Massive transfusion and nonsurgical hemostatic agents

Jeremy G. Perkins, MD, FACP; Andrew P. Cap, MD, PhD; Brendan M. Weiss, MD; Thomas J. Reid, MD, PhD; Charles E. Bolan, MD

Background: Hemorrhage in trauma is a significant challenge, accounting for 30% to 40% of all fatalities, second only to central nervous system injury as a cause of death. However, hemorrhagic death is the leading preventable cause of mortality in combat casualties and typically occurs within 6 to 24 hrs of injury. In cases of severe hemorrhage, massive transfusion may be required to replace more than the entire blood volume. Early prediction of massive transfusion requirements, using clinical and laboratory parameters, combined with aggressive management of hemorrhage by surgical and nonsurgical means, has significant potential to reduce early mortality.

Discussion: Although the classification of massive transfusion varies, the most frequently used definition is ten or more units of blood in 24 hrs. Transfusion of red blood cells is intended to restore blood volume, tissue perfusion, and oxygen-carrying capacity; platelets, plasma, and cryoprecipitate are intended to facilitate hemostasis through prevention or treatment of coagulopathy. Massive transfusion is uncommon in civilian trauma, occurring in only 1% to 3% of trauma admissions (10, 20, 21). As a result of a higher proportion of penetrating injury in combat casualties, it has occurred in approximately 8% of Operation Iraqi Freedom admissions and in as many as 16% during the Vietnam conflict. Despite its potential to reduce early mortality, massive transfusion is not without risk. It requires extensive blood-banking resources and is associated with high mortality.

Complications of Massive Transfusion

There are numerous problems associated with MT, including infectious, immunologic, and physiological complications related to the collection, testing, preservation, and storage of blood products (Table 1). These complications can exacerbate the underlying pathophysiology of injury and the number of transfusions required independently predicts for mortality (20, 28, 29). Trauma patients requiring transfusion generally receive uncrossmatched type O blood until type-specific products are available. The immediate safety of uncrossmatched type O blood use in trauma is well established with no acute hemolytic reactions reported (30–32). Although type-specific uncrossmatched blood has also been used successfully for MT (33, 34), acute hemolytic reactions have been associated with such blood products (35). Patients who have been transfused large volumes of type O stored “whole blood” (thus containing type O plasma) have been known to subsequently develop acute hemolytic reactions to type-specific blood, presumably from transfused isoagglutinins against type A or B antigens (36). Delayed serologic conversion and hemolytic reactions against blood alloantigens are also

Hemorrhage in trauma is a significant challenge, accounting for 30% to 40% of all fatalities, second only to central nervous system injury as a cause of death. However, hemorrhagic death is the leading preventable cause of mortality in combat casualties and typically occurs within 6 to 24 hrs of injury. In cases of severe hemorrhage, massive transfusion may be required to replace more than the entire blood volume. Early prediction of massive transfusion requirements, using clinical and laboratory parameters (12–14) combined with aggressive management of hemorrhage by surgical and nonsurgical means, has significant potential to reduce early mortality. Although the classification of massive transfusion varies (15–17), the most frequently used definition is ten or more units of blood in 24 hrs (18, 19). Transfusion of red blood cells is intended to restore blood volume, tissue perfusion, and oxygen-carrying capacity; platelets, plasma, and cryoprecipitate are intended to facilitate hemostasis through prevention or treatment of coagulopathy. Massive transfusion is uncommon in civilian trauma, occurring in only 1% to 3% of trauma admissions (10, 20, 21). As a result of a higher proportion of penetrating injury in combat casualties, it has occurred in approximately 8% of Operation Iraqi Freedom admissions and in as many as 16% during the Vietnam conflict (22, 23). Despite its potential to reduce early mortality, massive transfusion is not without risk. It requires extensive blood-banking resources (24–26) and is associated with high mortality (17, 21, 27). This review describes the clinical problems associated with massive transfusion and surveys the nonsurgical management of hemorrhage, including transfusion of blood products, use of hemostatic bandages/agents, and treatment with hemostatic medications.
During massive transfusion, however, there is often insufficient time or mixture of normal metabolic activity (58). Cells (RBCs) after transfusion with stored blood, red blood cell microchimerism (40) and transfusion-related immunomodulation (41). Microchimerism is the stable persistence of a minor population of allogeneic cells and can be detected for years after transfusion. It can occur in up to 10% of transfused trauma patients, although its consequences remain uncertain (40, 42). Transfusion-related immunomodulation, however, has been associated with increased risk of infection (43–47), acute lung injury/acute respiratory distress syndrome (48–51), systemic inflammatory response syndrome (28), and multiple organ failure (52, 53). The precise mechanisms for the development of these complications are unclear, although the age of stored blood, red blood cell microparticles, foreign antigens, foreign white blood cells, and bioactive lipids with neutrophil priming have all been implicated (41, 54–56).

Hyperkalemia is a common complication of MT. Increased levels of extracellular potassium develop during the storage of red blood cells with concentrations averaging 12 mEq/L at 7 days and increasing to 32 mEq/L after 21 days of storage (57). This excess extracellular potassium is gradually taken back into red blood cells (RBCs) after transfusion with restoration of normal metabolic activity (58). During massive transfusion, however, blood administered rapidly through central lines without sufficient time or mixing of normal metabolic activity (58). Cells (RBCs) after transfusion with stored blood, red blood cell microchimerism (40) and transfusion-related immunomodulation (41). Microchimerism is the stable persistence of a minor population of allogeneic cells and can be detected for years after transfusion. It can occur in up to 10% of transfused trauma patients, although its consequences remain uncertain (40, 42). Transfusion-related immunomodulation, however, has been associated with increased risk of infection (43–47), acute lung injury/acute respiratory distress syndrome (48–51), systemic inflammatory response syndrome (28), and multiple organ failure (52, 53). The precise mechanisms for the development of these complications are unclear, although the age of stored blood, red blood cell microparticles, foreign antigens, foreign white blood cells, and bioactive lipids with neutrophil priming have all been implicated (41, 54–56).

Hyperkalemia is a common complication of MT. Increased levels of extracellular potassium develop during the storage of red blood cells with concentrations averaging 12 mEq/L at 7 days and increasing to 32 mEq/L after 21 days of storage (57). This excess extracellular potassium is gradually taken back into red blood cells (RBCs) after transfusion with restoration of normal metabolic activity (58). During massive transfusion, however, blood administered rapidly through central lines without sufficient time or mixing of normal metabolic activity (58). Cells (RBCs) after transfusion with stored blood, red blood cell microchimerism (40) and transfusion-related immunomodulation (41). Microchimerism is the stable persistence of a minor population of allogeneic cells and can be detected for years after transfusion. It can occur in up to 10% of transfused trauma patients, although its consequences remain uncertain (40, 42). Transfusion-related immunomodulation, however, has been associated with increased risk of infection (43–47), acute lung injury/acute respiratory distress syndrome (48–51), systemic inflammatory response syndrome (28), and multiple organ failure (52, 53). The precise mechanisms for the development of these complications are unclear, although the age of stored blood, red blood cell microparticles, foreign antigens, foreign white blood cells, and bioactive lipids with neutrophil priming have all been implicated (41, 54–56).

Hyperkalemia is a common complication of MT. Increased levels of extracellular potassium develop during the storage of red blood cells with concentrations averaging 12 mEq/L at 7 days and increasing to 32 mEq/L after 21 days of storage (57). This excess extracellular potassium is gradually taken back into red blood cells (RBCs) after transfusion with restoration of normal metabolic activity (58). During massive transfusion, however, blood administered rapidly through central lines without sufficient time or mixing of normal metabolic activity (58). Cells (RBCs) after transfusion with stored blood, red blood cell microchimerism (40) and transfusion-related immunomodulation (41). Microchimerism is the stable persistence of a minor population of allogeneic cells and can be detected for years after transfusion. It can occur in up to 10% of transfused trauma patients, although its consequences remain uncertain (40, 42). Transfusion-related immunomodulation, however, has been associated with increased risk of infection (43–47), acute lung injury/acute respiratory distress syndrome (48–51), systemic inflammatory response syndrome (28), and multiple organ failure (52, 53). The precise mechanisms for the development of these complications are unclear, although the age of stored blood, red blood cell microparticles, foreign antigens, foreign white blood cells, and bioactive lipids with neutrophil priming have all been implicated (41, 54–56).

Hyperkalemia is a common complication of MT. Increased levels of extracellular potassium develop during the storage of red blood cells with concentrations averaging 12 mEq/L at 7 days and increasing to 32 mEq/L after 21 days of storage (57). This excess extracellular potassium is gradually taken back into red blood cells (RBCs) after transfusion with restoration of normal metabolic activity (58). During massive transfusion, however, blood administered rapidly through central lines without sufficient time or mixing of normal metabolic activity (58). Cells (RBCs) after transfusion with stored blood, red blood cell microchimerism (40) and transfusion-related immunomodulation (41). Microchimerism is the stable persistence of a minor population of allogeneic cells and can be detected for years after transfusion. It can occur in up to 10% of transfused trauma patients, although its consequences remain uncertain (40, 42). Transfusion-related immunomodulation, however, has been associated with increased risk of infection (43–47), acute lung injury/acute respiratory distress syndrome (48–51), systemic inflammatory response syndrome (28), and multiple organ failure (52, 53). The precise mechanisms for the development of these complications are unclear, although the age of stored blood, red blood cell microparticles, foreign antigens, foreign white blood cells, and bioactive lipids with neutrophil priming have all been implicated (41, 54–56).

Hyperkalemia is a common complication of MT. Increased levels of extracellular potassium develop during the storage of red blood cells with concentrations averaging 12 mEq/L at 7 days and increasing to 32 mEq/L after 21 days of storage (57). This excess extracellular potassium is gradually taken back into red blood cells (RBCs) after transfusion with restoration of normal metabolic activity (58). During massive transfusion, however, blood administered rapidly through central lines without sufficient time or mixing of normal metabolic activity (58). Cells (RBCs) after transfusion with stored blood, red blood cell microchimerism (40) and transfusion-related immunomodulation (41). Microchimerism is the stable persistence of a minor population of allogeneic cells and can be detected for years after transfusion. It can occur in up to 10% of transfused trauma patients, although its consequences remain uncertain (40, 42). Transfusion-related immunomodulation, however, has been associated with increased risk of infection (43–47), acute lung injury/acute respiratory distress syndrome (48–51), systemic inflammatory response syndrome (28), and multiple organ failure (52, 53). The precise mechanisms for the development of these complications are unclear, although the age of stored blood, red blood cell microparticles, foreign antigens, foreign white blood cells, and bioactive lipids with neutrophil priming have all been implicated (41, 54–56).
Coagulopathy in Massive Transfusion

Hemostasis is a complex process that requires the balanced interaction of the endothelium, platelets, coagulation factors, physiological anticoagulants, and fibrinolytic proteins (80, 81). The management of coagulopathy in massively transfused patients is often complicated by multiple simultaneous defects in the hemostatic pathway (Table 3) (26). Coagulopathy may be clinically recognized as abnormal “microvascular” bleeding of unjured mucosal or serosal surfaces or by prolonged bleeding at sites of vascular access and wound tissue surfaces after control of vascular bleeding (82). Standard clinical laboratory tests have poor correlation with in vivo coagulopathy.

Table 3. Factors contributing to the coagulopathy of trauma

| Acidemia | Decreased coagulation factor activity  
| Decreased thrombin generation  
| Activation of physiologic anticoagulation via protein C pathway  
| Impaired platelet aggregation  
| Enhanced fibrinolysis via increased tPA and depletion of plasma activator inhibitor-1  

| Hypothermia | Platelet dysfunction  
| Reduced platelet activation by the von Willebrand factor and platelet glycoprotein Ib-IX-V complex  
| Derangements of platelet adhesion and aggregation  
| Decreased thrombin generation on platelets  
| Reduced coagulation factor activity  

| Dilutional coagulopathy | Fibrinogen/coagulation factor deficiency  
| Thrombocytopenia  
| Anemia  
| Consumption of platelets and fibrinogen/coagulation factors  

| Dysregulation of intravascular coagulation | Consumption of antithrombin III  
| Acquired platelet dysfunction  
| Increased fibrinolysis  
| Increased tPA  
| Decreased α2 antiplasmin  

| tPA, tissue plasminogen activator.

Laboratory tests may be abnormal in the setting of coagulopathy, are the prothrombin time (PT) (97%), platelet count (72%), and the activated partial thromboplastin time (aPTT) (70%) (84). Thromboelastography is a method of measuring whole blood coagulation status from primary hemostasis to fibrinolysis, including plasma–platelet interactions. This technique has been proposed as a more accurate measure of coagulopathy and predictor of transfusion requirements than standard coagulation tests (85–87).

Coagulopathy is frequently present on admission in severely injured patients, particularly those with brain and/or penetrating injuries. When such coagulopathy is present, it is correlated with the need for MT as well as increased mortality (13, 27, 88–91). Coagulopathy leads to further hemorrhage and worsening physiological derangements, in turn prompting additional fluid resuscitation and transfusion. Such resuscitation contributes to more profound coagulopathy and thus leads to the “bloody vicious cycle” (92). The combination of severe injury, shock, acidosis, and hypothermia predictably leads to coagulopathic bleeding (93). Although multiple defects must be treated simultaneously, it is helpful to examine each of these components individually.

Acidosis. Acidosis, largely as a result of lactate production by hypoperfused tissues undergoing anaerobic metabolism (94), can develop during hemorrhagic shock (95, 96) and can be exacerbated by massive transfusion and crystalloid resuscitation. Stored RBCs are acidic with pH 7.16 at time of collection. Stored RBCs are acidic with pH 7.16 at time of collection. These data highlight the fact that restoration of adequate tissue perfusion is paramount to reverse the underlying lactic acidosis (103, 117).

Hypothermia. Trauma patients develop hypothermia from conductive, convective, evaporative, and radiative losses as a result of environmental and surgical exposure. In addition, temperature regulation is impaired during shock and anesthesia (118, 119). Hypothermia, defined as a core body temperature between 34°C and 36°C (mild), between 32°C and 34°C (moderate), and less than 32°C (severe) (120) is associated with an increased risk of uncontrolled bleeding and mortality in trauma patients (121–126). Although an-
imal studies have suggested that controlled hypothermia in hemorrhage may improve survival (127–129), hypothermia was associated with increased mortality in one randomized, clinical trial (130).

Because blood is stored at 4°C, hypothermia can quickly progress during MT (131). Fluid warmers are absolutely essential for preventing or limiting hypothermia (132). The multiple physiological consequences of hypothermia include impaired oxygen delivery by hemoglobin through leftward shift of the oxyhemoglobin dissociation curve (133), decreased cardiac output (134), increased risk of cardiac dysrhythmias, increased cardiac toxicity from electrolyte disturbances, and coagulopathy (135, 136).

Platelet dysfunction resulting from hypothermia was recognized in the 1980s (137) and also occurs through multiple mechanisms. Thromboxane A2 production, a measure of platelet activation by the von Willebrand factor and platelet glycoprotein Ib-IX-V complex, is greatly reduced at lower temperatures with a profound reduction in platelet activation at 30°C (138). Furthermore, defects in platelet adhesion, platelet aggregation, and thrombin generation on platelets have been observed at 33°C (139, 140). Multiple other hypothermia-induced platelet function defects have been documented, including decreased numbers of platelet alpha granules, up-regulation of platelet alpha-granule membrane protein, down-regulation of the GPIb-IX complex, and prolonged bleeding times (141, 142).

Hypothermia has a more modest effect on the coagulation cascade (143–147). There is a 10% reduction in coagulation factor activity for each 1°C drop in temperature (126), which prolongs clotting times at temperatures below 33°C (139). However, clinicians may underestimate the effect hypothermia on coagulation factor activity in vivo because PT and aPTT assays are performed at 37°C (148, 149). Finally, evidence of increased fibrinolysis has been described in the setting of profound hypothermia (143, 150), although this is most likely the result of diffuse intravascular coagulation from circulatory collapse (126, 151).

Platelet dysfunction and impaired coagulation enzyme activity are reversible with normalization of temperature to 37°C, highlighting the need to prevent and treat hypothermia aggressively (152). Currently, the goal during resuscitation is normalization of body temperature (153), and measures to prevent or reverse hypothermia are listed in Table 2.

**Consumption/Intravascular Coagulation.** Consumption of factors with the hemorrhagic phenotype of diffuse intravascular coagulation has been noted in early trauma (154, 155), particularly in association with extensive endothelial injury, massive soft tissue damage, fat embolization from long bone fractures, and brain injury (156, 157). Although local coagulation at the site of injury occurs through exposure of tissue factor and activation of factor VII, systemic activation of coagulation can result from release of thromboplastin into the circulation or widespread damage to the endothelium.

This systemic activation of coagulation may also trigger the immune system in patterns similar to those seen in septic patients (158). In addition to consumption of clotting factors, there is dysregulation of coagulation through consumption of antithrombin III (159), acquired platelet defects (160–162), and increased fibrinolysis (163) from increased tissue plasminogen activator (164) and decreased α2-antiplasmin (165).

**Dilutional Coagulopathy.** Dilutional coagulopathy develops in MT as a consequence of the replacement of shed whole blood with factor and platelet-poor fluids like crystalloids, colloids, and stored blood red blood cells (166). Coagulation factors are further diluted early in trauma by fluid shift from the extracellular to the vascular space, which is proportional to the grade of shock (167). The major etiologies of dilutional hemostatic defects associated with MT have varied over the decades as a result of significant changes in blood-banking practice. Transfusion support has shifted from the use of stored whole blood to the present-day use of fractionated component therapy. Each blood product contains different components, some of which may be functional (that is, platelets in fresh whole blood) but absent or nonfunctional in other blood products (that is, platelets in packed red blood cells or in whole blood stored >24–72 hrs). Strategies for managing the massively transfused patient must be adjusted to account for the contemporary changes in transfusion practice (168, 169).

The first report of a bleeding diathesis after MT of banked blood was in 1954, noting thrombocytopenia and bleeding, which was responsive to administration of platelet concentrates (170). Bleeding tendencies were documented in relation to the volume and rate of blood infusion, occurring commonly (33% to 78%) in adult patients receiving ten or more units of stored whole blood (171, 172). Based on reports in combat casualties during the Korean conflict, platelet dysfunction and deficiencies of labile coagulation factors (V and VIII) were implicated as sources of coagulopathy in MT with stored whole blood (173, 174). Although there was a strong correlation between thrombocytopenia and coagulopathy, multiple additional defects, including low fibrinogen or factor deficiencies (II, V, VII, VIII), were also felt to occur because not all patients with thrombocytopenia had bleeding, and not all patients with bleeding had thrombocytopenia (104, 175–177). Studies of MT with stored whole blood during the Vietnam conflict also concluded that dilutional thrombocytopenia was the major cause of microvascular bleeding (103), although significant thrombocytopenia (platelet counts <100 × 109/L) tended to develop later than would be predicted (that is, after 18–20 units of stored whole blood) (154, 166, 178). In addition to thrombocytopenia, platelet aggregation defects were also noted after MT with stored whole blood (179). In the 1970s, there was a change in practice from the use of stored whole blood to "modified whole blood" (with platelets and fibrinogen removed before storage, but with 1:1 ratios of red cells to plasma), which still resulted in thrombocytopenia as the most common cause of excessive bleeding in MT (180).

Since the advent of fractionated component transfusion practices in the 1980s, dilutional coagulation factor deficiencies have become more prominent (105, 181–184). Fibrinogen depletion develops earlier (at 1.4 blood volume replacement) than any other coagulation factor deficiency (181, 185, 186). Additionally, the optimal concentration of other coagulation factors to allow for enzyme-complex assembly is near the normal concentration of factors in plasma (187). Although platelets remain important (26, 188, 189), fresh-frozen plasma is currently considered the first choice in treating coagulopathy associated with MT (168).

Lowered hematocrit and dilution of RBCs may also contribute to coagulopathy. In addition to biochemical interactions with platelets and fibrin within the thrombus, erythrocytes contribute to hemostasis by allowing margination of platelets toward the capillary wall and endothelium (190). Local platelet con-
centrations along the endothelium are nearly seven times higher than the average blood concentration as a result of this effect (191). Anemia has been correlated with increased bleeding times in both nonthrombocytopenic and thrombocytopenic animal models (192). An acute drop in the hematocrit will increase bleeding times, which can be reversed with RBC transfusion (193), an effect also noted in thrombocytopenic patients with platelet counts <100 × 10^9/L (194, 195). The optimal hematocrit for platelet–vessel wall interactions is unknown but may be as high as 35% (169).

Dilutional coagulopathy may be inevitable in patients requiring a massive resuscitation as a result of the addition of preservative solutions to stored blood products after collection. Transfusion of stored red blood cells, plasma, and platelets in a 1:1:1 ratio results in a solution with a hematocrit of 30%, coagulation factor levels of approximately 60%, and platelets of 80 × 10^9/L (166). It should be noted that crystalloids and colloids (196) intended to restore volume and limit shock pathophysiology will greatly intensify dilutional effects if given in sufficient quantities (>20 mL/kg). In addition to dilutional effects, colloids such as hydroxyethyl starch are also known to increase coagulopathy by impairing von Willebrand factor activity in plasma (197, 198). For these reasons, some have advocated for limited use of crystalloids and colloids in severe trauma or massive hemorrhage (5).

**Management of Massive Transfusion**

Recognition of changes in transfusion practices over the decades is important when designing strategies to prevent or treat the complications of MT. Concepts from the era of whole blood transfusion may still be applicable, but as a consequence of component therapy, these are overlaid with the additional complexity of plasma to red blood cell (fresh-frozen plasma [FFP]:RBC) ratios. Blood products should be transfused recognizing that coagulopathy can be present on admission, develops early in patients requiring MT, and may be exacerbated by inappropriate transfusion strategies (168, 169).

**Plasma.** With the shift away from stored whole blood and “modified” whole blood, it is easier to understand the increasing focus on plasma for management of coagulopathy. Whole blood contains red cells and plasma in a 1:1 ratio, and transfusion of plasma in appropriate FFP:RBC ratios has been proposed as a means to both prevent and treat the coagulopathy of trauma. The impact of plasma has been shown in civilian trauma settings. Cinat et al. found that survivors received a FFP:RBC ratio of 1:1.8, whereas nonsurvivors received a ratio of 1:2.5 (17). Emerging data from combat casualties in Iraq also support the impact of plasma, showing a 65% mortality for patients in the lowest ratio group (1:8 FFP:RBC) as compared with a 19% mortality in patients in the highest ratio group (1:1.4) (199).

Empiric treatment with plasma has been based on washout equations with assumed stable blood volumes. It was recognized in the 1940s that if resuscitation is performed using factor-poor solutions (for example, stored red cells, crystalloid, or colloid), then infusion of one blood volume results in only 38% of the patient’s original blood remaining in circulation. In a two-blood volume infusion, only 13% remains (200). These values are reflective of the plasma and clotting factors remaining in circulation. Such calculations are appropriate in elective surgery or exchange transfusion settings where losses are replaced as they are occurring, but may not be appropriate for trauma settings where significant hemorrhage may have already occurred. Mathematical modeling taking into account initial loss of half a blood volume reveals that the original patient’s blood remaining would be 16% and 3% after one and two blood volumes transfused, respectively (23). It is also common for severely injured patients to receive multiple units of red blood cells before coagulopathy is recognized and plasma is requested. Thawing of plasma takes time, and although plasma is being prepared, patients often receive even more blood or crystalloids, which will further exacerbate coagulopathy. Thus, it has been suggested that plasma should be transfused early in the resuscitation to prevent dilutional coagulopathy (18, 27, 201). One way to incorporate plasma early is for the blood bank to provide “prethawed plasma” on admission. Prethawed plasma is FFP that has been thawed and then refrigerated (for up to 5 days) thus making it immediately available to patients on admission to the trauma bay. “Prethawed plasma” contains less of the labile factors V and VIII than FFP but for most purposes can be used interchangeably with FFP in trauma patients (166). Because plasma must be ABO-compatible, AB plasma (the universal plasma without anti-A or anti-B antibodies and a scarce resource given that only 5% of the population has this blood type) is often used until the blood type of the patient is known and type-specific plasma can be issued.

The optimal FFP:RBC ratio is unknown and randomized data are limited (202). Mathematical pharmacokinetic models for FFP transfusion have been developed suggesting that a ratio of 2:3 (203) or a more aggressive ratio of 1:1 (204) FFP:RBC will help to prevent the onset of dilutional coagulopathy. Resuscitation of exsanguinating patients is a challenging problem, which is worsened when clear MT protocols have not been developed (205). Although many institutions have MT protocols in place, adherence to such guidelines can still be difficult in a chaotic resuscitation. Successful resuscitation requires strong collaboration and effective communication among providers in the emergency room, operating room, intensive care unit, and blood bank (206).

**Platelets.** Although thrombocytopenia has been considered a delayed complication of MT, the phenomena of platelet dysfunction forces a reconsideration of the “adequate” platelet count necessary for hemostasis. Some have advocated that as a result of platelet dysfunction, platelets should be administered regardless of circulating counts in patients with surgical bleeding (188, 207). The currently recommended platelet transfusion threshold is 50 × 10^9/L for active bleeding or planned invasive procedures at risk for noncompressible bleeding (208). Improved survival, however, has been noted in patients with platelets counts >100 × 10^9/L after surgery for ruptured aortic aneurysm (209). Such observations, as well as expert opinions, have led to recommendations for a higher target platelet transfusion threshold of 100 × 10^9/L in cases of multiple high-energy trauma or central nervous system injury (93, 181, 189, 210–213).

One randomized trial in 1986 compared prophylactic pooled platelet transfusion with FFP in 33 massively transfused patients receiving modified whole blood. This trial applied a pooled platelet: RBC ratio of 0.5:1 and showed no difference in the development of microvascular bleeding (214). Mathematical modeling...
indicated to counter dilutional effects equally strong opinions that FWB was competitive (222, 223). This was met with contestations given the wide availability of components (221). After the development of microporous crystalline aluminosilicate microporous mesh bag containing zeolite beads designed to be applied directly to wounds, it is marketed as QuikClot (Z-Medica, Wallingford, CT) and works through absorption of water from blood, thus concentrating clotting factors and platelets (252, 253). Most data regarding the effectiveness of this agent in controlling hemorrhage come from animal models (254). The use of granular zeolite is known to result in an exothermic reaction. Significant thermal injuries have been observed in animal models (255, 256), and a case series has been published describing burns after the application of granular zeolite for the management of bleeding trauma patients (257). The manufacturer has modified the cation contained within the crystalline structure of the compound and is preloading the compound with water to control and decrease this exothermic reaction (258). Another undesirable aspect of this product is that removal of the granules from wounds can be time-consuming. As noted, the manufacturer of QuikClot has introduced an improved product that packages the zeolite within beads contained in a mesh bag intended to limit the potential for dispersal of the granules within the wound (259). Efforts are underway to improve training of prehospital personnel in the use of this product (260) because it is relatively lightweight and can be transported into the field for use in the prehospital setting. Although no clinical trials have been performed comparing it with other treatments, granular zeolite has been used successfully to control hemorrhage by U.S. military personnel. QuikClot has been included in the U.S. Marine Corps first aid kit and has also been fielded on a more limited basis by the U.S. Army during combat operations in both Iraq and Afghanistan (261, 262).

Advanced Bandages/Dressings. Gauze dressings, direct pressure, and tourniquets are effective methods for controlling hemorrhage in the prehospital setting but are frequently insufficient for proximal vascular injuries. Fibrin-impregnated bandages have been developed to enhance hemorrhage control in the prehospital setting. In animal models, fibrin-impregnated bandages have been shown to reduce blood loss (263–267). Fibrin sealant dressings have also been shown to rapidly control arterial hemorrhage in swine and prevent rebleeding for at least 7 days, indicating that such dressings may even provide the basis for an alternative to suture repair of vascular...
injuries (268). Two recently developed hemostatic dressings, fibrin sealant dressings (American Red Cross dressing described previously) and chitosan dressings (made from deacetylated chitin on a nonabsorbable backing, which primarily adheres to tissue), were compared with standard gauze Army field dressings in a swine model of exsanguinating arterial hemorrhage. Standard gauze dressings failed to achieve hemostasis, resulting in 100% mortality. Chitosan dressings achieved initial hemostasis in approximately 70% of treated animals but failed to maintain hemostatic integrity, resulting in the deaths of all animals. Fibrin sealant dressings achieved initial hemostasis in 100% of treated animals and durable hemostasis (96-h experiment duration) in five of six animals. Additionally, fewer fibrin dressings were required to achieve hemostasis compared with chitosan or gauze (269). The limitations of fibrin-impregnated bandages are cost ($1,000/bandage), brittleness with difficulty of application into complex wounds, and lack of FDA approval for routine use (although it is available to the U.S. military under an investigational new drug protocol). Research to augment the effectiveness of chitosan or gauze (269). The limitations of fibrin dressings were compared with chitosan or gauze (269). The limitations of fibrin-impregnated bandages are cost ($1,000/bandage), brittleness with difficulty of application into complex wounds, and lack of FDA approval for routine use (although it is available to the U.S. military under an investigational new drug protocol). Research to augment the effectiveness of fibrin bandages and reduce the amount of fibrin necessary has met with mixed success (270, 271).

Recombinant Factor VIIa. Recombinant factor VIIa (rFVIIa) is currently FDA-approved only for patients with congenital factor VII deficiency and hemophilia A or B with inhibitors. Within the past 7 yrs, there has been off-label use of rFVIIa for the management of other bleeding conditions marked by excessive hemorrhage or risk of hemorrhage. Randomized controlled trials (RCTs) in patients without hemophilia or factor VII deficiency have been conducted in various surgical populations, including esophageal varices, liver biopsy, partial hepatectomy with and without cirrhosis, liver transplantation, dental surgery, retropubic prostatectomy, major pelvic-rectalabular surgery, cardiac surgery, and burn grafting (272–284). Despite the early anecdotal success and enthusiasm of individual clinicians, none of these RCTs have shown a survival benefit for rFVIIa and ten of these 13 RCTs show no benefit in reducing transfusion requirements or blood loss.

The first case report of rFVIIa use in trauma was published in 1999 (285) and was soon followed by a series of controlled experimental animal studies using swine models of liver trauma, which showed prolongations in survival and decreased blood losses (286–290). One study in grade V liver injury in warm, noncoagulopathic swine, however, showed no benefit in blood loss from rFVIIa (291). These studies coincided with a number of subsequent case reports and case series of rFVIIa in trauma and uncontrolled hemorrhage (22, 292–313). The majority of publications suggested decreased blood loss and/or decreased transfusion requirements for patients, although some offered cautionary notes and limitations of rFVIIa, especially in acidosis, refractory coagulopathy, and hypothermia at temperatures approaching 30°C (106, 314–317). The only randomized trial to date of rFVIIa in trauma was published in 2005 (318). This study randomized 301 patients sustaining both blunt and penetrating injuries to placebo or rFVIIa to be administered after the eighth unit of blood. This trial showed a reduction of 2.6 units of RBC transfusions for the blunt trauma subgroup (p = .02) and a similar although nonsignificant trend in the penetrating injury subgroup. The incidence of adult respiratory distress syndrome was decreased for patients with blunt injury who received rFVIIa, although there were no differences in survival or in the incidence of thromboembolic events and multiorgan failure.

The thromboembolic complications associated with rFVIIa have received considerable attention with one large case series of rFVIIa use reporting a thromboembolic complication rate as high as 9.4% (319). One indirect comparison of adverse event reporting for rFVIIa and factor VII inhibitor bypass activity (an agent accepted to cause thromboembolic events) noted that rFVIIa had a higher estimated incidence of serious thromboembolic events than factor VII inhibitor bypass activity (320). A subsequent publication on the results of adverse event reporting also suggested that patients receiving rFVIIa are at risk of developing serious venous and arterial complications (321). It should be noted that neither of these reports took into account the rate of adverse events in equivalent control groups of patients who did not receive these agents. By contrast, a meta-analysis of RCTs published in 2006 suggested no overall increase in adverse events (322).

In light of the numerous data sets available and concern over the potential for adverse events, consensus statements have been developed to guide the use of rFVIIa in massive bleeding (323–325). The use of rFVIIa in blunt trauma has been supported with RCT data, although its use in uncontrolled bleeding in surgical patients has only been supported by case series. Adequately powered/randomized data do not exist to support the standard use of rFVIIa for penetrating trauma. In summary, the off-label use of rFVIIa is still considered controversial and should be used with caution and sound clinical judgment. An ongoing clinical trial sponsored by NovoNordisk on the use of rFVIIa in trauma may help to clarify its risks and benefits in this setting (326).

Antifibrinolytics. Because hyperfibrinolysis is a contributor to the coagulopathy of trauma, antifibrinolytics have the potential to reduce blood loss and improve outcomes in traumatic bleeding. Antifibrinolytic agents have been shown to reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery (327). The most extensively evaluated agents are aprotinin, epsilon aminocaproic acid, and tranexamic acid.

Aprotinin is a nonspecific serine protease derived from bovine lung and porcine gut. It was initially approved by the FDA for prophylactic use in patients undergoing on-pump coronary artery bypass grafting who are at high risk for perioperative blood loss (328), although the FDA suspended marketing of aprotinin in November 2007 as a result of reports of increased mortality in coronary bypass surgery (329). Its primary hemostatic activity results from the formation of a reversible enzyme-inhibitor complex with plasmin, thus inhibiting fibrinolysis. There are limited clinical trial data evaluating aprotinin in trauma patients. The Cochrane Collaboration performed a systematic review of antifibrinolytic drugs in trauma and only one study of 819 was suitable for analysis (330). In this study, 70 patients with pelvic or lower limb fractures and hypovolemic shock were randomized to aprotinin or placebo (331). Although the volume of blood transfused was decreased by 60% (relative risk [RR], −0.40; 95% confidence interval [CI], −0.91–0.11), differences in other outcomes were not apparent and the authors of the review concluded that there is no evidence to support the routine use of aprotinin in acute traumatic injury.

The lysine antifibrinolytics, aminocaproic acid and tranexamic acid, inhibit
plasmin binding to fibrin by occupying the lysine-binding sites of the proenzyme plasminogen. Aminocaproic acid is approved by the FDA for enhancing hemostasis in states of hyperfibrinolysis, and tranexamic acid is approved for patients with hemophilia undergoing tooth extraction (332, 333). In a Cochrane Review of antifibrinolytics for minimizing perioperative blood loss, tranexamic acid reduced the need for transfusion compared with control by approximately one third (RR, 0.61; 95% CI, 0.54–0.69) with similar although less pronounced benefit seen for aminocaproic acid (RR, 0.75; 95% CI, 0.58–0.96) (334). The Cochrane Review of antifibrinolytic drugs in acute traumatic injury revealed no studies of sufficient quality to assess the benefits in this population (330).

In summary, there is no evidence to support the prophylactic or empiric use of antifibrinolytic drugs to reduce allogeneic blood transfusion in patients sustaining acute traumatic injury (335). There is currently a major ongoing international trial, CRASH-2: Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (NCT00375258), to evaluate the use of tranexamic acid compared with placebo in trauma patients. Until these results are available, there remains no established role for the prophylactic or empiric use of antifibrinolytics in acute trauma.

Desmopressin. Desmopressin (DDAVP) is a synthetic analog of arginine vasopressin-1-deamino-8-d-arginine vasopressin and is FDA-approved for the management of mild hemophilia A and von Willebrand’s disease, type 1. DDAVP improves primary hemostasis through stimulation of the release of ultralarge von Willebrand factor multimers from endothelial cells, leading to an increase in plasma von Willebrand factor. DDAVP also increases the density of glycoprotein receptors on platelet surfaces and increases plasma factor VIII (336–338). DDAVP has been proven to be effective in reducing bleeding in the setting of uremia (339) and mild coagulopathy induced by hydroxyethyl starch (340). It has also been suggested that DDAVP may be effective in reducing hemorrhage after coronary artery bypass grafting in patients receiving aspirin before surgery (341, 342), but the results from more recent published studies on this benefit have been inconclusive (343). A Cochrane Review of DDAVP in reducing perioperative blood transfusions showed no benefit compared with controls (RR, 0.98; 95% CI, 0.88–1.10) (344). There are no studies in trauma patients using DDAVP, although its mode of action and limited benefits in other surgical populations make it unlikely to be as effective as a sole hemostatic agent in the trauma population.

CONCLUSIONS

The optimal management of massive transfusion and coagulopathy in trauma patients is complex and depends heavily on clinical judgment. This judgment, in turn, must be derived from a broad understanding of the expected complications as well as an individualized approach to the multitude of presentations and injuries of the specific patient. Currently, the challenges of performing studies in uncontrolled emergency settings present many obstacles and remain heavily influenced by the availability and nature of transfusion support. However, the continued high mortality rates associated with massive transfusion make ongoing research an indisputable necessity.

REFERENCES

transfusion rates in the care of acute trauma. *Transfusion* 2004; 44:809–813


43. Saaua A, Moore PA, Moore EE, et al: Multiple organ failure can be predicted as early as 12 hours after injury. *J Trauma* 1998; 45:291–301; discussion 301–303


75. Braasch D: Red cell deformability and capillary blood flow. *Physiol Rev* 1971; 51:679
86. Cannon WB: Acidosis in cases of shock, hemorrhage and gas infection. *JAMA* 1918; 70:531
110. Arthurs Z, Cuadrado D, Beekley A, et al: The impact of hypothermia on trauma care at...


165. Lahy JL, Ware AS, Seegers WH: Stability of prothrombin and Ac-globulin (Factor V) in stored human plasma as influenced by conditions of storage. *Am J Physiol* 1948; 154:122

166. Scott R Jr, Crosby WH: Changes in the coagulation mechanism following wound- ing and resuscitation with stored blood; a


200. Erber WN: Massive blood transfusion in the...


in patients with massive haemorrhage is ineffective. Vox Sang 2004; 86:120–124
324. Davis S: Use of Recombinant Factor VIIa in Uncontrollable Haemorrhage: A Position Statement of the NSW Therapeutic Assessment Group Inc. Sydney, Australia, NSW Therapeutic Assessment Group, 2002
344. Otto RJ, Metzler MH: Rewarming from experim