Sculpture garden along the river - Coagulopathy

Moderator: Tina Tomić Mahečić, Konstantina Triantafyllopoulou

Friday, May 01, 2026

1. COAGULOPATHY MANAGEMENT STANDARDIZED: SOLUCIONES CREATIVAS SIN POCT

Tina Tomić Mahečić

The coagulation point-of-care testing technology market has grown significantly over the last few years. However, these tools currently remain underused, even in countries where *Patient Blood Management* (PBM) is widely implemented, such as Germany[1].

In general, lab tests are very useful diagnostic tools, and they are employed in roughly 70% of medical decisions, even though they only represent around 2% of healthcare expenditure[2]. However, over 90% of preoperative prothrombin time (PT) and activated partial thromboplastin time (aPTT) determinations are requested unnecessarily[3].

In general, conventional coagulation tests are not consistently associated with a higher bleeding risk in minor surgeries or scheduled major surgeries.

PT and aPTT may be normal in the presence of factor level deficiencies. Standard laboratory tests underestimate factor XIII and vWF. Additionally, artefacts during venipuncture can alter coagulation times.

An exception is PT, which may be related to bleeding risk in patients with advanced liver disease undergoing abdominal surgery.

Standard coagulation tests	• Shortened PT and aPTT have no clinical relevance • Prolonged PT and aPTT are usually related to congenital or acquired deficiencies • Time to obtain the result is too long
PT	• The effect of some highly relevant coagulation factors such as FXIII or von Willebrand (vWF) are not contemplated • *In vitro* determination, not very significant as to what happens *in vivo*
aPTT	• It can be prolonged by multiple causes with no clinical relevance • It can be normal in patients with mild bleeding disorders (von Willebrand) • It can be prolonged due to artefacts in venipuncture

CAN WE PREDICT WHAT WILL BLEED?

In the context of elective surgery, a structured bleeding anamnesis provides more clinical value than routine analytical screening.

There are specific tools to assess bleeding risk, such as the ISTH-BAT *(International Society on Thrombosis and Haemostasis Bleeding Assessment Tool)*, a validated bleeding history questionnaire designed to identify patients with hereditary bleeding disorders[4]. ISTH-BAT presents the following features:

- It has a high negative predictive value (> 98%), meaning that a negative result virtually rules out a clinically relevant bleeding disorder.
- It cannot predict by itself perioperative bleeding risk; therefore, in case of a positive result, supplementary studies should be conducted.
- It allows to effectively distinguish hereditary platelet disorders and it is useful to identify patients requiring specific analytical evaluation, once von Willebrand disease has been preliminarily ruled out[5].

Given that ISTH-BAT is not able to detect acquired coagulation disorders, as happens with trauma patients, in these cases clinical signs and specific tools must be used to predict the risk for massive transfusion.

When approaching these patients, it is fundamental to consider that hemostasis varies between tissues and organs *(vascular bed-specific hemostasis)*, due to the different local expression of procoagulant and anticoagulant factors.

BRAIN TISSUE	LUNG, PANCREAS OR UROGENITAL SYSTEM
• It can induce prothrombotic states through the release of procoagulant phospholipids, microvesicles, and vWF.	• They can release large amounts of tissue-type plasminogen activator (tPA), and favour hyperfibrinolysis and bleeding.

In regard to therapy management in coagulopathy and perioperative or trauma bleeding in absence of point-of-care testing, measures aimed at restoring homeostasis should be considered and applied in the following order[6,7]:

1. Basic conditions: Temperature, pH, Calcium, clinical history review to check whether the patient receives anticoagulants or antiaggregants.

2. Hyperfibrinolysis control

- Tranexamic acid may be administered without significantly increasing the thrombotic risk in surgery patients with various conditions[8], providing there are no specific risk factors, such as liver cirrhosis or history of thrombosis.

3. Favouring clot formation

- Administration of fibrinogen concentrate (30-50 mg/kg), since fibrinogen decreases earlier than other coagulation factors and platelets[9] and because, unlike other factors, it is a substrate.
- Administration of platelets, taking into account that platelet concentrate is the blood product most commonly associated with reactions[10]. The target is a count over 50,000 platelets and >100,000 in case of traumatic brain injury or with a coexisting platelet deficiency.

4. Increasing thrombin production

- Administration of prothrombin complex concentrate (20-40 UI/kg).

5. Administration of FXIII and FVII

- As a final intervention on the coagulation cascade, the administration of factor XIII and factor VII may be considered.

In summary, in patients with trauma-induced coagulopathy, haemorrhage control must be achieved as early as possible, using coordinated strategies at a prehospital, hospital, and transfusion level. Additionally, an early correction of the so-called trauma “lethal diamond” is essential, formed by acidosis, hypothermia, coagulopathy, and hypocalcemia[11].

“TIME IS THE ENEMY OF BLEEDING PATIENTS”

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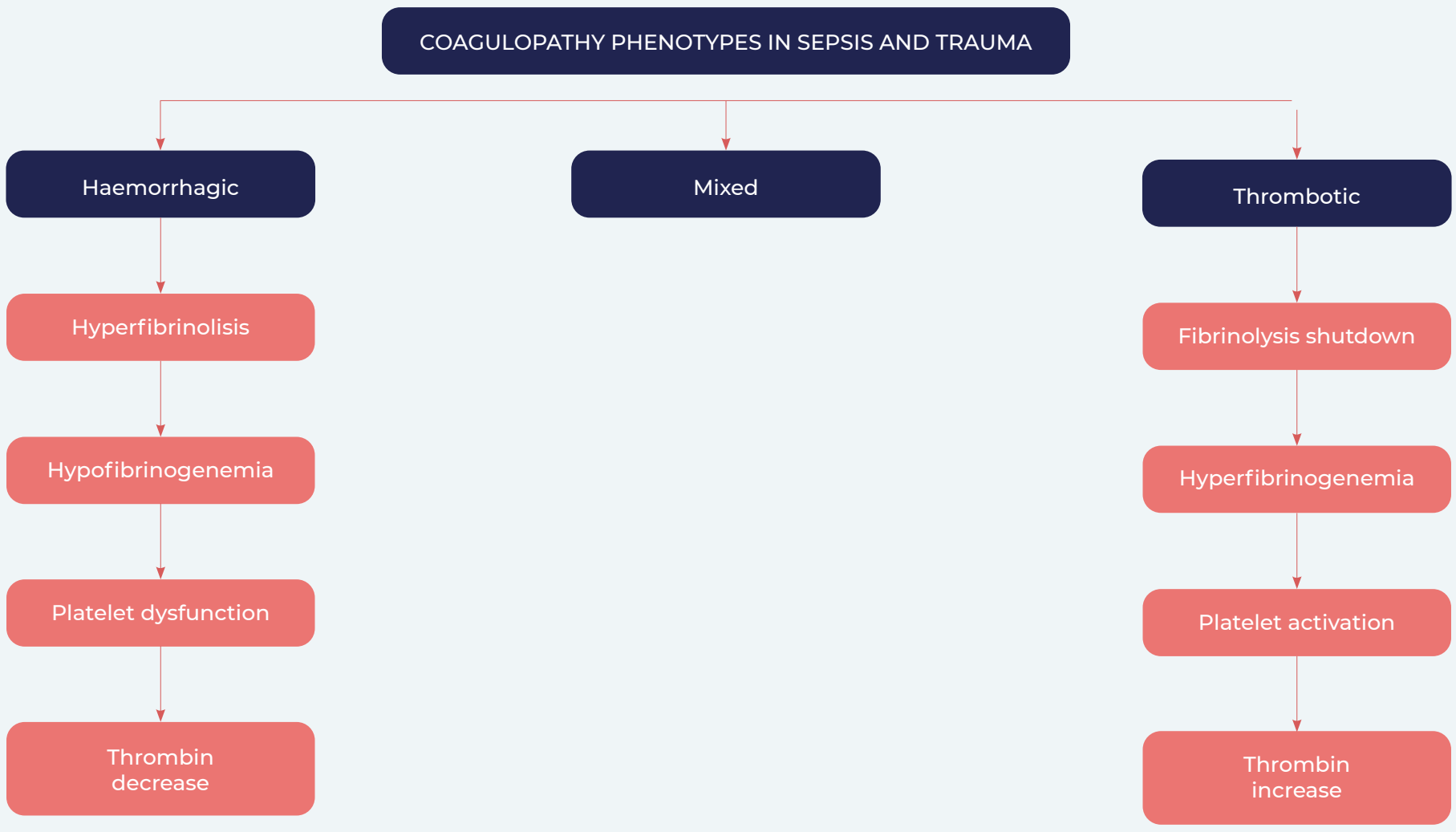
2. COAGULOPATHY MANAGEMENT INDIVIDUALISED (ROTEM/TEG/CLotPRO)

Dietmar Fries

Trauma- and sepsis-induced coagulopathy is not a uniform phenomenon. It comprises different phenotypes requiring specific therapy strategies. This variability exists both between different individuals and within the same patient along clinical evolution[12,13].



In this context, it is essential to consider the early decrease of fibrinogen during trauma haemorrhage and the subsequent need for an early assessment and correction of hypofibrinogenemia[14]. Among the different treatment options, fibrinogen concentrate is the most effective strategy:

- Replacement using cryoprecipitate achieves a faster correction than fresh frozen plasma[15].
- The FEISTY study demonstrated that fibrinogen replacement is achieved roughly 30 minutes earlier with fibrinogen concentrate than with cryoprecipitate[16].
- In the RETIC study, a strategy based on ROTEM-guided factor concentrates (fibrinogen, prothrombin complex concentrate, and FXIII) was associated with a 50% decrease in the need for massive transfusion when compared to a treatment based on fresh frozen plasma[17].
- The use of coagulation factor concentrates may explain the lower mortality rates observed in Austrian studies[17,18], compared to North American studies[19,20].

Blood product-based treatment allows for a more precise and individualized approach than whole blood transfusion, which poses several potential risks and issues:

Overtransfusion of unnecessary products	**Risk of complications: ARDS, among others[21]**	**Immune load**	**Risk of infections**	**Less useful life and more sensitivity to fibrinolysis[22]**	**Higher use of resources**	**Lack of sound evidence for many indications**

Whole blood is not the ideal solution, since not all haemorrhage cases require replacement of all blood products.

In this context, point-of-care tests are fundamental tools to individualize the haemostatic treatment. Unlike other diagnostic tests, they have been proven to significantly reduce mortality in trauma and heart surgery patients[23,24]. Moreover, different studies have shown that the empirical use of coagulation factors without functional monitoring does not improve clinical outcomes and may even increase thromboembolic complications[25,26]:

CRYOSTAT-2 study with cryoprecipitate[27]	**PROCOAG study with 4-factor prothrombin complex (4F-PCC)[28]**

As for tranexamic acid, it should not be administered indiscriminately to all trauma patients, but selectively, based on the fibrinolytic profile. In cases such as traumatic brain injury or multiorgan failure, hypofibrinolysis states are more common than hyperfibrinolysis. The PATCH-Trauma study, possibly because it did not specifically recruit hyperfibrinolytic patients, was not able to prove the efficacy of tranexamic acid administered in the prehospital setting[29]. Beyond an adequate indication, the time of administration of tranexamic acid is critical, since a delay in the administration is associated with a lower survival[30].

Recent European and German guidelines expressly recommend the addition of viscoelastic monitoring to transfusion algorithms[31–33]. Likewise, the DIVI German regulation considers these systems as part of the structural equipment recommended in advanced intensive care units[33].

In summary, rigid massive transfusion protocols should be avoided, and individualized strategies, guided by coagulation functional monitoring, should be adopted. Patients with a haemorrhage should only receive the blood products they really need, at the right time and in the right dose, in order to improve their clinical outcomes and to reduce complications associated to the transfusion treatment.

Furthermore, we should not forget that, once the haemorrhage has been corrected, antithrombotic prophylaxis must be implemented and monitored, because up to 50% of these patients present resistance to standard heparin doses.

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3. DIC IN CRITICALLY ILL PATIENTS

Julien Demisell

The International Society on Thrombosis and Haemostasis (ISTH) defines disseminated intravascular coagulation (DIC) as an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different severe conditions[34]. DIC represents the most advanced manifestation of coagulopathy and it is associated to multiorgan failure and death.

DIC is not a homogeneous entity and, depending on the underlying condition, a thrombotic or fibrinolytic phenotype may prevail[35]. In case of sepsis-related DIC, the thrombotic phenotype usually prevails.

- Sepsis affects 48.9 million people/year and over 20 million develop DIC[36].
- DIC is associated to a higher risk of complications and mortality[37,38].

Morbidity	Mortality	Severe acute kidney dysfunction

DIAGNOSIS OF DIC

Multiple diagnostic scales and biomarkers have been proposed for the diagnosis of DIC. Guidelines currently recommend a two-step diagnostic approach[39]:

1 SIC SCORE
(Sepsis-Induced Coagulopathy)

Evaluates sepsis-induced coagulopathy

2 CONFIRMATION WITH ISTH SCORE
(International Society of Thrombosis and Haemostasis)

Confirms the presence of DIC using the ISTH score

Platelets	PT/INR	Fibrinogen	D-Dimer

Limitations of DIC evaluation:

- Existence of multiple confusion factors in critical patients admitted to the ICU.
- Analytical alterations mainly detect late-stage changes, but not initial cellular events in the coagulopathy.

Because of this, and given that DIC is a dynamic process, septic patients must be continuously reassessed.

PATHOPHYSIOLOGY OF DIC

DIC is the result of immunothrombosis deregulation.

When compared to a healthy endothelium, with a protective, antithrombotic and antiinflammatory glycocalyx, in DIC we have a prothrombotic antifibrinolytic endothelium (fibrinolysis shutdown).

Tissue factor activation in endothelium and monocytes	Neutrophil activation, triggering endothelial damage and platelets	Loss of natural anticoagulants	Increase of plasminogen activator inhibitor (PAI-1) and fibrinolytic blockade

All of this leads to excessive activation of coagulation and hypofibrinolysis.

Neutrophil activation is currently put forward as a potential DIC biomarker, and there are ongoing studies aimed at evaluating its diagnostic and prognostic usefulness.

In sepsis, neutrophils are activated, and neutrophil NETosis and fluorescence appear, which may be the diagnostic criterion for sepsis-induced coagulopathy.

DIC TREATMENT

There are two main therapy strategies:

- Reducing coagulation activation using anticoagulants or thrombomodulin.
- Restoring fibrinolysis using plasma, plasma exchange or plasminogen.

1. Anticoagulants

Randomized clinical trials conducted over almost 20 years have failed to demonstrate a clear benefit of anticoagulants on sepsis-related mortality (OPTIMIST-TF pathway-, KyberSept -ATIII-, PROWESS-activated C Protein-)[40–42], probably due to several factors:

- Inclusion of heterogeneous populations, including patients with no DIC or with a haemorrhagic phenotype.
- Too late start of treatment.

2. Recombinant thrombomodulin (rhTM) (SCARLET TRIAL, fist randomized clinical trials with coagulopathy stratification in sepsis patients)

The efficacy of recombinant thrombomodulin has been assessed in patients with sepsis, cardiovascular dysfunction and/or respiratory condition and coagulopathy (INR > 1,4 and platelets 30–150 $\times 10^9$/L). rhTM was administered within 40 hours of inclusion in the study[43].

Although no significant reduction in mortality was observed within 28 days when compared to placebo, a separation of survival curves was actually confirmed, compatible with a potential clinical benefit in the patient subgroup still suffering from the coagulopathy at the time of administration. Around 20% of patients no longer presented a coagulopathy at that time. These findings suggest that both an adequate stratification of patients and the time of the intervention might be decisive for the therapy to be effective.

Furthermore, a post hoc analysis of the French cohort included in that trial suggested that patients with persistent sepsis-induced coagulopathy not receiving concomitant heparin may benefit from a treatment with rhTM[44].

3. Therapeutic plasma exchange

Plasma exchange has been shown to improve several pathophysiological and clinical parameters:

- Restoring balance between procoagulant and anticoagulant factors[44]
- Improvement of coagulation and endothelial protection[45]
- Increase of survival, both in adults and children[45,46]

4. Plasminogen supplementation

Plasminogen supplementation allows fibrinolytic capacity to be restored, which supports its potential therapeutic usefulness in sepsis-induced DIC. A recent study observed a non-significant reduction of mortality in the group treated with plasminogen (42%) versus the control group (60%)[47].

In summary, sepsis-induced DIC is a complex heterogeneous condition requiring a dynamic individualized approach. An early identification of the prevailing phenotype and an adequate selection of the therapy starting time may be key factors to improve the clinical outcomes.

CONCLUSIONS

- Early diagnosis of DIC is a challenge
- Identifying the right patient to administer the right treatment is key, and so the right scores must be defined or biomarkers must be used, such as fluorescence of neutrophil NETosis
- Treatment timing is fundamental for an optimal response
- New therapy goals must be developed:
- Anticoagulants?
- Restoration of plasminogen?

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