Published in final edited form as:
Hematology Am Soc Hematol Educ Program. 2010 ; 2010: 465–469. doi:10.1182/asheducation-2010.1.465.

Optimal Use of Blood Products in Severely Injured Trauma Patients

John B. Holcomb[1]

[1]Division of Acute Care Surgery and Center for Translational Injury Research, University of Texas Health Science Center, Houston, TX

Abstract

Injury is the leading cause of life years lost in the United States, and uncontrolled hemorrhage is the leading cause of potentially preventable death. Traditionally, these patients have been serially resuscitated with large volumes of crystalloid and/or colloids and red blood cells, followed by smaller amounts of plasma and platelets. Transfusion data coming first from the ongoing war in Iraq and Afghanistan and followed by multiple civilian studies have brought into question this tradition-based practice. Numerous recent retrospective single and multicenter studies have associated improved outcomes with earlier and increased use of plasma and platelets. These data have stimulated significant interest in studying massively transfused trauma patients. Most clinicians have concluded that the optimal timing and quantity of blood products in the treatment of hypothermic, coagulopathic, and acidotic trauma patients are unclear. Although there are strongly held opinions and long-standing traditions in their use, there are little quality data within which to logically guide resuscitation therapy. A multicenter prospective observational study is ongoing, and randomized trials are planned. This review will address the issues raised previously and describe recent trauma patient outcome data utilizing predetermined plasma:platelet:red blood cell transfusion ratios, and possibilities for future transfusion products and research.

Worldwide, injury is responsible for more than 5 million deaths per year. In the United States alone, injury accounts for over 150,000 deaths and over 3 million nonfatal injuries per year.[1] In the United States, traumatic injury is the leading cause of death for patients between the ages of 1 and 40.[2] Because trauma is a disease of young people, it is the leading cause of life years lost in the United States. Timing of intervention is important, because hemorrhagic deaths typically occur very early, usually within the first 6 hours of admission.[3,4] Only 25% of patients admitted to busy trauma centers receive a unit of red blood cells (RBCs), and, of those, only 25% of those are massively transfused (MT) (MT = ≥ 10 units of RBCs in 24 hours). Fortunately, this represents only 2% to 3% of all civilian trauma admissions, yet it is these few patients that have a mortality ranging from 40% up to 70% at leading trauma centers.[5–7] The 25% of patients presenting with severe traumatic injury and who are in shock are usually coagulopathic in the emergency department.[8,9] Shock and coagulopathy on admission have both been associated with massive transfusion and increased mortality. Interestingly, the mechanism of this trauma-induced coagulopathy has not been determined.[10] In summary, these patients are critically injured, at risk of immediate hemorrhagic mortality, occur infrequently, but constitute the largest group of

Correspondence, John B. Holcomb, MD, FACS, Vice Chair and Professor of Surgery, Chief, Division of Acute Care Surgery, Director, Center for Translational Injury Research, Jack H. Mayfield, M.D. Chair in Surgery, University of Texas Health Science Center, 6410 Fannin St., Ste. 1100, Houston, TX 77030; Phone: (713) 500-5493; Fax: (000) 000-0000; John.Holcomb@uth.tmc.edu.

Disclosures

Conflict-of-interest disclosure: The author declares no competing financial interests.
Off-label drug use: None disclosed.

potentially preventable deaths admitted to trauma centers. Reevaluation of long-accepted transfusion concepts, prompted by recent military and civilian data, has resulted in a resurgence of interest in transfusion medicine for injured patients. This recent interest has resulted in challenges to the status quo and lively scientific debate.

Background

Over the last 40 years, transfusion therapy evolved from use of predominately whole blood to largely component therapy. Although whole blood is still used in many developing countries and in military situations, component therapy predominates as the primary transfusion approach, primarily due to concerns for resource utilization and safety.[11,12] Unfortunately, this change occurred without strong evidence documenting at least equivalent clinical outcomes between whole blood and component therapy in MT patients.

We are unaware of any level 1 or level 2 data, focused on patient outcomes, which compare component therapy with whole blood in rapidly bleeding trauma patients. Previous transfusion guidelines were based on expert opinion in euvolemic patients requiring elective surgery and data from the modified whole blood era. Whereas component therapy does convey logistical, financial, and inventory management benefits, it is uncertain if it is clinically superior or even equivalent to whole blood, especially in the MT patients. Recent retrospective data from the ongoing conflict suggests that whole blood is superior to component therapy in the MT trauma patient.[12] Although whole blood is an approved and regulated product (by both the AABB and the US Food and Drug Administration, respectively), it is largely not available in civilian practice; instead, clinicians have moved to a balanced transfusion strategy of increased ratios of plasma:platelets:RBCs, utilizing an approach developed in Iraq called damage control resuscitation (DCR).[13]

How and why resuscitation of severely injured patients evolved from the exclusive use of whole blood to crystalloid and component therapy is an interesting story. Of perhaps greater interest is the rapid return to a balanced resuscitation practice of plasma, platelets, and RBCs (1:1:1) and minimal crystalloid. Resuscitation of trauma patients has been largely developed based on the wartime experiences of military physicians. Use of whole blood, saline, and artificial colloid was common in World War I. Cohn fractionation led to the widespread use of albumin and lyophilized plasma during World War II; and, early in World War II, it was believed that RBCs were not necessary.[14] Colonel Edward Churchill led the effort to reintroduce a balanced resuscitation with whole blood and plasma for optimal resuscitation of seriously injured and shocked combat casualties. In addition to using plasma and whole blood, in both World War I and World War II, hypotensive resuscitation was the norm. In Vietnam, aggressive crystalloid resuscitation became very popular (and became established in civilian practice); unfortunately, a practice wrongly ascribed to the teachings of Carrico and Shires.[15] When one reads their papers carefully, it is clear that they favored a balanced resuscitation, consisting of a slow infusion of limited crystalloid over 45 minutes, whereas whole blood was readied for transfusion. In fact, in 1968, Moore and Shires[16] strongly editorialized against the overzealous administration of crystalloid. Despite this caution, excessive crystalloid became the norm for almost 40 years, contributing to or creating a new set of surgical and critical care complications (acute respiratory distress syndrome [ARDS], multiple organ failure, and abdominal compartment syndrome).[17,18] Finally, in the late 1990s, clinicians started recognizing the deleterious effects of crystalloid and found beneficial effects associated with less infusion of crystalloid.[19–20] These discussions set the stage for a return to a balanced resuscitation, reminiscent of that described by Churchill[14] and Beecher[21] in World War II.

Damage Control Resuscitation

Prompted by new data from combat casualties, an evolution of opinion is occurring in the trauma, emergency medicine, anesthesia, and transfusion medicine communities regarding the optimal resuscitative approach to hemorrhagic shock. Borgman and colleagues[22] first described these efforts in their seminal paper relating improved survival in 252 MT combat casualties receiving close to a 1:1 ratio of fresh frozen plasma (FFP):RBC. In 2007, Holcomb and colleagues[13] called for a balanced strategy, calling it DCR, emphasizing (a) early and increased use of FFP, platelets, and RBC, while minimizing crystalloid use; (b) hypotensive resuscitation strategies; (c) avoiding hypothermia and acidosis and coagulopathy; (d) use of adjuncts like Ca^{2+}, THAM (tris-hydroxymethyl aminomethane), and recombinant activated clotting factor VII (rFVIIa); and (d) early definitive hemorrhage control. Soon after, Holcomb et al[7] described similar FFP:platelet:RBC ratio results in 466 MT civilian trauma patients. Multiple civilian trauma centers examined their own results and found similar results.[23–26] Perkins et al[27] focused on platelet ratios in combat casualties, and they clearly described the survival benefit, resulting in the Army Surgeon General establishing a clinical policy of 1:1:1 (FFP:platelets:RBCs) for combat casualties expected to receive a massive transfusion (platelets are given after 6 units of RBCs, either as 6 units of platelets or a single unit of aphresis platelets). Holcomb and colleagues[28] followed with a similar report in 643 civilian MT patients, showing improved survival with increased use of platelets. In summary, the current US military resuscitation practice is to use a balanced approach, using 1:1:1 as the primary resuscitation fluid for the most seriously injured casualties.[29] Achieving these exact ratios is extremely difficult, and it is unclear what the optimal ratios actually are. Nevertheless, a significant change has occurred in resuscitation practice. In many centers, crystalloids have become a carrier fluid for blood products, rather than a primary means of resuscitation. Lower volume resuscitation or a hypotensive resuscitation strategy, avoiding “popping the clot” with rapid rise in blood pressure prior to definitive hemorrhage control, is widely practiced. Anecdotally, as the early use of plasma and platelets has increased at trauma centers, the use of rFVIIa has gone down. It appears that rFVIIa may have been used to treat an iatrogenic resuscitation injury associated with overzealous crystalloid therapy. The DCR approach is intended to minimize exacerbating the multifactorial trauma-induced coagulopathy by replacing lost blood with plasma and platelet-containing products instead of early and large amounts of crystalloids and RBCs. Although there are no randomized data utilizing DCR, many centers have adopted these concepts, and it is quickly becoming a common resuscitation approach in severely injured patients.

Limited Literature Review

These suggested changes at first glance appear radical. However, on inspection of the literature supporting current practices, one finds generally underwhelming data supporting conventional practice. Until very recently, there have been very few studies in this area and none with large numbers of patients. The majority of consensus recommendations were based on elective surgery or oncology patients, rather than the typical MT trauma patient who presents hypovolemic, hypothermic, coagulopathic, and in shock. Current Advanced Trauma Life Support recommendations are based on a single paper from 1985, without a control group and comprising only 18 patients.[30] The influential paper by Counts et al,[31] published in 1979 and totaling 29 patients, admonished the use of plasma as a resuscitation product, yet utilized modified whole blood, not the RBCs we use today. Unfortunately, the admonishment against FFP transfusion is what was remembered, rather than the blood product that was transfused. The seminal work of Carrico and Shires[15] recommended minimal crystalloid (by today’s standards), while readying the *whole blood* transfusions for the seriously injured patient in shock. If one were to translate their work to the products

available today, their recommendations are very similar to those of DCR. Reed et al[32] have published in 1986 the only randomized controlled trial in MT patients, examining the efficacy of platelets compared with plasma in 33 trauma patients. This small study used modified whole blood; thus, one must be careful about translating their results directly to transfusion therapy today. Because fresh or even whole blood is no longer available at most Western institutions, practitioners have had to adjust to the availability of components only and transfuse plasma, RBCs, and platelets in a 1:1:1 ratio (reconstituted whole blood).

In summary, over the last 25 years, transfusion therapy in severely injured trauma patients was driven by 80 patients from three small, predominately uncontrolled studies, using blood products no longer available. In the years after the transition from whole blood to components, several studies suggested that increased plasma and platelets were required for patients with severe traumatic injury and hemorrhage[33–35] Unfortunately, these studies were not recognized for the important message they conveyed.

Survival Bias

Currently, there are multiple large military and civilian retrospective single and multicenter studies that associate a high ratio of plasma and platelets to RBCs with improved survival in MT trauma patients. Because the majority of these reports are retrospective and subject to bias, particularly survivorship bias, they must be interpreted with caution. Survivorship bias in this situation means that plasma and platelets were available only for those patients who were bleeding slowly enough to receive them and that rapidly bleeding patients died before receiving products. Snyder et al[36] have explored this issue; and, in an important single center study concluded that, after adjustment for survival bias, a high ratio of plasma:RBCs was not independently associated with survival. Most of the recent studies attempt to account for this by excluding those deaths within 30 to 60 minutes of arrival. This important issue will not be resolved with more retrospective studies.

The preponderance of the recent literature indicates patients in severe hemorrhagic shock likely benefit from increased ratios of plasma and platelets to RBCs. Other reports provide an alternative view, recommending a less aggressive approach.[37,38] It is appropriate and expected that data in this area are conflicting, because all of the studies are retrospective and confounded by multiple unmeasured variables. It is also understood that DCR should not be performed in patients who are not in hemorrhagic shock or who are not at high risk of massive transfusion, because the increased plasma and platelets could increase multiple organ failure, without a survival benefit. The AABB has recently performed an evidenced-based review for their plasma guideline project and has concluded that massive transfusion appears to be one situation in which giving increased amounts of plasma prevents death.[39]

Risk Versus Benefits

As the use of plasma and platelet transfusion increases, the risks associated with these products must be clearly understood, and placed within the framework of their potential benefit. Plasma, platelets, and RBC transfusion have been associated with increased risk of allergic reactions, transfusion-associated acute lung injury, transfusion-associated cardiac overload, and ARDS.[40] In patients without hemorrhagic shock, the risk of transfusion outweighs any potential benefit. However, for patients with severe traumatic injury and hemorrhagic shock, the survival benefit with increased plasma and platelet transfusion likely far exceeds the risks associated with their use. The risks associated with increased plasma and platelet use must also be put into perspective with the increased risk of thrombosis, sepsis, organ failure, and death-associated with RBC transfusion (especially aged products), which have been recently reviewed.[41,42] Interestingly, data are emerging that thawed plasma stored for 5 days at 4°C increases endothelial permeability, compared with freshly thawed

plasma.[43] These characteristics of plasma have not been reported previously and suggest that some of the beneficial effects of increased plasma in MT patients may be due to the ability of plasma to normalize injured endothelium by inhibiting endothelial permeability. The clinical consequences of this change in permeability are unknown. Platelet transfusions after 5 days of storage at room temperature may show a similar storage effect. In addition to the ratio questions raised by many authors, the clinical outcomes associated with various storage solutions are unknown. Likewise, the clinical risks associated with current inventory management practices appear real.[41] Unfortunately, there are no prospective studies in trauma patients that evaluated the potential clinical benefit versus the risks associated with transfusion of current blood products.

Ongoing Prospective Studies in Trauma Patients

Many centers have published their retrospective data describing increased plasma and platelet ratios on outcome, but there are no prospective data using modern components. To address this issue, the US Department of Defense has funded a 10-center prospective, observational study of trauma transfusion practices (PROMMTT study [PRospective, Observational, Multi-center Massive Transfusion sTudy]) at 10 major civilian trauma centers.[44] The PROMMTT study will record minute by minute what resuscitation products are transfused in what order, and the patient's complications and outcomes. Whereas the results are not yet known, enrollment is on target for 1200 transfused patients and 300 MT trauma patients in 12 months, proving that these studies are feasible in a reasonable period of time. Data collection ended in September 2010. These data will provide the basis for the first ever multicenter randomized study in trauma patients, finally establishing the scientific basis for subsequent transfusion studies. For the first time, we will have level 1 data guiding transfusion therapy in severely injured and massively injured trauma patients.

Future Products/Transfusion Concepts

The results of using increased plasma:platelets:RBC ratios in severely injured patients are hard to ignore. They suggest that a balanced resuscitation practice (DCR) is rapidly becoming widespread, without supporting level 1 data. This early and increased use of plasma and platelets does place significant stress on the blood banking system. In a logistically challenged system or remote/austere military environment, the supply chain of RBCs, frozen plasma, cryoprecipitate, and freshly drawn platelets will almost assuredly and understandably fail. Although one very viable option in many parts of the world is the institution of the walking blood bank and fresh whole blood transfusion, the military research community is considering reverse engineering of fresh whole blood. The monetary and logistical benefits of small, lightweight, ambient temperature storage, packages of dried plasma, platelets, fibrinogen, and RBCs—perhaps supplemented by prothrombin complex concentrate or other recombinant proteins—are obvious and significant. Immediate availability of disease-free products—with no requirement for biweekly transcontinental shipment on dry ice, freezers in the combat zone, in theater blood draws and component processing, and cold-monitored storage—is enormous. Similar benefits are expected in both large and small civilian hospitals, essentially providing decentralized (point-of-care) blood products. All of these products are either available, under various stages of development, and in animal or human testing stages.

Conventionally, transfusion of blood products is limited to the hospital setting. Rare systems have routinely placed RBCs on prehospital vehicles. However, with successful development of dried blood products, prehospital use becomes possible. With appropriate randomized studies documenting clinical benefit, utilizing these new products as the primary resuscitation fluid for seriously injured combat casualties is of great interest. Because the

number of yearly civilian deaths in the United States far exceeds that of the military (×300), this area of research is of intense interest in the civilian trauma community. Furthermore, it is intriguing to consider the possibility of only transfusing the exact product required, rather than the current practice of "throwing the kitchen sink" (1:1:1) at every massively bleeding patient. This goal-directed approach will depend on rapid availability of rugged, accurate, and validated coagulation tests that represent the entire spectrum of coagulation abnormalities associated with trauma patients. Much remains to be learned, not the least of which is how these products interact with each other, and if realistic animal models and then patients will benefit or at least do as well when compared with the current liquid products already in widespread use. The scientific and regulatory issues are not insignificant for this development pathway; however, many military and civilian clinicians and basic scientists consider this concept to be one of the most exciting and potentially fruitful areas of trauma research.

Conclusions

Trauma is the most common cause of death for patients age 1 to 40, and death from hemorrhagic shock is the most common cause of preventable death within 6 hours of admission. Data on which previous transfusion recommendations were based were relatively weak. Current data indicate that the early identification of coagulopathy and its treatment with RBCs, plasma, and platelets in a 1:1:1 unit ratio achieved with the use of fresh RBCs, thawed plasma, and platelets; limited use of crystalloids; and accompanied with rapid hemorrhage control may improve survival in the uncommon patient who presents with severe traumatic injury and life-threatening bleeding. These principles of DCR are routinely utilized at the author's institution and should only be applied to patients with life-threatening bleeding with hemorrhagic shock and should not be overused. Accurate predictive models that can be performed on admission may be able to identify the patients who will benefit from DCR, thus optimizing benefit and minimizing risk.[45,46] This is an area of active research and is likely one of the most important of current efforts. The US Department of Defense has funded a prospective observational transfusion trial at 10 busy trauma centers, and these data will start to answer many of the questions raised in this review. Prospective randomized studies are planned and required to definitively answer what resuscitation approach in the massively bleeding patient best balances benefit and risk. These randomized studies will establish a definitive standard of care based on level 1 data. From this standard, new products can be thoughtfully studied. We are currently overtreating many patients, exposing them to the myriad risks associated with blood products. This is because we do not understand the mechanism of trauma-induced coagulopathy, or how blood products work. When these mechanistic issues are worked out, we will be able to direct individual therapy to specific defects, minimizing exposure and maximizing results.

Forward-thinking researchers are planning the next evolution of blood products. Although one option is a return to whole blood use, some researchers are investigating the possibility of infusing multiple lyophilized products. The logistical benefits of small-volume, lightweight, ambient temperature storage; lyophilized products; and recombinant proteins are obvious and significant. Immediate availability of disease-free products, without a requirement for cold storage, is enormous. Future clinical trials in severely injured patients will involve these products.[47]

References

1. Trauma facts. The American Association for the Surgery of Trauma Web site. http://www.aast.org/TraumaFacts/dynamic.aspx?id=964.

2. Centers for Disease Control and Prevention. Deaths: final data for 2004. Atlanta, GA: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2007.
3. Demetriades D, Murray J, Charalambides K, et al. Trauma fatalities: time and location of hospital deaths. J Am Coll Surg. 2004; 198:20–26. [PubMed: 14698307]
4. Moore FA, Nelson T, McKinley BA, et al. Massive transfusion in trauma patients: tissue hemoglobin oxygen saturation predicts poor outcome. J Trauma. 2008; 64:1010–1023. [PubMed: 18404069]
5. Hess JR. Blood and coagulation support in trauma care. Hematology Am Soc Hematol Educ Program. 2007:187–191. [PubMed: 18024628]
6. Como JJ, Dutton RP, Scalea TM, Edelman BB, Hess JR. Blood transfusion rates in the care of acute trauma. Transfusion. 2004; 44:809–813. [PubMed: 15157244]
7. 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; 248:447–458. [PubMed: 18791365]
8. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma. 2003; 54:1127–1130. [PubMed: 12813333]
9. Brohi K, Cohen MJ, Ganter MT, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma. 2008; 64:1211–1217. [PubMed: 18469643]
10. Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma. 2008; 65:748–754. [PubMed: 18849786]
11. American Society of Anesthesiologists. Practice guidelines for blood component therapy: a report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. Anesthesiology. 1996; 84:732–747. [PubMed: 8659805]
12. Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. J Trauma. 2009; 66 Suppl:S69–S76. [PubMed: 19359973]
13. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma. 2007; 62:307–310. [PubMed: 17297317]
14. Churchill ED. The surgical management of the wounded in the Mediterranean theater at the time of the fall of Rome. Ann Surg. 1944; 120:268–283. [PubMed: 17858491]
15. Carrico CJ, Canizaro PC, Shires GT. Fluid resuscitation following injury: rationale for the use of balanced salt solutions. Crit Care Med. 1976; 4:46–54. [PubMed: 819213]
16. Moore FD, Shires G. Moderation. Anesth Analg. 1968; 47:506–508. [PubMed: 5691690]
17. American College of Surgeons. Advanced Trauma Life Support. 8th ed.. Chicago, IL: American College of Surgeons; 2008.
18. Moore FA, McKinley BA, Moore EE. The next generation in shock resuscitation. Lancet. 2004; 363:1988–1996. [PubMed: 15194260]
19. Wiedemann HP, Wheeler AP, et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006; 354:2564–2575. [PubMed: 16714767]
20. Cotton BA, Guy JS, Morris JA Jr, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock. 2006; 26:115–121. [PubMed: 16878017]
21. Beecher HK. Preparation of battle casualties for surgery. Ann Surg. 1945; 21:769–792. [PubMed: 17858614]
22. 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; 63:805–813. [PubMed: 18090009]
23. Maegele M, Lefering R, Paffrath T, Tjardes T, Simanski C, Bouillon B. Red blood cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiply injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft fur Unfallchirurgie. Vox Sang. 2008; 95:112–119. [PubMed: 18557827]

24. 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; 65:272–278. [PubMed: 18695461]
25. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. J Trauma. 2009; 66:41–49. [PubMed: 19131804]
26. Dente CJ, Shaz BH, Nicholas JM, et al. Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. J Trauma. 2009; 66:1616–1624. [PubMed: 19509623]
27. 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 Suppl:S77–S85. [PubMed: 19359974]
28. 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): 447–458. [PubMed: 18791365]
29. Impact of policy change on US Army combat transfusion practices. USAISR Web site. http://www.usaisr.amedd.army.mil/cpgs/DmgCntrlResus0903.pdf.
30. Harrigan C, Lucas CE, Ledgerwood AM, Walz DA, Mammen EF. Serial changes in primary hemostasis after massive transfusion. Surgery. 1985; 98:836–844. [PubMed: 4049256]
31. Counts RB, Haisch C, Simon TL, Maxwell NG, Heimbach DM, Carrico CJ. Hemostasis in massively transfused trauma patients. Ann Surg. 1979; 190:91–99. [PubMed: 464685]
32. 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; 203:40–48. [PubMed: 3510591]
33. Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. J Trauma. 1997; 42:857–862. [PubMed: 9191667]
34. Cinat ME, Wallace WC, Nastanski F, et al. Improved survival following massive transfusion in patients who have undergone trauma. Arch Surg. 1999; 134:964–970. [PubMed: 10487591]
35. Faringer PD, Mullins RJ, Johnson RL, Trunkey DD. Blood component supplementation during massive transfusion of AS-1 red cells in trauma patients. J Trauma. 1993; 34:481–487. [PubMed: 8487331]
36. 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; 66:358–364. [PubMed: 19204508]
37. Kashuk JL, Moore EE, Johnson JL, et al. Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer? J Trauma. 2008; 65:261–271. [PubMed: 18695460]
38. Scalea TM, Bochicchio KM, Lumpkins K, et al. Early aggressive use of fresh frozen plasma does not improve outcome in critically injured trauma patients. Ann Surg. 2008; 248:578–584. [PubMed: 18936570]
39. Roback JD, Caldwell S, Carson J, et al. Evidence-based practice guidelines for plasma transfusion. Transfusion. 2010; 50(6):1227–1239. [PubMed: 20345562]
40. Gajic O, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: benefit or harm? Crit Care Med. 2006; 34:S170–S173. [PubMed: 16617262]
41. Weinberg JA, McGwin G Jr, Griffin RL, et al. Age of transfused blood: an independent predictor of mortality despite universal leukoreduction. J Trauma. 2008; 65:279–284. [PubMed: 18695462]
42. Spinella PC, Carroll CL, Staff I, et al. Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries. Crit Care. 2009; 13:R151. [PubMed: 19772604]
43. 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–S63. [PubMed: 20622621]

44. PROMMTT. PRospective, Observational, Multi-center Massive Transfusion study. PROMMTT Web site. http://www.uth.tmc.edu/cetir/PROMMTT/.

45. Nunez TC, Voskresensky IV, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? J Trauma. 2009; 66:346–352. [PubMed: 19204506]

46. Nunez TC, Dutton WD, May AK, Holcomb JB, Young PP, Cotton BA. Emergency department blood transfusion predicts early massive transfusion and early blood component requirement. Transfusion. May 7. [Epub ahead of print.].

47. Holcomb JB. Traditional transfusion practices are changing. Crit Care. 2010; 14:162. [PubMed: 20550726]