Review

Coagulation abnormalities in critically ill patients

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Abstract

Many critically ill patients develop hemostatic abnormalities, ranging from isolated thrombocytopenia or prolonged global clotting tests to complex defects, such as disseminated intravascular coagulation. There are many causes for a deranged coagulation in critically ill patients and each of these underlying disorders may require specific therapeutic or supportive management. In recent years, new insights into the pathogenesis and clinical management of many coagulation defects in critically ill patients have been accumulated and this knowledge is helpful in determining the optimal diagnostic and therapeutic strategy.

Introduction

Coagulation abnormalities are commonly found in critically ill patients. A myriad of altered coagulation parameters are readily measurable, such as thrombocytopenia, prolonged global coagulation times, reduced levels of coagulation inhibitors, or high levels of fibrin split products. Prompt and proper identification of the underlying cause of these coagulation abnormalities is required, since each coagulation disorder necessitates very different therapeutic management strategies. This article reviews the most frequently occurring coagulation abnormalities in patients in the intensive care unit, with an emphasis on differential diagnosis, underlying molecular and pathogenetic pathways, and appropriate diagnostic and therapeutic interventions.

Incidence and relevance

The incidence of thrombocytopenia (platelet count $<150 \times 10^9$/l) in critically ill medical patients is 35% to 44% [1-3]. A platelet count of $<100 \times 10^9$/l is seen in 20% to 25% of patients, whereas 12% to 15% of patients have a platelet count $<50 \times 10^9$/l. In surgical and trauma patients, the incidence of thrombocytopenia is higher, with 35% to 41% of patients having less than 100×10^9/l platelets [4,5]. Typically, the platelet count decreases during the patient's first four days in the intensive care unit (ICU) [6].

The primary clinical relevance of thrombocytopenia in critically ill patients is related to an increased risk of bleeding. Indeed, severely thrombocytopenic patients with platelet counts of $<50 \times 10^9$/l have a 4- to 5-fold higher risk for bleeding compared to patients with higher platelet counts [1,3]. The risk of intracerebral bleeding in critically ill patients during intensive care admission is relatively low (0.3% to 0.5%), but 88% of patients with this complication have platelet counts below 100×10^9/l [7]. Moreover, a decrease in platelet count may indicate ongoing coagulation activation, which contributes to microvascular failure and organ dysfunction. Regardless of the cause, thrombocytopenia is an independent predictor of ICU mortality in multivariate analyses (relative risk, 1.9 to 4.2 in various studies) [1,3,4]. Several studies show that the severity of thrombocytopenia in critically ill patients is inversely related to survival. In particular, sustained thrombocytopenia over more than 4 days after ICU admission or a drop in platelet count of >50% during ICU stay correlates with a 4- to 6-fold increase in mortality [1,6]. The platelet count was shown to be a stronger independent predictor for ICU mortality than standard composite scoring systems, such as the Acute Physiology and Chronic Evaluation (APACHE) II score.

A prolonged global coagulation time (such as the prothrombin time (PT) or the activated partial thromboplastin time (aPTT)) occurs in 14% to 28% of intensive care patients [8,9]. Trauma patients, in particular, have a high incidence of coagulation time prolongation. A PT or aPTT ratio >1.5 was found to predict excessive bleeding [8]. A prospective study of trauma patients found that the presence of either a prolonged PT and/or aPTT was a strong and independent predictor of mortality [9].

Other coagulation test abnormalities frequently observed in ICU patients include elevated fibrin split products and reduced levels of coagulation inhibitors. Fibrin split products

aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; HIT = heparin-induced thrombocytopenia; ICU = intensive care unit; PT = prothrombin time.

Table 1

Differential diagnosis of thrombocytopenia in the intensive care unit

Differential diagnosis	Approximate relative incidence	Additional diagnostic clues
Sepsis	52%	Positive (blood) cultures, positive sepsis criteria, hematophagocytosis in bone marrow aspirate
DIC[a]	25%	Prolonged aPTT and PT, increased fibrin split products, low levels of physiological anticoagulant factors (antithrombin, protein C)
Massive blood loss	8%	Major bleeding, low hemoglobin, prolonged aPTT and PT
Thrombotic microangiopathy	1%	Schistocytes in blood smear, Coombs-negative hemolysis, fever, neurological symptoms, renal insufficiency
Heparin-induced thrombocytopenia	1%	Use of heparin, venous or arterial thrombosis, positive HIT test (usually ELISA for heparin-platelet factor IV antibodies), rebound of platelets after cessation of heparin
Immune thrombocytopenia	3%	Anti-platelet antibodies, normal or increased number of megakaryocytes in bone marrow aspirate, thrombopoeitin decreased
Drug-induced thrombocytopenia	10%	Decreased number of megakaryocytes in bone marrow aspirate or detection of drug-induced anti-platelet antibodies, rebound of platelet count after cessation of drug

Seven major causes of thrombocytopenia (platelet count $<150 \times 10^9$/l) are listed. Relative incidences are based on two studies in consecutive intensive care unit patients [1,6] but may vary depending on the population studied. Patients with hematological malignancies were excluded. [a]Patients with sepsis and disseminated intravascular coagulation (DIC) are classified as DIC. aPTT, activated partial thromboplastin time; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; PT, prothrombin time.

are detectable in 42% of a consecutive series of intensive care patients, in 80% of trauma patients and in 99% of patients with sepsis [10-12]. Low levels of coagulation inhibitors, such as antithrombin and protein C, are found in 40% to 60% of trauma patients and 90% of sepsis patients [12,13].

Causes of thrombocytopenia

There are many causes of thrombocytopenia in critically ill patients. Table 1 summarizes the most frequently occurring diagnoses recognized in intensive care patients with thrombocytopenia and their relative incidences, and Figure 1 shows an algorithm for a differential diagnostic approach.

Sepsis

Sepsis is a clear risk factor for thrombocytopenia in critically ill patients and the severity of sepsis correlates with the decrease in platelet count [14]. The principal factors that contribute to thrombocytopenia in patients with sepsis are impaired platelet production, increased consumption or destruction, or sequestration of platelets in the spleen. At first glance, impaired production of platelets from the bone marrow in septic patients, despite high circulating levels of platelet production-stimulating pro-inflammatory cytokines and thrombopoietin, might seem contradictory [15]. In a substantial number of patients with sepsis, however, marked hemophagocytosis may occur (Figure 2). This pathological process consists of active phagocytosis of megakaryocytes and other hematopoietic cells by monocytes and macrophages, hypothetically in response to high levels of macrophage colony stimulating factor in sepsis [16]. Platelet consumption probably also plays an important role in patients with sepsis. Thrombin is the most potent activator of platelets *in vivo*, and intravascular thrombin generation is a ubiquitous event in sepsis with or without evidence of overt disseminated intravascular coagulation (DIC).

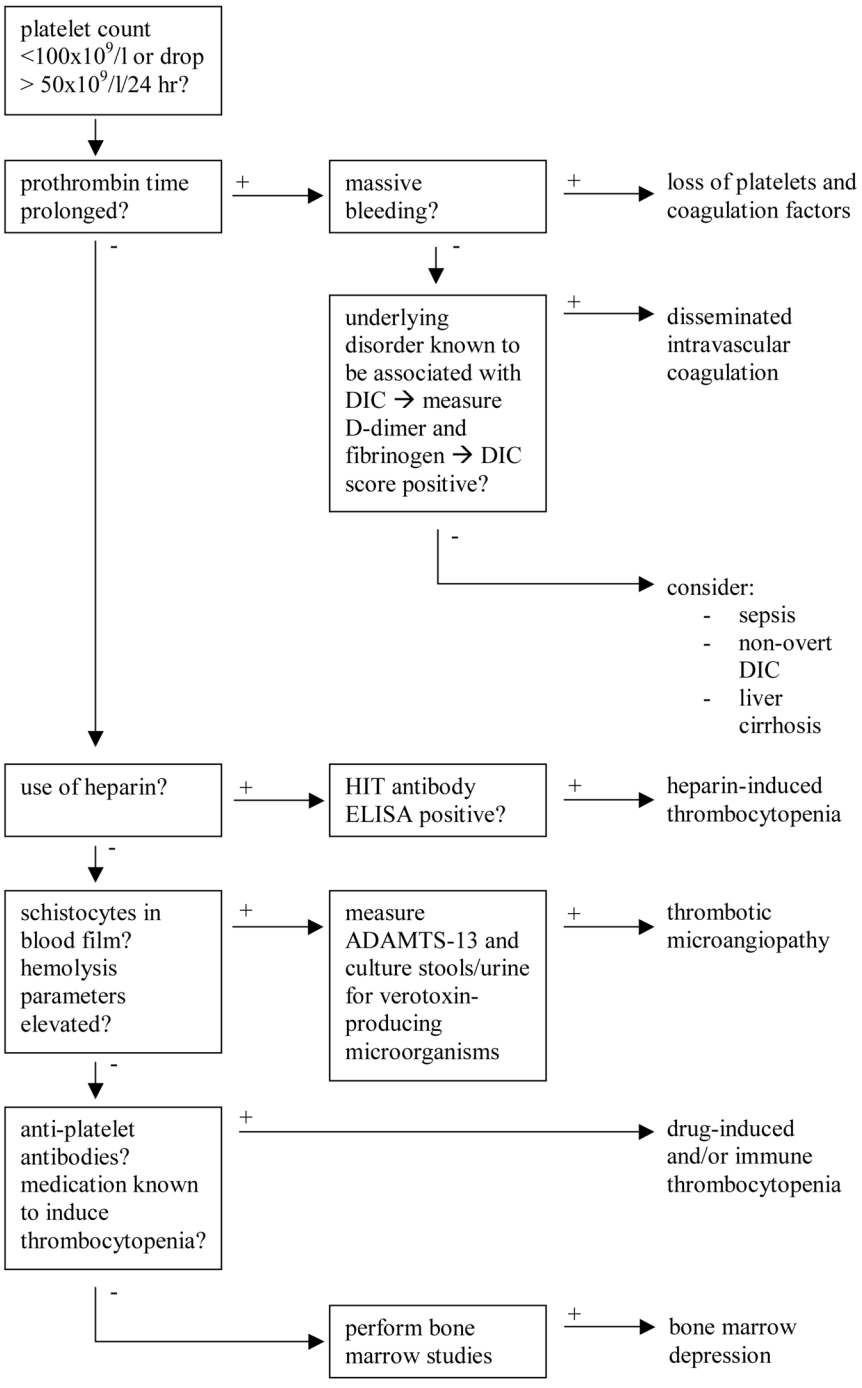
Disseminated intravascular coagulation

In patients with DIC, the platelet count is invariably low or rapidly decreasing [17]. DIC may complicate a variety of underlying disease processes, including sepsis, trauma, cancer, or obstetrical calamities, such as placental abruption, and this will be discussed in a separate paragraph.

Thrombotic microangiopathy

The group of thrombotic microangiopathies encompasses syndromes such as thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, severe malignant hypertension, and chemotherapy-induced microangiopathy [18]. A common pathogenetic feature of these clinical entities appears to be endothelial damage, which causes platelet adhesion and aggregation. The multiple clinical consequences of this extensive endothelial dysfunction include thrombocytopenia, mechanical fragmentation of red cells with hemolytic anemia and obstruction of the microvasculature of the kidney, brain and other organs (leading to renal failure and neurological dysfunction, respectively). Despite this common final pathway, the various thrombotic microangiopathies have different underlying etiologies. Thrombotic thrombocytopenic purpura is caused by deficiency of von Willebrand factor cleaving protease (ADAMTS-13), resulting in endothelial cell-attached ultra-large von Willebrand multimers that readily bind to

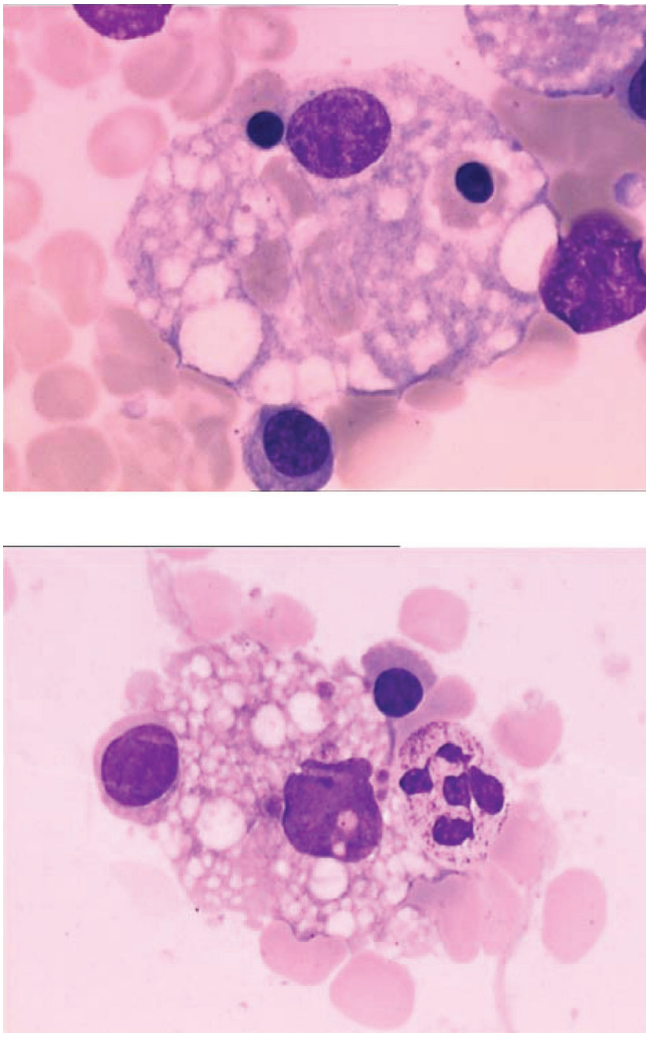
Figure 1



Differential diagnostic algorithm for coagulation abnormalities on the intensive care unit. DIC, disseminated intravascular coagulation; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia.

platelet surface receptors and cause platelet adhesion and aggregation [19]. In hemolytic uremic syndrome, a cytotoxin released upon infection with a specific serogroup of Gram-negative microorganisms (usually *Escherichia coli* serotype O157:H7) is responsible for endothelial cell and platelet activation. In cases of malignant hypertension or chemotherapy-induced thrombotic microangiopathy, direct mechanical or chemical damage to the endothelium may be responsible for the enhanced endothelial cell-platelet interaction. A diagnosis of thrombotic microangiopathy relies

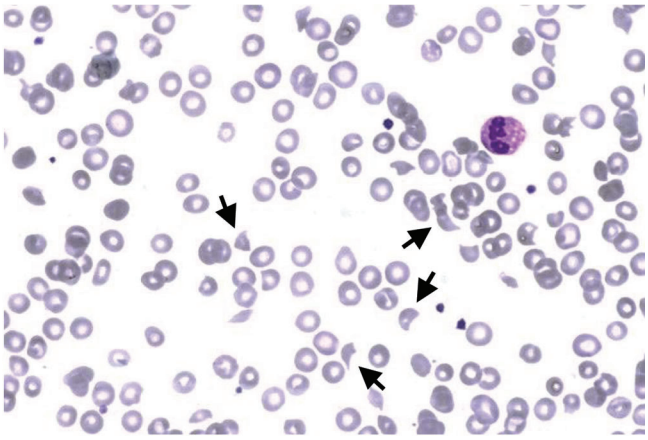
Figure 2



Typical examples of hematophagocytosis of bone marrow cells by macrophages. The bone marrow was obtained from a patient with severe sepsis (May-Grunwald-Giemsa staining, ×500). Courtesy of Bruno Francois and Frank Trimoreau, Dupuytren Hospital, Limoges, France.

upon the combination of thrombocytopenia, Coombs-negative hemolytic anemia, and the presence of schistocytes in the blood smear (Figure 3).

Figure 3



Blood smear from a patient with thrombocytopenic thrombotic purpura, due to deficiency of ADAMTS-13. The arrows indicate schistocytes generated by mechanical damage to red cells. Also note the reduced number of platelets, indicating thrombocytopenia. Giemsa staining, ×40. Courtesy of Dr J van der Lelie, Academic Medical Center, Amsterdam, the Netherlands.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is caused by a heparin-induced antibody that binds to the heparin-platelet factor-4 complex on the platelet surface [20]. This may result in massive platelet activation followed by a consumptive thrombocytopenia and arterial and venous thrombosis. The incidence of HIT may be as high as 5% of patients receiving heparin and is dependent upon the type and dose of heparin and the duration of its administration (usually more than 7 days, but may be sooner in patients treated with heparin in the previous 3 months). A consecutive series of critically ill ICU patients who received heparin revealed an incidence of 1% in this setting [21]. Unfractionated heparin carries a higher risk of HIT than low molecular weight heparin [22]. The risk of thrombosis in patients with HIT is 40-fold higher than in subjects without HIT [23] and the absolute risk of thrombosis is 25% to 60% (with fatal thrombosis in 4% to 5%) [24]. The diagnosis of HIT is based on the detection of HIT antibodies in combination with the occurrence of thrombocytopenia in a patient receiving heparin, with or without concomitant arterial or venous thrombosis.

It should be noted that the commonly used ELISA for anti-heparin-platelet factor 4 antibodies has a high negative predictive value (100%) but a very low positive predictive value (10%), especially in patients with a low pre-test likelihood of HIT [21]. False-positive results of this test may occur in 1% to 3% of patients on hemodialysis, 10% of medical patients, 20% of patients undergoing peripheral vascular surgery, and up to 50% of intensive care patients who have undergone cardiac surgery [25]. A more precise diagnosis may be made with a ^{14}C-serotonin release assay, but this test is not routinely available in most clinical settings [26].

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia is another frequent cause of thrombocytopenia in the ICU [4]. Thrombocytopenia may be caused by drug-induced myelosuppression, such as that caused by cytostatic agents, or by immune-mediated mechanisms. Drug-induced thrombocytopenia is a difficult diagnosis in the ICU since these patients are often exposed to multiple agents and have numerous other potential reasons

for platelet depletion. The diagnosis of drug-induced thrombocytopenia is often based upon the timing of initiation of a new agent in relationship to the development of thrombocytopenia, after exclusion of other causes of thrombocytopenia. In some cases, specific drug-dependent antiplatelet antibodies can be detected.

Causes of prolonged global coagulation times

It is important to emphasize that global coagulation tests, such as the PT and the aPTT, poorly reflect *in vivo* hemostasis. However, these tests are a convenient method to quickly estimate the concentration of one or at times multiple coagulation factors for which each test is sensitive (Table 2) [27]. In general, coagulation tests will prolong if the levels of coagulation factors are below 50%. The normal values and the sensitivity of these tests for deficiencies of coagulation factors may vary markedly between tests, depending upon the reagents used. Therefore, an increasing number of laboratories use the International Normalized Ratio instead of the prothrombin time. While this may allow for greater standardization between centers, it should be mentioned that the International Normalized Ratio has only been validated for control of the intensity of vitamin K antagonist therapy [28].

In the vast majority of critically ill patients, deficiencies of coagulation factors are acquired, mostly because of impaired synthesis, massive loss, or increased turnover (consumption). In addition, the presence of an inhibiting antibody should be considered. Circulating inhibitors can have major *in vivo* relevance (e.g., acquired hemophilia), or their presence may simply represent a clinically insignificant laboratory phenomenon. The presence of inhibiting antibodies can be confirmed by a simple mixing experiment. As a general rule, if a prolongation of a global coagulation test cannot be corrected by mixing 50% of patient plasma with 50% of normal plasma, then an inhibiting antibody is likely to be present.

Impaired synthesis is often due to liver insufficiency or vitamin K deficiency. The prothrombin time is very sensitive to both conditions, since this test is highly dependent on the plasma levels of factor VII (a vitamin K-dependent coagulation factor with a short half-life). Liver failure may be differentiated from vitamin K deficiency by measuring factor V, which is not vitamin K dependent. In fact, factor V plays an important role in various scoring systems for severe acute liver failure [29].

Uncompensated loss of coagulation factors may occur after massive bleeding, as in trauma patients or patients undergoing major surgical procedures. This is particularly common in patients with major blood loss where intravascular volume is rapidly replaced with crystalloids, colloids and red cells without simultaneous administration of coagulation factors. In hypothermic patients (e.g., trauma patients) measurement of the global coagulation tests may underestimate coagulation *in vivo*, since in the laboratory, test-tube assays are standardized and performed at 37°C.

Table 2

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Test result	Cause
PT prolonged, aPTT normal	Factor VII deficiency
	Mild vitamin K deficiency
	Mild liver insufficiency
	Low doses of vitamin K antagonists
PT normal, aPTT prolonged	Factor VIII, IX, or XI deficiency
	Use of unfractionated heparin
	Inhibiting antibody and/or anti-phospholipid antibody
	Factor XII or prekallikrein deficiency (no relevance for *in vivo* coagulation)
Both PT and aPTT prolonged	Factor X, V, II or fibrinogen deficiency
	Severe vitamin K deficiency
	Use of vitamin K antagonists
	Global clotting factor deficiency
	Synthesis: liver failure
	Loss: massive bleeding
	Consumption: DIC

aPTT, activated partial thromboplastin time; PT, prothrombin time.

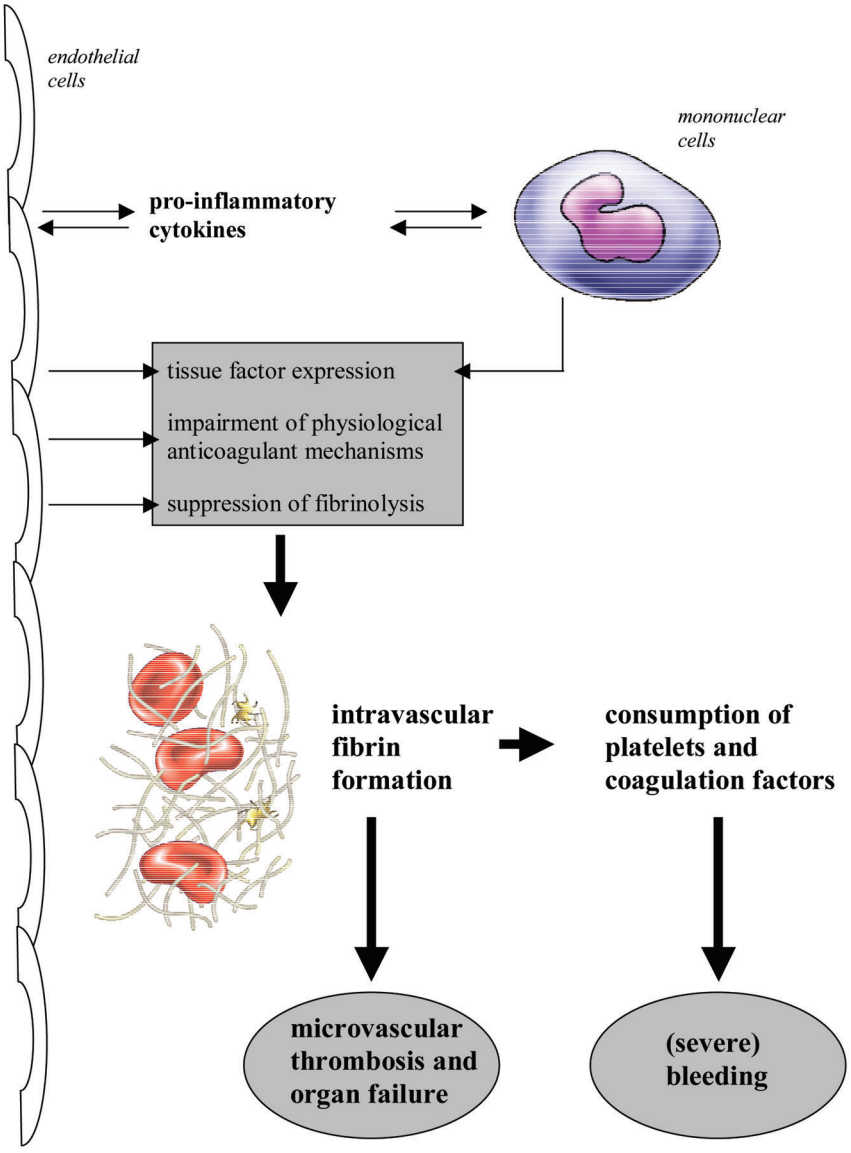
Consumption of coagulation factors may occur in the framework of DIC.

Disseminated intravascular coagulation

DIC is a syndrome caused by systemic intravascular activation of coagulation that occurs in a substantial proportion of consecutive intensive care patients [30]. Formation of microvascular thrombi, in concert with inflammatory activation, may cause failure of the microvasculature and thereby contribute to organ dysfunction [31]. Ongoing and inadequately compensated consumption of platelets and coagulation factors may pose a risk factor for bleeding, especially in perioperative patients. Triggers for the activation of the coagulation system are pro-inflammatory cytokines, expressed and released by mononuclear cells and endothelial cells. Thrombin generation proceeds via the (extrinsic) tissue factor/factor VIIa route concomitant with depression of inhibitory mechanisms of thrombin generation, such as antithrombin III and the protein C system. Impaired fibrin degradation, due to high circulating levels of plasminogen activator inhibitor type-1, further enhances intravascular fibrin deposition (Figure 4).

Patients with DIC have a low or rapidly decreasing platelet count, prolonged coagulation tests, low plasma levels of coagulation factors and inhibitors, and increased markers of fibrin formation and/or degradation, such as D-dimer or fibrin degradation products [32]. A diagnosis of DIC may be made

Figure 4



Schematic representation of the systemic activation of coagulation during a severe inflammatory response. Pro-inflammatory cytokines activate mononuclear cells and endothelial cells (which thereupon can also produce cytokines). Mononuclear cells and endothelial cells express tissue factor, the main initiator of coagulation. Simultaneously, impairment of the physiological anticoagulant mechanism and endogenous fibrinolysis, due to down-regulation of endothelial-bound proteins and endothelial cell perturbation, cause an insufficient counterbalance towards intravascular fibrin formation, which may contribute to organ failure. Simultaneously, consumption of platelets and clotting factors may cause serious bleeding.

using a simple scoring system based on a combination of routinely available coagulation tests (platelet count, PT, D-dimer levels and fibrinogen) [33]. The sensitivity and specificity of this DIC score were found to be 93% and 98%, respectively [30]. Furthermore, this DIC score was a strong and independent predictor of mortality in a large series of patients with severe sepsis [34].

Coagulation defects with normal routine coagulation tests

It is critically important to recognize that the routine coagulation tests, such as platelet count, global clotting assays, and measurement of coagulation factors, might miss clinically significant coagulation defects that can contribute to bleeding. The most important coagulation defects that may

remain undetected with routine coagulation tests are platelet dysfunction and hyper-fibrinolysis.

Platelet dysfunction is a frequent occurrence in critically ill patients, particularly those with uremia or severe liver failure. Another frequent cause for a defective platelet function is the use of anti-platelet agents, such as aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) or potent thrombin inhibitors, such as hirudin. Extracorporeal circuits may also cause serious platelet function defects, presumably due to platelet activation within these devices [35]. There is currently no accurate, routinely available test for platelet function in critically ill patients. The bleeding time is highly inaccurate in this situation [36] and the recently developed platelet function analyzers are poorly suited for the routine assessment of platelet function [37].

Hyper-fibrinolysis is a relatively rare condition that may occur in patients with specific types of cancer, such as acute promyelocytic leukemia or prostatic carcinoma [38]. Patients on extracorporeal circuits may also experience a marked activation of fibrinolysis due to release of plasminogen activators from endothelial cells. Critically ill patients that have been treated with thrombolytic agents have an intentionally induced hyper-fibrinolytic state [39]. Hyper-fibrinolysis may be suspected if levels of fibrin degradation products are inordinately high and fibrinogen levels are low. The diagnosis can be confirmed by detection of very low levels of plasminogen and α2-antiplasmin.

Management of coagulation abnormalities in critically ill patients

It is evident that the primary focus of attention in the treatment of a clinically relevant coagulopathy should be directed towards the management of the underlying condition. This underscores the critical importance of making a correct diagnosis of the underlying etiology of the acquired coagulopathy. In addition to proper treatment for the underlying disorder, further supportive measures to correct the coagulation defects are often required.

Most guidelines advocate a platelet transfusion in patients with a platelet count of $<30\text{-}50 \times 10^9$/l accompanied by bleeding or at high risk for bleeding, and in patients with a platelet count $<10 \times 10^9$/l, regardless of the presence or absence of bleeding. After platelet transfusion, the platelet count should rise by at least 5×10^9/l per unit. A lesser response may occur in patients with high fever, DIC, or splenomegaly, or may indicate allo-immunization of the patient after repeated transfusion. Platelet transfusion is particularly effective in patients with a thrombocytopenia due to impaired platelet production or increased consumption, whereas disorders of enhanced platelet destruction (e.g., immune thrombocytopenia) call for alternative therapies, such as steroids, immunoglobulin, or splenectomy. Thrombocytopenia due to HIT requires immediate cessation of heparin and institution of alternative anticoagulant treatment regimens, such as direct thrombin inhibitors (argatroban or lepirudin) [40]. The importance of starting treatment with direct thrombin inhibitors is underlined by a recent overview showing that the incidence of new thrombosis in patients with HIT who were treated by discontinuing heparin alone or with warfarin was 19% to 52% [40]. Vitamin K antagonists should be avoided in the initial treatment of HIT, since these agents may cause skin necrosis. In patients with a classic thrombotic microangiopathy due to low levels of von Willebrand cleaving protease (ADAMTS-13), plasmapheresis and immunosuppressive treatment should be initiated [18].

Fresh frozen plasma contains all coagulation factors and may be used to replenish deficiencies of these clotting factors. Most consensus guidelines indicate that plasma should only be transfused in case of bleeding, or if a high-risk of bleeding exists, and not based on laboratory abnormalities alone. For more specific therapy or if the transfusion of large volumes of plasma is not desirable, fractionated plasma of purified coagulation factor concentrate is available.

Prothrombin complex concentrates contain the vitamin K-dependent coagulation factors. Hence, these concentrates may be used if immediate reversal of vitamin K antagonist treatment is required. Also, prothrombin complex concentrates may be used if global replenishment of coagulation factors is necessary and large volumes of plasma may not be tolerated. One should realize, however, that only selected elements of coagulation factors are administered in such cases, and that important clotting factor deficiencies may remain (i.e., factor V or fibrinogen). In some cases, administration of purified coagulation factor concentrates, such as fibrinogen concentrate or cryoprecipitate, may be helpful.

Pro-hemostatic treatment can be used as adjunctive treatment in patients with major blood loss [41]. De-amino D-arginine vasopressin (desmopressin) is a vasopressin analogue that induces release of the contents of endothelial cells, including von Willebrand factor. Hence, the administration of de-amino D-arginine vasopressin results in a marked increase in the plasma concentration of von Willebrand factor and, by as yet unexplained additional mechanisms, a potentiation of primary hemostasis [42]. Relatively rare but important adverse effects of desmopressin include the occurrence of acute myocardial infarction (notably in patients with unstable coronary artery disease) and water intoxication with hyponatremia from its antidiuretic effect.

Anti-fibrinolytic agents, such as aprotinin and lysine analogues (ε-aminocaproic acid or tranexamic acid) may also be helpful in the prevention or management of bleeding. Anti-fibrinolytic agents have been found effective in the prevention of blood loss and transfusion in patients undergoing major surgical procedures and are relatively safe [43]. Aprotinin

may cause anaphylactic responses and lysine analogues should not be used in patients with hematuria since obstructive clots in the urinary tract have occurred.

Recombinant factor VIIa is a relatively new pro-hemostatic agent that has been licensed for the treatment of patients with hemophilia and inhibiting antibodies towards factor VIII or IX. Initial clinical studies in patients with other types of coagulation defects or patients with major bleeding due to surgery or trauma are promising [44,45]. A recently published large placebo-controlled trial of recombinant factor VIIa showed a significant reduction of red cell transfusion requirements in patients with severe blunt trauma. A trend towards a reduced incidence of multiple organ failure and acute respiratory distress syndrome was also observed in patients receiving recombinant factor VIIa [46]. A placebo-controlled, dose-finding trial in 400 patients with spontaneous intracranial hemorrhage indicated that administration of recombinant factor VIIa results in a reduction of hematoma size on repeated CT scans. A 35% reduction in mortality was found along with an improved disability score at 90 days follow up [47]. The initial clinical use of recombinant factor VIIa results in a surprisingly low incidence of thrombotic complications [45,48]. Based on this experience, off-label use of recombinant factor VIIa may be considered in the case of life threatening bleeding.

Supportive treatment of the coagulopathy associated with DIC is a complicated issue [17]. Administration of anticoagulants may theoretically be beneficial but its efficacy has never been proven in clinical trials. Restoration of dysfunctional physiological anticoagulant pathways by administration of (activated) protein C has beneficial effects on laboratory parameters but the effect on clinically relevant outcome parameters in clinical studies is variable. In patients with severe sepsis recombinant human activated protein C (drotrecogin alpha-activated) by continuous infusion over four days was effective [12]. All-cause mortality at 28 days after inclusion was 24.7% in the activated protein C group versus 30.8% in the placebo group (19.4% relative risk reduction). Predictably, the relative efficacy of activated protein C in the subgroup of patients with DIC was higher than in those without DIC and patients treated with activated protein C had a more rapid resolution of DIC than placebo-treated patients [34]. A recent trial confirms the notion that recombinant human activated protein C is not effective in patients with sepsis and low disease severity [49]. Interestingly, very recent data indicate that concomitant administration of prophylactic heparin in patients with severe sepsis may result in a slightly better 28-day survival, which was mostly due to increased morbidity and mortality in patients in whom prophylactic heparin was stopped during the infusion with recombinant human activated protein C (XPRESS study, presented by M Levi at the SCCM, San Francisco, 2006). Infusion of recombinant human activated protein C was associated with serious bleeding in 2.4% of patients (intracranial hemorrhage 0.6%), in comparison with 0.7% in placebo-treated patients (intracranial hemorrhage 0.1%) [50]. The concomitant administration of heparin seems not to result in an increase in serious bleeding complications.

In some countries, antithrombin concentrate is used as anticoagulant treatment in patients with DIC. Although there is no randomized controlled study showing a beneficial effect of antithrombin on mortality [51], retrospective subgroup analyses of studies in patients with sepsis indicate that administration of antithrombin in patients not receiving heparin and fulfilling the diagnostic criteria for DIC may be beneficial [52]. This hypothesis will be prospectively tested in an upcoming clinical trial with recombinant human antithrombin.

Conclusion

Abnormal tests of coagulation in critically ill patients occur frequently and should not be considered inconsequential. Coagulation abnormalities may significantly contribute to morbidity and mortality and require prompt analysis to establish the underlying cause and to initiate corrective and supportive treatment.

Competing interests

Drs Levi and Opal have participated in Eli Lilly sponsored trials before. Dr Levi has received speaker fees from Novo Nordisk and Eli Lilly and Co. Dr Opal has received speaker fees from Eli Lilly and Co.

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