Thrombocytopenia in critically ill patients due to vascular microthrombotic disease: pathogenesis based on “two activation theory of the endothelium”

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Abstract
The pathogenesis of thrombocytopenia in critically ill patients (TCIP) has not been established yet. Based on “two-activation theory of the endothelium”, TCIP is a manifestation of platelet activation and consumption in association with endotheliopathy. Endotheliopathy occurs in many critical illnesses. An injury to vascular endothelial cells (ECs) from pathogen or insult leads to endothelial dysfunction, which initiates the activation of two distinctly independent molecular pathways (i.e., inflammatory and microthrombotic). The activation of inflammatory pathway occurs due to the release of inflammatory cytokines from injured ECs. Inflammatory cytokines mediate inflammation. The activation of microthrombotic pathway is induced by the activation of platelets and endothelial exocytosis of unusually large von Willebrand factor multimers (ULVWF). Activated platelets are recruited by excytoxed ULVWF, which are anchored to ECs, and together assemble microthrombi consisting of platelets-ULVWF complexes. This microthrombogenesis leads to consumptive thrombocytopenia (i.e., TCIP) and disseminated intravascular microthrombosis (DIT). DIT triggers vascular microthrombotic disease (VMTD), which manifestations include hypoxic multi-organ dysfunction syndrome, and thrombotic microangiopathy (TMA). The combined syndrome due to the activation of both inflammatory pathway and microthrombotic pathway is called systemic inflammatory response syndrome (SIRS). Also, the true nature of “DIC” is endotheliopathy-associated DIT/VMTD (i.e., TTP-like syndrome).

Abbreviations
ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, rADAMTS13: recombinant ADAMTS13, AH/AHNS: acute hepatitis/acute hepatic necrosis syndrome, ARDS: acute respiratory distress syndrome, ARF: acute renal failure, CABG: coronary artery bypass graft, C-APLAS: catastrophic anti-phospholipoid antibody syndrome, CNS: central nervous system, CNSD: central nervous system dysfunction, DSS: dengue shock syndrome, DIC: disseminated intravascular coagulation, DIT: disseminated intravascular thrombosis, ECs: endothelial cells, E: gastroenteritis, HC: hepatic coagulopathy, HCP: hantavirus pulmonary syndrome, HCPs: hantavirus cardiopulmonary syndrome, HELLPs: hemolysis: elevated liver enzymes: and low platelet count syndrome, HFRS: hemorrhagic fever with renal syndrome, HUS: hemolytic-uremic syndrome, LDH: lactate dehydrogenase, MAHA: microangiopathic hemolytic anemia, aMAHA: atypical microangiopathic hemolytic anemia, MERS-CoV: middle east respiratory syndrome-coronavirus, MODS: multi-organ dysfunction syndrome, MOF: multi-organ failure, MRSA: methicillin-resistant staphylococcus aureus, NOMI: non-occlusive mesenteric ischemia, RMSF: Rocky mountain spotted fever, SARS-CoV: severe acute respiratory syndrome-coronavirus, SIRS: systemic inflammatory response syndrome, SFTS: severe fever with thrombocytopenia syndrome, TAMOF: thrombocytopenia-associated multiple organ failure, TCIP: thrombocytopenia in critically ill patients, TMA: thrombotic microangiopathy, TTP: thrombotic thrombocytopenic purpura, ULVWF: unusually large von Willebrand factor multimers, VMTD: vascular microthrombotic disease

Introduction
In the critically ill patient, thrombocytopenia is a very common hematological condition that occurs due to several different pathogenic mechanisms, and manifests with a broad clinical spectrum from benign presentation to life-threatening emergency. Mild to moderate thrombocytopenia plays a minor role in short-term clinical course, but the patient outcome related to the thrombocytopenia depends more upon the underlying pathologic disease.

Even after careful exclusion of the known etiology of thrombocytopenia, the cause of thrombocytopenia cannot be clearly determined in more than half of critically ill patients. This etiology-unidentified thrombocytopenia, encountered in critical illnesses (e.g., sepsis/septic shock, severe trauma, and complications of pregnancy, transplant and surgery), has been designated as “thrombocytopenia in critically ill patients” (TCIP) [1]. TCIP is now suspected to be an unfavorable indicator influencing the prognosis of the patient [2-4].

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TCIP in the critical care setting

The known mechanisms producing thrombocytopenia in critically ill patients include: 1) decreased production of the platelet due to transient bone marrow suppression or myelodysplasia (e.g., infection-associated), 2) increased destruction due to immune or non-immune response (e.g., drug or transfusion-induced), 3) increased utilization (e.g., disseminated intravascular coagulation - DIC), 4) increased consumption (e.g., heparin-induced thrombocytopenia, and thrombotic thrombocytopenic purpura - TTP), and 5) sequestration secondary to hypersplenism [5,6]. To date, TCIP is the term to use after the exclusion of known mechanisms.

The example of critical illnesses and conditions associated with TCIP is listed in Table 1. Thrombocytopenia is typically recognized after admission to the critical care unit for conditions such as sepsis, severe physical injury, acute respiratory distress syndrome (ARDS), and central nervous system dysfunction. In severe infection due to pathogen causing bacterial sepsis, viral pneumonia (e.g., Middle East respiratory distress syndrome due to coronavirus), and viral hemorrhagic fevers (e.g., Ebola, hantavirus, and dengue), TCIP occurs in advancing stage of the illness.

TCIP is mild to moderately severe usually with the platelet count not less than 20,000/µL. Hemorrhagic tendency has been uncommon unless it occurs with severe thrombocytopenia, DIC or hepatic coagulopathy. Thus, to some clinicians TCIP is considered to be not a serious issue in the management of critically ill patients.

The degree of thrombocytopenia has been correlated with the severity of clinical course. Increasing thrombocytopenia was associated with higher mortality and longer length of hospital stay, and the increase of the platelet count was an early sign of clinical improvement with higher mortality and longer length of hospital stay, and the serious issue in the management of critically ill patients.

Table 1. Examples of thrombocytopenia (TCIP)-associated conditions seen in critical care.

| Infectious agent | Causes | Involved organs | Associated syndromes |
|------------------|--------|-----------------|----------------------|
| Virus            | Ebola  | Lungs; liver; multi-organ | ARDS; hepatic necrosis; MODS |
|                  | H1N1 influenza | Brain; lungs; multi-organ | Encephalopathy; ARDS; MODS |
|                  | MERS-CoV | Lungs; multi-organs | ARDS; MODS |
|                  | SARS-CoV | Lungs; multi-organs | ARDS; MODS |
|                  | Hantavirus | Heart; lung; kidneys | HCPS; HPS; HFRS |
|                  | Dengue  | Adrenals; multi-organs | DDS; MODS |
|                  | SFTS virus | Multi-organs | SFTS; MODS |
| Bacteria         | Neisseria meningitides | Adrenals; Bowels; kidneys | Waterhouse-Friderichsen syndrome |
|                  | E.Coli O157:H7 | Multi-organs | Hemolytic-uremic syndrome; GE MODS; SIRS |
|                  | MRSA    | Lungs; multi-organs | ARDS; MODS; SIRS |
|                  | Klebsiella pneumonia | Lungs; multi-organs | ARDS; SIRS; TAMOF; C-APLAS |
|                  | Various bacterial sepsis | Lungs; multi-organs | |
| Rickettsia       | Rickettsia rickettsii | Skin; multi-organs | RMSF; MODS |
| Fungus           | Candida albicans | Multi-organs | MODS; SIRS |
| Parasite         | Plasmodium falciparum | Brain; multi-organs | Cerebral malaria; MODS; ARDS; SIRS |
|                  | Plasmodium vivax | Lungs; multi-organs | ARDS |
| Trauma           | Lungs/chest trauma | Motorcycle accident | |
|                  | CNS trauma | Head injury | ARDS; MODS; SIRS |
|                  | Lungs | Lungs; multi-organs | Encephalopathy; ARDS; MODS; SIRS |
|                  | Heart | Brain; lungs; multi-organ | |
| Surgery          | Cardiac surgery | CABG; open heart surgery | ARDS; myocardial ischemia; MODS |
|                  | Vascular surgery | Aortic aneurysm surgery | ARDS; MODS |
|                  | Bowel surgery | Mesenteric inflammation | NONE; MODS |
| Pregnancy        | Pre-eclampsia | Toxin (?) ; infection (?) | ARDS; HELLPs; Abruptio placenta; MODS |
| Transplant       | Liver transplant | Infection (?) | ARDS; MODS |
|                  | Kidney transplant | Infection (?) | ARDS; MODS |

Endothelium and critical illnesses

The endothelium is a delicate biological structure that lines the entire circulatory system. It maintains the integrity of the blood supply by protecting the human body from the invasion of pathogen and insult. It also guards the circulatory system against unneeded intravascular coagulation by preventing the intrusion of tissue factor (TF) at the basement membrane of ECs [15]. ECs do not express in vivo TF. In sepsis and other critical illnesses, the membrane barrier of ECs is not disrupted. Thus, TF does not enter into circulation from extravascular compartment, and intravascular coagulation (i.e., DIC) cannot be initiated. However, injured ECs become activated, and endothelial dysfunction leads to endotheliopathy triggering several molecular responses [16-22].

Endotheliopathy is associated with inflammation [23], platelet activation [24] and exocytosis of unusually large von Willebrand factor multimers (ULVWF) [25-27]. It is also associated with thrombocytopenia (i.e., TCIP) and disseminated intravascular microthrombosis (DIT) [28,29]. Other clinical syndromes associated with critical illnesses include SIRS [13,14], ARDS [19,22], MODS [4,6,11,12], "DIC" [30-32], thrombotic thrombocytopenic purpura (TTP)-like syndrome [33-39], hepatic coagulopathy, and others [36,40].

Current hypothesis for the pathogenesis of vascular microthrombosis, especially in sepsis, is based on the intricate interaction between inflammation and coagulation system. The release of endothelial cytokines would trigger TF-mediated activation of coagulation leading to disseminated intravascular micro blood clots, inducing to vascular microthrombosis (i.e., "DIC") [30,41,42].
Contrary to this concept, microthrombogenesis plays a key role in the pathogenesis of TTP and TTP-like syndrome. In endotheliopathy, the platelet is activated and excessive amounts of ULVWF are released from ECs [24-27,40]. The result is the formation of microthrombi made of platelet-ULVWF complexes, which also lead to vascular microthrombosis [26,27,34,36,40].

To annotate inflammation and circulatory disorder in the critical illness, a novel hypothesis of “two-activation theory of the endothelium” is proposed [36,40].

Two-activation theory of the endothelium

Endotheliopathy initiates two significant molecular events: 1) release of inflammatory cytokines (e.g., interleukin (IL)-1, IL-6, tumor necrosis factor-α, and others) [16-22], and 2) activation of the platelet and exocytosis of ULVWF [24-27]. The former triggers inflammation, which is called “activation of inflammatory pathway”, and the latter initiates microthrombogenesis, which is expressed as “activation of microthrombotic pathway”. These two independent responses are the essence of “two-activation theory of the endothelium” as illustrated in Figure 1. The manifestation of activated inflammatory pathway is inflammation with symptoms such as fever, myalgia, arthralgia, and malaise, and that of activated microthrombotic pathway is consumptive thrombocytopenia, hypoxemia, multi-organ dysfunction and multiple clinical syndromes as presented in Figure 1 and Table 1.

The activation of inflammatory pathway occurs due to release of cytokines in both sepsis and non-septic critical illnesses. Unlike in non-septic illnesses, sepsis also promotes inflammation through another loop of activated circulating immune cell pathway (e.g., macrophages, monocytes, neutrophils, and lymphocytes). This pathway also interacts with activated ECs as shown in Figure 1 [43,44]. This additional cytokine expression accentuates the inflammatory pathway that could result in “cytokine storm”. This mechanism explains why severe inflammation occurs in sepsis, which might lead to SIRS [11,13,14,45].

On the other hand, the activation of microthrombotic pathway is initiated by activated platelets and excessively exocytosed ULVWF that are anchored to ECs as long elongated strings [46,47]. If protease ADAMTS13, which cleaves ULVWF to smaller molecular weight VWF, is under expressed [36,48], activated platelets under shear stress of blood flow are recruited to the uncleaved ULVWF strings. This microthrombogenesis generates intravascular microthrombi consisting of platelet-ULVWF complexes at ECs [46,47]. This process sets off DIT and could lead to multiple clinical syndromes.

Endotheliopathy-associated vascular microthrombotic disease

DIT is the underlying pathology provoking vascular microthrombotic disease (VMTD) [36,40], which triggers hypoxic multi-organ dysfunction and thrombotic microangiopathy (TMA). Three kinds of disseminated VMTD are known to exist: 1) antibody-associated VMTD (i.e., acquired TTP), 2) gene mutation-associated VMTD (i.e., hereditary TTP), and 3) endotheliopathy-associated VMTD (TTP-like syndrome). Endotheliopathy-associated DIT/VMTD is the underlying pathologic condition producing TTP-like syndrome. It is characterized by TCIP, microangiopathic hemolytic anemia (MAHA)/atypical MAHA (if fewer schistocytes are present)/with without MODS.

Figure 1. Pathogenesis of TCIP and related syndromes in critically ill patients

Pathogen; Polytrauma; Surgery; Pregnancy; Transplant; Drug/Toxin

Activation of immune cells in sepsis → Endothelial Injury & activation → Endotheliopathy

Inflammatory pathway activation

Cytokine release & “Storm”

Fever

Inflammation

Microthrombotic pathway activation

Activated platelet & endothelial exocytosis of ULVWF

If ADAMTS13 is inefficient or insufficient, activated platelet-ULVWF complex strings anchored to ECs → Endotheliopathy-associated DIT

VMTD

TMA

TCIP

MAHA/aMAHA

TTP-like syndrome

SIRS

Multi-organ hypoxia

ARDS; MODS; AHNS

MOF; HC

TCIP

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Perhaps the dissimilar clinical features (e.g., central nervous system dysfunction in TTP and ARDS in TTP-like syndrome) are related to microthrombogenesis occurring at different sites, resulting in different clinical syndromes due to divergent localization of intravascular microthrombi, even among the TTP-like syndromes (Table 2). TTP seems to be the result of microvascular microthrombosis, but TTP-like syndrome is the result of vascular microthrombosis. In the former, microthrombogenesis occurs in the circulation and formed thrombomhi become lodged in microvasculatures [49], predominantly in the brain and kidneys. But in the latter, it occurs at ECs-anchored long elongated ULVWF strings [46,47] in smaller and larger vasculatures, commonly involving the lungs (i.e., ARDS), kidneys (i.e., acute renal failure, hemolytic-uremic syndrome), liver (i.e., acute hepatic necrosis syndrome), intestines (i.e., gastroenteritis), pancreas (i.e., acute pancreatitis), muscles (i.e., rhabdomyolysis), heart (i.e., acute myocardial ischemia), skin (i.e., purpura fulminans), and others.

**DIC** vs. DIT

According to the “two-activation theory”, DIT induced by microthrombogenesis is completely different from true DIC occurring as a result of activated TF coagulation pathway. DIT is a microthrombotic disorder, but true DIC is a coagulation disorder. Additionally, the current concept of pathologic coagulation (i.e., “DIC”) through TF pathway in the critical illness cannot be correct because in vivo sufficient TF is not available in the ECs. The characteristic difference between DIT and true DIC is shown in Table 3.

Donald McKay in early 1950s coined the term “DIC” [50] for a coagulation disorder that is caused by abnormally activated intravascular thrombotic state. He and his associates believed intravascular microthrombi in the luminal arterioles and capillaries in the pathologic tissue examination were micro blood clots made of platelets, coagulation factors and fibrins. His followers also supported the diagnosis of “DIC” with the laboratory result of prolonged prothrombin time and activated partial thromboplastin time, hypofibrinogenemia, and increased fibrin degradation products. The most of the coagulopathy associated with thrombocytopenia in the critical illnesses has been ascribed to “DIC” [51-53].

It should be emphasized that since no single laboratory test or set of tests is sensitive or specific enough to allow a definite diagnosis of**

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**Table 2. Genesis and characteristics of DIT/VMTD in TTP and TTP-like syndrome.**

| Event | Description | Laboratory Features | Hematologic Features |
|-------|-------------|---------------------|----------------------|
| Primary event | Hereditary ADAMTS13 gene mutation | ADAMTS13 activity: Markedly decreased (<5% of normal) | Consumptive thrombocytopenia (MAHA) |
| | Acquired ADAMTS13 antibody formation | ADAMTS13 antibody: Positive in acquired TTP | MAHA/MAHA |
| Secondary event | Excessive circulating ULVWF & platelet aggregation | Haptoglobin: Increased | Very common |
| | Microthrombogenesis leading to platelet-ULVWF complexes | Haptoglobin: Markedly decreased | Very common in sepsis/septic shock |
| Tertiary event | Microthrombi lodged in arteriolar capillary lumens | ADAMTS13 activity: Markedly decreased | Very common in sepsis/septic shock |
| | VMTD | LDH: Increased | Common |
| Final event | TMA (microthrombotic microangiopathy) | LDH: Markedly decreased | Common |
| | TTP | Hemoglobin: None to +++ | Common |

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**Table 3. Hematological and Clinical Characteristics of endotheliopathy-associated DIT and true DIC.**

|                      | Endotheliopathy-associated DIT (including "DIC" of McKay) | True DIC |
|----------------------|----------------------------------------------------------|----------|
| **Examples**         | TTP-like syndrome                                        | DIC associated with APL |
| **Nature of the disorder** | Microthrombosis made of platelet-ULVWF complexes | Coagulation activated by TF-FVIIa complexes |
| **Mechanism of the genesis** | Intravascular microthrombogenesis | Intravascular coagulation |
| **Inciting events** | Sepsis, complications of surgery, pregnancy, cancer, and transplant, and drugs/toxins leading to endotheliopathy | APL and drugs (?) leading to TF expression |
| **Hematological manifestations** | TTP-like syndrome | Hemorrhagic disorder of APL |
| **Pathogenesis**     | Activation of microthrombotic pathway | Activation of TF-FVIIa complex pathway |
| **Site of activation** | Intravascular membrane of the endothelium | In circulation of the Intravascular space |
| **Pathology**        | Endothelial activation/dysfunction → endotheliopathy | TF expression → coagulation and factor consumption |
| **Result of pathogenesis** | Formation of platelet-ULVWF microthrombi | Depletion of fibrinogen, FVIII, FV |
| **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** | Normal | Decreased |
| Fibrinogen            | Prolonged | Prolonged |
| PT; aPTT; TT          | Normal | Increased |
| FDP                   | Normal or markedly increased | Markedly decreased |
| **Thrombocytopenia**  | Moderately severe | Mild to very severe |
| **Associated clinical syndromes** | TTP-like syndrome, TMA, MODS, SIRS | Hemorrhagic disorder |
| **Associated hematologic features** | Schistocytes, MAHA, aMAHA, Consumptive thrombocytopenia, Hepatic coagulopathy | 0 - ++ |
| Schistocytes          | Often present | Absent |
| MAHA/aMAHA           | Always present | Present (?) |
| Consumptive thrombocytopenia | May occur | Unusual |
| Hepatic coagulopathy  | 0 - ++ (?) | 0 - ++ (?) |
| **Incidences in clinical practice** | Very common | Extremely rare |
| **Therapy**           | Contraindicated | May be needed for APL |
| Platelet transfusion  | TPE, rADAMTS13 (expected to be very effective) | Treat underlying pathology (e.g., ATRA in APL) |

"DIC" [54]. In most cases the diagnosis is based on the combination of results of non-specific abnormal coagulation profile in the patient with clinical conditions known to be associated with "DIC" [55].

In clinical medicine, "DIC" mainly has been diagnosed on clinical pretense and is accepted based on the scoring system of the International Society on Thrombosis and Haemostasis (ISTH). Because of the misconception of "DIC", DIT in the critically ill patient has been diagnosed as "DIC", "DIC" diagnosis has not been based on more reliable coagulation factor assay of FVIII and FV, which are typically depleted in true DIC [40,56-59] as seen in acute promyelocytic leukemia. In many patients with "DIC", the coagulation profile is perfectly normal and hemorrhagic tendency does not occur. Puzzled but conveniently, the concept of "chronic/compensated/ covert" was introduced. This description, however, cannot explain inexplicably extensive microthrombi in the absence of depleted coagulation factors.

"DIC" and endotheliopathy-associated DIT/VMTD (i.e., TTP-like syndrome) are exactly the same in their underlying risk factors and presentation. Both almost always occur in critical illnesses (e.g. sepsis/septic shock, trauma, immunologic and collagen-vascular diseases, and complications of surgery, pregnancy and transplant) [38,60,61]. Pathologically both are characterized by arteriolar and capillary hyaline microthrombi with variable fibroelastic proliferation [49,62]. Hematologically they also present with TCIP and MAHA/aMAHA. Therefore, "DIC" and DIT are exactly the same disorder.

**"DIC" perplexity explained**

Considering the different pathogenic mechanisms between DIC and DIT, "DIC" must have been started with a incorrect concept. Hence, "DIC" is a misnomer. For more than 60 years, this unfortunate misconception on "DIC" has created confusion in medical science and practice, including diagnostic dilemma [54,55] and treatment failures to date [63].

If one accepts the fact that "DIC" is a misnomer and its euonym must be endotheliopathy-associated DIT, "DIC" can be explained perfectly well by the concept of DIT. The only remaining question is how "DIC" sometimes is associated with hemorrhagic disorder. Another word, "What is the correct diagnosis for acute "DIC" that is associated with abnormal coagulation profile?" The hemorrhagic disorder in "DIC" can be explained by hepatic vascular microthrombosis. Endotheliopathy-associated DIT/VMTD can trigger acute hepatic necrosis syndrome leading to hepatic coagulopathy [40]. Indeed, hepatic coagulopathy shows exactly the same coagulation profile as seen in "acute DIC".

True DIC is very rare but perhaps occurs in acute promyelocytic leukemia, presumably due to TF expression from leukemic cells [64]. The predominant feature of true DIC is hemorrhagic disorder without MAHA/aMAHA, hypoxic organ dysfunction and MODS [56-58]. In differentiating true DIC from hepatic coagulopathy, the appropriate test is the assay of coagulation factors, especially FVIII and FV, which are depleted in true DIC. More importantly, in hepatic coagulopathy, FVIII is normal or increased although it is markedly decreased in true DIC [40,58,59]. Also, a markedly decreased liver dependent FVII occurs in hepatic coagulopathy. A suggested guideline for laboratory tests is presented in Table 4 to aid the differential diagnosis among complicated thrombopathies and coagulopathies [36].

**Conclusion**

In the critically ill patient, TCIP is the earliest sign suggestive of microthrombogenesis in progress. In addition to inflammation,
endotheliopathy-associated DIT/VMTD may lead to MODS, TMA, TTP-like syndrome and SIRS. "DIC" presents with the same clinical, pathologic and hematologic features as TTP-like syndrome. "DIC" should be correctly renamed as TTP-like syndrome.

Author disclosures

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