



Review

Trauma-Induced Coagulopathy: Overview of an Emerging Medical Problem from Pathophysiology to Outcomes

Gabriele Savioli ^{1,*} , Iride Francesca Ceresa ¹, Luca Caneva ², Sebastiano Gerosa ¹ and Giovanni Ricevuti ^{3,4}

¹ Emergency Department, IRCCS Policlinico San Matteo, PhD University of Pavia, 27100 Pavia, Italy; irideceresa@gmail.com (I.F.C.); seba.gerosa@gmail.com (S.G.)

² Anesthesia and Intensive Care, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy; l.caneva@smatteo.pv.it

³ Department of Drug Science, University of Pavia, 27100 Pavia, Italy; giovanni.ricevuti@unipv.it

⁴ Saint Camillus International University of Health Sciences, 00152 Rome, Italy

* Correspondence: gabrielesavioli@gmail.com; Tel.: +39-3409070001

Abstract: Coagulopathy induced by major trauma is common, affecting approximately one-third of patients after trauma. It develops independently of iatrogenic, hypothermic, and dilutive causes (such as iatrogenic cause in case of fluid administration), which instead have a pejorative aspect on coagulopathy. Notwithstanding the continuous research conducted over the past decade on Trauma-Induced Coagulopathy (TIC), it remains a life-threatening condition with a significant impact on trauma mortality. We reviewed the current evidence regarding TIC diagnosis and pathophysiological mechanisms and summarized the different iterations of optimal TIC management strategies among which product resuscitation, potential drug administrations, and hemostatis-focused approaches. We have identified areas of ongoing investigation and controversy in TIC management.

Keywords: early coagulopathy of trauma; acute coagulopathy of trauma-shock; trauma-induced coagulopathy; trauma-associated coagulopathy; major trauma; severe trauma; acute traumatic coagulopathy



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1. Introduction

Major trauma (MT) is one of the leading causes of mortality and morbidity globally and the leading cause of death in people younger than 40 years. Annually, traumatic injuries cause approximately 6 million deaths globally [1–3]. MT is also a frequent cause of hospitalization, as an estimated 24 million patients are hospitalized yearly. This also results in extensive out-of-hospital medical care for approximately 85 million patients worldwide [1–3]. Although the problem mainly affects low- and middle-income countries, high-income countries are also affected. For instance, in Europe major trauma is the third-leading cause of death in the general population and the first among younger patients. Traumatic injuries are also one of the main causes of disability, rendering major trauma a pathology with high direct and indirect costs [1–3]. Given its impact on mortality, a quick, efficient, and precise identification of bleeding causes, as well as of coagulopathy is of paramount importance for surgical management [4].

MT is an event that results in a single injury or multiple injuries of such magnitude that it constitutes a *quoad vitam* or *quoad valetudinem* (in regard to life or health) danger to the patient. Conventionally, trauma is defined as severe when the patient's injury severity score (ISS) exceeds 15. ISS is an assessment system that assigns a number based on the severity and location of the different injuries caused by trauma. This index was chosen because it displays excellent correlations with mortality, morbidity, the need for hospitalization, and hospital stay. ISS > 15 was selected on the basis of a proven increase in mortality. ISS can only be calculated after the patient has undergone diagnostic investigations, mainly in a hospital setting. To overcome this limitation, it is essential that a potential MT is

recognized as soon as possible in the pre-hospital phase, and triage criteria for MT should be implemented (Table 1).

Table 1. Triage criteria for severe trauma.

Physiological Criteria	Anatomical Criteria	Dynamic Criteria
Ejection from a vehicle	Penetrating head/neck/throat/abdomen/pelvic/armpit/groin trauma	Systolic blood pressure < 90 mmHg
Motorcycle crash with separation of the rider	Amputations above the wrist or ankle	Respiratory distress or respiratory rate of <10 or >29 breaths/min
Died in the same vehicle	Chest trauma with flap/flail chest	State of consciousness (GCS < 13)
CRASH intrusion >30 cm at the patient area	Neurological injury with paralysis of even a single limb	
Fall from height >2 m	Fractures of two or more long bones	
Pedestrian thrown or run over or hit at a speed >10 km/h	Suspected unstable fracture ring of pelvis:	Suspected unstable fracture
	High-energy impact	
	(Speed > 65 km/h)	Open or depressed skull fracture
Vehicle crash	Burn >20% of the body surface or airway/face	
	Extrication time > 20 min	

The criteria for activating the severe trauma protocol in our trauma center are presented, including physiological, anatomic, and dynamic criteria for defining probable severe trauma (one of the following criteria is sufficient). GCS, Glasgow coma score.

Post-traumatic hemorrhage is the most frequent cause of death in victims of severe trauma, in about 40% of cases. This is caused by two main mechanisms, but they can intertwine and present simultaneously [4–14].

The first mechanism is bleeding caused via direct injury of blood vessels, which involves hemorrhage that is dependent on physiological or anatomic factors. These include the hemodynamic state of the patient, in particular systolic blood pressure, the arterial or venous nature of the affected vessel, and the caliber of the vessel. In cases of injury of large-caliber arterial vessels, we can witness profuse hemorrhage with shock and exitus in an extremely short period, even before the arrival of the rescue crew.

Meanwhile, the second mechanism is secondary bleeding from the development of trauma-induced coagulopathy (TIC), which involves secondary bleeding from a widespread microvascular hemorrhage that is not localized to the site of the trauma. This represents a pathological entity in its own right, and its classification and pathogenesis will be discussed later.

Approximately 30% of patients with MT develop TIC upon arrival to the emergency department (ED). Although it was once believed that TIC begins hours or even days after the traumatic event, it is currently clear that it begins at the moment of trauma. Approximately 40% of trauma deaths result from bleeding, and 10% of these events appear avoidable [4–14].

2. Definition

Numerous definitions and terms have been proposed to identify coagulopathy resulting from trauma and describe the specific pathology of trauma-associated coagulopathy, including acute traumatic coagulopathy, early coagulopathy of trauma, acute coagulopathy of trauma shock, TIC, and trauma-associated coagulopathy [6,15–18].

TIC can be defined as a condition of endogenous hypercoagulation observed in the immediate post-traumatic period, that is, within 1 h of trauma. It is characterized by widespread microvascular hemorrhage opposed to events localized exclusively to the site of trauma [6,15–18].

3. Pathophysiology

Hemostasis is an essential physiological response to wound healing. It is a dynamic homeostatic process balancing pro- and anti-coagulation systems and fibrinolytic and fibrinolysis-inhibitory pathways, and it consists in the interaction between endothelial cells' walls, platelets, and clotting factors, with the endothelium taking an active part in this homeostatic process, together with several mediators, among which tissue factor pathway inhibitors, endothelial protein C receptors, the endothelial glycocalyx, thrombomodulin, nitric oxide, and tissue plasminogen activator (tPA) [19].

Despite continuing and recent advances in research into MT and the consequent increase in knowledge in the sector, the pathophysiological mechanisms that contribute to the development of TIC remain largely unknown. This is also associated with the multitude of complex systems that interact with each other [18–21]. A disturbance in hemostasis is induced by activation/dysregulation of the vascular endothelium, coagulation, natural anticoagulants, the pro-fibrinolytic and anti-fibrinolytic systems, and inflammation [19–21].

These phenomena are compounded by a number of external factors (such as hemodilution by the administration of crystalloids) and detrimental factors such as hypothermia, hydroelectrolytic imbalance, and acidosis. These detrimental factors are likely to self-feed and depend on both endogenous and exogenous factors [19–21].

For years, it was considered that TIC was solely attributable to the dilution of clotting factors caused by substantial fluid administration or massive transfusion, which further complicated the development of acidemia and hypothermia, which, together with TIC, contribute to the formation of the “lethal triad” and thus further aggravate the clinical picture (Figure 1).

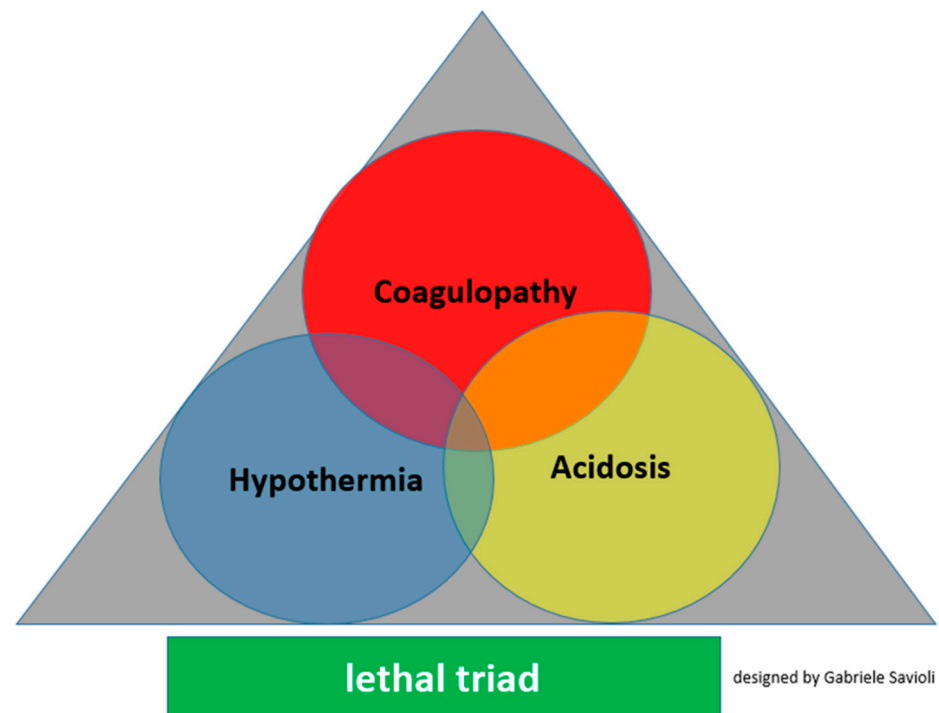


Figure 1. Lethal triad for major trauma.

Classically, the factors recognized as the only triggers of TIC were hemodilution, hypothermia, and acidemia. Although they are still recognized as TIC triggers, it has been found that TIC develops in the early stages of trauma before any medical intervention and the development of acidemia and hyperthermia. Thus, TIC is dependent on the first phase during the release of mediators by hypoperfused organs and damaged tissues.

With the increasingly greater body of research on the pathophysiological mechanisms of TIC, they have been discovered to be far more complex than initially inferred; additionally, fluid administration has been proven to contribute to the development of intracardiac thrombus without being the main cause, indicating a multifactorial etiopathogenesis.

A distinction can therefore be made between acute traumatic coagulopathy and coagulopathy disease induced by resuscitating maneuvers, which can coexist but possess different mechanisms and temporal phases [19–21].

We can schematically (Figure 2) claim that TIC consists of the following variables: a pathophysiological process linked to trauma (acute traumatic coagulopathy) iatrogenic factors (coagulopathy induced by resuscitation maneuvers) detrimental factors (both iatrogenic and pathophysiological)

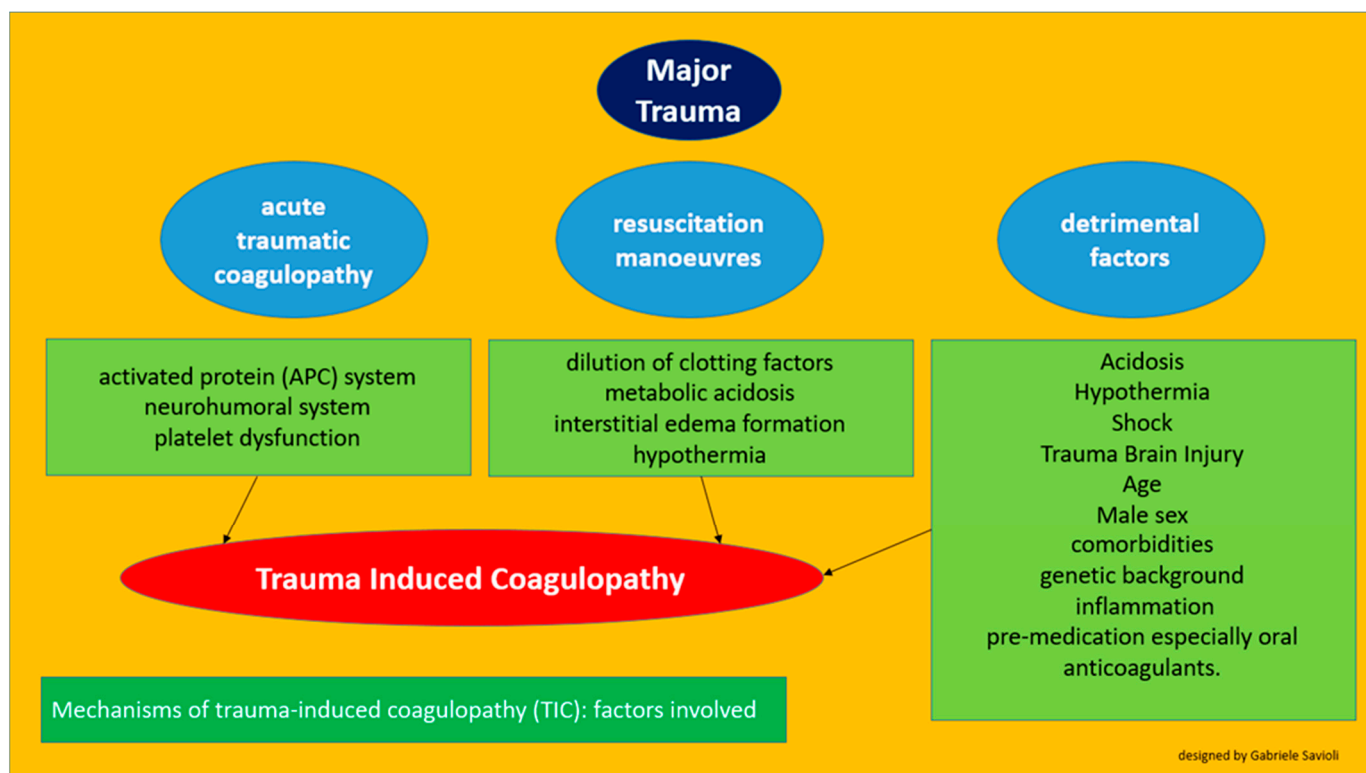


Figure 2. Factors involved in the development of trauma-induced cardiomyopathy.

3.1. Acute Traumatic Hypercoagulability

Injury to the wall of a vessel as a result of trauma can expose subendothelial collagen and activate tissue factors, which provide an adhesion platform for circulating platelets and support the interplay between the cellular and humoral components of the hemostatic system. This pro-coagulant activity is controlled by a counter-regulatory system of natural anticoagulants. The summed effect of these two opposing systems may trigger the coagulatory response at the site of endothelial injury while preventing uncontrolled microvascular thrombosis and tissue hypoperfusion by providing endogenous anticoagulation and fibrinolysis. Parts of the process are interconnected in a complex manner, with thrombin playing a central role by being able to partake in both coagulation and anti-coagulation pathways in addition to interacting with the inflammatory response.

3.1.1. Role of the C Protein

Several theories have been postulated regarding the pathophysiological process that triggers TIC [22–26]. Until recently, activated C protein (APC) had been considered one of the main players (Figure 3) [22–24]. It was believed that the APC system played the most im-

portant role in TIC development. APC is a physiological anticoagulant able to irreversibly inactivate factors Va and VIIIa, which are pro-coagulants. APC also enhances fibrinolysis by inhibiting plasminogen activator inhibitor-1 (PAI-1) and serves a cytoprotective function via anti-apoptotic and anti-inflammatory mechanisms [22,23].

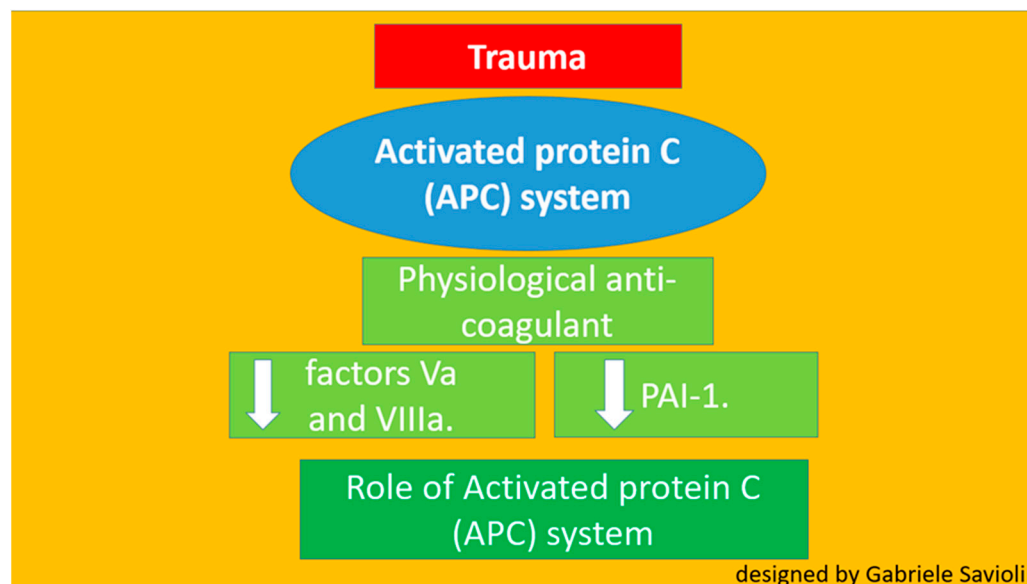


Figure 3. Role of protein C.

In the PROMMTT study, TIC at arrival to the emergency ward was associated with the depletion of the pro-coagulatory factors I, II, V, VII, VIII, IX, and X and with protein C system activation [24–26]. This apparent contradiction is not inexplicable considering the complexity of the response to trauma, encompassing the involvement of several dynamic physiological systems and the release of a multitude of co-interacting mediators.

3.1.2. Role of the Neurohumoral System

Trauma activates the neurohumoral system, leading to increased secretion of inflammatory cytokines and hormones, such as adrenaline and vasopressin. This increased secretion leads to the activation of endothelial cells, resulting in the release of tPA and Weibel–Palade bodies [25]. These factors bind to the endothelium, induce the release of von Willebrand factor, and encourage platelet recruitment [27–36].

In addition, the release of tPA and high amounts of plasmin contribute to the catabolism of fibrinogen. This catecholamine increase also damages the endothelium and causes glycocalyx degradation. The process, termed endotheliopathy, may also contribute to capillary leakage following trauma. Specifically, this process induces degradation of the endothelium and the consequent release of glycosaminoglycans such as heparin into circulation and thus activates the phenomenon most properly known as self-heparinization [27–29]. Endotheliopathy is present in about 5% of trauma patients and is associated with a high ISS (Figure 4).

Deceased adult patients of trauma have been reported to have presented high levels of adrenaline and syndecan-1. Some studies found high adrenaline levels and glycocalyx damage to be associated with endothelial damage, hyperfibrinolysis, and hypocoagulopathy. Syndecan-1 is an indicator for glycocalyx degradation, and elevated syndecan-1 is associated with an increase in inflammation and endothelial damage [29–33]. Recently both adrenaline and syndecan-1 were proven to be independent predictors of <24-h, 7-day, and 28-day mortality, even after adjustment for ISS [29–33].

Various pathophysiological mechanisms determine whether severe TIC leads to hypofibrinogenemia. In the early phases of trauma TIC induced hypofibrinogenemia is frequently observed. It has been demonstrated that fibrinogen concentrations are less than

2 g/L in approximately 15–20% of patients with TIC, and these low levels were linked to poor outcomes. However, fibrinogen levels may also increase with age [34–36].

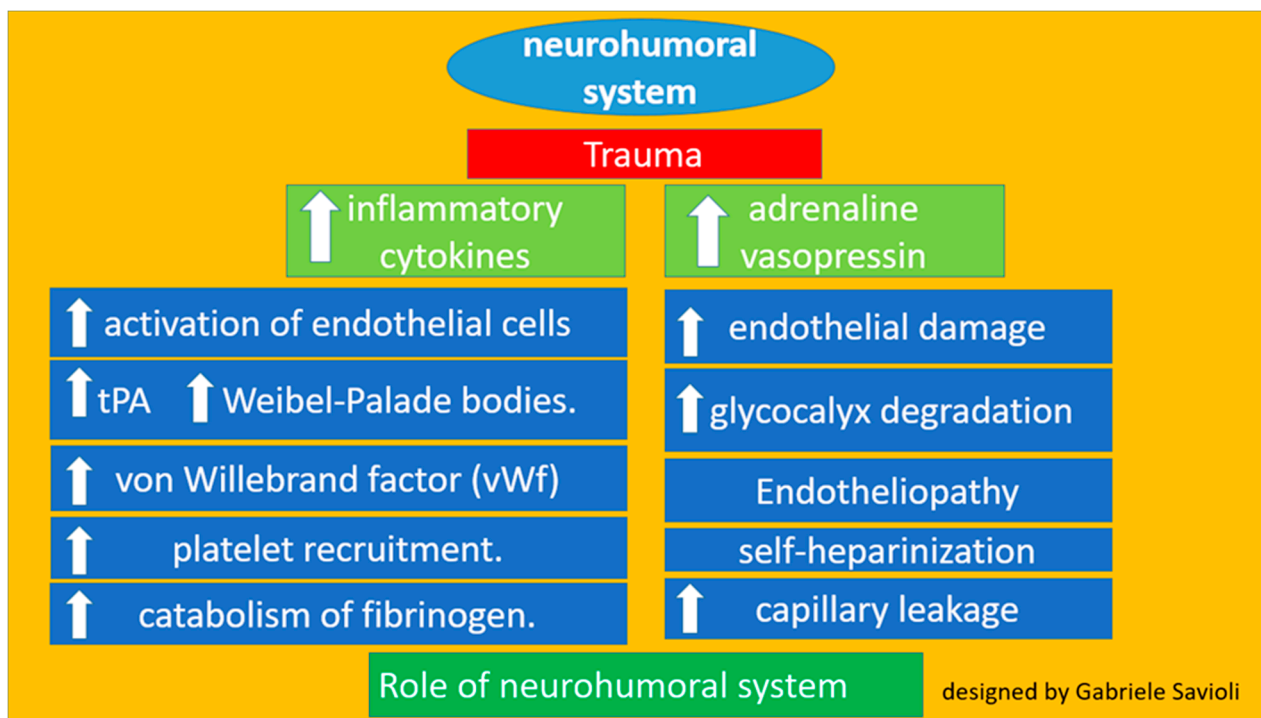


Figure 4. Role of the neurohumoral system.

3.1.3. Role of Platelets

Platelets produce a number of proteins involved in coagulation and fibrinolysis. The mechanisms by which the contradictory activities of secreted platelet proteins affect TIC are unclear. Precise data on platelet function in traumatic patients are scarce: platelet sample handling and specific assays availability are complicating factors in researching the subject [37–39].

Studies reported adenosine diphosphate (ADP), arachidonic acid, collagen, and thrombin receptor activating peptide to impair platelet aggregation, suggesting a prevalence of platelet dysfunction of up to 45.5% in patients with trauma on admission and to 91.1% during their stay in the intensive care unit [37–41]. The thrombin receptor pathway has been proposed to play an important role in platelet dysfunction in trauma [42–45]. However, the mechanisms and implications of these findings are unclear. Anemia, whether caused by hemorrhage or dilution, can also affect platelet adhesion. The available evidence suggests endotheliopathy and anemia to be triggers of platelets dysfunction in trauma.

Some cohorts of massively transfused trauma patients report that measuring platelet count at admission may be used as an outcome predictor, as their platelet count was inversely correlated with injury severity, morbidity, and mortality [37–45].

3.2. Coagulopathy Associated with Resuscitation Maneuvers

In post-trauma patients, aggressive resuscitation, as previously recommended, with crystalloid dilutes clotting factors and causes metabolic acidosis (hyperchloremic in the case of 0.9% NaCl administration) and interstitial edema. This also caused by microcirculation impairment and impaired oxygen tissue supply [46–48]. Colloids cause proteins to move from the blood to the interstitial space, therefore reducing plasma concentration of clotting factors, in particular of factor VII and von Willebrand factor, inhibiting platelet function, and reducing the interaction between factor XIII and fibrin polymers. It has been documented how administering crystalloids in trauma patients worsens TIC, acidemia,

and hypothermia, therefore inducing a reduction in thrombin coagulatory activity; it is, therefore, recommended to limit the use of crystalloids in order to reduce coagulation factors dilution effects [48–59]. The effects of hypothermia, to which hemorrhage and hypoperfusion contribute, will be discussed more extensively [48,49,51,55–58].

Finally, acidemia in patients after trauma, which occurs widely, depends on three factors: the use of crystalloids in resuscitation maneuvers, hypoperfusion, and the use of saline solution. In fact, hypoperfusion causes cells to switch from an aerobic mechanism to an anaerobic mechanism, resulting in the production of lactates and a consequent reduction of pH. Saline solution (0.9% NaCl) contains a higher concentration of chlorine than the body under physiological conditions, which could induce hyperchloremic metabolic acidemia [49–54].

3.3. Detrimental Factors Exacerbating Trauma Coagulopathy

Early trauma induced coagulopathy has been recently recognized as the result of the combination of bleeding-induced shock, tissue injury-related thrombin–thrombomodulin complex generation, and the activation of anticoagulant and fibrinolytic pathways; it is therefore a multifactorial primary condition.

3.3.1. Acidosis

Acidosis is a frequent and early event in patients after trauma that results from inadequate tissue oxygenation, which then activates anaerobic metabolism. Acidosis itself causes plasma protein dysfunction and leads to the rapid degradation of fibrinogen, and almost all stages of clotting are compromised in this setting. At pH less than 7.4, we observe:

- Changes of platelet shapes and structure;
- Reductions of clotting factor activity;
- Compromised thrombin production;
- Reductions of the fibrinogen concentration;
- Increased fibrinogen degradation (caused by increased fibrinolysis and increased factor XIII levels) without effects on fibrinogen production;
- Increased pro-inflammatory responses by platelet-mediated neutrophils;
- Bicarbonate administration to correct acidosis does not correlate with reversal of TIC [49–54].

3.3.2. Hypothermia

After trauma heat loss, reduced heat production, and fluid administration can induce hypothermia. Clinically significant reductions of platelet function and coagulation factor activity start at temperatures less than 36 °C and worsen dramatically at temperatures less than 33 °C. Hypothermia influences several key stages of the coagulation process, including the following:

- Negatively affects platelet function;
- Reduces the enzyme activity of clotting factors;
- Induces the activation of fibrinolysis;

The effects are reversible with the normalization of body temperature, which represents a first-level goal to be achieved, both through the use of thermal blankets, by other means of physically warming the patient, or the administration of hot liquids (40 °C).

Overall, the other two components of the lethal triad act on clotting in all phases. In particular, hypothermia extensively inhibits the early stages of the process, whereas acidosis extensively inhibits the propagation and thrombin generation phase. Regarding fibrinogen metabolism, hypothermia inhibits fibrinogen synthesis and acidosis accelerates its degradation. Regarding the response to therapy, we can note some differences in this case. Specifically, the effects of hypothermia are corrected when the body temperature is restored at least 36 °C, whereas the effects of acidosis cannot be immediately corrected with the normalization of pH [48,49,51,55–58].

3.3.3. Shock

There is agreement that shock is an independent risk factor for TIC even though the true frequency of shock in patients after trauma is unknown. Systolic blood pressure has been used in several studies as the parameter of choice to diagnose hypoperfusion. Traumatic brain Injury (TBI) decreases the precision of using blood pressure as a determinant for hypoperfusion. The systolic blood pressure goals differ depending on the areas involved in MT. In cases of head trauma, systolic pressure must reach 110 mmHg, whereas a value of 90 mmHg is desired when trauma occurs in other regions [22,59–63]. Despite the different kinds of injuries, shock and its effect on the sympathoadrenal system, the endothelium (including the glycocalyx), and hemostatic cells in blood circulation determine the phenotypic features that characterize the clinical conditions of patients with acute critical illness. Catecholamine-induced endothelial damage causes endothelial degradation, which results in glycocalyx shedding, which is the breakdown of tight junctions bringing about capillary leakage, and a pro-coagulant microvasculature that further reduces oxygen delivery because of increased tissue pressure and microvascular thrombosis, creating a vicious circle that ultimately leads to organ failure. Severe trauma, burn injury, and endotoxemia induce similar early genetic responses, indicating that the body response to various acute critical conditions accompanied by shock is relatively homogenous and most likely evolutionarily adapted [64–72].

3.3.4. TBI

TIC related to TBI usually occurs within minutes of head injury [18,73] it can be inferred that it is triggered by substances released, following brain damage, at the systemic level through the damaged blood–brain barrier (BBB). BBB is a semipermeable barrier consisting of cells (endothelial, smooth muscle, astrocytes, etc.) and an extracellular matrix [74] responsible for the (active and passive) control of fluids and macromolecules. Head trauma also increases the permeability of the BBB through secondary ischemic and inflammatory lesions. [75,76] Such lesions are mediated by intracellular signals of endothelial cell junction proteins, such as claudins [77–79] and junctional adhesion molecules. [80,81] The increase in permeability of the BBB causes fluid leakage with consequent cerebral edema. Cerebral edema in turn contributes to the release of substances involved in the triggering of systemic coagulopathy.

Among these substances it seems that brain-derived cellular microvesicles (BDMV) may play a role both as a diffusion factor and as a causal factor [72,73,82–84]. A study has shown in mouse models their rapid release into the circulation associated with a state of systemic hypercoagulability which rapidly evolves into consumption coagulopathy [85].

Their procoagulant power may be due to an abundant expression of the abundant tissue factor and phosphatidylserine [85].

Infusion of purified BDMV resulted in the initiation of a hypercoagulable state in non-trauma mice.

Some studies claim to have detected the fibrinolysis by-product D-Dimer along with other fibrinogen degradation products before detecting an alteration in prothrombin time (PT) and partial thromboplastin time (PTT), which reached their peaks approximately 3–6 h post TBI; some studies suggested these timeframes to be consistent with an early transition from a hypercoagulable to a hypocoagulable state [25,86–91]. However, many steps are required to fully understand the role of head trauma in activating TIC, particularly concerning its role in determining changes in fibrinolysis and platelet function. Regarding the changes of fibrinolysis inhibitors, few cases have been reported. Concerning platelet function, patients with TBI appear to have moderately low counts, but often, they are activated, permitting pro-coagulant activity [25,88–97].

3.3.5. Age, Male Sex and Comorbidities

Coagulopathy is modified by trauma-related factors such as age, sex, and comorbidities including diabetes and hypertension. Significantly different sympathoadrenal and

endothelial responses to MT in older and younger patients have been reported. Patient age also appears to significantly influence TIC, including the degree of endotheliopathy. This is congruent to the established correlation between old age and progressive disruption and dysfunction of the endothelium, with the greatest severity of disruption reported in smokers and patients with diabetes, atherosclerosis, or hypertension. Together with age, gender as well has a significant influence over the endogenous trauma-shock response; both age and male sex are independent predictors of multiple-organ failure, a complication closely related to endotheliopathy in major trauma patients [72,98–103]. Previously reported comorbidities can lead to worse outcomes, probably also because of endotheliopathy.

3.3.6. Other Factors

In addition to the aforementioned factors, the severity of coagulation disorders is influenced by environmental factors and the resulting therapeutic factors such as the genetic background, inflammation, and premedication, especially with oral anticoagulant use [101–103]. Concerning the involvement of anatomical regions, associations were found between TIC and the involvement of the abdominal region [93,101–103]. A recent study reported that a higher number of involved regions was correlated with the early development of TIC [93]. Some authors have highlighted the role of some biomarkers, in particular troponin and ultra-sensitive troponin, in highlighting worse outcomes, also due to bleeding, of trauma patients. Their early rise is in fact correlated with worse outcomes and ultra-sensitive troponin could play a role in stratifying even better patients at higher risk. Further studies will be needed to possibly better define a role of these biomarkers in early highlighting coagulopathy related to severe trauma [104–107].

Overall the pathophysiological mechanisms of trauma-induced coagulopathy are therefore multi-layered and complex (Figure 5).

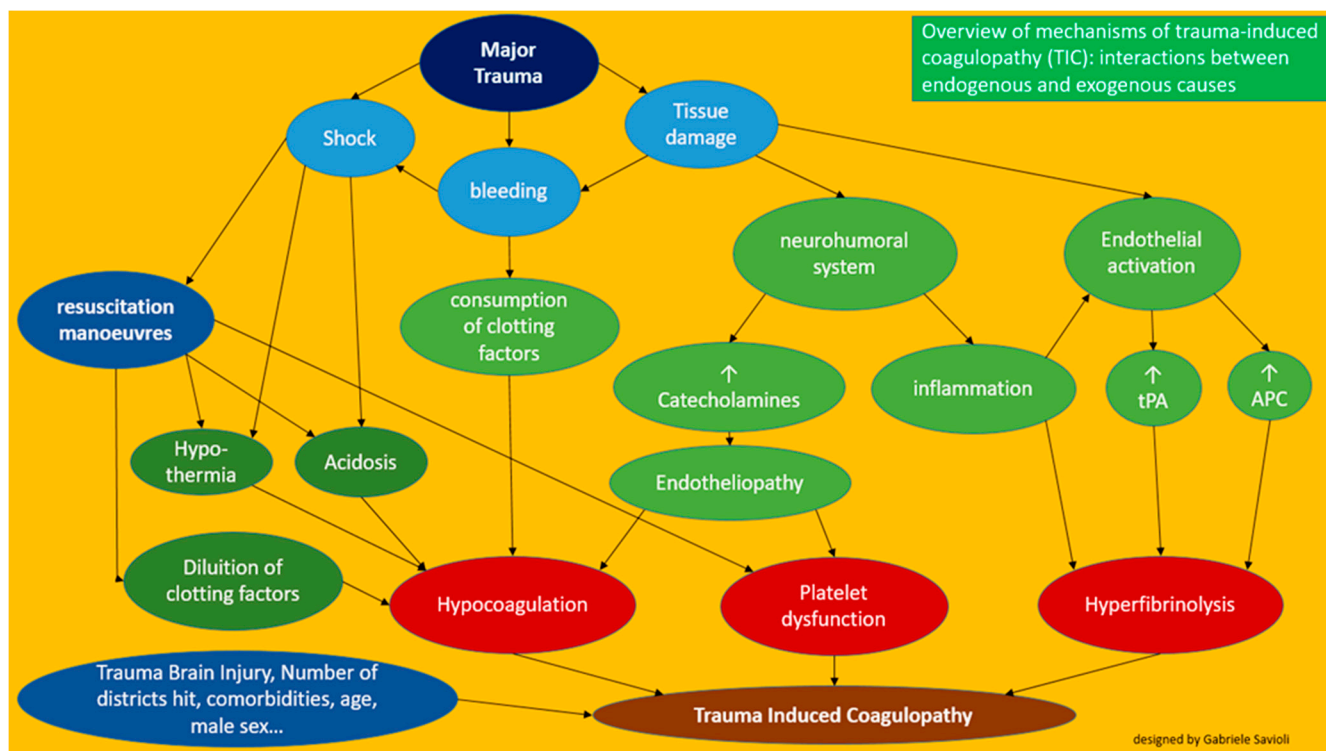


Figure 5. Overview of the mechanisms of trauma-induced coagulopathy (TIC).

4. Specials Clinical Forms of TIC

In addition to the aforementioned forms and severity of coagulopathy hyperfibrinolysis, hypocoagulation, then hypercoagulation (hypofibrinolysis)—some other forms are worthy of discussion [108–120].

4.1. Early Primary Hyperfibrinolysis

A limited number of patients experience rapid activation during the early manifestation process of coagulopathy and an uncontrollable pattern of fibrinolysis. This clinical picture is termed early primary hyperfibrinolysis. Hyperfibrinolysis is present in approximately 2.5–7% of all traumatized patients. Early diagnosis of this form presents many difficulties. Viscoelastic tests (see below) highlight only some cases, whereas occult hyperfibrinolysis appears to be more common. This condition may be associated with greater mortality, with some authors suggesting rates of 60–80%.

Early administration of anti-fibrinolytics is required as demonstrated by the CRASH two study. The administration of tranexamic acid (TXA) within the first 3 h in patients with active bleeding or those at risk of bleeding is strongly recommended (recommendation class 1A) according to the 2016 and 2019 European guidelines [9,101,121,122].

4.2. Late Hypercoagulability

Late coagulopathy has been observed as the hemostatic reaction following trauma, which normalized throughout recovery in uncomplicated patients, whereas patients with severe injuries may experience complications of massive coagulopathy. Recovery from coagulopathy and the return to normal clotting values may be delayed in such patients after severe trauma. A massive physiological response follows trauma, leading to a multitude of changes in the neurohumoral system, the natural pro- and anti-coagulation systems, and other previously reported systems. Distinguishing adaptive from maladaptive systemic inflammatory response to injury remains difficult.

From a clinical point of view, the identification of organ dysfunction could be a reliable indicator of maladaptive systemic inflammation. Multi-organ dysfunction syndrome is present in almost 30% of severely injured patients; it is associated with worse outcomes and a high mortality rate. It is important to remember that late hypercoagulopathy after trauma correlates with an increased risk of venous thromboembolism.

5. Diagnosis

5.1. Clinical Features

Although blood loss is sometimes noticeable, neither visual evaluation nor physiological parameters are effective guides to understand the degree of hemorrhage. Trauma dynamics is an important tool for identifying patients at risk of significant bleeding. For instance, a threshold of 6 m (20 ft) defines the critical fall height associated with major trauma according to the American College of Surgeons. Additional critical mechanisms include the high-energy deceleration effect and gunshot wounds. The dynamics of trauma combined with severity, the patient's clinical presentation, and the response to the initial resuscitation maneuvers should further lead to the decision to begin initial hemorrhage control as described in ATLS. An American study by Mutschler et al. analyzed the accuracy of this classification reporting that over 90% of all patients cannot be classified following the ATLS criteria of hypovolemic shock. This system is composed of four classes of patients depending on their vital parameters and state of consciousness [17,121,123–126].

The same group studied the effectiveness of the ATLS classification criteria and reported that it may underestimate sensory alterations in hypovolemic shock and overestimate the degree of tachycardia associated with hypotension. A three-class scheme with three kinds of response to initial volemic resuscitation was proposed. The first class consists of patients who respond with stable normalization of vital parameters. The second class, comprising transient responders after initial stabilization and volemic filling, subsequently present with unstable vital parameters of consciousness. The third class consists of non-

responders to volemic filling. The second and third classes are candidates for immediate surgical management of bleeding [17,124–128].

5.2. Laboratory Tests

TIC is diagnosed on the basis of laboratory abnormalities that do not necessarily correspond to distinct clinical phenotypes. Despite coagulation research progress and achievements, an established and verified test to predict and identify clinically relevant acquired coagulopathy is lacking. Current literature on TIC is mostly based on abnormalities of PT, aPTT, plasma fibrinogen concentration, and platelet count, either alone or in combination.

The early identification of coagulopathy in patients with trauma is important, as this can lead to better management and overall improvement in outcomes. The most commonly used tests are traditional clotting tests (aPTT and PT), along with the platelet count and fibrin monitoring. Originally, TIC was defined as an increase in clotting plasma variables such as the aPTT, PT, and international normalized ratio. Emerging evidence suggests that whole-blood viscoelastic tests, such as thromboelastography or rotational thromboelastometry, may better identify coagulopathy and the stage, type, and location of TIC. High ISSs are associated with increases in the severity of TIC and risk of poor outcomes.

Three stages of TIC can be proposed corresponding to more serious clinical frameworks and worse outcomes hyperfibrinolysis, hypocoagulation, then hypercoagulation (hypofibrinolysis). Viscoelastic tests can provide partial results in minutes. They also have the advantage of being able to diagnose, quantify, and classify fibrinolysis, thus allowing the use of anti-fibrinolytic and blood-resistant drugs such as concentrated fibrinogen.

Viscoelastic tests have also been revealed to prevent inappropriate hemotransfusion and hemostatic infusion of blood derivatives to non-coagulopathic patients [17,121,123–128]. In addition, the severity of TIC may vary with ongoing treatment, and viscoelastic tests are able to record these changes. Current hematochemical tests (PT, aPTT, fibrinogen, platelets), despite having the advantage of being universally available, require a long time for analysis. In addition, PT and aPTT are only useful for analysis in the early stages of clot formation, and they do not provide a complete view of actual pro-coagulant and anticoagulant activity, in particular on platelets, as well as hyperfibrinolytic activity.

The use instead of viscoelastic tests, such as thromboelastography and thromboelastometry, could remedy these problems, as they more quickly provide a more complete view of the entire clot process, giving a reflected view of the homeostatic process in vivo, including pertinent information regarding the analysis of platelets and fibrinogen, which not provided by routine hematochemical testing [17,121,123–128].

6. Outcomes

This section synthetically summarizes (because we discussed this topic elsewhere in the text) that patients who develop TIC have worse prognoses regardless of the initial severity. Among the worst complications they face include a higher need for hemotransfusion, a higher rate of hospitalization, a higher rate of hospitalization in intensive care, and a higher mortality rate. We can therefore observe that these patients have worse clinical outcomes and require more hospital and pre-hospital resources. As demonstrated with other pathologies as well, the lack of early recognition and treatment aggravates the outcome [129–134].

7. Hints for Therapy

Hypovolemic resuscitation, hypothermia prevention, and early clotting support are, together with damage control surgery, the cornerstones of damage control resuscitation (DCR). The convention of DCR largely arose following the discovery of the lethal triad of hypothermia, acidosis, and coagulopathy with the goal of avoiding the initiation of this cycle or reversing its progression. DCR is the strategy by which we attempt to correct

the early conditions that promote bleeding and compromise hemostasis and to limit the damage caused by hypoperfusion [135–141].

International guidelines state that the management of bleeding trauma should follow the principle that the normalization of coagulation parameters improves outcome. It is reasonable to suspect TIC to affect severely injured patients, and therefore a “best guess” treatment should be initiated; during resuscitation a goal-driven approach is considered optimal.

Coagulation support measures should be initiated immediately at admission, and it remains of paramount importance to rapidly assess the type and degree of coagulopathy in the individual patient along with identifying the most prominent causative factors in order to correctly treat the patient in a goal-driven fashion.

Early monitoring of coagulation is essential to detect trauma-induced coagulopathy and define the main causes. Early therapeutic intervention improves coagulation, reduces the need for red blood cell (RBC), fresh frozen plasma (FFP), and platelet transfusion, decreases the incidence of post-traumatic multi-organ failure, shortens the length of hospital stay, and potentially improves survival. The success of early intervention determines the best coagulation management to reduce transfusions and improve outcomes, including reductions of the risk of mortality [8,9,141–147].

Briefly, we will emphasize some aspects of management for the ED treatment of patients with TIC following the European guideline on the management of major bleeding and coagulopathy following trauma fifth edition published in 2019 (Figure 6) [124].

The first step in the EW is the clinical assessment of the extent of the hemorrhage. a combination of patient physiology, anatomical injury pattern, mechanism of injury and patient response to initial resuscitation can help estimating the severity of the bleeding. (4R,1C).

At the same time, adequate techniques to monitor and promote coagulation should be executed (R23/1B). A blood gas analysis should be performed as soon as possible to obtain hemoglobin (Hb), lactate and base deficit (BE), indicative parameters for shock and the magnitude of hemorrhage with coexisting coagulopathy (R8–9/1B). Blood sample should be collected for standard clotting parameters (prothrombin time, platelet count, and fibrinogen concentration) and/or point-of-care PT/international normalized ratio (INR) (R10/1C) and/or functional viscoelastic testing assays (R10/1C). The 2019 updated European trauma guideline, for the first time, considers standard clotting parameters and viscoelastic testing results as equivalent in the acute assessment of the bleeding trauma patient. Functional assessment of initiation and speed of clot formation, fibrinolytic activity and the functional levels of fibrinogen and platelets can be determined in whole blood by means of viscoelastic tests resulting in accelerate and tailored therapies.

Ongoing this first step, in trauma patients who are bleeding or who are at risk of significant hemorrhage tranexamic acid is to be administered as early as possible at a loading dose of 1 g infused over 10 min, followed by an intravenous (IV) infusion of 1 g over 8 h; administration should be started within 3 h after injury; TXA should not be given more than 3 h after injury (R22/1A).

Immediate bleeding control procedure is recommended in patients with an obvious bleeding source and those with hemorrhagic shock and a suspected source of bleeding (R5/1C) according to the classical damage control procedures (R18/1B) with closure/stabilization of the pelvic ring (R19/1B) and abdominal packing (R20/1B); angiographic embolization may be an option if available. Some clinical studies point out and the European Guidelines recommend performing immediate bleeding control procedure on patients with gunshot wounds and a suspected source of bleeding [122,148–151].

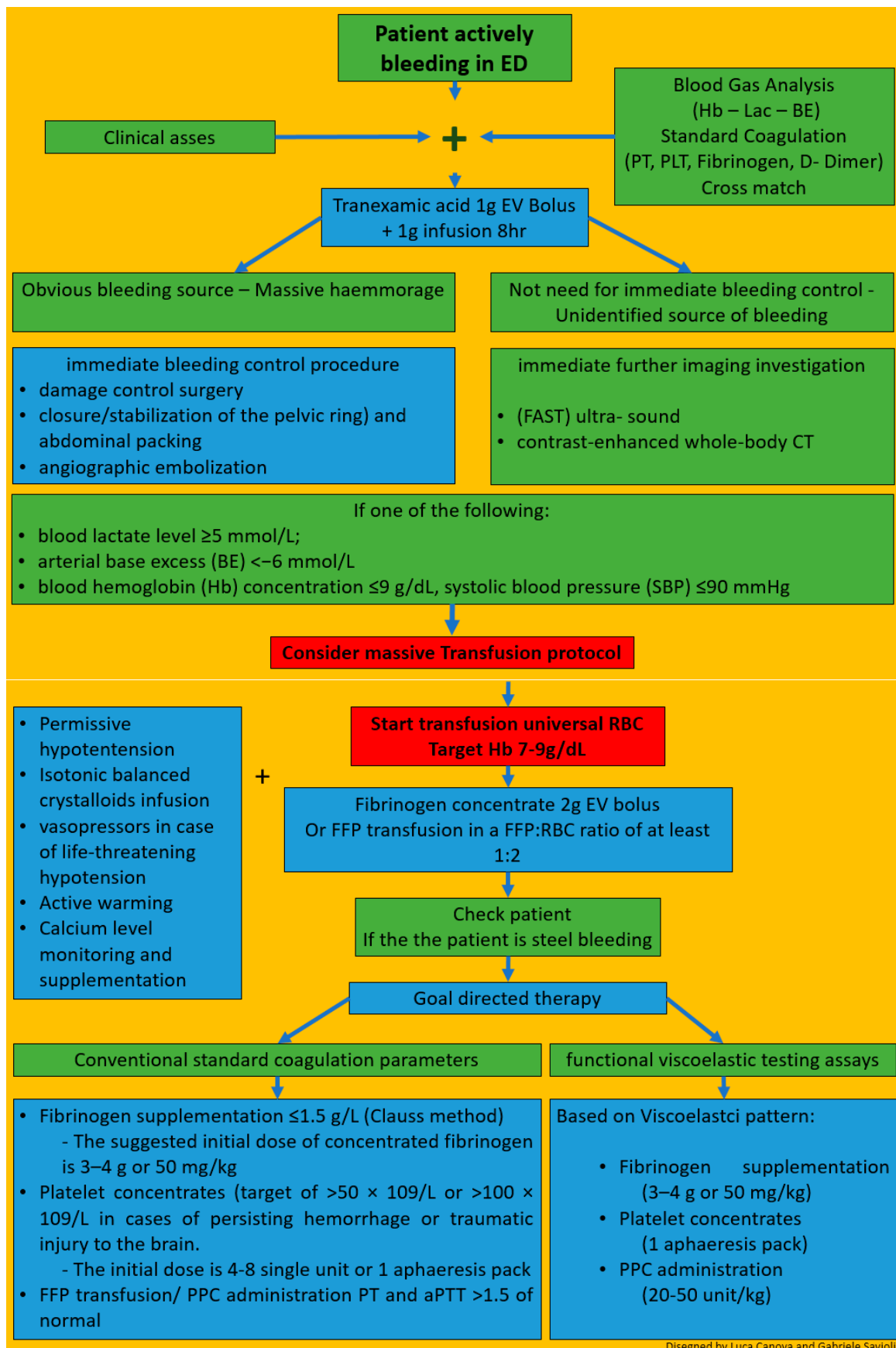


Figure 6. Overview of hints for therapy.

Immediate further imaging investigation such as: focused assessment with sonography in trauma (FAST) ultra- sound for the detection of free fluid in patients with torso trauma (R7–1C) and contrast-enhanced whole-body CT (WBCT) for the detection and identification of type of injury and potential source of bleeding. (R7–1B) is recommended in patients without a need for immediate bleeding control and an unidentified source of bleeding (R7–1B).

From a practical point of view if one of the following: blood lactate level ≥ 5 mmol/L; arterial base excess (BE) < -6 mmol/L; blood hemoglobin (Hb) concentration ≤ 9 g/dL, systolic blood pressure (SBP) ≤ 90 mmHg is present a predefined massive transfusion protocol MT should be started [152].

Concentrated red blood cells must be transfused to achieve a hemoglobin target of 7–9 g/dL.

Early management of patients with expected massive hemorrhage should follow one of these two strategies [8,9,139–147]: the empirical use of fresh frozen plasma (FFP) and packed red blood cell concentrates (pRBC) at a predefined ratio of at least 1:2 (R24/1C) or, alternatively, the use of fibrinogen concentrate and pRBC (R24/1C). Fibrinogen is the substrate for blood to clot and the first coagulation factor which reaches critical thresholds during acute and critical bleeding [17]. Administration of 2 g of fibrinogen to mimic the expected 1:1 ratio corresponding to the first four units of RBC and potentially correct hypofibrinogenemia, if present, has been proposed for initial coagulation support, while waiting for the results of viscoelastic or laboratory tests [152]. Endogenous fibrinogen has been shown experimentally not to be suppressed by fibrinogen administration. Moreover, recent studies have demonstrated a positive trend for survival and saving allogenic blood products when the fibrinogen concentrate approach was followed [153].

Simultaneously to reduce the blood loss, permissive hypotension is recommended with systolic target pressures 80–90 mm Hg (mean target pressure 50–60 mm Hg) in the absence of traumatic brain injury (TBI) until control of bleeding has been achieved (R12/1C). In the presence of TBI, a mean arterial pressure (MAP) ≥ 80 mm Hg is suggested to maintain an adequate cerebral perfusion pressure (R12/1C).

Isotonic balanced crystalloids should be given to achieve the perfusion target (R15/1A), associated with vasopressors in case of life-threatening hypotension and shock (R14/1C).

Heat lost must be avoided and technique to warm the patient should be employed (R17/1C). Calcium levels must be maintained within the reference ranges, especially in settings where a massive transfusion is needed (R30/1C).

After these first steps the patient has to be rechecked and if still bleeding these blind strategies should be replaced by a targeted and tailored strategy, guided either by conventional standard coagulation parameters or by the results from functional viscoelastic testing assays (R25/1B).

If functional viscoelastic testing is not available, the threshold for fibrinogen supplementation is ≤ 1.5 g/L with the Clauss method (R28/1C). The suggested initial dose of concentrated fibrinogen is 3–4 g or 50 mg/kg. Any repetition must be conducted using laboratory tests. The platelet concentrates should be transfused with a target of $>50 \times 10^9/L$ (R29/1C), or $>100 \times 10^9/L$ in cases of persisting hemorrhage or traumatic injury to the brain (R29/2C).

In this second phase, FFP transfusion should be based on PT and aPTT (>1.5 of normal) value and/or viscoelastic patterns (R26/1C). The administration of FFP in the absence of massive bleeding (R26/1B) or to correct hypofibrinogenemia is not advised (R26/1C).

Coagulation factor concentrates (PCC) has proven better than FFP in rapidly reversing vitamin K antagonists, as there is evidence of decreased hematoma formation in head trauma patients. PCC is therefore the preferred choice for vitamin k antagonists effect reversal. PCC are, for the first time, allowed by European updated Guidelines in case of lack of coagulation factors diagnosed by standard coagulation or, better, viscoelastic patterns (R26/1C).

The identification and management of patients pre-treated with anticoagulant agents, especially direct anticoagulant, continues to pose a major challenge despite accumulating experience and awareness [12,14–17,44,59,74,101–103,122,154–159]. Idarucizumab is indicated as an antidote for the thrombin inhibitor dabigatran (5 g intravenously (R35/1B)). In case of severe and life-threatening hemorrhage under preinjury factor-Xa inhibition, the recommended treatment is combined TXA 15 mg/kg (or 1 g) and PCC (25–50 units/kg) (R34/2C). The European Medicines Agency (EMA) supported the approval of factor-Xa antidote andexanet alfa and the agent became available in most European countries [160].

Platelet concentrates administration is recommended in case of documented platelet dysfunction and/or in patients with persistent bleeding previously treated with platelet inhibitors (R36/2C); this is to be considered in particular in patients with intracranial hemorrhage in need for an acute neurosurgical intervention (R36/2B) with the possible additional use of desmopressin (R36/2C).

8. Management of Patients with Severe Trauma in the ED

Briefly, we will emphasize some aspects of management for the ED treatment of patients with TIC.

The findings of this review highlighted the need for protocols for the management of coagulopathy regarding diagnostics and therapeutic pathways in patients with severe trauma in line with the most up-to-date guidelines. The usefulness of protocols for massive hemotransfusion and the need for bedside clotting analyzers have also been demonstrated. The European guidelines currently recommend to directly transfer patients to an appropriate trauma center for treatment and to follow a restricted volume replacement strategy during initial resuscitation [1–3,5–11,101,121,122,151,154,161–170]. Blood product optimal use procedures continue to evolve, and their development should be goal directed. Despite greater awareness and experience, the identification and management of patients under the effects of anti-coagulant agents remains a major challenge [12,14–17,59,74,101–103,122,154–159,162].

9. Conclusions

- TIC is a dynamic sequence coagulation disorder from hyperfibrinolysis, hypercoagulation to its final stage hypocoagulation. The early hypocoagulable state is not related to dilution nor to iatrogenic or hypothermic causes.
- TIC is present in approximately one-third of patients who report MT
- The physiopathology of TIC is complex and features several contributing causes. The role of protein C has been less emphasized
- The diagnosis and management of TIC often encompasses standard coagulation test and functional viscoelastic assays.
- Early initiation of antifibrinolytic therapy and balanced resuscitation of coagulation disorder is the mainstay of TIC
- TIC is related to worse outcomes, among which increased rates of transfusion, infection, thromboembolism, acute lung injury, multi-organ failure, and death.

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