Trombocytopenia: One of the Markers of Disseminated Intravascular Coagulation

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Key Words

Disseminated intravascular coagulation ·
Thrombocytopenia · Coagulation

Abstract

Disseminated intravascular coagulation (DIC) is a complication of a variety of severe underlying diseases and a contributing factor in multi-organ failure and death. DIC is diagnosed on the basis of clinical findings (organ failure, bleeding) and laboratory abnormalities. The laboratory data include (repeated) measurements of platelet count and global clotting tests, to which more specific and sensitive tests for activated coagulation are added. The focus of this paper is on thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{l}$) as a marker in DIC. First, in patients with suspected DIC it is imperative to consider alternative causes of thrombocytopenia, such as related to heparin use (heparin induced thrombocytopenia II) or thrombocytopenic purpura. Second, the observation of thrombocytopenia in relation to DIC should be interpreted as a marker of advanced or overt DIC and not as an early indicator. According to recommended guidelines measurements of platelet counts should always be coupled to a panel of coagulation markers and not be used as single marker of DIC (or other syndromes). In general, thrombocytopenia should not trigger platelet transfusions

except in patients with severe bleeding complications.

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Introduction

Disseminated intravascular coagulation (DIC) is a complex syndrome occurring in the course of a variety of severe underlying diseases [1]. DIC is a constellation of clinical signs and symptoms of bleeding and organ failure (liver failure, diminishing urine output) combined with laboratory markers of intravascular coagulation. Thus, the current working definition of the International Society of Thrombosis and Haemostasis (ISTH) reads: "DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction" [2]. The ISTH further distinguishes overt from non-overt (impeding) DIC and formulates criteria for its assessment. These criteria include general available laboratory tests plus at least one test for activated clotting that reflects the process of blood coagulation in the systemic circulation. Thus, the state of events in a venous (or arterial) blood sample taken from a peripheral vessel (arm) or from a high caliber blood vessel (jugular or subclavian vein) is considered representative for the state of activity of the blood coagulation system at a given point in time.

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From many previous studies it is known that in general overt DIC is associated with all features of activated coagulation including evidence of fibrin formation and turnover due to limited fibrinolysis and depletion of blood cells (leukocytes, platelets), in part due to interaction with the forming microvascular fibrin meshwork. Hence, to document DIC both clotting tests and platelet counts are routinely measured and the combined use of such tools is recommended by the ISTH. In addition, this policy follows and extends the previously adopted criteria from the Japanese Ministry of Health and Welfare. A recent comparison shows a reasonable concordance between the latter and ISTH criteria [3].

Mechanisms Involved in Overt DIC

Sepsis is one of the most important disorders that has been associated with DIC and has served as a model system of DIC. Since long the tight connection between pro-inflammatory cytokines and the onset of coagulation has been recognized and the mechanisms have been established in human and primate studies. The cytokines interleukin (IL) 1 and 6 are predominant inducers of cellular tissue factor expression, driving coagulation activation through NF κ B dependent mechanisms [4,5]. Similarly the initial activation of fibrinolysis is offset by induced expression and release in the blood of relative large amounts of plasminogen activator inhibitor 1 (PAI-1). These reactions are followed by alterations in function of several blood cells. Neutrophils are activated to release of numerous inflammatory agonists including elastase, which amplify the inflammatory response in tissues [6]. These cells are also relevant in localizing tissue factor that may add to the procoagulant forces upon passage to the subendothelial space. In addition, platelets are important players providing a catalytic surface for coagulation reactions, but also by liberating pro-inflammatory agonists including platelet activating factor, leukotrienes and CD 40L that may further localize and amplify the inflammatory response.

In the early phases of DIC overall clotting tests including prothrombin time and activated partial thromboplastin time are not sufficiently sensitive for detecting impending DIC. Under conditions of low grade inflammation induced by infusing lipopolysaccharide Reitsma et al detected subtle increments in the levels of a number of coagulation proteins in plasma [7]. The first 4-6 hours after acute LPS challenge are further dominated by increased levels of thrombin generation indices (F1+2, thrombin antithrombin complexes) and gradually impaired fibrinolysis due to PAI-1 increments. During this stage of DIC the platelet count may not be markedly lowered (see further).

In models of sepsis similar changes are being seen in the first 6 hours after *E. coli* challenge. In these sepsis models in baboons platelet and neutrophil counts do not show a clear bacterial dose response relationship [8]. The platelet count gradually diminishes during the 6 hour period to an average of about $165 \times 10^3/\mu\text{l}$, but major drops occur later, during the remaining 48 hours of observation, while leukocyte counts and fibrinogen levels return to normal values in surviving baboons. The typical pattern of DIC related to sepsis that emerges from these experiments is a first phase of an increased state of activity of inflammation and coagulation and a downregulated fibrinolysis, facilitating intravascular fibrin formation. This phase can be considered as non-overt DIC and can only be traced in patients by careful follow-up of laboratory tests including sensitive tests for thrombin and fibrin generation. It appears that detection of this state may be clinically relevant because non-overt DIC indicated increased mortality in intensive care patients (partly reviewed in [9]).

The next stage of DIC, between 6 and 48 hours in the baboon studies, is dominated by features of depletion of coagulation factors, continued fibrin formation and severe depletion of platelets. In addition, damage of the microvasculature is indicated by elevated markers of endothelial cell damage (such as von Willebrand factor, soluble thrombomodulin or soluble tissue factor) and increased markers of cell damage such as LDH [8]. During this stage of overt DIC diminishing concentrations of coagulation proteins and platelets can become clinically relevant in relation with an increased bleeding risk or overt bleeding. This type of "consumption coagulopathy" is associated typically with bleeding from puncture sites and mucous membranes, while the picture known as purpura fulminans is typically associated with massive cutaneous bleeding [9]. Another distinct type of overt DIC is the so-called defibrination syndrome which is marked by low fibrinogen levels and high turnover of fibrin due to increased fibrinolytic activity.

Thrombocytopenia as an Indicator of Severe Disease

When considering the diagnostic value of thrombocytopenia as an (isolated) laboratory marker it is important to assess its involvement in severe disease in general.

Thrombocytopenia is usually defined as a platelet count of $< 100 \times 10^3/\mu\text{l}$ and is a frequent phenomenon in critically ill patients. Studies show that counts $< 100 \times 10^3/\mu\text{l}$ are encountered in 20-40% of such patients, while levels $< 50 \times 10^3/\mu\text{l}$ are seen in 10-20% of critically ill individuals. The potential causes of thrombocytopenia have been clearly summarized by Drews and Weinberger [10] and a modification of their table gives an overview (Table 1).

In patients prone to develop DIC a number of other causes of thrombocytopenia may be present and are essential to consider in the diagnostic workup. At any time, artifacts due to EDTA phenomenon or insufficient anticoagulation in the tube should be ruled out and a repeated sample (citrate) obtained in case of doubt. In case a patient starts with a low platelet count to begin with, any pre-existing conditions including nutritional deficiencies, impaired production due to bone marrow failure, liver disease, immune thrombocytopenic purpura (ITP) and splenic sequestration should be taken into account, particularly when a low platelet count occurs in the absence of other signs of activated coagulation.

When in an individual with a previously normal platelet count, this level decreases progressively, all remaining causes should be considered. At this stage, again, the other laboratory markers become essential in distinguishing DIC from other causes, although some doubt may remain. For instance, in viral infections such as mumps, varicella and dengue hemorrhagic fever thrombocytopenia is a frequent (or even "obligatory") finding and clotting times may range

from normal in uncomplicated infections to prolonged in severe cases where DIC may contribute to organ failure or bleeding [11].

Thrombotic thrombocytopenic purpura (TTP)/ hemolytic uremic syndrome (HUS) should be discriminated on the basis of other clinical and laboratory findings. The classic combination includes microangiopathic hemolytic anemia, thrombocytopenia, neurological signs and symptoms and renal disease. In the laboratory schistocytes are prominent in the blood smear and LDH levels usually more pronounced than in DIC, while most conventional coagulation markers are normal. In HELLP syndrome hemolysis with a microangiopathic blood smear and elevated LDH and liver function levels are dominant laboratory features. In addition, in 15% of pregnant women with preeclampsia thrombocytopenia develops which may become severe in a subset of these patients. Here, DIC may be a complicating syndrome.

Finally, heparin induced thrombocytopenia (HIT) should always be considered in the differential diagnosis, particularly since many patients prone for DIC are also being administered low dose heparin and nowadays low molecular weight heparin (LMWH) to prevent deep venous thrombosis or counteract DIC. Type I HIT is fairly common and is characterized by a usually temporary decrease in platelet count in 15-20% of patients on heparin, to a count not lower than $100 \times 10^3/\mu\text{l}$. Type II HIT occurs in 1-3% of patients on unfractionated heparin, starts usually later, i.e. between days 5 and 10 after initiation and is characterized by an immune mediated mechanism where antibodies against a platelet factor 4- heparin complex form that deplete platelets but also trigger the blood coagulation system. This type of HIT is particularly harmful since it elicits potentially life threatening thrombotic complications in 30-80% of patients. Thus, timely suspicion is critical which should lead to immediate discontinuation of all sources of heparin or LMWH used at that moment. Screening for antibodies involved in HIT II should be done with commercially available tests and confirmed if positive by specific ELISA or serotonin release assay. However, the outcomes of testing should be viewed with caution because of limitations of sensitivity as well as specificity. It is crucial to realize that antibodies involved in HIT occur also on LMWH therapy, although less frequent than on unfractionated heparin. The management of HIT II is beyond the discussion of this paper.

Table 1. Thrombocytopenia and disease (modified from Drews RE, Weinberger SE. Thrombocytopenic disorders in critically ill patients. *Am J Respir Crit Care Med* 2000; 162: 347-51).

1	Decreased platelet production (bone marrow suppression)
	<ul style="list-style-type: none"> • Viral infections • Drugs and toxins • Nutritional deficiencies • Congenital or acquired disorders of hematopoiesis (bone marrow aplasia or hypoplasia, myelodysplastic syndromes) • Liver diseases
2	Increased platelet destruction due to immune or non-immune causes
	<ul style="list-style-type: none"> • Idiopathic • Drug-induced (heparin, quinidine, valproic acid) • Infection related (EBV, CMV, HIV, dengue hemorrhagic fever) • Alloimmune destruction (transfusions) • DIC • TTP- HUS • Antiphospholipid antibody syndrome • HELLP syndrome • Physical destruction (artificial surfaces, giant hemangiomas)
3	Dilutional or distributional
	<ul style="list-style-type: none"> • Massive blood loss and transfusion related • Splenic sequestration
4	Spurious thrombocytopenia
	<ul style="list-style-type: none"> • EDTA phenomenon • In vitro clotting due to insufficient anticoagulant in test tube

Thrombocytopenia and DIC; Interpretation and Management

As indicated, thrombocytopenia is a relevant marker of DIC, provided that the diagnosis DIC is supported by other laboratory tests and other causes of thrombocytopenia have

been reliably ruled out. It is important to note that in experimental models of sepsis the development of thrombocytopenia comes rather late in the time course. This might mean that thrombocytopenia is a late indicator or a marker of overt DIC, while it would probably not be reliable as marker of impending (non-overt) DIC. For this reason, it is imperative to monitor platelet counts in conjunction with other markers of DIC, including clotting tests and more sensitive markers of activated clotting (TAT complexes, fibrin monomers etc.). Thus, the recommended strategy by the ISTH committee to follow development of thrombocytopenia together with other clotting markers should be followed in general.

The next issue is whether a platelet count should have management consequences. In general, thrombocytopenia should not trigger platelet transfusions in patients with DIC, particularly not if HIT II is suspected, to avoid worsening clotting. Surgical bleeding does usually not occur at platelet counts of at least $50 \times 10^3/\mu\text{l}$, while spontaneous bleeding is unlikely at counts down to $10 \times 10^3/\mu\text{l}$. Therefore, a conservative approach to patients with DIC seems wise, avoiding unnecessary transfusions. In case of severe bleeding secondary to DIC platelet transfusions may however be warranted targeting for a count of $> 50 \times 10^3/\mu\text{l}$.

Conclusions

Thrombocytopenia is considered an important constituent of the panel of tests for diagnosing DIC, but it probably reflects a more advanced stage of DIC (overt DIC), rather than an early phase (non-overt DIC). The differential diagnosis is however of considerable importance, because other causes of thrombocytopenia such as related to the use of heparin (HIT), preeclampsia, HELLP, TTP/HUS or certain systemic infections are also well known severe underlying conditions in patients with thrombocytopenia. Considering the diagnosis of DIC in a patient the platelet count should be an integral part of the further workup (including white cell counts and the coagulation panel as proposed by the ISTH subcommittee on DIC [2]). In addition, daily monitoring of platelets and other markers of DIC is recommended to determine the course as a marker of ongoing disease and a predictor of mortality.

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