Resuscitation for Hypovolemic Shock

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KEYWORDS

• Hemorrhagic shock • Trauma • Coagulopathy • Damage control resuscitation
• Massive transfusion • Visoelastic hemostatic assays

KEY POINTS

- Massive hemorrhage in trauma causes inadequate tissue perfusion and coagulopathy.
- Early transfusion with balanced ratios of blood products results in improved coagulation profiles, less product and transfusions improved outcomes in trauma patients requiring massive transfusion.
- Damage control resuscitation for patients in hemorrhagic shock results in decreased morbidity and improved survival.
- Monitoring coagulation and basing resuscitation on visoelastic hemostatic assays results in decreased transfusions and improved survival.

INTRODUCTION: HISTORY OF HEMORRHAGIC SHOCK RESUSCITATION

The term "shock" originates from "choc," which was coined by French surgeon Henri François Le Dran in the eighteenth century to describe the destructive impact of gunshot.[1] It subsequently evolved to signify the suddenly worsening condition that can ensue after major trauma. In modern medical literature, shock denotes a lack of end-organ perfusion, which can result from multiple etiologies, but hemorrhage is the cause of acute hypovolemic shock resulting from nonburn trauma.

The first recorded human blood transfusion occurred in 1819,[2] but its use did not become common until almost 100 years later when the discovery of blood types[3] and development of techniques to crossmatch blood[4] allowed for widespread use. Crystalloid became the standard resuscitation fluid used for hemorrhagic shock in the nineteenth and early twentieth centuries[5–7] because of its availability and safety. However, with the high volume of severely injured combatants encountered during

Disclosure Statement: Dr B.A. Cotton has served as a consultant for Haemonetics Corporation, Braintree, MA, makers of TEG thromboelastogram. Dr K.J. Kalkwarf has no disclosures or conflicts.

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Surg Clin N Am 97 (2017) 1307–1321
http://dx.doi.org/10.1016/j.suc.2017.07.011
0039-6109/17/Published by Elsevier Inc.

World War I (WWI), Allied physicians soon that realized crystalloid transfusions resulted in "unsatisfactory" results because of dilution.[8] They preferred using limited whole-blood transfusions to maintain a low blood pressure and rewarming the patient.[9] This became the standard of care for resuscitation for the last 8 months of the Great War.[10] WWII physicians described similar practices of giving enough whole blood to achieve a systolic blood pressure of 85 mm Hg, along with appropriate skin color and warmth, while working to quickly stop bleeding.[11,12] They also used transfusions of recently developed reconstituted dried plasma to maintain blood pressure while preparing whole blood.[13]

By the time of the Vietnam War, there was a renewed interest in crystalloid administration based on subsequently refuted basic science[14,15] and animal models[16–19] of hemorrhage shock that showed improved survival from infusing Ringer lactate (LR) before whole-blood transfusion. As a result, trauma patients began receiving increasing quantities of crystalloid. Simultaneously, new blood fractionation techniques were being developed that allowed for whole blood to be separated into units of red blood cells (RBCs), plasma, and platelets. The ability to treat multiple patients with one unit of whole blood and the risk of hepatitis[20,21] associated with plasma at that time prompted medical leaders and groups[22,23] to advocate for specific component blood therapy for all transfusions despite no rigorous studies demonstrating the effects of such therapy in massively bleeding patients.[24,25] Although some studies performed at that time suggested "noninferiority in elective surgical cases," not a single study showed hemostatic potential in bleeding patients. Blood bankers demonstrated that they could administer component therapy safely, not necessarily that they should.

Trends away from whole-blood transfusions and toward large-volume crystalloid and RBC resuscitation continued throughout the last three decades of the twentieth century as a result of studies that said LR and more than six units of RBCs could be used without causing coagulopathy,[26] and others saying it was not important to augment blood transfusions with plasma[27,28] or platelets[29] unless there was clinical or laboratory coagulopathy. Another study declaring that it was safe to administer 2 L of crystalloid while waiting for blood[30] was widely propagated when it was adopted by the Advanced Trauma Life Support course.[31] Often forgotten is that these studies were conducted in patients receiving whole blood rather than RBCs and LR, as had become the standard practice in some busy trauma centers as early as the mid-1970s.[32] Concerns about human immunodeficiency virus transmission[33,34] and goals of therapy targeting "supranormal" resuscitation[35–40] led to continued propagation of transfusing large volumes of only crystalloid and RBCs during the 1980s and 1990s despite new tests making blood transfusions safe and large multicenter trails that showed no survival advantage to supranormal resuscitation.[41,42]

When examined critically, large-volume transfusion strategies resulted in increased morbidity including decreased intestinal perfusion along with increased abdominal compartment syndrome, cardiopulmonary dysfunction, multiple organ dysfunction, and death.[43–45] At the same time, coagulopathy was being identified in severely injured patients, independent of resuscitation,[46–48] and was found to be associated with increased mortality.[47,49,50] As a result, military surgeons returned to resuscitation techniques attempting to replicate the whole blood used in previous wars by including high ratios of plasma and platelets to RBCs. Results from data collected during conflicts in Afghanistan and Iraq showed that patients who received high ratios of plasma to RBCs had improved survival compared with those who received lower ratios.[51] As a result, the military developed damage control resuscitation (DCR) to reduce blood loss and coagulopathy. DCR is focused on limiting crystalloids, delivering whole blood or

high ratios of plasma and platelets, and maintaining permissive hypotension (Fig. 1). Massive transfusion (MT) protocols (MTP) were developed to achieve these goals of DCR and, in some instances, have been shown to improve survival independent of ratios. Finally, experts have recommended avoiding hypothermia and rapidly controlling hemorrhage with surgery and appropriate hemostatic adjuncts.[52]

DAMAGE CONTROL RESUSCITATION

Limit Crystalloid

Of all the three tenets of DCR, some trauma surgeons argue that the reduction in crystalloids over the last decade has had the greatest impact of improving survival. Despite decades of liberal use treating trauma patients, it is now known that infusing large volumes of crystalloid as a replacement for lost blood worsens the "vicious cycle of coagulopathy" resulting from hypoxia, acidosis, and hypothermia that was originally described 35 years ago.[32,53] Intravenous fluids are known to dilute clotting factors,[54] cool patients,[55] and create acidosis.[56] They also cause edema[57,58] and end-organ dysfunction[59] by disrupting cellular mechanisms and causing inflammation. This results in several complications including cardiac,[44] respiratory,[53] gastrointestinal,[60] and immune dysfunction; decreased wound healing[45]; increased anastomotic leak[44,61]; abdominal compartment syndrome[43,62]; open abdomens[53,63]; hyperfibrinolysis[64]; and mortality.[44,53,65] Limiting crystalloid also results in fewer overall blood transfusions for those with life-threatening injuries.[66–68]

Permissive Hypotension

The origins of the second tenet reach back to WWI and WWII, where physicians described increased blood loss and rebleeding when normal blood pressure is achieved before hemorrhage control.[9,11] The protective effect of hypotension was confirmed in animal models that showed decreased blood loss and improved mortality with limited resuscitation.[24,69–72] A study in swine demonstrated that rebleeding occurs at an average systolic blood pressure of 94 mm Hg and a mean arterial pressure of 64 mm Hg.[73] Randomized controlled trials confirmed the improvement in mortality from delaying resuscitation to a normal blood pressure until after operative control of

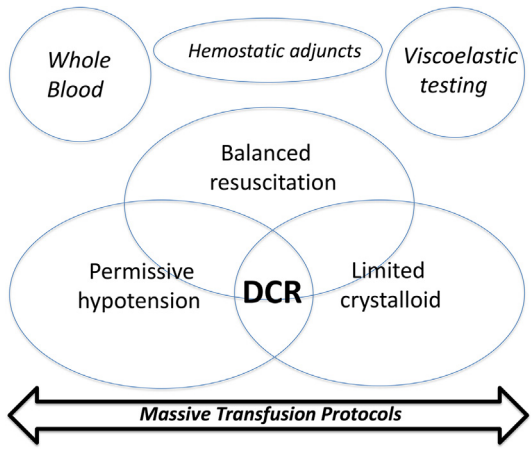


Fig. 1. The three tenets of DCR, brought together by massive transfusion protocols, and supported by several adjuncts.

bleeding[74] in penetrating[75] and blunt trauma patients.[76] A study in the 1990s from Houston randomized to receive prehospital fluid resuscitation (crystalloids) versus none in penetrating torso patients presenting with hypotension (blood pressure $\leq$90 mm Hg).[74] Fluid resuscitation in the "no fluids" arm was withheld until the patient entered the operating room. The patients who received delayed resuscitation had improved survival compared with those who received immediate fluid resuscitation.

Balanced (1:1:1) Resuscitation

The third and final tenet of DCR is the one that has been the most studied and most noted. The initial call to arms for DCR strongly advocated for a ratio of blood products that approximated whole blood (1:1:1).[52] Following publication of the initial military experience describing improved survival for those receiving higher ratios of plasma to RBCs,[53] the findings were replicated in the military experience[77] and multiple retrospective trials in civilians.[49,78–81] of those receiving a ratio or platelets: plasma/RBC (1:1:1). These studies included patients injured by blunt[82] and penetrating[83] mechanisms. The improvement in outcomes from plasma transfusions is attributed to decreasing inflammation, edema, and vascular permeability by repairing tight junctions and the glycocalyx of the vascular endothelium,[84,85] in addition to improving platelet function and clot formation.[86] Plasma also decreases blood hypercoagulability by modulating thrombin generation.[87] A limiting factor in fresh frozen plasma (FFP) administration has traditionally been the 45 minutes required to thaw it before transfusion. Prethawed[88] or liquid plasma[89] can be used to decrease this time[90,91] and 69% of level I and II American College of Surgeons Trauma Quality Improvement Program trauma centers now have plasma immediately available for MTP activations.[92] This has been shown to allow for earlier transfusions, balanced resuscitation, decreased overall blood product transfusions, and improved mortality.[90,93] Similar to higher ratios of transfused plasma, multiple studies have demonstrated improved survival for patients receiving balanced ratios of platelets.[94–99] Platelet inhibition and dysfunction is common after brain injury[100] and minor trauma.[101] It is associated with increased morbidity and mortality[102] because platelets improve wound healing, vascular integrity, and immune response.[98]

With the accumulation of trials demonstrating improved outcomes with balanced resuscitation, these practices quickly spread to civilian trauma practices throughout the United States, with MTP using a 1:1:1 ratio of plasma/platelets/RBCs blossoming from just a few institutions a decade ago[103] to more than 85% of major trauma centers today.[104] Retrospective reviews from trauma centers that implemented DCR showed an almost 50% reduction in crystalloid use at one center,[105] whereas another showed significantly less use of crystalloid and all blood components.[53] DRC is also associated with decreased morbidity from abdominal compartment syndrome,[63,105] infection,[105] and organ failure[106] and reduced mortality[53,105] from hemorrhage.[107]

In 2009, a study examining the time to transfusion of different blood components demonstrated a limitation of retrospective studies. Because of the time required to thaw FFP, the time to first transfusion of FFP (93 minutes) was significantly greater than the time to first RBC transfusion (18 minutes), despite attempting to achieve balanced ratios. As a result, patients who died early received RBCs but were not able to receive the appropriate ratio of FFP and platelets to achieve a balanced transfusion. In contrast, those who survived were eventually able to achieve the goal ratios, thus creating a survival bias.[108] The PROPPR trial was designed as a prospective, randomized, multicenter trial to overcome the selection bias of retrospective trials by evaluating the two most common resuscitation ratios[99] as determined by the

PROMMTT study, which observed transfusion practices in 10 level 1 trauma centers.[99] Although the PROPPR study showed no improvement in 24-hour survival for 1:1:1 versus 1:1:2 (plasma/platelet/RBC), it did show less death from exsanguination at 24 hours for higher ratios of plasma and platelets (9.2% in 1:1:1 group vs 14.6% in 1:1:2 group) and found no difference in complications for the group receiving higher ratios of plasma and platelets, alleviating concerns about their transfusion. The balanced plasma to RBC group also had decreased mortality at 3 hours, which is the median time to hemorrhagic death.[107,109–111]

ADJUNCTS TO DAMAGE CONTROL RESUSCITATION

Whole Blood

Whole blood is the optimal resuscitation fluid for patients who are massively bleeding. After first being successfully used to treat hemorrhagic shock in WWI, military doctors have successfully transfused more than a million units of whole blood during conflicts over the past century and it was preferentially used in civilian trauma until the 1970s when it fell out of favor because of concerns about safety and waste.[4,10,112,113] Recent military conflicts in Iraq and Afghanistan led to a resurgence of whole blood where more than 10,000 units were transfused[34] to the most severely injured patients.[114] Retrospective reviews of those who were transfused with warm fresh whole blood showed that it increased 24-hour and 30-day survival when compared with balanced component therapy.[115,116] These findings are supported by an in vitro study that showed whole blood is more hemostatic[117] and a pilot prospective randomized trial that showed it resulted in less transfusions of RBC, plasma, and platelets when patients with nonsurvivable head injuries were excluded.[118] The reason for the superiority is that a 500-mL unit of fresh whole blood has a hematocrit of 38% to 50%, a total of 150,000 to 400,000 platelets per microliter with full activity,[119] and 100% activity of clotting factors.[112] By comparison, transfusing one unit of plasma, platelets, and RBCs results in 660 mL of fluid with a hematocrit of 29%, a total of 88,000 platelets per microliter, 65% coagulation factor activity with reduced flow characteristics, and increased additives including anticoagulants (**Table 1**).[34,112]

Massive Transfusion Protocols

Based on experiences in WWII, Beecher[11] wrote, “about 2.5% (sic) of those wounded would fall into the group that is in bad enough condition to require special resuscitative care.” That proportion of civilian trauma admissions currently requires more than 10 units of blood within 24 hours of admission,[120] but two to three times that percentage of injured modern military combatants require an MT.[53,95] The mortality for patients

Table 1
Comparison of whole blood unit versus component therapy (reconstituted whole blood)

	Whole Blood (1 U)	1:1:1 Component Therapy (1 U Plasma, 1 U Platelets, 1 U RBC, 1 U Cryoprecipitate)	1:1:2 Component Therapy (1 U Plasma, 1 U Platelets, 2 U RBC, 1 U Cryoprecipitate)
Volume, mL	500	680	900
Hematocrit, %	38–50	29	38
Platelet count	>150,000	80,000	60,000
Coagulation factors, %	100	65	52
Fibrinogen, mg	1000	1000	1000

receiving MT is 20% to 65%,[53,120–121] but instituting MTPs has decreased mortality rates by more than 50%.[53,106,122,123] There are, however, side effects and risks associated with blood transfusions. Therefore, DCR should be reserved for patients who are in hemorrhagic shock or will require an MT.[124] The problem is determining which patients will eventually require an MT and which will not.

During WWII, Beecher[11] used increasing pulse, decreasing blood pressure, and cool skin as indications for a blood transfusion.[11] Based on this and experiences from previous wars,[8] the US military showed that a patient's baseline mental status (assuming no head injury)[125] and a normal radial pulse[126] could be used to reliability predict the need for transfusion and a life-saving intervention.[127] When ultrasound is available, the ABC Score is able to predict the need for an MT based on a scoring system that gives points for penetrating mechanism, positive focused assessment sonography for trauma, systolic blood pressure less than or equal to 90 mm Hg, and an arrival heart rate greater than 120 beats per minute.[128] This scoring system was verified in a rural hospital[129] and in a multicenter trial.[130] It is currently being used in civilian medical transport helicopters to determine if blood products should be given in the prehospital setting.[131] Although it has a tendency to overactivate the MTP, it misses less than 5% of MT or substantial bleeding scenarios.[130]

Viscoelastic Hemostatic Assays

Thrombelastography (TEG) was developed almost 70 years ago[132] to evaluate clot initiation, formation, strength, stability, and breakdown[57,133] in addition to evaluating the patient for hypocoagulable and hypercoagulable states.[134,135] It was not used to guide therapy for trauma patients until half a century later when it was shown to be easier to use, more cost efficient, and a better prognosticator of blood transfusion than conventional coagulation tests (CCT)[132,136] because it is able to evaluate the entire coagulation cascade[133] rather than just plasma.[134] There are two commercially available viscoelastic hemostatic assays (VHA): TEG and rotational thromboelastometry. Both use whole blood and rotation, but TEG rotates a cup with a fixed metal piston suspended in the blood sample, whereas rotational thromboelastometry rotates a metal pin in a blood sample contained in a stationary cup.[137] Rapid TEG (r-TEG) introduces tissue factor as an additional activator[138] and is thus able to provide initial results to guide resuscitation within 5 minutes, an almost 10-fold improvement over CCT and traditional TEG.[139] A series of retrospective trials demonstrate the superiority of VHA to CCT.[135,140,141] More recently, the Denver group noted improved survival for MTP patients that were randomized to resuscitation with VHA versus CCT.[142] In addition, r-TEG-guided resuscitation resulted in decreased transfusions of plasma, platelet, and cryoprecipitate compared with CCT. Both the Denver and Houston groups have published recommended treatment thresholds for r-TEG (**Table 2**).

Hemostatic Adjuncts

In addition to describing clot formation, VHA also provides information on fibrinolysis, or clot breakdown, that is not afforded by CCT. Posttraumatic fibrinolysis is a spectrum with excessive clot breakdown resulting in uncontrolled bleeding to one extreme and shutdown resulting in thrombus formation and subsequent organ dysfunction to the other.[143] Both extremes are associated with increased mortality and are diagnosed based on TEG LY30. Hyperfibrinolysis is a highly lethal state, commonly present on the verge of exsanguination,[143] for which mortality increases significantly with each percentage increase in LY30.[64] It is treated with tranexamic acid, a synthetic antifibrinolytic derivative that blocks plasminogen from binding with fibrin and thus inhibits dissolution of the fibrin clot.[144] Tranexamic acid is administered in the first

Table 2
Summary of recommended thresholds for treatment by r-TEG from two level-1 centers with extensive experience with r-TEG guided resuscitation

r-TEG Parameter	Interpretation	Treatment
ACT $\geq$128 s	Prolonged with factor deficiency, severe hemodilution	Plasma
K-time $\geq$2.5 min	Increased with hypofibrinogenemia $\pm$ platelet dysfunction	Plasma $\pm$ cryoprecipitate
α-angle $\leq$65°	Decreased with hypofibrinogenemia or platelet dysfunction	Cryoprecipitate (or fibrinogen concentrate)
MA $\leq$55 mm	Decreased with platelet dysfunction $\pm$ hypofibrinogenemia	Platelets $\pm$ cryoprecipitate
LY-30 $\geq$3%	Increased with accelerated fibrinolysis	Tranexamic acid or aminocaproic acid

Abbreviations: ACT, activated clotting time; LY-30, lysis 30 min after MA greater than 20 mm; MA, maximal amplitude.

3 hours after injury to patients with LY30 values greater than 3%, the percentage at which mortality increases significantly,[64,143] without increasing mortality.[145] Other hemostatic adjuncts for bleeding patients include prothrombin complex concentrate[146] and recombinant activated factor VII.[147]

Avoiding Hypothermia

In addition to providing the proper resuscitation fluid, it is also important to limit other causes of coagulopathy and blood loss by correcting hypothermia, not causing unnecessarily high blood pressure, and stopping surgical bleeding. Severely injured trauma patients are frequently hypothermic because of exposure and infusion of cold fluids. This worsens coagulopathy and increases mortality[32,148–150] because of decreased fibrinogen synthesis[151] and reduced platelet function.[152] As a result, it is necessary to implement warming techniques, including warmed intravenous fluids and heating blankets, to patients with hypothermia.[58]

SUMMARY

The current practice of hypovolemic shock resuscitation for trauma is similar to the protocols developed while treating thousands of severely injured soldiers during WWI and WWII. Deviation from these practices in the second half of the twentieth century has been rejected based on experiences and trials conducted over the last decade. Continued expansion of DCR into civilian practice will result some in some changes, but it is hoped not to the point that inferior care is provided and clinicians are not forced to relearn the same lessons in the future.

REFERENCES

1. Parrillo, Dellinger. Critical care medicine: principles of diagnosis and management in the adult. 4th edition. Philadelphia: Elsevier Health Sciences, 2013. p. 299.
2. Blundell J. Some account of a case of obstinate vomiting, in which an attempt was made to prolong life by the injection of blood into the veins. Med Chir Trans 1819;10(Pt 2):296–311.

3. Schmidt PJ. Transfusion in America in the eighteenth and nineteenth centuries. N Engl J Med 1968;279(24):1319–20.
4. Spinella PC. Warm fresh whole blood transfusion for severe hemorrhage: US military and potential civilian applications. Crit Care Med 2008;36(7):S340–5.
5. Jennings CE. The intra-venous injection of fluid for severe hæmorrhage. Lancet 1882;120(3081):436–7.
6. Jennings CE. The intra-venous injection of fluid for severe hæmorrhage. Lancet 1883;121(3102):228–9.
7. Pye-Smith RJ. Sheffield public hospital and dispensary: five cases of intravenous injection of saline fluid for hæmorrhage and collapse. Lancet 1892; 139(3582):913–5.
8. Fraser J, Cowell EM. Clinical study of blood pressure in wound conditions. JAMA 1918;70(8):520–35.
9. Cannon WB. Traumatic shock. New York: D. Appleton; 1923.
10. Hess JR, Thomas MJ. Blood use in war and disaster: lessons from the past century. Transfusion 2003;43(11):1622–33.
11. Beecher HK. Preparation of battle casualties for surgery. Ann Surg 1945;121(6): 769–92.
12. Beecher HK. Early care of the seriously wounded man. J Am Med Assoc 1951; 145(4):193–200.
13. Beecher HK. Resuscitation, and anesthesia for wounded men, the management of traumatic shock. Springfield (IL): Charles C. Thomas; 1949.
14. Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. Ann Surg 1961;154:803–10.
15. Shires T, Jackson DE. Postoperative salt tolerance. Arch Surg 1962;84:703–6.
16. Fogelman MJ, Wilson BJ. A different concept of volume replacement in traumatic hypovolemia observations on injured man and animal. Am J Surg 1960; 99(5):694–701.
17. Wolfman EF, Neill SA, Heaps DK, et al. Donor blood and isotonic salt solution. Effect on survival after hemorrhagic shock and operation. Arch Surg 1963;86: 869–73.
18. Shires T, Coln D, Carrico J, et al. Fluid therapy in hemorrhagic shock. Arch Surg 1964;88:688–93.
19. McClelland RN, Shires GT, Baxter CR, et al. Balanced salt solution in the treatment of hemorrhagic shock. JAMA 1967;199:830–4.
20. Davidsohn I. Speculation on future use of blood or blood component therapy. JAMA 1967;202(10):970–2.
21. Chaplin H Jr. Packed red blood cells. N Engl J Med 1969;281(7):364–7.
22. AMA Committee on Transfusion and Transplantation. Something old, something new. JAMA 1970;212(1):147.
23. Westphal RG. Rational alternatives to the use of whole blood. Ann Intern Med 1972;76(6):987–90.
24. Holcomb JB. Fluid resuscitation in modern combat casualty care: lessons learned from Somalia [review]. J Trauma 2003;54(5 Suppl):S46–51.
25. Holcomb JB. Reconstitution: reverse engineering. J Trauma 2011;70(5 Suppl): S65–7.
26. Shackford SR, Virgilio RW, Peters RM. Whole blood versus packed-cell transfusions: a physiologic comparison. Ann Surg 1981;193(3):337–40.
27. Counts RB, Haisch C, Simon TL, et al. Hemostasis in massively transfused trauma patients. Ann Surg 1979;190(1):91–9.

28. Lucas CE, Ledgerwood AM. Clinical significance of altered coagulation tests after massive transfusion for trauma. Am Surg 1981;47(3):125–30.
29. Reed RL 2nd, Ciavarella D, Heimbach DM, et al. Prophylactic platelet administration during massive transfusion. A prospective, randomized, double-blind clinical study. Ann Surg 1986;203:40–8.
30. Carrico CJ, Canizaro PC, Shires GT. Fluid resuscitation following injury: rationale for the use of balanced salt solutions. Crit Care Med 1976;4(2):46–54.
31. American College of Surgeons. Advanced trauma life support (ATLS) student course manual. 9th edition. Chicago: American College of Surgeons; 2012. p. 62–81.
32. Kashuk JL, Moore EE, Millikan JS, et al. Major abdominal vascular trauma-a unified approach. J Trauma Acute Care Surg 1982;22(8):672–9. RJ Lowe in Discussion.
33. Lee L, Moore EE, Hansen KC, et al. It's not your grandfather's field plasma. Surgery 2013;153(6):857–60.
34. Spinella PC, Pidcoke HF, Strandenes G, et al. Whole blood for hemostatic resuscitation of major bleeding. Transfusion 2016;56(S2):S190–202.
35. Bland R, Shoemaker WC, Shabot MM. Physiologic monitoring goals for the critically ill patient. Surg Gynecol Obstet 1978;147(6):833–41.
36. Shoemaker WC, Appel PL, Kram HB. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. Crit Care Med 1988;16(11):1117–20.
37. Fleming A, Bishop M, Shoemaker W, et al. Prospective trial of supranormal values as goals of resuscitation in severe trauma. Arch Surg 1992;127:1175–9 [discussion: 1179–81].
38. Bishop MH, Wo CCJ, Appel PL, et al. Relationship between supranormal circulatory values, time delays, and outcome in severely traumatized patients. Crit Care Med 1993;21:56–60.
39. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993;270(22):2699–707.
40. Bishop MH, Shoemaker WC, Appel PL, et al. Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. J Trauma 1995;38(5):780–7.
41. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 1995;333(16):1025–32.
42. Velmahos GC, Demetriades D, Shoemaker WC, et al. Endpoints of resuscitation of critically injured patients: normal or supranormal?: a prospective randomized trial. Ann Surg 2000;232(3):409–18.
43. Balogh Z, McKinley BA, Cocanour CS, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. Arch Surg 2003;138:637–42.
44. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg 2003;238(5):641.
45. Cotton BA, Guy JS, Morris JA Jr, et al. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock 2006;26:115–21.
46. MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. J Trauma 2003;55(1):39–44.

47. Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. J Trauma 2003; 54:1127–30.
48. Niles SE, McLaughlin DF, Perkins JG, et al. Increased mortality associated with the early coagulopathy of trauma in combat casualties. J Trauma 2008;64(6): 1459–63 [discussion: 1463–5].
49. Gunter OL Jr, Au BK, Isbell JM, et al. Optimizing outcomes in damage control resuscitation: identifying blood product ratios associated with improved survival. J Trauma 2008;65(3):527–34.
50. Pidcoke HF, Aden JK, Mora AG, et al. Ten-year analysis of transfusion in Operation Iraqi Freedom and Operation Enduring Freedom: increased plasma and platelet use correlates with improved survival. J Trauma Acute Care Surg 2012;73(6):S445–52.
51. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 2007;63(4):805–13.
52. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma Acute Care Surg 2007; 62(2):307–10.
53. Cotton BA, Reddy N, Hatch QM, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. Ann Surg 2011;254(4):598–605.
54. Maegele M, Lefering R, Yucel N, et al, AG Polytrauma of the German Trauma Society (DGU). Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury 2007;38:298.
55. Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: its pathophysiology and treatment in the injured patient. World J Surg 2007;31:1055–64.
56. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med 2013;369:1243–51.
57. Feinman M, Cotton BA, Haut ER. Optimal fluid resuscitation in trauma: type, timing, and total. Curr Opin Crit Care 2014;20(4):366–72.
58. Duchesne JC, Kimonis K, Marr AB, et al. Damage control resuscitation in combination with damage control laparotomy: a survival advantage. J Trauma 2010; 69:46–52.
59. Shah SK, Uray KS, Stewart RH, et al. Resuscitation-induced intestinal edema and related dysfunction: state of the science. J Surg Res 2011;166(1):120–30.
60. Lobo DN, Bostock KA, Neal KR, et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomized control trial. Lancet 2002;359:1812–8.
61. Schnüriger B, Inaba K, Wu T, et al. Crystalloids after primary colon resection and anastomosis at initial trauma laparotomy: excessive volumes are associated with anastomotic leakage. J Trauma Acute Care Surg 2011;70(3):603–10.
62. Balogh Z, McKinley BA, Cocanour CS, et al. Secondary abdominal compartment syndrome is an elusive early complication of traumatic shock resuscitation. Am J Surg 2002;184(6):538–43 [discussion: 543–4].
63. Hatch QM, Osterhout LM, Ashraf A, et al. Current use of damage control laparotomy, closure rates, and predictors of early fascial closure at the first takeback. J Trauma 2011;70(6):1429–36.
64. Cotton BA, Harvin JA, Kostousouv V, et al. Hyperfibrinolysis at admission is an uncommon but highly lethal event associated with shock and prehospital fluid administration. J Trauma Acute Care Surg 2012 Aug;73(2):365–70 [discussion: 370].

65. Ley EJ, Clond MA, Srour MK, et al. Emergency department crystalloid resuscitation of 1.5 L or more is associated with increased mortality in elderly and nonelderly trauma patients. J Trauma 2011;70:398–400.
66. Spinella PC, Perkins JG, Grathwohl KW, et al. Fresh whole blood transfusions in coalition military, foreign national, and enemy combatant patients during Operation Iraqi Freedom at a US combat support hospital. World J Surg 2008;32(1): 2–6.
67. Duchesne JC, Heaney J, Guidry C, et al. Diluting the benefits of hemostatic resuscitation: a multi-institutional analysis. J Trauma Acute Care Surg 2013; 75(1):76–82.
68. Shrestha B, Holcomb JB, Camp EA, et al. Damage-control resuscitation increases successful nonoperative management rates and survival after severe blunt liver injury. J Trauma Acute Care Surg 2015;78(2):336–41.
69. Kowalenko T, Stern S, Dronen S, et al. Improved outcome with hypotensive resuscitation of uncontrolled hemorrhagic shock in a swine model. J Trauma Acute Care Surg 1992;33(3):349–53.
70. Mabry RL, Holcomb JB, Baker AM, et al. United States army rangers in Somalia: an analysis of combat casualties on an urban battlefield. J Trauma Acute Care Surg 2000;49(3):515–29.
71. Burris D, Rhee P, Kaufmann C, et al. Controlled resuscitation for uncontrolled hemorrhagic shock. J Trauma 1999;46:216–23.
72. Holmes JF, Sakles JC, Lewis G, et al. Effects of delaying fluid resuscitation on an injury to the systemic arterial vasculature. Acad Emerg Med 2002;9:267–74.
73. Sondeen JL, Coppes VG, Holcomb JB. Blood pressure at which rebleeding occurs after resuscitation in swine with aortic injury. J Trauma 2003;54(5 Suppl): S110–7.
74. Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 1994;331(17):1105–9.
75. Wall MJ Jr, Granchi TS, Liscum K, et al. Delayed versus immediate fluid resuscitation in patients with penetrating trauma: subgroup analysis. J Trauma 1995; 39:173.
76. Schreiber MA, Meier EN, Tisherman SA, et al. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. J Trauma Acute Care Surg 2015;78(4):687.
77. Spinella PC, Perkins JG, Grathwohl KW, et al. Effect of plasma and red blood cell transfusions on survival in patients with combat related traumatic injuries. J Trauma 2008;64(2 Suppl):S69–77 [discussion: S77–8].
78. Duchesne JC, Hunt JP, Wahl G, et al. Review of current blood transfusions strategies in a mature level I trauma center: were we wrong for the last 60 years. J Trauma 2008;65:272–6 [discussion: 276–8].
79. Maegele M, Lefering R, Paffrath T, et al, Working Group on Polytrauma of the German Society of Trauma Surgery (DGU). Red-blood-cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiple injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie. Vox Sang 2008;95(2):112–9.
80. Teixeira PG, Inaba K, Shulman I, et al. Impact of plasma transfusion in massively transfused trauma patients. J Trauma 2009;66(3):693–7.
81. Brown LM, Aro SO, Cohen MJ, et al. A high fresh frozen plasma: packed red blood cell transfusion ratio decreases mortality in all massively transfused trauma

patients regardless of admission international normalized ratio. J Trauma 2011; 71(2 Suppl 3):S358–63.
82. Sperry JL, Ochoa JB, Gunn SR, et al. Inflammation the Host Response to Injury Investigators. An FFP: PRBC transfusion ratio >/=1:1.5 is associated with a lower risk of mortality after massive transfusion. J Trauma 2008;65:986.
83. Rowell SE, Barbosa RR, Diggs BS, et al. Effect of high product ratio massive transfusion on mortality in blunt and penetrating trauma patients. J Trauma 2011;71(2 Suppl 3):S353–7.
84. Pati S, Matijevic N, Doursout MF, et al. Protective effects of fresh frozen plasma on vascular endothelial permeability, coagulation, and resuscitation after hemorrhagic shock are time dependent and diminish between days 0 and 5 after thaw. J Trauma 2010;69(Suppl 1):S55–63.
85. Watson JJ, Pati S, Schreiber MA. Plasma transfusion: history, current realities, and novel improvements. Shock 2016;46(5):468–79.
86. Sillesen M, Johansson PI, Rasmussen LS, et al. Fresh frozen plasma resuscitation attenuates platelet dysfunction compared with normal saline in a large animal model of multisystem trauma. J Trauma Acute Care Surg 2014;76(4): 998–1007.
87. Cardenas JC, Cap AP, Swartz MD, et al. Plasma resuscitation promotes coagulation homeostasis following shock-induced hypercoagulability. Shock 2016; 45(2):166–73.
88. Zielinski MD, Johnson PM, Jenkins D, et al. Emergency use of prethawed Group A plasma in trauma patients. J Trauma Acute Care Surg 2013;74(1):69–75.
89. Matijevic N, Wang YW, Cotton BA, et al. Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma. J Trauma Acute Care Surg 2013;74(1):84–90 [discussion: 90–1].
90. Radwan ZA, Bai Y, Matijevic N, et al. An emergency department thawed plasma protocol for severely injured patients. JAMA Surg 2013;148(2):170–5.
91. Novak DJ, Bai Y, Cooke RK, et al. Making thawed universal donor plasma available rapidly for massively bleeding trauma patients: experience from the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial. Transfusion 2015;55(6):1331–9.
92. Camazine MN, Hemmila MR, Leonard JC, et al. Massive transfusion policies at trauma centers participating in the American College of Surgeons Trauma Quality Improvement Program. J Trauma Acute Care Surg 2015;78(6):S48–53.
93. Holcomb JB, Pati S. Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective. Hematology Am Soc Hematol Educ Program 2013;2013:656–9.
94. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008;248(3):447–58.
95. Perkins JG, Cap AP, Spinella PC, et al. An evaluation of the impact of apheresis platelets used in the setting of massively transfused trauma patients. J Trauma 2009;66:S77–85.
96. Zink KA, Sambasivan CN, Holcomb JB, et al. A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. Am J Surg 2009 May;197(5): 565–70 [discussion: 570].
97. Inaba K, Lustenberger T, Rhee P, et al. The impact of platelet transfusion in massively transfused trauma patients. J Am Coll Surg 2010;211:573–9.

98. Holcomb JB, Zarzabal LA, Michalek JE, et al. Increased platelet:RBC ratios are associated with improved survival after massive transfusion. J Trauma 2011; 71(2 Suppl 3):S318–28.
99. Holcomb JB, del Junco DJ, Fox EE, et al, PROMMTT Study Group. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg 2013;148(2):127–36.
100. Jacoby RC, Owings JT, Holmes J, et al. Platelet activation and function after trauma. J Trauma 2001;51:639–47.
101. Sirajuddin S, Valdez C, DePalma L, et al. Inhibition of platelet function is common following even minor injury. J Trauma Acute Care Surg 2016;81(2):328–32.
102. Wohlauer MV, Moore EE, Thomas S, et al. Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. J Am Coll Surg 2012; 214(5):739–46.
103. Malone DL, Hess JR, Fingerhut A. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. J Trauma 2006;60(6 Suppl):S91–6.
104. Hess JR, Holcomb JB. Resuscitating PROPPRly. Transfusion 2015;55(6): 1362–4.
105. Joseph B, Azim A, Zangbar B, et al. Improving mortality in trauma laparotomy through the evolution of damage control resuscitation: analysis of 1,030 consecutive trauma laparotomies. J Trauma Acute Care Surg 2017;82(2):328–33.
106. Cotton BA, Dossett LA, Au BK, et al. Room for (performance) improvement: provider-related factors associated with poor outcomes in massive transfusion. J Trauma 2009;67:1004–12.
107. Oyeniyi BT, Fox EE, Scerbo M, et al. Trends in 1029 trauma deaths at a level 1 trauma center: Impact of a bleeding control bundle of care. Injury 2017;48(1): 5–12.
108. Snyder CW, Weinberg JA, McGwin G Jr, et al. The relationship of blood product ratio to mortality: survival benefit or survival bias. J Trauma 2009;66(2):358–62.
109. Holcomb JB, Tilley BC, Baraniuk S, et al, PROPPR Study Group. 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(5):471–82.
110. Demetriades D, Kimbrell B, Salim A, et al. Trauma deaths in a mature urban trauma system: is “trimodal” distribution a valid concept? J Am Coll Surg 2005;201(3):343–8.
111. Fox EE, Holcomb JB, Wade CE, et al, PROPPR Study Group. Earlier endpoints are required for hemorrhagic shock trials among severely injured patients. Shock 2017;47(5):567–73.
112. Kauvar DS, Holcomb JB, Norris GC, et al. Fresh whole blood transfusion: a controversial military practice. J Trauma 2006;61(1):181–4.
113. Murdock AD, BersÈus O, Hervig T, et al. Whole blood: the future of traumatic hemorrhagic shock resuscitation. Shock 2014;41:62–9.
114. Holcomb JB. Damage control resuscitation [review]. J Trauma 2007;62(6 Suppl):S36–7.
115. Spinella PC, Perkins JG, Grathwohl KW, et al. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. J Trauma 2009;66(4 Suppl):S69–76.
116. Holcomb JB, Spinella PC. Optimal use of blood in trauma patients. Biologicals 2010;38(1):72–7.

117. Golan M, Modan M, Lavee J, et al. Transfusion of fresh whole blood stored (4 degrees C) for short period fails to improve platelet aggregation on extracellular matrix and clinical hemostasis after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1990;99(2):354–60.
118. Cotton BA, Podbielski J, Camp E, et al, Early Whole Blood Investigators. A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. Ann Surg 2013;258(4):527–32 [discussion: 532–3].
119. Repine TB, Perkins JG, Kauvar DS, et al. The use of fresh whole blood in massive transfusion. J Trauma 2006;60(6 suppl):S59–69.
120. Como JJ, Dutton RP, Scalea TM, et al. Blood transfusion rates in the care of acute trauma. Transfusion 2004;44(6):809–13.
121. Perkins JG, Schreiber MA, Wade CE, et al. Early versus late recombinant factor VIIa in combat trauma patients requiring massive transfusion. J Trauma 2007; 62(5):1095–9.
122. Biffl WL, Smith WR, Moore EE, et al. Evolution of a multidisciplinary clinical pathway for the management of unstable patients with pelvic fractures. Ann Surg 2001;233(6):843–50.
123. 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.
124. Holcomb JB. Traditional transfusion practices are changing. Crit Care 2010; 14(3):162.
125. Meredith W, Rutledge R, Hansen AR, et al. Field triage of trauma patients based upon the ability to follow commands: a study in 29,573 injured patients. J Trauma Acute Care Surg 1995;38(1):129–35.
126. McManus J, Yershov AL, Ludwig D, et al. Radial pulse character relationships to systolic blood pressure and trauma outcomes. Prehosp Emerg Care 2005;9(4): 423–8.
127. Holcomb JB. Manual vital signs reliably predict need for lifesaving interventions in trauma patients. J Trauma 2005;59:821–9.
128. Nunez TC, Voskresensky IV, Dossett LA, et al. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption). J Trauma 2009;66:346.
129. Krumrei NJ, Park MS, Cotton BA, et al. Comparison of massive blood transfusion predictive models in the rural setting. J Trauma Acute Care Surg 2012;72(1): 211–5.
130. Cotton BA, Dosseett LA, Haut EH, et al. Multicenter validation of a simplified score to predict massive transfusion in trauma. J Trauma 2010;69:S33–9.
131. Holcomb JB, Donathan DP, Cotton BA, et al. Prehospital transfusion of plasma and red blood cells in trauma patients. Prehosp Emerg Care 2015;19(1):1–9.
132. Plotkin AJ, Wade CE, Jenkins DH, et al. A reduction in clot formation rate and strength assessed by thrombelastography is indicative of transfusion requirements in patients with penetrating injuries. J Trauma 2008;64(2 Suppl):S64–8.
133. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. Blood Rev 2009;23(6):231–40.
134. Cotton BA, Minei KM, Radwan ZA, et al. Admission rapid thrombelastography predicts development of pulmonary embolism in trauma patients. J Trauma Acute Care Surg 2012;72(6):1470–5.

135. Holcomb JB, Minei KM, Scerbo ML, et al. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. Ann Surg 2012;256(3):476–86.
136. Kaufmann CR, Dwyer KM, Crews J, et al. Usefulness of thrombelastography in assessment of trauma patient coagulation. J Trauma 1997;42:716–22.
137. Cotton BA, Faz G, Hatch QM, et al. Rapid thrombelastography delivers real-time results that predict transfusion within 1 hour of admission. J Trauma 2011;71(2): 407–14 [discussion: 414–7].
138. Kashuk JL, Moore EE, Sawyer M, et al. Postinjury coagulopathy management: goal directed resuscitation via POC thrombelastography. Ann Surg 2010; 251(4):604–14.
139. Johansson PI, Stensballe J, Oliveri R, et al. How I treat patients with massive hemorrhage. Blood 2014;124(20):3052–8.
140. Kashuk JL, Moore EE, Wohlauer M, et al. Initial experiences with point-of-care rapid thrombelastography for management of life-threatening postinjury coagulopathy. Transfusion 2012;52:23.
141. Tapia NM, Chang A, Norman M, et al. TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. J Trauma Acute Care Surg 2013;74(2):378–86.
142. Gonzalez E, Moore EE, Moore HB, et al. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. Ann Surg 2016;263(6):1051–9.
143. Moore EE, Moore HB, Gonzalez E, et al. Rationale for the selective administration of tranexamic acid to inhibit fibrinolysis in the severely injured patient. Transfusion 2016;56(Suppl 2):S110–4.
144. Napolitano LM, Cohen MJ, Cotton BA, et al. Tranexamic acid in trauma: how should we use it? J Trauma Acute Care Surg 2013;74(6):1575–86.
145. CRASH-2 Collaborators, Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011;377: 1096–101.
146. Joseph B, Amini A, Friese RS, et al. Factor IX complex for the correction of traumatic coagulopathy. J Trauma Acute Care Surg 2012;72(4):828–34.
147. Spinella PC, Perkins JG, McLaughlin DF, et al. The effect of recombinant activated factor VII on mortality in combat-related casualties with severe trauma and massive transfusion. J Trauma 2008;64(2):286–93 [discussion: 293–4].
148. Jurkovich GJ, Greiser WB, Luterman A, et al. Hypothermia In trauma victims: an ominous predictor of survival. J Trauma 1987;27(9):1019–24.
149. Ferrara A, MacArthur JD, Wright HK, et al. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. Am J Surg 1990; 160:515–8.
150. Cosgriff NM, Ernest E, Sauaia A, et al. Predicting life-threatening coagulopathy in the massively transfused patient: hypothermia and acidosis revisited. J Trauma 1997;42(5):857–62.
151. Martini WZ, Holcomb JB. Acidosis and coagulopathy: the differential effects on fibrinogen synthesis and breakdown in pigs. Ann Surg 2007;246(5):831–5.
152. Hess JR, Holcomb JB. Transfusion practice in military trauma. Transfus Med 2008;18(3):143–50.