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Thrombocytopenia in the critically ill: considering pathophysiology rather than looking for a magic threshold

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Thrombocytopenia is a sensitive marker of severity in acute inflammatory disorders and is therefore a common laboratory finding in critically ill patients. A number of prospective and retrospective studies have provided a crude epidemiological picture of thrombocytopenia in the intensive care unit (ICU) and have assessed its prognostic value [1]. Using common platelet count thresholds of 100 or $150 \times 10^9/L$, the prevalence on ICU admission and the incidence of thrombocytopenia acquired during the ICU stay ranged from 8.3 to 67.1 % and from 13 to 41.2 %, respectively, depending on the type of ICU and the case mix of patients. Severe thrombocytopenia is defined as a platelet count $<50 \times 10^9/L$, with frequency ranging from 2.2 to 41.8 %. Thrombocytopenia in the ICU has been consistently associated with worse outcomes, and platelet count is part of some severity scores. Furthermore, when the platelet count declines over time, the so-called relative thrombocytopenia has also been suggested to be an accurate prognostic factor; For instance, Moreau et al. [2] already demonstrated that a 30 % decline in platelet count on day 4, but not the absolute platelet count at any time during ICU stay, was an

independent predictor of mortality. Besides prognostic considerations, the significance of thrombocytopenia in critically ill patients in terms of specific diagnostic procedures, clinical consequences, and the resulting therapeutic implications remains largely unclear in the ICU.

Some of these questions were addressed in a recent issue of *Intensive Care Medicine* by Thiolliere and coworkers [3], who performed a comprehensive and systematic analysis of thrombocytopenia occurring in the ICU. The definition of thrombocytopenia encompassed both absolute thrombocytopenia as a platelet count $<100 \times 10^9/L$ and relative thrombocytopenia as a 30 % decrease in platelet count over 4 days in nonthrombocytopenic patients. The prevalence of absolute thrombocytopenia was 8.9 %, and the incidence of relative thrombocytopenia was 6.7 %. Most importantly the study emphasized the similar prognostic values of absolute and relative thrombocytopenia. Of note, severe bleeding accounted for few deaths in patients with absolute thrombocytopenia, and even fewer in those with relative thrombocytopenia. This indicates that the prognostic value of thrombocytopenia is essentially related to the physiological process leading to platelet consumption rather than to the depth of thrombocytopenia itself. At the interface between thrombosis and inflammation, platelets have been implicated in the host response to infection [4]. Although devoid of nucleus, platelets are able to sustain the inflammatory and procoagulant processes encountered in the critically ill through the release of pro-inflammatory mediators and the expression of various membrane proteins with subsequent functional interactions with leukocytes [5, 6]. A number of clinical trials have addressed the efficacy of anticoagulant and antiplatelet drugs aimed at dampening platelet activation or the procoagulant activity responsible for sepsis-induced disseminated intravascular coagulation (DIC). Unfortunately all these products finally failed to demonstrate any survival gain, and so far, the treatment of DIC remains only supportive.

Table 1 Causes and mechanisms of thrombocytopenia in critically ill patients

Clinical setting	Potential mechanisms of thrombocytopenia	Comments
Sepsis	Disseminated intravascular coagulation	The most common mechanism of peripheral thrombocytopenia in the ICU
	Hemophagocytosis	Undetermined significance
	Antiplatelet antibodies	Undetermined significance
Hematological malignancy Solid tumor	Chemotherapy- or radiation-induced bone marrow insufficiency	Very common, often obvious in the medical history
	Hemophagocytic lymphohistiocytosis	Requires the association of hemophagocytosis with evidence of macrophage activation
	Bone marrow necrosis	Very rare
Cirrhosis Chronic alcoholism	Hypersplenism	Moderate pancytopenia
	Direct alcohol toxicity on megakaryocytes	
	Vitamin deficiency	
Acute renal failure	Defective production of thrombopoietin	Often accompanying macrocytosis
	Thrombotic microangiopathy (HUS, sclerosis renal crisis, malignant arterial hypertension)	Platelet transfusion contraindicated unless severe bleeding
	Renal replacement therapy	More common in continuous than intermittent methods
Neurological abnormalities	Thrombotic microangiopathy (TTP, malignant arterial hypertension)	Platelet transfusion contraindicated unless severe bleeding
Acute coronary syndrome Coronary angiography	GPIIb/IIIa inhibitors	Often sudden and profound drop in platelet count
	Intra-aortic balloon pump	Common but rarely of clinical significance
	TTP (clopidogrel)	Rare
Cardiac surgery	Perioperative platelet consumption, dilution	
	Extracorporeal circulation	
	Heparin-induced thrombocytopenia	Progressive thrombocytopenia with risk of arterial and venous thrombosis
ECMO	Membrane clotting	Rapidly resolves after membrane change
Trauma/hemorrhage Postoperative	Massive transfusion	
	Dilution	
	Platelet consumption	

ICU intensive care unit, HUS hemolytic–uremic syndrome, TTP thrombotic thrombocytopenic purpura, ECMO extracorporeal membrane oxygenation

Systematic extensive exploration of thrombocytopenia was a hallmark of this study, in which a vast majority of patients (79 %) were subjected to bone marrow aspiration regardless of absolute platelet count. As expected, the main mechanisms leading to decreased platelet count were most often peripheral. Bone marrow aspiration yielded a diagnosis not previously established in 22 % of patients, and this had a significant impact on management in only 11 % of patients, almost all of them having absolute thrombocytopenia. Interestingly, phagocytic histiocytes were observed in 24 (20 %) bone marrow smears and ultimately led to the diagnosis of hemophagocytic syndrome in 14 patients when confronted with other clinical and biological criteria defining the disease. This common cytological finding may either reflect bystander (or reactive) hemophagocytosis whose significance remains unclear or drive hemophagocytic syndrome with specific prognostic and therapeutic implications [7]. This example emphasizes a reasoned use of bone marrow aspiration depending on the pretest probability. Therefore, these results plead against systematic bone marrow exploration, which should be restricted to patients with absolute thrombocytopenia not explained by the clinical condition (Table 1), most especially if associated with other cytopenias or abnormal cell morphology.

Specific therapeutic intervention for thrombocytopenia is almost exclusively restricted to preventive platelet transfusion in order to avoid severe bleeding. Most of our knowledge in the field is based on studies performed in hematological patients with central thrombocytopenia in stable condition. In this setting, the risk of moderate to severe bleeding is more pronounced below a platelet count of $5\text{--}10 \times 10^9/\text{L}$, and the current standard of transfusion practice is aimed at maintaining platelet count above $10 \times 10^9/\text{L}$ in most patients with hypoproliferative thrombocytopenia [8–11]. The relationship between thrombocytopenia and bleeding is less stringent in critically ill patients, for whom the risk of severe bleeding is increased for platelet counts $<50\text{--}100 \times 10^9/\text{L}$ [12, 13]. Accordingly, platelet count $<50 \times 10^9/\text{L}$ was an independent risk factor for bleeding in the present study, but platelet counts <20 and $20\text{--}50 \times 10^9/\text{L}$ were associated with similar rates of severe bleeding (28 and 24 %, respectively), confirming that the risk of bleeding in the ICU is less dependent on the depth of

thrombocytopenia. Indeed, thrombocytopenia in critically ill patients is most often of peripheral origin and is less likely to favor severe bleeding because of sustained production of functional platelets. In addition, some factors related to the underlying condition such as renal failure, anticoagulant and antiplatelet agents, or invasive procedures may also increase the risk of bleeding.

Based on these results, should we transfuse all ICU patients at a threshold of $50 \times 10^9/\text{L}$, as advised in the present study? No prospective study has addressed this question, and indications for prophylactic platelet transfusion in the ICU remain highly unclear. For this reason, the French Society of Intensive Care Medicine recently proposed some recommendations for management of thrombocytopenia in the ICU [14]. In summary, there was generally no indication for prophylactic transfusion in patients with peripheral thrombocytopenia, for whom the benefit is questionable because of rapid consumption and short lifespan of transfused platelets, with a theoretical potential for sustaining or worsening an underlying thrombotic process. Furthermore, thrombotic microangiopathy represents a contraindication to prophylactic platelet transfusions, which have been occasionally associated with deterioration of clinical condition and sudden death. With respect to central thrombocytopenia, the experts agreed on prophylactic platelet transfusion for thresholds of $10\text{--}20 \times 10^9/\text{L}$. Of note, the question of the optimal platelet count for invasive procedures was not addressed, but it is our impression that the commonly recommended $50 \times 10^9/\text{L}$ threshold might be excessive for minor types of procedures such as vascular catheter insertion or lumbar puncture. Finally, these recommendations cannot encompass the diversity of clinical situations in the ICU. Thus, the decision for platelet transfusion remains a complex process that should involve not only absolute platelet count but also the mechanism of thrombocytopenia, the presence of alternative risk factors of bleeding, any history of serious bleeding, the need for invasive procedures, and the eventual refractoriness to platelet transfusion. Therein lies the difficulty in designing the still-elusive prospective interventional study awaited in the field.

Conflicts of interest None.

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