



# Blood and Coagulation Support in Trauma Care

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**Injuries are common and account for almost 15% of all blood use in the U.S. The historic view that the coagulopathy associated with severe injury was largely dilutional is being replaced by epidemiologic and molecular evidence for a distinct syndrome of trauma-associated coagulopathy. This coagulopathy of trauma is the sum of the effects of blood loss and dilution, coagulation factor and platelet consumption, hypothermic platelet dysfunction and acidosis-induced decreases in coagulation factor activity, and fibrinolysis. Preventing the coagulopathy of trauma is**

**best accomplished by preventing injury and hypothermia. Treating the coagulopathy of trauma requires its early recognition, prompt control of hemorrhage with local and systemic treatments, including in some patients the use of plasma instead of crystalloid solutions, and the prompt treatment of acidosis and hypothermia. The planned early use of allogenic plasma to treat many tens of thousands of massively transfused patients each year creates new demands for the immediate availability and improved safety of plasma products.**

## Importance of Injury, Injury Prevention, and Injury Care

Injury is the fifth leading cause of death worldwide and will become the second leading cause by 2020.<sup>1</sup> It is already the leading cause of death in individuals aged 5 to 45 years. Vehicular injury, self-inflicted injury, interpersonal violence (including war), work-related injury, falls, burns, and environmental disasters all contribute their share.

Primary prevention is the most effective way to limit injury. The importance of education, engineering controls, and the rule of law in prevention of injury cannot be overemphasized. Almost as many individuals die of vehicular injury in Egypt as in the U.S., but Egypt has one-quarter the population and one-tenth the number of vehicles.<sup>2</sup> Nevertheless, the majority of injuries in both countries are preventable.

Secondary prevention, the application of acute care to prevent death and disability following injury, is also highly effective.<sup>3,4</sup> The cost of trauma care is low per quality-adjusted life year saved compared with treatments in other common disease categories such as cardiovascular illness, stroke, or cancer interventional therapy. This care is best provided in regional centers.<sup>5</sup> The largest Level 1 trauma centers typically see more than 5000 direct admissions each year and are staffed around the clock with trauma surgeons, neurosurgeons, orthopedists, anesthesiologists, and a complete array of support staff. The work of these centers in patient care, medical education, and developing new knowledge is driving an international revolution in the quality of injury care.

Every year, 1 in 7 Americans is significantly injured. Two-thirds of those, or 1 person in 10 of the U.S. population, seek medical care for that injury, and 1 out of every 100 Americans is admitted to a hospital for injury care each year.<sup>6</sup> About 1 in every 10 patients admitted for injury, or 1 out of every 1000 Americans, receives blood products in the course of injury care. These individuals receive 10% to 15% of all of the blood transfused in the U.S.<sup>7</sup>

## Patterns of Injury-Related Death, Hemorrhage, and Blood Use

About 156,000 people die of injury each year in the U.S., and 93,000 of those fatalities involve physical trauma. Half of these individuals die before they reach the hospital.<sup>8</sup> Among those who reach the hospital alive and who will die during that hospital admission, 80% die within the first 24 hours after admission. The most frequent causes of death of patients who die in the field or in the hospital are profound neurologic injury and uncontrolled hemorrhage.

Control of hemorrhage is a critical aspect of trauma care.<sup>9</sup> In the field, bandages, direct pressure, and tourniquets control superficial and extremity hemorrhage. In the hospital, diagnostic imaging and surgical exploration allow the rapid identification of most other sites of bleeding. However, identification of sites of injury does not always allow immediate control of hemorrhage. Injuries such as deep hepatic lacerations and pelvic fractures with disruption of the pelvic venous plexus frequently require packing, and control of bleeding is obtained only slowly. These injuries can result in extensive and prolonged bleeding even in the hospital.

Patterns of blood use following traumatic injury are determined by the patterns of injury, the speed of transport to surgical care, and the availability of resources at the surgical center. At the University of Maryland R. Adams Cowley Shock Trauma Center in Baltimore in calendar year 2000, 91% of 5649 patients admitted directly from the scene of injury received no blood products.<sup>10</sup> About two-thirds of the remainder, 332 patients, received 10 U of red blood cells (RBCs) or less. However, 75% of the RBCs administered were given to the 146 patients who received more than 10 U and 50% of all the RBCs used were administered to 68 patients, who received more than 20 U of RBCs each. Thus, a select group of trauma patients receive massive transfusion, and it is these patients who are changing our thinking about blood use and resuscitation.

## ATLS Resuscitation and CAP, ASA, and ABC-T Task Force Transfusion Guidelines

The Advanced Trauma Life Support (ATLS) course of the American College of Surgeons suggests starting two large-bore IVs in patients who are significantly injured or appear to be going into shock and, if they are hypotensive, giving 2 L of crystalloid solution.<sup>11</sup> If such patients remain in shock, recover initially, but subsequently go back into shock, or have active ongoing bleeding of greater than 100 mL/minute, then RBCs should be given. These guidelines were based on the recognition that prolonged shock frequently led to renal failure that could be prevented by volume resuscitation and that many injured patients, who suffered decreases in their blood pressure, did not need blood at all.

Other groups have added guidelines for the administration of platelets and plasma. In 1994, the College of American Pathologists (CAP) advocated transfusion of plasma to keep the international normalized ratio (INR) below 1.5 and of platelets to maintain counts higher than  $50 \times 10^9/L$  in actively bleeding patients.<sup>12</sup> They suggested that such transfusions should be triggered by measured laboratory values. In 1996, the American Society of Anesthesiologists (ASA) also recommended administration of plasma to keep the INR below 1.5 and platelets to maintain counts higher than  $50 \times 10^9/L$  in hemodynamically normal but actively bleeding patients, and suggested that raising platelet counts to  $100 \times 10^9/L$  may be useful in multiply or massively injured patients.<sup>13</sup> They also emphasized the importance of the clinical assessment of coagulopathy and its rapid treatment in the face of ongoing bleeding. In 2007, the European Task Force for Advanced Bleeding Care in Trauma (ABC-T) repeated these recommendations and again noted that the evidence supporting them comes exclusively from observational studies and case series.<sup>14</sup> Implementing the laboratory-based treatment guidelines has had limited success, both because of the delay in the return of laboratory results relative to the rate of bleeding and because of the difficulty in achieving an INR of 1.5 with plasma alone.

## Damage Control

As trauma surgery advanced, critical care specialists became aware of a group of patients who were too badly injured to tolerate immediate anatomic correction of their injuries.<sup>15</sup> Such patients typically presented in shock with multiple serious injuries. Failure to control hemorrhage promptly in such patients resulted in a “Bloody Vicious Cycle” of hemorrhage, resuscitation, hemodilution, and coagulopathy, leading to more hemorrhage.<sup>16</sup> At the same time, acidosis from hypoperfusion and heat loss from environmental and surgical exposure combined with coagulopathy comprised a “Lethal Triad” that predicted imminent death. Patients who developed the “Lethal Triad” were extremely difficult to save, so prevention became a priority and led to the development of “damage control” surgery.<sup>17</sup>

Damage control is defined as the planned temporary sacrifice of normal anatomy to preserve vital physiology. Bleeding critical vessels are repaired or bypassed, smaller vessels are ligated, and sources of oozing are packed. Damaged gut is tied off, and injured ureters are diverted. The packed belly is left “open,” sealed with a plastic overwrap or “Bogata bag.” The whole procedure in the abdomen should take less than 40 minutes to keep heat loss to less than 1°C.<sup>18</sup> Such patients are then taken to the intensive care unit (ICU), where resuscitation continues. The goal is to have normotensive, normothermic patients with replete coagulation factors when they need to go back to the operating room to have the packing changed or removed. Sometimes several cycles are required to achieve full control of bleeding, and sometimes the process fails, but frequently patients are saved who would have died with conventional care.

## The Coagulopathy of Trauma

In the past, coagulopathy associated with trauma and massive transfusion was viewed as a largely dilutional event.<sup>19</sup> The loss of blood led successively to critical requirements for fluid volume, red cells, albumin, coagulation factors, and platelets. Critical dilution for coagulation factors occurred after the loss of 1.2 blood volumes and for platelets at 2 blood volumes. Hypothermia was known to slow the enzymatic reactions of the coagulation cascade. Occasionally, severe injury to the head, bones, and gravid uterus led to brain, fat, or amniotic fluid embolization with disseminated intravascular coagulation (DIC) and defibrination.<sup>20</sup> Complex coagulation problems in trauma patients were thought to result from combinations of these events.

As the molecular basis of clotting has become clearer, the effects at the molecular level of acidosis and hypothermia, consumption and fibrinolysis, and concentration and activity have also become clearer. Acidosis specifically interferes with the assembly of the coagulation factor complexes. These complexes normally assemble by coordinating calcium ions with vitamin K-dependent gamma carboxy-glutamic acid residues against negatively charged phospholipid rafts.<sup>21</sup> Excess protons destabilize this coagulation factor-phospholipid assembly and reduce the activity of the Xa-Va prothrombinase complex by 50% at pH 7.2, 70% at pH 7, and 90% at pH 6.8. Hypothermia does reduce the enzymatic activity of plasma coagulation proteins, but its greatest effect on clotting is by preventing the activation of platelets by traction on the glycoprotein Ib, IX, V complex by von Willebrand factor (VWF).<sup>22</sup> In tests of shear-dependent platelet activation, this pathway stops functioning in 50% of individuals at 30°C, and is markedly diminished in most of the rest.

Consumption of coagulation factors and platelets, seen in the past as DIC, is now thought to be highly localized at the site of injury. In this view, millions of endothelial microtears create enough exposure of tissue factor on the surfaces of normally subendothelial smooth-muscle cells

and fibroblasts to bind out most of the factor VII. The nanomole of tissue factor present in every square meter of fibroblasts or smooth-muscle cells means that all of the factor VII could be removed from the circulation by 3 to 30 square meters of endothelial disruption.<sup>23,24</sup> Simultaneous exposure of normally subendothelial type-3 collagen binds vWF and platelets. The  $250 \times 10^9$  platelets in a liter of blood can cover 1 square meter if lined up side by side as  $2 \times 2 \times 2 \mu\text{m}$  cubes. Injuries of this extent appear to occur in patients with moderate to severe lung contusions. The generation of thrombin at these many sites of injury leads to its binding to thrombomodulin on adjacent normal endothelial cells with the activation of protein C.<sup>25</sup> Reduced local thrombin concentrations at sites of injury lead to thin fibrin strands with high surface-to-volume ratios and prevent the activation of the thrombin-activated fibrinolysis inhibitor (TAFI). At the same time, low vascular flow leads to the release of tissue plasminogen activator (tPA) from intact endothelial cells. The consequence of these last three effects is increased fibrinolysis. This coagulopathy of trauma was first recognized in Vietnam casualties but is now receiving attention as the major contributor to preventable deaths.<sup>26</sup>

The coagulopathy of trauma—the sum of the effects of blood loss, dilution, acidosis, hypothermia, consumption, and fibrinolysis—is not only a distinct entity, it is present in most seriously injured patients when they arrive at the trauma center. About 2% of patients present to trauma centers with platelet counts below 50,000 and INRs greater than 1.5,<sup>27</sup> even before significant resuscitation attempts are implemented. Patients in stage IV shock frequently have lost 40% of their blood volume at the time of presentation. Resuscitation attempts, using crystalloid or colloid solutions before hemostasis is achieved, lead to hemodilution and further bleeding. Reaction rates of the coagulation factor complexes depend on the products of enzyme, cofactor, and substrate concentrations, so dilution leads to multiplicative increases in their reaction times. A 40% reduction in the concentration of three factors leads to an 80% reduction in the activity of their complex, and with three complexes necessary in the coagulation cascade, a greater than 90% reduction in coagulation activity. Acidosis in shock is initially best addressed by increasing tissue perfusion to increase oxygen delivery, but that requires the administration of volume to increase preload, which further dilutes procoagulant activity. Adding plasma-poor RBCs concentrates, usually the first blood product administered, further dilutes coagulation factor concentrations. Hypothermia, common in winter, in patients immobilized by their injuries, and in those exposed for treatment, leads to severe compromise in hemorrhage control. Jurkovich and his colleagues reported that survival was rare when severe bleeding and a core temperature below 32°C occurred in the same individual.<sup>28</sup>

## The Relationship Between Injury Severity and Coagulopathy

Brohi and his colleagues have described a series of 1088 trauma patients brought to the Royal London Hospital's Trauma and Critical Care Unit directly from the scene of injury by helicopter, for whom records of all fluid administered before hospital arrival, admission laboratory work, injury severity scores, and mortality data were available.<sup>29</sup> Dr. Brohi's group, using the definitions of the CAP for coagulopathy requiring the transfusion of blood products, found a prolonged prothrombin time (PT) or partial thromboplastin time (PTT) in 24% of this injured cohort. The amount of fluid administered before arrival at the hospital was small and did not differ between groups with or without coagulopathy and those who lived or died. In this series of predominantly blunt trauma patients, the frequency of coagulopathy was linearly related to the severity of injury. Moreover, at each level of injury severity, the presence of coagulopathy predicted worse outcome.

## Preventing and Correcting Coagulopathy with Blood Products

Hirshberg and his colleagues have used mathematic modeling to show that critical dilution of plasma coagulation factors will occur early in resuscitated trauma patients.<sup>30</sup> A blood-volume exchange of blood for crystalloid resuscitation fluid predicted an INR of 1.5. What this model and similar normovolemic exchange transfusion experience did not take into account is that trauma patients in profound shock are hypovolemic, often by as much as 30% to 50%, and that the same volume of exchange of a smaller intravascular volume will lead to even more rapid washout of coagulation factors and platelets. In the mathematic model, preventing coagulopathy required using RBCs and plasma in at least a fixed ratio of 2 U plasma for every 5 U of RBCs.

Clinically, trauma resuscitations start with crystalloid solutions. In the most severely injured patients, massive blood loss leads to the early use of uncross-matched group "O" RBCs, but modern RBC concentrates in additive solution contain only 30 to 50 mL of plasma/U. Their use leads to further coagulation factor dilution. Fresh frozen plasma (FFP) is typically made available only after the blood type has been established and plasma has been thawed, a combination of processes that may take more than an hour in some facilities. Thus, patients arrive coagulopathic and are made worse by their initial care.

Correcting established coagulopathy is often difficult. In a review of blood use and outcome at the Maryland Shock Trauma Center,<sup>10</sup> by the time patients had received 20 U of RBCs, they were typically receiving units of RBCs, plasma, and platelets at a 1:1:1 ratio. Such "reconstituted whole blood" is still dilute because of the way modern blood components are manufactured.<sup>31</sup> In this process, 450 mL of whole blood are collected into 63 mL of anticoagulant and separated into RBCs, platelets and plasma. The

RBCs are then filter-leukoreduced with the loss, 15 mL of RBCs and any remaining platelets in the RBC concentrate, followed by the addition of 100 mL of nutrient additive solution. The platelet units may also be leukoreduced, with additional losses. If the three resulting products were then recombined in a beaker, the resulting hematocrit would be 29%, the platelet count 88K, and the plasma coagulation factor activity would be 65%. In the body, only 90% of the RBCs and 70% of the platelets circulate. The result is that, with massive transfusion, severely injured trauma patients exist close to the transfusion triggers for all three products despite receiving each at the 1:1:1 ratio. Giving more of one product only dilutes the other two.

### Limiting the Effects of Coagulopathy

Seven different strategies have been tried to limit the effects of coagulopathy in massively injured and massively transfused patients. So-called hypotensive resuscitation was the first of these. Reducing the therapeutic goal for mean blood pressure meant that less fluid was given and less blood was lost. Trials in the prehospital and hospital resuscitation phase did not lead to worse outcomes.<sup>32,33</sup> Second, local modalities, including fibrin glue, hemostatic bandages, and the argon laser, all appear to reduce blood loss, even in the face of established coagulopathy.<sup>9</sup> Third, antifibrinolytics have been shown to reduce bleeding in many kinds of surgery. A small randomized trial suggested a benefit in trauma patients, and a large trial is underway.<sup>34</sup> Fourth, military surgeons have used fresh whole blood with its higher platelet counts, probably more active younger platelets, and less dilute plasma as an adjunct to damage-control surgery in the field.<sup>35</sup> Fifth, attempts to increase the early availability of plasma have focused on using thawed but still type-specific 5-day plasma.<sup>36</sup> This can speed plasma availability by more than half an hour. Sixth, recombinant activated factor VII (rVIIa) or, in Europe, combinations of fibrinogen and prothrombin complex concentrates<sup>37</sup> have been tried. Finally, the U.S. military has tried combinations of all of these approaches with the rapid identification of coagulopathic patients, prompt initiation of 1:1:1 resuscitation ratios with RBCs, prethawed universal donor AB plasma and apheresis platelets, conversion to fresh whole blood as soon as this can be obtained from a walking blood bank, and frequent use of rVIIa in conjunction with strict attention to avoiding hypothermia and treatment of acidosis.<sup>38</sup> The data from this effort have been widely presented and show a decrease in mortality with increasing ratios of units of plasma to RBCs administered. These data are deeply confounded by issues of treatment intensity, and an early attempt to recreate it from the records of civilian trauma centers has not been successful. In the military series, patients treated with fresh whole blood did not do better than those treated with equivalent numbers of units of RBCs and plasma. In the review from civilian trauma centers, patients treated with a 1:2 ratio of RBCs to plasma had a similar outcome as those treated with a 1:1 ratio. Interestingly, Johansson

and his colleagues at the University of Copenhagen have recently shown that pre-emptive use of plasma and platelets in a 1:1:1 ratio with RBCs reduced mortality from a historic 66% to 44% in a consecutive series of 50 patients with ruptured abdominal aortic aneurysms.<sup>39</sup>

### Risks and Benefits of Current and Evolving Strategies

Current resuscitation guidelines prevent the exposure of 91% of trauma patients to blood products and protect them from the many negative consequences of transfusion. The outcomes of these patients are generally excellent after allowances are made for patients who present with profound neurologic injury. Such patients should not be exposed to blood products without a clear expectation of benefit.

At the same time, 2% of civilian and 6% of military injured are coagulopathic at presentation, and most will be massively transfused. If conventional guidelines are followed, a large number of them will remain coagulopathic.<sup>40</sup> It is these patients who are likely to benefit from being identified early in the course of care and treated to prevent coagulopathy and its consequences. At this time, the available tools are blood components and local modalities, and perhaps antifibrinolytics and rVIIa.

### The Need for Better Blood Products

The use of plasma in initial resuscitation of the most seriously injured will require increased amounts of thawed AB plasma available for immediate issue and use.<sup>41</sup> As this component is already in short supply, more donors need to be recruited, more AB donors collected for double volumes of plasma by apheresis, and apheresis plasma licensed for 5-day thawed storage. If increasing fibrinogen and VWF concentrations turns out to be important for trauma patients, increased amounts of pre-pooled frozen cryoprecipitate will need to be available as well.

Because the volume of transfused products contributes to the coagulopathy of trauma, there may also a role for more concentrated plasma products. These products can be recombinant proteins, such as rVIIa; plasma derivatives, such as fibrinogen and balanced prothrombin complex concentrates; or simply freeze-dried single-donor plasmas, which can be reconstituted in reduced volumes of water. Safer plasma products are also a priority. Screening rare universal-donor AB plasma for transfusion-related acute lung injury (TRALI) risk may become cost effective.

### Conclusions

Trauma-associated coagulopathy is common in severely injured patients. It is associated with high mortality, which is partly preventable. The coagulopathic syndrome can be recognized from simple clinical measures available in the initial minutes of evaluation in a trauma center. Optimal treatment probably avoids initial large-volume crystalloid resuscitation and goes straight to resuscitation with RBCs and plasma. Platelets often need to be added early as well.

In some communities, trauma surgeons are changing practice based on these new insights and placing new demands on the blood supply. Better understanding of the coagulopathy of trauma, better tools for hemorrhage control, better evidence of optimal treatment, a better blood supply, and better blood products are all parts of a desired future.

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