CHAPTER 49

Transfusion therapy in the care of trauma and burn patients

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The oldest reports of successful blood transfusions for trauma come from the American Civil War. However, it was more than 50 years later, at the end of World War I, that recognizably modern blood banking was developed.1 Useful blood storage was possible only after three critical discoveries. First was the discovery that bacteria caused infections, which allowed the development of sterile fluid-handling techniques. Second was the discovery of ABO blood groups, which allowed donors and recipients to be crossmatched and universal donor blood types identified. Third, the discovery that citrate was a safe anticoagulant for human blood at low doses allowed blood donors and recipients to be separated in time and space, which in turn allowed the building of blood inventory and the institution of blood product quality control.2 Taking advantage of these discoveries and a transfusion bottle of his own design, Oswald H. Robertson then developed a system for delivering typed and syphilis-tested whole blood in bottles in ice chests to casualty clearing stations and base hospitals, and demonstrated the lifesaving value of stored blood transfusion for combat casualties.3 The approximately 30,000 Robertson bottle transfusions performed in 1918 were a model of how a blood transfusion service could function. After the war, organized blood banks disappeared because of their high overhead requirements, although direct transfusions continued, until individuals and institutions started to rebuild blood services. Lundy at the Mayo Clinic in 1935,4 Bethune and Duran-Jorda in the Spanish Civil War in 1936,5,6 Fantus at Cook County in 1937,7 and DeGowin at Iowa in 19388 all contributed to the rebirth of blood banking, but the largest impetus came from the London Blood Transfusion Service, the British Army, and the joint US Army, Navy, and American Red Cross programs in World War II. The London Blood Transfusion Service was able to provide half a million units of whole blood during the London Blitz of 1940,9 the British Army developed acid–citrate–dextrose (ACD) solution for the safe three-week storage of whole blood and showed that it could be delivered around the world,10 and the American war effort ultimately collected and processed 13 million whole blood collections.11 These efforts became the basis for national blood systems. During the Korean War (1950–1953), the US Army’s Surgical Research Team studied blood loss, the evolution of shock, and the effects of fluid resuscitation with the tracer deuterium heavy water.12 Furthermore, they reported on the safety of massive transfusion with stored universal donor blood and on the use of plastic bags for fluid and blood administration. A decade later in the Vietnam War, these concepts and products were integrated into systems for early resuscitation, rapid transportation, massive transfusion, and early surgical intervention, which reduced the death rate from wounds in field hospitals to 3%.[13,14] Altogether, the US armed forces transfused 600,000 units of whole blood or red cells in Vietnam.15 They further demonstrated the relative safety of the 100,000 units of group O universal donor red cells given, in that all seven fatal hemolytic transfusion reactions in Vietnam occurred in patients receiving crossmatched but mistransfused blood. By the end of the 1960s, ambulances in US cities were taking injured civilians to regional trauma centers.[16]

The Coconut Grove nightclub fire in Boston, Massachusetts, on November 28, 1942, was the critical event in the history of burn care. It led to the first burn resuscitation formula, the first systematic evaluation of the use of blood plasma in burn resuscitation, and the first burn unit in the United States.[17,18] The first two concepts remain controversial, but the ready availability of blood and blood components has improved survival among elderly burned patients and patients with associated medical problems who otherwise would not have tolerated a low hemoglobin level.19 Interoperative transfusion allowed wider more complete debridement procedures, rapidly reducing the inflammatory burden of irrevocably damaged tissue, and thereby decreasing the number of surgical procedures and the length of hospital care needed by a burned patient.20 The development of trauma centers and burn units in the late 1960s coincided with the development of blood bags and blood component therapy and with a general increasing demand for blood components in hospitals to support more advanced surgery and the war on cancer.[21] In an expanding blood supply system,[21] blood products were frequently in short supply, especially universal donor group O-negative red cells and group AB plasma. Managing a limited inventory of AB plasma meant keeping it frozen in the blood bank until the patient had a blood type and an indication in the form of a prothrombin time (PT) or activated partial thromboplastin time (aPPT) greater than 1.5 times normal.[22] By the time the American College of Surgeons’ Acute Trauma Life Support (ATLS) guidelines were written, the system of delaying plasma was so ingrained that many thought there was science behind it.[23,24]
A mistaken prejudice about injury and the physicians who cared for injured patients also shaped the development of trauma transfusion.24 In war, the banked blood was going to “our nation’s finest,” but in peacetime, injury was viewed as a problem to be prevented with engineering and social controls like collapsible steering columns and divided highways or seatbelt and helmet laws. The injured were assumed to be the poor and the drunk. The civilian health research establishment was slow to recognize the need for trauma research. In the 1960s, the National Academy of Sciences and the National Institutes of Health debated building a National Institute of Trauma to address the nation’s leading cause of early death and ultimately decided not to do so.26 The problems of trauma treatment were viewed as local and organizational, not national and scientific. Care of the injured was felt to revolve around prevention, rapid transport, and better surgical care, with little requirement for basic or translational research. The perceived needs did not blend with the molecular biology agenda of the time. As a result, injury research has been relatively underfunded compared to its impact for decades.27

The local and organizational issues surrounding trauma and burn care became the major focus of building in the 1970s and 1980s. Ultimately, 1082 trauma centers in the United States and Canada were accredited by the Committee on Trauma of the American College of Surgeons at various levels of service based on resources and programs, and 164 burn centers were built as well.28 The Committee on Trauma trained and accredited a generation of physicians and surgeons in the principles of ATLS, teaching basic injury epidemiology and a clinical approach focused on simple clinical skills such as managing the airway, checking for tension pneumothorax and hemopericardium, controlling accessible hemorrhage, rapidly moving patients to the operating room, and the resuscitation of hemorrhagic shock. Nationally, the program was viewed as a success as the number of moderately injured patients who died of surgically preventable causes decreased markedly.

The resuscitation of hemorrhagic shock became a focus of research.29 In animals, poor tissue perfusion secondary to hypovolemic hypotension became life threatening after approximately 30% blood loss, but perfusion could be restored by volume replacement with crystalloid fluids.30 With continued blood loss and volume replacement, red cell mass became critically low next after 60% of total blood volume blood loss. Red cell transfusion corrected this problem. Decreasing colloid osmotic activity led to blood flow-limiting edema after 120% blood volume removal. With concomitant albumin, volume, and red cell replacement, hemorrhagic complications occurred spontaneously after 180% volume, red cell, and albumin replacement that were related primarily to plasma coagulation factor deficiency, and platelets became limiting only after 220% removal and replacement of the other blood components. These isovolemic models of controlled hemorrhage and blood component replacement suggested that volume and oxygen transport were the critical early issues in the treatment of hemorrhagic shock and that coagulopathy was largely dilutional and a late complication. This logic was codified as the ATLS resuscitation algorithm, in which injured patients were given crystalloid fluids to maintain volume and red cells to maintain oxygen transport if more than 2L of crystalloid fluid were required to maintain blood pressure.31 Plasma was to be given based on laboratory measures of a prolonged PT or aPTT greater than 1.5 times normal, platelets when the platelet count was less than 50,000/µL, and cryoprecipitate when the fibrinogen was less than 100 mg/dL. Again, the system worked well for moderately injured patients and led to reduced overall mortality, especially from renal failure.

However, in severely injured patients with initially uncontrolled hemorrhage, the use of large volumes of crystalloid fluid led to massive tissue edema and severe coagulopathy. Tissue edema made closing wounds difficult. Attempting to close the abdomen over swollen bowel led to compression of the inferior vena cava, trapping blood in the legs, decreasing venous return to the heart, and worsening shock. Leaving the abdomen open led to prolonged hospitalizations, many complications, and secondary mortality. Cold crystalloid resuscitation caused hemodilution and hypothermia, which in turn caused coagulopathy and more bleeding, a phenomenon that came to be known as the bloody vicious cycle. The combination of acidosis, hypothermia, and coagulopathy was the triad of death. In the face of difficult-to-control bleeding, surgeons performed damage control laparotomies where normal anatomy was sacrificed in favor of stabilizing critical vascular integrity and limiting fecal, urinary, and biliary contamination in the hopes of getting the procedure performed in less than 40 minutes.32 Nevertheless, for patients who needed 10 units of red blood cells (RBCs), mortality was typically 40%, and for those who needed 20 units, it was 50%.33

In the past two decades, three areas of clinical investigation led to the use of more plasma and less crystalloid in the resuscitation of severely and profoundly injured patients. The first line involved reducing the amount of crystalloid fluid given for volume expansion because there were situations in which it was not necessary and certain patients appeared to do better without the extra volume. The second line involved experiences, almost entirely military, in which dramatically better hemostasis was achieved with the use of fresh whole blood. The third involved the purposeful administration of plasma early in resuscitation to prevent coagulopathy, because once coagulopathy had developed it proved difficult to treat with conventional blood components.

A dramatic demonstration that crystalloid resuscitation could be deadly was conducted by Bickell and colleagues in a model of aortic tear in swine.34 In the model, a loop of stainless-steel suture was placed in the aorta and brought out through the skin. A week later, with the animal awake, the suture was torn out to create an 0.45 cm aortic tear. Pigs sustaining this injury typically lay down, dropped their blood pressure to 30 Torr systolic for an hour while the injury bleeding clotted firmly, and then the blood pressure slowly returned to normal with 85% of the animals surviving. Attempting to resuscitate the swine with crystalloid raised their blood pressure, causing further bleeding and hemodilution that preventing the bleeding from ever clotting and resulted in 100% fatality. On the basis of this demonstration, a large study was performed in patients in Houston sustaining penetrating trucal trauma.35 Moderately hypotensive patients were randomized to be either resuscitated or not prior to exploratory surgery. Mortality was higher (69 vs. 60%, p = 0.04) in the resuscitated group. A second smaller randomized study conducted by Dutton and colleagues also showed no benefit to early resuscitation in the short time between admission and exploratory surgery in moderately hypotensive injured patients in a level 1 trauma center.36

US military experience with the use of fresh whole blood to treat battlefield casualties in situations where platelets were not available also led to a widening appreciation of the ability of whole blood to rapidly achieve hemostasis in badly injured soldiers. In the first Iraq war, Somalia, Bosnia, Kosovo, and then Afghanistan and the second Iraq war, situations repeatedly occurred where casualties with
In one early and informative case from Mogadishu in 1993, a soldier was bitten by a great white shark, losing the back of a thigh. By the time he arrived at the American combat support hospital, he was in profound shock. His surgeons proceeded to give him all 50 units of RBCs in additive solution that were available in the country, leading to more free bleeding with each unit he was given until they ran out. At that time, they switched his resuscitation to fresh whole blood collected from the arms of group O soldiers in his unit, and with the administration of each successive unit, his coagulopathy improved until he stopped bleeding altogether after 16 units of fresh whole blood. Stories like this one spread rapidly among surgeons, and the dramatic photographs of the extent of the injury and success of the hemorrhage control further emphasized the take-home messages that red cells alone can lead to a profound dilutional coagulopathy and that fresh whole blood can correct it.

The recognition that crystalloid fluids and red cells did not prevent coagulopathy led to many attempts at more balanced resuscitation. Hiipala wrote about the importance of early administration of plasma in the massively bleeding trauma patient in the 1990s, but groups like the British Committee for Standards in Haematology continued to advocate for limiting plasma use and strict transfusion triggers. However, with the descriptions of the acute coagulopathy of trauma in 2003 and reports of even more devastating injuries from improvised explosive devices in the second Iraq war at the same time, the need to prevent and reverse coagulopathy early in resuscitation came to the fore. The US military published its first theater guideline recommending early initiation of balanced hemostatic resuscitation in 2004; held a small international expert panel in San Antonio, Texas, in May 2005; and published a national recommendation in 2007 stating red cells, plasma, and platelets be given in 1:1:1 ratios to the most seriously injured. Since that time, Holcomb has led a series of consecutively more rigorous studies of the resuscitation of massive hemorrhage—the Trauma Outcomes Group study (2009), the Prospective Observational Multicenter Massive Transfusion Trial (PROMMTT, 2012), and the Pragmatic Randomized Optimal Plasma and Platelet Ratios trial (PROPPR, 2015)—that constitute the best evidence for resuscitation of massive hemorrhage using balanced ratios of conventional blood products. The American College of Surgeons has followed with educational projects such as the Educational Initiative on Critical Bleeding in Trauma and the Trauma Quality Improvement Project for 2012, and with requirements that hospitals and trauma centers have massive transfusion protocols and that they utilize hemostatic ratios of blood products. In Northern Europe, a similar process has been led by Johansson through his work at the University of Copenhagen and in the Scandinavian Conferences on Critical Bleeding.

The epidemiology of physical injury

Injury is common, and over the last decade mortality has increased. In the United States, approximately one individual in 10 receives a significant physical injury requiring medical attention every year, and one in 100 is hospitalized because of such an injury annually. Approximately one in 1000 individuals receives a blood transfusion for injury each year, and just over 180,000 people die of physical injury annually. Costs are greater than $400 billion each year. About 95,000 of these deaths are the result of unintentional injury, with the remainder divided between suicides using physical methods and deaths from injuries purposely inflicted by others. Injury is the third leading cause of death overall, and because it occurs so frequently in children and young adults, it is the leading cause of loss of years of productive life through age 75. As noted, to deal with these injuries, the United States and Canada have built more than a thousand trauma centers and more than a hundred burn centers.

Motor vehicle–related injuries, interpersonal violence, and falls are the most common causes of fatal injuries. Work and recreational accidents also contribute to the toll. All of the common causes of injury are subjects of ongoing efforts at primary prevention through engineering and social controls, but faster cars, higher caliber handguns, and a rising elderly population limit the decline in the overall incidence of both injuries and deaths.

Half of all injury-related deaths in civilians occur outside the hospital, either because of rapid death from massive injury or because they occur in remote or unobserved locations so that movement to advanced care is too late. In the Vietnam War, 85% of battlefield deaths occurred in the field with 40% occurring essentially instantaneously, 65% being dead within five minutes, 80% within 30 minutes, and 90% within two hours of injury. For civilian casualties that arrive at the hospital alive and subsequently die a hemorrhagic death, a similar compression of early deaths occurs with 50% of such patients dead in two hours and 80% dead in six hours (Figure 49.1). Later deaths are caused largely by central nervous system injury or multiple organ failure. Autopsy series of those who die in the field suggest that 15 to 20% have a potentially correctable hemorrhagic cause of death.

Blood use in the injured is strongly related to injury severity. In an examination of blood usage rates in a trauma center, only 8% of all admissions received RBCs, and only 3% of all admissions received 10 or more units. Increased anatomic injury severity was strongly associated with increased RBC use and mortality. Nevertheless, there does not appear to be an upper limit to the number of RBC units that can be successfully transfused, and survivorship after massive transfusion was 60%, after 20 units of RBC was about 50%, and after hypermassive transfusion for trauma is reported in the 15–20% range. This means that massive transfusion is not a marker of therapeutic futility.
Because of the spatial distribution of the population in the United States and Canada, only about half of seriously injured patients are treated initially in level 1 trauma centers. Blood products for the immediate care of the severely injured are often limited in smaller facilities to liquid red cells and frozen plasma, and plasma administration is often delayed. The consequences of this delay creates a need for alternative blood products for austere environments such as freeze-dried plasma and frozen platelets.30 These products and their potential uses will be discussed in greater detail in this section.

**Trauma-associated coagulopathy**

The human coagulation system is slow and weak. Sustain a small laceration, and it typically takes at least five minutes for bleeding to stop. Brush the clot, and it bleeds again. The clotting system is also limited in capacity. The effectors of blood coagulation, fibrinogen and platelets, exist in limited amounts in the whole body. For fibrinogen, that amount is about 300 mg/dL in 3 L of plasma or about 9 g of fibrinogen altogether in the blood of healthy individuals. Platelets are present in similarly small amounts. The normal 250,000 platelets/μL fill only 0.2% of the blood volume or 10 mL of the normal 5 L of blood. Laid out side-by-side as 3 x 3 μm discs, all the platelets in the circulation will cover only 10 m². However, the body has 100 m² of capillaries in the lung and 3000 m² of capillaries altogether. Thus, the body starts with 2 teaspoons of fibrinogen and 2 teaspoons of platelets, and initial blood losses after severe injury can mean that 40% of that is already lost before care ever begins. Only blood product transfusion can provide more of these critical materials rapidly.

Furthermore, the physiology of massive injury leads to rapid degradation of the body’s already limited coagulation capacity. Dilution, acidosis, hypothermia, consumption, and fibrinolysis all contribute to an inability to take full advantage of the limited blood-clotting resources that the body starts out with.51 In combination, they insure that many severely and most profoundly injured patients are coagulopathic when they arrive at medical care.

Loss of coagulation factors and platelets starts with the acute blood loss of injury, which can be in excess of 40% in patients arriving in deep shock. Attempts to raise blood pressure with asanguinous fluid to sustain tissue perfusion will lead to further blood loss through uncontrolled defects in vascular integrity. Dilution of platelet counts and coagulation factor concentrations occurs naturally as remaining intravascular blood is watered down by physiologic vascular refill. Normally, blood pressure pushes water into the tissues, which returns through the lymphatic circulation. As blood pressure falls in hemodynamic shock, water moves back into the vascular space down a concentration gradient to dilute the colloidal osmotic activity of plasma proteins.

Acidosis, which develops rapidly with tissue hypop冲洗，has profound effects on plasma coagulation. Normally, activated plasma coagulation factors assemble into complexes on negatively charged phospholipid rafts on the surfaces of exposed subendothelial cells, platelets, and endothelium in ways that increase the clotting activity of the enzymes in these complexes by 10,000 to a millionfold. The increased concentration of protons that are low pH destabilizes these coagulation factor complexes and reduces their activities. The reduction is 50% at pH 7.2, 70% at pH 7.0, and 80% at pH 6.8.32 All these levels are commonly seen in patients suffering severe hemorrhagic shock.

Hypothermia also affects the plasma coagulation enzymes, reducing their activities by about 10% per degree Celsius, but it has a much greater effect on platelet activation. Normally, platelets activate when they adhere to exposed subendothelium through bridging von Willebrand factor. The von Willebrand factor binds to the platelet glycoprotein receptor Ib with one end and to type III collagen on the other, creating traction and torsion of the receptor leading to platelet activation. However, this receptor torsion–platelet activation coupling is lost with mild cooling and is essentially gone at 30 °C.52 In the past, the combination of a low core temperature and severe injury with uncontrolled bleeding was viewed as fatal, but now the combination of extracorporeal blood warming, avoidance of blood dilution, and an array of hemorrhage control strategies allows many trauma patients who present with severe hypothermia to survive.

Consumption of platelets and coagulation factors can occur both within wounds and diffusely with the embolization of tissue factor–bearing tissue fragments and phospholipids and with the diffusion of thrombin. In high-energy blunt or penetrating trauma, the extent of endothelial disruption may extend to billions of endothelial microtears, each associated with the exposure of tissue factor–bearing cells and subendothelial basement membrane collagen. Under these circumstances, factors VII, VIII, and V and platelets can be depleted. Factor VII is present normally in only nanomolar amounts, so the exposure of a few hundred grams of mesothelial cells presents enough tissue factor to bind all of the factor VII available. Factors VIII and V are classically consumable factors, activated by thrombin and inactivated by protein C. The blood can be exposed to multiple cycles of activation and inactivation in its course through injured tissue with resultant consumptive loss of much procoagulant activity. Finally, platelet activity can be consumed with either reduction in platelet number or depletion of platelet granule contents, membrane, and energy. Severely injured patients typically present with normal numbers of platelets that then decline over the first hour in the hospital, and their remaining platelets appear to have reduced activity, a phenomenon called platelet fatigue.54

Fibrinolysis, in the context of trauma-associated coagulopathy, is the early and inappropriate breakdown of fibrin clot, resulting in the loss of hemostasis and the substrate for further coagulation and vascular healing. Pathologic fibrinolysis following trauma is typically caused by plasmin or neutrophil elastase. Plasmin is activated by tissue plasminogen activator released in response to low blood flow, and its breakdown is delayed by early destruction of plasminogen activator inhibitor by protein C. Neutrophil elastase is released in large amounts in injured tissue, and its signature fibrin fragments are found in large amounts following severe injury.

In severely injured patients, all of these activities limiting stable clot formation can be going on at once. In a review of the risks for uncontrolled coagulopathy following injury, Cosgrove and colleagues found that the risks were additive.53 Patients with severe injury but without shock, acidosis, or hypothermia were rarely coagulopathic. With profound injury, about 10% were coagulopathic at presentation; and with shock requiring resuscitation, the rate increased to 40%. With profound injury and hypothermia coagulopathy was present in 50%, and with acidosis in 60% of all patients. However, when three or more of these factors were present simultaneously, the incidence of coagulopathy increased to 85–98%. Thus, the most severely injured patients will develop coagulopathy.

What was not widely recognized until a decade ago is that about one in four of severely and profoundly injured patients arrive at the hospital with coagulopathy already established. In 2003, Brohi and his colleagues described a thousand patients arriving at the Royal
London Hospital by helicopter from motor vehicle collisions on the London ring-road; they had received only 400 mL of crystalloid fluids on average before arrival, and yet one-quarter had their prothrombin time (PT) prolonged beyond 1.5 times normal.56 Moreover, the quarter with the prolonged PT had a fourfold excess in-hospital mortality. Brohi called the finding the acute coagulopathy of trauma. A month later, MacLeod and her colleagues from the Ryder Trauma Center in Miami reported a similar finding in 20,000 patients seen over a five-year period.57 In their series, 28% of all seriously injured patients had a prolonged PT that was associated with a 35% excess in-hospital mortality, and 8% had a prolonged partial thromboplastin time (PTT) that was associated with a 426% excess in-hospital mortality. In 2009, Hess and his colleagues described the prevalence of abnormal coagulation, which was measured at admission in 35,000 direct admissions to the Cowley Shock Trauma Center in Baltimore over a seven-year period; this measured at admission in 35,000 direct admissions to the Cowley Shock Trauma Center in Baltimore over a seven-year period; this coagulation showed greater prevalence of abnormalities of the PT, PTT, fibrinogen, and platelet count with increasing injury severity, and the increasing severity of each of the abnormalities was associated with increasing in-hospital mortality. At the highest levels of injury severity observed, the prevalence of abnormal admission coagulation tests was 45%, and in-hospital mortality was 80%. In a search for clinical and mechanistic drivers of the acute trauma of coagulopathy, Cohen and his colleagues from the Prospective Observational Multicenter Massive Transfusion Trial (PROMMTT) found that the fraction of 1198 severely injured patients with an INR ≥1.3 was 42% and that they generally had depressed concentrations of factors I, II, V, and VIII, and evidence of increased concentrations of activated protein C.59 Decreased concentrations of platelets on admission are much less frequent. As noted, most patients with severe injury present with normal platelet counts, but when the admission counts are low, they are associated with very high in-hospital mortality.

There has been an argument in the literature about whether the acute coagulopathy of trauma is a separate pathophysiologic entity or is just the early and hypocoagulable form of disseminated intravascular coagulation (DIC).60 The International Society of Thrombosis and Hemostasis used trauma as their example of the early and vascular coagulation (DIC).61,62 The autopsy series suggest that such patients may represent 8–19% of all injury deaths, and the deaths represent a combination of missed diagnostic and therapeutic opportunities that in turn result in delayed hemorrhage control. As these deaths clearly overlap with the excess mortality associated with the acute coagulopathy of trauma, designing resuscitation systems to limit coagulopathy is a priority.

In an instructive case, a young soldier seen in the combat support hospital in Baghdad with massive injuries from an improvised explosive device received 18 units of RBCs in the approximately 50 minutes of his hospital care and died before type-specific plasma was thawed. In reviewing the case among the hospital staff in Baghdad, the surgeons pointed to the need to get plasma into the patient sooner, whereas the supporting transfusion service pointed to the limited supplies of universal donor group AB fresh frozen plasma (FFP) and the potentially massive waste of plasma products associated with the legal requirement to use thawed FFP within six hours of thawing. The transfusion service had adopted the protocol of first obtaining the patient’s ABO type and only then thawing type-specific plasma to provide the best matched product, limit frozen plasma wastage, and balance usage by ABO type. However, the end result was dead patients. An outside consultant suggested that the problem could be partially ameliorated by the simple expedient of relabeling thawed FFP as thawed plasma, which can be kept for five days; that keeping four units of AB plasma thawed at all times would provide a buffer of plasma for immediate use; and that patients might benefit as well from prompt initial treatment of the acute coagulopathy of trauma. After confirming the legal definitions of thawed plasma and assuring a continuing supply of AB FFP, this plan was adopted. It was further agreed that units of red cells and plasma would be given alternately to the profoundly injured to keep the combined hematocrit of the administered products close to 30% and provide an easy protocol for administration in the chaotic situation of a massive injury resuscitation (Figure 49.2).

The clinical results were dramatic. All involved in the immediate care of the subsequent wounded casualties thought that they did better. More patients appeared to survive initial resuscitation, their tissues handled better in the operating room with less spontaneous bleeding and edema, and the required duration of ventilator support

**Figure 49.2** (A) Whole blood–derived blood components processed by the platelet-rich plasma method have the average contents shown above. (B) Giving RBC, plasma, and platelets in a 1:1:1 unit ratio results in a hematocrit (Hct) of 29%, a plasma concentration of 65%, and a platelet concentration of about 90 K/mcL. An additional unit of RBC dilutes the plasma to 52% and the platelet count to 60 K/mcL while raising the Hct unnecessarily. Source: Data from Arman and Hess, 2003 (Transfus Med Rev 2003 Jul;17[3]:223–31) and Kornblith et al., 2014 (J Trauma Acute Care Surg 2014 Dec; 77[6]:818–27).
was shorter because patients appeared to get less blood and fluids altogether. Other surgical groups in theater, both US and allied and in Iraq and Afghanistan, adopted the procedures, and by the end of 2004 the use of 1:1 unit ratios of red cells and plasma for resuscitation had become a theater guideline. A retrospective review of cases performed at the Baghdad hospital showed a strong correlation between the ratio of plasma units to red cells given and survival.63

Because the 1:1:1 resuscitation strategy was at variance both with conventional surgical dogma as outlined in the ATLS manual and with evolving transfusion medicine doctrine as exemplified by the drive to reduce plasma usage generally, the authors felt it necessary to gather a panel of experts and review the findings. Expert review panels were recruited and asked to develop data and position papers on critical issues surrounding early massive transfusion for trauma. The meeting took place at the US Army Institute of Surgical Research in San Antonio on May 25–27, 2005, and the results were published as a supplement to the Journal of Trauma in September 2006.64 There were several major findings. First, there was essential agreement on the epidemiologic association of injury severity, number of units of RBCs transfused, and admission coagulation measures with time to death and in-hospital mortality between the German Trauma Registry and the US Miami and Baltimore Trauma Registries.65 Second, in contacting 80 academic trauma centers, formal massive transfusion protocols were rare.66 Third, a number of high-volume trauma centers, including those in Sydney, Baltimore, and Helsinki, had learned to switch their resuscitation blood orders from emergency unencounted to type-compatible 1:1:1 as soon as a blood type was available. Fourth, concerns about the safety of red cell and plasma transfusion were widespread, especially among groups writing standards, but the size of the associated risks and the effects of risk reduction strategies such as leukoreduction were not known. Fifth, for the group of severely injured patients with ongoing massive uncontrolled hemorrhage, resuscitation with a 1:1:1 unit ratio of red cells–plasma–platelets was recommended as long as resuscitation was running ahead of available laboratory data. Finally, it was widely admitted that there was a general lack of useful data to allow the identification of injured patients at risk for massive transfusion, and also regarding what the best clinical and laboratory tests were to guide subsequent transfusion and what safety and efficacy trade-offs were involved in blood product–based resuscitation. Early balanced resuscitation appeared to reduce morbidity and mortality, no group was performing such resuscitation in an ideal way, and the trauma community was poorly positioned to gather the data that would be needed to justify the costs and risks of such a commitment of resources. The meeting was a watershed event.

In the five years following the conference, a number of retrospective studies of massive bleeding were published that described differences in outcome associated with differences in resuscitation on large, essentially consecutive series of patients. Borgman and his colleagues published the results of the Baghdad series showing a 50% reduction in mortality with high-plasma versus low-plasma resuscitation of combat injuries. Johansson and colleagues reported a 33% drop in massive transfusion mortality at the University of Copenhagen Hospital after instituting hemorrhage control resuscitation.67 Cotton and colleagues reported a 40% improvement in 30-day survival after damage control laparotomy when damage control resuscitation was used.68 Holcomb and the Trauma Outcomes Group gathered 466 cases of massive transfusion from the records of 16 trauma centers, which showed a strong relationship of the plasma-to–red cell transfusion ratio with outcome.69 Also noted was a strong relationship of platelet count on admission and platelet transfusion to outcome. However, all of these important studies were subject to the criticism that it was impossible to separate out the effects of receiving blood products from the effects of surviving long enough to receive the products, or survival bias.70 In a review of 10 published series, Stansbury and her epidemiologic colleagues pointed out a number of reasons for believing that the reported effect of a high plasma-to–RBC ratio was real, most importantly the declining overall mortality, but ultimately concluded that randomized and prospective data would be necessary to overcome the biases introduced by patient selection and time to treatment differences.71

Obstacles to conducting randomized trials in trauma patients are multiple. They include problems with study design, informed consent, study team building, and support. The trials of recombinant human blood-clotting factor VIIa (rFVIIa) conducted by its manufacturer and of hypertonic saline by the Resuscitations Outcomes Consortium provided experience and object lessons. In the rFVIIa hemorrhage trials, informed consent turned out to be a particular problem as half of all hemorrhage deaths occurred in the first two hours after arrival in the trauma center and the mean time to obtaining consent from next of kin or another legally authorized representative was three hours. This meant that a $40 million trial with a planned mortality of 40% had only 11% mortality and a statistically negative outcome in the patients who could be consented.72 The hypertonic saline trials provided experience with conducting large publically funded resuscitation research under the exception from informed consent (EFIC) rules of the US government. They were successfully conducted and showed no benefit for this low-volume resuscitation technique.73

The first large prospective trial of hemostatic trauma resuscitation, PROMMTT, was observational only.74 Designed to gather data in preparation for a randomized trial, in 15 months it screened 12,560 patients with highest level trauma team activations at 10 level 1 trauma centers and enrolled 1245 patients with apparent uncontrolled hemorrhage who survived at least 30 minutes and received at least one unit of red cells within six hours of admission. A subset of 905 of these patients who went on to receive at least three blood products in the next six hours became the analysis cohort. In the first six hours of observation, 95 patients died, including 77 of uncontrolled hemorrhage, whereas in the period between six hours after admission and 30 days only 18 of 125 further deaths were associated with uncontrolled bleeding. A Cox proportional hazards analysis showed that deaths in the first six hours were strongly associated with the ratio of plasma to red cell units given, with hazard ratios for death four times greater in the patients receiving plasma-to–red cell ratios less than 0.5. However, even with the strong association with outcome, the centers had trouble delivering plasma in a timely manner, with 65% of patients receiving no plasma in the first hour, 40% receiving no plasma in the first two hours, and 20% receiving none in the first three hours. Infusion times for platelets were even slower. Median time to hemorrhagic death was 2.6 hours. Ultimately, 25% of patients in the evaluation cohort died, of whom only a third died of hemorrhage, and most of them during the first six hours when active resuscitation was occurring. The study showed that it was possible to gather accurate time of transfusion data on large numbers of trauma patients in a short time period, but that the process was labor intensive, required screening large numbers of patients to enroll the few patients likely to benefit, and even in the best centers was still subject to risks of survival bias because of long delays in delivering plasma and platelets to the bedside. However, the size of the possible therapeutic
benefit of timely administration of balanced resuscitation appeared to be as large as a 75% reduction in hemorrhage-related mortality.

The PROMMTT study suggested that a prospective randomized test of 1:1:1 transfusion in severely injured and massively bleeding trauma patients was possible. However, such a trial would require access to more than 10,000 trauma patients and the ability to screen patients and enroll those at high risk for active ongoing hemorrhage while simultaneously excluding those with severe head injury unlikely to benefit from resuscitation. It would need to submit them to randomized treatment quickly with EFIC, and to treat them promptly with blood products available within minutes after arrival so that there was no delay between the time of randomization and treatment to create survival bias.

The PROPPR study was conducted between August 2012 and January 2014. It screened 14,000 patients and enrolled 680 who had an Assessment of Blood Consumption score of 2 or more and no evidence of unsurvivable head injury. The 12 participating trauma centers had to prove that their transfusion service could make six units of universal donor RBCs and plasma available within 10 minutes of notification and have six more available within 20 minutes of patient arrival. The patients were randomized to receive plasma–platelets–red cells in either 1:1:1 or 1:1:2 unit ratios and followed to 24-hour and 30-day mortality endpoints. The trial was completed with better than 97% protocol compliance and 100% follow-up for the primary endpoint.

The results are complicated only in the sense that the US Food and Drug Administration (FDA) required that the primary endpoints be 24-hour and 30-day survival as a condition of granting the permission to conduct the study under EFIC rules. The study results were not significant at these primary endpoints. However, over the course of resuscitation from 10 minutes to three hours, a significantly greater proportion of patients treated with the 1:1:1 ratio survived, and the absolute difference in mortality was significant at the end of resuscitation and persisted from three hours to the end of the study (Figure 49.3). The number of hemorrhage deaths occurring during resuscitation was reduced by almost 50%, and the relative reduction in total deaths over 30 days was 18%. Overall mortality in the treated arm was 18%, down from 40% to 70% in series reported a decade ago.

What the PROPPR study did not tell was whether the benefit of balanced hemostatic resuscitation was the result of the extra plasma, the platelets, or both. It addresses only the difference between resuscitation with a 1:1:1 ratio of blood components and a 2:1:1 ratio. Planned blood sampling at admission and two hours after admission will miss most of the intermediate differences that led to excess early deaths in the 2:1:1 arm.

Rapid delivery of balanced hemostatic resuscitation is the new standard of care. It has been adopted by the American College of Surgeons in their Trauma Quality Improvement Guidelines for Massive Transfusion Protocols required for trauma center accreditation. It is required for Patient Blood Management program accreditation through the AABB. It saves lives, and it saves blood.

**Clinical approach to the trauma patient**

There are general phases of trauma care: prehospital, emergency room, operative care, and postoperative care. The phases of care are more blurred now as hemostatic resuscitation has been pushed further forward even into the prehospital phase of care with the provision of red cell and plasma products to some helicopter emergency patient transport systems, and associated with improved outcomes and minimal wastage.

Half of all civilian trauma deaths occur in the prehospital environment. Rapid movement of patients from the area where injury occurred to a trauma center provides the greatest benefit because most rapidly fatal injuries are truncal and require surgical or radiographically guided access for care. Nevertheless, opportunities exist and should not be lost to limit extremity bleeding through the use of tourniquets. Neck, scalp, and truncal soft tissue bleeding can be reduced by the application of direct pressure and hemostatic bandages. Keeping patients warm and limiting blood dilution are also important goals. The administration of crystalloid

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**Figure 49.3** Mortality in the resuscitation phase of the PROPPR trial comparing resuscitation with a 1:1:1 unit ratio of RBC–plasma–platelets with a 2:1:1 ratio as a Kaplan–Meier plot with 95% Hall–Wellner confidence intervals. Data from Holcomb et al. (2015).
fluids in the field to prevent acute renal failure does not appear to be necessary with modern casualty evacuation times, and raising blood pressure is associated with the loss of more of the patient’s blood through vascular defects. In situations where red cells and plasma are available in the field or in transport, they can be given, but only about 15% of patients undergoing helicopter transport to trauma centers appear to be candidates for transfusion even when blood products are available.78

In the emergency room, there is an emphasis on rapid and systematic evaluation. The primary survey (ABCDEs) of airway, breathing, circulation, neurologic disability, and full exposure is followed by a more systematic evaluation and the mobilization of teams to deal with specifically identified problems. Hypotension and penetrating injury suggest major internal bleeding and urgent need to move to the operating room (OR), as do significant tachycardia and the presence of fluid in body cavities assessed in a focused ultrasonographic survey for trauma (FAST). A combination of these two pairs of signs as the Assessment of Blood Consumption score has close to 80% power to predict massive transfusion and served as a major inclusion criterion in the PROPPR study.79 For patients with less urgent needs to go directly to the OR, staged further studies leading to a complete secondary survey of the patient are the next goal. Hemorrhage remains a concern. There are multiple body cavities where it is possible to lose enough blood to cause shock from hypovolemia: pleural spaces and the mediastinum in the chest; peritoneal and retroperitoneal spaces in the abdomen, pelvis, and thighs; as well as subcutaneous spaces. Whole-body imaging is important for patients stable enough to tolerate it, and computerized tomographic (CT) scanning identifies additional sites of injury such as intracranial bleeding, pericardial hemorrhage, major vascular disruption, major organ fracture or laceration, and bowel, biliary, and urinary tract disruption that need prompt attention. Moreover, musculoskeletal injuries are frequent and need at least initial stabilization to make patients movable for nursing care. Simply placing a pelvic binder to hold the pelvic ring together can often limit venous bleeding and prevent further arterial injury in the early phases of patient assessment.

In the OR, time remains of the essence. The historic problem that 40 minutes of wide-open abdominal exposure in a hemorrhaging trauma patient led to the loss of a degree centigrade in core temperature through evaporative cooling from the exposed wet tissue surfaces is not true anymore as balanced resuscitation prevents gut swelling with evisceration and has the result that fluid and body warmers can now keep up. However, the requirement to obtain hemorrhage control can supersede the demands of normal operative patient setup, so that vascular access for resuscitation may be limited and resources for patient warming altogether missing in the early phases of emergently opening a body cavity for hemorrhage control. As a result, a decision on the goals of the exploratory surgical procedure needs to be made early. Massive organ disruption or soft tissue injury may lead to a decision to pack wounds for hemorrhage control with the concomitant need to change or remove packing a day (or at most two days) later and therefore a need to leave the wound open. The decision to pursue only hemorrhage control, restoration of critical organ perfusion, and limitation of wound contamination with bowel tie-off and bile and urinary drainage is classic damage control. However, damage control surgery rates are plummeting as iatrogenic resuscitation injury is avoided.80 More frequently, surgical exposure allows the identification of correctable sources of bleeding that can be dealt with by vascular repair or ligation, repair or removal of injured organs, and closure.

Increasingly, close collaboration between surgeons and interventional radiologists (IRs) has led to procedures that are partially performed by one specialty and partially by the other. These procedures occur with the patient being moved in the middle of the procedure from the OR to the IR suite or can occur in modern hybrid ORs where the interventional radiology cameras can be brought to the patient and the two groups can work together simultaneously.81 Transfusion support for such highly complex and high-blood-loss situations is similar to other massive transfusion situations and involves ongoing balanced resuscitation shaped to the clinical situation and the available laboratory data.

At the end of such procedures, patients are moved to recovery rooms or directly to intensive care units (ICUs) for continued resuscitation. Bleeding is often slowed but not stopped, and provision for continuing blood product support and planning for potential return of frank hemorrhage if packing fails or is reinitiated with unpacking is prudent. In the recovery room or ICU, bleeding is usually slow enough that its replacement can be guided by laboratory measures. It is still important to remember that the limitations of resuscitation imposed by multiple different blood components diluting each other make it prudent to avoid components such as platelets in additive solution that do not maximize plasma dose.

Clinical approach to the mass casualty trauma situation

Mass casualty trauma situations are uncommon, and those requiring large amounts of blood are rare. In the United States between the years 1975 and 2000, there were only four such events that required more than 100 units of RBCs to treat all of the resulting casualties in their first 24 hours of care.82 The largest domestic use of RBCs for a mass casualty event was 224 units given for injuries from falling glass from the World Trade Towers into crowds of pedestrians below. The London and Madrid train bombings used even more RBCs (338 and 696, respectively) on the first day, but each involved the care of hundreds of casualties spread across multiple hospitals in a large urban area. Blood use in the Boston Marathon 2013 bombings has been described.83

The rarity of massive blood use in masscasuality events is to be contrasted with the frequency of massive blood use in a single individual when polytrauma or transplant more commonly creates situations where one individual uses more than 100 units of RBCs in 24 hours. A critical difference between these situations is the need to have well-practiced protocols to maintain the unique identity of each patient in masscasuality settings. The use of universal donor products in disaster situations where casualties may be unidentified or, more importantly, misidentified is an important precaution. It should be remembered that more than 100,000 universal-donor whole blood and red cell units were given in the Vietnam War and that all seven fatal acute hemolytic reactions there were associated with the misidentification of recipients of crossmatched red cells. Mass casualty trauma situations are major media events, and the media frequently encourage the population to donate blood as a response to disaster. During the Clapham Junction railway disaster in London in 1988, the number of volunteer donors responding effectively shut down the Richmond blood center. The 600,000 extra units of blood collected nationwide after the September 11, 2001, terrorists attacks were unnecessary and largely had to be destroyed.
**Initial resuscitation of the burn patient**

The resuscitation of patients with severe burns is different than that of patients with penetrating and/or blunt force trauma. Trauma patients in hemorrhagic shock with ongoing acute blood loss are generally resuscitated with blood products. Burn patients typically have a higher initial hemoglobin concentration associated with redistribution of plasma water into the interstitium and intracellular space. Therefore, their initial resuscitation utilizes crystalloid and occasionally colloid solutions, and blood product transfusion is rare during burn resuscitation. However, later during the treatment course, cumulative blood loss associated with eschar excision and grafting, anemia of critical illness, and laboratory testing increases. It is during this latter period in the hospital course that attention should be given to the type and quantity of blood transfusions given to patients with severe burns.

In the initial period (24–48 hours after injury), resuscitation is conducted according to standard burn resuscitation formulas; however, no single formula replaces the role of the physician, who must continually assess the adequacy of resuscitation. Utilizing the Parkland formula, most patients receive 2 to 4 mL/kg of fluid per percentage of total body surface area (BSA) burned in the first 24 hours after injury. This fluid is generally lactated Ringers’ solution. The first half of the calculated volume is given over the first eight hours from injury, not from the beginning of resuscitation; the rest is given over the next 16 hours.64,85 Children also should receive maintenance fluids containing dextrose in addition to the resuscitative fluid. The presence of inhalation injury can increase the volume of fluid to achieve adequate resuscitation. Whether colloid is used in the first 24 hours is determined on a case-by-case basis; administration of colloid should not be routine, but is utilized in the severely burned patient who is not hemodynamically responsive to crystalloid resuscitation. Urinary output of 0.5–1 mL/kg/hour is the most commonly used measure of resuscitation adequacy.

Release of vasoactive mediators from injured tissue results in a diffuse capillary leak starting soon after injury. This loss of microvascular integrity results in extravasation of crystalloid and colloid solutions for the first 18 to 24 hours after injury. This pathophysiologic process explains the enormous fluid volumes given to burned patients for the first 24 hours, which can be up to 40 L. This is the reason that most burn resuscitation formulas incorporate the use of colloid after 24 hours; microvascular integrity is restored at that time, and colloid remains largely intravascular. Colloid, generally 5% albumin, is infused at a dose based on burn size (generally, 0.3 to 0.5 mL/kg per percentage of total BSA burned over 24 hours). During this period, crystalloid utilization decreases markedly.

**Transfusion therapy in the care of the severely burned**

Patients with less than 10% total BSA burns rarely receive transfusions.86 Those with increasing burn size, age, and presence of anticoagulants significantly increase the use of blood transfusions, but deciding when to transfuse can be difficult.87 The hypermetabolic response to severe burn significantly alters normal physiologic parameters that are commonly relied upon to determine transfusion indications. When considering transfusions in burn patients, several factors are evaluated, including the acuity of the anemia, the risk–benefit of transfusions, blood loss mitigation techniques, and potential physiologic benefit.

During the initial resuscitative period, burned patients will have an acute blood loss anemia that is not associated with large-volume blood loss, but rather from destruction of erythrocytes within the cutaneous circulation and by hemorrhage into the burn wound. This initial anemia is typically not significant enough to require transfusion, as evident by data showing an average of 5.3 ± 0.3 days from admission to the first transfusion.88 The critical point of highest blood loss, and subsequently the use of large-volume transfusions, occurs during burn wound excision and grafting. Further blood loss can occur from postoperative dressing changes. During burn wound excisions, most estimates suggest that 1 mL of reconstituted whole blood will be used for each square centimeter of excised wound. Therefore, if 1000 cm² will be excised, approximately two units of packed RBCs and two units of FFP should be available. Platelets are rarely transfused unless the platelet count is less than 10,000/mm³ in the absence of other coagulopathies.

Efforts made to mitigate the use of transfusions during eschar excision include the use of hemostatic techniques such as topical thrombin, epinephrine-soaked gauze, tourniquets, and fibrin sealants.89,90 It is well known that intraoperative blood loss is the limiting factor of the extent of excision and grafting performed. Initial steps to control hemorrhage use electrocautery devices or pressure. Thrombin spray and laparotomy pads saturated with thrombin and epinephrine can be applied directly to the wound bed to limit intraoperative blood loss. The use of tourniquets for excision and grafting of extremities can further decrease blood loss, but should be tempered by the risk of ischemia resulting in graft loss.91 Recently, the use of activated thrombin mixed with fibrin that is sprayed onto the wound has become popular and may prove effective. Results of preliminary studies of the use of intraoperative blood recovery techniques show recovery and reinfusion of approximately 40% of shed blood without adverse inflammatory or infectious complications.92 As in the care of trauma patients, the importance of normothermia in preventing coagulopathy is recognized, and patients are actively warmed or more importantly not allowed to get cold at the time of surgery.

Data from a multicenter study evaluating the effects of blood transfusion in severe burns revealed that 70% of blood transfusions for burn victims occur outside of the operating room.3 These transfusions are done to treat the persistent anemia of chronic illness that affects most critically ill patients, including burn patients. This anemia is multifactorial in origin and due in part to mild ongoing blood loss from dressing changes and phlebotomy, impaired RBC production from erythropoietin insensitivity, malnutrition, and metabolic demands. As with operative excisions, some efforts can be undertaken to mitigate this anemia as well. Minimizing blood draws and using pediatric blood collection tubes can decrease blood volumes wasted. Maintaining adequate nutrition is important for all patients, and some studies have identified up to 13% of critically ill patients as deficient in nutrients necessary for erythropoiesis.93 Administration of exogenous erythropoietin has been extensively studied in multiple critically ill populations but has yet to show any efficacy in patients with burns.

Transfusing patients with thermal injuries must be tempered with the known risks and benefits of blood and blood products. Increasing hemoglobin concentrations is the only method to increase oxygen carrying capacity, but the known transfusion-associated morbidity documented in multiple specialties is also seen in burn patients. The safety of a restrictive transfusion strategy demonstrated in the Transfusion Requirements in Critical Care (TRICC) trial has been investigated in patients with thermal
Adjuncts in transfusion therapy for trauma and burn patients

Tranexamic acid

Tranexamic acid (TXA) and e-aminocaproic acid are lysine analogs used as antifibrinolytics. Newly formed fibrin polymer has exposed lysine residues that serve as binding sites for plasmin and facilitate the plasmin-dependent breakdown of fibrin polymer. During normal coagulation, a strong thrombin burst activates the thrombin-activated fibrinolysis inhibitor (TAFI), which removes these lysine residues to prevent fibrin breakdown. However, after trauma and especially with the acute coagulopathy of trauma, the intensity of thrombin activation is reduced and as a result TAFI is not activated. However, activation of plasmin by tissue plasminogen activator secreted in response to hypotension and inactivation of plasminogen activator inhibitor by activated protein C lead to high plasmin activity. The combination of high plasmin activity and widely available plasmin binding sites on fibrin leads to rapid degradation of fibrin polymer. Using TXA to inhibit fibrinolysis stabilizes newly formed clot and reduces blood loss.

TXA has been demonstrated to reduce blood loss in several nontrauma settings such as in knee and hip joint replacement, in craniosynostosis surgery, and after tooth removal in patients with hemophilia. Knee and hip joint replacement trials have shown reduced blood drainage after surgical site irrigation with a suspension of the drug. In infants undergoing craniosynostosis surgery, a randomized trial demonstrated an almost 50% reduction in blood loss and red cell replacement requirements with intravenous administration. In hemophilia patients undergoing dental extraction, oral wash with a suspension of the drug reduced duration of bleeding.

For trauma patients, the international CRASH II trial and the MATTERs study are the basis for recommendations for wide use of the drug. The CRASH II trial was a large simple randomized trial of TXA use or nothing in 20,211 trauma patients in 274 hospital in 40 countries. Use of the drug led to a 1.5% reduction in overall mortality with a reduction in the odds of hemorrhagic mortality by 15%. However, in patients treated more than three hours after injury, mortality was increased. The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation study (MATTERs) is a retrospective review of 896 consecutive admissions to a British Army medical facility in Afghanistan that demonstrated better survival in patients treated with TXA. The mortality benefit observed in patients receiving TXA was almost 50% in those receiving more than 10 units of RBCs.

Despite occasional reports of thrombotic complications after TXA administration, a large meta-analysis of randomized trials of the drug did not reveal excess thrombosis or mortality after its use. This suggestion of broad safety has led to recommendations that TXA be given in prehospital situations. A large Australian study of the use of TXA in the prehospital setting and in facilitating the movement of patients from remote locations to trauma surgical centers is underway, and in the United States, the Resuscitation Outcomes Consortium is starting a trial of TXA in head-injured patients. The drug is rapidly becoming a standard of care.

Plasma-derived coagulation factors

In Central Europe, especially in Austria, recent work has focused on using plasma-derived coagulation factor concentrates to rapidly restore activity in the coagulation system in severely injured patients. The two products that have received the most attention are four-factor prothrombin complex concentrates (PCCs) and fibrinogen concentrates. Chapter 27 describes these products.

Four-factor PCCs provide enough factors VII, X, and II to reconstitute the extrinsic pathway coagulation enzymes, and fibrinogen concentrate provides both fibrinogen and factor XIII. Given early in the course of trauma, they appear effective in multiple uncontrolled case studies, but the exact effects of the lack of factors V, VIII, and XI are unknown. Moreover, the factor concentrates are expensive.

The potential advantages of using these pharmaceutical plasma-derived products are several. Their excellent storage properties and ease of reconstitution mean that they can be kept on the anesthesiologist’s cart or even used in the field, ambulance, or helicopter. Their high concentrations of extrinsic pathway factors allow rapid restoration of extrinsic pathway function, the most common coagulation defect seen in severely injured patients with the acute coagulopathy of trauma. They are blood-type independent, are immunologically well tolerated, contain low concentrations of other proteins, have low volume, and are virologically safe because of pathogen reduction steps integrated into their manufacture.

Disadvantages include the need for reconstitution, which can take 20 minutes and requires another set of hands; the lack of other plasma proteins; and the lack of the full complement of coagulation factors. Although reconstitution is relatively easy, the anesthesiologist is busy managing other aspects of the care of these most severely injured trauma patients, and time to reconstitution delays
the onset of therapy. Also, severely injured patients need volume, so PCCs have frequently been given with other colloids such as starches, which interfere with platelet coagulation. Finally, the PCCs lack factors I, V, VIII, XI, and XIII, and the most seriously injured patients often have deficits of factors I, V, and VIII, with those that do having very high mortality.

As noted, factors I and XIII are present in fibrinogen concentrate, so fibrinogen concentrate is typically given with PCCs, but fibrinogen concentrates have also been given alone. Healthy individuals have relatively low fibrinogen concentrations, which become markedly higher in the days following injury. Providing fibrinogen early to severely injured patients who are still capable of generating a normal thrombin burst takes advantage of the normal extra thrombin capacity to lay down the added extra fibrin to make stronger clots. For this reason, fibrinogen has been viewed as an attractive field medical agent to be given early to reduce blood loss in patient transport. These concepts have been demonstrated in animal studies and small human trials where they are clearly better than classic ATLS resuscitation. However, how the advantages of rapid restoration of extrinsic pathway function and increased fibrinogen balance with the problems created by missing factors and the modest time delay involved in mixing is not known. Direct comparisons with 1:1:1 blood product resuscitation are needed.

Recombinant activated human factor VII

Recombinant activated human coagulation factor VII (rVIIa) was developed as a factor VIII bypass activity for use in the treatment of hemophilia patients with inhibitors. It saw use in trauma first in Israel, then more widely, and finally was tested in randomized trials. The failure of the drug to alter mortality in the randomized trials was discussed in this chapter in relation to time to death in trauma patients with uncontrolled hemorrhage and the trial requirements for informed consent.

rVIIa is grown in mammalian cell culture, isolated and activated by chromatography, and freeze dried. Milligram doses reproduce the normal nanomolar concentrations of the active factor in plasma, but the half-life is only two hours. A quarter of severely injured patients had an abnormal PT in the early reports of the acute coagulopathy of trauma and appeared likely to benefit from treatment, but an isolated elevated PT was associated with only a modest increase in mortality. Early trials showed that the drug reduced blood loss in situations such as prostate surgery, but as a vitamin K-dependent coagulation factor, rVIIa’s activity is highly pH dependent and is reduced in acidic patients and environments.

The combination of inappropriate claims that the drug was a universal hemostat, failure to demonstrate a mortality benefit in the randomized trauma trials, an alleged association with increased posttrauma thrombosis, and perceived high cost have reduced usage.108 If the drug has a use, it is probably early after injury rather than late, and in combination with products such as fibrinogen concentrates to reduce bleeding in transport. Avoiding crystalloid use and more balanced forms of resuscitation have largely replaced the need for rVIIa in trauma center care.

Hemorrhage control bandages

It is possible to make excellent hemorrhage control bandages that provide for rapid control of even arterial bleeding when applied to accessible sites with appropriate pressure. Dry fibrin sealant dressings (DFSDs) containing fibrinogen and thrombin freeze-dried on an absorbable mesh backing have been approved for use, and even better prototypes have been demonstrated.109 Many of the same hemostatic effects can be achieved with hydrophobically modified chitosan and other synthetic hemostatic agents, which can be made into wound-adhering bandages and are inexpensive as well.110

Animal experiments with the Army/American Red Cross DFSD prototype showed reduced blood loss and improved survival in experimental models of grade V liver injury and groin injury. In its one human use in a groin injury with femoral artery rupture above a level compatible with tourniquet, it proved lifesaving. Nevertheless, its relatively high cost and use of plasma-derived products created manufacturing problems. The currently available licensed versions use lower concentrations of thrombin and fibrinogen that are less effective against arterial hemorrhage, but can still be used in liver surgery. Making low-cost synthetic hemorrhage-control bandages with appropriate short-term stability and midterm biodegradation will be a major advance in the care of large superficial wounds, accessible but not-tourniquet-compatible hemorrhage, and wound stabilization and hemorrhage control during trauma and other forms of surgery.

Artificial oxygen carriers

Hemoglobin and perfluorocarbon-based oxygen carriers have a long and complex history. Cell-free hemoglobin can support life for a few hours in patients with profound hemolysis from clostridial sepsis, in animals following exchange transfusion to lethally low hematocrits, and occasionally in patients given hemoglobin-based blood substitutes. However, most patients do not tolerate the materials, and 11 randomized trials using four different commercial products all had excess mortality in the treated groups.111 For this reason, it is hard to imagine a public health agency such as the FDA approving a material that consistently kills more people than it helps.

Tetrameric cell-free hemoglobin will stay in the circulation for several hours and functions in oxygen delivery during that time, but all the while it dissociates into dimers that are cleared by haptoglobin binding and glomerular filtration and oxidizes to met-hemoglobin and hemichromes, heme, iron, and globin precipitates. Free hemoglobin leads to renal proximal tubular injury as its classic toxicity. It also binds endothelium-derived nitric oxide, causing vasoconstriction and increased vascular resistance; serves as a primary nutrient for bacterial pathogens such as Streptococcus aureus and Escherichia coli; and presents bacterial endotoxin to the immune system in a more active form. Hemoglobin breakdown products cause oxidative injury, including monococyte and endothelial activation, excitatory neurotoxicity, and the production of lyso phospholipids and cyclic endoperoxides with secondary immune consequences.112

Modified hemoglobins, whether internally cross-linked tetramers, polymerized tetramers, or conjugates, can be made to reduce one or more of these extracellular toxic mechanisms, but usually at the expense of exacerbating another. The polymerized bovine and human hemoglobins could not eliminate vasoactivity, but lost cooperativity and some oxygen carrying capacity as a result and had inflammatory side effects as well. Polyethylene glycol-conjugated hemoglobin is highly osmotically active, meaning that it has both limited bulk oxygen carriage and significant colligative interference with plasma coagulation proteins. Even though these oxygen carriers carry oxygen, they do not improve the outcome of injured patients.

Oxygen can be dissolved in perfluorocarbon oils, and the oils can be emulsified to be miscible in water, but a safe and effective combination of these properties has not been achieved. The original
product, a mixture of perfluorodecalin and perfluorotriprolyl amine emulsified with a polar detergent (Fluosol, Green Cross Corp., Tokyo, Japan), failed a human trial in patients refusing red cell transfusion for religious reasons. The product had the side effect that the perfluorocarbon lipids could not be metabolized or excreted, and so they accumulated in liver, spleen, and marrow macrophages at a rate of a pound per dose, and a dose functioned for only a few hours. Subsequent development of the volatile perfluorocarbon oils perfluorocetyl bromine and perfluorodichloro octane, which had high oxygen solubility and low vapor pressures compatible with both air breathing and simultaneous excretion of the fluorocarbon through the lung, failed because the high dose of emulsion necessary to carry useful amounts of oxygen led to complement activation, fever, and hypotension.

Despite the well-understood physicochemical limitations of all available alternative oxygen carriers and the well-characterized toxicities of the second-generation products that have undergone human trials, there continues to be interest in these blood substitute materials. Approximately 100 articles are published each year on their possible roles in trauma resuscitation. This literature largely ignores the toxicities and colligative activities of all such alternative oxygen carriers that make them largely incompatible with the restoration of blood coagulation function at the heart of modern trauma care.

Summary
The reduction in blood transfusion in the care of burned patients has been dramatic (three- to fivefold), as burn surgeons have learned to manage blood loss and accept lower transfusion triggers. This is an example of patient blood management evolving in a surgical field largely independent of transfusion medicine.

In the last decade, improvements in trauma resuscitation and trauma care have led to an almost 50% reduction in the incidence of hemorrhagic deaths in trauma centers carrying out damage control resuscitation. These improvements center on the early administration of balanced hemostatic resuscitation with plasma and platelets aimed at early correction of the acute coagulopathy of trauma. These improved outcomes have been validated in the PROPPR study, a large randomized clinical trial.

The challenges of extending these improvements in care to injured patients arriving in smaller centers and to soldiers and civilians in the field will center on developing ways to deliver current blood products earlier in care and the wider use of hemo-static adjuncts such as tranexamic acid, hemo static bandages, and fibrinogen concentrates. It will require a national commitment to collecting the amounts of universal donor blood products needed to make the system work. This will be facilitated by developing a new generation of blood products such as freeze-dried plasma, more effective plasma derivatives, and frozen platelets.

Key references
A full reference list for this chapter is available at: http://www.wiley.com/go/simon/transfusion