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Review

Are we giving enough coagulation factors during major trauma resuscitation?

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Abstract

Hemorrhage is a major cause of trauma deaths. Coagulopathy exacerbates hemorrhage and is commonly seen during major trauma resuscitation, suggesting that current practice of coagulation factor transfusion is inadequate. Reversal of coagulopathy involves normalization of body temperature, elimination of the causes of disseminated intravascular coagulation (DIC), and transfusion with fresh-frozen plasma (FFP), platelets, and cryoprecipitate. Transfusion should be guided by clinical factors and laboratory results. However, in major trauma, clinical signs may be obscured and various factors conspire to make it difficult to provide the best transfusion therapy. Existing empiric transfusion strategies for, and prevailing teachings on, FFP transfusion appear to be based on old studies involving elective patients transfused with whole blood and may not be applicable to trauma patients in the era of transfusion with packed red blood cells (PRBCs). Perpetuation of such concepts is in part responsible for the common finding of refractory coagulopathy in major trauma patients today. In this review, we argue that coagulopathy can best be avoided or reversed when severe trauma victims are transfused with at least the equivalent of whole blood in a timely fashion.

Keywords: Acidosis; Blood coagulation factors; Disseminated intravascular coagulation; Hemorrhage; Hypothermia; Plasma; Transfusion; Wounds and injuries

Uncontrolled hemorrhage is responsible for 40% of trauma deaths [1]. Coagulopathy is a component of the trauma triad of death that also includes hypothermia and acidosis [2–4]. Given that a mainstay of trauma management is the replacement of lost and consumed coagulation factors, the very fact that coagulopathy is commonly seen during trauma resuscitation points to a logical conclusion: we are not giving enough coagulation factors during major trauma resuscitation.

Causes of Coagulopathy

The causes of trauma- and resuscitation-related coagulopathy are complex, not fully understood, and include disseminated intravascular coagulation (DIC), dilution, hypothermia, and major metabolic derangements.

Disseminated intravascular coagulation

DIC is a common complication of brain and extensive tissue injuries. Thromboplastin in blood and exposed endothelium trigger disseminated coagulation. Based on the prothrombin time (PT), activated partial thromboplastin time (APTT), plasma fibrinogen and D-dimers, and platelet counts, Kearney et al [5] found that 41% of trauma patients with head injury and 25% of those without head injury had DIC. Keller et al [6] found that the incidence of coagulopathy correlated with the Glasgow Coma Scale (GCS) score. May et al [7] found that 81% of patients with a GCS $\leq$6 were coagulopathic, as were all those with a GCS $<$5. The incidence of coagulopathy was 21% in patients with an injury severity score (ISS) of 15–29, 41% in patients with ISS 30–44, 59% in patients with ISS 45–59, and 79% in those with ISS 60–75 [7].

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Coagulopathy was associated with an increased mortality over and above that of the ISS [7]. Brohi et al [8] found that 24.4% of 1088 trauma patients on admission had a coagulopathy (PT >18 seconds, APTT >60 seconds, or thrombin time >15 seconds [1.5 × normal]), having received only minimal fluid therapy in the field. Increased fibrinolysis naturally accompanies widespread activation of the coagulation system. Furthermore, in patients with head injury, α_2-plasmin inhibitor, which inactivates plasmin, a key enzyme in fibrinolysis, is greatly reduced due to consumption [9] and possibly dilution and reduced production.

Treatment of patients with DIC includes the prevention of further tissue injuries and hypoxia, and the transfusion of cryoprecipitate, fresh-frozen plasma (FFP), and platelets.

Dilutional coagulopathy

By definition, dilutional coagulopathy occurs when lost blood is replaced with fluids that do not contain adequate coagulation factors. It is a recognized complication of massive transfusion and is, arguably, preventable. Dilution sometimes starts at the scene of the accident, beginning with a severely injured patient being resuscitated with crystalloid solution, followed by several units of packed red blood cells (PRBCs) in the emergency department, before admission coagulation test results become available. When fluid resuscitation prior to arrival at the hospital was the norm, 33% to 55% of major trauma patients had an admission blood sample that indicated an APTT >55 seconds and a PT >18 seconds [10]. These results in a hemorrhaging patient would trigger a call for FFP. After a 20- to 30-minute thawing process, the FFP would be used up, and further delay would be incurred, especially if one "went by the book," and insisted on laboratory confirmation in the next blood sample for guidance. Today, even when no fluid resuscitation is administered at the scene of the accident, the above sequence is often played out in the hospital, with similar results.

The treatment of dilutional coagulopathy is the transfusion of coagulation factors (and platelets).

Hypothermia

Despite aggressive prevention strategies, most severely injured patients initially develop hypothermia. Hypothermia impairs platelet aggregation [11] and potentiates coagulopathy in factor-deficient plasma. Johnston et al [12] found that at 35°C, without dilution, there were decreases of function in all factors, such that factors XI and XII are only functioning at 65% of normal, and at 33°C, their activities are 17% and 32%, respectively. At 32°C and without dilution, the PT performed without pre-warming the blood sample to 37°C is 1.5 × normal [13]. Using blood from healthy volunteers, Wolberg et al [14] found at 33°C a modest but nonstatistically significant reduction in coagulation enzyme cascade enzyme activities, and a significant reduction in platelet aggregation and adhesion after activation by thrombin. Below 33°C, enzyme activities were also significantly reduced. The PT and APTT normally do not reflect hypothermia-induced coagulopathy because blood samples are prewarmed to 37°C before measurements. Patients (n = 28) with high Trauma Score (15 or 16) and Abdominal Injury Severity Score ≥9 had significantly less blood loss when body temperature was maintained above 35°C when compared to patients (n = 29) whose temperature was 33 and 35°C (540 ± 580 mL vs. 1820 ± 1160 mL; $P < .003$) [15]. In patients with an ISS >25, mortality rates of 100%, 69%, 40%, and 7% were associated with core temperatures of <32°C, <33°C, <34°C, and >34°C, respectively [16]. In most situations, great effort must be taken to prevent and reverse hypothermia (without inducing hyperthermia) during trauma resuscitation. Indeed, in recent years, clinicians have been increasingly employing warming blankets, fluid warmers, staged laparotomy, etc., with improved outcome [3].

In our opinion, until normothermia is restored, it may be useful to treat all of the other causes of coagulopathy more aggressively to reduce any additive or synergistic effects.

Acidosis

Meng et al [17] found that the rate of activated factor X formation by activated factor VII/tissue factor complex and the activity of activated factor VII alone on phospholipid (found in cell membranes) vesicles are substantially reduced in a pH <7.4 environment. A decreased pH also decreased the rate of prothrombin activation by activated factor X/activated factor V complex on phospholipid vesicles. Interestingly, they found that these activities increased in an alkaline environment. Viuff et al [18] found significantly reduced clot formation rate based on thrombelastography (angle α) in normal blood acidified to pH of 7 in vitro. Djaldetti et al [19] observed that healthy platelets incubated at a pH of 5.5 transform into spheres deprived of pseudopodia and aggregating tendency, while at a pH of 9, the platelets underwent internal organelle transformation similar to that caused by thrombin, and developed pseudopodia that facilitated aggregation. Impaired hemostatis at a pH of 7.2 had also been demonstrated by Dunn et al [20]. Cosgriff et al [21] found that among patients with an ISS >25 and pH <7.1, half had a PT and/or APTT ≥2 × the control value.

Reversal of acidosis depends on improved tissue perfusion, avoidance of hypoventilation and excessive saline use [22], and, in severe cases, may require titrated bicarbonate administration. Although never proven, aggressive correction of coagulopathy due to other causes may lessen the impact of acidosis on the overall coagulopathic picture.

Difficulties in Preventing or Reversing Coagulopathy During Major Trauma Resuscitation

Apart from correction of hypothermia and bleeding control, an important step for eliminating and preventing coagulopathy is the replenishment of consumed and lost factors (and platelets) through FFP, cryoprecipitate (and platelet) transfusion. Blood products are expensive and potentially dangerous. Ideally, they should be given only if microvascular bleeding is present and PT and APTT are $>1.5 \times$ control [23]. Unfortunately, diffuse bleeding in severely injured patients is often occult and anatomically ill-defined, and PT and APTT results are rarely reported quickly. Further complicating the task of requesting for FFP is the time required to deliver, thaw, and transfuse FFP, and the refusal of some blood banks to accept unused FFP. Another difficulty is created by the perpetuation in books and reviews of a "conservative" attitude toward FFP use during major trauma resuscitation.

Current attitude toward the use of FFP in major trauma resuscitation

By not taking into consideration the practical problems discussed above, many authors provide inappropriate FFP transfusion strategies in the face of severe traumatic hemorrhage. Empiric strategies (e.g., 1 unit of FFP for every 5–6 units of PRBCs [24–26], at least 1 unit for every 4 units of PRBCs [27] or every 10 units of PRBC [28]) have been advocated by some, while others have proposed that a minimum of 2 units of FFP should be given based on a PT $\geq 1.8 \times$ control, or that 1–2 units of FFP for every 2 units of PRBCs should henceforth be given until the PT is controlled [29]. These strategies appear to be fundamentally flawed in severe trauma. It seems counterintuitive that one could transfuse with the equivalent of blood deficient in clotting factors (as would be the case with any of these empiric formulae), and still expect that a hemorrhaging patient would not eventually suffer worsening coagulation deficiency. In our opinion, all of these recommendations are too conservative when applied to major trauma resuscitation. If they were not, coagulopathy would not be so commonly associated with severe trauma. For the record, this conservative attitude on FFP use in major trauma resuscitation appears not to be the culmination of rigorous and statistically robust studies, but to be based on research and expert opinions that were extrapolated from the non-trauma literature, or are no longer relevant today. Previous work had suggested that despite major blood loss, dilutional coagulopathy develops late during surgery. However, the often cited studies to support this claim were on patients undergoing plasma-exchange transfusion, showing that one third of their coagulation factors were still present in their plasma after an entire blood volume has been replaced under normovolemic conditions [30,31]. Translating these findings to major trauma patients, who receive transfusion *after*, not concurrently with the onset of, blood loss, may not be appropriate. To take an extreme example, if a patient should hypothetically be drained of all his blood after trauma, then is given an entire blood volume of PRBCs and colloid (or crystalloid equivalent) devoid of coagulation factors, he should not still have one third of his normal factor levels. Other frequently cited studies on dilutional coagulopathy were also on elective surgical patients [32–35]. Trauma patients suffer an initial contraction of blood volume, whereas in elective patients, normovolemia is maintained. As a result, for the same volume of bleeding, the degree of factor loss is much reduced in the latter. Upon volume resuscitation initially with crystalloid/colloid and PRBCs, the trauma patient's plasma coagulation factors are more severely diluted. Trauma patients have 3 more reasons why they may be more prone to coagulopathy: hypothermia, consumptive coagulopathy, and acidosis are generally absent in elective cases, but are common among trauma patients.

Prior to the late 1980s, blood transfusion was in the form of whole blood, and the main hemostatic consequence of mass transfusion was thrombocytopenia [32–34]. Coagulopathy developed later than thrombocytopenia (but did nonetheless) because whole blood is roughly equivalent to 1 unit of PRBCs plus 1 unit of FFP (minus the platelets and portions of some labile coagulation factors). A whole generation of clinicians was trained to believe that dilution of coagulation factors with massive transfusion occurred late. Then, beginning in the late 1980s, whole blood was almost completely replaced by PRBCs that have virtually no coagulation factors. Despite this important change, the doctrine that FFP is required late in the resuscitation process continues to be preached. We do not see the logic behind the notion that thrombocytopenia develops before coagulopathy [36]. First, there is no prospective study on this subject in severely injured patients in this era of using PRBCs rather than whole blood. Second, with its considerable reserve marginalized in blood vessels and stored in the spleen, platelets do not get depleted quickly. By the time significant thrombocytopenia develops, why should the coagulation factors, many of which do not have the capacity to acutely increase to a great extent, not also have decreased to significantly low levels?

Although the conservative approaches to FFP dosing during major trauma resuscitation promulgated in textbooks and reviews are inconsistent with our experience and that of many of our frontline colleagues, convincing published data to refute (or support) them are not available. Prospective, let alone randomized, blinded, controlled, intention-to-treat–analyzed trials are difficult to conduct in severe trauma. Unfortunately, trauma does not wait for such data, and decisions must be made every day in emergency and operating rooms, and in intensive care units on how to combat coagulopathy. While some academics may decry "the lack of convincing evidence" that increased use of FFP during major trauma resuscitation improves outcome, many of our

colleagues already are convinced that current recommendations in textbooks and in review papers are inadequate or impractical.

Proposing a More Aggressive Coagulation Factor Transfusion Strategy

Data demonstrating high incidences of coagulopathy in patients with a high ISS even before fluid resuscitation had begun [8] argue strongly for a more aggressive coagulation factor replacement strategy right from the start for severe cases. If neglected, further dilution of coagulation factors occurs as resuscitation begins and catching up becomes very difficult. Some may argue that FFP, cryoprecipitate, and platelet transfusion in the absence of microvascular bleeding is tantamount to mismanagement. Strictly speaking, we are not in disagreement with this "textbook" recommendation, and concur that if it is certain that there is no microvascular bleeding, and the patient's clinical picture is stable, coagulation factors should not be given. Likewise, if coagulation test results are available quickly (as might be provided by an accurate point-of-care device), the porter service is efficient, and a fast warmer that does not denature plasma protein is available, then one could have the luxury of waiting for the test results before deciding on the need for FFP transfusion. We also agree that the recommendation of one unit of FFP for every 4–10 units of PRBC [24–29] is appropriate in patients who are not severely injured and coagulopathic, as long as we are still in the early phase of resuscitation, when temporary natural protective mechanisms such as increased mobilization of coagulation factors and hypercoagulabiliy are in effect.

What we would like to see replace the current textbook teachings is a factor transfusion strategy that is adopted ideally before, and definitely no later than, the point when loss of approximately 1 blood volume within a relatively short period of time has occurred, or when the PT and APTT are $>1.5 \times$ control, and hemorrhage is unabated, or when the ISS is ≥ 30 [8]. From that point onward, 1 unit of FFP (and possibly platelets) should be given for every unit of PRBCs given, with little or no crystalloid or colloid. In other words, we recommend transfusing with the equivalent of whole blood. In the not uncommon situation when factor concentration is already much less than 40% (APTT >55 seconds, PT >18 seconds), and the patient is still bleeding, FFP may need to be given even more aggressively, in the ratio of 1–1.5 units of FFP for every unit of PRBCs transfused. Given the inherent delays in readying FFP, the window of opportunity for preventing coagulopathy in a hemorrhaging patient could be small. In order not to have to play "catch up," it is much better to proactively adopt an aggressive strategy in coagulation factor transfusion before factor levels decline to a critical level, especially if bleeding is severe and control of bleeding is nowhere near imminent. Should significant hypothermia be present, maximum rewarming is required, and coagulation factors should be topped up probably even more aggressively to avoid the additive or synergistic effect of hypothermia and low plasma coagulation factor concentration (our unproven view). In the thick of a major resuscitation when control of the hemorrhage is not yet at hand, it is better to not risk a downward-spiraling coagulopathy from which the patient never recovers, not to mention the guaranteed increased exposure to blood products, than to avoid the theoretical risks of unnecessary exposure to blood products. Obviously, trauma resuscitation is a complex and dynamic process, one that should not be managed with inflexible dogma and a few simple formulas. The best way to use blood products sensibly and efficiently is by maintaining vigilance, a flexible attitude, and the appropriate use of laboratory measurements of complete blood count and coagulation indices. In our experience with severe trauma, one is far less likely to end up giving way too much FFP before realizing it, than to lose a fight against refractory coagulopathy.

Although, as mentioned earlier, no blinded prospective randomized controlled trial is available on how FFP should be given, less robust data [3,10,37–45] are available that support or are consistent with the kind of "aggressive" FFP strategies we are proposing.

Hewson et al [37] retrospectively reviewed 64 massively transfused patients (8 had multiple trauma) and identified that significant, albeit transient as a result of successful resuscitation, coagulopathy occurred after crystalloid administration, and that the APTT was closely correlated with the number of liters of crystalloid infused and the duration of antecedent hypotension. They recommend that in patients with major and ongoing bleeding, FFP and PRBC should be given in a 1:1 ratio to avoid a dilutional coagulopathy [37].

Faringer et al [10] echoed the experience of many clinicians that during the massive transfusion of PRBCs, critically abnormal coagulation test results were commonly noted. They retrospectively studied 44 trauma patients and found that 33% of those with blunt trauma and brain injuries and 55% of those with penetrating trauma and no brain injuries had a PT >18 seconds and APTT >55 seconds on arrival in the emergency department, after having received only electrolyte solutions as pre-hospital therapy. They found that the magnitude of blood loss, and not the mechanism of injury, primarily influenced the development of coagulopathy during massive transfusion. They recommended early correction of coaglulation abnormality.

Phillips et al [38] retrospectively reviewed the records of 56 patients who had received more than 31–39 units of blood (90% was in the form of PRBCs) till death or 36 hours after admission. They identified a 77% mortality rate among patients who developed coagulopathy as defined by microvascular bleeding. They argued for an aggressive use of FFP for prophylaxis in these patients.

Harvey et al [39] retrospectively reviewed 43 patients who received 19.2 ± 10.4 units of PRBCs in 24 hours. Twenty of them were trauma patients. The 43 patients used

824 units of PRBCs, 457 units of FFP, and 370 units of platelets. Overall survival rate was 60%. Severe coagulopathy occurred in 19 patients (44%) with a mortality rate of 74%. They recommended targeting component replacement such that PT and APTT are under 1.5 × normal, and their "best guess" strategy is the replacement of 5 units of FFP and 10 units of platelets per 10 units of PRBCs, after the initial 10 units of PRBCs have been transfused.

Mitchell et al [40] retrospectively reviewed the records of 30 penetrating trauma patients who received 11.7 ± 4.9 (SD) (range 8 to 43) liters of crystalloid, 7.6 ± 3 (range 4 to 45) units of PRBCs, and 7.0 ± 3.6 (range 1 to 30) units of FFP during the first 24 hours of admission. They found that nonsurvivors demonstrated, among others, a greater incidence of coagulopathy (62% vs. 4.5%). They recommended that FFP and platelets should be given aggressively on an empiric basis without delaying for laboratory confirmation of coagulopathy.

Cinat et al [3] retrospectively analyzed survival following massive transfusion (50–114 units of PRBCs over 24 hours) in patients who had undergone trauma. They compared the periods 1988–1992 and 1993–1997. Survival increased during the more recent years ($P = .03$). They attributed the improvement to more aggressive correction of coagulopathy, more efficient use of warming measures, decreased operative times for the initial operation, the use of staged laparotomy, and increased use of component therapy. They found that FFP use was 1 unit per 1.8 units of PRBCs in survivors versus 2.5 units of PRBCs for nonsurvivors.

Leslie and Toy [41] retrospectively reviewed 39 patients (25 involved in trauma) given 10 or more units of PRBCs in 24 hours, and found that after transfusion of 12 units of PRBCs, 100% of patient had a PT >1.5 × mid-range of normal, compared to 36% of patients given <12 units.

Horst et al [42] retrospectively reviewed 154 trauma patients and found prolongation of coagulation indices with increasing transfusion of plasma-poor red blood cells. Coagulopathy was diagnosed clinically in 43 patients, 32 (74%) of whom died.

Using a computer model of exanguination, Hirshberg et al [43] concluded that dilutional coagulopathy is common and occurs early. They determined that FFP transfusion should begin early using an FFP:PRBC ratio of 2:3 [43]. Using a mathematical model of normovolemic hemodilution, Singbartl et al [44] determined that a critically low fibrinogen level is sometimes breached before critically low hematocrit and platelet concentrationa. Our own simulation shows similar results and confirms what would seem intuitively obvious that the equivalent of whole blood is required to prevent dilution coagulopathy, and further supplementation with FFP is needed to correct established dilution coagulopathy.

Implicit endorsement of increased FFP use can also be found in the claim that whole blood is superior to PRBCs for trauma resuscitation [45], and in the effectiveness of staged laparotomy [2]. During the initial laparotomy and in the intensive care unit, re-warming, aggressive use of platelets, cryoprecipitate, and FFP to normalize the fibrinogen level and the PT and APTT, monitoring for signs of abdominal compartment syndrome, and stabilization of vital parameters, etc., are carried out. Retrospective studies have documented reduction in operative times, and salvage rates of 20% to 60% in patients who formerly would probably have died in the operating room [2,46–48]. Could the superiority of the delayed resuscitation ("scoop-and-run") technique for penetrating torso trauma be due not just to the prevention of the re-opening of bleeding sites, but also to the prevention of hypothermic and dilutional coagulopathy caused by zealous transfusion of fluids by ambulance and emergency staff?

Platelets are similarly vulnerable to depletion during major resuscitation. However, platelets do not require thawing and can be given very quickly (catching up is easier). As such, thrombocytopenia is rarely ever a downward spiral from which one never recovers.

While arguing for more liberal use of FFP, we are acutely aware of inappropriate FFP transfusion practices in the past. Any suggestion for increased FFP use should be tempered by the warning against repetition of past abuses. Whether or not more liberal use of FFP in trauma would lead to decreased net bleeding and better outcome (our view), or result in increased exposure of patients to blood products with negative implications, is best resolved by clinical studies. Blood product requirements may also be reduced with the use of recombinant activated factor VII. However, this potent (and impressive) agent still requires coagulation factors for thrombin generation. Moreover, it is expensive, is not yet approved for trauma resuscitation, and the optimal timing of its use is not well defined. Just as antibiotics have not eliminated sepsis, activated factor VII is not likely to solve all of our patients' bleeding problems [49]. Its eventual broad availability and better guidelines are eagerly anticipated. Meanwhile, we should not forget that we currently have a serious problem of coagulopathy in severely injured patients, caused, in part, by the underuse of coagulation factors.

References

[1] Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. J Trauma 1995;38:185–93.
[2] Gentilello LM, Pierson DJ. Trauma critical care. Am J Respir Crit Care Med 2001;163:604–7.
[3] Cinat ME, Wallace WC, Nastanski F, et al. Improved survival following massive transfusion in patients who have undergone trauma. Arch Surg 1999;134:964–8.
[4] Eddy VA, Morris JA Jr, Cullinane DC. Hypothermia, coagulopathy, and acidosis. Surg Clin North Am 2000;80:845–54.
[5] Kearney TJ, Bentt L, Grode M, et al. Coagulopathy and catecholamines in severe head injury. J Trauma 1992;32:608–11.
[6] Keller MS, Fendya DG, Weber TR. Glasgow Coma Scale predicts coagulopathy in pediatric trauma patients. Semin Pediatr Surg 2001; 10:12–6.

[7] May AK, Young JS, Butler K, et al. Coagulopathy in severe closed head injury: is empiric therapy warranted? Am Surg 1997;63:233–6.
[8] Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003;54:1127–30.
[9] Kushimoto S, Yamamoto Y, Shibata Y, et al. Implications of excessive fibrinolysis and α2-plasmin inhibitor deficiency in patients with severe head injury. Neurosurgery 2001;49:1084–90.
[10] Faringer PD, Mullins RJ, Johnson RL, et al. Blood component supplementation during massive transfusion of AS-1 red cells in trauma patients. J Trauma 1993;34:481–7.
[11] Gubler KD, Gentilello LM, Hassantash SA, et al. The impact of hypothermia on diltutional coagulopathy. J Trauma 1994;36:847–51.
[12] Johnston TD, Chen Y, Reed RL II. Functional equivalence of hypothermia to specific clotting factor deficiencies. J Trauma 1994;37: 413–7.
[13] Reed RL II, Johnston TD, Hudson JD, et al. The disparity between hypothermic coagulopathy and clotting studies. J Trauma 1992;33: 465–70.
[14] Wolberg AS, Meng ZH, Monroe DM III, et al. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma 2004;56:1221–8.
[15] Bernabei AF, Levison MA, Bender JS. The effects of hypothermia and injury severity on blood loss during trauma laparotomy. J Trauma 1992;33:835–9.
[16] Jurkovich GJ, Greiser WB, Luterman A, et al. Hypothermia in trauma victims: an ominous predictor of survival. J Trauma 1987; 27:1019–24.
[17] 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;55:886–91.
[18] Viuff D, Johansson PI, Holcomb JB, et al. In vitro evaluation of the impact of colloid hemodilution, acidosis, and hypothermia on the effect of recombinant factor VIIa (NovoSeven). Presented at the Advanced Technology Applications for Combat Casualty Care 2004 Conference, St. Pete Beach, FL, August 16–18, 2004.
[19] Djaldetti M, Fishman P, Bessler H, et al. pH induced platelet ultrastructural alterations. Arch Surg 1979;114:707–10.
[20] Dunn EL, Moore EE, Breslich DJ, et al. Acidosis induced coagulopathy. Surg Forum 1979;30:471–8.
[21] 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;42:857–61.
[22] Ho AMH, Karmakar MK, Contardi LH, et al. Excessive use of normal saline in managing traumatized patients in shock. J Trauma 2001;51:173–7.
[23] Practice guidelines for blood component therapy. A report by the American Society of Anesthesiologists Task Force on blood component therapy. Anesthesiology 1996;84:498–501.
[24] Stern SA, Bobek EMK. Resuscitation: management of shock. In: Ferrera PC, Colucciello SA, Marx JA, et al, editors. *Trauma Management: An Emergency Medicine Approach*. St. Louis, MO: Mosby; 2001:75–102.
[25] Montenegro LM, Jobes DR. Complications of massive transfusion. In: Atlee JL, editor: *Complications in Anesthesia*. Philadelphia, PA: Saunders; 1999:668–73.
[26] Waldspurger Robb WJ. Massive transfusion in trauma. AACN Clin Issues 1999;10:69–74.
[27] Turner DAB. Emergency anaesthesia. In: Aitkenhead AR, Rowbotham DJ, Smith G, editors. *Textbook of Anaesthesia*. 4th ed. Edinburgh, UK: Churchill Livingstone; 2001:619–28.
[28] http://www.usc.edu/hsc/medicine/surgery/trauma/Trauma_Protocols/5MASSBLD.html, accessed Aug 18, 2004.
[29] Murphy WG, Davies MJ, Eduardo A. The haemostatic response to surgery and trauma. Br J Anaesth 1993;70:205–13.
[30] Flaum MA, Cuneo RA, Applebaum FR, et al. The hemostatic imbalance of plasma-exchange transfusion. Blood 1979;54:694–702.
[31] Domen RE, Kennedy MS, Jones LL, et al. Hemostatic imbalances produced by plasma excahnge. Transfusion 1984;24:336–9.
[32] Murray DJ, Olson J, Strauss R, et al. Coagulation changes during packed red cell replacement of major blood loss. Anesthesiology 1988;69:839–45.
[33] Laks H, Handin RI, Martin V, et al. The effects of acute normovolemic hemodilution on coagulation and blood utilization in major surgery. J Surg Res 1976;20:225–30.
[34] Umlas J, Sakhuja R. The effect on blood coagulation of the exclusive use of frozen red cell transfusions during and after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1975;70:519–23.
[35] Murray DJ, Pennell BJ, Weinstein SL, et al. Packed red cells in acute blood loss: dilutional coagulopathy as a cause of surgical bleeding. Anesth Analg 1995;80:336–42.
[36] Barker SJ. Anesthesia for trauma. Anesth Analg 2003;96(Suppl):1–6.
[37] Hewson JR, Neame PB, Kumar N. Coagulopathy related to dilution and hypotension during massive transfusion. Crit Care Med 1985;13: 387–91.
[38] Phillips TF, Soulier G, Wilson RF. Outcome of massive transfusion exceeding two blood volumes in trauma and emergency surgery. J Trauma 1987;27:903–10.
[39] Harvey MP, Greenfield TP, Sugrue ME, et al. Massive blood transfusion in a tertiary referral hospital. Clinical outcomes and haemostatic complications. Med J Aust 1995;163:356–9.
[40] Mitchell KJ, Moncure KE, Onyeije C, et al. Evaluation of massive volume replacement in the penetrating trauma patient. J Natl Med Assoc 1994;86:926–9.
[41] Leslie SD, Toy PTCY. Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. Am J Clin Pathol 1991;96:770–3.
[42] Horst HM, Dlugos S, Fath JJ, et al. Coagulopathy and intraoperative blood salvage (IBS). J Trauma 1992;32:646–53.
[43] Hirshberg A, Dugas M, Banez EI, et al. Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation. J Trauma 2003;54:454–63.
[44] Singbartl K, Innerhofer P, Radvan J, et al. Hemostasis and hemodilution: a quantitative mathematical guide for clinical practice. Anesth Analg 2003;96:929–35.
[45] Bernstein DP. Transfusion therapy in trauma. In: Capan LM, Miller SM, Turndorf H, editors. *Trauma Anesthesia and Intensive Care.* New York, NY: Lippincott; 1991:167–205.
[46] Morris JA, Eddy VA, Blinman TA, et al. The staged celiotomy for trauma: issues in packing and reconstruction. Ann Surg 1993;217: 576–84.
[47] Moore EE, Burch JM, Franciose RJ, et al. Staged physiologic restoration and damage control surgery. World J Surg 1998;22:1184–90.
[48] Sharp KW, Locicero RJ. Abdominal packing for surgically uncontrollable hemorrhage. Ann Surg 1992;215:467–75.
[49] Ho AMH, Dion PW, Karmakar MK. Use of recombinant activated factor VII in patients with severe coagulopathy and bleeding (letter). Anesthesiology 2003;98:1025–6.