Disseminated intravascular coagulation: is it fact or fancy?

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'Disseminated intravascular coagulation (DIC)' occurs commonly in critical illnesses such as sepsis, trauma, cancer, and complications of surgery and pregnancy. Mortality is very high. The pathogenesis has been ascribed to tissue factor-initiated coagulation disorder, resulting in disseminated microblood clots that are made of platelets, plasma factors, fibrins, and blood cells. True DIC depletes coagulation factors and consumes platelets, and activates fibrinolysis. 'DIC' is assumed to orchestrate thrombocytopenia, microangiopathic hemolytic anemia and hypoxic multiorgan dysfunction syndrome, and causes hemorrhagic disorder due to depleted coagulation factors. In contrast, disseminated intravascular microthrombosis (DIT) occurs in thrombotic thrombocytopenic purpura (TTP) and TTP-like syndrome due to ADAMTS13 deficiency or insufficiency. The pathogenesis is due to formation of intravascular 'microthrombi' composed of complexes of platelets and unusually large von Willebrand factor multimers. Interestingly, DIT also occurs in the same critically ill patients as 'DIC' does. Following activation of complement system, the terminal complex C5b-9 causes endotheliopathy via channel formation to the endothelial cell membrane. Endotheliopathy activates microthrombotic pathway and initiates microthrombogenesis, leading to endotheliopathy-associated DIT. DIT results in TTP-like syndrome with hematologic phenotype of consumptive thrombocytopenia, microangiopathic hemolytic anemia, and multiorgan dysfunction syndrome. In reinterpretation of 'DIC', the true lesion is 'microthrombi' but not microblood clots. Thus, 'DIC' is endotheliopathy-associated DIT. This concept reconciles all the clinical features of 'DIC', and dramatically changes our understanding of pathophysiological mechanism in hemostasis and thrombosis. This new paradigm should assist the physician with correct diagnostic evaluation and treatment intervention. *Blood Coagul Fibrinolysis* **29:330–337**

Blood Coagulation and Fibrinolysis 2018, **29**:330–337

Keywords: antimicrothrombotic agent, disseminated intravascular coagulation, disseminated intravascular microthrombosis, endotheliopathy, microthrombogenesis, thrombocytopenia, thrombotic thrombocytopenic purpura, thrombotic thrombocytopenic purpura-like syndrome, vascular microthrombotic disease

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Received 28 October 2017 **Revised** 20 January 2018
Accepted 5 February 2018

Introduction

Disseminated intravascular coagulation (DIC) has been an enigma in medical science and practice for more than 60 years. No accurate diagnostic test has been available for this disorder [1,2], and its pathogenesis is still poorly understood [3]. Anticoagulation therapy has not been effective [4]. Therapeutic intervention counteracting the activated tissue factor (TF) pathway has been proved unsuccessful [5].

In a healthy person, homeostatic checks and balances exist between procoagulant and anticoagulant forces. In certain pathological conditions, TF-initiated coagulation cascade could become excessively activated and develop a life-threatening hemorrhagic disorder, as seen in DIC associated with acute promyelocytic leukemia (APL). On the other hand, pathological microthrombogenesis, which is completely different from TF-initiated coagulation, could trigger equally serious thrombosis, as seen in disseminated intravascular microthrombosis (DIT) [i.e., thrombotic thrombocytopenic purpura (TTP) and TTP-like syndrome] [6]. The former is a hemostatic coagulation disorder, but the latter is a pathological microthrombotic disorder.

Coagulation and thrombosis in critical care

The current concept that the platelet and von Willebrand factors (VWF) participate in both hemostasis and thrombotic disorder to assemble similar (if not the same) blood clots has impeded identifying their accurate pathophysiological functions [7]. The pathological thrombotic disorder seen in many critical illnesses such as sepsis has been termed DIC and has been accepted as hemostatic coagulation disorder developing through the activated TF pathway [8]. This hypothesis has had a major negative impact on the care and outcome of critically ill patients.

In 1924, Moschcowitz [9] first recognized a thrombotic blood disorder characterized by disseminated hyaline microthrombi in terminal arterioles and capillaries of many organs of a young woman who died at the Beth Israel Hospital in New York City. Later, Singer *et al.* [10] named this disorder TTP attributing to generalized platelet thrombosis. TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and often with hypoxic dysfunction of the brain and kidneys. A quarter century later, in 1950, McKay [11] coined the term 'DIC' for another blood disorder

 DOI:10.1097/MBC.0000000000000727

observed in a woman who died of extensive vascular thrombosis associated with hemorrhage progressing to multiorgan dysfunction. Quotation marks have been put for 'DIC' to separate it from true DIC seen in APL. Since McKay's original proposal for the term, 'DIC' in reported cases has been characterized by thrombocytopenia, MAHA and hyaline microthrombi in arterioles and capillaries, and sometimes with severe coagulopathy and hemorrhagic disorder. Today 'DIC' is firmly recognized as a serious coagulation disorder, typically occurring in critical illnesses including sepsis/septic shock, trauma, cancer, collagen vascular disease, and complications of surgery, pregnancy, and transplant [12,13].

More recently, TTP-like syndrome/atypical TTP also has been recognized without clear distinction from TTP. The involvement of the brain and kidneys was not as common as in TTP and atypical phenotypes occurred due to the involvement in multiorgans [14–17], such as the kidneys, pancreas, lungs [15,18], heart [17], muscles [19], liver [20], and others [15,21]. Also, often fewer schistocytes were present on the blood film in association with intravascular hemolysis [14–16], which has been called atypical MAHA (aMAHA). In retrospect, just as in 'DIC', TTP-like syndrome has occurred in critical illnesses such as sepsis/septic shock, cancer, collagen vascular disease, complications of surgery, pregnancy, and transplant [15,16,20,21–24], and often responded to therapeutic plasma exchange (TPE) if treated in early stage of TTP-like syndrome [16,18,19,21,22].

Pathogenesis of disseminated intravascular microthrombosis

In the early 1980s, Moake *et al.* [25] made a very important observation that unusually large von Willebrand factor multimers (ULVWF) contributed to the pathogenesis of TTP. Furlan *et al.* [26] and Tsai [27] independently published the presence of VWF cleaving protease, and subsequently the deficient role of this protease ADAMTS13 due to anti-ADAMTS13 antibody was established in TTP. However, clinical hematologists have been baffled about similarity and dissimilarity between antibody-positive TTP and acquired antibody-negative TTP-like syndrome. The latter has been associated with acute respiratory distress syndrome, hemolytic-uremic syndrome, acute myocardial ischemia, pancreatitis, rhabdomyolysis, the syndrome of hemolysis, elevated liver enzymes and low platelet count (HELLPs), and others (Table 1 and Fig. 1).

Unlike antibody-associated TTP, TTP-like syndrome occurs as a result of endotheliopathy [24,28] as illustrated in Table 1. The nature of microthrombi in endotheliopathy-associated DIT is similar to TTP. In both disorders, microthrombi are composed of platelet-ULVWF complexes in the intravascular space. However, in TTP, microthrombi are formed in microcirculation [6], but in endotheliopathy-associated DIT, they are formed on the intravascular membrane of endothelial cells *in situ* [24,28]. If this distinction is understood, the endothelial pathogenesis promoting by microthrombogenesis can readily explain TTP-like syndrome. The salient role of endotheliopathy in the molecular pathogenesis of TTP-like syndrome is very clear in critical illnesses [24,28] as shown in Table 1, and Fig. 1.

Endotheliopathy develops as the result of complement activation in critical illnesses. Terminal C5b-9 (membrane attack complex) attacks the host bystander endothelial cells and produces channel (pore) formation on the endothelial membrane, leading to endothelial injury and dysfunction. This 'unprotected' complement activation is suspected to be due to downregulated CD59.

Endotheliopathy triggers molecular events, leading to activation of two independent pathways (i.e., inflammatory and microthrombotic) according to the novel thesis of 'two-activation theory of the endothelium' (Fig. 1) [24,28]. In short, two important molecular events are; first, release of inflammatory cytokines (e.g., IL-1, IL-6, tumor necrosis factor-α, and others) [29,30], and second, activation of the platelet [31] and excessive endothelial exocytosis of ULVWF [32,33]. The former triggers inflammation through 'activation of inflammatory pathway'. The latter mediates microthrombogenesis via 'activation of microthrombotic pathway' as illustrated in Fig. 1. In microthrombogenesis, exocytosed ULVWF become anchored as long elongated strings to endothelial membrane [34] and recruit activated platelets to form 'microthrombi' composed of platelet-ULVWF complexes. This process causes pathological phenotype of DIT, which is the pathology of endotheliopathy-associated vascular microthrombotic diseases (VMTD), and lead to various clinical phenotypes of multiorgan dysfunction syndrome (MODS) occurring in TTP-like syndrome.

Microthrombogenesis due to hyperactive ULVWF (i.e., megakaryocytic and endothelial) occurs at two different locations; DIT in antibody-positive TTP takes place in microcirculation [6] due to ADAMTS13 deficiency, but DIT in endotheliopathy-associated VMTD (i.e., TTP-like syndrome) develops on the endothelial membrane due to ADAMTS13 insufficiency [24,28]. The predominant organ localization is much more variable in TTP-like syndrome, which is related to endothelial heterogeneity [35] among different TTP-like syndromes. Perhaps the physical configuration of microthrombi between TTP and TTP-like syndrome may be very different because their difference in sites of microthrombogenesis. Antibody-associated TTP is a 'microvascular' disease since microthrombi in circulation become lodged within arteriolar and capillary microvasculatures in the brain and kidneys. Instead, TTP-like syndrome is a 'vascular' disease because microthrombi are anchored to the

Table 1 Genesis and characteristics of thrombotic thrombocytopenic purpura and thrombotic thrombocytopenic purpura-like syndrome due to disseminated intravascular microthrombosis/vascular microthrombotic disease

	ADAMTS13 gene mutation-associated VMTD (hereditary TTP) ADAMTS13 antibody-associated VMTD (acquired TTP)	Endotheliopathy-associated VMTD (TTP-like syndrome)
Primary event	Hereditary *ADAMTS13* gene mutation	Sepsis due to pathogens (e.g., viruses; bacteria; fungi; rickettsia; parasites)
	Acquired ADAMTS13 antibody formation	Polytrauma (e.g., chest/lungs; bones; skull/brain)
		Pregnancy complications (e.g., preeclampsia; abruptio placenta)
		Cancer (e.g., stomach; breast; lung)
	↓	Transplant (e.g., liver; kidney; bone marrow)
		Drug and chemical (e.g., cyclosporine; mytomycin C; Shiga toxin)
		↓
Secondary event	Excessive circulating ULVWF and platelet aggregation	Endothelial injury and platelet activation→ Eendotheliopathy
	↓	↓
	Microthrombogenesis leading to platelet-ULVWF complexes	Cytokine release and cytokine storm → Inflammation → SIRS
		Endothelial exocytosis of ULVWF and anchored to ECs as long elongated strings
	↓	↓
Tertiary event	Microthrombi lodged within arteriolar capillary lumens	Vascular microthrombogenesis leading to platelet-ULVWF complexes
	↓	↓
	VMTD	VMTD
	↓	↓
Final event	TMA (microthrombotic microangiopathy)	TMA (microthrombotic angiopathy)
	↓	↓
	TTP	TTP-like syndrome
Hematologic features		
Platelet	Consumptive thrombocytopenia	Consumptive thrombocytopenia
Red blood cell	MAHA	MAHA/aMAHA
Clinical syndromes		
Inflammation/fever	Unlikely present	Very common
ARF/HUS	ARF is common	HUS occurs due to Shiga toxins or infections
Encephalopathy	Common without sepsis or trauma	Common with sepsis, trauma, and toxin, etc.
ARDS	Absent	Often present with sepsis, trauma, transplant, etc.
Myocardial infarction	Absent	May be present with sepsis
Rhabdomyolytsis	Absent	May be present with sepsis
Pancreatitis	Absent	May occur in sepsis
Acute fulminant hepatitis	Absent	Common, especially due to viral hepatitis
HELLP syndrome	Absent	Common in pregnancy
Adrenal insufficiency	Absent	Common in sepsis (e.g., meningococcus) with septic shock
SIRS	Absent	Commonly present, especially in sepsis
Hepatic coagulopathy	Unlikely to occur	Common
DIC (see the text)	Does not occur	Does not occur
Laboratory features		
ADAMTS13 activity	Markedly decreased (<5% of normal)	May be mild-to-moderately decreased (20–70% of normal)
ADAMTS13 antibody	Positive in acquired TTP	Negative
LDH	Increased	Increased
Haptoglobin	Markedly decreased	Markedly decreased
Schistocytosis	++ to ++++	None to +++
Response to TPE	Very good response	Excellent and fast response if treated in early stage

ARDS, acute respiratory distress syndrome; ARF, acute renal failure; DIC, disseminated intravascular coagulation; ECs, endothelial cells; HELLP, hemolysis, elevated liver enzyme; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; MAHA/aMAHA, microangiopathic hemolytic anemia/atypical MAHA; rADAMTS13, recombinant ADAMTS13; SIRS, systemic inflammatory response syndrome; TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura; ULVWF, unusually large von Willebrand factor multimers; VMTD, vascular microtrombotic disease.

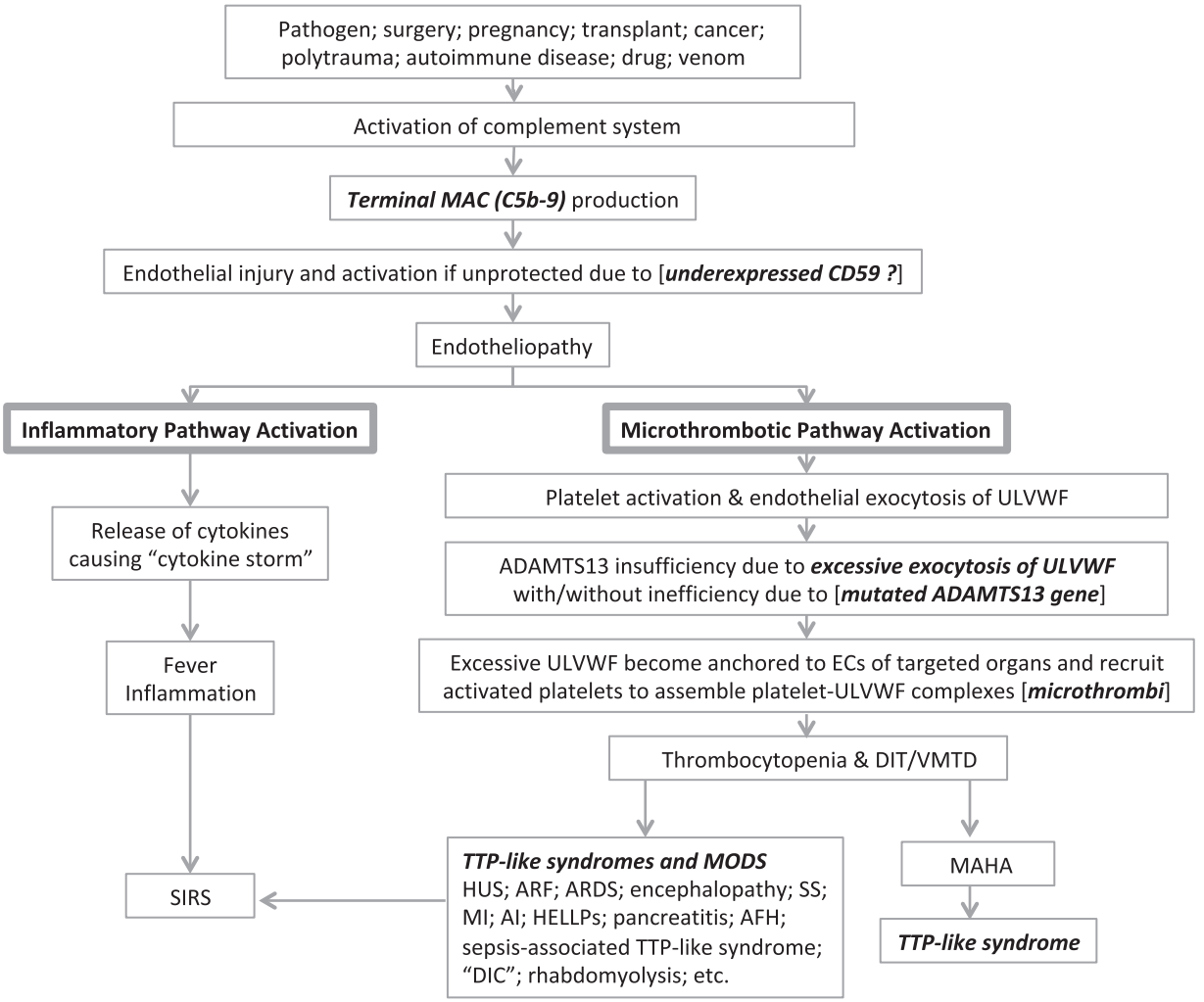
membrane of endothelial cells *in situ* of smaller and larger vasculatures.

Reinterpretation of 'disseminated intravascular coagulation'

The 'two activation theory of the endothelium' supports the pathogenesis of TTP-like syndrome is the result of endotheliopathy-associated DIT. This theory also could apply in solving the enigmatic puzzle of 'DIC' occurring in critically ill patients. Moschcowitz first reported his case of DIT seen in a critically ill patient. It could have been due to either antibody-associated TTP or TTP-like syndrome. Retrospectively, we cannot be certain which one is correct. Many years later, McKay encountered a patient with extensive intravascular microthrombosis and coined the term 'DIC'. Currently, the pathogenesis of 'DIC' is accepted to be due to activation of TF-initiated coagulation [8]. However, clinical, pathological, and laboratory features support it is the result of pathological microthrombogenesis, leading to endotheliopathy-associated DIT [28]. Each clinician saw the same condition of pathological microthrombotic disorder from different perspectives.

In retrospect, 'DIC' and endotheliopathy-associated DIT (i.e., TTP-like syndrome) are exactly the same in their

Fig. 1



Molecular pathogenesis of thrombotic thrombocytopenic purpura-like syndrome. Based on 'two activation theory of the endothelium' showing the molecular events of endotheliopathy-associated vascular microthrombotic disease (i.e., thrombotic thrombocytopenic purpura-like syndrome) and many associated clinical syndromes, complement activation can occur through three different pathways. In addition to lysis of pathogen by terminal product C5b-9 (membrane attack complex), membrane attack complex induces endotheliopathy to the host if unprotected by CD59 in endothelial cells. Activated inflammatory pathway is severe in sepsis but is minimal if organ involvement is limited. Activated microthrombotic pathway results in endotheliopathy-associated disseminated intravascular microthrombosis/vascular microthrombotic disease. The excess of unusually large von Willebrand factor multimers develops when partial ADAMTS13 deficiency occurs due to heterozygous gene mutation and/or its insufficiency due to excessive release of unusually large von Willebrand factor multimers. This theory explains all the manifestations of vascular microthrombotic disease. Systemic inflammatory response syndrome is the combined syndrome of activated inflammatory and microthrombotic pathways. ADAMTSD13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AFA, antifibrinolytic agent; AFH, acute fulminant hepatitis; AI, adrenal insufficiency; APL, acute promyelocytic leukemia; aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; ARF, acute renal failure; ATRA, all-trans retinoic acid; DIC, disseminated intravascular coagulation; DIC, false disseminated intravascular coagulation; DIT, disseminated intravascular thrombosis; ECs, endothelial cells; FDP, fibrin degradation products; FFP, fresh frozen plasma; FVIIa, activated factor VII; FVIII, factor VIII; HC, hepatic coagulopathy; HELLPs, hemolysis, elevated liver enzymes, and low platelet syndrome; HUS, hemolytic uremic syndrome; IL, interleukin; LDH, lactate dehydrogenase; MAC, membrane attack complex; MAHA, microangiopathic hemolytic anemia; MI, myocardial infarction; MODS, multiorgan dysfunction syndrome; PF, purpura fulminans; PT, prothrombin time; rADAMTS13, recombinant ADAMTS13; SIRS, systemic inflammatory response syndrome; SS, stroke syndrome; TCIP, thrombocytopenia in critically ill patient; TF, tissue factor; TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura; ULVWF, unusually large von Willebrand factor multimers; VMTD, vascular microthrombotic disease; vWF, von Willebrand factor.

underlying risk factors, and clinical and pathological features; clinically, both disorders always occur in association with critical illnesses; their pathology is characterized by arteriolar and capillary hyaline microthrombi with variable fibroblastic proliferation [6,36]; and hematological features are consumptive thrombocytopenia and MAHA/aMAHA. Can we accept now that 'DIC' is a microthrombotic disorder?

If these findings were not sufficient enough to convince 'DIC' is endotheliopathy-associated 'DIT', followings are more arguments for it.

Other arguments for endotheliopathy-associated disseminated intravascular microthrombosis

Table 2 summarizes hematologic and clinical characteristics between endotheliopathy-associated DIT (i.e., TTP-like syndrome and 'DIC') and true DIC (e.g., APL). The table is self-explanatory. Endotheliopathy-associated DIT is a thrombotic disorder, but the predominant feature of true DIC is a hemorrhagic disorder without MAHA and MODS [37–39]. Related to 'DIC' mystery, a few more comments are appropriate to refute the TF-initiated pathogenesis of 'DIC'.

First, the Subcommittee for DIC of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis has introduced a DIC scoring system to better establish the diagnosis of 'DIC' [2,40]. It still is unsatisfactory because there is no gold standard for diagnosis of DIC and in the scoring system 'DIC' must be diagnosed on the grounds of clinical pretense. It should be emphasized that no single laboratory test or set of tests is sensitive or specific enough to allow a definitive diagnosis of 'DIC' [1]. In many cases, the diagnosis is based on the combination of results of nonspecific abnormal coagulation profile in the patient with a clinical condition known to be associated with 'DIC' [3].

Second, TF encryption/decryption theory [41,42], thiol path TF regulation theory [43], and TF transfer hypothesis from leukocytes [44,45] have been advanced to support how TF can participate in activation of coagulation cascade. But these theories are still controversial because insufficient supply of TF *in vivo* in endothelial cells cannot explain the pathologic coagulation in 'DIC' instigating extensive vascular microthrombosis.

Third, the abnormal coagulation profile, showing prolonged prothrombin time, activated partial thromboplastin time, hypofibinogenemia, and increased fibrin degradation products, is not specific for 'DIC', but also

Table 2 Hematologic and clinical characteristics of endotheliopathy-associated disseminated intravascular microthrombosis and true disseminated intravascular coagulation

	Endotheliopathy-associated DIT and 'DIC' of McKay	True DIC
Examples	TTP-like syndrome	DIC associated with APL
Nature of the disorder	Microthrombosis made of platelet-ULVWF complexes	Clots due to coagulation activated by TF–FVIIa complexes
Proposed mechanism of thrombogenesis	Intravascular microthrombogenesis	Intravascular coagulation
Inciting events	Sepsis, complication of surgery, pregnancy, trauma, or cancer, and transplant, and drugs/toxins leading to endotheliopathy	APL and drugs [39] leading to TF expression
Hematological manifestations	Thrombocytopenia and MAHA	Thrombocytopenia and depleted FVIII and FV
Pathogenesis		
Mechanism	Activation of microthrombotic pathway	Activation of TF–FVIIa complex pathway
Site of activation	Intravascular surface of the endothelium	In circulation of the Intravascular space
Pathology	Endothelial activation/dysfunction → endotheliopathy	TF expression → coagulation factor consumption
Result of pathogenesis	Formation of platelet-ULVWF microthrombi	Depletion of fibrinogen, FVIII, FV, and platelet
Essence of pathology	Arteriolar and capillary luminal hyaline microthrombi	Incoagulable blood/unstable blood clots
Effect on the involved organs	Vascular microthrombosis leading to organ hypoxia	Hemorrhage leading to organ damage
Coagulation tests		
Fibrinogen	Normal	Decreased
PT	Normal	Prolonged
aPTT	Normal	Prolonged
FDP	Normal	Increased
FVIII activity	Normal to markedly increased	Markedly decreased
Thrombocytopenia	Moderately severe	Mild to very severe
Associated clinical syndromes	Various organ phenotypes of TTP-like syndrome TMA MODS SIRS	Hemorrhagic disorder
Associated hematologic features		
Schistocytes	0 – +++	0
MAHA/aMAHA	Always present	Absent
Consumptive thrombocytopenia	Always present	Present due to consumption and APL
Hepatic coagulopathy	May occur	Unexpected
Incidence in clinical practice	Very common	Extremely rare
Therapy		
Platelet transfusion	Contraindicated	May be needed for chemotherapy of APL
Treatment	TPE; rADAMTS13 (expected to be very effective)	Treat underlying pathology (e.g., ATRA in APL)

APL, acute promyelocytic leukemia; aPTT, activated partial thromboplastin time; ATRA, all-trans retinoic acid; DIC, disseminated intravascular coagulation; DIT, disseminated intravascular thrombosis; FDP, fibrin degradation products; FVIIa, activated factor VII; FVIII, factor VIII; MAHA/aMAHA, microangiopathic hemolytic anemia/atypical MAHA; MODS, multiorgan dysfunction syndrome; PT, prothrombin time; rADAMTS13, recombinant ADAMTS13; SIRS, systemic inflammatory response syndrome; TF, tissue factor; TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura; ULVWF, unusually large von Willebrand factor multimers.

occurs in other acquired coagulopathies. In addition, this coagulation profile strangely develops only in some patients with 'acute DIC'. For this reason, the 'chronic/compensated/covert' and other concepts [2,40,46,47], including 'low grade DIC', has been proposed to explain the variable coagulation profile from normal to mildly abnormal in patients with 'DIC'. However, this conceptual designation cannot explain inexplicably extensive microthrombosis in the patient who presents with normal coagulation profile.

Fourth, numerous clinical trials (e.g., TF pathway inhibitors, activated protein C, antithrombin III, and others) based on TF-initiated coagulation theory and modulating septic response to infection have not been successful to improve the survival in sepsis [5].

It is no wonder why progress has not been made in designing a diagnostic test(s) for 'DIC' and no effective treatment has been found after more than a half century. These facts also put a question mark not only on TF-initiated coagulation and inflammation theory of 'DIC' but also on the pathogenesis of sepsis itself.

'Acute disseminated intravascular coagulation' is likely due to 'disseminated intravascular microthrombosis with hepatic coagulopathy'

One remaining very important question is, 'What is the correct diagnosis for acute/uncompensated/overt 'DIC' presenting with an abnormal coagulation profile?' The answer is self-evident if one understands the nature of DIT. In endotheliopathy-associated DIT, hepatic coagulopathy could occur due to acute fulminant hepatic failure/acute hepatic necrosis syndrome as seen in viral hemorrhagic fevers [24,28] and other critical illnesses [48–53]. Acute 'DIC' is consistent with the diagnosis of endotheliopathy-associated DIT progressing to hepatic coagulopathy. McKay [11] also recognized that hemorrhage in 'DIC' is frequently associated with both acute and chronic hepatic diseases that could lead to fatal complication. He asserted that 'DIC' and liver disease could occur concurrently.

Indeed, the medical literature is replete with the reports of DIT (i.e., TTP-like syndrome) and/or 'DIC', occurring in association with HELLPs, acute fulminant hepatic failure, hepatic encephalopathy, pancreatitis and hepato-renal syndrome and others. When organ phenotype of hepatic dysfunction occurs in endotheliopathy-associated DIT, which is likely due to acute hepatic necrosis syndrome, an abnormal coagulation profile could be easily misinterpreted as acute 'DIC'.

Differential diagnosis between disseminated intravascular microthrombosis and true disseminated intravascular coagulation

Once the difference between microthrombogenesis and TF-initiated coagulation is understood, the differential diagnosis among DIT, DIT-associated hepatic coagulopathy, and true DIC can be accomplished with proper coagulation tests as shown in Table 3. DIT occurs in both TTP and TTP-like syndrome. True DIC is an extremely rare disorder if we relocate 'DIC' associated with critical illnesses to the column of TTP-like syndrome.

In differentiating true DIC from DIT-associated hepatic coagulopathy, the most important test is the assay of coagulation factors [24,28,38,39,54,55]. In true DIC, factors VIII, and V are markedly decreased, but, in DIT-

Table 3 Differential hematologic features among thrombopathies and coagulopathies

	TTP-like syndrome (DIT)	DIT associated with HC (e.g., sepsis) = acute 'DIC'	True DIC (e.g., APL)	Pathologic fibrinolysis (e.g., amyloidosis)
Thrombocytopenia	Always present	Always present	Always present	Not present
MAHA/aMAHA	Always present	Always present	Very unlikely to be present	Not present
Fibrinogen	Normal	Decreased	Always decreased	Always decreased
Factor VIII	Normal	Normal or markedly increased	Markedly decreased	Decreased
Factor V	Normal	Decreased	Decreased	Normal or decreased
Factor X	Normal	Decreased	Usually normal	?
Factor VII	Normal	Markedly decreased	Normal	Normal
Factor IX	Normal	Decreased	Normal	Normal
FDP	Normal	Increased	Increased	Increased
Prothrombin time	Normal	Prolonged	Prolonged	Prolonged
Activated partial thromboplastin time	Normal	Prolonged	Prolonged	Prolonged
Thrombin time	Normal	Prolonged	Prolonged	Prolonged
Thrombosis form	Microthrombi	Microthrombi	Friable macrothrombi (?) or not formed	Absent
Bleeding: Character Treatment	Rare; petechiae; No need of treatment	May cause serious bleeding; Controllable with FFP	Common, serious bleeding; Abrogated with ATRA and chemotherapy	Slow and persistent bleeding; Treatable with AFA
Hypoxic organ dysfunction	Present	Present	Not present	Not present
Platelet transfusion	Contraindicated	Contraindicated	May be used with ATRA	Not needed

AFA, antifibrinolytic agent; APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; 'DIC', false disseminated intravascular coagulation; DIT, disseminated intravascular thrombosis; FDP, fibrin degradation products; FFP, fresh frozen plasma; HC, hepatic coagulopathy; MAHA/aMAHA, microangiopathic hemolytic anemia/atypical MAHA; TTP, thrombotic thrombocytopenic purpura.

associated hepatic coagulopathy, factor VIII is normal or more likely markedly increased. It is likely due to endothelial exocytosis of ULVWF as some of them are cleaved by ADAMTS13 to smaller VWF, which protect factor VIII from degradation. In hepatic coagulopathy, factor VII is markedly decreased, although it is normal in true DIC. A suggested guideline for laboratory tests is presented in Table 3 to aid in differential diagnosis among complicated thrombopathies and coagulopathies.

Treatment consideration

Once 'DIC' is correctly redefined as endotheliopathy-associated DIT (i.e., TTP-like syndrome), the treatment of choice is TPE at this time. Indeed, sepsis has been managed with TPE, sometimes with significant benefit [56–58] although it has been tried without understanding of the concept of microthrombogenesis. Unfortunately, TPE may not be readily available in urgent situation and carries with its own shortcomings such as inconvenience, time consuming nature, delayed treatment, and volume overload, especially in urgent septic patients. TPE for TTP-like syndrome has been an effective treatment if it is initiated in early stage of the disorder [16,18,21,22,59–62].

The better treatment might be targeted antimicrothrombotic agent such as recombinant ADAMTS13. Currently, it is being investigated for the treatment of hereditary TTP. As TPE worked well in TTP-like syndrome when it was initiated in early stage of the disorder, a good response to recombinant ADAMTS13 is anticipated for TTP-like syndrome, including 'DIC'. Proper clinical trials are needed. Unlike TPE, once approved, it could become readily accessible at on-care site of the hospital.

High mortality associated with 'DIC' in critical care patients could have been related to platelet transfusions, as well as masked hepatic coagulopathy and heparin treatment. The platelet transfusion is contraindicated because it aggravates on-going microthrombogenesis, and heparin increases hemorrhage associated with hepatic coagulopathy. Fresh frozen plasma should be beneficial for hepatic coagulopathy.

Recombinant activated factor VII has shown potential role in severe hemorrhage associated with 'DIC' [63–65]. Perhaps it was effective because hemorrhagic syndrome was due to hepatic coagulopathy, in which factor VII is the lowest factor among liver dependent factors, factors II, V, VII, IX, and X, and is responsible for hemorrhagic disorder. However, potentially serious complication of recombinant activated factor VII treatment in endotheliopathy-associated DIT is the development of life-threatening thrombo-hemorrhagic syndrome.

Conclusion

Shall we call 'DIC' is fancy and endotheliopathy-associated DIT (TTP-like syndrome) fact? This paradigm changes would have an immediate impact on the diagnosis, treatment and prognosis of 'DIC' and save many lives. Unconvinced? Then, the enigma of 'DIC' should be reevaluated with appropriate coagulation studies to confirm or refute its claim as endotheliopathy-associated DIT (i.e., TTP-like syndrome).

Acknowledgements

Conflicts of interest

The author J.C.C., MD has neither actual nor potential personal or financial conflicts of interest in regard to this article.

References

1 Slofstra SH, Spek CA, ten Cate H. Disseminated intravascular coagulation. *Hematol J* 2003; **4**:295–302.
2 Wada H, Matsumoto T, Hatada T. Diagnostic criteria and laboratory tests for disseminated diagnostic criteria and laboratory tests for disseminated intravascular intravascular coagulation. *Expert Rev Hematol* 2012; **5**: 643–652.
3 Franchini M, Lippi G, Manzato F. Recent acquisitions in the pathophysiology, diagnosis and treatment of disseminated intravascular coagulation. *Thromb J* 2006; **4**:4.
4 Iba T, Gando S, Thachil J. Anticoagulant therapy for sepsis-associated disseminated intravascular coagulation: the view from Japan. *J Thromb Haemost* 2014; **12**:1010–1019.
5 Marshall JC. Why have clinical trials in sepsis failed? *Trends Mol Med* 2014; **20**:195–203.
6 Tsai HM. Pathophysiology of thrombotic thrombocytopenic purpura. *Int J Hematol* 2010; **91**:1–19.
7 Sadler JE. von Willebrand factor: two sides of a coin. *J Thromb Haemost* 2005; **3**:1702–1709.
8 Levi M, van der Poll T. A short contemporary history of disseminated intravascular coagulation. *Semin Thromb Hemost* 2014; **40**:874–880.
9 Moschcowitz E. An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries: an undescribed disease. *Arch Intern Med* 1925; **36**:89–93.
10 Singer K, Bornstein FP, Wile SA. Thrombotic thrombocytopenic purpura; hemorrhagic diathesis with generalized platelet thromboses. *Blood* 1947; **2**:542–554.
11 McKay DG. Progress in disseminated intravascular coagulation. *Calif Med* 1969; **111**:186–198; 279–290.
12 Levi M, Scully M. How I treat disseminated intravascular coagulation. *Blood* 2018; **131**:845–854.
13 Boral BM, Williams DJ, Boral LI. Disseminated intravascular coagulation. *Am J Clin Pathol* 2016; **146**:670–680.
14 Chang JC, Newman RS. Redefining the syndromes of thrombotic microangiopathy. *Ther Apher Dial* 2004; **8**:73–74.
15 Chang JC. The understanding of thrombotic thrombocytopenic purpura: dyadic, triadic, pentadic, and other manifestations. *J Clin Apher* 2004; **19**:2–4.
16 Chang JC, Shipstone A, Llenado-Lee MA. Postoperative thrombotic thrombocytopenic purpura following cardiovascular surgeries. *Am J Hematol* 1996; **53**:11–17.
17 Sarode R. Atypical presentations of thrombotic thrombocytopenic purpura: a review. *J Clin Apher* 2009; **24**:47–52.
18 Chang JC, Aly ES. Acute respiratory distress syndrome as a major clinical manifestation of thrombotic thrombocytopenic purpura. *Am J Med Sci* 2001; **321**:124–128.
19 Qahtani SA. Acute renal failure and severe rhabdomyolysis in a patient with resistant thrombotic thrombocytopenic purpura. *Int J Gen Med* 2011; **4**:687–689.
20 Thomas MR, Robinson S, Scully MA. How we manage thrombotic microangiopathies in pregnancy. *Br J Haematol* 2016; **173**:821–830.
21 Chang JC, Kathula SK. Various clinical manifestations in patients with thrombotic microangiopathy. *J Investig Med* 2002; **50**:201–206.
22 Booth KK, Terrell DR, Vesely SK, George JN. Systemic infections mimicking thrombotic thrombocytopenic purpura. *Am J Hematol* 2011; **86**:743–751.
23 Lopes da Silva R. Viral-associated thrombotic microangiopathies. *Hematol Oncol Stem Cell Ther* 2011; **4**:51–59.
24 Chang JC. A thought on possible pathogenesis of Ebola viral hemorrhagic disease and potential treatments: could it be thrombotic thrombocytopenic purpura-like syndrome? *J Ther Aph Dialysis* 2016; **20**:93–98.

25 Moake JL, Rudy CK, Troll JH, Weinstein MJ, Colannino NM, Azocar J, *et al.* Unusually large plasma factor VIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. *N Engl J Med* 1982; **307**:1432–1435.

26 Furlan M, Robles R, Lämmle B. Partial purification and characterization of a protease from human plasma cleaving von Willebrand factor to fragments produced by in vivo proteolysis. *Blood* 1996; **87**: 4223–4234.

27 Tsai HM. Physiologic cleavage of von Willebrand factor by a plasma protease is dependent on its conformation and requires calcium ion. *Blood* 1996; **87**:4235–4244.

28 Chang JC. Thrombocytopenia in critically ill patients due to vascular microthrombotic disease: pathogenesis based on 'two activation theory of the endothelium'. *Vascul Dis Ther* 2017; **2**:1–7.

29 Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. *Blood* 2003; **101**:3765–3777.

30 Zhang C. The role of inflammatory cytokines in endothelial dysfunction. *Basic Res Cardiol* 2008; **103**:398–406.

31 Janicek MJ, Van den Abbeele AD, Hollenberg NK, Kassis AI, Holman BL, Tumeh SS. Platelet activation and aggregation after endothelial injury. Assessment with indium-111-labeled platelets and angiography. *Invest Radiol* 1990; **25**:988–993.

32 Valentijn KM, van Driel LF, Mourik MJ, Hendriks GJ, Arends TJ, Koster AJ, Valentijn JA. Multigranular exocytosis of Weibel–Palade bodies in vascular endothelial cells. *Blood* 2010; **116**:1807–1816.

33 Huang J, Roth R, Heuser JE, Sadler JE. Integrin alpha(v)beta(3) on human endothelial cells binds von Willebrand factor strings under fluid shear stress. *Blood* 2009; **113**:1589–1597.

34 Mourik MJ, Valentijn JA, Voorberg J, Koster AJ, Valentijn KM, Eikenboom J. von Willebrand factor remodelling during exocytosis from vascular endothelial cells. *J Thromb Haemost* 2013; **11**:2009–2019.

35 Aird WC. Endothelial cell heterogeneity. *Cold Spring Harb Perspect Med* 2012; **2**:a006429.

36 Sueishi K, Takeuchi M. Pathology of disseminated intravascular coagulation. *Nihon Rinsho* 1993; **51**:30–36.

37 Kotiah SD. Acute promyelocytic leukemia: clinical presentation. Available at: http://emedicine.medscape.com/article/1495306-clinical. [Accessed 31 January 2018]

38 Cooperberg AA. Acute promyelocytic leukemia. *Can Med Assoc J* 1967; **97**:57–63.

39 Chang JC, Gross HM, Jang NS. Disseminated intravascular coagulation due to intravenous administration of hetastarch. *Am J Med Sci* 1990; **300**:301–303.

40 Wada H, Thachil J, Di Nisio M, Mathew P, Kurosawa S, Gando S, *et al.* The Scientific Standardization Committee on DIC of the International Society on Thrombosis Haemostasis. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. *J Thromb Haemost* 2013; **11**:761–767.

41 Rao LV, Kothari H, Pendurthi UR. Tissue factor encryption and decryption: facts and controversies. *Thromb Res* 2012; **129 (Suppl 2)**: S13–S17.

42 Chen VM, Hogg PJ. Encryption and decryption of tissue factor. *J Thromb Haemost* 2013; **11 (Suppl 1)**:277–284.

43 Versteeg HH, Ruf W. Thiol pathways in the regulation of tissue factor prothrombotic activity. *Curr Opin Hematol* 2011; **18**:343–348.

44 Rauch U, Bonderman D, Bohrmann B, Badimon JJ, Himber J, Riederer MA, Nemerson Y. Transfer of tissue factor from leukocytes to platelets is mediated by CD15 and tissue factor. *Blood* 2000; **96**:170–175.

45 Østerud B, Bjørklid E. The tissue factor pathway in disseminated intravascular coagulation. *Semin Thromb Hemost* 2001; **27**: 605–617.

46 Taylor FB Jr, Wada H, Kinasewitz G. Description of compensated and uncompensated disseminated intravascular coagulation (DIC) responses (nonovert and overt DIC) in baboon models of intravenous and intraperitoneal *Escherichia coli* sepsis and in the human model of endotoxemia: toward a better definition of DIC. *Crit Care Med* 2000; **28 (9 Suppl)**:S12–S19.

47 Asakura H. Classifying types of disseminated intravascular coagulation: clinical and animal models. *J Intensive Care* 2014; **2**:20.

48 Panackel C, Thomas R, Sebastian B, Mathai SK. Recent advances in management of acute liver failure. *Indian J Crit Care Med* 2015; **19**:27–33.

49 Kularatne SA, Imbulpitiya IV, Abeysekera RA, Waduge RN, Rajapakse RP, Weerakoon KG. Extensive haemorrhagic necrosis of liver is an unpredictable fatal complication in dengue infection: a postmortem study. *BMC Infect Dis* 2014; **14**:141.

50 Talwani R, Gilliam BL, Howell C. Infectious diseases and the liver. *Clin Liver Dis* 2011; **15**:111–130.

51 Samanta J, Sharma V. Dengue and its effects on liver. *World J Clin Cases* 2015; **3**:125–131.

52 El Sayed SM, Abdelrahman AA, Ozbak HA, Hemeg HA, Kheyami AM, Rezk N, *et al.* Updates in diagnosis and management of Ebola hemorrhagic fever. *J Res Med Sci* 2016; **21**:84.

53 Mammen EF. Coagulation abnormalities in liver disease. *Hematol Oncol Clin North Am* 1992; **6**:1247–1257.

54 Senzolo M, Burra P, Cholongitas E, Burroughs AK. New insights into the coagulopathy of liver disease and liver transplantation. *World J Gastroenterol* 2006; **12**:7725–7736.

55 Castellone D. Available at: http://www.aniara.com/Blog/Coagulation-Corner/archives/2010/11/LIVER-DISEASE-AND-COAGULATION-OUTCOMES.aspx. [Accessed 2010]

56 Rimmer E, Houston BL, Kumar A, Abou-Setta AM, Friesen C, Marshall JC, *et al.* The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis. *Crit Care* 2014; **18**:699.

57 Hadem J, Hafer C, Schneider AS, Wiesner O, Beutel G, Fuehner T, *et al.* Therapeutic plasma exchange as rescue therapy in severe sepsis and septic shock: retrospective observational single-centre study of 23 patients. *BMC Anesthesiol* 2014; **14**:24.

58 Reeves JH. A review of plasma exchange in sepsis. *Blood Purif* 2002; **20**:282–288.

59 Nguyen TC, Han YY. Plasma exchange therapy for thrombotic microangiopathies. *Organogenesis* 2011; **7**:28–31.

60 Nguyen TC, Kiss JE, Goldman JR, Carcillo JA. The role of plasmapheresis in critical illness. *Crit Care Clin* 2012; **28**:453–468.

61 Sakamaki Y, Konishi K, Hayashi K, Hashiguchi A, Hayashi M, Kubota E, *et al.* Renal thrombotic microangiopathy in a patient with septic disseminated intravascular coagulation. *BMC Nephrol* 2013; **14**:260.

62 Chang JC, Gupta S. Acute respiratory distress syndrome and nonocclusive mesenteric ischemia as major clinical manifestations of thrombotic thrombocytopenic purpura: complete remission following exchange plasmapheresis. *J Clin Apher* 1998; **13**:190–192.

63 Franchini M, Manzato F, Salvagno GL, Lippi G. Potential role of recombinant activated factor VII for the treatment of severe bleeding associated with disseminated intravascular coagulation: a systematic review. *Blood Coagul Fibrinolysis* 2007; **18**:589–593.

64 Palomino MA, Chaparro MJ, de Elvira MJ, Curiel EB. Recombinant activated factor VII in the management of massive obstetric bleeding. *Blood Coagul Fibrinolysis* 2006; **17**:226–227.

65 Martínez J, Cid AR, de la Rubia J, Gimeno R. Treatment of intra-abdominal bleeding with recombinant activated factor VII in a patient with disseminated intravascular coagulation secondary to septic shock. *Blood Coagul Fibrinolysis* 2005; **16**:297–299.