Fluid and Blood Therapy in Trauma

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Neither Dr. Novikov nor Dr. Smith has a conflict of interest with any of the products named in this article.

Learning Objectives: 1) To understand the timing, extent, and the immediate goals for the initial fluid resuscitation in trauma victims, individualized to specific patients. 2) To review the factors influencing choice of fluid for the initial and ongoing resuscitation. 3) To discuss factors influencing the decision for initiating transfusion therapy, choice of blood products, and immediate and delayed risks and benefits of transfusion therapy. 4) To become familiar with the current state of therapies intended for the most severely injured patients, including recombinant factor VIIa and massive blood transfusion protocols.

Abstract

Initial fluid resuscitation in conjunction with temporary hemostasis should aim at maintenance of vital organ perfusion above critical levels. Judicious use of fluids is indicated in this early stage. Complete volume replacement is done once permanent hemostasis has been achieved. Mild (20%-40%) hemodilution produces hypercoagulability, while further hemodilution results in hypocoagulability. Resuscitation using balanced crystalloid solutions and balanced colloid solutions preserves coagulation better than resuscitation with 0.9% saline or saline-based colloids; it reduces blood loss and improves acid-base profile. Hypertonic saline is popular in the prehospital setting and is also beneficial for ongoing in-hospital resuscitation. Both hetastarch and hypertonic fluids have favorable effects on endothelial swelling, microcirculation, and immunologic function; both are equally or more efficient than standard mannitol-based therapy in head trauma patients with intracranial hypertension. Large volumes of high-molecular-weight hetastarch are associated with coagulopathy. Patients are surprisingly resistant to acute normovolemic anemia, even in the presence of cardiovascular risk factors.

Hemodilution down to hemoglobin of 7 g/dL is safe for most patients, provided they are not actively bleeding, are adequately volume-resuscitated, and high inspired oxygen concentrations are used. On the other hand, with transfusion of stored red blood cells, the immediate increase in oxygen delivery often does not translate to increased oxygen consumption and might even worsen tissue acidosis. Red blood cell transfusion might be an independent risk factor for mortality and other complications. Late immunologic effects of allogeneic blood transfusion are poorly understood. Warm blood transfusion from a “walking blood bank” is popular in the military trauma setting and might be more efficient than standard transfusion therapy. In the setting of ongoing severe hemorrhage, massive transfusion protocols with concomitant administration of red blood cells, plasma, and platelets should be implemented. Recombinant factor VIIa is a new exciting modality of treating transfusion-associated coagulopathy and hard-to-control bleeding in trauma patients; its exact place in trauma care remains to be determined.

Initial evaluation of an acutely volume-depleted trauma patient will include a primary and secondary survey according to Advanced Trauma Life Support protocol, an estimate of blood volume deficit (Table 1), rate of the ongoing blood loss, and an evaluation of cardiopulmonary reserve and coexisting hepatic or renal dysfunction. The major goal in resuscitation is to stop the bleeding, replete intravascular volume, and restore tissue oxygenation. Perfusion pressure and oxygenated blood flow to vital organs are important determinants of outcome.

Management priorities in an acutely bleeding trauma patient include ventilation and oxygenation, assessment of perfusion, estimation of volume-replacement requirements, establishment or verification of adequate intravenous access, measurement of blood pressure, placement of electrocardiogram (ECG), pulse oximeter and capnograph, and laboratory studies. Placement of arterial line and close monitoring of systolic pressure variability, temperature, urine output, arterial blood gases, hemoglobin, hematocrit, electrolytes, and parameters of coagulation is routine in severely injured mechanically ventilated patients. Consideration is given to use of additional monitors (e.g., central venous catheter, pulmonary artery catheter, transesophageal echocardiography) and provision of anesthesia as needed.

For induction of anesthesia in hemodynamically unstable patients, etomidate or ketamine is useful. Titrated opioids, scopolamine, midazolam, and amnestic concentrations of volatile agents can then be used for maintenance of general anesthesia until the intravascular volume deficit has been corrected and bleeding is under control. Neuromuscular relaxants and other agents are given as clinically indicated.
Timing and Aggressiveness of Fluid Resuscitation

Early aggressive fluid resuscitation aimed at restoration of “normal” hemodynamics has been the mainstay of trauma management for years. However, in animal models of uncontrolled hemorrhage, this strategy leads to increased duration and volume of bleeding and decreased survival. The proposed mechanisms include dilution of clotting factors, decreased blood viscosity, and blow-out of hemostatic plugs with increasing blood pressure (Table 2). Hypotensive resuscitation, where the rate of fluid infusion is carefully titrated to a predetermined level of lower-than-normal blood pressure, has been advocated in patients who are not pregnant and do not have traumatic head injury. The question of immediate versus delayed fluid resuscitation for hypotensive trauma patients was addressed in a landmark randomized clinical trial that demonstrated improved survival, shorter hospital stay, and fewer postoperative complications in patients who did not receive fluid resuscitation until arrival to the operating room. The study was limited to isolated penetrating torso injuries, and the receiving trauma center had a rapid response time such that most patients were in the operating room within 1 hour of injury. Benefits of delayed fluid resuscitation in the prehospital setting include minimal delay in transfer and surgical intervention and avoidance of increased blood pressure or hemodilution, which could disrupt the clot or alter resistance to flow around a partially formed thrombus. To date, no human study has shown detrimental effects of delayed or hypotensive resuscitation on survival, but so far the conclusive evidence on its superiority in trauma or ruptured abdominal aortic aneurysm is lacking.

Consequently, in uncontrolled hemorrhagic shock, resuscitation is aimed at restoration of radial artery pulse, restoration of mental function, and systolic blood pressure of 80 mm Hg, until the bleeding is surgically controlled. Higher blood pressures (systolic blood pressure >100 mm Hg, mean arterial pressure >70 mm Hg) are generally sought in head-injured and in pregnant patients. This approach provides satisfactory resuscitation of the trauma patient until surgical control of bleeding is achieved.

### Table 1. Estimation of Blood Volume Deficit in Trauma Patients

<table>
<thead>
<tr>
<th>Site</th>
<th>Volume (mL)</th>
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<tbody>
<tr>
<td>Unilateral hemothorax</td>
<td>3,000</td>
</tr>
<tr>
<td>Hemoperitoneum with abdominal distention</td>
<td>2,000–5,000</td>
</tr>
<tr>
<td>Full-thickness soft tissue defect, 5 cm²</td>
<td>500</td>
</tr>
<tr>
<td>Pelvic fracture</td>
<td>1,500–2,000</td>
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<tr>
<td>Femur fracture</td>
<td>800–1,200</td>
</tr>
<tr>
<td>Tibia fracture</td>
<td>350–650</td>
</tr>
<tr>
<td>Smaller fracture sites</td>
<td>100–500</td>
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### Fluid Options

#### Crystalloids

There is controversy concerning which intravenous solutions should be used for resuscitation (see also the article in this issue by Dr. Boldt). During hemorrhage, a compensatory increase in reabsorption of fluid into capillaries partially restores the intravascular compartment, but depletes the interstitial space. To replete the intravascular and interstitial compartments, crystalloid solutions such as isotonic 0.9% saline or lactated Ringer’s (LR) solution are traditionally used.

Glucose-containing solutions are avoided because hyperglycemia is associated with aggravation of central nervous system injury and increased mortality, especially in trauma patients. In large human interventional studies in both surgical and medical intensive care unit (ICU) settings, intensive insulin therapy guided by specific target glucose levels has been shown to improve in-hospital survival, with the benefit preserved over a 4-year follow-up, to prevent critical illness neuropathy, decrease the need for long-term ventilation, and shorten ICU stay. The most prominent effect has been achieved with glucose levels below 110 mg/dL even despite the increased incidence of hypoglycemia. Paradoxically, the effect was most prominent in nondiabetic patients. The effect is seemingly more dependent on the strict glucose control than on the dose of insulin, even though nonhypoglycemic effects of insulin are generally well recognized and might play a role. It should be noted that in observational studies, patients with more severe traumatic brain injury have higher blood glucose levels; that is, hyperglycemia might be a marker of injury severity and predictor of the outcome rather than the causative agent. Improved outcome with strict glucose control might then be effects of insulin infusion rather than lowering of the glucose level. Some animal studies have suggested that hyperglycemia induced by rapid glucose infusion does not worsen different markers of neurologic injury, survival, and neurologic sequelae of head trauma. Other studies refute these results and find euglycemia protective regardless of the insulin dose used. In any case, the routine use of glucose-containing solutions is not justified, and hyperglycemia is treated aggressively with insulin.

There are not enough clinical data to compare outcomes with 0.9% saline versus LR in trauma. LR is mildly hypotonic with respect to plasma and may be detrimental if given in large volumes to patients with head injury (Table 3). Because LR contains 3 mEq/L of calcium, it traditionally has been contraindicated for coinfusion with or dilution of packed red blood cells (RBCs). This view has been challenged by several authors. It has been shown that dilution of RBCs with LR in ratio up to 2:1 (RBC to LR) with subsequent incubation at 37°C for up to 2 hours does not lead to clot formation, and dilution of RBCs to hematocrit of 35% does not slow down the passage of blood through the standard 170-micron filter. Hepatic conversion of lactate to bicarbonate should increase the blood buffering capacity while large volumes of 0.9% saline (>30 mL/kg) lead to hyperchloremic acidosis. The same concepts hold true when comparing hetastarch diluted in 0.9% saline (Hespan) with balanced crystalloid solution-based hetastarch (Hextend). Hyperchloremic metabolic acidosis is produced because high chloride solutions displace serum bicarbonate in the extracellular volume. Unlike lactate acidosis, patients with hyperchloremic metabolic acidosis have a normal anion gap and elevated serum chloride.

The effects of crystalloid solutions on the coagulation system are complex. With hemodilution up to 20% to 40%, crystalloids produce a hypercoagulable state because of dilution of anticoagulant factors such as antithrombin and by platelet activation. After 60%
hemodilution, both crystalloids and colloids produce a hypocoagulable state. However, animal studies point to attenuation of hypocoagulability and increased blood loss in uncontrolled hemorrhagic shock treated with 0.9% saline as opposed to LR. A head-to-head comparison of these two crystalloid solutions in patients undergoing abdominal aortic aneurysm repair found an increased need for bicarbonate, platelets, and blood products in patients receiving 0.9% saline compared with LR. There was no difference in outcomes. In major abdominal surgery, there was no difference in coagulation parameters in patients receiving 0.9% saline or LR.

At MetroHealth Medical Center, 0.9% saline is used primarily in head trauma patients and is the only crystalloid used in blood transfusion lines; LR is used for most other purposes.

### Colloids Versus Crystalloids

The choice of crystalloid or colloid solutions for resuscitation of trauma patients requiring surgery is unresolved (Table 3). Factors influencing choice of asanguinous fluids include effects on coagulation, metabolic state, alterations in macro- and microcirculation, volume distribution, and organ function (e.g., kidney function and splanchnic perfusion). The crystalloid/colloid controversy has been focused primarily on outcome. There is increasing evidence that mortality is not the correct measure when assessing the ideal volume-replacement strategy. Rather, measures such as organ perfusion, organ function, degree of inflammation, immunologic aspects, and wound healing may be more appropriate.

Colloid solutions are more effective plasma expanders than crystalloids. They increase the plasma oncotic pressure, which serves to retain water in the intravascular compartment and minimize interstitial edema in vital organs such as the lung, heart, and brain. Intraoperative use of colloid solutions has been associated with improved outcome and decreased hospital stay, possibly because of decreased tissue edema, nausea, vomiting, and pain. Hextend (6% hydroxyethyl starch in a physiologically balanced medium of electrolytes, glucose, and lactate) has a median serum half-life of more than 30 hours. Thus, less overall fluid volume is required and less peripheral edema is produced for the same degree of intravascular volume expansion.

Hextend may be beneficial after head injury. For example, in a model of severe traumatic brain injury in pigs, Hextend, used as the sole resuscitation fluid, prevented an increase in intracranial pressure model of severe traumatic brain injury in pigs, Hextend, used as the sole resuscitation fluid, prevented an increase in intracranial pressure (vs. 0.9% saline). For example, in a model of severe traumatic brain injury in pigs, Hextend, used as the sole resuscitation fluid, prevented an increase in intracranial pressure (vs. 0.9% saline).

Most colloids produce coagulopathy at relatively lower degrees of hemodilution compared with crystalloid. Colloids also prevent, to a variable degree, naturally occurring platelet activation and hypercoagulability. Hextend (6% hetastarch in 0.9% sodium chloride) has been shown to have adverse effects on hemostasis, including impaired platelet aggregation, type I von Willebrand-like syndrome with decreased factor VIII coagulant activity, decreased von Willebrand factor antigen, and factor VIII-related ristocetin cofactor. This colloid was withdrawn from the authors’ hospital formulary and replaced with Hextend, which is associated, both in vitro and in vivo, with better thromboelastographic parameters of

<table>
<thead>
<tr>
<th>Table 3. Asanguinous Fluid Options for Trauma.</th>
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<tbody>
<tr>
<td><strong>Lactated Ringer’s (LR)</strong></td>
</tr>
<tr>
<td><strong>0.9% Saline</strong></td>
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<tr>
<td><strong>Hespan (6% hetastarch in 0.9% saline)</strong></td>
</tr>
<tr>
<td><strong>Hextend (6% hetastarch in balanced electrolyte solution)</strong></td>
</tr>
<tr>
<td><strong>Low- and medium-molecular-weight hetastarch</strong></td>
</tr>
<tr>
<td><strong>Albumin (5%)</strong></td>
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<tr>
<td><strong>Dextran and gelatins</strong></td>
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<tr>
<td><strong>Hypertonic saline</strong></td>
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pRBCs, packed red blood cells; SAFE, saline versus albumin fluid evaluation; ICP, intracranial pressure; CPP, cerebral perfusion pressure.
interstitial lung edema. It has been suggested that hetastarch 130/0.4-based volume replacement.

In a randomized, double-blind trial comparing fluid resuscitation with albumin or 0.9% saline on mortality in 6,997 ICU patients (SAFE [saline versus albumin fluid evaluation] study), use of either solution resulted in similar outcomes at 28 days. The relative risk of death, proportion of patients with new single-organ and multiple-organ failure, days spent in the ICU, days spent in the hospital, days of mechanical ventilation, and days of renal-replacement therapy were similar between groups. However, there was increased mortality in head-injured patients randomized to the albumin (59 of 241 patients, 24%) as compared with the saline group (38 of 251 patients, 15%).

Hetastarch is the most intensively studied plasma substitute. The different hetastarch preparations are defined by concentration, molar substitution, mean molecular weight, and the C2/C6 ratio of substitution. In particular, medium-molecular-weight hetastarches with lower molar substitution appear promising compared with first-generation hetastarches. Several hetastarch solutions are available in Europe. In the United States, only the first-generation high-molecular-weight 6% hetastarch with a high molar substitution (Hesperan and Hextend, mean molecular weight = 450 kD) are approved. In Canada, a medium-molecular-weight 10% hetastarch (Pentastarch, mean molecular weight = 270 kD) is available.

In addition to the starch average molecular weight, the weight distribution, degree, and pattern of substitution all can influence the effect on the coagulation. In general, smaller molecule size starches as opposed to the larger ones, and starches diluted in balanced salt solutions as opposed to 0.9% saline, produce less coagulopathy and platelet dysfunction. However, at least in some studies, no clinically relevant differences have been observed.

Large amounts of high-molecular-weight 6% hetastarch (>15–20 mL/kg) are traditionally avoided because of the well-documented risk of coagulopathy, increased blood loss and transfusion requirements, and mortality. These effects are mediated by dose-dependent decrease in factor VIII and von Willebrand factor, and inactivation of glycoprotein IIb-IIIa. Hextend, approved for use in United States in 1999, appears to be different than Hesperan in its effects on hemostasis. Hextend is the first reported hydroxyethyl starch solution that increases platelet reactivity. It is not clear if this effect is explained completely by the calcium-containing solvent.

Albumin is derived from pooled human plasma, heated and sterilized by ultrafiltration. Its molecular weight is approximately 69 kD. Albumin is generally accepted to be safe in terms of transmission of infectious diseases with little effect on coagulation. Albumin may have some additional specific effects aside from its volume-replacing properties such as transport function for various drugs and endogenous substances or effects on membrane permeability secondary to free radical scavenging. In patients with impaired vascular endothelial integrity, albumin may pass into the interstitial compartment with resultant endothelial swelling and impaired microcirculatory perfusion.

Dextran has been largely abandoned for fluid resuscitation because of the negative effects on coagulation and high anaphylactic potential. Similarly, gelatins were abandoned in the United States because of the high incidence of hypersensitivity reactions.
**Hypertonic Fluids**

Use of hypertonic solutions for critically ill patients has been investigated for more than 2 decades. The obvious rationale is that a minimal volume of hypertonic saline will draw intracellular water into the extracellular space. Not surprisingly, volume expansion with hypertonic saline is both more efficient and better sustained than with normosmolar fluids. In comparison of the peak hemodilution in healthy volunteers, 7.5% saline and 7.5% saline in 6% Dextran were 4.4 and 6.2 times more effective than similar volumes of 0.9% saline, respectively. Area under the hemodilution time curve was 7 times larger for 7.5% saline in dextran and 3.8 times larger for 7.5% saline than for 0.9% saline. As expected, addition of colloid to the hypertonic saline increased the magnitude and markedly prolonged the duration of volume expansion. When a 30-minute infusion of 4 mL/kg of 7.5 saline in 6% dextran was compared with 25 mL/kg of LR, the peak volume expansion was similar, about 7 mL/kg. However, 30 minutes later, the volume expansion with hypertonic saline-dextran was 3 times higher than with LR (5.1 ± 0.9 vs. 1.7 ± 0.6 mL/kg). At 2 hours, for each milliliter of the fluid infused, the remaining intravascular volume expansion was 0.07 mL for LR and 0.7 mL for hypertonic saline-dextran. Hypertonic fluids are especially advantageous in military trauma and other situations (e.g., prehospital, helicopter) when the weight-to-benefit ratio is crucial.

In hemorrhagic shock or local ischemia, cells swell, absorb water, chloride, and sodium, and lose the resting membrane potential. They return to normal volume, electrolyte balance, and resting potential with hypertonic saline better than with isotonic resuscitation. Capillary lumens narrow as a result of this swelling and return to normal diameter with hypertonic resuscitation but not with LR. Further, hypertonic saline restores intravascular volume and hemodynamics while decreasing extravascular volume and tissue edema. With LR, extravascular volume increased by 60% of the infused volume at the end of the infusion and by 43% at 2 hours, while with hypertonic saline-dextran, extravascular water decreased by 170% and 430%, respectively. In brain injury associated with pulmonary edema, hypertonic saline depletes tissue water content better than mannitol. This feature may be crucial in situations such as head trauma.

Prehospital infusion of 250 mL of 7.5% saline, with or without dextran, followed by a usual fluid resuscitation to hypotensive trauma patients was compared with LR. The bolus of hypertonic fluid resulted in improved blood pressure, decreased fluid requirements, and increased survival to discharge, especially in patients with Glasgow Coma Scale <8. The rise in the circulating blood volume and cardiac output is immediate, although a transient decrease in blood pressure because of vasodilatation may occur. Hypertonic solutions increase cardiac contractility, venous return, and coronary blood flow. Moreover, hypertonic saline/dextran solution is effective in treating dehydration and massive hemorrhage in animals with preexisting dehydration.

Hypertonic solutions used in clinical studies vary. The most common regimen is 100 to 250 mL or 1.5 to 2 mL/kg of 7.2% to 7.5% saline with or without colloid. The U.S. military recommends 7.5% saline in Europe, 7.5% saline in 6% dextran 70 is used. Other regimens include single boluses of 30 mL of 23.4% saline, 75 mL of 10% saline, or continuous infusions of 3% saline. For most studies in head trauma, regardless of concentration used, the dose of sodium chloride infused with a single fluid bolus in adult patients ranges approximately from 7 to 15 g, or 120 to 300 mEq. Accordingly, results are fairly uniform. A single infusion of hypertonic saline will decrease intracranial pressure by around 70% or 10 to 25 mm Hg and increase the cerebral perfusion pressure by 10 to 30 mm Hg, both effects evident in a matter of minutes, reaching maximum effect by 20 to 60 minutes, and lasting for 1.5 to 4 hours, sometimes longer. Similar effects have been observed in patients with stroke and subarachnoid hemorrhage. Effects of hypertonic saline on intracranial and cerebral perfusion pressure were more rapid and more profound than a comparable volume of 20% mannitol, and lasted longer.

In a study of trauma patients whose elevated intracranial pressure was refractory to all other modalities, 2 mL/kg of hypertonic saline was compared with a similar volume of 20% mannitol. In the hypertonic saline group, the number of episodes of elevated intracranial pressure was reduced by almost a half and their cumulative duration by about a third as compared with patients treated with mannitol. Similarly, patients in the hypertonic saline group required 50% less volume of cerebrospinal fluid drainage to maintain target intracranial and cerebral perfusion pressure, and the success rate in achieving these targets was 90% in the hypertonic saline group versus only 30% in the mannitol group. The clinical outcome at 90 days was, however, similar in both groups.

In a striking study on pediatric head-injured patients whose elevated intracranial pressure had been refractory to all other modalities, including mannitol and barbiturate coma, continuous infusion of 3% saline for the mean of 7.6 days (range, 4–18 days) led to a rapid and sustained improvement in intracranial and cerebral perfusion pressure. The treatment was surprisingly well tolerated, even though on average the serum sodium was 171 mEq/L (range, 157–187 mEq/L) and serum osmolality was 365 mOsm/L (range, 330–431 mOsm/L).

A cohort study in patients with traumatic brain injury and hypotension compared 7.5% saline/6% dextran 70 with conventional crystalloid fluid treatment. With the hypertonic fluid, there was a trend for improved survival to discharge in all the subgroups (odds ratios: 1.6–1.8). For patients with initial Glasgow Coma Scale score <8, the odds ratio for survival until discharge was 2.12 with hypertonic saline-dextran versus conventional treatment. On the other hand, in a randomized controlled trial of patients with traumatic brain injury who were comatosed (Glasgow Coma Scale score <9) and hypotensive (systolic blood pressure <100 mm Hg), at 6 months after injury the patients who received prehospital resuscitation with 250 mL of 7.5% saline had almost identical neurologic function compared with the ones resuscitated with conventional fluid. There was no significant difference between the groups in favorable outcomes or in any other measure of postinjury neurologic function.

Hypertonic saline has some immune modulating effects. For example, hypertonic saline resuscitation in traumatic hemorrhagic shock in humans blunts the usual response in distribution of monocyte receptors, decreases tumor necrosis factor-α, and increases anti-inflammatory interleukins (IL-1ra and IL-10).

Currently, there are insufficient data to determine whether hypertonic crystalloid is better than isotonic crystalloid for the resuscitation of patients with trauma, burns, or those undergoing surgery. In this meta-analysis, the pooled relative risk for death in trauma patients was 0.84 (95% confidence interval [CI]: 0.69–1.04); in patients with burns, 1.49 (95% CI: 0.56–3.95), and in patients undergoing surgery, 0.51 (95% CI: 0.09–2.73). In the one trial that gave data on disability using the Glasgow outcome scale, the relative risk for a poor outcome was 1.00 (95% CI: 0.82–1.22).

**Red Cell Transfusions**

Oxygen-carrying blood substitutes are reviewed by Drs. Como and Malangoni, and by Dr. Schubert in separate articles in this issue. To date, these substitutes are not commercially available. In this
section, we will briefly answer four questions. First, what level of anemia is dangerous to a normovolemic patient, and what other variables are involved? Second, what are the risks and benefits of correcting this anemia with available RBC concentrates? Third, what are the net clinical outcomes of transfusion? And fourth, what is a reasonable approach to transfusion in the trauma patient?

The lower limit of anemia is not established in humans. Observational studies of surgical patients refusing transfusion for religious reasons suggest that the risk of mortality and/or morbidity becomes extremely high with hemoglobin levels below 5 to 6 g/dL. After adjusting for age, cardiovascular disease, and Acute Physiology and Chronic Health Evaluation II (APACHE) score, the odds of death in patients with a postoperative hemoglobin level <8 g/dL increase by factor of 2.5 for each gram decrease in hemoglobin level. A retrospective cohort study of patients who declined red cell transfusions for religious reasons demonstrated that in patients with a postoperative hemoglobin level of 7.1 to 8.0 g/dL, none died and 9% had a morbid event such as myocardial infarction, arrhythmia, or congestive heart failure. In patients with a postoperative hemoglobin level of 4.1 to 5.0 g/dL, 34% died and 58% had a morbid event or died. Of note, age, systolic blood pressure at admission, Glasgow Coma Scale score, and type of trauma were more important predictors of mortality than religious objection to blood.

Normally, oxygen delivery exceeds oxygen consumption 3- to 4-fold. Consumption is thus independent of delivery over a wide range of hemoglobin concentrations. “Critical hematocrit” (or hemoglobin) is defined as the threshold below which the body oxygen consumption becomes dependent on oxygen delivery.

Several factors help maintain tissue oxygenation in acutely anemic patients. Sympathetic stimulation increases hear rate and contractility. Decreased blood viscosity increases venous return and lowers systemic vascular resistance, thus increasing the stroke volume. Indeed, the observed increase in stroke volume closely parallels the calculated one as should be produced by the decreased blood viscosity. Redistribution of blood flow to vital organs may protect them even if whole-body perfusion/oxygen delivery is falling. Oxygen extraction ratio by most organs, including the brain, increases. Mobilization of capillary flow increases the oxygen extraction, as only about one third of capillaries are usually perfused. The oxygen dissociation curve shifts to the right as a result of increased production of 2,3-diphosphoglyceric acid (2,3-DPG) and tissue acidosis (if anaerobic metabolism occurs). The heart does not have a large oxygen-extraction reserve, and compensates for anemia by increasing coronary blood flow. In dogs with normal coronary arteries, lactate production and subendocardial ischemia occur at hematocrit of 9%; in the presence of a critical left anterior descending artery stenosis, coronary blood flow in the affected area remains constant and ischemic changes become evident at hematocrit of 17%. Similar numbers were reported by other investigators.

In a series of human experiments with acute normovolemic hemodilution to hemoglobin 5 g/dL, subcutaneous tissue perfusion increased and oxygen tension remained stable, even in the subjects who were mildly hypoperfused at baseline. Transient and asymptomatic ECG changes were observed in only 3 of 55 volunteers, all at hemoglobin of <7 g/dL, in conjunction with movement or tachycardia. Subtle cognitive function impairment appeared only at or below hemoglobin 6 g/dL and was readily reversible with breathing 100% oxygen. The same authors used invasive monitoring to investigate the effects of an acute normovolemic hemodilution in awake volunteers and in patients without cardiovascular comorbidities (mean age, 50 years; range, 35 to 69 years) undergoing major surgery with general anesthesia. Gradual hemodilution resulted in increased cardiac index and stable oxygen delivery down to hemoglobin of approximately 7.5 to 8 g/dL in men and 5.5 to 6 g/dL in women. Below this level, and down to 4.5 to 5.4 g/dL, oxygen delivery decreased in parallel to the fall in oxygen-carrying capacity. Tissue oxygen extraction ratio increased from 23% to 30%, and oxygen consumption increased by approximately 12%. pH and base excess both also increased, and there was a trend to a lower lactate level.

The cardiovascular and metabolic response to acute, severe isovolemic anemia was studied in elderly patients (76 ± 2 years; range, 66 to 88 years), many of them with diabetes and other significant risk factors, undergoing major abdominal surgery. Patients were hemodiluted from hemoglobin of 11.6 to 8.8 g/dL before surgery. Hemoglobin further decreased on average to 7.7 g/dL because of surgical blood loss. Oxygen consumption was stable throughout surgery, and signs of myocardial ischemia such as ST segment changes, arrhythmias, and hypotension were absent.

In patients separating from cardiopulmonary bypass, hemodilution to hematocrit of 15% resulted in decreased mean arterial blood pressure and oxygen delivery, increased cardiac output and oxygen extraction ratio, and stable oxygen consumption across the tested range.

Of note, in awake, normovolemic patients, heart rate increases linearly with normovolemic anemia. In patients under general anesthesia, however, anemia does not induce tachycardia. The increased cardiac output is due to increased stroke volume alone.

An increase in the heart rate should raise suspicion for hypovolemia.

In a literature review published in 1994, the authors sought reports on Jehovah’s Witnesses with hemoglobin <8 g/dL or hematocrit <24%. With the exception of three patients who died after cardiac surgery, all of the deaths attributed to anemia occurred when hemoglobin was lower than 5 g/dL. There were 25 survivors with hemoglobin of >5 g/dL, adding to the anecdotal evidence of human tolerance to anemia.

In surgical patients without cardiovascular comorbidities, there are anecdotal reports of survival without major complications despite extreme levels of normovolemic anemia. For example, in a 41-year-old woman who refused blood transfusion, hematocrit dropped from 47 to 8% at the end of surgery and to 6.4% on postoperative day 2; and in a 58-year-old man whose hemoglobin dropped to 1.1 g/dL for 30 minutes because of unexpected blood loss and unavailability of blood during elective surgery. It is important to stress that both these patients were adequately volume-resuscitated.

Less data are available in patients with coronary artery or valvular heart disease. In observational studies, any level of anemia has been associated with increased perioperative mortality, more so in patients with preexisting cardiovascular disease. However, anemia might be a result of and a marker for ill health rather than a cause for the adverse outcome. For example, in patients undergoing cardiopulmonary bypass, after correction for comorbidities, only nadir hematocrit of lower than 14% (17% for high-risk patients) was an independent risk factor of adverse outcome.

Under normal conditions, oxygen dissolved in the blood accounts for only about 2% of the blood oxygen content. With hemodilution and thus relatively larger plasma volume, and especially if high inspired oxygen concentrations are used, dissolved O2 becomes clinically relevant. In a series of experiments on pigs, hyperoxia improved tolerance of extreme anemia and decreased critical hemoglobin levels from 2.4 when breathing room air to 1.5 g/dL FiO2 = 0.6 and to 1.2 g/dL at FiO2 = 1.0. There was 100% mortality at critical hemoglobin and FiO2 = 0.21, whereas switching to 100% oxygen increased oxygen delivery and resulted in 100% survival at 6 hours.

In healthy human volunteers breathing room air, acute normovolemic hemodilution from 12.7 to 5.7 g/dL resulted in hypotension, tachycardia, and cognitive changes.
administration decreased heart rate and restored cognitive function even though the blood pressure did not change.

More relevant is the question of whether correcting anemia with stored RBCs will improve the oxygen consumption and how will it affect outcome. First, despite the immediate improvement in the oxygen-carrying capacity of the blood and oxygen delivery, transfusion may not improve the target tissue oxygen utilization, unless the patient has already reached the critical hemoglobin concentration. Second, older RBC units have low levels of 2,3-DPG. Their ability to release the transported oxygen in the peripheral tissues is compromised; it takes many hours to restore the normal levels of 2,3-DPG. Third, older RBCs lack the normal deformability and thus impair the capillary flow. These effects are clinically significant. For example, in cardiac patients with hemoglobin 7.5 to 8.5 g/dL, transfusion of one to two red cell units increased the calculated oxygen delivery but did not increase oxygen consumption or tissue oxygenation.118 In an ICU study of critically ill septic patients, transfusion of three red cell units failed to improve the tissue oxygenation for up to 6 hours.119 More importantly, there was an inverse correlation between age of blood units and tissue pH. Transfusion of red cell units older than 15 days consistently worsened the tissue acidosis.119

Two main approaches factor into the decision to transfuse. First is the so-called transfusion trigger, which is establishing ahead of time, based on our experience and assumptions, a certain level of anemia at which, for the given patient, there is a favorable risk-benefit ratio of the transfusion. Second are the real-time physiologic data such as hemodynamic instability despite normovolemia, decreased mixed venous oxygen saturation, evidence of target organ ischemia, and direct or indirect measurement of brain oxygenation.

In a landmark trial, critically ill euvolemic patients with hemoglobin <9 g/dL were randomized to transfusion trigger of hemoglobin 7 or 10 g/dL.120 Patients in both the restrictive and liberal arms of the study had an average of two or more units of blood transfused prior to randomization. Patients in the restrictive arm received 54% less transfusions and their chance to receive any transfusion after randomization was diminished by 33%. Shock was diagnosed more often in the restrictive group. Patients in the restrictive arm had a one-third less incidence of acute respiratory distress syndrome (ARDS) and 35% less cardiac complications such as heart attacks and pulmonary edema. Multiple-organ failure scores decreased mixed venous oxygen saturation, evidence of target organ ischemia, and direct or indirect measurement of brain oxygenation.

In another study, cardiac patients, a post hoc analysis of 24,112 patients with acute coronary syndrome pooled from three large cardiology trials revealed an increase in 30-day mortality with transfusion at hematocrit higher than 25%.121 In one study of elderly patients admitted for acute myocardial infarction, transfusion was beneficial if the admission hematocrit was below 33% and detrimental at hematocrit higher than 36%.122 However, it is difficult to extrapolate data from this specific population to the typical trauma patient.

The updated American Society of Anesthesiologists practice guidelines recommend transfusion if hemoglobin concentration is below 6 g/dL and do not recommend transfusion with hemoglobin concentration above 10 g/dL. The decision to transfuse in the 6 to 10 g/dL hemoglobin concentration range should be individualized according to presence of organ ischemia, rate and magnitude of potential or actual bleeding, intravascular volume status, and risk factors for complications of inadequate oxygenation, such as low cardiopulmonary reserve and high oxygen consumption123 (Table 4). Although some authorities recommend using mixed venous oxygen saturation (SvO2) <50% or mixed venous oxygen tension (PvO2) <32 mm Hg as a trigger for transfusion, clinical and laboratory evidence is more frequently used. Use of recombiant factor VII, more effective use of blood salvage devices, and possibly other means of bleeding control may significantly decrease the need for allogeneic transfusion in the future.

One unit of packed RBCs will usually increase the hematocrit by approximately 3% or the hemoglobin by 1 g/dL in a 70-kg nonbleeding adult. Available options are type O-negative, type-specific, typed and screened, or typed and cross-matched packed RBCs. Type O-negative red cells have no major antigens and can be given reasonably safely to patients with any blood type. Unfortunately, only 8% of the population has O-negative blood, and blood bank reserves of O-negative, low-antibody titer blood are usually very low. For this reason, O-positive red cells are frequently used. This is a reasonable approach in males but may be a problem in childbearing-aged females. If 50% to 75% of the patient's blood volume has been replaced with type 0 blood (e.g., approximately 10 units of red cells in an average size adult patient), one should continue to administer type O red cells. Otherwise, risk of a major cross-match reaction increases because the patient may have received enough anti-A or anti-B antibodies to precipitate hemolysis if A, B, or AB units are subsequently given.

Obtaining type-specific red cells requires 5 to 10 minutes in most institutions, and "temporizing" measures can sometimes be employed to gain the necessary time. Switching to a type-specific blood transfusion as soon as possible would spare the scarce supply of O-type blood, reduce the risk of hemolytic transfusion reaction,126 and allow continuation with a type-specific and cross-matched blood transfusion once it becomes available. If one can wait 15 minutes, typed and screened blood should be available. A full cross-match generally requires about 45 minutes and involves mixing donor cells with recipient serum to rule out any unexpected antigen/antibody reactions.

**Table 4. Approach to Transfusing Red Blood Cells (RBCs)**

Based on the American Society of Anesthesiologists Practice Guidelines125 and Review of the Literature.

- Transfuse RBCs if hemoglobin <6 g/dL
- Do not transfuse RBCs if hemoglobin >10 g/dL
- Decision to transfuse RBCs should be individualized based on:
  1. Presence of organ ischemia (e.g., altered mental status, myocardial ischemia, acidosis, low mixed venous oxygen saturation)
  2. Rate of bleeding
  3. Magnitude of bleeding
  4. Intravascular volume status
  5. Cardiopulmonary reserve
Coagulation Factors and Platelets

The primary cause of bleeding after trauma is surgical, while the second leading cause is hypothermia and dilutional coagulopathy. Murray et al. have shown that microvascular bleeding and clinical evidence of coagulopathy occurred in the setting of massive transfusion and was associated with decreased coagulation factor levels, decreased fibrinogen, and elevated prothrombin times. Microvascular bleeding in this instance was treated with fresh-frozen plasma. Two units of fresh-frozen plasma (10–15 mL/kg) will achieve 30% factor activity in most adults. Coagulation factor deficiencies may be present because of other causes such as preexisting defects or disseminated intravascular coagulopathy from tissue injury.

Cryoprecipitate and factor concentrates may be indicated to correct specific factor deficiencies. Cryoprecipitate is rich in fibrinogen as well as factors VIII, XIII, and von Willebrand factor. Thrombocytopenia is treated with platelet concentrates. Because platelets are suspended in plasma, one unit of single-donor apheresis platelets or four to five multiple donor platelet units will provide factor levels similar to one unit of fresh-frozen plasma.

Dilutional thrombocytopenia and microvascular bleeding is likely after 1.5 to 2.0 blood volumes have been transfused. For example, Leslie and Toy showed that platelet count was reduced to <50,000/mcL after administration of 20 units of red cells. Platelet transfusions are usually indicated in the presence of clinical bleeding and a platelet count <75,000 to 100,000/mcL. Platelet concentrates are stored at room temperature (thus a higher risk of bacterial contamination) and contain about 70% of the platelets in a unit of fresh-frozen plasma.

Transfusion of single-donor pooled platelet units, equivalent each to six units of stored at room temperature (thus a higher risk of bacterial contamination), is considered more likely to cause infection, but the increased risk is offset by decreased platelet contamination. Transfusion of single-donor pooled platelet units, equivalent each to six units of platelets in the unit of fresh-frozen plasma, has become routine at many institutions.

Prothrombin time, activated partial thromboplastin time, fibrinogen, and fibrin degradation products are monitored because deficiencies may be present because of dilution, preexisting defects, or disseminated intravascular coagulopathy. Point-of-care testing including tests of platelet function (e.g., thromboelastography, platelet works) and rapid reporting of coagulation test results are useful to guide decisions regarding administration of fresh-frozen plasma, platelets, or cryoprecipitate. Modifications to the thromboelastograph include the addition of recombinant human tissue factor as an activator that accelerates the rate of thrombin formation and time required to evaluate clot strength and platelet function.

Treatment of coagulopathy with factor VIIa (FVIIa) is gaining popularity, especially in patients in clear danger of exsanguination, and in Jehovah’s Witnesses who refuse blood products. FVIIa was developed initially for use in hemophiliacs who developed inhibitors to factor VIII, and it is licensed only for this use. FVIIa combines with tissue factor at the site of endothelial damage to activate factor X, which promotes conversion of prothrombin to thrombin and to trigger platelet activation. This “thrombin burst” depends on adequate levels of fibrinogen and mainly occurs at site of injury, thus limiting the risk of thrombotic events. FVIIa can also bind to activated platelet membranes where it activates factor X directly, which leads to a massive rise in thrombin generation at the platelet surface. The dose currently recommended for bleeding episodes in patients with hemophilia is 90 mcg/kg. The dose used at Maryland Shock Trauma Hospital is 100 mcg/kg, rounded to the nearest vial (R. Dutton, personal communication, 2007). Pharmacokinetics of FVIIa based on two-compartment model is compatible with initial half-life of 0.6 hours and terminal half-life of 2.4 hours. If needed, continuous infusion of FVIIa can be used. Of note, the use of FVIIa for reversal of coagulopathy and/or treatment of bleeding in nonhemophiliac patients is off-label.

The first case report of FVIIa use in a trauma patient complicated with coagulopathy was reported in Israel in 1999. Initial anecdotal and small series reports suggested a striking effectiveness of the intervention. Results of two parallel industry-supported multicenter trials on blunt and penetrating trauma patients requiring transfusion of more than six units of RBCs were published together. Patients received the first dose immediately after the sixth dose of RBCs was transfused. Patients with severe head injury and patients with severe acidosis or requiring massive transfusion before arrival to the hospital were excluded. A total of 277 cases were eligible for analysis. Trends to decreased transfusion requirements and to decreased incidence of mortality, multiple organ failure (MOF) and ARDS were observed, all more pronounced in the patients who survived the first 48 hours. One hundred thirty-six patients (49%) were considered coagulopathic. In a subgroup analysis limited to coagulopathic patients, FVIIa reduced transfusion requirements significantly, and again, this effect was most pronounced in patients who had survived the first 48 hours. In the same subgroup, combined end point of death, MOF, and ARDS occurred in 6% patients treated with FVIIa as opposed to 23% of patients treated with placebo.

In a retrospective review of the use of FVIIa in 81 patients with acute traumatic hemorrhage, the authors concluded that early administration of FVIIa, before the development of massive blood loss and severe shock, may increase the rate of clinical response. Depth of hemorrhagic shock, profound acidosis, and prothrombin time >17.6 seconds were associated with futile administration of FVIIa. So far all the studies enrolled the actively bleeding patients only after a certain limit of transfusion had been reached: 6 units of packed RBCs in the NovoSeven phase II trial, 10 units of packed RBCs, 8 units of fresh-frozen plasma, and an apheresis unit of platelets in the series published by Dutton et al.

Apparently, the common feeling among the active investigators in the field is that at this late stage of shock, FVIIa will most probably reverse the coagulopathy and stop the bleeding, but will not reliably prevent major complications and death. Earlier stratification of the patients and prompt administration of FVIIa might improve outcomes. Careful evaluation of the safety profile of FVIIa as well as its risk (cost)-benefit ratio are needed. In a review of 285 patients treated with FVIIa (242 trauma patients), 27 (9.4%) had thromboembolic complications; 9 of these events were considered highly related to the treatment. Of the nine complications, only two patients died; furthermore, in only one did the treatment likely contribute to the demise of the patient. Almost all the thromboembolic complications occurred in conjunction with a high-energy local vascular injury. Subsequently, the authors have tried to minimize the use of the drug in patients with known carotid or mesenteric vascular injury. Considering that the patients represent the highest-risk group and their expected mortality is very high, the overall risk-benefit ratio was very favorable.

There are no studies specifically addressing patients with head trauma. However, a randomized study of 399 patients with spontaneous hemorrhage demonstrated a significant reduction in the volume of hematoma, and drastically improved survival and functional outcome. Cryoprecipitate is a highly concentrated source of fibrinogen: 10 pooled units (50 mL) contain about 150 times more fibrinogen than a 250-mL bag of fresh-frozen plasma. Additionally, cryoprecipitate contains high concentrations of factor VIII and von Willebrand factor, which further enhance platelet adhesion and coagulation. Depending on the local protocol, it is usually given later in resuscitation, after 10 or more units of RBCs, 1 bag (10 pooled units) for every 10 units of RBCs.
Massive Blood Transfusion

Massive transfusion protocols are employed in order to provide the large quantities of blood products required for the resuscitation of rapidly exsanguinating trauma patients. These protocols are designed to stabilize blood volume, support tissue, and prevent or correct coagulation deficits often associated with hemorrhagic shock.

Different definitions of massive transfusion threshold exist (Table 5), such as one total blood volume loss (and replacement) in 24 hours, roughly equivalent to 10 units of whole blood, or 4 or more units replaced in 1 hour with continuing bleeding, 50% blood volume loss in 3 hours (equivalent to 5 units of whole blood), 50 units lost in 48 hours, 20 units lost in 24 hours, or blood loss exceeding 150 mL/min. Massive transfusion protocols have been modified and now generally consist of administering red cells and plasma initially, then adding platelet units, cryoprecipitate, and FVIIa at regular intervals later in the protocol. The reason behind designing massive transfusion protocols is to prevent coagulopathy rather than wait for coagulopathy to develop. Mathematical modeling has shown that initial resuscitation with more than five units of red cells together with crystalloid inevitably leads to dilutional coagulopathy. Ongoing resuscitation with red cells, fresh-frozen plasma, and platelets in a 1:1:1 ratio just barely keeps up. A mix of one unit of packed RBCs, an apheresis unit of platelets, and a unit of thawed plasma together have an approximate hematocrit of 29%, about 65% of initial coagulation factor activity, and platelet count of about 88,000/mcL. Some authors make a strong case that most trauma patients have enough oxygen-carrying capacity reserve, but are severely coagulopathic on their arrival to the hospital or before the surgery. Indeed, coagulopathy as measured by the regular tests is severely coagulopathic on their arrival to the hospital or before the patients have enough oxygen-carrying capacity reserve, but are limited by the very specific logistic limitations in the war theater, but seems to be safe and possibly even much more effective than transfusion of the stored blood components.

### Table 5. Definitions of Massive Transfusion

- One blood volume loss in 24 hours (equivalent to 10 units of whole blood)
- Four or more units replaced in 1 hour with continuing bleeding
- 50% blood volume loss in 3 hours (equivalent to 5 units of whole blood)
- 50 units lost in 48 hours
- 20 units lost in 24 hours
- Blood loss exceeding 150 mL/min.

Adapted from Repine et al.

### Table 6. Massive Transfusion Protocol

<table>
<thead>
<tr>
<th>Shipment</th>
<th>Red Cells</th>
<th>Packed Plasma</th>
<th>Thawed</th>
<th>Platelets</th>
<th>Cryo</th>
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<tbody>
<tr>
<td>1a</td>
<td>5 (O-Neg)</td>
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</tr>
</tbody>
</table>

Numbers refer to units per shipment for red cell, plasma, platelets, and cryoprecipitate (cryo).

*rFVIIa, recombinant factor VIIa (lyophilized powder with diluent), 100 mcg/kg rounded to the nearest whole vial.

Adapted from Dr. J. E. Forestner, Parkland Memorial Hospital, Dallas, and modified from Dr. R. Dutton.

Complications of Transfusions

In several high-quality retrospective trauma patients, transfusion was a very strong predictor of mortality even after meticulous adjustment for age and severity of trauma and shock. No randomized studies were conducted in trauma patients to clarify the issue, and the design for such a study would be extremely difficult. Mechanisms are also debated. Several strategies might be used to decrease the rate of complications such as cell salvage, preoperative erythropoietin, oxygen-carrying red blood cell substitutes, and lower transfusion triggers (Table 7). Immunomodulation by allogeneic blood transfusion has long been recognized, but the practical implications are uncertain. In cadaveric kidney recipients, transfusion of RBCs increased graft survival and the effect persisted after 5 years. Decreased natural killer cytotoxicity and various T-cell subpopulations could be demonstrated 2 decades after blood transfusion. Infection risk may increase 10-fold, and immunologic effects are still evident 1 month after transfusion. Transfusions, especially of nonleukoreduced blood, have been associated with a poor wound healing, failure of bowel anastomosis, sepsis, MOF, and death. These effects are more significant with transfusions of older blood cells. Blood banks discard RBC units after 42 days of storage, but cells older than 14 days have been shown to increase the rate of the complications. Observational studies report a several-fold increase in infection, pulmonary complications, ARDS, ventilator-associated pneumonia, MOF, and mortality, but it is not clear what kind of leukoreduction, if any, was used. Figures 1 and 2 illustrate the age of RBC units issued by the blood bank to consecutive trauma patients in our hospital, a tertiary care, Level 1 trauma center.

Immunomodulation is dose-dependent, regarding both the number of units transfused (usual threshold being three to four units of packed RBCs) and the degree of leukodepletion. For the last several years the blood provided to U.S. hospitals by the American Red Cross is leukoreduced unless requested otherwise. In most other developed countries, universal leukoreduction was adopted years ago. Thus, old findings might not apply to the current practice. One
has to recognize that “leukoreduced” does not mean free from leukocytes. Buffy-coat reduction removes about 70% of white blood cells, whereas filtering the blood removes more than 99.9%, leaving several million leukocytes per unit of RBC. The incidence of microchimerism (long-term survival of the donor white blood cells in the recipient body) is approximately 30% and is not diminished by leukoreduction. Storage of blood with leukocytes allows them to release significant amounts of cytokines. Thus, early leukoreduction should reduce the inflammatory impact of the transfused blood.

Bedside leukoreduction has also been associated with an impressive reduction in the risk of perioperative infection associated with blood transfusion. Current American Red Cross standards require that RBC units be leukodepleted no later than 5 days after donation, and contain no more than 5 x 10^6 white blood cells per unit. Leukoreduction seems to decrease the rate of febrile reactions and postoperative infections. Cell salvage is an important way to reduce allogeneic blood consumption. It reduces the postoperative infections and mortality in some studies, but others do not confirm the results.

Transfusion-related acute lung injury (TRALI) is a rare and underreported transfusion reaction presenting as ARDS and has to recognize that “leukoreduced” does not mean free from leukocytes. Buffy-coat reduction removes about 70% of white blood cells, whereas filtering the blood removes more than 99.9%, leaving several million leukocytes per unit of RBC. The incidence of microchimerism (long-term survival of the donor white blood cells in the recipient body) is approximately 30% and is not diminished by leukoreduction. Storage of blood with leukocytes allows them to release significant amounts of cytokines. Thus, early leukoreduction should reduce the inflammatory impact of the transfused blood.

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Transfusion-related acute lung injury (TRALI) is a rare and underreported transfusion reaction presenting as ARDS and noncardiogenic pulmonary edema during or after transfusion of blood. All blood products, except albumin, have been implicated. The severity of TRALI depends on the susceptibility of the patient to develop a more clinically significant reaction as a result of an underlying disease process, and on the nature of triggers in the transfused blood components, including granulocyte-binding alloantibodies (immune TRALI) or neutrophil-priming substances such as biologically active lipids (nonimmune TRALI). Immune TRALI, which occurs mainly after the transfusion of fresh-frozen plasma and platelet concentrates, is a rare event (about 1 incident per 5,000 transfusions) but if it happens, requires mechanical ventilation in about 70% (severe TRALI) and is fatal in 6% to 9% of the cases. Nonimmune TRALI, which occurs mainly after the transfusion of stored platelet and erythrocyte concentrates, seems to be characterized by a more benign clinical course, with oxygen support sufficient as a form of therapy in most cases, and a lower mortality than immune TRALI. Other causes of acute lung injury should be excluded in order to definitively diagnose TRALI. To prevent further antibody-mediated cases, the evaluation of TRALI should include leucocyte antibody testing of implicated donors. However, further studies are necessary to determine the prevention of this serious transfusion complication.

The adverse effects of hypothermia in the trauma patient include major coagulation derangements, peripheral vasoconstriction, metabolic acidosis, compensatory increased oxygen requirements during rewarming, and impaired immune response. Standard coagulation tests are temperature-corrected to 37°C and may not reflect hypothermia-induced coagulopathy. Hypothermia impairs coagulation because of slowing of enzymatic rates and reduced platelet function. Even worse, different steps in coagulation cascade are affected to different degrees, disrupting synchronization of the cascade. Hypothermia can cause cardiac dysrhythmias and even cardiac arrest from electromechanical dissociation, standstill, or fibrillation, especially with core temperatures below 30°C. Hypothermia also impairs citrate, lactate, and drug metabolism; increases blood viscosity; impairs RBC deformability; increases intracellular potassium release; and causes a leftward shift of the oxyhemoglobin dissociation curve. A mortality of 100% has been reported in trauma patients whose body temperature fell below 32°C, regardless of severity of injury, degree of hypotension, or fluid replacement. In our own study of 880 acute trauma victims, hypothermia, and especially hypothermia toward the end of the surgery, was an independent predictor of mortality. The importance of fluid warming cannot be overestimated in the trauma patient (see article in this issue by Drs. Smith and Wagner). It requires 16 kCal of energy to raise the tem-perature of 1
liter of crystalloid infused at 21°C to body temperature and 30 kCal to raise the temperature of cold 4°C blood to 37°C. Infusion of 4.3 liters of crystalloid at room temperature to an anesthetized adult trauma patient who cannot increase heat production can result in a decrease of 1.5°C in core temperature. Similarly, infusion of 2.3 liters of red cells could result in a core temperature decrease of between 1°C and 1.5°C.176,177 Because the thermal stress of infusing fluids at normothermia is essentially zero, it follows that use of fluid-warming devices effective at delivering normothermic fluids to the patient at clinically relevant flow rates permits more efficient rewarming of hypothermic trauma patients than using other methods such as the patient’s own metabolically generated heat or externally provided heat such as convective warming.178

Citrate Intoxication, Hyperkalemia, and Acid-Base Abnormalities

Blood is stored in citrate phosphate dextrose with adenine or Adsol at 4°C. Citrate binds calcium (that is why it is added to the RBCs in the first place) and citrate intoxication sharply decreases the serum levels of ionized calcium.179 Administration of calcium is warranted during massive transfusion if the patient is hypotensive and measured serum ionized serum calcium is low or large amounts of blood are infused rapidly (50–100 mL/min). Ionized serum calcium levels will usually return to normal when hemodynamic status is improved.

The potassium level in stored blood rises with length of storage and can be as high as 78 mmol/L after 35 days. The potential for clinically important hyperkalemia still exists in patients receiving blood administered at rates >120 mL/m² and in patients with severe acidosis. Monitoring the ECG for signs of hyperkalemia is always warranted, and treatment of hyperkalemia with calcium chloride, bicarbonate, glucose, and insulin may be life-saving.

The pH of bank blood decreases to about 6.9 after 21 days of storage because of accumulation of CO₂, lactic acid, and pyruvic acid by RBC metabolism. Thus, the acidosis seen in stored blood is partly respiratory and partly metabolic. The respiratory component is of little consequence with adequate patient ventilation. The metabolic component is not usually clinically significant. It is unwise to administer sodium bicarbonate on an empiric basis because there is already a pool of bicarbonate generated from the metabolism of citrate, which is present in large quantities in stored blood.

Hemolytic Transfusion Reactions

Immediate reactions occur from errors involving ABO incompatibility. More than half of these errors happen after the blood has been issued by the blood bank, which highlights the importance of verifying and identifying each and every donor unit for recipient compatibility. Intravascular hemolysis occurs when recipient antibody coats and immediately destroys the transfused red cells. Classic signs of hemolytic transfusion reaction are masked by general anesthesia. The only evidence may be hemoglobinuria, hypotension, and a bleeding diathesis. Treatment is supportive and involves stopping the transfusion and maintaining systemic and renal perfusion.

Microaggregates

Microaggregates begin forming after approximately 2 days of blood storage. During the first 7 days, microaggregates are mostly platelets or platelet debris. After the first week, the larger fibrin-white blood cell-platelet aggregates begin to accumulate.181 Whether these microaggregates contribute to lung dysfunction during blood transfusion and whether they need to be removed by micropore filters is controversial.

Infection

The risk of infection after transfusion of a single unit of blood product in developed countries was approximately 1:2-3 × 10⁴ for hepatitis C, 1:30-200 × 10⁴ for hepatitis B, 1:1.5-4.7 × 10⁶ for human immunodeficiency virus, 1:2-8 × 10⁴ for bacterial contamination with platelet units, and 1:28-143 × 10⁴ for packed RBCs; several cases of possible transfusion-transmitted variant Creutzfeldt-Jacob disease have been described.182 The risk per unit for Yersinia, malaria, babesiosis, and Chagas disease is estimated at <1:1,000,000. Other types of infectious diseases such as toxoplasmosis and cytomegalovirus, Epstein-Barr virus, and bacterial infections may also be transmitted by transfused blood and blood products. Each unit of fresh-frozen plasma or platelets has the same risk of infection as a unit of packed red cells.
End Points of Resuscitation

Blood and fluid resuscitation is continued until perfusion has been improved and organ function has been restored. Manifestations of improved perfusion include improved mental status, increased pulse pressure, decreased heart rate, increased urine output, resolution of lactic acidosis and base deficit, brisk capillary refill, and improvement in oxygen delivery, oxygen consumption, and central venous or pulmonary artery oxygen saturation (Table 8).

Blood and Fluid Warmers

Fluid and blood resuscitation of the trauma patient is best accomplished with large-gauge intravenous catheters and effective fluid warmers with high thermal clearances. Because alterations in red cell integrity are not apparent until 46°C, several models of fluid warmers with set points of 42°C are now commonly used. Countercurrent water and other fluid warmers using 42°C set points will not damage red cells, will result in consistently warmer fluid delivery, and will allow the clinician to maintain thermal neutrality with respect to fluid management over a wide range of flow rates.

Summary

Fluid management is a challenging task in trauma patients undergoing urgent and emergent surgery. The major goal is to stop the bleeding and replete intravascular volume to optimize blood pressure and tissue oxygen delivery. Choice, volume, and timing of intraoperative fluid resuscitation are based on correlates of hypoperfusion such as tachycardia, hypotension, low pH, base deficit, and lactate.

The bleeding trauma patient requires rapid evaluation and treatment to ensure adequate tissue perfusion and successful outcome. Resources such as thermally efficient warmers, effective transfusion services, and rapid availability blood products (RBCs, thawed plasma, platelets, cryoprecipitate), FVIIa, and coagulation tests are practical aspects of trauma resuscitation that deserve priority. Preventing hypothermia and recognizing other complications of massive transfusion, as well as following trends in vital signs, urinary output, central venous pressures, and arterial and central venous blood gas analysis, are of vital importance in managing patients with hemorrhagic shock.

### Table 8. Resuscitation End Points Within the First 24 Hours after Trauma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mixed venous oxygen tension</td>
<td>&gt;35 mm Hg</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (central venous or pulmonary artery)</td>
<td>&gt;65%</td>
</tr>
<tr>
<td>Base deficit</td>
<td>&gt; -3 mmol/L</td>
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<tr>
<td>Lactate</td>
<td>&lt;2.5 mmol/L</td>
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</tbody>
</table>


### References

18. Talmor D, Shapira Y, Artru AA, et al. 0.45% saline and 5% dextrose in water, but not 0.9% saline or 5% dextrose in 0.9% saline, worsen brain edema two hours after closed head trauma in rats. Anesth Analg 1999;88(6):1225-9.


92. Ware ML, Nemani VM, Meeker M, et al. Effects of 23.4% sodium chloride
95. Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline
96. Rizoli SB, Rhind SG, Shek PN, et al. The immunomodulatory effects of
97. Battison C, Andrews PJ, Graham C, Petty T. Randomized, controlled trial on
98. Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in
99. Licker M, Ellenberger C, Sierra J, et al., Cardiovascular response to acute

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