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REVIEW ARTICLE

The coagulopathy of trauma

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Abstract Trauma is a leading cause of death, with uncontrolled hemorrhage and exsanguination being the primary causes of preventable deaths during the first 24 h following trauma. Death usually occurs quickly, typically within the first 6 h after injury. One out of four patients arriving at the Emergency Department after trauma is already in hemodynamic and hemostatic depletion. This early manifestation of hemostatic depletion is referred to as the coagulopathy of trauma, which may distinguished as: (i) acute traumatic coagulopathy (ATC) and (ii) iatrogenic coagulopathy (IC). The principle drivers of ATC have been characterized by tissue trauma, inflammation, hypoperfusion/shock, and the acute activation of the neurohumoral system. Hypoperfusion leads to an activation of protein C with cleavage of activated factors V and VIII and the inhibition of plasminogen activator inhibitor-1 (PAI-1), with subsequent fibrinolysis. Endothelial damage and activation results in Weibel–Palade body degradation and glycocalyx shedding associated with autoheparinization. In contrast, there is an IC which occurs secondary to uncritical volume therapy, leading to acidosis, hypothermia, and hemodilution. This coagulopathy may, then, be an integral part of the "vicious cycle" when combined with acidosis and hypothermia. The awareness of the specific pathophysiology and of the principle drivers underlying the coagulopathy of trauma by the treating physician is paramount. It has been shown that early recognition prompted by appropriate and aggressive management can correct coagulopathy, control bleeding, reduce blood product use, and improve outcome in severely injured patients. This paper summarizes: (i) the current concepts of the pathogenesis of the coagulopathy of trauma, including ATC and IC, (ii) the current strategies available for the early identification of patients at risk for coagulopathy and ongoing life-threatening hemorrhage after trauma, and (iii) the current and updated European guidelines for the management of bleeding and coagulopathy following major trauma.

Keywords Trauma · Hemorrhage · Coagulopathy · Mechanisms · Diagnosis · Predictors · Treatment · Guideline

Introduction

Trauma is among the major health care issues of modern societies and the leading cause of death in persons under the age of 40 years [1]. Currently, trauma results in the annual death of more than five million people worldwide, accounting for approximately 10 % of all deaths in general, but this number is set to increase to more than eight million by 2020 [2]. Despite substantial improvements in the care for the acutely injured, uncontrolled post-traumatic hemorrhage is still responsible for more than 50 % of all trauma-related deaths in both civilian and military settings within the first 48 h after hospital admission [3], and has also been determined to be the most common cause of preventable deaths [4–6].

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Several studies independent from each other have demonstrated that one out of four severely injured patients presents to the Emergency Department (ED) with hemodynamic and hemostatic depletion [7–10]. This early manifestation of hemostatic depletion has been referred to as acute traumatic coagulopathy (ATC) and is associated with higher transfusion requirement, greater incidence of organ failure, longer intensive care unit (ICU) and in-hospital stays, as well as mortality compared to cases with similar injuries but absence of coagulopathy [7–9]. Vice versa, it has been shown that the early recognition of ATC accompanied by appropriate and aggressive management can correct coagulopathy, control bleeding, reduce blood product use, and improve outcome in severely injured patients [11, 12].

Apart from ATC, there is an iatrogenic coagulopathy (IC) which occurs secondary to uncritical volume therapy, leading to acidosis, hypothermia, and dilution. This coagulopathy may, then, be an integral component of the so-called "vicious cycle" when combined with acidosis and hypothermia. The awareness of the specific pathophysiology and of the principle drivers underlying the coagulopathy of trauma by the treating physician is paramount. Meanwhile, the current German S3 Guideline "Polytrauma" recognizes the coagulopathy of trauma as a distinct clinical entity with a strong impact on outcome [13, 14].

The appropriate management of the massively bleeding trauma patient includes the early identification of the bleeding sources, followed by adequate measures to minimize blood loss, restore tissue perfusion, and achieve hemodynamic stability [15]. According to a recent analysis of trauma data documented in the German TraumaRegister DGU®, the C-priority, e.g., circulation with hemorrhage control and coagulation management, is still not adequately addressed during primary survey and initial resuscitation between the ED and ICU admission [16]. This manuscript summarizes: (i) the current concepts of the pathogenesis of the coagulopathy of trauma, including ATC and IC, (ii) the current strategies available for the early identification of patients at risk for coagulopathy and ongoing life-threatening hemorrhage after trauma, and (iii) the current and updated European guidelines for the management of bleeding and coagulopathy following major trauma.

Principle mechanisms and drivers of early ATC

A summary of the current concept of the pathogenesis of the coagulopathy of trauma including both ATC and IC with its principle mechanisms and drivers has recently been presented (Fig. 1) [17]. Early ATC has recently been recognized as a multifactorial primary condition resulting from a combination of tissue trauma, inflammation, and hypoperfusion/shock thus triggering the activation of the so-called "protein C pathway", endothelial injury, sympathoadrenal activation, and platelet dysfunction. This condition may be modified by individual and patient-related factors such as pre-existing comorbidities, inflammation, genetic precondition, and medications (in particular, anticoagulants). In an aging population, ED physicians and (neuro-)surgeons are confronted with a growing number of trauma patients, including traumatic brain injury (TBI) patients, receiving antithrombotic and antiplatelet medication for other diseases, such as cardiovascular diseases, prior to injury.

Activation of the "protein C pathway"

Significant clinical and animal data suggest that activation of the so-called "protein C pathway" is a principle component to ATC which occurs when tissue injury is associated with tissue hypoperfusion/shock [18–21] (Fig. 2). Protein C is a vitamin K-dependent glycoprotein circulating in plasma which is activated on the surface of endothelial cells by thrombin bound to its own receptor, the endothelial protein C receptor (EPCR), and the transmembrane glycoprotein thrombomodulin (TM), forming the so-called thrombin–thrombomodulin (TTM) complex [17, 18]. While the mechanisms for this enhanced activation remain an open experimental question, some data suggest that tissue hypoperfusion/shock leads to an increased expression of TM and EPCR on the endothelial surface. EPCR binds protein C to the endothelial cell surface and enhances the rate of protein C activation by the TTM complex by 5- to 20-fold [22]. Once activated, protein C has dual anticoagulant actions, thereby driving ATC: (i) it proteolytically cleaves peptide bonds in activated procoagulant factors V and VIII that act as cofactors in the activation of factors X and II, and (ii) it promotes fibrinolysis through the inhibition of plasminogen activator inhibitor-1 (PAI-1). In addition to its anticoagulant function, it is also a profound antiinflammatory, reducing inflammation via binding through PAR-1 and EPCR and decreasing leukocyte nuclear factor-kB activation [23]. Finally, activated protein C has been shown to cleave extracellular histones [24, 25]. Cofactor protein S increases the activity of activated protein C. Protein S and factor V are required for the regulation of the tenase complex, which leads to an inactivation of factor VIII; protein S participates in the regulation of the prothrombinase complex, which leads to an inactivation of factor V.

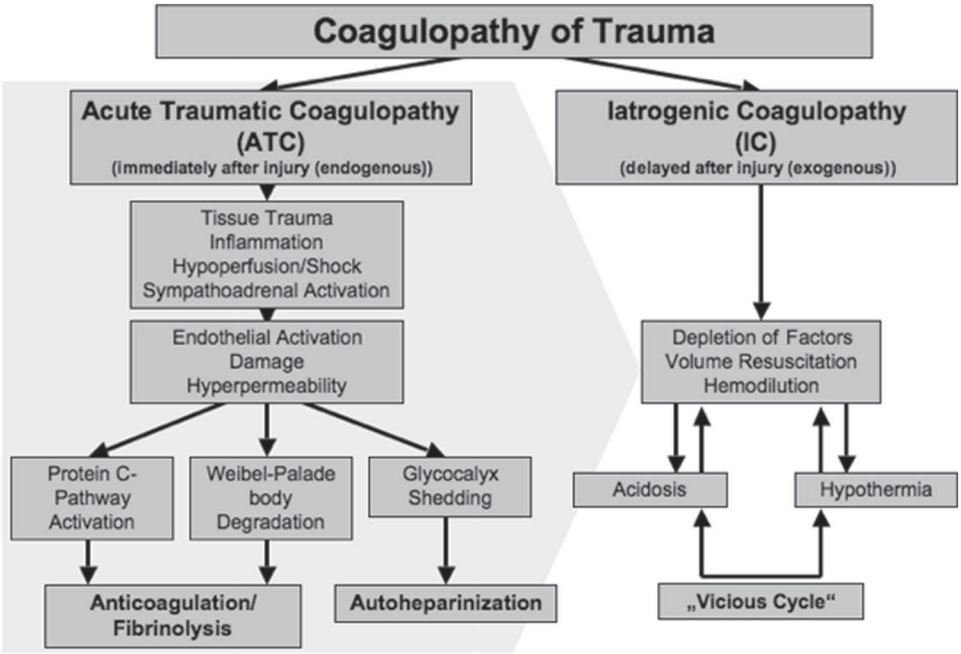

Fig. 1 The current understanding of the coagulopathy of trauma. The principle drivers of acute traumatic coagulopathy (ATC) have been characterized by tissue trauma, inflammation, hypoperfusion/shock, and the acute activation of the neurohumoral system. Hypoperfusion leads to an activation of protein C with cleavage of activated factors V and VIII and the inhibition of plasminogen activator inhibitor-1 (PAI-1), with subsequent fibrinolysis. Endothelial damage and activation results in Weibel–Palade body degradation and glycocalyx shedding associated with autoheparinization. In contrast, there is an iatrogenic coagulopathy (IC) which occurs secondary to uncritical volume therapy, leading to acidosis, hypothermia, and dilution. This coagulopathy may be an integral part of the "vicious cycle" when combined with acidosis and hypothermia (modified from [17])

Endothelial injury

Recent evidence suggests that ATC may also be linked to the disruption of the vascular endothelium and its glycocalyx. The endothelial glycocalyx covers the endothelium as a negatively charged antiadhesive and anticoagulant surface layer, thus protecting the endothelium and maintaining vascular barrier function [26]. Tissue trauma, inflammation, hypoperfusion, and sympathoadrenal activation result in systemic endothelial activation and damage, and subsequently leading to early coagulopathy and endothelial hyperpermeability. Injury and damage to the endothelium triggers the release of small molecules into the circuitry, reflecting endothelial glycocalyx degradation (syndecan-1) [27], endothelial cell damage [soluble thrombomodulin (sTM), vascular endothelial growth factor (VEGF)], and Weibel–Palade body degranulation [tissue plasminogen activator (tPA), angiopoietin-2 (Ang-2)] [28].

The entire endothelial glycocalyx contains approximately one liter of non-circulating plasma with significant amounts of heparin-like substances. When degradated, this ultimately leads to autoheparinization [29]. Johansson and coworkers reported evidence of high-degree autoheparinization among severely injured trauma patients [30], as well as associations of increasing magnitude of injury in patients with high syndecan-1 levels with progressive protein C depletion, increasing sTM, hyperfibrinolysis, and prolonged activated partial thromboplastin times (aPTT) [27]. These results may indicate the link between endothelial glycocalyx degradation and ATC.

Hyperfibrinolysis

Under physiological conditions, the coagulation system modulates fibrinolysis in that blood clots are maintained stable for a given time to control bleeding and to promote adequate wound healing. High concentrations of thrombin inhibit plasmin activation via the activation of thrombin-activated fibrinolysis inhibitor (TAFI) and plasminogen activator inhibitor-1. Vice versa, if the thrombin burst is weak, TAFI remains unactivated. Furthermore, if thrombin encounters thrombomodulin on endothelial cells, protein C may be activated, which then inactivates PAI-1.

Hyperfibrinolysis (HF) has been identified as a major contributor of mortality in bleeding trauma patients [31, 32]. Hyperfibrinolysis diagnosed via thrombelastography (TEG) is present in 7–20 % of adult trauma patients and is associated with increased mortality [33, 34]. Raza and coworkers reported. from their cohort of trauma patients, that only 5 % had severe fibrinolysis on thrombelastometry

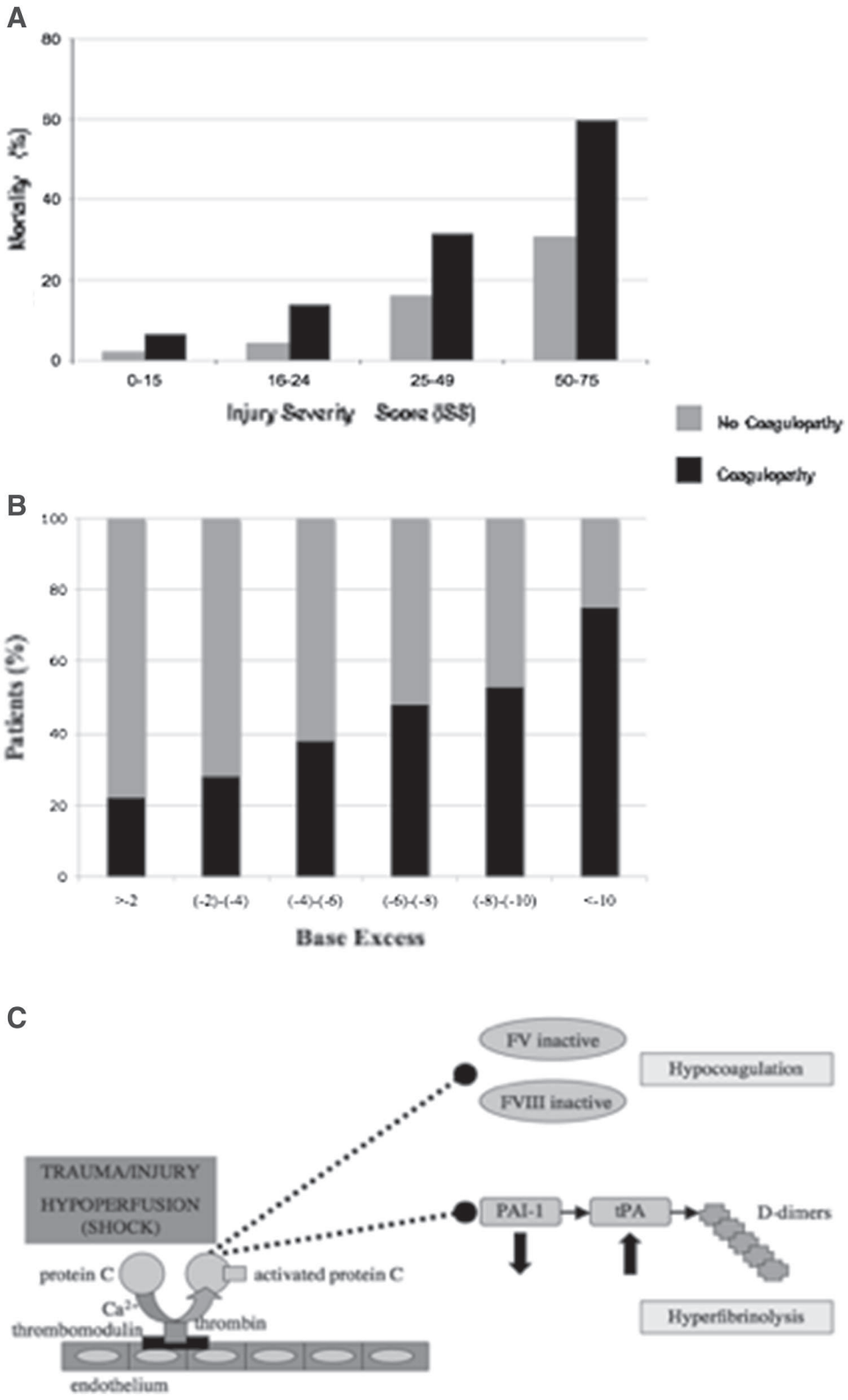

Fig. 2 Activation of the "protein C pathway" when (tissue) injury is associated with (tissue) hypoperfusion/shock. The frequency of coagulopathy/coagulopathy-associated mortality as a function of injury severity [reflected by the Injury Severity Score (ISS); **a**] and hypoperfusion/shock [reflected by base excess (BE); **b**] upon Emergency Department (ED) arrival. Combined trauma and hypoperfusion/shock may lead to a hypocoagulable state via the formation of an anticoagulant complex [thrombin–thrombomodulin (TTM) complex], which converts protein C into activated protein C, leading to an inactivation of the coagulation factors Va and VIIIa. Activated protein C in surplus also consumes PAI-1, which may lead to an increase in tissue plasminogen activator (tPA), together with hyperfibrinolysis and an increase in systemic d-dimer concentrations (**c**) (modified from [9–11, 18])

(TEM), but 57 % had evidence of "moderate" fibrinolysis, with PAP complex levels elevated to over twice the normal levels without lysis on TEM, indicating that fibrinolytic activation occurs in the majority of trauma patients [35]. If present, HF occurs early (<1 h) and is associated with massive transfusion requirements, coagulopathy, and

hemorrhage-related death. Schöchl and coworkers reported a mortality rate of 88 % in trauma patients with hyperfibrinolysis present upon Emergency Room (ER) admission as detected by viscoelastic testing [31]. Even a small reduction of the maximum amplitude in TEG (>15 %) is likely to be associated with higher transfusion requirements, including massive transfusion, coagulopathy, and hemorrhage-related death [32].

Platelet dysfunction

The question of early platelet dysfunction in ATC remains unclear, but may be secondary to the attenuation of platelet stimulation to adenosine diphosphate (ADP) agonism. Wohlauer and coworkers prospectively assessed platelet function in the assembly and stability of the thrombus within 30 min of injury using whole blood samples from 51 trauma patients versus healthy controls using point-of-care thrombelastography-based platelet functional analysis [36]. There were significant differences in the platelet response between trauma patients and healthy volunteers, such that there was impaired aggregation to these agonists. In trauma patients, the median ADP inhibition of platelet function was 86.1 % compared with 4.2 % in healthy volunteers. After trauma, the impairment of platelet function in response to arachidonic acid was 44.9 % compared with 0.5 % in volunteers. This study indicated that platelet dysfunction is manifest after major trauma and before substantial fluid or blood administration. In another study, Kutcher and coworkers prospectively collected blood from 101 patients with critical injury upon ER arrival and thereafter, and functionally assessed the responsiveness to ADP, thrombin receptor-activating peptide, arachidonic acid (AA), and collagen using multiple-electrode impedance aggregometry [37]. Of the 101 enrolled patients, 46 (45.5 %) had below-normal platelet response to at least one agonist at admission ("platelet hypofunction") and 92 patients (91.1 %) had platelet hypofunction some time during their ICU stay. Admission platelet hypofunction was associated with low Glasgow Coma Scale (GCS) scores and a nearly 10-fold higher early mortality.

Coagulation factor deficiency (depletion of factors)

Coagulation factor abnormalities occur quickly after trauma, with fibrinogen levels reaching critical levels first. As the major substrate, fibrinogen is essential for clotting. A prospective cohort study from the UK reported declining levels of fibrinogen below the critical levels of <1.5, 1.0, and 0.8 g/l in 14, 5, and 3 % of trauma patients, respectively [38]. In another study involving 45 trauma patients, over half displayed coagulation abnormalities within 25 min after injury [39]. In general, these coagulation abnormalities appear to occur more pronounced in patients with higher levels of injury, including acidosis and higher transfusion requirement. Critical factor V levels, as also often seen in trauma patients, may be related to the activation of protein C and the cleavage of factor V, as descibed earlier (Fig. 2c).

Iatrogenic coagulopathy (IC)

The "vicious cycle": hypothermia, acidosis, and hemodilution

The traditionally so-called "lethal triad" comprising coagulopathy, hypothermia, and acidosis may be extended to the "lethal quartet" if hemodilution is added, thus emphasizing the detrimental role of uncritical overuse of fluid resuscitation in the acute phase, resulting in further dilution of coagulation factors.

Direct loss and the consumption of coagulation factors, dilution, hypothermia, acidosis and fibrinolysis, and the release of anticoagulation factors, e.g., activated protein C, all interfere with coagulation and diminish hemostasis. There seems to be an additive effect among the clinical drivers of the process, as the probability of life-threatening coagulopathy increases with the number of drivers present. Cosgriff and coworkers [40], for example, have shown that the conditional probability of developing coagulopathy after trauma was 1 % in moderate injury without the presence of additional triggers, but this increased to 39 % in severe injury [Injury Severity Score (ISS) > 25] combined with hypotension, to 58 % when injury occurred with acidosis (pH < 7.1), and to 98 % in cases of ISS >25 together with hypotension (systolic blood pressure <70 mmHg), hypothermia (<34 °C), and acidosis (pH < 7.1).

Hypothermia and acidosis

Meng and coworkers frequently demonstrated the effects of temperature and pH on coagulation factor and complex activity [41, 42]. Both temperature and acidosis contribute to coagulopathy by reducing the pace of plasma coagulation factor biochemical reactions (Fig. 3). This activity is slowed down by approximately 5 % with each 1 °C drop in temperature. The von Willebrand factor (vWF)–glycoprotein Ib interaction, which activates platelets, is absent in 75 % of individuals at 30 °C [43, 44]. Similarly, drops in pH to values of 7.2 have been shown to reduce coagulation factor complex activities by half, and can be reduced to 20 % of normal activity at pH 6.8 [43]. Hypothermia primarily inhibits the initiation of thrombin generation and

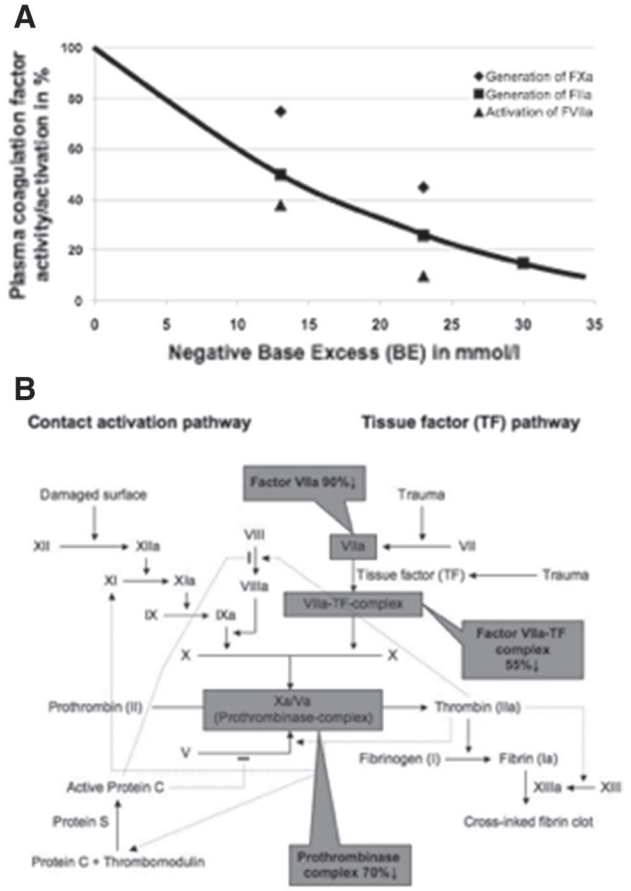

Fig. 3 Effect of acidosis on coagulation factor and complex activity. Acidosis contributes to coagulopathy by reducing the pace of plasma coagulation factor biochemical reactions. **a** Exemplary correlation between coagulation factor FIIa and FXa generation and FVIIa activation with negative BE assuming non-respiratory acidosis. **b** Exemplary decrease in plasma coagulation factor/complex activity if the pH drops from 7.4 to 7.0 in the context of the classical Y-shaped "cascade model of coagulation" (adopted from Rolf Zander [Mainz/Germany] and modified from [11, 42])

fibrinogen synthesis, with no effect on fibrinogen degradation [45]. Acidosis disrupts the interplay of coagulation factors with the negatively charged phospholipids on the surface of activated platelets [46].

Hemodilution

Dilution may occur both physiologically and iatrogenically. In trauma-associated physiologic hemodilution, the unopposed osmotic activity of plasma in states of hypotension is prompted by a water shift into the intravascular space, thus diluting plasma proteins until equilibrium is re-established. In this scenario, each protein is diluted to the same amount and their interactions, for example, the intrinsic "tenase complex" comprising combined factors IXa, VIIIa, and X, are reduced proportionally to their individual factor concentrate changes. In this model, Monroe calculated a 37 % reduction in single factor concentration to result in a 75 % reduction in the overall complex activity [47].

Iatrogenic dilution is caused by unguided and often overadministration of fluids in the acute phase of trauma care. In patients derived from the TraumaRegister DGU®, coagulopathy upon ER admission was observed in >40 % of patients with >2,000 ml, in >50 % with >3,000 ml, and in >70 % with >4,000 ml of fluids administered during the pre-hospital phase of care [9]. More recently, a pre-hospital intravenous colloid:crystalloid ratio ≥1:2 and the amount of pre-hospital intravenous fluids ≥3,000 ml have been identified as independent contributors to hemostatic abnormalities after trauma [48]. This dilution is accompanied by consumption and inactivation not only of coagulation factor substrates but also coagulation enzymes, with magnitudes matching the degree of individual injury [49].

Coagulopathy of traumatic brain injury (TBI)

Traumatic brain injury (TBI) is often associated with hemocoagulative disorders, but incidence rates vary considerably. A recent meta-analysis of 34 studies has indicated that one out of three patients suffering from TBI displays signs of coagulopathy [50]. While hemocoagulative disorders may occur in >60 % of patients with severe TBI [51], in mild head injury, coagulopathy is uncommon (<1 %) [52]. Step-wise logistic regression analysis has identified the following independent risk factors for the development of coagulopathy after blunt TBI: (i) severity of head trauma as reflected by AIS_{head} (Abbreviated Injury Scale for head), (ii) GCS score at the scene ≤8 points, (iii) hypotension ≤90 mmHg at the scene or upon ED arrival, (iv) pre-hospital intravenous fluid administration ≥2,000 ml, and (v) age ≥75 years [53]. It has been observed that the number of patients with isolated TBI and coagulopathy may double within the first 24 h post-trauma and that hemostatic abnormalities reflected by impaired global coagulation parameters may continue until the third day after injury or even longer [54]. The time interval to the onset of coagulopathy decreases substantially with increasing magnitude of injury.

Meanwhile, coagulopathy upon ED arrival in TBI has been identified as a powerful predictor related to outcome and prognosis [50, 53, 54]. The risk of dying among patients with coagulopathy after TBI is about ten times higher than in patients without coagulopathy, and the risk of unfavorable outcome in surviving patients is even more than 30 times higher if coagulopathy is present upon ED arrival [50]. A recent observational study derived from Italian EDs demonstrated that pre-injury antiplatelet therapy may substantially aggravate the post-traumatic

sequelae. In this study, pre-injury antiplatelet therapy increased the risk of intracranial hemorrhage worsening by two-fold [55].

The complex pathophysiological mechanisms of the coagulopathy of TBI are still undefined and the nature of these abnormalities seem to differ from non-TBI patients with multiple somatic injuries. The current hypothesis for the development of coagulopathy of TBI includes a combination of both hypo- and hypercoagulable states promoted by the magnitude and the extent of the traumatized brain tissue, resulting in secondary injury via subsequent ischemic or hemorrhagic lesioning [50, 56, 57]. The proposed underlying mechanisms of the coagulopathy of TBI may overlap, in part, with those listed above for the coagulopathy of somatic injuries and may comprise hyperfibrinolysis, shock, and hypoperfusion, thus triggering the protein C pathway, disseminated intravascular coagulation, platelet dysfunction, but also, and in addition, the substantial release of tissue factor (TF) into the systemic circulation [56, 57].

Diagnosis, monitoring, and predicting coagulopathy, ongoing bleeding, and massive transfusion

In accordance with the recently updated European guideline for the management of bleeding and coagulopathy following major trauma, there is broad consensus that monitoring and measures to support coagulation should be initiated as early as possible [15].

Standard coagulation tests

The current guideline suggests the early, repeated, and combined measurement of standard laboratory coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and platelets for routine practice to detect and monitor post-traumatic coagulopathy [15]. However, it has to be acknowledged that these standard tests only monitor the initiation phase of the blood coagulation process, and represent only the first 4 % of thrombin generation [58]. Therefore, it may be possible that the standard coagulation screen appears normal while the overall state of blood coagulation is abnormal. Furthermore, standard coagulation tests do not provide any clinically relevant information on the dynamics and the sustainability of the clot formation. The delay in the detection of traumatic hemocoagulative disorders may also influence the initiation of treatment and outcome, and turnaround times for viscoelastic tests have been shown to be substantially shorter as compared to standard coagulation tests, with time differences of between 30 and 60 min or even longer [15]. Davenport and coworkers, for example, reported median laboratory prothrombin time turnaround times of 78 (62–103) min in their local setting [59]. The updated guideline suggests either serum lactate or base deficit (BD) measurements as sensitive tests to estimate and monitor the extent of bleeding and shock, while single measurements of hematocrit as an isolated laboratory marker for bleeding are obsolete [15].

Advanced Trauma Life Support® (ATLS): classification of hemorrhage

The updated European guideline further suggests to assess the extent of traumatic hemorrhage by using a combination of patient physiology, anatomical injury pattern, mechanism of injury, and the patient's response to initial volume resuscitation based upon the Advanced Trauma Life Support® (ATLS) program [15]. The ATLS classification of hemorrhage is based upon an estimated blood loss as a percentage, together with corresponding vital signs [60]. For each class, ATLS allocates therapeutic recommendations, for example, the administration of intravenous fluids and blood products. Although the ATLS classification of hemorrhage is recognized as a useful guide in hemorrhagic shock, its clinically validity has recently been questioned by two analyses independently from each other on two large-scale trauma databases, the UK TARN (Trauma Audit and Research Network) registry and the German TraumaRegister DGU®, which had included >140,000 trauma patients in total. According to both analyses, ATLS seems to: (i) overestimate the degree of tachycardia associated with hypotension and (ii) underestimate mental disability in the presence of hypovolemic shock [61–63]. In the study by Mutschler and coworkers on 36,504 trauma patients, only 3,411 patients (9.3 %) could be adequately classified according to ATLS, whereas 33,093 did not match the combination of all three criteria given by ATLS [63].

Scoring systems and algorithms

The early identification of trauma patients at risk for ongoing bleeding and massive transfusion is of fundamental clinical importance in order to: (i) rapidly address and correct the coagulopathy of trauma, including potential triggers, for example, acidosis and hypothermia, (ii) allow the early activation of massive transfusion protocols, and (iii) allow the early mobilization of resources, for example, blood bank resources in the civilian setting as well as activation of whole blood donation in the military setting. To date, several groups have, independently from each other, introduced scoring systems/algorithms for transfusion, including massive transfusion, in civilian and military trauma populations [64]. The models developed so far

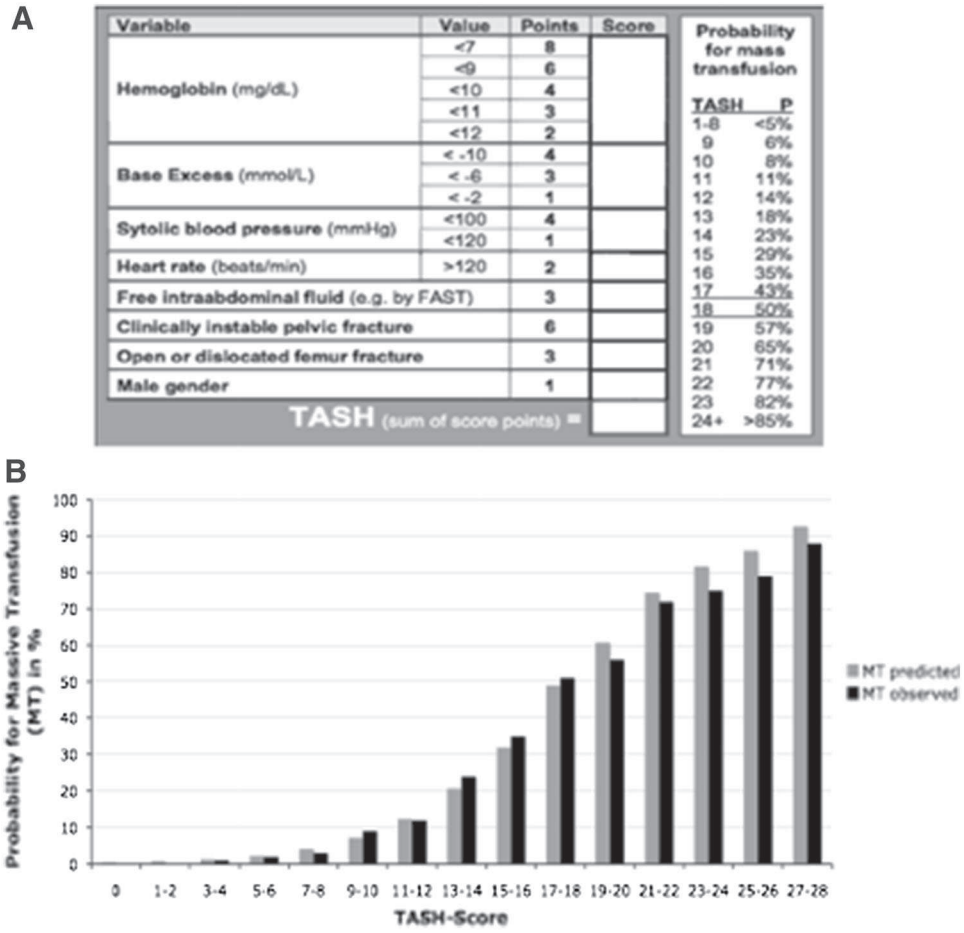

Fig. 4 The Trauma-Associated Severe Hemorrhage (TASH)-Score. **a** It uses eight independent but weighted variables to identify patients who will require a massive transfusion. The possible range of the scores is between 0 and 28, where each point corresponds to a risk for massive transfusion as a percentage. **b** The results from the revalidation study on data from 5,835 severely injured patients derived from the TraumaRegister DGU® with respect to predicted versus observed rates of massive transfusion (*MT*)

suggest combinations of physiologic, hemodynamic, laboratory, injury severity. and demographic triggers identified on the initial evaluation of the bleeding trauma patient. Many of these models use a combination of dichotomous variables readily accessible after ED arrival but others rely on time-consuming calculations or complex algorithms and may have limited real-time application. Weighted and more sophisticated systems including greater numbers of variables perform in a more superior fashion. A common limitation to all models is their retrospective nature and prospective validations are still needed.

The Trauma-Associated Severe Hemorrhage (TASH)-Score was initially developed and validated on the basis of data from 6,044 severely injured blunt trauma patients derived from the TraumaRegister DGU® database [65] to provide a surrogate for life-threatening hemorrhage after multiple injury (Fig. 4). Recently, the performance of the score was internally revalidated on data from 5,834 patients derived from the same registry [66]. The TASH-Score uses eight independent but weighted variables to identify patients who will require a massive transfusion: systolic blood pressure, gender, hemoglobin, FAST exam (focused assessment with sonography for trauma), heart rate, base excess (BE), and extremity and pelvic fractures. The possible range of the calculated scores is between 0 and 28, where each point corresponds to a risk for massive transfusion as a percentage. The TASH-Score is transformed into a probability for massive transfusion using the following logistic function: $(p = 1/[1 + \exp(5.4 - 0.3*\text{TASH})])$. By its update, the high performance of the score was not only restored but enhanced, reflected by an increased area under the receiving operator characteristic curve (AUROC) of 0.905. At a cutoff of >16 out of 28 points, the correct classification rate is >90 %. Brockamp and coworkers recently conducted a retrospective internal and external validation of six scoring systems and algorithms, including the TASH-Score (four civilian and two military systems), to predict the risk of massive transfusion at a very early stage after trauma on a single dataset of severely injured patients derived from the TraumaRegister DGU® database 2002–2010 and have reemphasized the clinical validity of the TASH-Score [67]. Meanwhile, the score has also been externally validated on data derived from other databases and registries [68, 69]. The TASH-Score can be calculated within less than 8 min upon arrival of the trauma patient to the ED [70].

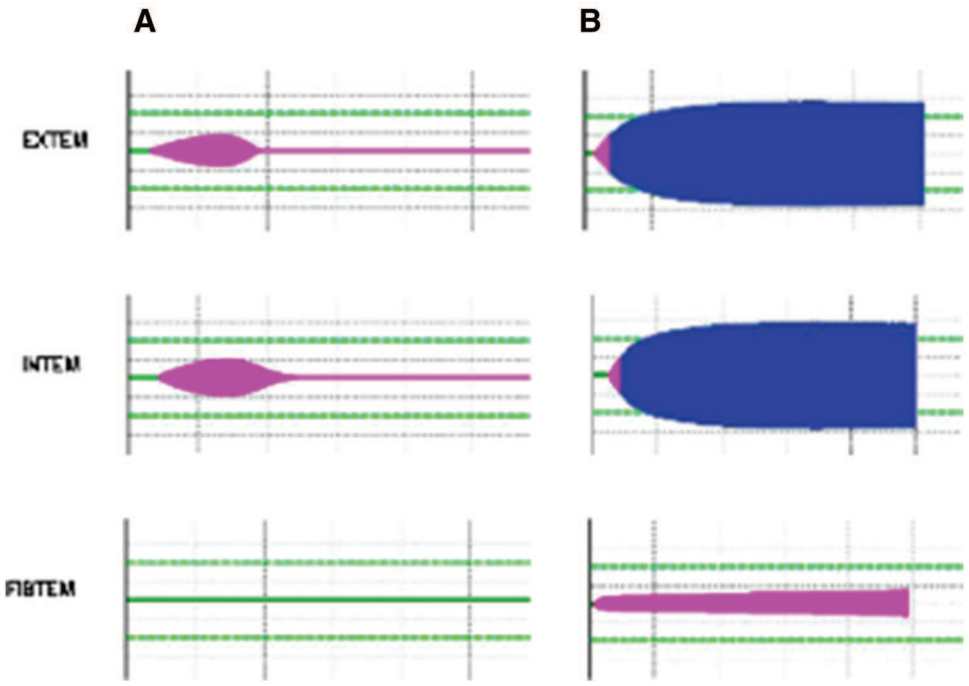

Fig. 5 Exemplary three-channel rotational thrombelastometry (ROTEM®) result from a severely injured and exsanguinating trauma patient upon Emergency Department (ED) arrival (**a**) in comparison to a reference result (**b**). Note the delayed and insufficient clot formation with breakdown in the EXTEM and INTEM tests, with no signal in the FIBTEM test, suggesting fibrinolysis in panel **a**. The EXTEM test activates hemostasis via tissue factor (TF) and is a screening test for the (extrinsic) hemostasis system. The INTEM test activates the contact phase of hemostasis and, in the absence of heparin, is a screening test for the hemostasis system. The FIBTEM test represents an EXTEM-based assay for the fibrin part of the clot. FIBTEM eliminates the platelet contribution to clot formation by inhibiting platelets with cytochalasin D. FIBTEM allows for the detection of fibrinogen deficiency or fibrin polymerization disorders

A novel approach: viscoelastic methods

The use of viscoelastic methods to assist in characterizing the coagulopathy and in guiding hemostatic therapy is emphasized by the updated European guideline and the grade of recommendation has been lifted from grade 2C in 2010 to grade 1C in 2013 [15]. Figure 5 displays an exemplary 3-channel rotational thrombelastometry (ROTEM®) result from a severely injured and exsanguinating trauma patient upon ED arrival in comparison to a reference result. Early variables of clot firmness assessed by viscoelastic methods have been demonstrated to be good predictors for the need of massive transfusion and outcome [31, 32, 34, 71, 72]. These tests may also be useful in the detection of coagulation abnormalities associated with the preinjury intake of direct thrombin inhibitors. Despite the rapidly increasing number of publications on the use of viscoelastic methods for the early detection of hemostatic disorders after trauma, controversy still remains on the standardization of this technology. Another limitation is the lack of sensitivity for platelet dysfunction. If the latter is anticipated, viscoelastic methods should be supplemented by other point-of-care platelet function tests, such as whole blood impedance aggregometry [15]. Undisputable advantages of this technology remain its rapid availability in the ED or at the bedside, thus improving the availability of real-time point-of-care data to guide therapy, as well as its ability to visualize the dynamics and the sustainability of the clot formation.

Management of bleeding and coagulopathy following major trauma: a brief summary of the updated European guideline 2013

The European guideline for the management of bleeding and coagulopathy following major trauma was first developed and published in 2007 and updated in 2010 and 2013 [15]. Table 1 provides a summary of the current recommendations with regard to time management, initial resuscitation, assessment, and intervention, for both surgery and hemostasis. Major changes to the previous version of the guideline published in 2010 consider (i) the grade 1A recommendation for tranexamic acid (TXA) based upon the results of the CRASH-2 trial [73], (ii) the grade 1C recommendation to use viscoelastic methods to characterize coagulopathy and to guide hemostatic therapy (previously a grade 2C recommendation), and (iii) the grade 1B recommendation to avoid plasma in patients without substantial bleeding.

Table 1 Current European guideline for the management of bleeding and coagulopathy following major trauma [15]

R#	Time management
R1	Minimize time to OR if urgent surgery bleeding control is needed *(1A)*
R#	Initial resuscitation (bleeding control, ventilation and volumes)
R2	Use tourniquet to stop life-threatening bleeding from open extremity injuries *(1B)*
R3	Use normoventilation if no signs of imminent cerebral herniation *(1C)*
R13	Target SBP 80-90 mmHg until major bleeding is stopped with no TBI; MAP ≥80 mmHg with TBI *(1C)*
R14	Initiate fluid therapy in hypotensive bleeding trauma patient and use crystalloids *(1A/1B)*
	If colloids use within prescribed limits; hypertonic solutions have no advantage *(1B/2B)*
	Use hypertonic solutions in hemodynamically unstable patients with penetrating torso trauma *(2C)*
R15	Use vasopressors to maintain target arterial pressure in the absence of a response to fluids *(2C)*
	Infuse an inotropic agent if myocardial dysfunction *(2C)*
R14	Avoid hypotonic solutions in severe head trauma *(1C)*
R16	Reduce heat loss and warm the patient to achieve and maintain normothermia *(1C)*
	Hypothermia at 33–35 °C for ≥48 h be applied in TBI once bleeding has been controlled *(2C)*
R#	Assessment/investigation/monitoring
R4	Clinically assess hemorrhage via physiology, injury pattern/mechanism and fluid response *(1C)*
R7	Use early imaging (ultrasonography or CT) for free fluid if suspected torso trauma *(1B)*
R6	Initiate further investigation if hem-shock and an unidentified bleeding source *(1B)*
R9	Use CT for hemodynamically stable patients *(1B)*
R23	Initiate monitoring and measures to support coagulation as early as possible *(1C)*
R29	Measure platelet function if treated/suspected of being treated with antiplatelet agents *(2C)*
R12	Use repeated and combined measurement of PT, APTT, fibrinogen and platelets *(1C)*
	Perform viscoelastic methods to characterize coagulopathy and to guide hemostatic therapy *(1C)*
R11	Use serum lactate or BD as sensitive tests to estimate/monitor the extent of hem-shock *(1B)*
R25	Monitor ionised calcium levels *(1C)*
R32	Measure anti-factor Xa activity if treated/suspected of being treated with anti-factor Xa agents *(2C)*
R10	Not use single Hct measurements as an isolated laboratory marker for bleeding *(1B)*
R#	Immediate intervention (surgery)
R5	Undertake immediate bleeding control procedure if hem-shock and bleeding source is identified *(1B)*
R8	Undergo intervention if significant free intra-abdominal fluid and hem-shock *(1B)*
R18	Abdominal bleeding control by packing, surgery and local hemostatic procedures *(1C)*
R19	Undertake pelvic ring closure and stabilisation if pelvic ring disruption in hem-shock *(1B)*
R20	Use preperitoneal packing, embolisation and/or surgery if hem-shock despite pelvic stabilisation *(1B)*
R21	Use "Damage control (DC)" surgery if deep hem-shock, ongoing bleeding and coagulopathy *(1B)*
R22	Use topical hemostatics with surgery/packing for venous/moderate arterial bleeding in parenchyma *(1B)*
R#	Immediate intervention (hemostasis)
R17	Target hemoglobin (Hb) of 7–9 g/dl *(1C)*
R26	Use plasma ((FFP) or pathogen-inactivated plasma) or fibrinogen in massive bleeding *(1B/1C)*
	If further plasma, use plasma:red blood cell ratio of at least 1:2 *(2C)*
	Avoid plasma in patients without substantial bleeding *(1B)*
R28	Administer platelets for platelet count $>50 \times 10^9$/l; $> 100 \times 10^9$/l in ongoing bleeding and/or TBI *(1C/2C)*
	Use initial dose of 4–8 single platelet units or one aphaeresis pack *(2C)*
R29	Use platelets if platelet dysfunction is documented with continued microvascular bleeding (2C)
R27	Use fibrinogen concentrate (dose 3–4 g)/cryoprecipitate (50 mg/kg) if thromboelastometric signs of functional fibrinogen deficit or fibrinogen level <1.5–2.0 g/l *(1C)*
	Guide repeated doses by viscoelastic monitoring and laboratory assessment of fibrinogen levels *(2C)*

Table 1 continued

R#	Immediate intervention (hemostasis)
R24	Use TXA as early as possible if bleeding/risk of bleeding at 1 g × 10 min, followed by 1 g × 8 h *(1A)*
	Use TXA in the bleeding trauma patient within 3 h after injury *(1B)*
	Consider administration of the first dose of TXA en route to the hospital *(2C)*
R31	Use PCC if bleeding with thromboelastometric evidence of delayed coagulation initiation if a concentrate-based goal-directed strategy is applied (2C)
R33	Consider rFVIIa if bleeding/traumatic coagulopathy persist despite best-practice *(2C)*
	Not use rFVIIa with intracerebral hemorrhage caused by isolated head trauma *(2C)*
R25	Maintain ionised calcium levels within the reference range during massive transfusion (1C)

The recommendations (R) were formulated and graded according to Guyatt and coworkers [79]

APTT activated partial thromboplastin time, *BD* base deficit, *CT* computed tomography, *Hb* hemoglobin, *Hct* hematocrit, *hem-shock* hemorrhagic shock, *OR* operating room, *PCC* prothrombin complex concentrate, *PT* prothrombin time, *SBP* systolic blood pressure, *TBI* traumatic brain injury, *TXA* tranexamic acid

Balanced transfusion with 1:1:1 (the "ratio" concept)

Back in 2005 and based upon reports from the Iraq War, an international panel of experts, during a conference at the United States Army's Institute for Surgical Research, introduced a new concept for the resuscitation of patients with massive hemorrhage and recommended the immediate administration of blood products in a balanced 1:1:1 ratio for packed red blood cell concentrates (pRBC), plasma, and platelets [74, 75]. This strategy aims to correct for both the early coagulopathy of trauma as well as the volume status of patients in hemorrhagic shock, overall targeting preventable hemorrhage-related deaths. Over the recent years, numerous retrospective studies have suggested improved outcomes when using this strategy in patients with massive hemorrhage and, to date, the 1:1:1 transfusion strategy has been widely adopted by trauma centers around the globe. However, substantial methodological limitations to these studies exist, including a number of potential co-founders, thus introducing relevant bias (in particular, survivorship bias), significant heterogeneity among the different studies, as well as their mostly retrospective nature, which, in summary, still preclude any definitive conclusion on the potential benefit of this strategy with regard to efficacy and safety. Indeed, several studies have even raised concerns regarding the potential increase in morbidity associated with this approach, in particular when patients were overtriaged to 1:1:1 in cases where massive transfusion was unlikely [76]. Borgman, together with coworkers from the German TraumaRegister DGU®, stratified severely injured trauma patients for their individual risk for massive transfusion according to the TASH-Score and reported a survival benefit for high-risk patients (TASH-Score ≥ 15 points) when treated according to the high ratio concept, whereas the same concept was associated with increased morbidity in patients at low risk for massive transfusion according to the TASH-Score [77]. The current and updated European guideline for the management of bleeding and coagulopathy following major trauma suggests an optimal plasma:red blood cell ratio of at least 1:2 as a grade 2C recommendation [15].

A novelty within the updated 2013 guideline is the further quest for treatment pathways. These pathways should include the local implementation of (i) evidence-based treatment algorithms for the bleeding trauma patient, (ii) checklists to be used to guide the clinical management of the bleeding trauma patient, and (iii) strategies to assess the adherence to these institutional algorithms in routine quality management [15].

The European guideline is an integral component to the European "STOP the Bleeding Campaign", an international initiative launched in 2013 [78]. This campaign aims to increase awareness of the phenomenon of hemostatic abnormalities after trauma and its appropriate management by (i) publishing European guidelines for the management of the bleeding trauma patient, (ii) promoting and monitoring the implementation of these guidelines, and (iii) preparing promotional and educational material, organizing activities, and developing health quality management tools. The campaign aims to reduce the number of patients who die within 24 h after arrival in the hospital due to exsanguination by a minimum of 20 % within the next 5 years. The acronym "STOP" stands for Search for patients at risk of coagulopathic bleeding, Treat bleeding and coagulopathy as soon as they develop, Observe the response to interventions, and Prevent secondary bleeding and coagulopathy.

Conflict of interest None are declared.

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