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CORRESPONDENCE

Unraveling the secret of re-balancing homeostasis in sepsis: a critical view on extracorporeal blood purification modalities

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Two recent reports in Intensive Care Medicine raise important questions regarding a potential mortality hazard of extracorporeal blood purification for the treatment of septic shock.

Garbero et al. report the results of the COMPACT-2 trial investigating high volume coupled plasma filtration and adsorption (CPFA) in 115 patients suffering from septic shock [1]. The study was prematurely determined due to a potential harmful effect of CPFA as mortality in the intensive care unit (ICU) was 54% in the treatment and 29% in the control group. In particular, early mortality after 3 days was more than twice as high in the CPFA group and a significant treatment dose—response effect on mortality even suggested a putative causal relationship.

Just a few days earlier, Wendel-Garcia and colleagues reported equally concerning results in a propensity score matched analysis, studying hemoadsorption by means of the CytoSorb adsorber in 96 patients suffering from severe refractory septic shock [2]. In May of this year, a small trial of patients affected by coronavirus disease 2019 (COVID-19) with severe acute respiratory distress syndrome (ARDS) undergoing extracorporeal membrane oxygenation (ECMO) therapy noted a mortality increase of 58% in patients randomized to receive additive cytokine adsorption, albeit as secondary outcome [3].

Alarmingly, in the short period of a few months, three rigorously conducted investigations, sharing the same intervention, have suggested that indiscriminate removal of circulating mediators from the blood might be unexpectedly harmful in patients with septic shock. Potential effectors of this observation require careful consideration. Both CPFA and full blood hemoadsorption have the potential to remove both injurious and protective substances involved in the pathophysiology of sepsis. It is, therefore, conceivable that extraction of protective factors diminishes beneficial physiological responses such as immune homeostasis restoration, endothelial integrity re-establishment as well as a reduction of coagulopathy.

Earlier this year, we reported results of a randomized controlled trial exploring additive therapeutic plasma exchange (TPE) in patients with severe refractory septic shock, finding rapid hemodynamic improvement following this intervention [4]. In contrast to CPFA and CytoSorb hemoadsorption, TPE combines two therapeutic measures in a singular intervention [5]. It effectively removes injurious mediators such as proinflammatory cytokines, endothelial destabilizing factors (e.g. Angiopoietin-2, Heparanase-1) and molecules involved in intravascular coagulation (e.g. von-Willebrand factor) (Fig. 1). Simultaneously, the exchange of septic plasma with that from healthy donors leads to a replenishment of protective but consumed factors involved in anti-inflammatory processes (e.g. immunoglobulins), in endothelial stabilization (e.g. Angiopoietin-1, Heparanase-2) and in anti-coagulation (e.g. Antithrombin-III, Protein C, ADAMTS-13). Larger randomized studies investigating additive use of TPE in septic shock are under way.

Given the unmet medical need to improve our therapeutic strategies against the pathological host response in sepsis, we believe that the appealing concept of blood purification should endure under the pervasive Hippocrates umbrella *"First do not harm"*. In conceptualizing

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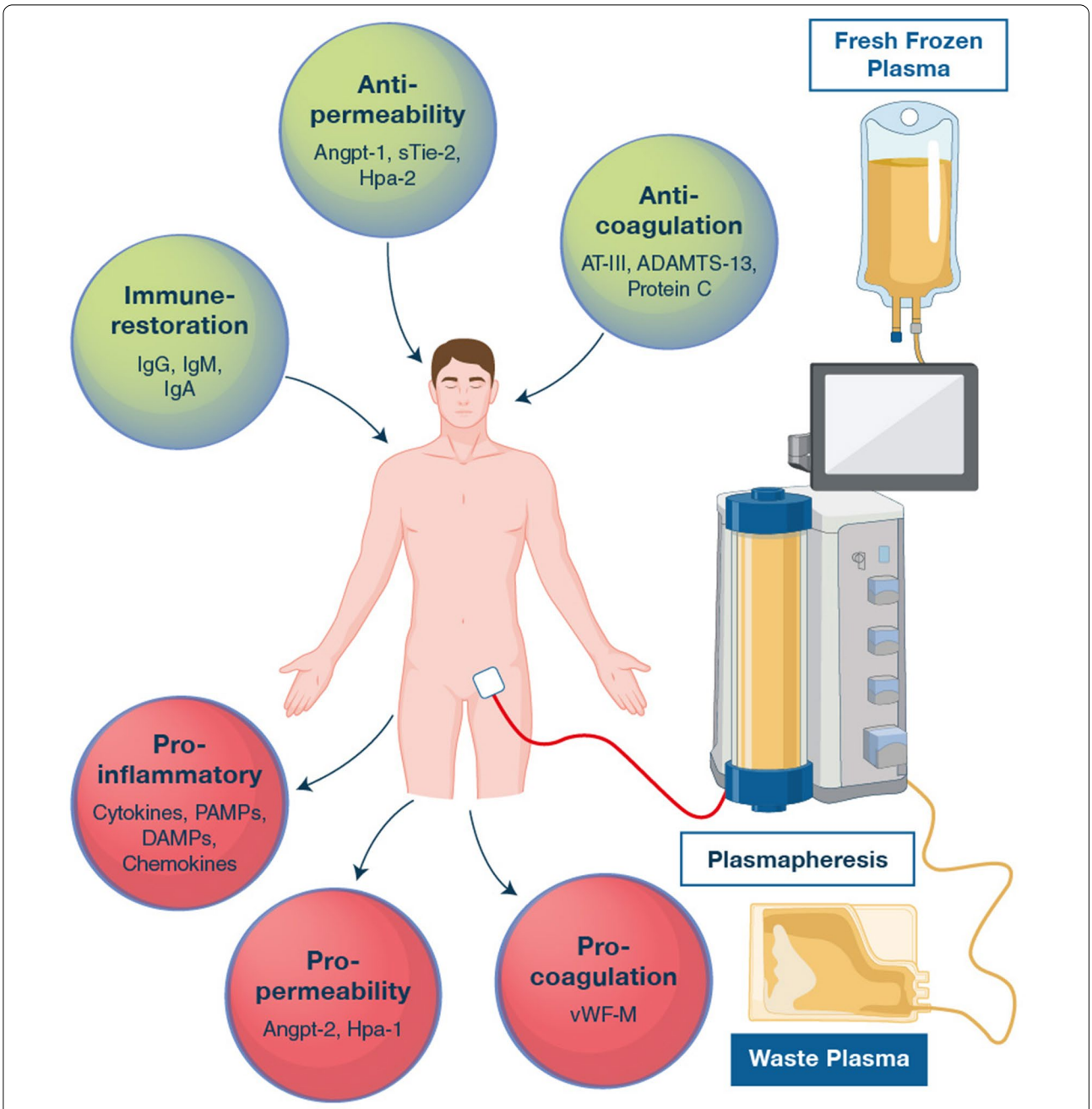

Fig. 1 Molecular mechanisms targeted by additive therapeutic plasma exchange (TPE) in septic shock. Demonstrated are molecular mechanisms involved in the pathological host response of sepsis, that are influenced by use of TPE. Protective, but consumed factors that are replenished by TPE are shown in green. Excessive injurious mediators, which are removed by TPE, are indicated in red. *Angpt-1* Angiopoietin-1, *Angpt-2* Angiopoietin-2, *ADAMTS13* A disintegrin and metalloprotease with thrombospondin-1-like domains 13, *AT-III* Antithrombin-III, *DAMPs* Damage-associated molecular patterns, *Hpa-1* Heparanase-1, *Hpa-2* Heparanase-2, *PAMPs* Pathogen-associated molecular patterns, *sTie2* a Soluble receptor of tyrosine kinase with immunoglobulin-like and EGF-like domains 2, *vWF-M* (Ultra) large von Willebrand factor multimers

future studies, we suggest to consider options that not only unselectively remove but also replace consumed counterbalancing factors.

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Conflicts of interest
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