Review Article

The Diagnosis and Treatment of Acute Traumatic Bleeding and Coagulopathy

Marc Maegele

Summary

Background: Uncontrolled bleeding with trauma-induced coagulopathy (TIC) is still the most common avoidable cause of death in multiple trauma. The aging of the population has led to an increasing number of bleeding trauma patients with pre-existing anticoagulation. Such patients are not treated uniformly, even in major trauma centers.

Methods: This review is based on a selective search of the literature (Medline/PubMed, Cochrane Reviews) and summarizes current treatment recommendations, including those of the newly revised European trauma guidelines.

Results: The treatment of traumatic hemorrhage begins at the site of the accident, with compression, tourniquets, pelvic binders, and rapid transport to a certified trauma center. The early use of tourniquets was shown to lessen the transfusion requirement (packed red blood cells: 2.0 ± 0.1 vs. 9.3 ± 0.6 ; $p < 0.001$; fresh frozen plasma concentrates: 1.4 ± 0.08 vs. 6.2 ± 0.4 ; $p < 0.001$), while external pelvic stabilization was shown to reduce mortality (19.1% vs. 33.3%). Upon the patient's arrival in the hospital, steps are taken to measure, monitor, and support clotting function. Bleeding is controlled surgically according to the principles of damage control. Modern clotting management consists of goal-oriented, individualized therapy, including the use of point-of-care viscoelastic test procedures. Idarucizumab can be used as an antidote to the thrombin inhibitor dabigatran, andexanet alpha as an antidote to factor Xa inhibitors.

Conclusion: The evidence-based treatment of patients with hemorrhage from severe trauma, in accordance with the existing guidelines, can improve the clinical outcome. Corresponding algorithms, adapted to local logistics and infrastructure, must be developed and implemented.

Cite this as:

Maegele M: The diagnosis and treatment of acute traumatic bleeding and coagulopathy. Dtsch Arztebl Int 2019; 116: 799–806. DOI: 10.3238/arztebl.2019.0799

In spite of improvements in the care of trauma patients, uncontrolled bleeding with coagulopathy as a complication remains a relevant clinical problem (1) and the most common avoidable cause of death after polytrauma (2). Death by bleeding out occurs rapidly—at a median of 1.65 hours after hospital admission (3)—and one in every four patients with severe trauma presents at admission to the shock room with laboratory-defined signs of coagulopathy (4). Systemic clotting problems may already be present at admission to the shock room or they may develop thereafter and rapidly get worse (5, 6). The therapeutic focus is on identifying acute bleeds and systemic clotting problems early and treating them in a targeted manner (7, 8). In the context of a subgroup analysis of the PROPPR study in the USA, each 15-min reduction of the time needed to control the bleed/correct the coagulopathy was associated with lowered mortality (relative risk [RR]: 0.97; 95% confidence interval [0.94; 0.99] and multi-organ failure (RR 0.94; [0.91; 0.97] (e1). The clinical care of bleeding trauma patients with accompanying coagulopathy is inconsistent, even in large trauma centers (e2-e4), although implementation of and adherence to standardized algorithms are associated with a better treatment result (e5-e7). The present article summarizes the current understanding of the pathophysiology and the recently updated treatment recommendations for the control of traumatic bleeding including complicating clotting problems.

Method

This review article is based on a selective search of the recent literature in the databases Medline (PubMed) and Cochrane Reviews, using different combinations of the relevant search terms (“bleeding/hemorrhage,” “coagulopathy,” “management,” “mortality,” “outcome,” “transfusion,” “trauma”). Because of the topicality of the subject we considered primarily publications from the past 5 years. Additionally we considered the recently revised and updated European guideline on the management of major bleeding and coagulopathy following trauma: fifth edition (ET-GL 2019 [8] with level of recommendation by number and level of evidence by character [recommendation / evidence level 1A–2C]). The recommendations given below follow the classification of Guyatt and colleagues with regard to their evidence levels (9).

Department of Orthopedic Surgery, Trauma Surgery, and Sports Medicine, Cologne Merheim Medical Center, Witten/Herdecke University, Cologne: Prof. Dr. med. Marc Maegele

FIGURE 1

Current concept of the pathophysiology of trauma-induced coagulopathy (after 5, 6, 8, 10). As a result of endothelium-bound thrombin–thrombomodulin complex (TTC) formation the so called protein-C pathway is activated and the clotting factors FV and FVII are inactivated, with concomitant hyperfibrinolysis as a result of increased tissue plasminogen activation (6, 13). More recent studies have indicated—even independently of this activation pathway—a systemic trauma-related release of tissue plasminogen activators (14). Subsequent to a glycocalyx injury, subendothelial heparin is systemically released in the sense of autoheparinization. Almost all trauma patients present disturbed thrombocyte function at some point during their stay in intensive care (15) (modified from [e25]).

Mechanisms of acute trauma-induced coagulopathy

Although coagulopathy in the context of traumatic injuries was initially understood as a secondary development, more recent data indicate an independent, multifactorial, and primary entity (5, 6, 10). The updated German clinical practice guidelines on the treatment of polytrauma/severe injuries now acknowledge trauma-induced coagulopathy (TIC) as an independent pathology with a notable effect on survival (7). *Figure 1* shows the current concept for the pathophysiological understanding of TIC. Especially systemic endotheliopathy, triggered by hemorrhagic shock and systemic inflammation, is now considered to be a central pathophysiological element (5, 6, 11). Initial thrombin deficiency is usually not present in a bleeding trauma patient (12). Platelet function defects have recently moved into the scientific focus (e8, e9). Plasma concentrations of most clotting factors fall only slowly during acute hemorrhages and are often—even in a scenario of halved plasma volume—still within their reference ranges. By contrast, fibrinogen as a substrate of the clotting process decreases significantly as early as during the prehospital treatment phase, depending on the severity of the injury, and is the first factor to reach critical concentrations (16). Fibrinogen concentrations

lowered as a result of trauma have been measured in the prehospital setting and consistently found to be associated with increased mortality and a poor treatment result at hospital admission (17). Further administration of fluids will trigger the fatal triad of existing coagulopathy, hypothermia, and acidosis.

Prehospital measures to control traumatic bleeding

The treatment of traumatic bleeding and associated coagulopathy, including TIC, starts at the site of the accident (18). Depending on the extent of blood loss, the classic ABCDE scheme may well have to be abandoned and control of the C component (circulation/critical bleeding) prioritized even before securing the airway, in the sense of a modified C-ABCDE scheme (*eTable*). Adequate therapeutic options are available to control external bleeding, whereas internal bleeding can often not be managed during prehospital care. In such cases, immediate transport prioritization with rapid surgical intervention in hospital is the only reasonable option that holds any hope of success (19). The crucial prehospital measures for the treatment and control of critical traumatic bleeding are summarized in the left column of *Table 1*. In this setting, manual and direct compression of the wound surface and/or supplying blood vessels is the most important measure in achieving

TABLE 1

Overview of the main measures for treatment and control of critical and trauma-related bleeding during prehospital care and the shock room phase

Prehospital care phase (treatment bundle: prehospital phase)	Shock room phase (treatment bundle: shock room)
Controlling the bleeding <ul style="list-style-type: none"> – Manual compression and compression bandage – Wound packing* – Tourniquet – Pelvic binder – Tamponade (nasal tamponade) 	Diagnostic evaluation <ul style="list-style-type: none"> – Clotting diagnostics: standard tests (Hb value, Quick value, PTT value, platelet count, fibrinogen measurement according to Clauss, calcium), viscoelastic testing methods (ROTEM), platelet function tests – Blood gas analysis: base deficit [BD], lactate value, pH value – Imaging: FAST ultrasound and computed tomography
Restrictive volume therapy <ul style="list-style-type: none"> – Permissive hypotension – No TBI: BP_{syst} 80–90 mm Hg/MAP 50–60 mm Hg – TBI: MAP ≥ 80 mm Hg – Volume replacement using crystalloids; vasopressors 	Controlling the bleed <ul style="list-style-type: none"> – Damage control procedures – Angioembolization – REBOA (?)
If patient is in shock <ul style="list-style-type: none"> – TXA 1 g bolus intravenously 	Clotting stabilization/clotting function support <ul style="list-style-type: none"> – TXA 1 g bolus infusion for patients in shock if not given during prehospital phase; if required, another 1 g as infusion over 8 h – Targeted administration of clotting stabilization factors/hemostatic drugs (see Figure 2) – Fibrinogen concentrate ≤ 1.5 g/L according to Clauss – Optimization of overall conditions for coagulation (normothermia and normocalcemia, prevention of acidosis) Transfusion therapy <ul style="list-style-type: none"> – In massive transfusion, FFP:pRBC at least 1:2; restrictive administration of pRBC (target Hb value 7–9 g/L) – FFP administration in PT and/or aPTT > 1.5 of norm (not to be given to patients without massive bleeding and not for treatment of hypofibrinogenemia!) – Platelet administration with aim > 50 × 10⁹/L (in sustained bleeding and TBI: > 100 × 10⁹/L) Antagonizing anticoagulant activity see Table 2

* Packing the wound with sterile dressings; if required, also hemostatic agents (zeolite, kaolin, or chitosan; these have a tissue adherent/mucoadhesive or clot stabilizing effect and have to be applied directly to the bleeding source/wound area).

aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma concentrates; Hb, hemoglobin; MAP, mean arterial pressure; pRBC, packed red blood cell concentrates; PT, prothrombin time; REBOA, resuscitative endovascular balloon occlusion of aorta – placing and blocking a balloon catheter in the aorta via the femoral artery; TBI, traumatic brain injury; TXA, tranexamic acid

timely control of the bleeding (R2/1A). If the source of the bleeding is deep within the injured tissue, the wound should be packed with sterile dressing materials. In some cases, compression is combined with physically acting hemostatics or drugs to stabilize clotting.

Although wound compression should be preferred primarily, the use of tourniquets is a proven means of controlling severe bleeding from injuries of the extremities (R2/1B). The primary use of tourniquets is especially useful in life-threatening hemorrhage or multiple sources of bleeding on one limb, if the source of the bleeding is not accessible, if concomitant and critical A, B, or C problems arise, and in the context of a mass event with multiple casualties (18). The tourniquet should be applied under sufficient analgesia in as distal a position as possible, but at least a hand width proximal to the injury, and it should be kept tight until the bleeding ceases; the time of application should be documented. If indicated and appropriately applied, the use of a tourniquet was associated with improved stability of the circulation at

admission to the shock room (BP_{syst} 120 ± 2 vs 112 ± 2 mm Hg, p = 0.003), a reduced need for transfusion (packed red blood cells [pRBC]: 2.0 ± 0.1 vs 9.3 ± 0.6, p < 0.001; fresh frozen plasma concentrates [FFP]: 1.4 ± 0.08 vs 6.2 ± 0.4, p < 0.001), and a non-increased risk for complications, e.g., nerve injuries and infections (e10).

With increasing severity of the overall injury, rates of complex pelvic injuries with bleeding mostly from the venous peritoneal plexus increase; only 10–15% of all pelvic bleeds are arterial (e11, e12). The use of pelvic binders has been found to be an effective measure to control bleeding in complex and unstable fractures of the pelvic ring (R2/1B). If these are applied correctly at the level of both trochanters, the pelvic volume is reduced and counterpressure to the bleed is established (eFigure). The patient's trouser pockets should be emptied before the binder is applied, and the patient's pulse should be monitored distally before and after application. Patients with initial pelvic stabilization by means of a pelvic binder subsequently required fewer blood transfusions

(2462 ± 2215 mL vs. 4385 ± 3326 mL; $p < 0.01$), spent fewer days in the acute setting and in intensive care (16.11 ± 12.54 vs. 19.55 ± 26.14 days and 5.33 ± 5.42 vs. 8.36 ± 11.52 days), and displayed a positive trend in terms of survival (e13). In a retrospective analysis of 104 hemodynamically unstable trauma patients with relevant single injury of the pelvis, external stabilization was undertaken in 45.2% of cases (e14). In the group receiving external pelvic stabilization, 19.1% of patients died, whereas mortality in the group not receiving external stabilization was 33.3%. In view of the low sensitivity and specificity of manual checks for pelvic stability, the indication for applying a binder should be defined generously. Severe bleeding in the oromaxillofacial region, especially in the context of falls or physical violence, can be controlled either by compressing the nostrils—in most cases, more effectively by packing—or, in case of emergency, by using blocked bladder catheters (18). The prehospital administration of blood products depends on the context, risks, and logistical challenges (e15–e18). In a retrospective analysis of >55 000 US military datasets from the Iraq and Afghanistan conflicts (2001–2017), a reduction in mortality by 44% over time was associated primarily with three key interventions (e19):

- Application of tourniquets
- Reduction of prehospital transport time to less than 60 min
- Early use of blood products

Treatment in specialized centers

A white paper of the German Trauma Society (*Deutsche Gesellschaft für Unfallchirurgie*, DGU) set out recommendations for the structure, organization, and equipment for the care of severely injured patients in Germany, and their implementation was initiated in the context of the project TraumaNetwork DGU (20). The ET-GL 2019 recommends the direct admission of bleeding trauma patients to an appropriate trauma center (R1/1B). The TraumaNetwork DGU ensures the vertical transfer after primary stabilization in a trauma center providing a basic level of care. If a bleeding trauma patient's circulation cannot be stabilized during the prehospital phase then the measures at the site of the accident will have to be discontinued in favor of immediate transport to a suitable trauma center (18), in order to keep the interval between injury and control of bleeding as short as possible (R1/1A). To prevent further blood loss, permissive hypotension with systolic target pressures of 80–90 mm Hg (mean target pressure 50–60 mm Hg) in patients without traumatic brain injury is an option until bleeding is controlled (R12/1C). In patients with traumatic brain injury, mean arterial pressure ≥ 80 mm Hg is recommended in order to compensate for the cerebral perfusion pressure (R12/1C). Volume replacement in hypotensive and bleeding trauma patients still consists of isotonic balanced crystalloids (R15/1A); in life-threatening bleeding and shock, administration of vasopressors

should be considered to achieve the target pressure (R14/1C).

Acute management of bleeding at the trauma center

Clinical assessment and immediate surgical treatment
The extent of traumatic bleeding should be assessed by using a combination of clinical assessment of the patient's physiology at admission, the anatomical injury pattern, and the mechanism of the injury suffered (R4/1C). The Advanced Trauma Life Support (ATLS) classification of hemorrhagic shock has limitations regarding risk stratification (e20), but has been upgraded in the latest edition of the manual by the inclusion of base deficit as an additional criterion (21, 22). The bolus response to defined fluid administration in the context of “permissive hypotension” up to control of the bleeding is subject to criticism (R13/1B). The importance of imaging methods to detect free fluids in thorax and abdomen as well as to locate possible bleeding sources is still emphasized (FAST ultrasound [R7/1C], contrast-enhanced whole-body computed tomography [R7/1B]). Patients with an obvious bleeding source and patients in severe hemorrhagic shock and a suspected bleeding source should immediately be put through a procedure to control the bleeding (R5/1C), employing the usual damage control methods (T18/1B) with closure and stabilization of the pelvic ring (R19/1B) and packing (T20/1B). The assumption is that around 10% of extremely severely injured patients will benefit from this approach; there are no individual predictive factors for therapeutic success (e21). Where the relevant infrastructure exists, angiographic embolization techniques should be considered (R20/1B); to gain time under extreme conditions in life-threatening pelvic bleeding, retrograde endovascular balloon occlusion of the aorta (REBOA) is an option until definitive care can be given (R20/2C).

Early diagnosis of coagulopathies

Targeted measures to establish, monitor, and support the clotting function should be initiated immediately after hospital admission (R23/1B). Initially lowered hemoglobin can be used as an indicator for a severe hemorrhage with accompanying coagulopathy (R8/1B); repeated measurements are required, however, since an initial result within the reference levels can mask an existing hemorrhage (R8/1B). Sensitive parameters for the establishment and monitoring of shock depth and severity of the bleed are lactate and base deficit (BD) (R9/1A). The routine diagnostic work-up for coagulopathies should—because of their dynamics—be undertaken early and repeated at short intervals, taking account of the standard variables of clotting function (prothrombin time [PT; Quick], platelet count, and fibrinogen concentration) and/or point-of-care PT/international normalized ratio (INR) (R10/1C) and/or functional viscoelastic testing methods (R10/1C). For the first time, the updated European trauma guidelines consider the standard parameters of clotting function and viscoelastic testing

FIGURE 2

Treatment recommendation	Interpretation	
Consider administration of fibrinogen (fibrinogen concentrate)	A10 < 45 mm (A5 < 35 mm) or MCF < 55 mm	A10 < 10 mm (A5 < 9 mm) or MCF < 12 mm
Prothrombin complex—consider (PCC) administration (Prothrombin complex concentrate) Caution: Low thrombocyte count and low fibrinogen prolong CT	CT > 80 s and A10 ≥ 45 mm (A5 ≥ 35 mm) or MCF ≥ 55 mm	Normal A10 (A5 ≥ 9 mm) or normal MCF
Consider administration of antifibrinolytic (tranexamic acid)	any sign of hyperfibrinolysis in EXTEM und FIBTEM!
Conservative therapy/ consider transfusion	A10/MCF too high	

Algorithm based on point-of-care-rotational thrombelastometry (ROTEM) including consensus-based thresholds for using clot-stabilizing factor concentrates and hemostatic drugs in the early care of bleeding severely injured patients (7, 24). In Germany, the method of choice is point-of-care ROTEM, while in the USA, thromboelastography is used more frequently; the two are comparable in terms of the testing principle. Deviations in the measurements and reference ranges occur as a result of technical differences and use of different start reagents. Both methods reactivate the initially inhibited clotting process in the patient's blood in a test tube by adding an activator and display this visually as a curve in a temporal dynamic. By adding different activators/inhibitors to the patient's blood sample, partial stages of hemostasis can be examined. In contrast to the usual standard parameters of clotting function (Quick/INR and aPTT), which are limited to the initiation phase, viscoelastic testing methods yield information about initiation of clotting (clotting time [CT]), the dynamics of clot formation, the firmness and stability of the clot (maximum clot firmness [MCF]), and thrombolysis. The amplitude shows the firmness and stability of the clot that is forming. If, in a scenario of significant bleeding, hypofibrinogenemia with viscoelasticity-based confirmation of a functional fibrinogen deficit (lowered FIBTEM amplitude) becomes apparent, administration of fibrinogen concentrate should be considered (R28/1C), usually at an initial dose of 3–4 g (R28/2C). Provided fibrinogen concentrations have been compensated, administration of prothrombin complex concentrates (PCC) should be considered if viscoelasticity testing confirms delayed initiation of clotting (prolonged EXTEM-CT) (R27/2C). EXTEM, ROTEM test to check the extrinsic clotting system via sample activation by adding tissue thromboplastin (tissue factor): enables the assessment of clotting factors I, II, V, VII, X, platelet function, and fibrinolysis; FIBTEM, sample activation as in EXTEM test, with addition of cytochalasin D for the purpose of blocking platelet activation: enables the assessment of fibrin polymerization and fibrinolysis; A10, test result after 10-min test period; aPTT, activated partial thromboplastin time; CT, clotting time; MCF, maximum clot firmness. Modified from (24) and (e22).

as equivalent during diagnostic evaluation (8). By using the latter, the functional clotting properties of the patient's blood in terms of formation, firmness, and dissolution of the clot can be documented at the bedside, providing a relevant time advantage (e22, e23). In suspected platelet dysfunction, additional point-of-care approaches are recommended to investigate platelet function (R11/2C).

Acute coagulation-stabilizing treatment

Acute treatment in a setting where a massive transfusion is to be expected includes on the one hand the empirical administration of FFP and pRBC at a prede-

finied ratio of at least 1:2 (R24/1C) in the sense of the damage control resuscitation (DCR) concept or, alternatively, administration of fibrinogen concentrate and pRBC (R24/1C). These strategies should, as early as possible, give way to a targeted and individualized therapeutic concept, guided by the usual (above-mentioned) standard parameters of clotting function or on the basis of viscoelastic testing (R25/1B). Regarding the latter, studies have shown a positive trend in terms of survival and also a reduction in the need for allogenic blood products (23). In contrast to the conventional standard parameters of clotting function (Quick/INR and aPTT) limited to the initiation phase

TABLE 2

Current options for neutralizing the anticoagulant effect of anticoagulant drugs taken before the accident/injury*

Clotting inhibitors	Strong recommendation based on moderate to strong evidence	Conditional recommendation based on (very) weak to moderate evidence
Vitamin K antagonists (VKAs)	Vitamin K Prothrombin complex concentrates (PCC)	Fresh frozen plasma concentrates (FFP) if PCC is contraindicated or not available
Direct factor-Xa inhibitors (apixaban, edoxaban, and rivaroxaban)	Andexanet alfa, recommended for approval by the European Medicines Agency (EMA) in March 2019 and available in Germany since 1 September 2019	PCC Tranexamic acid (TXA) Active charcoal within 2 h after ingestion in intubated patients with enteral access and/or low risk of aspiration
Direct thrombin inhibitors (dabigatran)	Idarucizumab	PCC if idarucizumab not available Hemodialysis if idarucizumab not available or in event of overdose of dabigatran Active charcoal within 2 hours after ingestion in intubated patients with enteral access and/or low risk of aspiration
Unfractionated heparins	Protamine sulfate	
Low-molecular-weight heparins (LMWHs)	Protamine sulfate	Recombinant factor VIIa in patients treated with danaparoid or if protamine is contraindicated or not available
Pentasaccharides		PCC Recombinant factor VIIa if PCC contraindicated or not available
Platelet aggregation inhibitors		Desmopressin in bleeds in patients treated with ASA/cyclooxygenase-1- or ADP receptor antagonists Platelet concentrates in bleeds in patients treated with ASA or ADP receptor inhibitors in event of a (neuro-)surgical intervention

ADP, adenosine diphosphate; ASA, acetylsalicylate; *modified from (e24)

and minimum thrombin generation, viscoelastic testing yields immediate treatment-relevant information about the dynamics and sustainability of the clot structure and stability, including (hyper-)fibrinolysis. Viscoelastic testing can be carried out in the shock room/operating theater with no delay, and the results can immediately be considered in the therapeutic decision (24). *Figure 2* shows the current recommendations for guiding treatment with coagulation-stabilizing substances and blood products in bleeding trauma patients, using POC rotational thrombelastometry (ROTEM) on the basis of consensus-based thresholds (24). In the course of clotting management based on FFP, the use of FFP should be guided by the standard parameters PT and aPTT (>1.5 of normal) and/or viscoelastic signs of a lack of clotting factors (R26/1C). Giving FFP to patients without massive hemorrhages (R26/1B) or to treat hypofibrinogenemia is expressly not recommended (R26/1C). In consideration of the standard values, the threshold for fibrinogen substitution is ≤ 1.5 g/L as measured according to Clauss (R28/1C).

The recommendation based on the CRASH-2 trial is early use of the antifibrinolytic tranexamic acid (TXA) in bleeding trauma patients or in the presence of a risk for significant hemorrhage: TXA should be given as a bolus within 3 h after the injury (1 g intravenously over 10 min), followed by an infusion (1 g over 8 h) (R22/1A). Administration of TXA can be considered even before transfer to the hospital (R22/1C). Substitution of clotting factor XIII to stabilize the clot can be considered, but currently no detailed recommendations exist (R27/2C). The use of

recombinant factor VIIa as first-line treatment is not recommended (R31/1B); it can be considered if bleeding continues despite the deployment of the listed and conventional strategies and after correction of acidosis, temperature, fibrinogen level, and platelet count (R31/2C). The threshold values for transfusion of pRBC with an Hb target value of 7–9 g/L (R16/1C) and platelet concentrates with a target of $> 50 \times 10^9/L$ (R29/1C), or $> 100 \times 10^9/L$ in sustained bleeding or traumatic brain injury (R29/2C), remain valid. It is self-evident that acidosis and hypothermia should be avoided (R17/1C) and that monitoring and correction of lowered calcium concentrations should be performed in the context of a massive transfusion (R30/1C). The crucial immediate measures to control the bleeding and stabilize coagulation in the setting of shock room treatment are summarized in the right-hand column of *Table 1*.

Bleeding trauma patients receiving anticoagulation

Demographic change means that the number of bleeding trauma patients who are taking anticoagulant drugs can be expected to rise (25). If previous treatment is known or suspected, laboratory chemical screening (R10/1C) is recommended, and in the case of a sustained bleed it is advised to neutralize the effects (R32/1C). Although the anticoagulant effect of vitamin K-dependent antagonists can be detected by measuring the INR and can be neutralized by emergency administration of prothrombin complex concentrates (PCC) and oral vitamin K (R33/1A), the current trend is towards prescribing direct and non-vitamin K-dependent

Key messages

- Uncontrolled bleeding with complicating trauma-induced coagulopathy (TIC) is still the most common avoidable cause of death after polytrauma.
- Bleeding is controlled and treated on the basis of the current AWMF (Association of the Scientific Medical Societies in Germany) clinical practice guidelines on polytrauma/treatment of severely injured patients and the European trauma guidelines, updated in 2019.
- The treatment of trauma-related bleeding starts at the site of the accident with compression, tourniquets, and a pelvic binder to prevent further blood loss, followed by rapid transport to a certified trauma center.
- Targeted measures for the surgical control of bleeding and for the diagnostic evaluation, monitoring, and support of the clotting function should be initiated immediately after hospital admission in the shock room.
- For patients taking oral anticoagulants, the antidote for vitamin K antagonists is administration of vitamin K and prothrombin complex concentrates (PCC); for patients taking the thrombin inhibitor dabigatran, the available antidote is idarucizumab; and the antidote for Factor Xa is andexanet alfa.

oral anticoagulants (apixaban, dabigatran, edoxaban, and rivaroxaban) in the setting of various underlying cardiologic and neurologic disorders. In the setting of acute bleeding emergencies, idarucizumab is an antidote for the thrombin inhibitor dabigatran (5 g intravenously [R35/1B]), and clotting activity levels can be estimated by using thrombin time ([R35/2C] for the qualitative estimate), ecarin clotting time, and diluted thrombin time [R35/2C]) (25); factor-Xa inhibitors (apixaban, edoxaban, and rivaroxaban) by using calibrated chromogenic anti-factor-Xa activity tests (R34/2C) (25). These methods are not universally available, react differently depending on the anticoagulant in use, and often do not detect the entire therapeutic range, so that demonstration of presence and neutralization of effects remain a challenge, especially in the emergency setting (25). In the event of life-threatening bleeding in patients treated with factor-Xa inhibitors, the recommended treatment is TXA 15 mg/kg (or 1 g) intravenously and PCC (25–50 units/kg) (R34/2C).

In March 2019 the European Medicines Agency (EMA) recommended approval of the factor-Xa antidote andexanet alfa; the substance has been available in Germany since 1 September 2019. Sustained bleeding in patients treated with platelet function inhibitors and in documented inhibition should be treated with platelet concentrates (R36/2C); this should be considered in particular in patients with intracranial bleeds who require neurosurgery (R36/2B). Administration of desmopressin can also be considered

(R36/2C). Close collaboration with a hemostaseologist is strongly advised. *Table 2* summarizes the current recommendations for dealing with anticoagulants in the context of bleeding trauma patients.

Adherence to ethical guidelines

For this article, the author did not undertake studies in humans or animals. For the cited studies, the respective reported ethical guidelines apply.

Conflict of interest statement

Marc Maegele has received lecture honoraria, fees for participating in expert and advisory panels, and financial funding for participating in conferences and undertaking scientific projects from Abbott Laboratories, Astra Zeneca, Bayer, Biotest, CSL Behring, IL-Werfen/TEM-International, LFB Biomedicaments France, and Portola.

Manuscript received on 13 June 2019, revised version accepted on 6 September 2019

Translated from the original German by Birte Twisselmann, PhD

References

1. Cannon JW: Hemorrhagic Shock. *N Engl J Med* 2018; 378: 370–9.
2. Schoeneberg C, Schilling M, Hussmann B, et al.: Preventable and potentially preventable deaths in severely injured patients: A retrospective analysis including patterns of errors. *Eur J Trauma Emerg Surg* 2017; 43: 481–9.
3. Oyeniyi BT, Fox EE, Scerbo M, et al.: Trends in 1029 trauma deaths at a level 1 trauma center. *Injury* 2017; 48: 5–12.
4. Fröhlich M, Mutschler M, Caspers M, et al.: Trauma-induced coagulopathy upon emergency room arrival: Still a significant problem despite increased awareness and management? *Eur J Trauma Emerg Surg* 2019; 45: 115–24.
5. Chang R, Cardenas JC, Wade CE, et al.: Advances in the understanding of trauma-induced coagulopathy. *Blood* 2016; 128: 1043–9.
6. Kornblith L, Moore H, Cohen M: Trauma-induced coagulopathy: Past, present and future. *J Thromb Haemost* 2019; 17: 852–62.
7. S3-Leitlinie Polytrauma/Schwerverletzten-Behandlung AWMF Register-Nr. 012/019. www.awmf.org/leitlinien/detail/ll/012-019.html (last accessed on 30 May 2019).
8. Spahn D, Bouillon B, Cerny V, et al.: The European Guideline on management of major bleeding and coagulopathy following trauma: 5th edition. *Crit Care* 2019; 23: 98.
9. Guyatt G, Gutterman D, Baumann MH, et al.: Grading strength of recommendations and quality of evidence in clinical guidelines: Report from an American College of Chest Physicians task force. *Chest* 2006; 129: 174–81.
10. Maegele M, Schöchl H, Cohen MJ: An update on the coagulopathy of trauma. *Shock* 2014; 41 (Suppl 1): 21–5.
11. Johansson PI, Stensballe J, Ostrowski SR: Shock induced endotheliopathy (SHINE) in acute critical illness—a unifying pathophysiologic mechanism. *Crit Care* 2017; 21: 25.
12. Cardenas J, Rahbar E, Pommerening M, et al.: Measuring thrombin generation as a tool for predicting hemostatic potential and transfusion requirement following trauma. *J Trauma Acute Care Surg* 2014; 77: 839–45.
13. Davenport R, Guerreiro M, Frith D, et al.: Activated protein C drives the hyperfibrinolysis of acute traumatic coagulopathy. *Anesthesiology* 2017; 126: 115–27.
14. Chapman M, Moore EE, Moore H, et al.: Overwhelming tPA release, not PAI-1 degradation, is responsible for hyperfibrinolysis in severely injured trauma patients. *J Trauma Acute Care Surg* 2016; 80: 16–23.
15. Kutcher ME, Redick BJ, MacCreary RC, et al.: Characterization of platelet dysfunction after trauma. *J Trauma Acute Care Surg* 2012; 73: 13–9.
16. Floccard B, Rugeri L, Faure A, et al.: Early coagulopathy in trauma patients: An on-scene and hospital admission study. *Injury* 2012; 43: 26–32.
17. Rourke C, Curry N, Khan S, et al.: Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost* 2012; 10: 1342–51.
18. Helm M, Kulla M, Ströhr A, Josse F, Hossfeld B: Prähospital Management traumatischer Blutungen: Maßnahmen gemäß der S3-Leitlinie Polytrauma zur lokalen Blutungskontrolle. *Notfall Rettungsmedizin* 2018. www.springermedizin.de/praehospital-management-traumatischer-blutungen/15781652 (last accessed on 30 May 2019).

19. Kulla M, Bernhard M, Hink D, et al.: Treatment options for the critical bleeding in the out-of-hospital setting. *Der Notarzt* 2015; 31: 47–53.
20. Ruchholtz S, Lewan U, Debus F, et al.: TraumaNetzwerk DGU: Optimizing patient flow and management. *Injury* 2014; 45: 89–92.
21. American College of Surgeons Committee on Trauma: ATLS Student Manual. 10th Edition Chicago, IL: American College of Surgeons; 2018.
22. Standl T, Annecke T, Cascorbi I, Heller AR, Sabashnikov A, Teske W: The nomenclature, definition and distinction of types of shock. *Dtsch Arztebl Int* 2018; 115: 757–68.
23. Wikkelsø A, Wetterslev J, Møller AM, Afshari A: Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database Syst Rev* 2016; 22: 8: CD007871.
24. Inaba K, Rizoli S, Veigas PV, et al.: Consensus conference on viscoelastic test-based transfusion guidelines for early trauma resuscitation: Report of the panel. *J Trauma Acute Care Surg* 2015; 78: 1220–9.
25. Maegele M, Grottko O, Schöchl H, Sakowitz O, Spannagl M, Koscielny J: Direct oral anticoagulants in emergency trauma admissions—perioperative management, and handling hemorrhage. *Dtsch Arztebl Int* 2016; 113: 575–82.

Corresponding author

Prof. Dr. med. Marc Maegele
Klinik für Orthopädie, Unfallchirurgie und Sporttraumatologie
Klinikum Köln-Merheim, Kliniken der Stadt Köln gGmbH
Institut für Operative Medizin (IFOM)
Universität Witten/Herdecke
Ostmerheimer Str. 200
51109 Köln, Germany
Marc.Maegele@t-online.de

Cite this as:

Maegele M: The diagnosis and treatment of acute traumatic bleeding and coagulopathy. *Dtsch Arztebl Int* 2019; 116: 799–806. DOI: 10.3238/arztebl.2019.0799

► [Supplementary material](#)

For eReferences please refer to:

www.aerzteblatt-international.de/ref4719

eTable and eFigure:

www.aerzteblatt-international.de/19m0799

Supplementary material to:

The Diagnosis and Treatment of Acute Traumatic Bleeding and Coagulopathy

by Marc Maegele

Dtsch Arztebl Int 2019; 116: 799–806. DOI: 10.3238/arztebl.2019.0799

eReferences

- e1. Chang R, Kerby J, Kalkwarf K, et al.: Earlier time to hemostasis is associated with decreased mortality and role of complications: Results from the pragmatic randomized optimal platelet and plasma ratio trial. *J Trauma Acute Care Surg* 2019; 87: 342–9.
- e2. Schäfer N, Driessen A, Fröhlich M, et al.: Diversity in clinical management and protocols for the treatment of major bleeding trauma patients across European level I trauma centres. *Scand J Trauma Resusc Emerg Med* 2015; 23: 74.
- e3. Fuller G, Bouamra O, Woodford M, et al.: Recent massive blood transfusion practice in England and Wales: View from a trauma registry. *Emerg Med J* 2012; 29: 118–23.
- e4. Etchill E, Sperry J, Zuckerbraun B, et al.: The confusion continues: Results from an American Association for the Surgery in Trauma survey on massive transfusion practices among United States trauma centers. *Transfusion* 2016; 56: 2478–86.
- e5. Nunn A, Fischer P, Sing R, et al.: Improvement of treatment outcomes after implementation of a massive transfusion protocol: A level 1 trauma center experience. *Am Surg* 2017; 83: 394–8.
- e6. Bawazeer M, Ahmed N, Izadi H, et al.: Compliance with a massive transfusion protocol (MTP) impacts patient outcome. *Injury* 2015; 46: 21–8.
- e7. Hwang K, Kwon J, Cho J, et al.: Implementation of trauma center and massive transfusion protocol improves outcomes for major trauma patients: A study at a single institution in Korea. *World J Surg* 2018; 42: 2067–75.
- e8. Hofer V, Wrigge H, Wienke A, et al.: Thrombozytenfunktionsstörung bei Traumapatienten, ein unterschätztes Problem? Ergebnisse einer monozentrischen Untersuchung. *Der Anaesthesist* 2019; 68: 368–76.
- e9. Verni CC, Davila A Jr, Balian S, et al.: Platelet dysfunction during trauma involves diverse signaling pathways and an inhibitory activity in patient-derived plasma. *J Trauma Acute Care Surg* 2019; 86: 250–9.
- e10. Smith AA, Ochoa JE, Wong S, et al.: Prehospital tourniquet use in penetrating extremity trauma: Decreased blood transfusions and limb complications. *J Trauma Acute Care Surg* 2019; 86: 43–51.
- e11. Felix S, Hanschen M, Biberthaler P: Blutungskontrolle bei Beckenverletzungen. *Trauma Berufskrankh* 2016; 18: 173–80.
- e12. Culemann U, Ostern HJ, Pohlemann T: Current treatment of pelvic ring fractures. *Unfallchirurg* 2014; 117: 145–59.
- e13. Hsu SD, Chen CJ, Chou YC, et al.: Effect of early pelvic binder use in the emergency management of suspected pelvic trauma: A retrospective cohort study. *Int J Environ Res Public Health* 2017; 14: 1217.
- e14. Esmer E, Esmer E, Derst P, et al.: Influence of external pelvic stabilization on hemodynamically unstable pelvic fracture. *Unfallchirurg* 2017; 120: 312–9.
- e15. Shackelford SA, Del Junco DJ, Powell-Dunford N, et al.: Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. *JAMA* 2017; 318: 1581–91.
- e16. Sperry JL, Guyette FX, Brown JB, et al.: Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. *N Engl J Med* 2018; 379: 315–26.
- e17. Moore HB, Moore EE, Chapman MP, et al.: Plasma-first resuscitation to treat hemorrhagic shock during emergency ground transportation in an urban area: A randomized trial. *Lancet* 2018; 392: 283–91.
- e18. Fenger-Eriksen C, Fries D, David JS, et al.: Pre-hospital plasma transfusion: A valuable coagulation support or an expensive fluid therapy? *Crit Care* 2019; 23: 238.
- e19. Howard JT, Kotwall RS, Stern CA, et al.: Use of combat casualty care data to assess the US military trauma system during the Afghanistan and Iraq conflicts, 2001–2017. *JAMA Surg* 2019; 154: 600–8.
- e20. Mutschler M, Nienaber U, Brockamp T, et al.: A critical reappraisal of the ATLS classification of hypovolaemic shock: Does it really reflect clinical reality? *Resuscitation* 2013; 84: 309–13.
- e21. Lamb CM, MacGoey P, Navarro AP, Brooks AJ: Damage control surgery in the era of damage control resuscitation. *Brit J Anaesth* 2014; 113: 242–9.
- e22. Maegele M: Moderne Gerinnungstherapie beim blutenden Schwerverletzten. *Med Klin Intensivmed Notfmed* 2019; 114: 400–9.
- e23. Gratz J, Grüting H, Thorn S, et al.: Protocolised thromboelastometric-guided haemostatic management in patients with traumatic brain injury: A pilot study. *Anaesthesia* 2019; 74: 883–90.
- e24. Maegele M, Schöchl H, Menovsky T, et al.: Coagulopathy and haemorrhagic progression in traumatic brain injury: Advances in mechanisms, diagnosis and management. *Lancet Neurol* 2017; 16: 630–47.
- e25. Stensballe J, Henriksen H, Johansson PI: Early haemorrhage control and management of trauma-induced coagulopathy: The importance of goal-directed therapy. *Curr Opin Crit Care* 2017; 23: 503–10.

eTABLE

Primary survey according to the ABCDE scheme once the immediate threat to the patient's life has been averted
Rapid documentation of the vital functions and immediate initiation of lifesaving measures (treat-first-what-kills-first principle!) *

A = Airway & Cervical Spine Control	Airway problem? Open airway by using jaw thrust, chin lift, Guedel airway, manual stabilization of cervical spine. Patient is not to move or be moved! Immediate measure: Open and secure the airways!
B = Breathing & Ventilation	Ventilation problem? Shallow breathing (?), symmetrical respiratory excursions, inspection of thorax (effect of external force?), palpation, pain, instabilities, percussion, auscultation (4 points, breath sounds present, weakened, absent?) Immediate measures: Secure and optimize pulmonary gas exchange. Every trauma patient receives O ₂ (5–10 L; SpO ₂ > 95 %), frequency? (12 > BF < 30: assisted ventilation). Endotracheal intubation; if required, alternative airway Caution: Tension pneumothorax with weak/absent breath sounds, respiratory failure, and shock > immediate decompression of the thorax!
C = Circulation & Hemorrhage Control Severe/directly life-threatening hemorrhage needs immediate care!! (even when neglecting the ABCDE scheme > C-ABCDE!)	Circulation problem? Visible external bleeding? Peripheral pulse palpable? If not, carotid pulse! Pulse quality, skin texture, recapillarization time(> / < 2 s), investigation for internal bleeding > thorax, abdomen, pelvis (pelvic stability: test only once if at all!), femur (increase in circumference? instability?) Immediate measures: Stabilize circulation and reduce/prevent further blood loss. Hemostasis by manual compression, compression bandage, tourniquets. If required, pelvic binder
D = Disability & Neurological Status	Disability (cerebral pressure signs?)?, traumatic brain injury?, spinal injury?, GCS (continuous monitoring!), pupillary reaction/width? Vomiting, bradycardia, breathing changes
E = Exposure & Environment	Accompanying injuries? Immediate measure: Hypothermia prophylaxis!

*In the acute phase this is done on site, often with no knowledge of medical history or diagnosis. BF, breathing frequency; GCS, Glasgow Coma Scale; SpO₂, oxygen saturation as measured by pulse oximetry

eFigure: a) Unstable anterior and posterior pelvic ring fracture in the radiological anteroposterior projection before and b) after correct application of a pelvic binder at the level of the two trochanters. After application, the anterior pelvic ring is shown as closed and the pelvic volume thereby reduced. c) Emergency surgical stabilization was undertaken by applying a supra-acetabular external fixator in a triangular configuration involving the right femur in the presence of a simultaneous right femoral shaft fracture following the damage control approach.