Damage control resuscitation: A sensible approach to the exsanguinating surgical patient

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Background: **The current wars in Iraq and Afghanistan have resulted in the highest rates of combat casualties experienced by the U.S. military since the Vietnam conflict. These casualties suffer wounds that have no common civilian equivalent and more frequently require massive transfusion (greater than 10 units of packed red blood cells [PRBCs] in less than 24 hrs) than civilian injured.**

Discussion: **Military surgeons have found that traditional approaches to resuscitation, particularly in terms of the ratio of blood products to each other and the timing of these products, often fail to effectively treat the coagulopathy that is present on arrival in these casualties. This observation has been concurrently noted in the civilian trauma literature. These experiences have ignited interest in an alternative approach to the resuscitation of these most grievously injured patients. This approach includes the use of permissive hypotension; the prevention and aggressive treatment of hypothermia with both passive and active warming measures; the temporization of acidosis with use of exogenous buffer agents; the immediate use of thawed plasma in ratios approaching 1:1 with PRBCs; the early use of platelets, often given well before 10 units of PRBCs have been transfused; the early use of recombinant Factor VIIa; and, in military settings, the use of fresh whole blood as a primary resuscitation fluid. This strategy has been called "damage control resuscitation" to emphasize its pairing with damage control surgical techniques.**

Summary: **Review of the published support for this strategy reveals that additional trials are needed to study and optimize these techniques. (Crit Care Med 2008; 36[Suppl.]:S267–S274)**

KEY WORDS: damage control resuscitation; massive transfusion; exsanguination; fresh thawed plasma; fresh whole blood; hemostatic resuscitation; hypotensive resuscitation; permissive hypotension; coagulopathy; lethal triad

The term "resuscitation" has evolved in modern medical lexicon to encompass the entire spectrum of care delivered to a surgical patient in physiological distress or shock. Far from just the amount and type of fluids used, this spectrum of care includes a standard and finite set of invasive interventions during the initial primary survey of the injured patient, the diagnostic means used to discover sources of injury and shock, the advanced surgical interventions used to treat these injuries, the reversal of hypothermia, the correction of acidosis, and the replacement of intravascular volume, oxygen-carrying capacity, and coagulation factors. However, for the purposes of this article, "resuscitation" refers to the non-surgical strategies used to prevent or reverse anemia, coagulopathy, acidosis, and hypothermia in the presentation and initial 24 to 48 hrs of care of the severely injured patient.

With the advent of modern blood centrifuge, preservation, and banking, the major logistic hurdle involved in having rapidly available blood products on hand for injured patients was largely overcome. At roughly the same time, it was discovered that relatively simple isotonic crystalloid solutions could provide initial and, in many cases, adequate resuscitation for most injured casualties. The administration of isotonic crystalloid solutions to acutely injured patients has become a standard practice that remains in the Advanced Trauma Life Support courses taught today (1). Until recently, massive transfusion guidelines for the ratio of various products administered were based on the assumption that the coagulopathy encountered in severely injured patients was primarily from dilution of blood clotting constituents and did not occur until at least one blood volume had been transfused (2).

The notions that substantial volumes of isotonic crystalloid solutions are acceptable for severely injured patients and that coagulopathy is primarily a byproduct of resuscitation have recently been challenged (3). Several recent articles from major civilian and military trauma centers have demonstrated that severely injured casualties have a significant coagulopathy on presentation (4–6). Not surprisingly, these severely injured patients are also the ones most likely to experience hypothermia and acidosis. Adherence to the traditional practice of administering isotonic crystalloids followed by packed red blood cells (PRBCs) until a either a predetermined threshold of PRBCs is reached or until fresh frozen plasma can be thawed results in a worsening of all three aspects of the "lethal triad."

In many of the classic papers that describe reversing the "lethal triad" of hypothermia, acidosis, and coagulopathy with "damage control" approaches, the authors break down the various aspects of the damage control process into sequences or steps for simplicity (7–9). An unfortunate byproduct of describing the damage control sequence in phases is the potential inference that correction of the hypothermia, acidosis, and coagulopathy is the "secondary resuscitation," which does not begin in earnest until the patient reaches an intensive care unit.

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The emphasis in many of these papers is on the very concept of delaying definitive surgical treatment until the patient's hypothermia, acidosis, and coagulopathy are treated and on the surgical techniques used to perform an abbreviated operation. The intraoperative resuscitation strategies described often featured initial resuscitation with crystalloid, transition to PRBCs for continued evidence of shock, and addition of plasma and platelets into the resuscitation strategy only after a certain threshold of PRBC numbers (for example, 8–10) had been reached (8).

That this resuscitation strategy fails to treat and in fact worsens the hypothermia, acidosis, and coagulopathy that are associated with severe trauma has been recently noted by several authors, including surgeons deployed in the global war on terrorism (10, 11). An alternative strategy, aptly named "damage control resuscitation" to emphasize its pairing with damage control surgical techniques, is described and is currently in use in Operations Iraqi and Enduring Freedom. This strategy includes the tolerance of moderate hypotension (systolic blood pressure approximately 90 mm Hg); the trauma system-wide emphasis on the recognition and prevention of hypothermia; the temporization of acidosis (or at least prevention of worsening acidosis); and the emphasis on immediate correction of coagulopathy as the most treatable arm of the "lethal triad." The treatment of coagulopathy features appropriate choices of resuscitation fluids; the amounts and ratio of these products to one another; the timing of the delivery of these products; and the use of adjuncts to resuscitation (for example, recombinant Factor VIIa). Clearly, for this resuscitation strategy to be successful, it must be married to the treatment of immediately life-threatening conditions (for example, tension pneumothorax) and the rapid surgical control of hemorrhage.

The majority (>90%) of trauma patients treated in both civilian and military settings do not require damage control surgical techniques or massive transfusion (defined as >10 units PRBCs in 24 hrs for this article) (12). Although it has been demonstrated that up to 28% of these patients may have an abnormal ProTime on arrival (5), more recent data suggest that thromboelastography may be superior to standard assays (such as ProTime and partial thromboplastin time) in detecting a hypercoagulable state early after injury in less severely injured patients (13). Hence, managing hypercoagulability may be more critical in the majority of less severely injured trauma patients. The need for massive transfusion is relatively rare, occurring in only 1% to 2% of civilian trauma patients (14), but up to 7% of patients in current military settings (11). However, these patients are the most at risk for early death from hemorrhage and stand to benefit from alternative strategy that begins to treat their physiological derangements as soon as they arrive (and preferably before they arrive).

Permissive Hypotension

The concept that the combination of the patient's natural coagulation cascade, hypotension, and vessel spasm will temporarily arrest traumatic hemorrhage is perhaps no better illustrated than in the combat casualty with proximal limb amputations from an explosion. These patients often arrive without apparent bleeding from traumatically amputated limbs, only to have rapid arterial bleeding resume once resuscitation begins and hypotension is corrected to normal systolic pressures. This bleeding will sometimes overwhelm tourniquet control (15). This phenomenon was well known and previously described by World War I and II era surgeons (16). Several terms have been coined to describe the strategy of allowing hypotension in trauma victims before the establishment of surgical hemorrhage control. These terms include hypotensive resuscitation, deliberate hypotension, and permissive hypotension; undoubtedly there are others. Both animal and human clinical studies have also supported this concept, although mixed results have been noted in clinical studies (17–28). Nevertheless, current military doctrine and training emphasize minimizing fluid and blood product delivery in the prehospital setting in combat casualties who have a palpable radial pulse and have normal mental status (29, 30). This approach is also used in the trauma bays at forward surgical teams and combat support hospitals to prevent unnecessary blood loss before surgical control is obtained.

Hypothermia

The dramatic and negative association that hypothermia has with the survival of severely injured trauma patients is well described. Severe trauma-related hypothermia (temperature <32°C) has been associated with 100% mortality (31). The effect of hypothermia on the coagulation system is multifactorial (32, 33). Moderate hypothermia (32°C to 34°C) directly reduces coagulation factor activity approximately 10% for each degree Celsius decrease in temperature while markedly affecting platelet function (34–36). Severely injured trauma patients with hemorrhagic shock typically have uncoupling of normal metabolic pathways, resulting in the loss of homeothermic ability. This loss of thermoregulation can be exacerbated in the prehospital setting by environmental factors, prolonged extrication or scene time, intoxication, and convective heat losses (for example, open helicopter door during flight). Both civilian and military trauma centers have linked the presence of hypothermia on arrival with increased mortality (37–39).

Hypothermia in combat casualties was identified as a theaterwide trauma system problem in Operation Iraqi Freedom (40, 41). Several measures were subsequently put in place system-wide to prevent hypothermia. First, simple hypothermia prevention measures were disseminated to the combat medics on the battlefield. These measures included emphasis on external hemorrhage control as the first priority, limiting removal of clothing to areas of the body that require treatment, wrapping treated casualties in wool or solar blankets, and the use of inline fluid warmers such as the Thermal Angel (Estill Medical Technologies, Dallas, TX). Measures to prevent and treat hypothermia at the initial levels of surgical care (forward surgical teams and combat support hospitals) include the use of standardized heat-loss prevention kits (use of solar blankets, heated blankets, and body bag[s]), the use of warmed blood products and fluids, and the use of fluid warmers/rapid infusers (for example, the Thermal Angel [Estill Medical Technologies, Inc., Dallas, TX] and the Belmont Rapid Infuser [Belmont Instrument Corporation, Billerica, MA]). Since institution of standardized hypothermia prevention measures, the rate of patients arriving to the combat support hospitals with hypothermia has dropped from 7% to less than 1% (41).

Hence, severe hypothermia has become a relative rarity in Operation Iraqi Freedom. The system measures in place allow prevention of additional heat loss in prehospital settings and prevention and

treatment of hypothermia are the standard care a casualty receives on arrival to the hospital. Aside from the standardized use of maximum warming settings on rapid infusers, the need for active rewarming measures such as continuous arteriovenous rewarming (42, 43) or body cavity lavage of warmed fluids has been largely obviated. Cardiopulmonary bypass, used in extreme cases of hypothermia for controlled active rewarming, is not available in the combat support hospitals in Iraq or Afghanistan.

Acidosis

The contribution of acidosis to the "bloody vicious cycle" (44) is well known if not entirely or clearly understood (45). *In vitro* studies have demonstrated substantially reduced clot formation rate as detected by thromboelastography in normal blood brought to a pH of 7 (46), and platelets incubated in a low pH (5.5) form spheres devoid of aggregating tendency, whereas at a higher pH (9.0) they form pseudopodia that increase aggregation properties (47). Martini et al. demonstrated that acidosis reduced fibrinogen concentration, platelet counts, and thrombin generation in an animal model (48, 49). Meng et al. demonstrated reduced rates of activated Factor X formation by activated Factor VII/tissue factor complex in an acidic (pH <7.4) environment (50). Multiple clinical studies have also linked varying degrees of acidosis with coagulopathy and poorer outcomes in trauma patients (6, 45, 51–53).

Effective reversal of acidosis can be challenging in the severely injured or still actively hemorrhaging trauma patient and is essentially dependent on rapid control of hemorrhage and restoring global tissue perfusion. Several end points of resuscitation have been identified as goals for therapy. These end points traditionally include serum lactate and base deficit (54, 55), which reflect global tissue perfusion. Newer technologies such as the use of near-infrared spectroscopy (56–60), skeletal muscle acid-base status (61), and more sophisticated measures of global acid-base status (62) have been proposed and are under study. The ability to restore these end points to normal ranges has been shown to have prognostic significance (54, 58). Several techniques to temporarily ameliorate the negative effects of acidosis on the coagulation system have been proposed such as the administration of exogenous bicarbonate or tris-hydroxymethyl aminomethane. These interventions have had mixed results in studies and alone appear insufficient in reversing acidosis-induced coagulopathy (63, 64).

Perhaps more important than interventions to directly reverse acidosis is avoiding interventions that worsen acidosis. One potentially preventable and easily correctable cause of acidosis is hypoventilation. A second preventable cause of iatrogenic acidosis involves the choice of resuscitation fluid. The two most commonly used isotonic crystalloid solutions in emergency rooms and prehospital settings are lactated Ringer's and normal saline. Both of these fluids are labeled with pH ranges as low as 4.5 for normal saline (NS) and 6.0 for lactated Ringer's (LR). In a fairly extensive review of animal research, case reports, case series, and clinical studies, Ho and colleagues demonstrated that use of large amounts of NS in trauma patients with shock contributes to metabolic acidosis (65), which as discussed can significantly worsen coagulopathy. This effect was not demonstrated with LR, although large volumes can also cause this effect. Several other recent animal studies have demonstrated superiority of LR over NS as a resuscitation fluid in hemorrhagic shock (66–68).

Nevertheless, the choice of LR as a resuscitation fluid, particularly for severely injured patients requiring damage control surgical approaches and massive transfusion, has other drawbacks. LR in large volumes provides little to no direct contribution to improved coagulation or oxygen-carrying capacity. Use of this fluid may be detrimental in patients with an uncontrolled surgical hemorrhage source (20–22, 24). LR has also recently been demonstrated to dramatically activate the immune system and potentially contribute to secondary cellular injury (69–73).

Coagulopathy

As discussed, considerable attention has been given to reversing the effects of the hypothermia and acidosis in the "lethal triad." Unfortunately, the therapies available to directly reverse these problems (when they are severe) are either invasive or cumbersome, as is the case in hypothermia, or relatively lacking in efficacy, as is the case in acidosis. Hence, preventing worsening hypothermia and acidosis are the strategies of choice, and the ultimate correction of hypothermia and acidosis is generally linked to the overall resuscitation of the patient. The remaining member of the "lethal triad," coagulopathy, has also been demonstrated to be present on arrival in severely injured trauma patients (4–6, 10, 74). Unlike its counterparts, there are a number of effective therapies and products available to directly treat coagulopathy. The renewed interest in therapies for coagulopathy reflects a realization that of the three parts of the "lethal triad," coagulopathy is perhaps the most readily treatable; and until recently, standard massive transfusion practices have undertreated it (11, 75–77).

Fresh Whole Blood

The key question driving current resuscitation research is "what is the optimal resuscitation fluid for a severely injured trauma surgical patient?" The simplest and idealized answer to this question may be "give the patient back the fresh whole blood that he lost." The reality is much more complex, particularly because modern experience with fresh whole blood as a resuscitation fluid is relatively small, and in all cases, the fresh whole blood was given in conjunction with a number of other more commonly used stored blood components. Nevertheless, a review of the literature of fresh whole blood offers some perspectives. First, animal studies evaluating whole blood have demonstrated that whole blood restores myocardial function better than PRBCs administered after severe hemorrhage in dogs (78); and fresh whole blood is the best 24-hr hypotensive resuscitation fluid after severe hemorrhage in swine (79). Manno and colleagues demonstrated that use of blood less than 48 hrs old reduced blood loss and transfusion requirements in neonates undergoing cardiac surgery (80). Erber and colleagues published a small series suggesting a benefit of unrefrigerated whole blood in severely hemorrhaging surgical patients (81). More recently, the U.S. Army has accumulated a great deal of experience using fresh whole blood in combat casualties in Operations Iraqi Freedom and Enduring Freedom (82). The safety of a fresh whole blood program using rapid screening assays for infectious diseases has been demonstrated (83). Although data directly evaluating the efficacy of fresh whole blood use versus component therapy have yet to be published, initial evaluation of the data and anecdotal reports of "unexpected

survivors" suggest there may be a survival benefit to the use of fresh whole blood in massive transfusion (12, 15). This analysis is ongoing, and additional prospective studies are required to answer this question (75, 84). More details on the emergence of fresh whole blood transfusions are addressed elsewhere in this supplement.

The dramatic experiences reported by physicians using fresh whole blood to treat combat casualties, although anecdotal, have refocused resuscitation research toward strategies to mimic the delivery of whole blood by adjusting ratios of standard blood components and using adjuncts such as recombinant Factor VIIa. Unfortunately, the sum of combining standard blood component therapy does not equal the whole of a unit of fresh whole blood. Analysis of a unit of fresh whole blood reveals it contains approximately 500 mL of warm blood with a hematocrit of 38% to 50%, a platelet count of 150,000 to 400, essentially full coagulation function, and 1500 mg of fibrinogen. Combining one unit of PRBCs, one unit of platelets, one unit of fresh frozen plasma, and a ten-pack of cryoprecipitate provides 660 mL of fluid with a hematocrit of 29%, platelet count of 87,000, coagulation activity of approximately 65%, and 750 mg of fibrinogen (12, 85).

Additional problems have been identified with component therapy. Increasing blood transfusion rates correlate with increasing mortality in both civilian and military trauma patients (14, 86). Injury severity alone does not account for this correlation. A growing body of trauma and critical care literature demonstrate the detrimental effects of red blood cell transfusion on patient survival. Degradation of stored red blood cells over time, termed "storage lesion" (87), has been implicated in decreased red blood cell aggregation (88), increased inflammatory mediators (89), decreased 2,3-DPG activity and splanchnic ischemia (90), pneumonia and other infections (91), multiple organ failure (92), and mortality (93, 94). Currently, the average age of transfused red blood cells in Operation Iraqi Freedom is 33 days (83), indicating that substantial storage lesion is likely present in the blood being transfused into combat casualties. Hence, the military has developed strategies to minimize the amount of red blood cell transfusions that are necessary by aggressively treating coagulopathy on patient arrival and, in some cases, preferentially switching to fresh whole blood as a primary resuscitation modality rather than just a logistic necessity (12).

Blood Product Ratios

The focus on providing the optimal resuscitation fluid has also dramatically altered the use of standard blood components. Busy trauma centers, including those in Iraq and Afghanistan, now routinely thaw Type AB or A fresh frozen plasma each morning (relabeled "fresh thawed plasma," this product has a shelf-life of 4 to 5 days; most is used the day it is thawed). These products are delivered to the trauma bay and operating room in standard resuscitation packs for delivery early in a severely injured trauma patient's course (95). The optimal ratios of red blood cells to plasma and platelets has yet to be elucidated in prospective trials; nevertheless, retrospective data from Operation Iraqi Freedom demonstrate a survival benefit when plasma to red blood cell ratios approach 1:1 (96). A similar trend has been demonstrated in an unpublished study done at 16 major civilian trauma centers (John B. Holcomb, MD, COL, Commander, U.S. Army Institute of Surgical Research, personal communication, December 3, 2007). The early use of ratios of plasma to red blood cells of 2:3 or approaching 1:1 have also been suggested in other published studies (76, 97–99). Researchers are also exploring the use of freeze-dried plasma products or the use of purified protein concentrates that use variable amounts of factors. These products are potentially safer from an infectious disease perspective, target factor replacement without the additional volume, and are logistically appealing given their small size.

Recombinant Factor VIIa

The use of recombinant Factor VIIa remains a topic of considerable debate, and large, multicenter, prospective trials are ongoing to elucidate both efficacy and safety issues. Factor VIIa's efficacy has considerable support in anecdotal and animal research (100–111). Boffard and colleagues' prospective trial demonstrated reduction of blood transfusions with administration of Factor VIIa in blunt trauma patients but no effect on mortality (112). There is still considerable debate about the appropriate timing of drug delivery, the selection of patients to receive the drug, and whether additional blood components can be delivered with the drug to enhance its effect (113, 114). The drug appears to be less effective in the setting of acidosis (50) but remains effective in all but the most severely hypothermic settings (115). Recent reports regarding a potential for increased thromboembolic events has sounded a note of caution on the medication's liberal use until randomized, prospective trials conclude (116, 117). The use of recombinant Factor VIIa in damage control resuscitation should take these factors into account. The risk of subsequent thromboembolic events must be balanced against the more acute threat of exsanguination. Identification of the appropriate patient population in whom to use the medication will require completion of ongoing randomized, prospective trials and perhaps additional studies.

Prospective Identification of Patients Who Require Damage Control Resuscitation

Because less severely injured trauma patients may theoretically manifest hypercoagulability, identification of candidates for damage control resuscitative techniques must be based on rapidly obtainable clinical parameters. In combat settings, in which roughly 95% of casualties present with a penetrating trauma mechanism, we have found certain patterns of injury that reliably predict need for massive transfusion and damage control surgical and resuscitative techniques. These patterns tend to be obvious and include patients with multiple proximal amputations (particularly thigh-level), truncal hemorrhage combined with a proximal amputation, and abdominal evisceration with hypotension. Penetrating mechanism has been shown to be an independent predictor of need for massive transfusion in combat casualties (6).

Other measurable parameters that have been suggested as predictors of massive transfusion requirements include a base deficit less than 6 (51), an international normalized ratio 1.5 or greater (5, 6, 76), a systolic blood pressure less than 90 mm Hg in combat trauma patients and less than 110 mm Hg in civilian trauma patients (118–120), hemoglobin less than 11 (6), temperature less than 96°F or 35°C to 36°C (37, 39, 121), and a weak or absent radial pulse (122). Patients with any of these clinical parame-

ters, certainly if they are in combination or otherwise match physical examination findings, should be considered for immediate transition from a "standard" resuscitation mode to a damage control resuscitation mode (86).

Summary

Employment of damage control resuscitation begins as soon as the patient is identified as being at risk for death from hemorrhage. The patient will require rapid transfer to an operating room for initiation of damage control surgical techniques and early administration of increased amounts of thawed plasma and red blood cells than traditionally taught. Some authors recommend ratios approaching 1:1 (although further investigation needs to be performed before definitive conclusions can be made); minimization of crystalloid infusion; activation of massive transfusion or exsanguination prevention guidelines, which feature automatic delivery of predefined transfusion "packs" containing plasma, red blood cells, platelets, and potentially cryoprecipitate; consideration for early administration of recombinant Factor VIIa; institution of hypothermia prevention and treatment; and potentially the use of tris-hydroxymethyl aminomethane or other agents to buffer severe acidosis if present (10, 11). Validated end points of resuscitation such as correction of lactate and/or base deficit should be used to guide resuscitation. The use of thromboelastography (currently used in some combat support hospitals in Iraq) can potentially identify specific deficits in the patient's clotting cascade and decrease unnecessary transfusion of products.

Future Directions

It should be noted that the majority of the current published data examining the damage control resuscitation strategy are Class II or III data (retrospective observational studies) and that current prospective studies are underway. Many unanswered questions remain regarding the optimal resuscitation strategy for severely injured trauma patients. What are the optimal ratios of plasma, PRBCs, platelets, and fibrinogen-containing products? When should Factor VIIa be given, and can the administration of Factor VIIa with other products enhance its efficacy? Is there a role for other hemostatic agents (for example, tranexamic acid)? It is critical that these questions be studied through well-designed, multiinstitutional, randomized, prospective trials. This is a challenge; the resuscitation of severely injured patients in modern civilian and military trauma centers involves a complex interaction of multiple providers performing simultaneous interventions in which team dynamics, communication, logistics, provider experience, trauma center volume, as well as individual patient factors impact on the ultimate outcomes.

Perhaps the ultimate frontier of resuscitation research, and the ultimate "damage control" approach, is suspended animation. A number of researchers are currently investigating suspended animation using profound hypothermia, hydrogen sulfide, and nitric oxide (123–144). Although years away, the suspended animation approach may eventually provide salvage to trauma patients who arrive to surgical care at the limits of physiological reserve. Currently, this set of patients may undergo emergency department thoracotomy with predictably dismal results.

REFERENCES

1. Advanced Trauma Life Support for Doctors: Student Course Manual [Student Edition]. Seventh Edition. American College of Surgeons, 2004
2. Rabinovici R, Frankel H, Kaplan L: Trauma evaluation and resuscitation. *Curr Probl Surg* 2003; 40:599–681
3. Moore FA: Evidence-based medical information technology: The next generation. *J Trauma* 2007; 63:1195–1205
4. Brohi K, Singh J, Heron M, et al:. Acute traumatic coagulopathy. *J Trauma* 2003; 54:1127–1130
5. MacLeod JB, Lynn M, McKenney MG, et al: Early coagulopathy predicts mortality in trauma. *J Trauma* 2003; 55:39–44
6. Schreiber MA, Perkins J, Kiraly L, et al: Early predictors of massive transfusion in combat casualties. *J Am Coll Surg* 2007; 205:541–545
7. Rotondo MF, Schwab CW, McGonigal MD, et al: 'Damage control': An approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma* 1993; 35:375–382
8. Rotondo MF, Zonies DH: The damage control sequence and underlying logic. *Surg Clin North Am* 1997; 77:761–777
9. Shapiro MB, Jenkins DH, Schwab CW, et al: Damage control: collective review. *J Trauma* 2000; 49:969–978
10. Hess JR, Holcomb JB, Hoyt DB: Damage control resuscitation: The need for specific blood products to treat the coagulopathy of trauma. *Transfusion* 2006; 46:685–686
11. Holcomb JB, Jenkins D, Rhee P, et al: Damage control resuscitation: Directly addressing the early coagulopathy of trauma. *J Trauma* 2007; 62:307–310
12. Repine TB, Perkins JG, Kauvar DS, et al: The use of fresh whole blood in massive transfusion. *J Trauma* 2006; 60(Suppl): S59–S69
13. Park MS, Martini WZ, Dubick MA, et al: Thromboelastography is superior to PT and PTT for the assessment of hypercoagulability and fibrinolysis after injury in burned vs. trauma patients. *J Trauma* 2007; 63:1429
14. Como JJ, Dutton RP, Scalea TM, et al: Blood transfusion rates in the care of acute trauma. *Transfusion* 2004; 44:809–813
15. Beekley AC, Starnes BW, Sebesta JA: Lessons learned from modern military surgery. *Surg Clin North Am* 2007; 87:157–184, vii
16. Cannon W, Frawer J, Cowell E: The preventive treatment of wound shock. *JAMA* 1918; 70:618–621
17. Sondeen JL, Coppes VG, Holcomb JB: Blood pressure at which rebleeding occurs after resuscitation in swine with aortic injury. *J Trauma* 2003; 54(Suppl):S110–S117
18. Sondeen JL, Pusateri AE, Hedner U, et al: Recombinant factor VIIa increases the pressure at which rebleeding occurs in porcine uncontrolled aortic hemorrhage model. *Shock* 2004; 22:163–168
19. Bickell WH, Shaftan GW, Mattox KL: Intravenous fluid administration and uncontrolled hemorrhage. *J Trauma* 1989; 29:409
20. Bickell WH, Bruttig SP, Millnamow GA, et al: The detrimental effects of intravenous crystalloid after aortotomy in swine. *Surgery* 1991; 110:529–536
21. Bickell WH, Bruttig SP, Millnamow GA, et al: Use of hypertonic saline/dextran versus lactated Ringer's solution as a resuscitation fluid after uncontrolled aortic hemorrhage in anesthetized swine. *Ann Emerg Med* 1992; 21:1077–1085
22. Bickell WH: Are victims of injury sometimes victimized by attempts at fluid resuscitation? *Ann Emerg Med* 1993; 22:225–226
23. 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: 1105–1109
24. Bickell WH, Stern S: Fluid replacement for hypotensive injury victims: How, when and what risks? *Curr Opin Anaesthesiol* 1998; 11:177–180
25. Dutton RP: Low-pressure resuscitation from hemorrhagic shock. *Int Anesthesiol Clin* 2002; 40:19–30
26. Dutton RP: The role of deliberate hypotension. *Hosp Med* 2005; 66:72–73
27. Holcomb JB: Fluid resuscitation in modern combat casualty care: Lessons learned from Somalia. *J Trauma* 2003; 54(Suppl): S46–S51
28. Dutton RP, Mackenzie CF, Scalea TM: Hypotensive resuscitation during active hem-

orrhage: Impact on in-hospital mortality. *J Trauma* 2002; 52:1141–1146
29. Rhee P, Koustova E, Alam HB: Searching for the optimal resuscitation method: Recommendations for the initial fluid resuscitation of combat casualties. *J Trauma* 2003; 54(Suppl):S52–S62
30. *Emergency War Surgery*. Third U.S. Revision, 2004
31. Jurkovich GJ, Greiser WB, Luterman A, et al: Hypothermia in trauma victims: an ominous predictor of survival. *J Trauma* 1987; 27:1019–1024
32. Johnston TD, Chen Y, Reed RL: Functional equivalence of hypothermia to specific clotting factor deficiencies. *J Trauma* 1994; 37: 413–417
33. Patt A, McCroskey BL, Moore EE: Hypothermia-induced coagulopathies in trauma. *Surg Clin North Am* 1988; 68:775–785
34. Hess JR, Lawson JH: The coagulopathy of trauma versus disseminated intravascular coagulation. *J Trauma* 2006; 60(Suppl): S12–S19
35. Kettner SC, Kozek SA, Groetzner JP, et al: Effects of hypothermia on thrombelastography in patients undergoing cardiopulmonary bypass. *Br J Anaesth* 1998; 80:313–317
36. Kettner SC, Sitzwohl C, Zimpfer M, et al: The effect of graded hypothermia (36 degrees C–32 degrees C) on hemostasis in anesthetized patients without surgical trauma. *Anesth Analg* 2003; 96:1772–1776
37. Arthurs Z, Cuadrado D, Beekley A, et al: The impact of hypothermia on trauma care at the 31st combat support hospital. *Am J Surg* 2006; 191:610–614
38. Gentilello LM, Jurkovich GJ, Stark MS, et al: Is hypothermia in the victim of major trauma protective or harmful? A randomized, prospective study. *Ann Surg* 1997; 226:439–447
39. Martin RS, Kilgo PD, Miller PR, et al: Injury-associated hypothermia: An analysis of the 2004 National Trauma Data Bank. *Shock* 2005; 24:114–118
40. Beekley AC: United States military surgical response to modern large-scale conflicts: The ongoing evolution of a trauma system. *Surg Clin North Am* 2006; 86:689–709
41. Eastridge BJ, Jenkins D, Flaherty S, et al: Trauma system development in a theater of war: Experiences from Operation Iraqi Freedom and Operation Enduring Freedom. *J Trauma* 2006; 61:1366–1372
42. Gentilello LM, Rifley WJ: Continuous arteriovenous rewarming: report of a new technique for treating hypothermia. *J Trauma* 1991; 31:1151–1154
43. Gentilello LM, Cobean RA, Offner PJ, et al: Continuous arteriovenous rewarming: rapid reversal of hypothermia in critically ill patients. *J Trauma* 1992; 32:316–325
44. Kashuk JL, Moore EE, Millikan JS, et al: Major abdominal vascular trauma—a unified approach. *J Trauma* 1982; 22:672–679
45. Cosgriff N, Moore EE, Sauaia A, et al: Predicting life-threatening coagulopathy in the massively transfused trauma patient: Hypothermia and acidoses revisited. *J Trauma* 1997; 42:857–861
46. Engstrom M, Schott U, Romner B, et al: Acidosis impairs the coagulation: A thromboelastographic study. *J Trauma* 2006; 61: 624–628
47. Djaldetti M, Fishman P, Bessler H, et al: pH-induced platelet ultrastructural alterations. A possible mechanism for impaired platelet aggregation. *Arch Surg* 1979; 114: 707–710
48. Martini WZ, Pusateri AE, Uscilowicz JM, et al: Independent contributions of hypothermia and acidosis to coagulopathy in swine. *J Trauma* 2005; 58:1002–1009
49. Martini WZ, Holcomb JB: Acidosis and coagulopathy: the differential effects on fibrinogen synthesis and breakdown in pigs. *Ann Surg* 2007; 246:831–835
50. Meng ZH, Wolberg AS, Monroe DM III, et al: The effect of temperature and pH on the activity of factor VIIa: Implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. *J Trauma* 2003; 55:886–891
51. Davis JW, Parks SN, Kaups KL, et al: Admission base deficit predicts transfusion requirements and risk of complications. *J Trauma* 1996; 41:769–774
52. Davis JW, Kaups KL: Base deficit in the elderly: A marker of severe injury and death. *J Trauma* 1998; 45:873–877
53. Dunn EL, Moore EE, Breslich DJ, et al: Acidosis-induced coagulopathy. *Surg Forum* 1979; 30:471–473
54. Elliott DC: An evaluation of the end points of resuscitation. *J Am Coll Surg* 1998; 187: 536–547
55. Husain FA, Martin MJ, Mullenix PS, et al: Serum lactate and base deficit as predictors of mortality and morbidity. *Am J Surg* 2003; 185:485–491
56. Cohn SM, Crookes BA, Proctor KG: Near-infrared spectroscopy in resuscitation. *J Trauma* 2003; 54(Suppl):S199–S202
57. Cohn SM: Near-infrared spectroscopy: potential clinical benefits in surgery. *J Am Coll Surg* 2007; 205:322–332
58. Cohn SM, Nathens AB, Moore FA, et al: Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. *J Trauma* 2007; 62:44–54
59. Crookes BA, Cohn SM, Burton EA, et al: Noninvasive muscle oxygenation to guide fluid resuscitation after traumatic shock. *Surgery* 2004; 135:662–670
60. Crookes BA, Cohn SM, Bloch S, et al: Can near-infrared spectroscopy identify the severity of shock in trauma patients? *J Trauma* 2005; 58:806–813
61. Sims C, Seigne P, Menconi M, et al: Skeletal muscle acidosis correlates with the severity of blood volume loss during shock and resuscitation. *J Trauma* 2001; 51:1137–1145
62. Martin M, Murray J, Berne T, et al: Diagnosis of acid-base derangements and mortality prediction in the trauma intensive care unit: The physiochemical approach. *J Trauma* 2005; 58:238–243
63. Martini WZ, Dubick MA, Pusateri AE, et al: Does bicarbonate correct coagulation function impaired by acidosis in swine? *J Trauma* 2006; 61:99–106
64. Weil MH, Tang W: Management of acidosis: The role of buffer agents. *Crit Care* 1997; 1:51–52
65. Ho AM, Karmakar MK, Contardi LH, et al: Excessive use of normal saline in managing traumatized patients in shock: A preventable contributor to acidosis. *J Trauma* 2001; 51:173–177
66. Healey MA, Davis RE, Liu FC, et al: Lactated ringer's is superior to normal saline in a model of massive hemorrhage and resuscitation. *J Trauma* 1998; 45:894–899
67. Kiraly LN, Differding JA, Enomoto TM, et al: Resuscitation with normal saline (NS) vs. lactated Ringer's (LR) modulates hypercoagulability and leads to increased blood loss in an uncontrolled hemorrhagic shock swine model. *J Trauma* 2006; 61:57–64
68. Todd SR, Malinoski D, Muller PJ, et al: Lactated Ringer's is superior to normal saline in the resuscitation of uncontrolled hemorrhagic shock. *J Trauma* 2007; 62: 636–639
69. Alam HB, Sun L, Ruff P, et al: E- and P-selectin expression depends on the resuscitation fluid used in hemorrhaged rats. *J Surg Res* 2000; 94:145–152
70. Alam HB, Stanton K, Koustova E, et al: Effect of different resuscitation strategies on neutrophil activation in a swine model of hemorrhagic shock. *Resuscitation* 2004; 60: 91–99
71. Ayuste EC, Chen H, Koustova E, et al: Hepatic and pulmonary apoptosis after hemorrhagic shock in swine can be reduced through modifications of conventional Ringer's solution. *J Trauma* 2006; 60:52–63
72. Rhee P, Koustova E, Alam HB: Searching for the optimal resuscitation method: Recommendations for the initial fluid resuscitation of combat casualties. *J Trauma* 2003; 54(Suppl):S52–S62
73. Watters JM, Tieu BH, Todd SR, et al: Fluid resuscitation increases inflammatory gene transcription after traumatic injury. *J Trauma* 2006; 61:300–308
74. Hess JR, Lawson JH: The coagulopathy of trauma versus disseminated intravascular coagulation. *J Trauma* 2006; 60(Suppl): S12–S19
75. Ho AM, Karmakar MK, Dion PW: Are we giving enough coagulation factors during major trauma resuscitation? *Am J Surg* 2005; 190:479–484
76. Ketchum L, Hess JR, Hiippala S: Indications for early fresh frozen plasma, cryoprecipitate, and platelet transfusion in trauma. *J Trauma* 2006; 60(Suppl):S51–S58
77. Malone DL, Hess JR, Fingerhut A: Massive transfusion practices around the globe and a suggestion for a common massive trans-

fusion protocol. *J Trauma* 2006; 60(Suppl): S91–S96
78. Barbee RW, Kline JA, Watts JA: A comparison of resuscitation with packed red blood cells and whole blood following hemorrhagic shock in canines. *Shock* 1999; 12: 449–453
79. Sondeen JL, Wade C, Dubick M, et al: Fresh whole blood is the best 24-hour hypotensive resuscitative fluid in severe hemorrhage in swine. *Shock*, In press
80. Manno CS, Hedberg KW, Kim HC, et al: Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. *Blood* 1991; 77:930–936
81. Erber WN, Tan J, Grey D, et al: Use of unrefrigerated fresh whole blood in massive transfusion. *Med J Aust* 1996; 165:11–13
82. 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 U.S. combat support hospital. *World J Surg* 2007
83. Spinella PC, Perkins JG, Grathwohl KW, et al: Risks associated with fresh whole blood and red blood cell transfusions in a combat support hospital. *Crit Care Med* 2007; 35: 2576–2581
84. Kauvar DS, Holcomb JB, Norris GC, et al: Fresh whole blood transfusion: A controversial military practice. *J Trauma* 2006; 61: 181–184
85. Armand R, Hess JR: Treating coagulopathy in trauma patients. *Transfus Med Rev* 2003; 17:223–231
86. Eastridge BJ, Malone D, Holcomb JB: Early predictors of transfusion and mortality after injury: A review of the data-based literature. *J Trauma* 2006; 60(Suppl):S20–S25
87. Offner PJ: Age of blood: Does it make a difference? *Crit Care* 2004; 8(Suppl 2): S24–S26
88. Hovav T, Yedgar S, Manny N, et al: Alteration of red cell aggregability and shape during blood storage. *Transfusion* 1999; 39: 277–281
89. Silliman CC, Clay KL, Thurman GW, et al: Partial characterization of lipids that develop during the routine storage of blood and prime the neutrophil NADPH oxidase. *J Lab Clin Med* 1994; 124:684–694
90. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; 269:3024–3029
91. Offner PJ, Moore EE, Biffl WL, et al: Increased rate of infection associated with transfusion of old blood after severe injury. *Arch Surg* 2002; 137:711–716
92. Zallen G, Offner PJ, Moore EE, et al: Age of transfused blood is an independent risk factor for postinjury multiple organ failure. *Am J Surg* 1999; 178:570–572
93. Purdy FR, Tweeddale MG, Merrick PM: Association of mortality with age of blood transfused in septic ICU patients. *Can J Anaesth* 1997; 44:1256–1261
94. Weinberg JA, McGwin G, Cherry SA, et al: Transfusions in the less severely injured: does age of transfused blood affect outcomes? [Abstract] *J Trauma* 2007; 63:1437
95. Gonzalez EA, Moore FA, Holcomb JB, et al: Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma* 2007; 62:112–119
96. 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
97. Hirshberg A, Dugas M, Banez EI, et al: Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation. *J Trauma* 2003; 54:454–463
98. Ho AM, Dion PW, Cheng CA, et al: A mathematical model for fresh frozen plasma transfusion strategies during major trauma resuscitation with ongoing hemorrhage. *Can J Surg* 2005; 48:470–478
99. Gunter OL, Au BK, Mowery NT, et al: Optimizing outcomes in damage control resuscitation: Identifying blood product ratios associated with improved survival [Abstract]. *J Trauma* 2007; 63:1432
100. Dutton RP, Hess JR, Scalea TM: Recombinant factor VIIa for control of hemorrhage: Early experience in critically ill trauma patients. *J Clin Anesth* 2003; 15:184–188
101. Dutton RP, McCunn M, Hyder M, et al: Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2004; 57:709–718
102. Dutton RP, Stein DM: The use of factor VIIa in haemorrhagic shock and intracerebral bleeding. *Injury* 2006; 37:1172–1177
103. Dutton RP: Factor VII and the brain: Time to get this research done! *Crit Care* 2007; 11:161
104. Ho AM, Dion PW, Karmakar MK: Use of recombinant activated factor VII in patients with severe coagulopathy and bleeding. *Anesthesiology* 2003; 98:1025–1026
105. Holcomb JB, Neville HL, Fischer CF, et al: Use of recombinant FVIIa for intraperitoneal coagulopathic bleeding in a septic patient. *Curr Surg* 2003; 60:423–427
106. Klemcke HG, Delgado A, Holcomb JB, et al: Effect of recombinant FVIIa in hypothermic, coagulopathic pigs with liver injuries. *J Trauma* 2005; 59:155–161
107. Martinowitz U, Holcomb JB, Pusateri AE, et al: Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. *J Trauma* 2001; 50:721–729
108. Martinowitz U, Kenet G, Segal E, et al: Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma* 2001; 51:431–438
109. Martinowitz U, Kenet G, Lubetski A, et al: Possible role of recombinant activated factor VII (rFVIIa) in the control of hemorrhage associated with massive trauma. *Can J Anaesth* 2002; 49:S15–S20
110. Martinowitz U, Michaelson M: Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. *J Thromb Haemost* 2005; 3:640–648
111. Schreiber MA, Holcomb JB, Hedner U, et al: The effect of recombinant factor VIIa on coagulopathic pigs with grade V liver injuries. *J Trauma* 2002; 53:252–257
112. Boffard KD, Riou B, Warren B, et al: Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: Two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma* 2005; 59:8–15
113. Perkins JG, Schreiber MA, Wade CE, et al: Early versus late recombinant factor VIIa in combat trauma patients requiring massive transfusion. *J Trauma* 2007; 62:1095–1099
114. Rizoli SB, Boffard KD, Riou B, et al: Recombinant activated factor VII as an adjunctive therapy for bleeding control in severe trauma patients with coagulopathy: Subgroup analysis from two randomized trials. *Crit Care* 2006; 10:R178
115. Kheirabadi BS, Delgado AV, Dubick MA, et al: In vitro effect of activated recombinant factor VII (rFVIIa) on coagulation properties of human blood at hypothermic temperatures. *J Trauma* 2007; 63:1079–1086
116. Dutton RP, Stein DM, Hess JR, et al: Recombinant factor VIIa and thromboembolic events. *JAMA* 2006; 296:43–44
117. O'Connell KA, Wood JJ, Wise RP, et al: Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006; 295:293–298
118. Eastridge BJ, Owsley J, Sebesta J, et al: Admission physiology criteria after injury on the battlefield predict medical resource utilization and patient mortality. *J Trauma* 2006; 61:820–823
119. Eastridge BJ, Salinas J, McManus JG, et al: Hypotension begins at 110 mm Hg: Redefining 'hypotension' with data. *J Trauma* 2007; 63:291–297
120. Holcomb JB, Niles SE, Miller CC, et al: Prehospital physiologic data and lifesaving interventions in trauma patients. *Mil Med* 2005; 170:7–13
121. Gentilello LM: Advances in the management of hypothermia. *Surg Clin North Am* 1995; 75:243–256
122. Holcomb JB, Salinas J, McManus JM, et al: Manual vital signs reliably predict need for life-saving interventions in trauma patients. *J Trauma* 2005; 59:821–828
123. Alam HB, Chen Z, Ahuja N, et al: Profound hypothermia protects neurons and astrocytes, and preserves cognitive functions in a swine model of lethal hemorrhage. *J Surg Res* 2005; 126:172–181
124. Alam HB, Casas F, Chen Z, et al: Development and testing of portable pump for the induction of profound hypothermia in a swine model of lethal vascular injuries. *J Trauma* 2006; 61:1321–1329
125. Alam HB, Chen Z, Li Y, et al: Profound hypothermia is superior to ultraprofound

hypothermia in improving survival in a swine model of lethal injuries. *Surgery* 2006; 140:307–314
126. Alam HB, Rhee P, Honma K, et al: Does the rate of rewarming from profound hypothermic arrest influence the outcome in a swine model of lethal hemorrhage? *J Trauma* 2006; 60:134–146
127. Behringer W, Kentner R, Wu X, et al: Thiopental and phenytoin by aortic arch flush for cerebral preservation during exsanguination cardiac arrest of 20 minutes in dogs. An exploratory study. *Resuscitation* 2001; 49:83–97
128. Behringer W, Safar P, Wu X, et al: Survival without brain damage after clinical death of 60–120 mins in dogs using suspended animation by profound hypothermia. *Crit Care Med* 2003; 31:1523–1531
129. Bellamy R, Safar P, Tisherman SA, et al: Suspended animation for delayed resuscitation. *Crit Care Med* 1996; 24(Suppl): S24–S47
130. Blackstone E, Morrison M, Roth MB: H2S induces a suspended animation-like state in mice. *Science* 2005; 308:518
131. Blackstone E, Roth MB: Suspended animation-like state protects mice from lethal hypoxia. *Shock* 2007; 27:370–372
132. Chen Z, Chen H, Rhee P, et al: Induction of profound hypothermia modulates the immune/inflammatory response in a swine model of lethal hemorrhage. *Resuscitation* 2005; 66:209–216
133. Holzer M, Behringer W: Therapeutic hypothermia after cardiac arrest. *Curr Opin Anaesthesiol* 2005; 18:163–168
134. Karplus H: Suspended animation and resuscitation. A historical review in the light of experimental hypothermia. *J Forensic Med* 1966; 13:68–74
135. Nozari A, Safar P, Wu X, et al: Suspended animation can allow survival without brain damage after traumatic exsanguination cardiac arrest of 60 minutes in dogs. *J Trauma* 2004; 57:1266–1275
136. Richards V, Pinto D, Coombs P: Studies in suspended animation by hypothermia combined with hyperbaric oxygenation. *Ann Surg* 1963; 158:349–362
137. Roth MB, Nystul T: Buying time in suspended animation. *Sci Am* 2005; 292:48–55
138. Satava RM: Looking forward. *Surg Endosc* 2006; 20(Suppl 2):S503–S504
139. Svensson LG: Antegrade perfusion during suspended animation? *J Thorac Cardiovasc Surg* 2002; 124:1068–1070
140. Szabo C: Hydrogen sulphide and its therapeutic potential. *Nat Rev Drug Discov* 2007; 6:917–935
141. Teodoro RO, O'Farrell PH: Nitric oxide-induced suspended animation promotes survival during hypoxia. *EMBO J* 2003; 22: 580–587
142. Tisherman SA, Rodriguez A, Safar P: Therapeutic hypothermia in traumatology. *Surg Clin North Am* 1999; 79:1269–1289
143. Tisherman SA: Suspended animation for resuscitation from exsanguinating hemorrhage. *Crit Care Med* 2004; 32(Suppl):S46–S50
144. Traynor J: Suspended animation. *Health Serv J* 2002; 112:17, 19