Curr Anesthesiol Rep (2016) 6:72–78
DOI 10.1007/s40140-016-0145-x

Damage Control Resuscitation: More Than Just Transfusion Strategies

Catherine Heim[1] · Marc P. Steurer[2] · Karim Brohi[3]

Published online: 2 February 2016

Abstract Trauma hemorrhage continues to carry a high mortality worldwide. The contemporary damage control resuscitation (DCR) paradigm supports actively bleeding trauma patients until hemorrhage control is achieved. The principles of DCR center on early hemorrhage control and limiting ongoing blood loss by adopting strategies limiting fluid administration, reducing blood pressure targets, and maintaining hemostasis through balanced transfusion strategies. Application of DCR strategies has dramatically reduced mortality from trauma hemorrhage and also seems to reduce the incidence and severity of complications such as organ failure and infection. While much of the discussion around DCR focuses on control of coagulopathy and the delivery of a balanced transfusion, the other principles are at least as important. Avoiding clear fluids solutions, especially at the most critical timepoints, require experience and a coordinated, practiced, multidisciplinary approach. The anesthesiologist therefore has a central role to play in the successful delivery of DCR, and perioperative management of fluid administration and the patient's cardiovascular status can make all the difference between a good and bad outcome. In this article, we discuss the principles of DCR with a focus on areas of trauma anesthesiology management.

Keywords Trauma · Hemorrhage · Damage control resuscitation · Trauma anesthesiology · Anesthesia · Hemostatic resuscitation · Blood · Plasma · Crystalloids · Permissive hypotension

Introduction

Hemorrhage remains a leading cause of death in the severely injured. Management of the massively bleeding trauma patient has significantly changed over the last two decades with the emergence of the 'Damage Control' paradigm. The original principle of damage control surgery (DCS) was the 'planned temporary sacrifice of normal anatomy to preserve vital physiology' [1]. This use of abbreviated surgical procedures, focusing on rapid hemostasis rather than anatomic repair, led to improvements in survival for the most severely injured [1]. Damage control resuscitation (DCR) is a more recent development of the DCS concept. DCR describes the extension of the damage control principles beyond surgery, including resuscitation strategies spanning the pre-hospital care through to the operating room and intensive care unit. The principle aim of DCR is to define a systematic approach to major trauma in order to minimize blood loss and ultimately optimize outcome [2]. DCR strategies are applicable to patients who are actively bleeding and focus on

This article is part of the Topical Collection on *Anesthesia for Trauma*.

✉ Catherine Heim
Catherine.Heim@chuv.ch

Marc P. Steurer
marc.steurer@ucsf.edu

Karim Brohi
k.brohi@qmul.ac.uk

[1] Anesthesia Department, Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 46, 1011 Lausanne, Switzerland

[2] Department of Anesthesia and Perioperative Care, San Francisco General Hospital, UCSF, 1001 Potrero Ave, Room 3C-38, San Francisco, CA 94110, USA

[3] Centre for Trauma Sciences, Queen Mary University of London, 2 Newark St, London E1 2AT, UK

maintaining hemostatic competence and central perfusion while hemorrhage control is achieved.

Often, DCR is simplified as DCS in combination with a formula-guided blood transfusion strategy. However, recent efforts in resuscitation focus on minimizing the coagulopathic response to trauma and preservation of endothelial integrity, as well as maintenance of circulating volume [3, 4••]. Anesthesia for the severely injured, bleeding patient plays a central role in achieving good outcomes and requires specific considerations and carefully assessment of hemostatic and physiologic reserves. Goals and limits often differ from those used in elective settings and a close collaborative approach between the surgical, anesthesia and ICU team is required. The aim of this publication is to describe the principles of the anesthetic considerations of the DCR concept. We focus on the principles required to support rapid hemostasis while limiting inflammatory dysfunction and thus improving survival and reducing subsequent complications such as organ failure and infection.

Indication for DCR

The DCR approach applies to patients who are actively bleeding. The aim is to protect hemostatic competence and maintain core perfusion such that physiologic reserves are maintained as far as possible. Patient selection is critical and no single parameter for identification has been determined. The critical decision is whether a patient is actively bleeding or not. Patients who are in hemorrhagic shock but are not actively bleeding (that is they have bled but this has now stopped) require standard resuscitation to restore systemic perfusion. In contrast, it is impossible to normalize systemic perfusion in actively bleeding patients and thus the paradigm changes to a DCR approach.

Patients with signs of severe hemorrhagic shock and active bleeding should be included into the damage control pathway. Active bleeding is best recognized as a poor dynamic response to initial attempts at volume resuscitation. Rapid identification of patients in compensated hemorrhagic shock warrants an experienced clinician, integrating the mechanism of trauma and potential injuries and the hemodynamic response to a fluid challenge. More sensitive measures for volume status as invasive monitoring are difficult to establish during the phase of ongoing bleeding and are not recommended as inferring unnecessary delay to surgical hemostasis. Blood gas values such as lactate and base deficit provide an indication of the depth of shock [5•] but do not in themselves describe whether bleeding is ongoing or not. They may be of use in patients who initially appear well but who are at the limit of hemodynamic compensation for the blood loss. Similarly the presence of coagulopathy implies significant trauma and depth of shock but does not in itself specify that bleeding is still ongoing.

Factors that may further trigger a damage control approach are hypothermia, metabolic acidosis, an inaccessible major vascular injury or the need for time-consuming procedures in a patient with suboptimal response to resuscitation [6••, 7, 8]. In most civilian trauma centers, less than 10 % of the trauma population qualifies for this approach. Patients must be selected carefully as inappropriate application of DCR can lead to significant morbidity, wasting of blood products, and hospital resource use.

The Principles of Damage Control Resuscitation

Together with DCS, the following strategies can be summarized as the three conceptual pillars of DCR:

- Limited fluid administration
- Permissive hypotension
- Hemostatic resuscitation

Limited Fluid Administration

Aggressive fluid resuscitation to restore normal blood pressure and systemic perfusion has been the mainstay of the approach for hemorrhagic shock for a long time. It is now recognized that aggressive crystalloid resuscitation in the actively bleeding patient leads to increased bleeding and dilutional coagulopathy. Crystalloid resuscitation during hemorrhage may temporarily increase blood pressure but counteracts local vasoconstriction and the innate primary hemostasis, causing more hemorrhage and re-bleeding from spontaneously clotted vessels [9, 10]. The term “bloody vicious cycle” had been coined, describing the sequence of hypotension, fluid bolus, re-bleeding, and deeper hypotension. This cyclical crystalloid resuscitation rapidly leads to a severe dilutional coagulopathy. Large volumes of crystalloids may also have adverse immunological and inflammatory effects (Fig. 1). Large shifts in extracellular volume and osmolarity can lead to cellular swelling, impairing enzyme function vital to intracellular signaling mechanisms and ultimately to organ function [11].

Crystalloid-based resuscitation leads to increased concentration of circulating pro-inflammatory cytokines, potentiating the inflammatory mediators [12]. Inducing shedding of the endothelial glycocalyx high volumes of crystalloids may increase reperfusion injury, all of which may subsequently contribute to infectious complications and organ failure. Further, high volumes of crystalloids in hemorrhagic shock have also been associated with cardiac

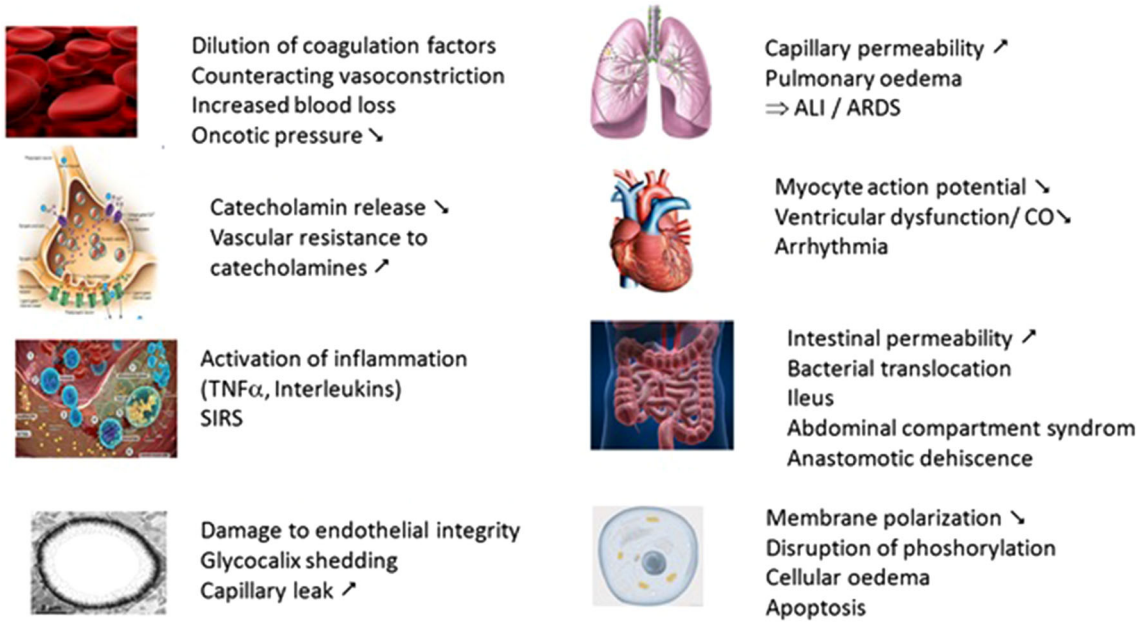

Fig. 1 The consequences of aggressive crystalloid resuscitation

dysfunction, decreased cardiac output, and higher mortality as compared to blood-based resuscitation. Stroke volume may be reduced by 20 % despite adequate filling pressures, if volume restoration was achieved by crystalloid loading [13, 14].

Synthetic colloids such as gelatines, dextran solutions, and hydroxyethyl starches have no benefit over crystalloids and have their own specific complications. In the situation of shock with inflammatory widening of the endothelial cell gap, macromolecular solutions will further leak into the interstitial space, contributing to additional intravascular dehydration through osmosis. Synthetic colloidal solutions induce or enhance established coagulopathy by impairing fibrin polymerization and blockade of the fibrinogen receptor GIIb-IIIa, impairing platelet function [15]. A set of large RCT's in critically ill patients has further shown a correlation of starches with adverse outcome [16–19]. It is therefore recommended that during ongoing surgical bleeding, clear fluids should be limited to minimal amounts until definitive control of hemorrhage has been achieved.

Permissive Hypotension

Reducing blood pressure targets is a key method of reducing fluid administration during active hemorrhage. Permissive hypotension (PH) is a strategy to reduce blood loss by limiting blood pressure temporarily to a vital minimum. In massively bleeding patients, raising blood pressure to normal levels before achieving surgical hemostasis has been shown to increase bleeding by displacing clots formed during the body's attempt of primary hemostasis [9].

The specific blood pressure targets remain unclear and probably vary from patient to patient and at different phases of an individual patient's care. There's a known lack of correlation between the hemodynamics of the macrocirculation and end-organ perfusion, indicating that systolic blood pressure (SBP) is of limited value for the assessment of organ perfusion. The often used cut-off of a SBP of 90 mmHg as marker of shock has been based on expert opinion. In animal models re-bleeding occurred when SBP was raised to above 80–90 mmHg and a significant correlation between the blood pressure at the initiation of resuscitation and the re-bleeding pressure was demonstrated [9, 20]. Similarly there is no hard data supporting that a mean arterial pressure (MAP) of 60 mmHg is required to preserve heart and brain perfusion. Animal studies have also shown that PH aiming at values of 60 % of baseline MAP does not reduce regional organ perfusion as compared to normotensive resuscitation but resulted ultimately in less bleeding [21•]. In the actively hemorrhaging patient, such targets will most likely lead to over-resuscitation, increasing bleeding and ultimately worsening tissue perfusion.

Without high-grade evidence, the European Guidelines for trauma resuscitation recommend aiming at a SBP of 80 mm Hg during ongoing hemorrhage [6••]. However, it should be emphasized that such low pressures should be maintained for the shortest possible time in order to limit further exacerbation of hypoperfusion and the inflammatory response. The importance of early surgical hemostasis

and the need for the DCR concept being applied as a whole has to be underlined.

In the exsanguinating patient, even lower than normal blood pressures are often difficult to achieve. The use of vasopressors for hemodynamic support during resuscitation after injury, however, is controversial. Arterial hypotension is the body's attempt to improve microcirculation by opening maximally the capillary bed. Vasopressors will significantly further decrease perfusion of microcirculation via their alpha-receptor-mediated action [22]. A prospective multicenter study on blunt trauma patients indicated an increased mortality with early vasopressors, regardless of the drug used [23]. Interestingly, research in septic shock failed to improve sublingual microcirculation with increasing doses of Noradrenaline [24]. Hemorrhagic shock should therefore be treated primarily by surgical hemostasis and volume replacement.

Hemostatic Resuscitation

Preserving hemostatic competence is the central tenet of the DCR approach. Coagulopathy is common in trauma patients and has two principle origins—an endogenous coagulopathy due to the injury pathophysiology, and a dilutional coagulopathy due to volume resuscitation (with fluid or red blood cells).

The recognition of the early endogenous coagulation disorder of severely injured patients in hemorrhagic shock has significantly contributed to the change in resuscitation paradigms over the last decade. The presence of this acute traumatic coagulopathy (ATC) has been identified as a surrogate marker of the extent and severity of tissue trauma and hypoperfusion. It correlates with transfusion requirements, incidence of organ failure, and increased mortality [25]. Up to 30 % of injured patients present with impaired coagulation at their arrival to the care facility, even before the onset of hypothermia, acidosis or a dilution of coagulation factors occurs [26, 27]. Trauma itself induces an endogenous coagulopathic state as part of a maladaptive response to tissue destruction and shock. ATC can be seen as an imbalance of the dynamic equilibrium between pro- and anticoagulant factors, platelets, endothelium, and fibrinolysis. Exposed tissue factor, released from the injured subendothelium, fibrin, and activated platelets serve as catalyzer for a massive stimulation of thrombin generation, fibrinogen depletion, and the activation of fibrinolytic processes [26–28]. Thrombin is a key element for conversion of fibrin to fibrinogen and platelet activation. Additionally, it is a potent stimulator of endothelial t-PA, activating fibrinolysis; another key feature of ATC [29]. Hypoperfusion and cellular hypoxia play a crucial role in the pathogenesis of ATC, leading to systemic anticoagulation via activated protein C [29] . Activated protein C plays a key role in the cleavage of factor Va and VIIIa. It activates fibrinolysis by binding PAI-1 and reduces the inhibition of t-PA [30–33]. During resuscitation efforts, ATC is secondarily exacerbated by iatrogenic dilution of coagulation factors and worsening hypothermia and acidosis, combining to the multifactorial trauma induced coagulopathy (TIC) [34].

Early identification of patients with ATC may be of value for the timely initiation of hemostatic resuscitation. Early blood product-based resuscitation, tackling coagulation disorders, has shown to reduce the overall need of blood products, the incidence of posttraumatic multi-organ failure and in return shorten the length of hospital stay and improve patients' survival [35–38]. To date, none of the vast array of published clinical scoring systems has proven reliable in identifying patients at risk of ATC. Standard plasma-based coagulation tests are not useful in the setting of acute trauma-related hemorrhage because of the absence of assessment of the cellular components of coagulation, the interaction with the cellular phospholipid surfaces as well as the lack of identification of fibrinolysis. Further, long turn-around times invalidate these tests as point-of-care assays in the rapidly changing setting of massive bleeding. Point-of-care viscoelastic tests as thromboelastometry (ROTEM® or TEG®) have been useful in early detection of ATC with moderately or severely injured patients exhibiting typical features [39, 40]. In the absence of timely laboratory assessment, in patients with evidence of impaired end-organ perfusion, expressed as base deficit and in combination with extensive tissue trauma, initiation of hemostatic resuscitation may be indicated even before biologic or viscoelastic confirmation of ATC.

Balanced resuscitation with high-dose plasma administration appears to reduce the severity of dilutional coagulopathy and may also have anti-inflammatory properties and the potential to restore the shed glycocalyx [41, 42••]. Most centers therefore currently follow a resuscitation strategy centered on the balanced administration of blood products. There is an ongoing debate about the optimal transfusion ratios of fresh frozen plasma (FFP) and platelets that should be administered alongside packed red blood cells (PRBCS). In the recent multicenter RCT PROPPR, a ratio of 1:1:1 FFP:PLT:PRBC has shown a relative risk reduction for mortality of 25 % as compared to 1:1:2 [43]. This difference, however, did not reach statistical significance and the optimal ratio of products remains unclear. Many recommend switching to a goal directed approach as soon as possible, ideally guided by viscoelastic tests [6••]. Although validated treatment algorithms are lacking, this strategy is supported by a decreased risk of infection and mortality when applying a restrictive, targeted transfusion strategy [44]. A plasma-free resuscitation approach has been described, based on crystalloids in combination with factor concentrates [45]. While the latter might provide

advantages in terms of readiness of products and safety issues, data suggest that plasma-based resuscitation is better at preserving endothelial integrity when compared to the crystalloid-based approach.

Fibrinogen, the final key component in the coagulation cascade acts as ligand for platelet aggregation, ensuring effective clotting and platelet function [46, 47]. During resuscitation of hemorrhagic shock, fibrinogen is the first coagulation factor to critically deplete and low fibrinogen levels are associated with poor outcome [48–50]. Plasma-based volume resuscitation provides approximately 500 mg of fibrinogen per unit FFP and has proven to be insufficient in adequately rising plasmatic fibrinogen levels [49]. Viscoelastometry-guided substitution of fibrinogen during hemostatic resuscitation has shown to increase survival and reduce the need for blood products [36].

Fibrinolysis is a key feature of ATC and is induced by inhibition of plasmin via the thrombin-activated fibrinolysis inhibitor (TAFI) and PAI-1. Hyperfibrinolysis occurs within the first hour after trauma and is associated with a mortality rates as high as 90 % [51, 52, 53••]. The CRASH 2 trial, a large multicenter RCT including over 20,000 patients, showed a significant mortality reduction from bleeding after the administration of tranexamic acid (TXA) in trauma patients at risk of major hemorrhage [54]. Benefits have been maximal if administrated within 1 h after the injury without any increase in thromboembolic events. Early administration of TXA to severely bleeding trauma patients constitutes a key element in many pre-hospital treatment algorithms today.

Hypothermia impairs coagulation mainly by inhibition of platelet adhesion and aggregation, inhibition of thrombin generation, and fibrinogen synthesis [55]. At lower levels, altered enzyme activity will act aggravatingly. Additionally, hypothermia impairs the oxidative killing function of neutrophils via activation of the autonomic nervous system. During DCR aggressive measures should be taken to prevent further heat loss, aiming at a core body temperature above 35 °C. Acidosis is a surrogate marker of the systemic hypoperfusion of the microcirculation. A low pH decreases cardiac contractility, attenuates adrenergic receptor responsiveness, and impairs kidney perfusion. Further, acidosis impairs coagulation by reducing thrombin generation and accelerating fibrinogen degradation, leading ultimately to a reduced availability of fibrinogen. Additionally, acidosis weakens the interplay of coagulation factors with activated platelets. Administration of bicarbonate has not proven to be efficacious to reverse the acidosis-induced coagulation impairments. Restoration of the microcirculatory perfusion appears to be the only valuable strategy [55]. Early and consistent application of DCR principles to patients should reduced the depth and duration of hypothermia and acidosis experienced by bleeding trauma patients.

Tissue oxygen delivery is directly dependant on the hemoglobin concentration. Compensatory mechanisms, including changes in flow in macro- and microcirculation, can compensate for acute anemia. Erythrocytes also contribute to hemostasis via a rheological effect on platelet margination and by supporting thrombin generation [46]. However, the ideal threshold for hemoglobin during and after traumatic hemorrhage to sustain optimal tissue oxygenation and hemostasis is unknown. Rapid administration of high amounts of blood products raises logistic challenges. The implementation of a major hemorrhage protocol (MHP) is recommended, which allows for a rapid and consistent availability of blood products [6••]. The institution of a MHP has shown to be associated with a reduction of organ failure and improved 30-day-survival after severe trauma.

Post-operative Critical Care

Principles of damage control aim at rapid hemostatic procedures of as short as possible duration, allowing for bringing patients early to the less aggressing and more controlled environment of ICU. Therefore, patients in the damage control pathway are expected to arrive in the ICU in a critical and under-resuscitated state. The goal of the initial treatment in ICU is to reverse the sequela inherent to damage control principles. Rapid restoration of optimal organ oxygen delivery by normalization of microcirculation, correction of coagulopathy, and rewarming are key for optimal outcome. Speed of lactate clearance is a validated marker of outcome in this stage [56].

Early and optimal flow of information about the situation and specific needs between the surgical, anesthetic and ICU teams is key for the optimal follow-up management. Therefore, trauma resuscitation requires prolonged collaboration in a multidisciplinary resuscitation strategy, starting in the pre-hospital setting and continuing through emergency departments and operating theaters to the ICU.

Conclusion

For the actively bleeding injured patient, the primary goal is the early control of hemorrhage. The conduct of anesthesia and resuscitation is central to the maintenance of hemostatic competence and therefore the ability to achieve hemorrhage control. DCR provides a framework to support central circulation and coagulation during this critical phase. The delivery of the principles of limited fluid administration, PH, and hemostatic resuscitation are

challenging and require an experienced and practiced team working to agreed procedures and guidelines. The principles and practice of DCR continue to evolve as we improve our understanding of the pathophysiology of the bleeding trauma patient.

Compliance with Ethics Guidelines

Conflict of Interest Catherine Heim, Marc P. Steurer, and Karim Brohi 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
- •• Of major importance

1. Rotondo MF, Schwab CW, McGonigal MD, et al. 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. J Trauma. 1993;35:375–82 **discussion 82-3**.
2. Hodgetts TJ, Mahoney PF, Kirkman E. Damage control resuscitation. J R Army Med Corps. 2007;153:299–300.
3. Pierce A, Pittet JF. Inflammatory response to trauma: implications for coagulation and resuscitation. Curr Opin Anaesthesiol. 2014;27:246–52.
4. •• Peng Z, Pati S, Potter D, et al. Fresh frozen plasma lessens pulmonary endothelial inflammation and hyperpermeability after hemorrhagic shock and is associated with loss of syndecan 1. Shock 2013;40:195–202. *Promising results in animal study comparing plasma based resuscitation to crystalloid resuscitation of hemorrhagic shock. FFP inhibits endothelial cell hyperpermeability and inflammation as compared to in an animal model.*
5. • Mutschler M, Nienaber U, Brockamp T, et al. Renaissance of base deficit for the initial assessment of trauma patients: a base deficit-based classification for hypovolemic shock developed on data from 16,305 patients derived from the TraumaRegister DGU(R). Critical Care 2013;17:R42. *Retrospective, registry-based study underlining the value of early blood gases for decision –making in trauma patients.*
6. •• Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Critical Care 2013;17:R76. *Comprehensive overview of recommendations and their rationales for interventions in the early management of bleeding trauma patients.*
7. Shapiro MB, Jenkins DH, Schwab CW, Rotondo MF. Damage control: collective review. J Trauma. 2000;49:969–78.
8. Asensio JA, McDuffie L, Petrone P, et al. Reliable variables in the exsanguinated patient which indicate damage control and predict outcome. Am J Surg. 2001;182:743–51.
9. Sondeen JL, Coppes VG, Holcomb JB. Blood pressure at which rebleeding occurs after resuscitation in swine with aortic injury. J Trauma. 2003;54:S110–7.
10. Smail N, Wang P, Cioffi WG, Bland KI, Chaudry IH. Resuscitation after uncontrolled venous hemorrhage: does increased resuscitation volume improve regional perfusion? J Trauma. 1998;44:701–8.
11. Lang F, Busch GL, Ritter M, et al. Functional significance of cell volume regulatory mechanisms. Physiol Rev. 1998;78:247–306.
12. Powers KA, Zurawska J, Szaszi K, Khadaroo RG, Kapus A, Rotstein OD. Hypertonic resuscitation of hemorrhagic shock prevents alveolar macrophage activation by preventing systemic oxidative stress due to gut ischemia/reperfusion. Surgery. 2005;137:66–74.
13. Gibson JB, Maxwell RA, Schweitzer JB, Fabian TC, Proctor KG. Resuscitation from severe hemorrhagic shock after traumatic brain injury using saline, shed blood, or a blood substitute. Shock. 2002;17:234–44.
14. Conahan ST, Dupre A, Giaimo ME, Fowler CA, Torres CS, Miller HI. Resuscitation fluid composition and myocardial performance during burn shock. Circ Shock. 1987;23:37–49.
15. Sorensen B, Fries D. Emerging treatment strategies for trauma-induced coagulopathy. Br J Surg. 2012;99(Suppl 1):40–50.
16. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA. 2013;309:678–88.
17. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124–34.
18. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–11.
19. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9 % NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Crit Care. 2012;16:R94.
20. Kowalenko T, Stern S, Dronen S, Wang X. Improved outcome with hypotensive resuscitation of uncontrolled hemorrhagic shock in a swine model. J Trauma. 1992;33:349–53 **discussion 61-2**.
21. • Schmidt BM, Rezende-Neto JB, Andrade MV, et al. Permissive hypotension does not reduce regional organ perfusion compared to normotensive resuscitation: animal study with fluorescent microspheres. World J Emerg Surg 2012;7(Suppl 1):S9. *Permissive hypotension during resuscitation of hemorrhagic shock was associated with less bleeding and equivalent organ perfusion as compared to normotensive resuscitation.*
22. Taylor AE, Moore TM. Capillary fluid exchange. Am J Physiol. 1999;277:S203–10.
23. Sperry JL, Minei JP, Frankel HL, et al. Early use of vasopressors after injury: caution before constriction. J Trauma. 2008;64:9–14.
24. Dubin A, Pozo MO, Casabella CA, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. Crit Care. 2009;13:R92.
25. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma. 2003;54:1127–30.
26. Maegele M, Lefering R, Yucel N, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury. 2007;38:298–304.
27. Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma. 2008;65:748–54.
28. Brohi K, Cohen MJ, Ganter MT, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma. 2008;64:1211–7 **discussion 7**.
29. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg. 2007;245:812–8.

30. Jansen JO, Scarpelini S, Pinto R, Tien HC, Callum J, Rizoli SB. Hypoperfusion in severely injured trauma patients is associated with reduced coagulation factor activity. J Trauma. 2011;71: S435–40.
31. Cohen MJ, Call M, Nelson M, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. Ann Surg. 2012;255:379–85.
32. Davenport R, Brohi K. Fibrinogen depletion in trauma: early, easy to estimate and central to trauma-induced coagulopathy. Crit Care. 2013;17:190.
33. Frith D, Brohi K. The pathophysiology of trauma-induced coagulopathy. Curr Opin Crit Care. 2012;18:631–6.
34. Nienaber U, Innerhofer P, Westermann I, et al. The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. Injury. 2011;42:697–701.
35. Schochl H, Nienaber U, Maegele M, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care. 2011;15:R83.
36. Riskin DJ, Tsai TC, Riskin L, et al. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. J Am Coll Surg. 2009;209:198–205.
37. Johansson PI, Sorensen AM, Larsen CF, et al. Low hemorrhage-related mortality in trauma patients in a Level I trauma center employing transfusion packages and early thromboelastography-directed hemostatic resuscitation with plasma and platelets. Transfusion. 2013;53:3088–99.
38. Rugeri L, Levrat A, David JS, et al. Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. J Thromb Haemost. 2007;5:289–95.
39. Davenport R, Manson J, De'Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med. 2011;39:2652–8.
40. Innerhofer P, Westermann I, Tauber H, 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;44:209–16.
41. Haywood-Watson RJ, Holcomb JB, Gonzalez EA, et al. Modulation of syndecan-1 shedding after hemorrhagic shock and resuscitation. PLoS One. 2011;6:e23530.
42. •• Holcomb JB, Tilley BC, Baraniuk S, 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. *First large RCT to compare transfusion ratios in trauma patients. 1:1:1 showed a relative mortality risk reduction of 25 % without however reaching statistical significance.*
43. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2012;4:CD002042.
44. Peyrou V, Lormeau JC, Herault JP, Gaich C, Pfliegger AM, Herbert JM. Contribution of erythrocytes to thrombin generation in whole blood. Thromb Haemost. 1999;81:400–6.
45. Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. Anesth Analg. 2011;112:1289–95.
46. Furie B, Furie BC. Mechanisms of thrombus formation. N Engl J Med. 2008;359:938–49.
47. Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg. 1995;81:360–5.
48. 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.
49. Hagemo JS, Stanworth S, Juffermans NP, et al. Prevalence, predictors and outcome of hypofibrinogenaemia in trauma: a multicentre observational study. Crit Care. 2014;18:R52.
50. Kashuk JL, Moore EE, Sawyer M, et al. Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. Ann Surg. 2010;252:434–42.
51. Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. J Thromb Haemost. 2013;11:307–14.
52. Schochl H, Frietsch T, Pavelka M, Jambor C. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thromboelastometry. J Trauma. 2009;67:125–31.
53. •• Collaborators C-T, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376:23–32. *RCT with over 20,000 patients showing significant mortality reduction from bleeding after early antifibrinolytic therapy without increase in thromboembolic events.*
54. Martini WZ. Coagulopathy by hypothermia and acidosis: mechanisms of thrombin generation and fibrinogen availability. J Trauma. 2009;67:202–8 **discussion 8-9**.
55. Meiler SE. Long-term outcome after anesthesia and surgery: remarks on the biology of a newly emerging principle in perioperative care. Anesthesiol Clin. 2006;24:255–78.
56. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. J Trauma. 1993;35:584–8 **discussion 8-9**.