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UNDERSTANDING THE DISEASE

# Trauma-induced coagulopathy

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Trauma is a major cause of mortality worldwide, and bleeding is the leading preventable cause of death. About one-quarter of patients with severe trauma develop a clotting disorder termed trauma-induced coagulopathy (TIC) which is fatal in 30–50% of cases [1]. Understanding TIC pathophysiology is essential to reducing trauma-related mortality [2].

## Pathophysiology of TIC

The normal coagulation response initiates when the vascular endothelium is injured. This activates platelets, which adhere to the injury site, forming the initial platelet clot, and the coagulation cascade, amplified by activated platelets, leading to a thrombin burst that cleaves fibrinogen into fibrin. Fibrin monomers crosslink onto the aggregated platelets, further stabilising clot formation. In normal conditions, anticoagulation and fibrinolytic processes limit excessive clot formation to maintain vascular patency. Figure 1 in the electronic supplementary material describes the cell-based coagulation model in detail (ESM Fig.1 S1).

TIC originates from severe tissue damage combined with haemorrhagic shock [3], resulting in an inability to form and maintain clots leading to excessive bleeding and worsening shock and spiralling into a vicious cycle. In TIC, the cell-mediated regulation of haemostasis is impaired. The endogenous TIC differs from the iatrogenic exogenous resuscitation-induced coagulopathy caused by dilution of coagulation factors with clear fluids and blood products. However, this component may also be present in TIC.

Extensive tissue and endothelial cell damage causes loss of the endothelial glycocalyx and increased tissue factor (TF) expression [4], which both activate coagulation (Fig. 1 and ESM Fig. S1). Dying cells release intracellular components, such as cell-free DNA, histones, and high mobility group box protein 1 (HMGB-1), that signal tissue injury and are therefore termed “damage-associated molecular patterns” (DAMPs).

In about half of patients with TIC, platelets are dysfunctional in their adhesion and aggregation capabilities. This platelet dysfunction, known as "platelet exhaustion", is not revealed by the platelet count, which is often normal. Exhaustion has been attributed to platelet overactivation from TF, von Willebrand factor, and DAMPs [5]. Platelet dysfunction impairs haemostasis even if the blood levels of coagulation factors are maintained within the normal range.

The inflammatory response to major traumatic injury results from a large release of DAMPs, not only from damaged or necrotic tissues but also from active release by activated immune cells such as neutrophils. DAMPs are potent pro-inflammatory mediators that activate platelets and leukocytes [6], but also the complement system, resulting in increased levels of C3a and C5a [7]. In turn, innate immune cells and complement factors trigger the release of cytokines, further amplifying the inflammatory response and leading to a prolonged systemic perpetuating cycle [8]. In localised tissue injury, the inflammatory response is self-limited and promotes tissue repair. However, following severe tissue damage, this response may be overactivated, excessively prolonged, and lose its compartmentalisation, resulting in a systemic response.

Interestingly, platelets interact bidirectionally with circulating leukocytes by forming platelet-leukocyte aggregates (PLAs) [5]. PLAs are potent activators of the immune response, stimulating leukocytes to migrate

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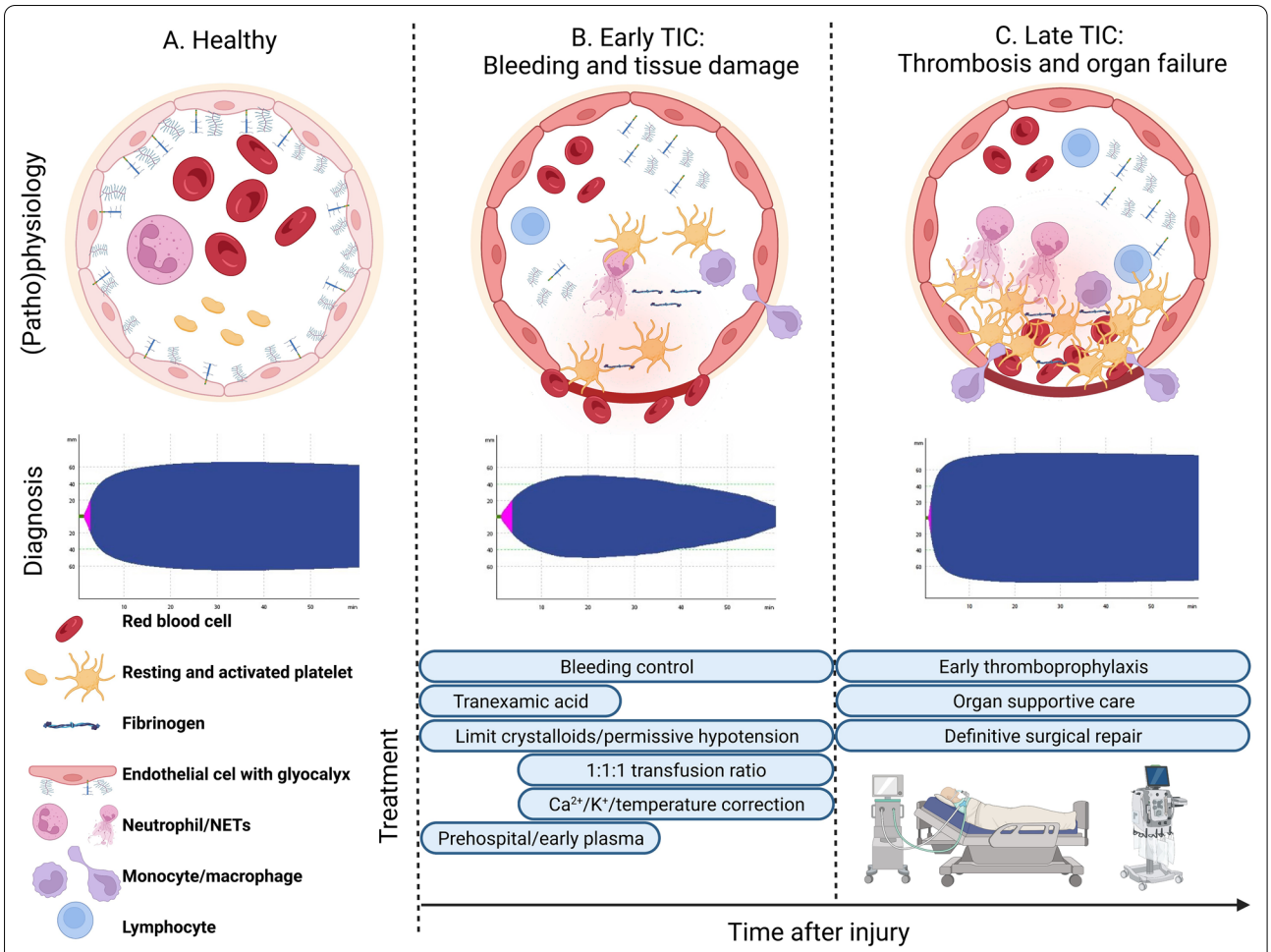


**Fig. 1** Pathophysiology, diagnosis and treatment of TIC. **A** The normal endothelial cell function limits spontaneous coagulation processes from occurring. **B** Trauma-induced coagulopathy (TIC) arises from severe tissue damage and haemorrhagic shock. TIC is characterised by widespread endothelial cell activation with glycocalyx release, impairment of platelet function, consumption of coagulation factors, dysregulated anticoagulation and hyperfibrinolysis. Together, these factors result in an inability to form and maintain clots. Also, immune cells are activated and crosstalk with activated platelets. For example, neutrophils produce neutrophil extracellular traps (NETs), and macrophages migrate to the injury site. See ESM Fig. S1 for a detailed description of the cell-based coagulation model. TIC is often defined as a prothrombin ratio $\geq$ 1.2. Viscoelastic haemostatic assays (VHAs; see also ESM Fig. S2) during active bleeding may show a hypocoagulable profile without or with fibrinolysis, as illustrated here. Early TIC can be treated with bleeding control, early administration of tranexamic acid, limiting crystalloid infusion and administering balanced blood transfusion of red blood cells with early plasma and platelet products whilst maintaining adequate electrolyte levels and temperature. **C** After haemostasis, TIC may shift towards a more hypercoagulable profile. The timing of this shift can vary from minutes to hours after injury and is patient- and injury-specific. Inflammation, endothelial and platelet dysfunction may result in (micro)thrombosis and organ dysfunction during this phase

towards the injury site. On the other hand, extracellular traps (ETs) (Fig. 1B) from activated neutrophils and macrophages are released, promoting platelet aggregation and thrombin formation[5].

Coagulation factors are usually depleted in TIC due to systemic consumption, dilution, and degradation by overproduction of several proteins of the anticoagulation and fibrinolytic systems (ESM Fig. S1), mainly activated protein C (APC) and plasmin. APC degrades coagulation factors FVa and FVIIIa and promotes the activity of tissue plasminogen activator, which converts plasminogen to plasmin. High plasmin production degrades fibrin and fibrinogen, leading to hyperfibrinolysis [9]. Moreover, reduced thrombin formation alters clot formation resulting in a thick loose fibrin network that is more prone to lysis [10]. The resulting breakdown of newly formed clots further amplifies bleeding [3].

Several coagulation reactions require ionised calcium as a cofactor. In TIC, calcium is consumed during coagulation and inactivated by citrate-containing blood products, further worsening coagulation disturbances.

When patients survive their initial traumatic bleeding and injuries, TIC shifts from a hypocoagulable to a hypercoagulable profile (Fig. 1C), with a consequent increased risk of thromboembolic events and organ dysfunction[11]. This shift occurs within minutes to hours after injury. It is initiated by the persistence of endothelial damage, activated immune cells and platelets, and circulating DAMPs that create a procoagulant environment.

## Diagnosis and management of TIC

TIC is classically defined as a prothrombin ratio of 1.2 or higher [1]. However, this single parameter cannot describe the complex series of coagulation changes associated with TIC. Fibrinogen levels below 1.5 g/L are common due to fibrinogen consumption and lysis and are associated with poor outcomes [12]. Conventional coagulation tests (CCTs) do not assess platelet dysfunction. D-dimer's levels are commonly increased due to the general response to severe trauma and are not sufficiently specific to assess fibrinolysis in TIC. Viscoelastic haemostatic assays (VHAs), such as rotational thromboelastometry (ROTEM) or thromboelastography (TEG) (ESM Fig. S2), separately assess the contributions of platelets and fibrinogen to clot formation and are rapidly available (5–20 min). For these reasons, VHAs are becoming increasingly popular for TIC management. The European Task Force for Advanced Bleeding Care in Trauma supports using VHAs but does not recommend specific therapeutic thresholds [13]. In a recent trial [14], VHA-guided augmented therapy did not result in better outcomes than CCT-guided augmented therapy (ESM Fig. S3).

Damage control haemostatic interventions (Fig. 1B) are essential to halt TIC progression. They include permissive hypotension to minimise fluid infusion and dilution of coagulation factors, early administration of tranexamic acid to limit the production of plasmin and reduce fibrinolysis [13], and early activation of massive transfusion protocols employing a balanced transfusion strategy of 1:1:1 red blood cells, plasma, and platelets [15]. Based on pathophysiology, replacing fibrinogen and calcium as essential components of the coagulation cascade is also necessary. Correcting hypothermia and acidosis to facilitate enzymatic coagulation reactions is common practice, even without direct support from clinical trials.

After the bleeding has ceased, prevention of thrombotic events due to hypercoagulability from late TIC is indicated. Thromboprophylaxis within 24 h from haemostasis is recommended (Fig. 1C) [13].

## Knowledge gaps and future development

Ongoing trials (ESM Fig. S3) investigate the early use of fibrinogen or cryoprecipitate and the administration of specific coagulation factors to correct TIC. More investigations are needed into the role of inflammation, the mechanisms of hypercoagulability and organ dysfunction during late TIC. A better understanding of the complex and time-dynamic pathophysiology of TIC may help reduce potentially preventable deaths due to trauma-induced shock and organ dysfunction in the future.

**Supplementary Information**
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