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UNDERSTANDING THE DISEASE

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Understanding platelet dysfunction in sepsis

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Introduction

Sepsis is defined as the systemic response to infection and is associated with a significant mortality rate. The role of platelets in sepsis remains incompletely understood (Fig. 1). Under normal conditions approximately 1×10^{11} platelets are produced daily; however, during physiological stress, this may increase over 20 times [1].

Pro-inflammatory cytokines activate the coagulation system. This response, in combination with endothelial damage, leads to platelet activation [2].

In addition, bacteria may trigger platelet activation either directly by releasing endotoxins, or indirectly by binding to plasma proteins to form complexes that become ligands for platelet receptors [1].

Activated platelets enhance leukocyte recruitment and aggregation between leucocytes, platelets and the endothelium. This improves the efficacy of leukocyte phagocytosis and formation of neutrophil extracellular traps (NETs) which both act via proteolytic activity to destroy microbes in the microvasculature tissue.

Sepsis may result in hypercoagulation due to fibrin deposition, and platelet activation. This leads to the formation of micro-thrombi, as a host defence mechanism against pathogens in which platelets play a crucial role. However, the formation of micro-thrombi and the subsequent recruitment of immune cells into the microvasculature may also result in the development of renal, lung and liver dysfunction and progressive failure. In extreme situations, this may progress to disseminated intravascular coagulation (DIC), with severe thrombocytopenia and coagulation system impairment [1, 2].

Platelet dysfunction during sepsis correlates with a poorer prognosis. Thus the number, morphology and function may be used as biomarkers for risk stratification of patients with sepsis.

Platelet concentration

Thrombocytopenia, traditionally defined as a platelet count less than 150×10^9/L, is a common haematological alteration in critical illness [3]. In patients with sepsis, thrombocytopenia is associated with a higher vasopressor

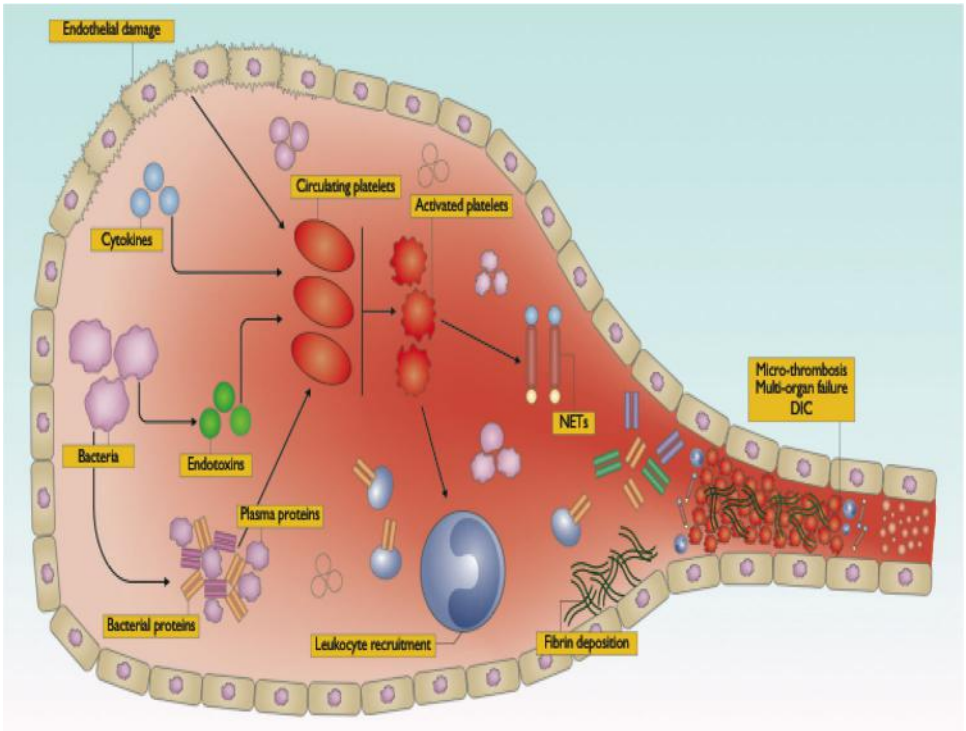

Fig. 1 The role of platelet in sepsis

requirement and a lower PaO_2/FiO_2 ratio [4]. In addition, in patients with community-acquired pneumonia admitted to the intensive care unit (ICU), a lower admission platelet count is associated with a higher incidence of septic shock and an increased mortality rate [5].

The evaluation of the trend of the platelet count over time is also important. Indeed, a late thrombocytopenia in ICU may indicate septic patients with a greater risk of mortality, even if it could represent a non-specific response to stress during the ICU stay [6].

Platelet volume indices (PVIs)

PVIs such as mean platelet volume (MPV) (normal range 7.5–11.5 fL) and platelet distribution width (PDW) (normal range 9–14 fL) are routinely measured by haematology analysers. In sepsis, it has been reported that a higher MPV is demonstrable in patients with sepsis compared to those with localised infection, suggesting that an increased MPV could be related to a more invasive infection or to failure of antibiotic therapy. In an observational study of the MPV trend in patients during their ICU admission, survivors demonstrated a decrease in MPV whereas in non-survivors the MPV increased [7]. In neonatal sepsis higher MPV and PDW were observed compared to healthy controls with non-survivors having demonstrably higher MPV and PDW than survivors [8].

Immature platelet fraction (IPF)

Immature platelets differ from mature platelets as a result of their larger shape and the presence of larger amounts of RNA. A greater number of circulating immature platelets correlates directly with increased megakaryocyte activity. The fraction of immature to mature platelets rises when platelet production is increased and is therefore a measure of the thrombopoiesis rate.

The IPF has been used as a prognostic indicator in DIC [9] and acute coronary syndrome. Recent studies have evaluated the value of IPF measurements in patients with bacterial infection and sepsis. One trial demonstrated that IPF was significantly higher in adult patients with neutrophilia and positive blood cultures than in those with negative blood cultures [10]. Another study found a significant difference in the IPF in ICU patients who develop sepsis compared to those who did not [11]. In patients admitted to the ICU without infection, an increase in IPF preceded the onset of sepsis by a median of 2 days [11]. The daily evaluation of the IPF may therefore be used to predict the development of sepsis and therefore commence treatment at the earliest opportunity.

Platelet aggregation

The proportion of circulating platelets that are in an activated state can be measured using assays of platelet

aggregability. Recently this has been measured using point-of-care testing, such as whole blood impedance aggregometry (multiplate). Contradictory literature exists but overall it appears that platelet aggregation is reduced in patients with sepsis. This could be related to the consumption of platelets, endothelial dysfunction, coagulation factor impairment or a combination of factors.

Platelet aggregability was found to be reduced in patients attending the emergency department (ED) and the ICU with severe sepsis or septic shock compared to those with isolated SIRS or uncomplicated sepsis [12]. Further evaluations demonstrated that preserved platelet function was associated with a mortality of 10 %, whereas impaired platelet function was associated with a mortality of 40 % [13].

Thrombopoietin (TPO)

TPO is the humoral growth factor for megakaryocyte proliferation and differentiation. The levels of TPO are increased in inflammatory states as a result of IL-6 stimulation [14]. In adult patients on the ICU, TPO levels were significantly higher in patients with septic shock compared to those with less severe sepsis [14]. In the ED the plasma TPO concentration was significantly higher in patients with SIRS secondary to infection compared to those with non-septic SIRS [15]. Similarly in patients being treated for burn injuries, those complicated by sepsis demonstrated higher TPO plasma levels than those without [13]. These studies suggest that the presence of higher TPO plasma concentrations can identify severe forms of sepsis and differentiate inflammation caused by infection and non-infective causes.

Conclusions

The platelet is intimately involved in the pathogenesis of sepsis, participating in the immune response and interacting with bacteria. Platelet abnormalities occur frequently in critical illness, especially in septic patients, and are associated with poorer outcomes.

In clinical practice the value of serial measurements of platelet numbers, volume indices and the immature fraction are underappreciated and consequently underutilised. The key role of the platelets in sepsis-induced multiple organ failure requires more study and may lead to novel therapeutic strategies.

Compliance with ethical standards

Conflicts of interest The authors have no competing financial interests to disclose.

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