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Emergency Blood Transfusion for Trauma and Perioperative Resuscitation: Standard of Care

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Keywords

Massive transfusion · Factor concentrates · Coagulation · Perioperative bleeding

Abstract

Uncontrolled and massive bleeding with derangement of coagulation is a major challenge in the management of both surgical and seriously injured patients. The underlying mechanism of trauma-induced or -associated coagulopathy is tissue injury in the presence of shock and acidosis provoking endothelial damage, activation of inflammation, and coagulation disbalancing. Furthermore, the combination of ongoing blood loss and consumption of blood components that are essential for effective coagulation worsens uncontrolled hemorrhage. Additionally, therapeutic actions, such as resuscitation with replacement fluids or allogeneic blood products, can further aggravate coagulopathy.

Of the coagulation factors essential to the clotting process, fibrinogen is the first to be consumed to critical levels during acute bleeding and current evidence suggests that normalizing fibrinogen levels in bleeding patients improves clot formation and clot strength, thereby controlling hemorrhage.

Three different therapeutic approaches are discussed controversially. Whole blood transfusion is used especially in the military scenario and is also becoming more and more popular in the civilian world, although it is accompanied by a strong lack of evidence and severe safety issues. Transfusion of allogeneic blood concentrates in fixed ratios without any targets has been investigated extensively with disappointing results. Individualized and target-controlled coagulation management based on point-of-care diagnostics with respect to the huge heterogeneity of massive bleeding situations is an alternative and advanced approach to managing coagulopathy associated with massive bleeding in the trauma as well as the perioperative setting.

Introduction

Massive bleeding remains a key problem in trauma, but also for perioperative complications [1]. Not only in traumatic injury but also prehospitally and early, i.e., within 24 h in hospital [2], it is a major preventable cause of death [3]. In the trauma setting, as many as six out of every ten deaths occurring within the first 3 h of injury are due to massive bleeding [4].

Our understanding of trauma-induced coagulopathy (TIC) has evolved over recent years. As TIC is initialized by a combination of cellular hypoxia/shock and tissue damage, this entity is present in about 30% of trauma patients on arrival in the emergency department but may also appear intraoperatively. TIC is graver when both severe tissue injury and shock are present, thus provoking endothelial damage, deterioration of the immune and the coagulation systems [5]. The "lethal triad" of coagulopathy, metabolic acidosis, and hypothermia, initially regarded as the cause of life-threatening post-injury bleeding, worsens TIC [5]. Hemostatic disturbance includes fibrinogen depletion, inadequate thrombin generation, impaired platelet (PLT) function, and fibrinolytic dysreg-

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Table 1. Contemporary "massive transfusion" concepts (modified, [13])

Traditional definition	≥10 pRBC/24 h
Modern definition	≥10 pRBC/6 h ≥4 pRBC/1 h loss of ≥50% of blood volume/3 h
Substantial bleeding	≥1 pRBC within 2 h and ≥5 pRBC or bleeding-related death within 4 h
Resuscitation intensity	Number of units infused within 30 min of arrival 1 unit = 1 L crystalline solution, 0.5 L colloid, 1 pRBC, 1 plasma, or 6 platelets (= 1 pooled or apheresis unit)
CAT-positive	≥3 pRBC CAT24h: in any 1 h within 24 h of arrival CAT1h: within 1 h CAT4h: in any 1 h within 4 h

CAT, critical administration threshold; pRBC, packed red blood cells.

ulation [6]. Still, there is a wide, time-dependent spectrum of post-injury fibrinolysis. In addition to hyperfibrinolysis, there can be physiologic fibrinolysis, hypofibrinolysis, or "fibrinolysis shutdown" [5, 7]. Additionally, perioperative and traumatic bleedings are different: a coagulopathy is frequently an initial problem in TIC; perioperatively, this is rare; mostly there is a singular and localized source for the bleeding. Known perioperative triggers of coagulopathy might be operation on/damage of the "4P" (pulmo, pancreas, placenta, prostate) but also brain, liver, or malignancies. Another cause is tissue hypoxia, as it is known to induce tPA release from endothelial cells [8]. Therefore, hemostatic management in these settings should be different. The aim of this review is to give an update on current options for treatment of perioperative and traumatic bleeding.

Definitions

There is no internationally accepted definition of "critical" bleeding. However, for postpartum hemorrhage (PPH) critical bleeding is defined as a blood loss of more than 1.5 L since that amount (about ¼ of the body's blood volume) may affect hemodynamics [9]. Nevertheless, visual estimation of blood loss is notoriously wrong; this is true perioperatively [10] and in the trauma setting [11]. Weighing blood-soaked swabs, use of calibrated containers, and other interventions will be helpful [12] but are not commonly utilized. The definition often used in trauma for "massive transfusion" is a patient requiring/being transfused more than 10 packed red blood cell (pRBC) in 24 h; this has never been validated as a marker of bleeding severity and does not account for early deaths [13]. A more rational definition might be ≥4 pRBC in 1 h [14, 15] or a „critical administration threshold (CAT)" of ≥3 pRBC in 1 h (CAT1h) or in one of the first 4 h (CAT4h) [16]. Table 1 lists contemporary concepts for massive transfusion (modified, [13]). "Coagulopathy" is defined by an international normalized ratio >1.2, >1.4, or >1.5, but there is still no evidence to back up these definitions [17]. Deterioration of standard laboratory tests (SLT) like prothrombin time, partial thromboplastin time, international normalized ratio, or fibrinogen is used for the definition of TIC. However, these parameters are often misleading and not causally related to the underlying pathology [18]. TIC is a multifactorial entity that includes two distinct components: endogenous acute traumatic coagulopathy and iatrogenic resuscitation-associated coagulopathy [1]. Figure 1 illustrates a model of our current understanding of TIC's pathophysiology (modified, [19]). Nevertheless, there is still no clear definition of TIC [3, 5]. "Hyperfibrinolysis" is most often defined by viscoelastic tests as a percentage drop in amplitude of the maximal amplitude; although a clear definition on hyperfibrinolysis is pending, ≥3% is associated with increased mortality and transfusion requirements during uncontrolled hemorrhage [20].

Diagnosis (Table 2)

Initially, hemorrhage is a volume problem [18]. With ongoing massive bleeding, coagulation will be increasingly compromised. Regardless of its primary cause, every bleeding will result in coagulopathy if no early intervention is successfully applied. Yet not all coagulation factors will be equally influenced. Even for the singular specialty of PPH, it was shown that coagulopathy is not observed

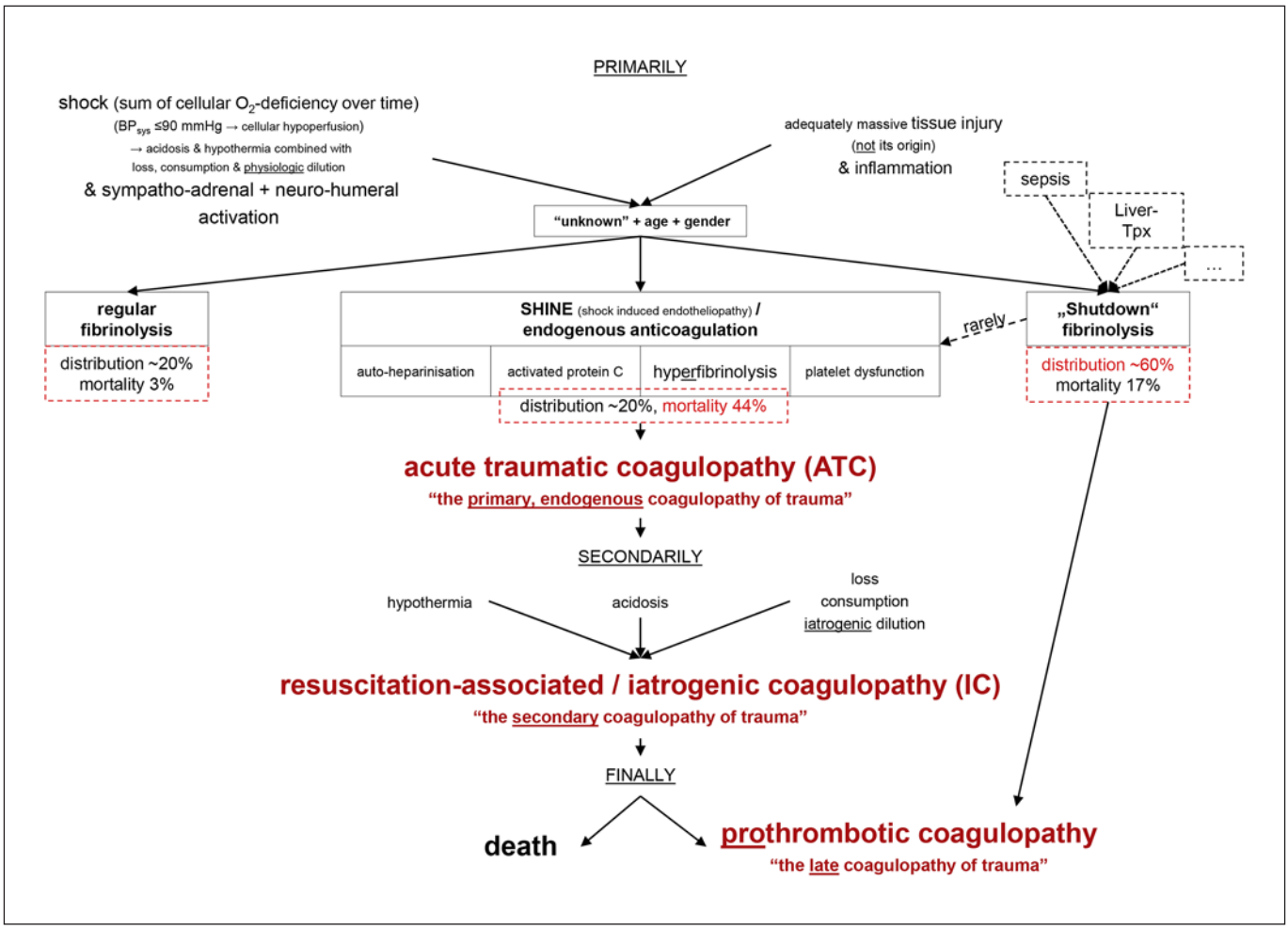

Fig. 1. Current understanding of the pathophysiology of TIC. The percentages refer to the Moores' publication [82], similar results were published by other authors (modified, [19]). BP_{sys}, systolic blood pressure; Tpx, transplantation.

in all women who suffer obstetric hemorrhage and cannot be predicted solely by blood loss. Additionally, different etiologies cause different disturbances in coagulation [21]. However, fibrinogen, the most abundant coagulation factor, is the first to reach critically low levels in severe bleeding events [5].

If SLT are useful for the diagnosis of coagulopathy or to guide hemostatic therapy is questionable [20, 22, 23]; their turnaround times of 45–60 min disqualify SLT, as median time to death due to exsanguination was 106 min [24]. However, if no other laboratory test is available, SLT may be preferable to no testing [22].

In general, it is recommended to initiate testing when bleeding problems occur [20]. Currently, a time- and patient-near diagnosis of the underlying pathology is possible only with whole-blood "point-of-care" tests: for primary hemostasis that is a PLT function analysis (Multiplate™, ROTEMplatelet™, TEG-Platelet Mapping™) and for secondary hemostasis it is viscoelastic testing (VET). PLT function tests by impedance aggregometry seem to be "useful point-of-care tests which identify anti-PLT medication use and PLT dysfunction in trauma patients" [25]. A specific evaluation of PLT function can be advantageous also in the perioperative setting if bleeding complications arise [20]. In elective cardiac surgery, the devices provided similar predictability for postoperative chest tube drainage and red blood cell (RBC) transfusion requirements [26]. However, the different devices correlate poorly with each other [20] and also had different clinical associations [27]. Currently, these tests might be regarded as an add-on to VET. A growing number of tools are available for VET (e.g., thrombelastography [TEG™], thromboelastometry [ROTEM™], elastic motion thromboelastometry [ClotPro™], sonorheology [Quantra™]). VET provides information about several aspects of the coagulation process, including clot initiation, clot strength, and fibrinolysis. In a systematic review and meta-analysis, the use of VET in the perioperative

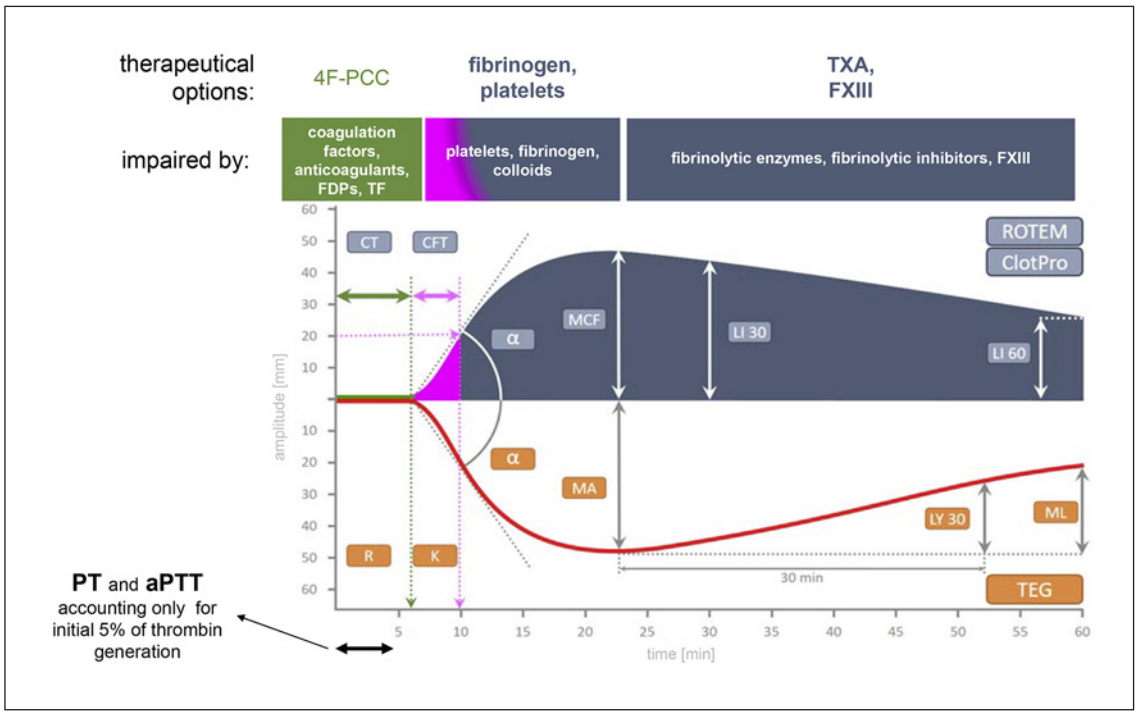

Fig. 2. Simplified diagnostic and therapeutic capabilities of VET (modified, [83]). Note: The Quantra™ system is not included in the figure as it measures comparable parameters but traces completely different curves.

period was seen to be associated with a statistically significant reduction in mortality (7.3% vs. 12.1%; RR = 0.64, p = 0.03), risk for acute kidney injury (10.5% vs. 17.6%; RR = 0.53, p = 0.005), volume of RBCs transfused (MD = −1.63 U, p = 0.02), risk for PLT transfusion (23.9% vs. 27.3%; RR = 0.74, p = 0.006), risk for fresh frozen plasma (FFP) transfusion (RR = 0.57, p = 0.001), and volume of FFP transfused (MD = −0.90, p = 0.0003) [28]. This precision-based therapeutic approach to the individual patient's hemostatic derangements is called "goal-directed" [15, 29]. VET should be repeated after therapeutic intervention; diagnosis and therapy are possible in a timely interval enabling a "theragnostic" approach [30] (Fig. 2). Standardization of VET is being addressed with controlled cartridge systems [15]. While laboratory devices are subject to a detailed quality control, this might not always be the case with VET usage by non-laboratory personnel. Inherently, VET's measuring principle integrates all factors participating in hemostasis and fibrinolysis and does not allow a selective assessment of single components; by selectively blocking of PLT function, the only exception is the measurement of fibrinogen (i.e., FIBTEM/functional fibrinogen/FIB-test). Additionally, VETs currently do not measure PLT function, impaired primary hemostasis (e.g., von Willebrand disease), or anticoagulant pharmaceuticals (ClotPro™ does the latter) [20]. The results of different VETs are not interchangeable, different generations of the same device (i.e., ROTEM™ delta vs. ROTEM™ sigma or TEG™ 5000 vs. TEG™ 6s) and even use of different cartridges might result in different values [20, 30, 31]. Of note, VET should complement, not replace, clinical judgment [32]. What needs treatment is the bleeding patient in the given situation, and not a reference value.

Therapy (Table 2)

If major bleeding is aggravated by coagulopathy, the negative impact on outcome and survival is significant [20]. Stopping the coagulopathy, even better preventing the development of one, is the main goal of coagulation management.

The Basics

As an enzymatic process, plasmatic hemostasis is strongly influenced by temperature and pH. Maintaining a core temperature ≥34°C (preferably normothermia) and a pH ≥7.2 is essential [33]. Calcium is coagulation factor IV and a cofactor for almost every enzymatic step in primary hemostasis; ionized Ca^{2+} should be kept at ≥0.9 mmol/L (preferably normocalcemia) [33].

The optimal fluid for volume replacement in hemorrhaging patients remains to be found. Both crystalline solutions and colloids impair hemostasis, the latter to a greater extent. Additionally, the optimal arterial blood

Table 2. Summary of cited studies of the Diagnosis and Therapy sections

More EE et al. Nat Rev Dis Primers. 2021 [5]	TIC	Review
Walsh M et al. J Clin Med. 2021 [15]	Blood component therapy	Narrative review
McNamara H et al. Anaesthesia. 2019 [21]	PPH	Observational
Haas T et al. Br J Anaesth. 2015 [22]	Perioperative use of SLT	Review
Gratz J et al. J Clin Med. 2020 [23]	Thrombin generation	Laboratory, healthy volunteers
Holcomb JB et al. JAMA. 2015 [24]	ratio	Pragmatic, phase 3, multisite, randomized, clinical
Connelly CR et al. J Surg Res. 2017 [25]	POC platelet function	Prospective, observational
Petricevic M et al. Anaesthesia. 2016 [26]	POC platelet function	Prospective, observational
George MJ et al. Transf Med. 2018 [27]	POC platelet function	Prospective, clinical
Santos AS et al. J Clin Anesth. 2020 [28]	VET	Systematic review and meta-analysis
Adam EH et al. Transfus Med Hemother. 2020 [29]	Plasma transfusion	Systematic review
Leal-Noval SR et al. Expert Rev Clin Pharmacol. 2020 [30]	Fibrinogen concentrate	Review
Baksaas-Aasen K et al. Ann Surg. 2019 [31]	ROTEM/TEG algorithms in trauma	Prospective, observational, multicenter
Bugaev N et al. J Trauma Acute Care Surg. 2020 [32]	TEG/ROTEM in bleeding, coagulopathic patients	Practice management guideline from the Eastern Association for the Surgery of Trauma
Lier H et al. J Trauma. 2008 [33]	Acidosis, hypocalcemia, anemia, and hypothermia in trauma	Review
Richards JE et al. Anesth Analg. 2021 [34]	Vasopressors in trauma	Review
Spahn DR et al. Crit Care. 2019 [35]	Management of major bleeding and coagulopathy following trauma	European guideline, fifth edition
Kozek-Langenecker SA et al. Eur J Anaesthesiol. 2017 [36]	Management of severe perioperative bleeding	Guidelines from the European Society of Anaesthesiology, first update
Trentino KM et al. BMC Med. 2020 [39]	Mortality in restrictive and liberal haemoglobin thresholds	Overview of systematic reviews
Ducrocq G et al. JAMA. 2021 [40]	Restrictive versus liberal blood transfusion in patients with acute myocardial infarction and anemia	Randomized
Whitlock EL et al. BMJ. 2015 [42]	Single unit perioperative transfusion	Retrospective population based
Goel R et al. JAMA Surg. 2018 [43]	Perioperative RBC and VTE	Registry study (NSQIP)
Turan A et al. Can J Anaesth. 2013 [44]	Massive transfusion in non-cardiac surgery	Registry study (NSQIP)
Levy JH et al. Semin Thromb Hemost. 2020 [45]	Plasma and PCC	Review
Innerhofer P et al. Lancet Haematology. 2017 [46]	First-line CFC or FFP in TIC	Single-center, parallel-group, open-label, randomized
German Medical Association 2020 [47]	Therapy with blood components and plasma derivatives	Cross-sectional guidelines
Marietta M et al. Blood Transfus. 2016 [49]	Solvent/detergent plasma versus FFP	Systematic review
Garrigue D et al. J Thromb Haemost. 2018 [50]	French lyophilized plasma versus FFP in TIC	Randomized, open-label
Cardenas JC et al. Blood Adv. 2018 [51]	Platelet transfusion in trauma	Substudy of the prospective, randomized PROPPR trial
Fields AT et al. Shock. 2021 [52]	Effects of trauma patient plasma on healthy platelet aggregation	Laboratory
Thiele T et al. Semin Thromb Hemost. 2020 [53]	Perioperative platelet transfusion	Review
Lippi G et al. Semin Thromb Hemost. 2020 [54]	Platelet transfusion thresholds	Review
Ponschab M et al. Anaesthesia. 2015 [55]	Ratio versus whole blood	Laboratory
McQuilten ZK et al. Transfus Med Rev. 2018 [58]	Blood products in massive transfusion	Systematic review
Kleinveld DJB et al. Transfusion. 2021 [59]	Platelet-to-red blood cell ratio and mortality in bleeding trauma patients	Systematic review and meta-analysis
Hashmi ZG et al. Transfusion. 2021 [60]	Blood product use for trauma resuscitation	Registry study
Hagen KG et al. Transfusion. 2021 [61]	Civilian whole blood	Retrospective, Norwegian university hospital
Khurrum M et al. J Trauma Acute Care Surg. 2021 [62]	WB + PCC versus WB alone	Registry study (NSQIP)
Meizoso JP et al. J Trauma Acute Care Surg. 2018 [63]	TXA and trauma	Retrospective, observational
Benipal S et al. West J Emerg Med. 2019 [64]	TXA in developed settings	Systematic review and meta-analysis
Hu W et al. CNS Drugs. 2019 [65]	TXA and cerebral hemorrhage	Systematic review and meta-analysis
Collins PW et al. Br J Anaesth. 2017 [67]	VET in PPH	Double-blind, randomized, controlled
Stabler SN et al. J Trauma Acute Care Surg. 2020 [68]	FC in trauma	Systematic-review and meta-analysis
Wu F et al. Shock. 2019 [69]	FC and glycocalyx	In vitro
Schlimp CJ et al. Scand J Trauma Resusc Emerg Med. 2016 [70]	FC in trauma	Retrospective, comparative
Baksaas-Aasen K et al. Intensive Care Med. 2021 [71]	VET in trauma	Randomized, controlled
Lv K et al. World J Emerg Surg. 2020 [72]	FC and TBI	Retrospective
Görlinger K et al. Korean J Anesthesiol. 2019 [73]	Evidence-based algorithms for ROTEM-guided bleeding management	Review
Frigo MG et al. Transfus Med. 2021 [74]	PPH	Comparative
Erdoes G et al. Anaesthesia. 2021 [75]	PCC	European consensus statement
Coleman JR et al. J Am Coll Surg. [76]	WB and thrombin generation	Observational
Schochl H et al. Crit Care. 2014 [77]	PCC in trauma	Observational
van den Brink DP et al. J Thromb Haemost. 2020 [78]	PCC	Systematic review and meta-analysis
Larsen JB et al. Semin Thromb Hemost. 2021 [79]	Thrombin	Review
Grottke O et al. Anesthesiology. 2019 [80]	PCC	Porcine trauma model
Listyo S et al. J Clin Med. 2020 [81]	FXIII	Observational, descriptive of prospectively collected samples

pressure target for resuscitation of patients with hemorrhagic shock is unknown. In the resuscitation of traumatic shock, it is necessary to target an appropriate balance with intravascular volume and vascular tone [34]. In those patients, permissive hypotension by a limited number of crystalloids in combination with norepinephrine or arginine vasopressin, aiming at a cerebral perfusion pressure of 60–70 mm Hg, and supported by blood-saving measures like cell recovery is a current recommendation [34–36].

Red Blood Cells, Plasma, and Platelets

Anemia refers to a drop in the total hemoglobin (Hb) concentration. Of note, the Hb level provides an estimate of the circulating red cell mass, but reveals nothing about tissue oxygenation, which RBC transfusion is meant to address [37]. Working from a suggestion made in 1942 [38], namely the "10/30 rule," requiring a Hb of 10 g/dL and a hematocrit of 30% has been the goal of transfusion for decades. Currently, a restrictive transfusion threshold is recommended in nearly all critically ill patients [39], even in the case of myocardial infarction [40], and recommendations increasingly focus on unwanted side effects. Yet, the "critical" Hb will, for ethical reasons, probably never be found in a randomized controlled trial. A retrospective analysis of mostly Jehovah's witnesses concerning mortality and morbidity in patients with very low postoperative Hb levels declining blood transfusion suggested "the risk of mortality increases sharply as Hb decreases below 5 to 6 g/dL, but in the Hb ranges of 6 to 8 g/dL, despite presence of a trend toward increased risk of death, the clinical importance of the risk becomes less clear, especially when the risks associated with blood transfusions are considered" [41]. Transfusion of as little as one unit was associated with an odds ratio (OR) of 2.33 (95% confidence interval [CI], 1.90–2.86) for perioperative stroke/myocardial infarction, and the odds of stroke/myocardial infarction markedly increased with transfusion of four or more units [42]. The American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) analyzed 750,937 patients; RBC caused a significantly increased risk for venous thromboembolism with an adjusted OR of 2.1 (95% CI, 2.0–2.3). This association remained statistically significant across all surgical subspecialties analyzed and was dose-dependent [43]. Another NSQIP report analyzed 971,455 patients undergoing non-cardiac surgery for morbidity and mortality after massive transfusion: 30-day postoperative mortality for non-transfused patients was 1.2%, for low transfusion (1–4 units) 8.9%, and for massive transfusion (≥5 units) 21.5% [44]. Current guidelines recommend a perioperative Hb range of 7–9 g/dL for most patients and for cardiovascular compromised patients in the range of 8–9 g/dL [40].

Although plasma is used extensively in the treatment of bleeding patients, evidence from randomized controlled trials comparing its effect with that of other therapeutic interventions is currently lacking [29, 45]. Transfusion of FFP is frequently ineffective for correction of the outcome-related pathologies of bleeding, hypofibrinogenemia, low fibrin polymerization, and poor clot strength [46]. Nevertheless, plasma is recommended by multiple international guidelines, especially for massive transfusions [29, 47]. This requires at least 30 mL/kg body weight (BW) at 30–50 mL/min [47]. Plasma was inferior in a prospective randomized study as compared to a coagulation factor-based resuscitation strategy [46]. It is known that freezing and thawing reduces the concentration of coagulation factors by approximately 10% and that pathogen-inactivation causes additional impairment of certain plasma components [29, 48]. Whether the clinical effects of FFP, freeze-dried plasma, and solvent/detergent plasma are comparable remains to be proven [49, 50].

There is little evidence for beneficial effects of PLT transfusion. Neither does an impairment of PLT-dependent clotting predict the need for PLT transfusion, nor do PLT transfusions reverse these impairments [5]. A qualitative and quantitative dysfunction of PLT is an integral part of acute traumatic coagulopathy [1, 5, 15]. Current literature increasingly distinguishes between PLT number and function [35, 36, 47]. In a subgroup analysis of the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial (see below), the group receiving PLT had significantly lower incidences of both 24-hour (5.8% vs. 16.9%; $p = 0.01$) and 30-day mortality (9.5% vs. 20.2%; $p = 0.001$). It is noteworthy that the median PLT count pretransfusion was 243×10^9/L [51]. Shock-/hypoxia-mediated soluble factors impair PLT aggregation, and tissue injury-mediated soluble factors amplify PLT aggregation [52]. Based on expert opinions, for massive bleeding a PLT count of $>100 \times 10^9$/L is recommended [53] but "a more individualized (personalized) approach based on assessment of the overall hemostatic balance seems … reasonable" [54].

Ratio

"Ratio" refers to the proportion of RBC to FFP to PLT. A caveat is the use of single-donor PLT concentrates in the USA and some other countries. Many European countries use pooled or apheresis PLT matching 4–6 single-donor concentrates, i.e., a US ratio of 1:1:1 equals 4–6:4–6:1. Ratio-driven concepts are based on the idea that mixing plasma, pRBC, and PLT in a fixed ratio produces whole blood. However, it has been shown in the past that this conception is wrong [1, 55]; "the reality of this approach is that the sum of the component parts does not equal the composition of whole blood" [56].

US and European guidelines differ regarding the role of ratio-driven therapy. Based on military experience, the US Department of Defense initialized the PROPPR trial published in 2015 [24]. Among patients with severe trauma and major bleeding, early administration of RBC, FFP, and PLT in a 1:1:1 ratio compared with a 2:1:1 ratio did not result in significant differences in mortality at 24 h or at 30 days. Subgroup analysis revealed more

patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 h (predominantly within the first 3 h [4]). This result was later specified in a commentary: reduced hemorrhagic mortality at 3 h after trauma center admission was possible only when components were available within 8 min of calling the blood bank and crystalloid and artificial colloid fluid use were markedly restricted [57]. The PROPPR trial has received significant scrutiny because of the lack of benefit in overall mortality. The trial has also received criticism for inconsistencies and confounding variables [15]. A 2018 systematic review concluded, from the limited evidence available, that there is insufficient basis to recommend a 1:1:1 over a 2:1:1 ratio or standard of care for adult patients with critical bleeding requiring massive transfusion [58]. A current meta-analysis of 5 RCTs with 1,757 patients noted a significantly improved 24-hour mortality (OR 0.69 [0.53–0.89]) and 30-day mortality (OR 0.78 [0.63–0.98]) for a high PLT:RBC compared with a low PLT:RBC ratio [59]. Of note, these improved outcomes are limited to patients with traumatic injury undergoing a massive transfusion, and any ratio-driven approach entails the risk of transfusing blood components that are not necessary and may be harmful [5].

Whole blood (WB) may resolve many logistical challenges involving multiple blood component administration, eliminate the need to keep track of transfusion ratios, and decrease the likelihood of transfusion errors during critical moments of resuscitation [1, 15, 56]. Of note, even in the USA, only a quarter of the American College of Surgeons (ACS)-certified trauma centers transfuse WB [60]. Since 2017, 205 patients were transfused with low titer group O whole blood at the University Hospital in Bergen, Norway; the wastage rate was 30% [61]. There is substantial evidence that WB is safe and feasible, but it has not been shown to be superior to component therapy in any large or randomized studies [56]. Additionally, a recent trial found that the use of 4-factor prothrombin complex concentrate (PCC) as an adjunct to WB is associated with a reduction in transfusion requirements and ICU LOS as compared to WB alone in the resuscitation of trauma patients [62]. Little evidence of superiority, some major safety issues (e.g., alloimmunization), and no authorization in most European countries limit its application.

Tranexamic Acid

Tranexamic acid (TXA) is a synthetic lysine analog acting on plasminogen via competitive block of the lysine binding sites. TXA inhibits the binding of plasminogen (the proenzyme) to plasmin (i.e., blocking activation of plasmin) and it also inhibits the binding of plasmin (the active form) to fibrin (i.e., blocking fibrinolysis) [19]. The sole licensed indication of TXA is hyperfibrinolytic bleeding and here, TXA is highly effective. As the body's reaction to severe trauma is a wide spectrum of hyperfibrinolysis (sustained excessive fibrinolytic activity), physiologic fibrinolysis (initial activation followed by a more gradual decline in fibrinolytic activity), hypofibrinolysis (a blunted initial response and low fibrinolysis activity early after injury), and "fibrinolytic shutdown" (initial activation and a rapid transition to a low fibrinolytic state) and this reaction switches time-dependently [7]; an antifibrinolytic agent like TXA cannot be the "magic bullet" for every bleeding. After resuscitation, all phenotypes converge into a low fibrinolytic state due to a post-resuscitation acquired fibrinolysis resistance [7]. Additionally, there is an increased risk of fibrinolysis shutdown among severely injured trauma patients receiving TXA [63]. Side effects, especially thromboembolic incidence rates, in modern, developed care settings might be different than what was observed in the major trials [64, 65]. Therefore, considering the many questions that remain unanswered, cautious, individualized use of TXA is recommended for ongoing, severe bleeding of more than 1,500 mL and/or hemorrhagic shock [19, 66]. An initial dose of 1 g or 15 mg/kg BW is recommended [19].

Coagulation Factor Concentrates

Not all blood components are depleted equally in hemorrhage [15]. An European expert meeting concluded that fast and targeted therapy for bleeding-induced coagulation factor deficiency is only possible with coagulation factor concentrates as the concentrations of coagulation factors, including fibrinogen, in FFP are too low to increase, or possibly even maintain, already low plasma concentrations in a bleeding patient [3]. A non-targeted, empirical approach to fibrinogen replacement is unlikely to be an optimal and cost-effective strategy [67].

Fibrinogen

Fibrinogen, coagulation factor I, is the precursor of fibrin and is an important mediator of PLT aggregation, namely via the PLT receptor glycoprotein IIb/IIIa [4]. It is the first factor to reach critical levels [23, 68]. Rapid depletion and dysfunction of fibrinogen are an integral part of TIC [1, 4, 15]. Fibrinogen supplementation should be administered only if significant bleeding is accompanied by a functional fibrinogen deficiency [30]. Fibrinogen can be substituted with FFP, cryoprecipitate, or fibrinogen concentrate (FC). FFP contains a low fibrinogen concentration of ~2.5 g/dL with wide variation in a large volume of 250 mL. The need to be thawed, no viral inactivation, and severe side effects (TRALI, TACO, TRIM [29]) are severe limitations. Current guidelines no

longer recommend the use of plasma for the treatment of hypofibrinogenemia [35]. Cryoprecipitate should be given at a dose of 50 mg/kg BW or 1 U/10 kg BW. It contains ~15 g/dL with wide variation and has side effects like those of FFP. Increasing evidence indicates a benefit of FC [4] with 25–50 mg/kg BW. It contains a defined concentration (15–20 mg/mL [29]) in a small volume, is immediately available, pathogen-inactivated, and has no known side effects. However, some countries still lack accreditation for acquired hypofibrinogenemia. Recently, it was shown that fibrinogen (not plasma) enhances endothelial barrier integrity [69]. The treatment of severe trauma patients with FC during bleeding management in the first 24 h after hospital admission does not lead to higher fibrinogen levels post-trauma beyond that occurring naturally due to the acute phase response, indicating no increased risk for thromboembolism [46, 70, 71]. Preemptive or prophylactic FC administration in patients without moderate or severe bleeding is not recommended [30].

Consistently, international guidelines label a fibrinogen <1.5–2 g/L as an indication for substitution [35, 36]. In an emergency, a standard dose of 3–4 g (50 mg/kg BW) may be administered and subsequently adjusted per the results of VET [3, 35, 36]. A fibrinogen level of 2–2.5 g/L seems to be adequate for hemostasis [67, 69, 72]. In an evidence-based algorithm for ROTEM™ (A5)-guided bleeding management, FC is indicated with an EXTEM A5 <35 mm and FIBTEM A5 <9 mm (trauma) or <12 mm (PPH) with a target of ≥12 mm (trauma) or ≥16 mm (PPH) [73]. For TEG™ 5000, a functional fibrinogen MA <20 mm (trauma [31]) or <6–9 mm (PPH [74]) might be indicative.

Prothrombin Complex Concentrate

PCC contains the vitamin K-dependent factors II, VII, IX, and X (4-factor PCC) or II, IX, and X (3-factor PCC). Following the initial approval for hemophilia B, the vial is standardized on factor IX; the content of the other coagulation factors can vary significantly among the different preparations [75]. The concentration of clotting factors is approximately 25-fold that of plasma [15, 29]. Even in severely bleeding trauma patients, thrombin generation might be sufficient to achieve adequate hemostasis [3, 23]. This might be different for trauma patients in shock [76]. Administration of PCC results in a dose-dependent increase in the endogenous thrombin potential for 3 days, indicating a possible risk for thromboembolism [23, 77]. In a systematic review and meta-analysis, PCC administration was not associated with a reduction in mortality in all patient groups taken together (OR 0.83; 95% CI, 0.66–1.06; $p = 0.13$; $I^2 = 0\%$). However, the trauma subgroup showed a significant reduction in mortality when PCC was added to FFP, but not when PCC was administered as a stand-alone therapy (OR 0.64; 95% CI, 0.46–0.88; $p = 0.007$; $I^2 = 0\%$; p for heterogeneity = 0.81) [78]. Yet, due to the very short half-life and almost immediate inhibition in fluid phase by antithrombin, thrombin itself remains elusive, and only indirect measurement of thrombin generation is possible [79]. As the clotting times of VET are not sensitive to reduced anticoagulant levels (e.g., antithrombin), their use as a surrogate remains debatable [80]. For coagulopathic, severe bleeding, an initial bolus of 25 IU/kg BW appears to be effective and for those patients with an increased risk for thromboembolism an initial half-dose bolus of 12.5 IU/kg BW followed by a second dose if microvascular bleeding persists [75]. In an evidence-based algorithm for ROTEM-guided bleeding management, PCC substitution is indicated with an EXTEM CT >80 s and FIBTEM A5 ≥9 mm (trauma) or ≥12 mm (PPH) [48].

Other Concentrates and Combinations

Nearly 30% of trauma patients exhibit FXIII of less than 60% on admission [46]. FXIII activity <70% is associated with an increased need for allogeneic transfusion and with bleeding complications in different scenarios [81].

In the prospective, randomized RETIC trial, time until first medication and time until normalization of bleeding were crucially shorter for coagulation factor concentrates (FC, PCC, and FXIII, guided by VET) versus FFP. The study was terminated early as the a priori planned interim analysis showed an unacceptably high incidence of treatment failure and an increased risk for massive transfusion for patients randomly allocated to the FFP group [46].

An European expert meeting suggested 1 g TXA as soon as possible and within 3 h of trauma followed by FC, blindly while awaiting fibrinogen level results, and finally PCC if bleeding continues, fibrinogen level is normalized, and clotting time is prolonged per VET [3].

Conclusion

Every hospital should have a massive transfusion protocol or major hemorrhage protocol that is adapted to its own resources and abilities and provides a clear framework as to facilitate a coordinated response by a large multi-disciplinary team during a time-critical situation [4, 29]. Table 3 is an example for such a protocol without VET; one using VET needs to be device-specific [20].

Hemostatic resuscitation as part of damage control is a key management strategy for massive bleeding. European guidelines recommend an initial ratio-driven ap-

Table 3. Exemplary table of an escalating scheme of hemostaseological therapeutic options for coagulopathic bleeding

1. Stabilization of concomitant factors (prophylaxis and therapy)	Core temperature ≥34°C (preferably normothermia) pH ≥7.2 Ionised Ca^{2+} >0.9 mmol/L (preferably normocalcemia)
2. Earliest inhibition of possible (hyper-)fibrinolysis (always before fibrinogen!)	Tranexamic acid initially 1 g (15 mg/kg BW), repeat if required
3. Substitution of oxygen carriers	RBC in massive bleeding, aim: Hb 7–9 g/dL (4.3–5.5 mmol/L)
4. Substitution of coagulation factors (for ongoing, severe bleeding)	Fibrinogen 30–60 mg/kg BW, aim: ≥200 mg/dL (≥2.0 g/L) and If needed, FXIII 20 IE/kg BW, aim: >60% and/or FFP ≥30 mL/kg BW If needed, 4-factor PCC 25 IE/kg BW
5. Substitution of platelets for primary hemostasis	PC, aim for bleeding requiring transfusion: 70–100 Gpt/L
6. If necessary, thrombin burst	On a case-by-case basis, if other therapeutic options fail, and after consideration and correction of concomitant factors If needed rFVIIa, initially 90 µg/kg BW
Within 24 h after stopping the hemorrhage, a pharmacological thrombosis prophylaxis is recommended	

Particularly, this scheme is drafted for hospitals without "point of care" VET, without knowing "What exactly is missing"; this (like every ratio-driven) approach entails the risk of transfusing components that are not needed! Escalating, i.e., if step 1 is not sufficient, add step 2. If steps 1 + 2 are not enough, add step 3. Patients requiring massive transfusion or suffering from hemorrhagic shock may benefit of a ratio of FFP:RBC ≥1:2 or combined application of FFP, PC, and factor concentrates.

proach, followed as quickly as possible by a goal-directed approach [35, 36]. This is called a "hybrid approach" or the "Copenhagen concept" [15]. However, this hybrid approach does not combine all benefits of these different strategies. Quite the opposite was shown in a randomized controlled trial: patients who initially received plasma at a dosage of 30 mL/kg BW followed by coagulation factor concentrates presented significantly higher morbidity values and allogeneic blood transfusion including the need for massive transfusion as compared to patients receiving solely factor concentrates. The guiding principle is not to initiate massive transfusion with early administration of allogeneic blood products, but to avoid it with an individualized and goal-directed resuscitation strategy.

We have come a long way in treating massive bleeding, but many questions remain.

Conflict of Interest Statement

H.L. has received travel expenses and lecture fees from Bayer Vital, blood donation service west (DRK = German Red Cross), CSL Behring, Ferring, IL Werfen, NovoNordisk. D.F. has received travel expenses and lecture fees from Braun, CSL Behring, Cytosorbents, Instrumental Laboratories, LFB-France, Medscape, Mitsubishi Pharma, Octapharm, Portola, TEM-Innovation.

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