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Changing Paradigms in Hemostatic Resuscitation: Timing, Extent, Economic Impact, and the Role of Factor Concentrates

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Abstract Damage-controlled hemostatic resuscitation has become a standard of care for critically injured patients. Recently completed PROPRR trial demonstrated hemostatic benefits of 1:1:1 Platelets:FFP:RBC transfusion approach, although overall mortality did not decrease. Improved logistics of resuscitation (decreased crystalloid administration), optimization of blood product delivery with adoption of massive transfusion protocols (short time to first unit of plasma transfused), and better early post-MTP management are the factors that contributed to lower than expected mortality in this study. Liquid plasma and pre-thawed Type A fresh frozen plasma (FFP) are safe alternatives to universal donor Type AB FFP and have been adopted by few trauma centers in North America due to shortage of AB FFP supply.

Keywords Damage-controlled resuscitation · Massive transfusion · 1:1:1 Ratio · Liquid plasma · Factor concentrates in trauma · Goal-directed coagulopathy management

Introduction

Damage control resuscitation (DCR) is an approach to managing critically injured and massively hemorrhaging patients, that emerged from military practice. It has been rapidly adopted by civilian trauma centers in North America and Europe. Historically, DCR consisted of two main components: hypotensive resuscitation and hemostatic resuscitation. Hypotensive resuscitation was used to limit crystalloid and artificial colloid administration with their potential for hemodilution, hypothermia, and platelet dysfunction. Hemostatic resuscitation with blood products was aimed at prevention and correction of dilutional coagulopathy. As resuscitation science has advanced with earlier deployment of blood products, hemostatic resuscitation has become the main thrust.

The concept of hemostatic resuscitation became a cornerstone of trauma care in the last decade since the discovery of trauma-induced coagulopathy (TIC). Numerous retrospective studies, initially in military and later in civilian settings, demonstrated a probable survival benefit from administering high ratios of units of fresh frozen plasma (FFP) and platelets to red blood cells (RBCs). This pattern of resuscitation was rapidly adopted by North American and European trauma centers. Academic societies guiding trauma care also advanced this changing practice in newly issued guidelines.

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PROPPR Trial—What Does It Mean for Your Practice

Despite many retrospective studies and a prospective observational study demonstrating benefit from high FFP-to-RBC ratios, no data existed from a randomized prospective clinical trial addressing the optimal ratios of FFP to RBC that might improve hemostasis without increasing the incidence of transfusion-related complications. The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial was designed and executed to answer these questions [1••]. This multicenter clinical trial compared outcomes from the two most common transfusion ratios of PLT, FFP, and RBC, 1:1:1 versus 1:1:2. The key points from this landmark study are important to understand:

Patients in the 1:1:1 ratio group had significantly *decreased mortality due to exsanguination* (difference, −5.4 % [95 % CI, −10.4 % to −0.5 %], P = .03), demonstrating that better hemostasis was indeed achieved with higher FFP ratios.

While overall (all cause) mortality was not different between two groups (Fig. 1), the study was underpowered for this endpoint, which was in part attributable to lower-than-expected mortality in the control group. This fact leads to another very important observation: *both* arms of the study received good-quality resuscitation consistent with DCR principals. Timely initiation of MTP and median time to the first batch of blood product was 8 min. Both groups received minimal crystalloids with median volume of 6 l over first 24 h after admission. At 24 h, cumulative ratios of blood products in both groups were similar, approaching 1:1 ratio. It appears that after termination of MTP and initiation of local standard of care patients in the 1:2 group received more FFP, achieving ratios close to intervention group but at later time (Fig. 2).

Since the wide adoption of early empiric high ratio FFP transfusion for trauma, there has been a concern regarding transfusion related complications (TRALI, sepsis, respiratory failure). Pre-specified analysis of complications in high and low FFP ratio group showed no difference, confirming that a 1:1 ratio appears to have the same safety profile as a 1:2 ratio. This noteworthy observation likely was related to the endothelium preserving properties of FFP and the limited volume of crystalloids in both study groups.

The 1:1:1 study arm received platelets early during resuscitation. According to the study protocol, platelets were transfused first when new batch of blood products was delivered in this group, whereas in the lower ratio group, it was the 13th product administered. Nevertheless, most patients in both groups received platelets. It is not clear if this sequence conferred a benefit, or that the use of platelets was partially responsible for decreased overall mortality in the study comparing to the common practice of administering PRBC and FFP first during MTP.

Logistical and Economical Challenges for Blood Banks in Massive Transfusion Era

Wide adoption of massive transfusion protocols is leading to increased demand for FFP. The American College of Surgeons requires adoption and practical implementation

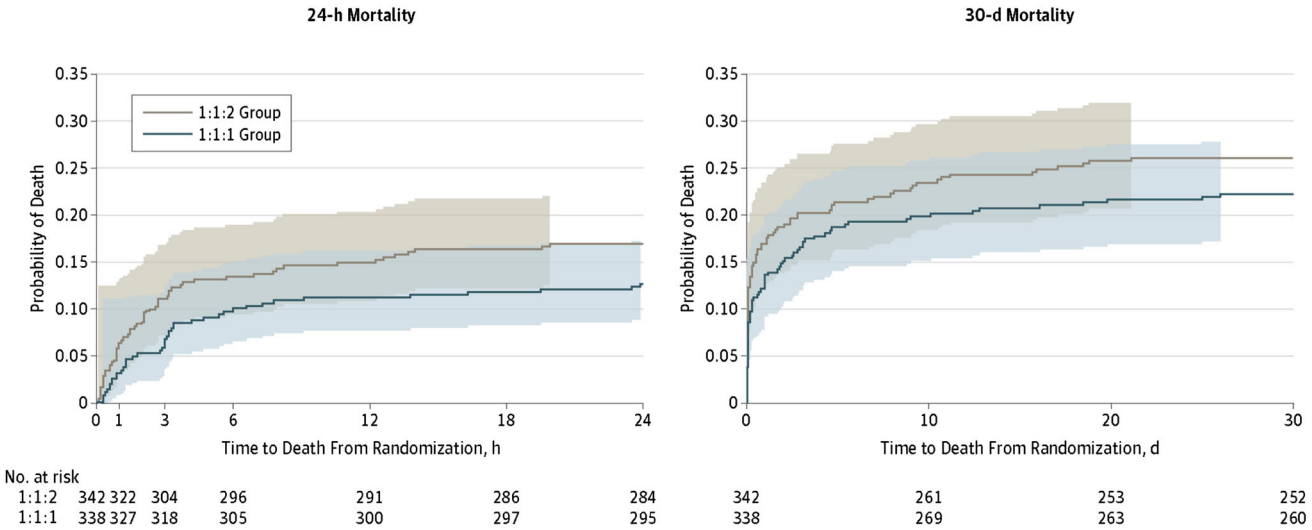

Fig. 1 PROPRR trial: Kaplan–Meier curves for mortality at 24 h and 30 days. The *colored areas* indicate 95 % confidence bands. For 24-h mortality, the Cox proportional hazards regression model, adjusted for site as a random effect, produced a hazard ratio (HR) of 0.72 (95 % CI 0.49–1.07). For 30-day mortality, the Cox proportional hazards regression model, adjusted for site as a random effect, produced an HR of 0.83 (95 % CI 0.61–1.12). From Holcomb et al. [1••], with permission of the American Medical Association. Copyright ©2015 American Medical Association. All rights reserved (Color figure online)

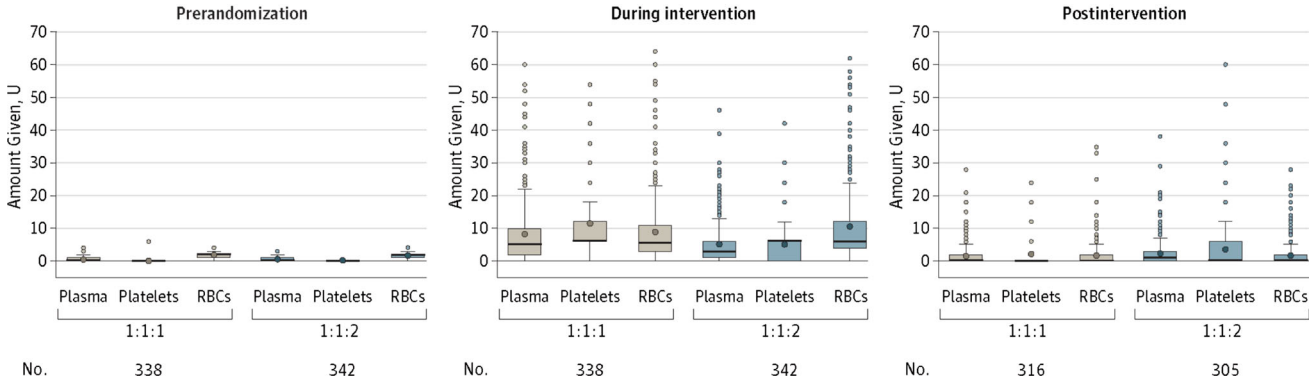

Fig. 2 PROPRR trial: distribution of blood product amounts within period up to 24 h after admission. The *lower* and *upper edges* of the *boxes* are the 25th and 75th percentiles, the whiskers extend to ± 1.5 × the interquartile range, and the points outside are the outliers. The *thick lines inside the box* represent the median, and the *circles* represent the mean. Five or 6 U pools of whole blood-derived platelets were considered equivalent to 1 U of apheresis platelets (e.g., an adult dose of platelets). From Holcomb et al. [1••], with permission of the American Medical Association. Copyright ©2015 American Medical Association. All rights reserved

of a MTP as a fundamental requirement for ACS trauma center accreditation in the United States. MTPs per se have been shown to decrease utilization and wastage of blood products overall [2].

Demand for FFP, especially the universal donor AB FFP, that has been traditionally used in initial stages of hemostatic resuscitation has increased, putting additional strain on already limited pool of donors (AB donors are only 4 % of US population) and is overwhelming the supply capacity with increased utilization of 27 % between 2006 and 2001 [3]. One common MTP requirement is maintenance of a limited supply of pre-thawed universal donor plasma in case of MTP activation, as obtaining an ABO blood type typically takes 25 min and thawing type specific plasma typically takes 25 min more. Thawed FFP units have a limited shelf life of only 5 days and, if not utilized for trauma, have to be withdrawn for general use, which will lead to thawing another batch and repeating this cycle. This can lead to increased utilization and wastage especially in smaller hospitals and less busy trauma centers where the frequency of MTP activations is low. In order to alleviate this shortage and minimize wastage several strategies have been proposed and tested recently [4•].

Liquid (never frozen) AB plasma (LQP) has been proposed as an alternative to thawed AB FFP. It has a shelf life of 26 days, giving an obvious advantage in response time [5•]. Limited in vitro and in vivo experience with this product has been favorable so far [6, 7].

Another alternative is to use a thawed male Group A plasma for the initial stages of the MTP. The safety of this approach has been studied recently [8]. Transfusion reactions due to anti-B antibody were not observed, and several small safety studies suggested that group A FFP is generally a safe option for emergent transfusion [8, 9]. Furthermore, transfusion of Group O apheresis platelets with potentially higher antibody load (anti-A and anti-B antibody) has been accepted as a generally safe practice and became routine.

Pre-hospital Plasma Transfusion: Current Experience and Challenges of Implementation

The pathophysiological basis of coagulopathy and bleeding following injury is believed to be an interplay of hypoperfusion, endothelial injury, and an inflammatory response and starts immediately after the injury, independent of hypothermia, bleeding, and coagulation factor dilution. Within the framework of DCR, major improvements have been achieved in the last decade with regard to delivery time of plasma products to bleeding trauma patients after hospital admission [10, 11•]. The next logical step would be treatment of coagulopathy as early as the pre-hospital setting. While pre-hospital transfusion of plasma and plasma products had been conducted in military campaigns, little evidence of outcome improvement has been shown [12–14].

A recent retrospective study done in Houston compared trauma patient receiving pre-hospital transfusion—RBCs and plasma during aeromedical transport—with those receiving only in-hospital transfusion. The pre-hospital group had some evidence of better outcomes such as improved acid–base status on admission, decreased use of blood over 24 h, and some reduction in 6-h mortality for a subset of the most critically injured. However, no 24-h or 30-day mortality benefit was noted [15].

Distributing plasma to pre-hospital services, whether ground or air platforms, creates logistical difficulties for transfusion services and necessitates a rigorous process of training and quality control [16]; plasma products used in military milieus, such as freeze-dried plasma (FDP), can serve as potential alternative to liquid plasma products [13, 17]. FDP has also been shown to be feasible for use in civilian setting in a pre-hospital environment in Norway [18]. Another approach, which is logistically appealing, is administration of fibrinogen concentrate. There is some

evidence for improved outcomes in combat casualties receiving higher ratios of fibrinogen to RBCs [19]. This approach is supported by some European authors, who have wider experience in using fibrinogen concentrate for trauma patients and is currently undergoing prospective investigation in the Fibrinogen in Trauma Induced Coagulopathy (FIinTIC) study [20•, 21].

There are currently three Department of Defense funded randomized prospective trials underway meant to compare efficacy and utility of air and ground pre-hospital plasma transfusion as compared to standard crystalloid infusion: Prehospital Air Medical Plasma (PAMPer), Control of Major Bleeding after Trauma (COMBAT), and Prehospital use of Plasma for Traumatic Hemorrhage (PUPTH) [22–24]. It is hoped that the studies will provide the necessary evidence to justify the emerging concept of early prehospital plasma transfusion.

Goal-Directed Coagulopathy Management Versus Predetermine Ratios: Theory and Practice

Currently, three main approaches to massive blood transfusion in trauma are described. These are the blind use of a predetermined blood component ratio, a laboratory-directed goal-directed approach, and the use of bedside or laboratory-based viscoelastic testing to direct variation from a standard resuscitation strategy. In fact, most groups start with ratio-based approach and move to a laboratory or viscoelastic guided strategy as soon as data are available.

Following the implementation of DCR, major differences arose between most North American trauma centers and some European centers in the approach to treating massively bleeding trauma patients. The predetermined approach, known as the "1:1:1" approach, has become very popular, mainly in the US, and has several appealing aspects to it. It enables the clinician to treat massive hemorrhage rapidly, while supplying the patient with coagulation factors and much needed volume at the same time, mitigating the need to use crystalloid or colloids. It has been studied extensively in the military and civilian setting, with over 30 studies culminating in the aforementioned randomized PROPRR study, showing, with different degrees of significance and methodological robustness, mortality, and morbidity advantage over giving a lower ratio of plasma and platelets [25, 26].

The Central European goal-directed approach relies heavily on viscoelastic testing which attempts to identify specific deficiencies in the coagulation system and assigns specific coagulation products such as fibrinogen concentrate, prothrombin complex concentrate (PCC), and tranexamic acid. Proponents of this approach site higher potency of PCC over FFP, decreased danger of exposure to allogeneic blood products, and decreased waste of blood products [27•, 28, 29]. A randomized control study comparing the two approaches has never been conducted, and given regulatory obstacles is highly unlikely to be done. However, these two approaches are not mutually exclusive, and indeed many centers are combining the use of the proportional ratio system in the acute massive exsanguination phase, transitioning into a goal directed therapy as soon as the patient's clinical situation allows [30].

Role of Plasma and Fibrinogen Concentrates

Contrary to North American and British teachings, in Europe, management of trauma-induced hemorrhage relies mainly of administration of fibrinogen and 4-factor concentrates and is commonly guided by viscoelastic testing of coagulation (ROTEM® or Rapid TEG®)—a goal-directed approach to coagulation therapy. Proponents of this approach claim that viscoelastic testing can identify specific coagulation deficiencies in the settings of trauma such as decreased fibrinogen or platelet function and hyperfibrinolysis and deliver targeted individualized therapy in form of factor concentrates. Such therapy claims to address three major derangements of coagulation cascade related to trauma: improvement in clot stability (fibrinolysis), clot strength, and thrombin generation. There are a few reports published describing this approach with visually appealing algorithms, but except for a handful of case reports, there are no prospective trials confirming efficacy or superiority of this method. Even if performed, such a study is likely to be underpowered for primary outcome and definition of control group will be challenging. Some experts make an argument not to wait for a "perfect" study but to adapt individualized approach on the basis of existing evidence from trauma, basic science, and other clinical situations where it has been showed to be of benefit (cardiothoracic surgery and liver transplantation) [31••]. In general, if adopted, TEG tends to encourage giving more plasma, more platelets, and more fibrinogen, just like formula-based resuscitation. More importantly, there is emerging evidence that high plasma ratio DCR may not have significant influence on coagulation abnormalities diagnosed by viscoelastic testing during massive transfusion protocols [32]. In this prospective multicenter observational study, viscoelastic markers of coagulation did not change significantly with administration of high ratio of FFP, except cases when, in addition to plasma and platelets, cryoprecipitate was administered boosting fibrinogen levels (in excess of 4 g/l total fibrinogen transfused).

The 2013 European guidelines for management of bleeding and coagulopathy following major trauma strongly recommends using PCC for the emergency reversal of vitamin-K antagonists (VKA) as well as suggest using PCC and fibrinogen concentrate-based goal-directed therapy [33••]. Evidence for the use of PCC in reversal of warfarin induced VKA are present, mainly in neurosurgical trauma [34, 35]. For bleeding trauma patients with unsuspected VKA influence using PCC under viscoelastic testing, goal-directed approach is widely practiced in some European centers, mainly for its thrombin generation capabilities and the theoretical reduction in exposure risk to allogeneic blood products. Evidence for this approach's utility is mainly observational in nature and might not be generalized to different patient population [36•, 37, 38]. A 4-complex concentrate (Kcentra®) was only approved in April 2013 by the US Food and Drug Administration for use in emergency reversal of VKA in the bleeding patient, and most of its use for trauma patients in the US has been reported in connection with head injury, sometimes in addition to FFP [39–41]. There have been some studies conducted in the US on the perioperative use of PCC in patients with elevated INR, both trauma and non-trauma, irrespective of VKA use [42, 43].

Conclusions

Hemostatic resuscitation of injured patients with high fixed ratios of PRBC, FFP, and PLTs is becoming a standard of trauma care in North America. High demand for plasma in initial stages of resuscitation prompted introduction of liquid plasma and group A FFP as safe and viable alternatives to a universal donor AB FFP. Prehospital plasma administration is a next frontier of hemostatic resuscitation with few ongoing studies evaluating efficacy and safety of this approach. Goal-directed hemostatic resuscitation with aid of viscoelastic testing is more valuable in later stages, when hemodynamic stability is achieved. Administration of PCC and fibrinogen concentrate guided by viscoelastic testing has been strongly recommended by European Guidelines on Management of Bleeding and Coagulopathy but has not been adopted in the United States as it is based primarily on small observational studies.

Compliance with Ethics Guidelines

Conflict of Interest Roman Dudaryk, Nadav Sheffy, and John R. Hess declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
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1. •• Holcomb JB, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313:471–82. doi:10.1001/jama.2015.12. *Largest prospective randomised clinical trial of 2 most commonly used transfusion ratios of hemostatic resuscitation. This study demonstrated better controlled of hemostasis and safety of 1:1:1 ratio although did not show survival benefit that reached statistical significance.*
2. Cotton BA, et al. Room for (performance) improvement: provider-related factors associated with poor outcomes in massive transfusion. J Trauma. 2009;67(5):1004–12.
3. Yazer M, Eder AF, Land KJ. How we manage AB plasma inventory in the blood center and transfusion service. Transfusion. 2013;53(8):1627–33.
4. • Dudaryk R, et al. What is new in the blood bank for trauma resuscitation. Curr Opin Anaesthesiol. 2015. 28(2):206–9. *A consise review of blood components used for resuscitation of trauma patients.*
5. • Allen CJ, et al. Liquid plasma use during "super" massive transfusion protocol. J Surg Res. 2015;199(2):622–8. *Prospective observational study examined effects of liquid plasma availability on quality of massive transfusion protocols. This study demostrated that liquid plasma improves target ratios of early plasma administration, especially in the settings of high volume massive transfusion.*
6. Cao Y, et al. Never-frozen liquid plasma blocks endothelial permeability as effectively as thawed fresh frozen plasma. J Trauma Acute Care Surg. 2014;**77**(1):28–33; discussion 33.
7. Norda R, et al. The impact of plasma preparations and their storage time on short-term posttransfusion mortality: a population-based study using the Scandinavian Donation and Transfusion database. J Trauma Acute Care Surg. 2012;72(4):954–60.
8. Zielinski MD, et al. Multicenter comparison of emergency release group A versus AB plasma in blunt-injured trauma patients. Clin Transl Sci. 2015;8(1):43–7.
9. Stubbs JR, et al. How we provide thawed plasma for trauma patients. Transfusion. 2015;55(8):1830–7.
10. Murthi SB, et al. Transfusion medicine in trauma patients: an update. Expert Rev Hematol. 2011;4(5):527–37.
11. • Mehr CR, et al. Balancing risk and benefit: maintenance of a thawed Group A plasma inventory for trauma patients requiring massive transfusion. J Trauma Acute Care Surg. 2013;74(6):1425–31. *Group A plasma can be safely used as an alternative to AB FFP in trauma patients requiring massive transfusion.*
12. Malsby RF 3rd, et al. Prehospital blood product transfusion by U.S. army MEDEVAC during combat operations in Afghanistan: a process improvement initiative. Mil Med. 2013;178(7):785–91.
13. Glassberg E, et al. Freeze-dried plasma at the point of injury: from concept to doctrine. Shock. 2013;40(6):444–50.
14. Morrison JJ, et al. En-route care capability from point of injury impacts mortality after severe wartime injury. Ann Surg. 2013;257(2):330–4.
15. Holcomb JB, et al. Prehospital transfusion of plasma and red blood cells in trauma patients. Prehosp Emerg Care. 2015;19(1):1–9.
16. Hervig T, et al. Prehospital use of plasma: the blood bankers' perspective. Shock. 2014;41(Suppl 1):39–43.

17. Sailliol A, et al. The evolving role of lyophilized plasma in remote damage control resuscitation in the French Armed Forces Health Service. Transfusion. 2013;53(Suppl 1):65s–71s.
18. Sunde GA, et al. Freeze dried plasma and fresh red blood cells for civilian prehospital hemorrhagic shock resuscitation. J Trauma Acute Care Surg. 2015;78(6 Suppl 1):S26–30.
19. Stinger HK, et al. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. J Trauma. 2008;64(2 Suppl): S79–85 **discussion S85**.
20. • Schochl H, Schlimp CJ, Maegele M. Tranexamic acid, fibrinogen concentrate, and prothrombin complex concentrate: data to support prehospital use? Shock. 2014;41(Suppl 1):44–6. *Review of the evidence advocation pre-hospital use of TXA and factor concentrates.*
21. Maegele M, et al. Injectable hemostatic adjuncts in trauma: fibrinogen and the FIinTIC study. J Trauma Acute Care Surg. 2015;78(6 Suppl 1):S76–82.
22. Chapman MP, et al. Combat: initial experience with a randomized clinical trial of plasma-based resuscitation in the field for traumatic hemorrhagic shock. Shock. 2015;44(Suppl 1):63–70.
23. Brown JB, et al. Taking the blood bank to the field: the design and rationale of the Prehospital Air Medical Plasma (PAMPer) trial. Prehosp Emerg Care. 2015;19(3):343–50.
24. Reynolds PS, et al. Prehospital use of plasma in traumatic hemorrhage (the PUPTH trial): study protocol for a randomised controlled trial. Trials. 2015;16(1):321.
25. Ho AM, et al. Prevalence of survivor bias in observational studies on fresh frozen plasma:erythrocyte ratios in trauma requiring massive transfusion. Anesthesiology. 2012;116(3):716–28.
26. Bhangu A, et al. Meta-analysis of plasma to red blood cell ratios and mortality in massive blood transfusions for trauma. Injury. 2013;44(12):1693–9.
27. • Schochl H, Schlimp CJ. Trauma bleeding management: the concept of goal-directed primary care. Anesth Analg. 2014;119(5):1064–73. *Concise description of goal-directed European approach to managment of TIC with factor and fibrinogen concentrates guided by visco-elastic testing.*
28. Görlinger K, et al. Reduction of fresh frozen plasma requirements by perioperative point-of-care coagulation management with early calculated goal-directed therapy. Transfus Med Hemother. 2012;39(2):104–13.
29. Fries D, Innerhofer P, Schobersberger W. Time for changing coagulation management in trauma-related massive bleeding. Curr Opin Anaesthesiol. 2009;22(2):267–74.
30. Johansson PI, et al. How I treat patients with massive hemorrhage. Blood. 2014;124(20):3052–8.
31. •• Spahn DR. TEG(R)- or ROTEM(R)-based individualized goal-directed coagulation algorithms: don't wait–act now! Crit Care. 2014;18(6):637. *Good review of goal-directed coagulation management in trauma using viscoelastic testing.*
32. Khan S, et al. Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage. Intensive Care Med. 2015;41(2):239–47.
33. •• Spahn DR, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care. 2013;17(2):R76. *Updated European Guidelines with emphasis on the use of goal-directed coagulopathy management. This document also recommends to use factor concentrates (PCCs) and fibrinogen concentrate as a primary modality to correct trauma-induced coagulopthy.*
34. Cartmill M, et al. Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergencies. Br J Neurosurg. 2000;14:458–61.
35. Konig S, et al. Coagulopathy and outcome in patients with chronic subdural haematoma. Acta Neurol Scand. 2003;107: 110–6.
36. • Schochl H, et al. Use of rotation thromboelastometry (ROTEM) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. Anaesthesia. 2010;65(2):199–203. *A review of goal-directed approach to the management of trauma induced coagulopathy.*
37. Grassetto A, De Nardin M, Ganzerla B, et al. ROTEM®-guided coagulation factor concentrate therapy in trauma: 2-year experience in Venice, Italy. Crit Care. 2012;16:1–2.
38. Innerhofer P, et al. The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. Injury. 2013;44(2):209–16.
39. Joseph B, et al. Use of prothrombin complex concentrate as an adjunct to fresh frozen plasma shortens time to craniotomy in traumatic brain injury patients. Neurosurgery. 2015;76(5):601–7 **discussion 607**.
40. Yanamadala V, et al. Reversal of warfarin associated coagulopathy with 4-factor prothrombin complex concentrate in traumatic brain injury and intracranial hemorrhage. J Clin Neurosci. 2014;21(11):1881–4.
41. Edavettal M, et al. Prothrombin complex concentrate accelerates international normalized ratio reversal and diminishes the extension of intracranial hemorrhage in geriatric trauma patients. Am Surg. 2014;80(4):372–6.
42. Quick JA, et al. Less is more: low-dose prothrombin complex concentrate effective in acute care surgery patients. Am Surg. 2015;81(6):646–50.
43. Joseph B, et al. Prothrombin complex concentrate versus fresh-frozen plasma for reversal of coagulopathy of trauma: is there a difference? World J Surg. 2014;38(8):1875–81.