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EDITORIAL

Hemostasis disorders: from bleeding to thrombosis

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For decades, we have spoken of coagulopathy as if it were a binary phenomenon—patients either bled or clotted. This simplistic view is being replaced by a more integrated one: coagulation is not a binary switch, but a fragile highly regulated network that oscillates between activation and inhibition. Across critical illnesses—from hematologic malignancy and sepsis to extracorporeal support and thrombotic microangiopathies—dysregulation, rather than deficiency, appears to be the common denominator (Fig. 1).

The burden of imbalance

In critically ill patients, the coexistence of bleeding and thrombosis remains one of the most challenging paradoxes. As an example, in a large population-based cohort of 76,803 patients with hematologic malignancies in Ontario [1], the incidence of venous thromboembolism (VTE) was threefold higher in intensive care unit (ICU) patients than in non-ICU patients (3.7% vs. 1.2%), while major bleeding affected 7.6% versus 2.4%, respectively. After adjustment, critical illness remained independently associated with VTE (adjusted OR 2.92, 95% CI 2.62–3.25). VTE risk was also higher in certain malignancy subtypes and in patients with prior thrombosis, whereas severe thrombocytopenia and late-stage admissions were associated with a lower incidence. These findings highlight the delicate balance between thrombosis and bleeding in critically ill patients with hematologic cancers.

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When correction misses the target

The PLOT-ICU international cohort [2] refined our understanding of this disequilibrium. Among 1166 ICU patients from 52 centers worldwide, thrombocytopenia occurred in 43% and was independently associated with increased 90-day mortality (adjusted OR 1.7). Roughly one in four thrombocytopenic patients received platelet transfusions—mostly prophylactically. Yet, as emphasized in *Ten Tips on Sepsis-Induced Thrombocytopenia* [3], platelets are not passive fragments to be replenished, but active immune and hemostasis actors. Their fall in number mirrors their migration to sites of injury, their engagement in immune defense, and their consumption in microthrombosis.

This explains why "adding what's missing" often fails. In the PACER trial [4], withholding prophylactic platelet transfusion before ultrasound-guided central venous catheter placement in patients with severe thrombocytopenia ($10–50 \times 10^9$/L) resulted in more bleeding and failed to meet non-inferiority compared with transfusion. Procedural safety, the authors concluded, depends less on a numeric threshold than on the patient's global hemostatic profile.

The same story repeats with antifibrinolytics. In the TREATT trial [5], more than 600 patients with hematologic malignancies and persistent thrombocytopenia received either tranexamic acid or placebo. However, the treatment did not reduce the incidence of bleeding or transfusion (31.7% vs. 34.2%), nor did it increase thrombosis. For many of us in the ICU, this feels familiar. We see platelets fall, fibrinogen drop, and our instinct is to replace what is missing. Yet, both PACER and TREATT tell a different story. When the problem lies in regulation rather than quantity, adding more of the missing piece rarely helps. What matters is not the number of platelets or the dose of tranexamic acid, but

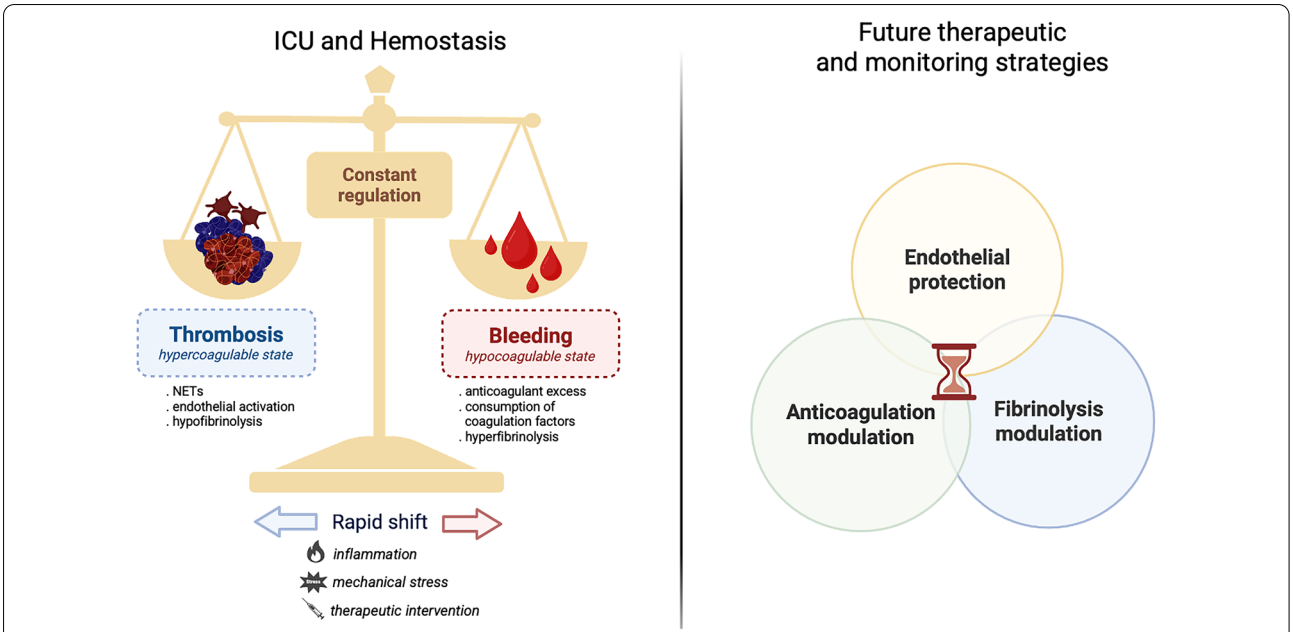

Fig. 1 Future strategies in the therapy and monitoring of hemostasis disorders in critical illness

the physiological setting—inflammation, consumption, endothelial stress—in which these components are trying to act.

Timing of intervention

The OPTIMAS trial [6] extended this logic to thrombosis prevention. Among 3,621 patients with atrial fibrillation—related ischemic stroke, early initiation of direct oral anticoagulants (≤4 days) was non-inferior to delayed initiation (7–14 days) for preventing recurrent stroke or intracranial hemorrhage. The results challenge long-standing recommendations advocating delayed anticoagulation and show that restoring balance early—before clot propagation or endothelial remodeling—may be both safe and effective.

A similar lesson emerges from extracorporeal life support. In this setting, static thresholds are meaningless [7]. Here, consumptive coagulopathy—driven by contact activation, inflammation, and mechanical injury—links microthrombosis and bleeding in a self-perpetuating loop. Vandenbriele et al. [8] elegantly described how complete withdrawal of heparin paradoxically worsens bleeding, whereas low-dose unfractionated heparin may halt the cycle by damping contact activation and factor consumption. Supporting this, prospective studies have shown that increases in tPA, D-dimer, and plasmin–antiplasmin complexes often preceded hemorrhagic events—confirming a shift toward pathologic hyperfibrinolysis [9, 10]. This profibrinolytic shift, together with the consumptive pattern suggests that bleeding in ECMO patients is not merely iatrogenic, but the downstream expression of contact pathway-driven hemostatic exhaustion.

The evolving spectrum of thrombotic microangiopathies

At the other end of the spectrum, thrombotic thrombocytopenic purpura (TTP) exemplifies uncontrolled microvascular coagulation. In a large international cohort of 1,525 immune-mediated TTP patients [11], early administration of caplacizumab, combined with plasma exchange and immunosuppression, improved survival (98.5% vs 94%), shortened time to platelet recovery, and decreased refractoriness. The benefit was greatest when the treatment was initiated within 3 days of the first exchange, with major bleeding reported in only 2.4% of patients, mostly older adults. This real-world cohort confirms that early modulation of von Willebrand factor can transform outcomes in TTP, at the manageable price of mild bleeding.

By contrast, the MAGMAT trial [12] tested magnesium sulfate as an adjunctive endothelial stabilizer in TTP, hypothesizing a cytoprotective effect. Among 73 participants, magnesium did not shorten the time to platelet normalization (median 4 days in both groups) or improve survival, though it was well tolerated. These contrasting findings suggest that targeting the molecular trigger, not simply supporting endothelium or platelets, alters the course of the disease.

Redefining balance

New tools are emerging to capture this dynamic state. Daily point-of-care ultrasound, as shown by Wu et al. [13], can detect early catheter-related thrombosis and guide timely intervention. Beyond imaging, biomarkers may soon be integrated into predictive models using machine learning to track the oscillations between hyper- and hypocoagulable states in real time.

What all these studies collectively demonstrate is that coagulopathy is not a laboratory abnormality, but a syndrome of dysregulation. Platelets, fibrin, and endothelium form a constantly adapting network. When inflammation, mechanical stress, or therapeutic intervention disrupts this equilibrium, the patient can shift within hours from thrombosis to bleeding. Understanding and monitoring this temporal evolution—rather than reacting to static thresholds—is the next frontier of critical care hematology.

The therapeutic implications are profound. Future strategies will likely combine moderate anticoagulation, fibrinolysis modulation, and endothelial protection, rather than oscillating between transfusion and withdrawal (Fig. 1). Precision medicine in coagulation will not come from a single biomarker, but from interpreting trends—integrating clinical, biological, and temporal data to anticipate where the balance will tip next.

In short, the modern view of coagulopathy moves beyond correction to orchestration—aligning the multiple components of hemostasis rather than replacing them. The path forward is not about adding platelets, antifibrinolytics, or heparin in isolation, but about retiming their use within the evolving landscape of critical illness. What these studies teach us is simple yet revolutionary: in coagulopathy, time, not numbers, is the true therapeutic variable.

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Declarations

Conflicts of interest

JH has received honoraria for lectures from Pfizer PFE France, Sanofi Aventis France, Inotrem, MSD, Octapharma and Shionogi and serves on the Steering Committees for Bayer and AngioDynamics. AC has no COI to declare. TI participated in advisory boards of Japan Blood Products Organization, Asahi Kasei Pharmaceuticals, and Toray Medical.

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