.[24] Most clinicians feel that after trying blood components, if the patient is still significantly bleeding and has evidence of hyperfibrinolysis syndrome, such as that seen in trauma within the first 3 hours or in metastatic prostate carcinoma and/or in acute promyelocytic leukemia, an antifibrinolytic such as tranexamic acid

DOI: 10.1093/ajcp/aqw195

may be administered. Epsilon aminocaproic acid must not be used without concomitant heparin according to the package insert. If the DIC shows primarily hypercoagulability, such as deep vein thrombosis or pulmonary emboli of metastatic carcinoma or other chronic DIC conditions (retained dead fetus syndrome, intra-abdominal aortic aneurysm), then heparin therapy may be considered.

Although plasma-derived AT at a dose between 1,500 and 3,000 IU/d for 3 days has been shown to decrease 28-day mortality in DIC by 10% and can be used in Japan for the treatment of sepsis with DIC to bring the plasma AT concentration to more than 80%, the FDA has not approved AT concentrate for this purpose in the United States.[25]

Not everything works out as expected because, in October 2011, Eli Lilly pulled its recombinant activated protein C (drotrecogin alfa) off the market after 9 years because it was eventually shown not to improve mortality when administered for septicemia in humans. On the other hand, human soluble thrombomodulin (TM) has been successfully used for the treatment of sepsis-DIC in Japan since 2008, and recombinant TM is undergoing phase III clinical trials in the United States for severe sepsis with coagulopathy.[26]

A review of experimental treatments in DIC can be found in a 2014 article by Levi and van der Poll,[1] and several have yet to be tested in DIC in humans once the recombinant proteins or monoclonal antibodies are approved for human use. Reducing the levels of factor XII and/or PK did not affect coagulopathy or bleeding in bacterially induced sepsis in animals but did block the usual finding of shock. However, blocking TF or factor VIIa through specific monoclonal antibodies resulted in complete inhibition of thrombin generation and the prevention of DIC in chimpanzees infused with *E coli*. Recombinant TFPI has been shown to block thrombin generation in inflammation and prevent mortality during endotoxin-induced DIC in animals. Interestingly, mice with a plasminogen activator deficiency that are challenged with endotoxin have more extensive fibrin deposition in organs, while those with PAI-1 deficiency have no microvascular thrombosis when challenged with endotoxin. TAFI, like PAI-1, may also contribute to microvascular thrombosis-induced ischemia in organs resulting in MODS. Activated protein C, when blocked, enhances the inflammatory response but, if increased by administering recombinant activated protein C, will decrease inflammatory activation in animals infused with *E coli*.

In summary, the clinical course of DIC ranges from asymptomatic to life threatening. It is caused by excessive activation of coagulation so that the anticoagulation system is overwhelmed, secondary to a wide variety of clinical conditions. The pathogenesis involves the generation of high levels of thrombin, potentially leading to microvascular thrombosis, as well as the consumption of coagulation factors and the increased generation of plasmin, which could generate a hemorrhagic diathesis. Bleeding is related to several factors, including the consumption of factors, platelets, and fibrinogen, as well as the generation of D-dimers. Typical laboratory tests performed to evaluate DIC include PT, aPTT, platelet count, fibrinogen, and D-dimer. MAHA is a feature that can be appreciated by the presence of large numbers (four or more per high-power field) of schistocytes on the peripheral blood smear. Therapy involves supportive care and treatment of the underlying condition.[27]

Corresponding author: Leonard I. Boral, MD, MBA, University of Kentucky Medical Center, Dept of Pathology and Laboratory Medicine, 800 Rose St, Lexington, KY 40536.

References

1. Levi M, van der Poll T. A short contemporary history of disseminated intravascular coagulation. *Semin Thromb Hemost*. 2014;40:874-880.
2. Kenne E, Nickel KF, Long AT, et al. Factor XII: a novel target for safe prevention of thrombosis and inflammation. *J Intern Med*. 2015;278:571-585.
3. Worm M, Kohler EC, Panda R, et al. The factor XIIa blocking antibody 3F7: a safe anticoagulant with anti-inflammatory activities. *Ann Transl Med*. 2015;3:247.
4. Kurosawa S, Stearns-Kurosawa DJ. Complement, thrombotic microangiopathy and disseminated intravascular coagulation. *J Intensive Care*. 2014;2:65.
5. Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. *J Leukoc Biol*. 2007;81:1-5.
6. Taylor FB Jr, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86:1327-1330.
7. Rodgers GM. Acquired coagulation disorders. In: Greer JP, Arber DA, Glader BE, et al, eds. *Wintrobe's Clinical Hematology*. 13th ed. Philadelphia, PA: Wolters Kluwer, Lippincott Williams & Wilkins Health; 2014:1186-1217.
8. Duncan CJSS. What caused the Black Death? *Postgraduate Med J*. 2005;81:315-320.
9. Singh B, Hanson AC, Alhurani R, et al. Trends in the incidence and outcomes of disseminated intravascular coagulation in critically ill patients (2004-2010): a population-based study. *Chest*. 2013;143:1235-1242.
10. Levi M, van der Poll T. Disseminated intravascular coagulation: a review for the internist. *Int Emerg Med*. 2013;8:23-32.
11. Levi M. Disseminated intravascular coagulation. In: Hoffman R, Benz EJ, Silberstein LE, et al, eds. *Hematology: Basic Principles and Practice*. 6th ed. Philadelphia, PA: Saunders/Elsevier; 2013:2001-2012.
12. Crawley JT, Zanardelli S, Chion CK, et al. The central role of thrombin in hemostasis. *J Thromb Haemost*. 2007;5:95-101.
13. Levi M, Seligsohn U, Disseminated intravascular coagulation. In: Kaushansky K, Lichtman MA, Prchal JT, et al, eds. *Williams Hematology*. 9th ed. New York, NY: McGraw-Hill; 2016.

DOI: 10.1093/ajcp/aqw195

14. Gando S. Hemostasis and thrombosis in trauma patients. *Semin Thromb Hemost*. 2015;41:26-34.
15. Schmaier AL, Miller JL. Coagulation and fibrosis. In: McPherson RA, Pincus MR, eds. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 22nd ed. Philadelphia, PA: Elsevier/Saunders; 2011:785-800.
16. Bakhtiari K, Meijers JC, de Jonge E, et al. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med*. 2004;32:2416-2421.
17. Gando S, Iba T, Eguchi Y, et al. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. *Crit Care Med*. 2006;34:625-631.
18. Sarode R, Bandarenko N, Brecher ME, et al. Thrombotic thrombocytopenic purpura: 2012 American Society for Apheresis (ASFA) consensus conference on classification, diagnosis, management, and future research. *J Clin Apher*. 2014;29:148-167.
19. Cataland SR, Wu HM. How I treat: the clinical differentiation and initial treatment of adult patients with atypical hemolytic uremic syndrome. *Blood*. 2014;123:2478-2484.
20. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113:2386-2393.
21. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117:4190-4207.
22. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med*. 2011;365:147-156.
23. McKenzie SE, Sachais BS. Advances in the pathophysiology and treatment of heparin-induced thrombocytopenia. *Curr Opin Hematol*. 2014;21:380-387.
24. Wada H, Thachil J, Di Nisio M, et al. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. *J Thrombos Haemost*. 2013;11:761-767.
25. Iba T, Saitoh D. Efficacy of antithrombin in preclinical and clinical applications for sepsis-associated disseminated intravascular coagulation. *J Intensive Care*. 2014;2:66.
26. Ikezoe T. Thrombomodulin/activated protein C system in septic disseminated intravascular coagulation. *J Intensive Care*. 2015;3:1.
27. Hunt BJ. Bleeding and coagulopathies in critical care. *N Engl J Med*. 2014;370:847-859.

DOI: 10.1093/ajcp/aqw195