Purpose of review
This review presents a synopsis of best current knowledge with reference to the updated German and European guidelines and recommendations on the management of severe trauma hemorrhage and trauma-induced coagulopathy as well as a viscoelastic-based treatment algorithm based upon international expert consensus to trigger the administration of hemostatic agents and blood products.

Recent findings
Uncontrolled hemorrhage and trauma-induced coagulopathy are the major causes for preventable death after trauma and early detection and aggressive management have been associated with improved outcomes. However, best practice to treat this newly defined entity is still under debate. In the acute phase, the clinical management usually follows the ‘Damage Control Resuscitation’ concept, which advocates the empiric administration of blood products in predefined and fixed ratios. As an alternative, several European but also a few US trauma centers have instituted the concept of ‘Goal-directed Coagulation Therapy’ based upon results obtained from early point-of-care viscoelastic testing.

Summary
Current guidelines urge for the implementation of evidence-based local protocols and algorithms including clinical quality and safety management systems together with parameters to assess key measures of bleeding control and outcome.

Keywords
blood products, empiric therapy, goal-directed therapy, hemostatic agents, trauma-induced coagulopathy, trauma-hemorrhage, viscoelastic testing

INTRODUCTION
Despite substantial improvements in the care for the severely injured, uncontrolled hemorrhage and trauma-induced coagulopathy (TIC) are still the major causes for preventable death after trauma [1–7]. With frequencies slightly declining over the last decade because of improved prehospital care and increased awareness, approximately one out of four severely injured patients admitted to the trauma bay is bleeding with variable degrees of laboratory coagulopathy [8,9]. Early detection and aggressive management of this newly identified entity have been associated with improved outcomes [10] and current guidelines urge for the implementation of evidence-based local protocols and algorithms including clinical quality and safety management systems together with parameters to assess key measures of bleeding control and outcome [11,12]. Meanwhile, the German S3 Guideline on the Treatment of Patients with Severe and Multiple Injuries recognizes TIC as an own clinical entity with substantial impact on survival after trauma (S3-DGU GoR A [11]).
There has been speculation about the potential mechanisms underlying TIC but much of the data continue to be rather correlative than causative with robust links still lacking [13–17,18]. The current understanding of TIC is summarized in Fig. 1. However, only little data have been reported linking the laboratory-based abnormalities with true clinically evident coagulopathic bleeding, and therefore TIC continues to be a significant diagnostic and therapeutic challenge. Recent surveys confirm a substantial diversity and heterogeneity in the clinical diagnosis and management of acute trauma hemorrhage and TIC across trauma centers in Europe and abroad [19*,20,21]. In the acute phase, the clinical management of severe and bleeding trauma patients usually follows the ‘Damage Control Resuscitation’ (DCR) concept which advocates the empiric administration of blood products in predefined ratios and the concept of GDCT based upon results obtained from early POC viscoelastic testing.

GDCT based upon viscoelastic testing allows better characterization of the existing coagulopathy with supplementation of hemostatic agents and blood products according to the individual patient’s needs.

Implementation and adherence to evidence-based guidelines are essential for improved patient outcomes.

KEY POINTS

- Uncontrolled hemorrhage and TIC are the major causes for preventable death after trauma, and early detection and aggressive management have been associated with improved outcomes.
- Current treatment concepts include the DCR concept, which advocates the empiric administration of blood products in predefined ratios and the concept of GDCT based upon results obtained from early POC viscoelastic testing.
- GDCT based upon viscoelastic testing allows better characterization of the existing coagulopathy with supplementation of hemostatic agents and blood products according to the individual patient’s needs.
- Implementation and adherence to evidence-based guidelines are essential for improved patient outcomes.

As an alternative, several European but also a few US trauma centers have instituted the concept of ‘Goal-directed Coagulation Therapy’ (GDCT) based upon results obtained from early point-of-care (POC) viscoelastic testing [30–35]. Viscoelastic tests provide rapid information about the underlying deficiencies with particular focus on the different aspects of hemostasis such as initiation, dynamics, and sustainability of clotting thus allowing targeted coagulation monitoring and therapy according to the individual’s needs [36–40, 41*,42*,43–48]. To date, a number of individualized algorithms and treatment protocols have been suggested but mostly based upon retrospective registry data or expert opinion [31,33–35]. Early viscoelastic variables of clot firmness have been

**FIGURE 1.** Current concept of the mechanisms underlying trauma-induced coagulopathy (TIC).
shown to be good predictors for the need of massive transfusion and mortality in surgical and trauma patients [36,39,40,46,48] and a recently updated Cochrane review provided, apart from the known reductions in transfusion requirement [49,50], for the first time, a survival benefit with the use of viscoelastic testing in adults or children with bleeding [51*].

**GERMAN AND EUROPEAN RECOMMENDATIONS AND GUIDELINES TO MANAGE TRAUMA-INDUCED COAGULOPATHY**

A synopsis of best current knowledge with reference to the updated German and European guidelines and recommendations on the management of severe trauma hemorrhage and TIC is presented:

1. **S3 Guideline on the Treatment of Patients with Severe and Multiple Injuries**: [English Version of the German Guideline S3 Leitlinie Polytrauma/Schwerverletzten-Behandlung/Association of the Scientific Medical Societies in Germany (AWMF) Register-Nr. 012/019 (07/2016) sponsored by the German Society for Trauma Surgery/Deutsche Gesellschaft für Unfallchirurgie (DGU); S3-DGU; [11]).

2. **The European Guideline on Management of Major Bleeding and Coagulopathy following Trauma, fourth edition 2016 (EU GRADE; [12*]).**

The evidence statements for the recommendations given for the S3-DGU guideline (AWMF Register-Nr 012/019) are based upon the AWMF-Regelwerk ‘Leitlinien’ and the evidence classification system of the Oxford Center of Evidence-Based Medicine (CEBM), Version March 2009, wherein priority is given to studies with the highest Level of Evidence (LoE) available [52]. Within this system, three grades of recommendations (GoRs) are possible, for example, A (strong recommendation), B (recommendation), and 0 (open recommendation), where the wording corresponds to ‘must’, ‘should’, or ‘can’. The GoRs indicate to what extent recommended actions lead to a patient-relevant benefit or avoidance of harm, respectively. The recommendations given by the European trauma guideline are graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [53]. The number associated with the recommendation reflects the strength of the recommendation being ‘Grade 1’ considered as the authors group’s ‘strong recommendation’ and being ‘Grade 2’ considered as the authors group’s ‘weak recommendation/suggestion’; the following letter reflects the quality of the scientific evidence ranging from A (high-quality evidence) to C (low-quality evidence).

Surgical, interventional, and other local hemostatic measures associated with trauma-hemorrhage and bleeding control such as damage control procedures in case of severe injury with deep hemorrhagic shock and ongoing bleeding as well as the use of tourniquets, peritoneal packing, and angiographic embolization are discussed elsewhere [12*].

**INITIAL RESUSCITATION OF THE BLEEDING TRAUMA PATIENT**

In normotensive trauma patients with absent signs for volume deficit, fluid replacement therapy can be neglected (S3-DGU GoR 0 [11]), but intravenous lines be inserted (S3-DGU GoR A [11]). In severely injured and hypotensive trauma patients, volume replacement should be initiated, at a reduced level if there is uncontrollable bleeding, in order to keep the circulation stable at target blood pressure and not exacerbate the bleeding until the bleeding can be controlled (S3-DGU GoR B [11]; EU GRADE 1B [12*]). The updated S3-DGU guideline and the European trauma guideline suggest for adult trauma patients with active bleeding to conduct ‘permissive hypotension’ with target mean arterial pressure (MAP) of 65 mmHg and/or with target systolic blood pressure (SBP) of 80–90 mmHg until major bleeding control has been achieved (S3-DGU GoR B [11]; EU GRADE 1C [12*]). Low evidence suggests to tolerate even lower MAPs as 50 mmHg until surgical control is achieved but only after injuries to the central nervous system (CNS) or underlying cardiovascular diseases have been excluded ([54]; S3-DGU GoR 0 [11]). The fluid of choice in the hypotensive bleeding trauma patient is isotonic crystalloid solution (EU GRADE 1A [12*]); the use of colloids be restricted due to their adverse effects on hemostasis (EU GRADE 2C [12*]). Specific recommendations apply for patients with traumatic brain injury (TBI; [11,12*]).

**DIAGNOSIS, MONITORING, AND INITIATION OF MEASURES TO SUPPORT COAGULATION FUNCTION**

Both guidelines recommend that monitoring and measures to support coagulation be initiated immediately or at latest upon hospital admission (S3-DGU GoR A [11]; EU GRADE 1B [12*]) as the time elapsed between injury and bleeding control also be minimized (EU GRADE 1A [12*]). The extent of trauma hemorrhage should be clinically assessed by using a combination of patient physiology,
anatomical injury, mechanism of injury, and the individual’s response to initial resuscitation as outlined in the ‘Advanced Trauma Life Support’ protocol ([55]; EU GRADE 1C [12*]). This concept suggests four classes of hypovolemic shock based upon initial presentation, which triggers specific strategies for initial fluid resuscitation [55]. Early and repeated imaging such as computed tomography (CT) and ultrasound, for example, in the context of focused assessment sonography in trauma (FAST), is recommended to detect or exclude extravasal fluid (EU GRADE 1B [12*]).

**Laboratory parameters**

Low initial hemoglobin (Hb) is considered indicative for severe bleeding associated with coagulopathy and repeated Hb measurements are recommended as an initial value within the reference ranges may mask the bleeding (EU GRADE 1B [12*]). Laboratory parameters to assess and monitor volume deficits and shock include lactate, ScvO2, hematocrit, and base excess. The updated S3-DGU guideline as well as the European trauma guideline advocate repeated and independent measurements of base excess (BE) and/or lactate as sensitive tests to assess adequate perfusion, to estimate and monitor the extent of bleeding and shock, and to guide volume replacement therapy (S3-DGU GoR A [11]; EU GRADE 1B [12*]). A BE of less than −6 mEq/l is considered as an alert criteria for TIC being strongly associated with hypofibrinogenemia. The reliability of lactate may be lower when trauma is coincided with alcohol consumption; in these cases BE may be a superior predictor. Recent data from the TraumaRegister DGU showed that BE upon admission may be superior over the Advanced Trauma Life Support classification of hemodynamic shock in predicting the need for volume including transfusion and mortality [56].

The routine practice should include the early and repeated monitoring of coagulation, using either conventional coagulation assays (CCAs) such as prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet counts and fibrinogen (S3-DGU GoR A [11]; EU GRADE 1A [12*]), and/or viscoelastic tests (EU GRADE 1C [12*]). The S3-DGU guideline recommends the additional and early use of viscoelastic testing in the diagnosis and therapy of TIC in bleeding trauma patients (S3-DGU GoR GPP [11]). As early variables of clot firmness have been associated with outcome in bleeding trauma patients, a rapid and more complete monitoring of the individual’s coagulation profile including fibrinolysis may facilitate a more accurate targeting of therapy as compared with isolated CCAs [12*]. In addition, CCAs only monitor the initiation phase of the clotting process and only 4% of the overall thrombin generation [57]. Fibrinogen levels deteriorate before other routine coagulation parameters and massive transfusion in the early phase of severe trauma [58] and low levels on admission have frequently been associated with poor outcome [59–61].

**INITIAL COAGULATION MANAGEMENT INCLUDING MASSIVE TRANSFUSION**

**Massive transfusion**

The European trauma guideline currently advocates one of the two following strategies for the initial management of patients with bleeding and (expected risk of) massive transfusion: first, plasma [fresh frozen plasma (FFP) or pathogen-inactivated plasma] in a plasma:packed red blood cell (pRBC) ratio of at least 1:2 (EU GRADE 1B [12*]), or second, fibrinogen concentrate and pRBC according to the individual Hb level (EU GRADE 1C [12*]). The S3-DGU guideline suggests that the indication to transfuse a bleeding trauma patient be judged upon individual criteria, severity of injury including extent of blood loss as well as cardiovascular function and oxygenation (S3-DGU GoR B [11]). If transfusion is guided by FFP, an FFP:pRBC:platelets ratio of 4:4:1 should be targeted (S3-DGU GoR B [11]). Further resuscitation measures should be continued using a goal-directed strategy guided by CCAs and/or viscoelastic assays (EU GRADE 1C [12*]).

**Plasma-based versus factor-concentrate based strategies**

In the absence of massive transfusion and if a plasma-based coagulation resuscitation strategy is used, the European trauma guideline recommends plasma (FFP or pathogen-inactivated plasma) be administered to maintain PT and aPTT less than 1.5 times the normal control (EU GRADE 1C [12*]). It is emphasized that plasma transfusion be avoided in patients without substantial bleeding (EU GRADE 1B [12*]). If a factor concentrate-based strategy is executed, both guidelines recommend the treatment with fibrinogen concentrate (or cryoprecipitate) if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficit or a fibrinogen level less than 1.5–2.0 g/l (S3-DGU GoR B [11]; EU GRADE 1C [12*]). This trigger has recently been confirmed by results from a clinical trial in trauma patients with life-threatening hemorrhagic disorders [62*]. Once fibrinogen levels have been corrected and provided that fibrinogen levels are within the reference ranges
but coagulation initiation is still delayed based on evidence from viscoelastic monitoring, the European trauma guideline suggests the administration of prothrombin complex concentrates (PCCs) or plasma in the bleeding trauma patient (EU GRADE 2C [12*]). A factor-based strategy should be monitored and guided by appropriate measures (S3-DGU GoR GPP [11]) and repeated factor doses should be guided by viscoelastic monitoring and laboratory assessment of fibrinogen levels (EU GRADE 2C [12*]). A target level for Hb of 7–9 g/dl (EU GRADE 1C [12*]) is suggested whereas platelet concentrations should be kept more than 50 × 10^9/l (EU GRADE 1C [12*]); in patients with TBI and/or ongoing bleeding more than 100 × 10^9/l (EU GRADE 2C [12*]).

Viscoelastic tests (ROTEM) to guide hemostatic therapies
Thromboelastometry (ROTEM) is increasingly being used to diagnose, monitor, and guide treatment strategies in trauma hemorrhage but currently, no uniformly accepted guidelines exist for how this technology should be integrated into clinical care [63]. In September 2014, an international multidisciplinary group of leaders mostly from Europe but also from the USA in the field of trauma coagulopathy and resuscitation was assembled for a 2-day consensus conference in Philadelphia, USA [64*,65]. A summary document was reviewed by the panel in an open forum followed by a Delphi consensus regarding viscoelastic thresholds for triggering the initiation of specific treatments including fibrinogen, platelets, plasma, and PCCs in the acutely bleeding trauma patient. Figure 2 summarizes the consensus, which corresponds to a S2k guideline according to the system of the AWMF and which informs, for the first time, on specific triggers for clinical decision-making.

Tranexamic acid
Fibrinolysis has been identified as an integral component to the pathogenesis of TIC [66,67] and based

### ROTEM-based algorithm for the use of hemostatic agents and blood products during early trauma care

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider fibrinogen administration</strong> (fibrinogen concentrate or cryoprecipitate)</td>
<td>EXTEM: A10 &lt; 45 mm (A5 &lt; 35 mm) or MCF &lt; 55 mm</td>
</tr>
<tr>
<td><strong>Consider plasma transfusion</strong> (or prothrombin complex concentrate (PCC)) (Note: Low platelets and low fibrinogen may also prolong CT)</td>
<td>EXTEM: CT ≥ 80 sec and A10 ≥ 45 mm (A5 ≥ 35 mm) / MCF ≥ 55 mm</td>
</tr>
<tr>
<td><strong>Consider platelet transfusion</strong></td>
<td>EXTEM: A10 &lt; 45 mm (A5 &lt; 35 mm) or MCF &lt; 55 mm</td>
</tr>
<tr>
<td><strong>Consider antifibrinolytics</strong></td>
<td>Any evidence of hyperfibrinolysis in EXTEM or FIBTEM!</td>
</tr>
<tr>
<td><strong>Consider withholding transfusion</strong></td>
<td>EXTEM: Abnormal high A10/MCF</td>
</tr>
</tbody>
</table>

**FIGURE 2.** ROTEM-based algorithm for the use of hemostatic agents and blood products during early care for the severely injured with bleeding and TIC [64*,65]. TIC, trauma-induced coagulopathy.
Recombinant activated coagulation factor VII and desmopressin

Because of insufficient high-level of evidence and failure in large clinical trials, recombinant activated coagulation factor VII (rFVIIa) is currently recommended only for off-label use if major bleeding and TIC persist despite all other attempts to control the bleeding and best practice use of conventional hemostatic measures ([69]; EU GRADE 2C [12*]). It needs to be emphasized that rFVIIa acts on the individual’s own coagulation system provided there are sufficient numbers of platelets and fibrinogen concentrations [70]. The European trauma guideline argues against the routine use of desmopressin (DDAVP) in the bleeding trauma patient (EU GRADE 2C [12*]).

ENVIROMENTAL CONDITIONS

Even small reductions in pH and temperature result in reduced coagulation enzyme kinetics [71–73]. The S3-DGU as well as the European trauma guideline recommends to avoid hypoxemia and acidosis rather than to correct (S3-DGU GoR B [11]; EU GRADE 1A [12*]) as experimental simple correction of the arterial pH with bicarbonate was not sufficient for reversal of coagulopathy due to acidosis [74,75]. Likewise, both guidelines suggest the early application of measures to reduce heat loss and warm the hypothermic patient in order to achieve and maintain normothermia (S3-DGU GoR B [11]; EU GRADE 1C [12*]). Ionized calcium levels should be monitored and maintained within the normal reference ranges during (massive) transfusion (S3-DGU GoR B [11]; EU GRADE 1C [12*]).

CONCLUSION

Early detection and aggressive multidisciplinary management of acute trauma-hemorrhage and TIC are still challenging. Implementation and adherence to evidence-based guidelines are essential for improved patient outcomes.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Management of trauma-induced coagulopathy Maegel et al.


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Important article indicating a survival benefit with the use of viscoelastic testing in adult bleeding.


53. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommenda-


Important article which informs on the target for fibrinogen supplementation.

63. David JS, Durand M, Levrat A, et al. Correlation between laboratory coagula-

64. Inaba K, Rizoli S, Vegas PV, et al. 2014 consensus conference on viscoelas-

First time consensus on viscoelastic test-based transfusion guidelines and trigger values for the administration of blood products and hematocrit agents.


