

SECTION III.

TRANSFUSION: CLINICAL PRACTICE

Fluid and Blood Therapy in Trauma

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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.¹ 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.² 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.²

Table 1. Estimation of Blood Volume Deficit in Trauma Patients

Site	Volume (mL)
Unilateral hemothorax	3,000
Hemoperitoneum with abdominal distention	2,000–5,000
Full-thickness soft tissue defect, 5 cm ³	500
Pelvic fracture	1,500–2,000
Femur fracture	800–1,200
Tibia fracture	350–650
Smaller fracture sites	100–500

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^{3,4} and decreased survival.³ 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.⁵ 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 trauma⁶ or ruptured abdominal aortic aneurysm⁷ 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.⁸ 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 2. Disadvantages of Immediate Fluid Resuscitation

Decreased blood viscosity
Blow-out of hemostatic plug
Dilution of coagulation factors
Increased blood loss
Delayed transport to definitive care

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^{9,10} and increased mortality, especially in trauma patients.¹¹ 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,^{12–14} with the benefit preserved over a 4-year follow-up,¹⁵ to prevent critical illness neuropathy, decrease the need for long-term ventilation, and shorten ICU stay.¹⁶ 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.^{17–19} Other studies refute these results and find euglycemia protective regardless of the insulin dose used.²⁰ 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.^{21,22} 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,²² and dilution of RBCs to hematocrit of 35% does not slow down the passage of blood through the standard 170-micron filter.²¹ 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.²³ The same concepts hold true when comparing hetastarch diluted in 0.9% saline (Hespan) with balanced crystalloid solution-based hetastarch (Hexend).^{24,25} Hyperchloremic metabolic acidosis is produced because high chloride solutions displace serum bicarbonate in the extracellular volume. Unlike lactic 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.^{26–28} After 60%

Table 3. Asanguinous Fluid Options for Trauma.

Lactated Ringer's (LR)	Preferred isotonic crystalloid solution for most trauma resuscitations. Do not mix with blood or use in blood lines because LR contains calcium.
0.9% Saline	Preferred isotonic crystalloid solution for head trauma. Only solution used in blood transfusion lines and to dilute pRBCs. May cause hyperchloremic metabolic acidosis (with normal anion gap) due to excess chloride displacing serum HCO ₃ .
Hespan (6% hetastarch in 0.9% saline)	High-molecular-weight hetastarch. Not recommended because of adverse effects on hemostasis. Half-life, 30 hours. Abandoned at authors' institution in favor of Hextend.
Hextend (6% hetastarch in balanced electrolyte solution)	High-molecular-weight hetastarch. Half-life, 30 hours. Less coagulopathy and platelet dysfunction compared with Hespan. Maximum dose, 10–15 mL/kg
Low- and medium-molecular-weight hetastarch	Colloid solutions with less coagulopathy and platelet dysfunction compared with high-molecular-weight hetastarch. Low-molecular-weight hetastarch associated with improved muscle oxygen tension, lower markers of inflammation, and endothelial activation compared with LR. Available in Europe and Canada. Not currently available in United States.
Albumin (5%)	Little effect on coagulation. May pass into interstitial compartment if impaired vascular integrity with resultant endothelial swelling and impaired microcirculatory perfusion. Increased mortality after head trauma in SAFE study (vs. 0.9% saline). ⁴⁶
Dextrans and gelatins	Colloid solutions largely abandoned in United States because of negative effects on coagulation and potential for anaphylaxis and hypersensitivity reactions
Hypertonic saline	Variety of solutions/concentrations. May be combined with colloid to prolong duration of action. Efficiently restores intravascular volume and decreases extravascular volume and tissue edema. Decreases ICP and increases CPP. Especially advantageous in prehospital situations and in head trauma with refractory increased ICP. Not associated with improved neurologic outcomes.

pRBCs, packed red blood cells; SAFE, saline versus albumin fluid evaluation; ICP, intracranial pressure; CPP, cerebral perfusion pressure.

hemodilution, both crystalloids and colloids produce a hypocoagulable state.²⁹ However, animal studies point to attenuation of hypercoagulability and increased blood loss in uncontrolled hemorrhagic shock treated with 0.9% saline as opposed to LR.³⁰ 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.³¹ In major abdominal surgery, there was no difference in coagulation parameters in patients receiving 0.9% saline or LR.³²

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).^{33,34} 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.³⁵

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,^{36,37} 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.³⁸ 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 and maintained cerebral perfusion pressure similar to LR combined with mannitol, while the brain tissue Po₂ and neurologic outcomes were significantly better³⁹; when compared with the crystalloid plus mannitol standard of care, total fluid requirements were reduced and no adverse effect on the coagulation profile was observed. Compared with 0.9% saline, volume resuscitation with Hextend was associated with less metabolic acidosis and longer survival in an animal model of septic shock.⁴⁰

Most colloids produce coagulopathy at relatively lower degrees of hemodilution compared with crystalloid.^{27–29} Colloids also prevent, to a variable degree, naturally occurring platelet activation and hypercoagulability. Hespan (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.^{41,42} This colloid was withdrawn from the authors' hospital formulary and replaced with Hextend, which is associated, both in vitro⁴³ and in vivo,⁴⁴ with better thromboelastographic parameters of

dynamic clot formation. Hextend does not inhibit platelet function, which may be because of its solvent containing 2.5 mmol/L of calcium chloride dihydrate.⁴⁵ In a randomized double-blind study of intraoperative fluid replacement, LR produced hypercoagulability, Hespan produced a hypocoagulable state, and Hextend had the least effect on thromboelastographic profile.⁴⁴

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.⁴⁶ 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%).

The effects of colloid versus crystalloid on tissue oxygen tension have been studied.⁴⁷ In patients scheduled for major abdominal surgery, volume replacement with low-molecular-weight hetastarch (mean molecular weight, 130 kD; degree of substitution, 0.4), as compared with LR, has resulted in significantly improved muscle oxygen tension, possibly from reduced endothelial swelling and improved microcirculation. The difference between the groups was apparent despite similar hemodynamics and oxygenation profile, and was progressively increasing during the surgery and through the next-day morning.

The influence of different volume-replacement regimens on inflammation and endothelial activation in elderly patients undergoing major abdominal surgery was assessed.⁴⁸ Patients were randomized to receive LR, 0.9% saline, or low-molecular-weight hetastarch 130/0.4. Fluids were given to keep central venous pressure between 8 and 12 mm Hg. Although hemodynamics were similar in all groups, markers of inflammation and endothelial injury and activation were significantly higher after crystalloid than after hetastarch 130/0.4-based volume replacement.

Resuscitation with crystalloid fluids alone may reduce the plasma oncotic pressure, promote water shift from intravascular to interstitial space, and result in tissue edema.⁴⁹ It has been suggested that decreased colloid oncotic pressure from infusion of crystalloid solutions would result in adverse pulmonary outcomes because of interstitial pulmonary edema. In a retrospective study of 512 trauma patients requiring surgery within 24 hours of admission to a Level 1 trauma center, it was shown that, compared with Hextend, resuscitation with crystalloid fluids was not associated with increased duration of mechanical ventilation, worsened alveolar-to-arterial oxygen gradient, or oxygen index after surgery. The low mortality rate in both groups supported the effectiveness of both fluid-management strategies in maintaining tissue homeostasis.⁵⁰

A meta-analysis failed to detect any differences in survival between crystalloid and colloid resuscitation overall, although it is recognized that many studies of specific solutions have been underpowered.⁵¹ Further, pooling old-to-very old underpowered studies in a meta-analysis is of limited value to clinicians caring for trauma patients.⁵²

Hetastarch accumulates in the body. Because preparations of hetastarch are actually a mixture of complex molecules of different size and structure, only an average half-life of the particular mix can be calculated. Hetastarch is slowly metabolized by intravascular alpha-amylase. For example, median serum half-life of Hextend is about 30 hours. The smaller hydroxyethyl starch molecules are rapidly eliminated by glomerular filtration. Hemodilution is observed for 24 to 48 hours after short-term infusion. A varying amount of

hetastarch is taken up by the reticuloendothelial system.

Pruritus has been reported after hetastarch infusion.⁵³ Life-threatening anaphylactic reactions may occur with different kinds of hydroxyethyl starch preparations, but appear to be rare.⁵⁴⁻⁵⁶ A dose limitation exists for all hetastarch preparations ranging from 20 mL/kg (10% hetastarch 200/0.5) to 50 mL/kg (6% hetastarch 130/0.4).

Different Colloid Formulations

The crystalloid/colloid debate has been enlarged to a colloid/colloid debate because several preparations exist including albumin, dextrans, gelatins, and hetastarch solutions (Table 3). Colloid solutions are reviewed in detail by Dr. Boldt in a separate article. Because of their varying physicochemical properties, these solutions differ widely with regard to their pharmacokinetic and pharmacodynamic properties as well as to their hemodynamic efficacy and side effects.

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.⁵⁵ In particular, medium-molecular-weight hetastarches with lower molar substitution appear promising compared with first-generation hetastarches.⁵⁷ 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 (Hespan 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.⁵⁸ 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.²⁹ However, at least in some studies, no clinically relevant differences have been observed.⁵⁹

Large amounts of high-molecular-weight 6% hetastarch (>15–20 mL/kg) are traditionally avoided because of the well-documented risk of coagulopathy,⁶⁰ increased blood loss and transfusion requirements,^{61,62} and mortality.^{61,63} These effects are mediated by dose-dependent decrease in factor VIII and von Willebrand factor, and inactivation of glycoprotein IIb-IIIa.⁶² Hextend, approved for use in United States in 1999, appears to be different than Hespan in its effects on hemostasis.^{44,64} 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.^{64,65}

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.^{66,67} In patients with impaired vascular endothelial integrity, albumin may pass into the interstitial compartment with resultant endothelial swelling and impaired microcirculatory perfusion.⁶⁸⁻⁷⁰

Dextrans have 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 different populations of 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.⁷¹ As expected, addition of colloid to the hypertonic saline increased the magnitude and markedly prolonged the duration of volume expansion.^{71,72} 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.⁷³ 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,⁷⁴ absorb water, chloride, and sodium, and lose the resting membrane potential.⁷⁵ They return to normal volume, electrolyte balance, and resting potential with hypertonic saline better than with isotonic resuscitation.⁷⁵ Capillary lumens narrow as a result of this swelling⁷⁶ and return to normal diameter with hypertonic resuscitation but not with LR.⁷⁷ Further, hypertonic saline restores intravascular volume and hemodynamics while decreasing extravascular volume and tissue edema.⁷³ 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.⁷⁸ 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.⁷⁹ 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,⁸⁰ although a transient decrease in blood pressure because of vasodilatation may occur.^{81,82} Hypertonic solutions increase cardiac contractility, venous return, and coronary blood flow.^{82,83} Moreover, hypertonic saline/dextran solution is effective in treating dehydration⁸⁴ and massive hemorrhage in animals with preexisting dehydration.⁸⁵

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.^{86–88} Similar effects have been observed in patients with stroke⁸⁹ and subarachnoid hemorrhage.⁹⁰ Effects of hypertonic saline on intracranial and cerebral perfusion pressure were more rapid⁸⁶ and more profound than a comparable⁹¹ or double⁸⁷ volume of 20% mannitol, and lasted longer.^{87,92}

In a study of trauma patients whose elevated intracranial pressure was refractory to all other modalities,⁹¹ 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,⁹³ 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.⁹⁴ 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 comatose (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.⁹⁵ 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 humans⁹⁶ 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.⁹⁷ 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.⁹⁸ 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.⁹⁸ 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 heart 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.⁹⁹ 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%.¹⁰⁰ Similar numbers were reported by other investigators.¹⁰¹

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.¹⁰² 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.¹⁰³ Subtle cognitive function impairment appeared only at or below hemoglobin 6 g/dL and was readily reversible with breathing 100% oxygen.¹⁰⁴ 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.¹⁰⁵

The cardiovascular and metabolic response to acute, severe isovolemic anemia was studied in elderly patients (76 \pm 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.¹⁰⁶ 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.¹⁰⁷

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.^{99,108} An increase in the heart rate should raise suspicion for hypovolemia.

In a literature review published in 1994,¹⁰⁹ 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 37% to 8% at the end of surgery and to 6.4% on postoperative day 2¹¹⁰; 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.¹¹¹ 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.¹¹²

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 $\text{FiO}_2 = 0.6$ and to 1.2 g/dL at $\text{FiO}_2 = 1.0$. There was 100% mortality at critical hemoglobin and $\text{FiO}_2 = 0.21$, whereas switching to 100% oxygen increased oxygen delivery and resulted in 100% survival at 6 hours.¹¹³⁻¹¹⁶ 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.¹¹⁷ Oxygen

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 euvoletic 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 adjusted to death and change of score after randomization were lower with the restrictive protocol. Mortality was lower with the restrictive strategy in patients younger than 55 years and with APACHE II score of ≤20, and similar or nonsignificantly lower for all other subgroups, including separate analysis for patients with trauma¹²¹ and cardiovascular disease.¹²² Surprisingly, the trend to decreased incidence of infections and bacteremia in the restrictive group did not reach statistical significance, possibly because of transfusion before randomization, which would blunt the difference between the groups. Rate of pneumonia was about 20% in both groups. Rates of all other individual complications were nonsignificantly lower in the restrictive compared with the liberal transfusion group. Overall, the rate of complications was about 10% lower in the restrictive versus the liberal transfusion group.

Regarding the effect of anemia and transfusions on mortality in 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%.¹²³ 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%.¹²⁴ 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 consumption¹²⁵ (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 recombinant 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 O 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.²

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^{127,128} 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 Toy¹²⁹ 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 blood. One unit of platelets, equivalent to 50 mL, increases the platelet count in an average adult by 5,000 to 10,000/mcL. Transfusion of single-donor pooled platelet units, equivalent each to six units of random donor platelet units, 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.¹³⁰ 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.¹³¹ 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.¹³² 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 1999.¹³³ 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.¹³⁴ 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.¹³⁵ 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,¹³⁶ 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,¹³⁴ 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.¹³⁷

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.¹³⁸ 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.¹³⁹

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.^{140,141} 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.¹⁴² 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.¹⁴³ 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 common in trauma patients,¹⁴⁴⁻¹⁴⁶ especially in the ones showing signs of hypoperfusion and acidosis,^{145,147} and is strongly associated with mortality.¹⁴⁴⁻¹⁴⁶ For the trauma patient in hemorrhagic shock with ongoing bleeding, the benefits of administering blood products in the absence of confirmatory laboratory tests usually outweigh the risks of transfusion. The logistics of such transfusion protocols need to involve several departments including anesthesia, surgery, and blood bank (transfusion medicine). Further experience with a large number of patients is needed in order to prove definite benefit from use of such protocols in trauma patients.¹⁴⁸ The protocol being established at the authors' institution is shown in Table 6. Of note, the military employs a protocol of transfusing the fresh, warm, whole blood collected in real time from the "walking blood bank." The practice is dictated mainly 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.^{149,150}

Table 5. Definitions of Massive Transfusion
<ul style="list-style-type: none"> • 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.¹⁵⁰

Table 6. Massive Transfusion Protocol					
Shipment Red Cells	Packed Plasma	Thawed	Platelets	Cryo	rFVIIa
1a	5 (O-Neg)	5			rFVIIa*
1b	5	5	5		
2	5	5		10	
3	5	5	5		
4	5	5			
5	5	5	5	10	
6	5	5			
7	5	5	5		
8	5	5		10	
9	5	5	5		
10	5	5			

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.^{151,152} 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.¹⁵³ Decreased natural killer cytotoxicity and various T-cell subpopulations could be demonstrated 2 decades after blood transfusion.¹⁵⁴ Infection risk may increase 10-fold, and immunologic effects are still evident 1 month after transfusion.¹⁵⁵ Transfusions, especially of nonleukodepleted blood, have been associated with a poor wound healing,¹⁵⁶ failure of bowel anastomosis,¹⁵⁷ sepsis, MOF,¹⁵⁸ and death. These effects are more significant with transfusions of older blood cells.¹⁵⁹ 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.¹⁵⁹ Observational studies report a several-fold increase in infection, pulmonary complications, ARDS, ventilator-associated pneumonia, MOF, and mortality,¹⁶⁰ 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

Table 7. Clinical Strategies to Reduce Complications of Transfusion Therapy

Complication	Clinical Strategies to Reduce Complication
Impaired oxygen release from hemoglobin	Warm all IV fluids and blood. Avoid alkalosis. Maintain normothermia (core temperature 36°C–37°C)
Dilutional coagulopathy	Thawed plasma for prothrombin >1.5 × normal and clinically excessive bleeding. Platelets for thrombocytopenia <75,000/mcL and clinically excessive bleeding.
Hypothermia	Warm all IV fluids and blood. Warm room >28°C. Convective warming. Humidify all inspired gases.
Decreased ionized calcium	Treat with calcium chloride, 20 mg/kg, in setting of massive transfusion and hypotension
Hyperkalemia	Monitor ECG and treat with calcium chloride, 20 mg/kg, if hemodynamically significant. Otherwise, monitor and treat with glucose and insulin and/or bicarbonate.
Hemolytic transfusion reaction	Check and recheck every donor unit. Once occurred, stop transfusion and maintain systemic perfusion and renal blood flow. Alkalinize urine. Watch for DIC. Send suspected unit to blood bank for crossmatch.
Infection	Lower transfusion trigger. Red cell salvage. Avoid indiscriminate blood product transfusions. Oxygen-carrying red blood cell substitutes.*
Transfusion-induced immunosuppression	Lower transfusion trigger. Red cell salvage. Leukoreduction. Avoid indiscriminate blood product transfusions. Oxygen-carrying red blood cell substitutes.*

IV, intravenous; ECG, electrocardiogram; DIC: disseminated intravascular coagulation.

*Not currently available.

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.¹⁶¹ 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.¹⁶² Current American Red Cross standards require that RBC units be leukodepleted no later than 5 days after donation, and contain no more than 5×10^6 white blood cells per unit. Leukoreduction seems to decrease the rate of febrile reactions and postoperative infections.^{163–165} 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 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 leukocyte antibody testing of implicated donors. However, further studies are necessary to determine the prevention of this serious transfusion complication.^{166,167}

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.^{168–170} Standard coagulation tests are temperature-corrected to 37°C and may not reflect hypothermia-induced coagulopathy.^{171–173} 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.¹⁷⁴ 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.¹⁷⁵

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 temperature of 1

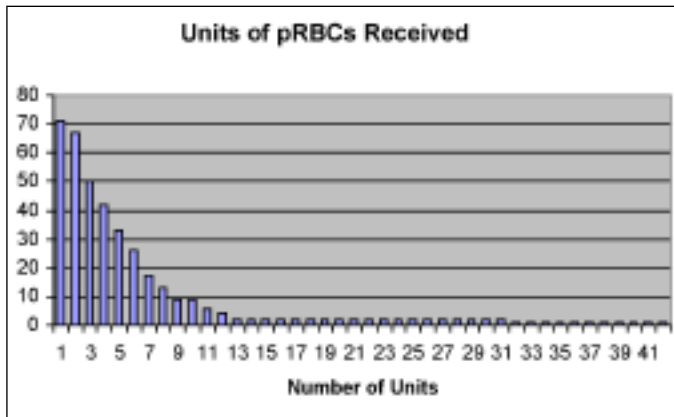


Figure 1. Number of packed red blood cell units (pRBCs) transfused per patient. Data are from 115 trauma patients requiring emergency surgery at MetroHealth Medical Center between June 2003 and June 2004. A total of 2,595 units were transfused.

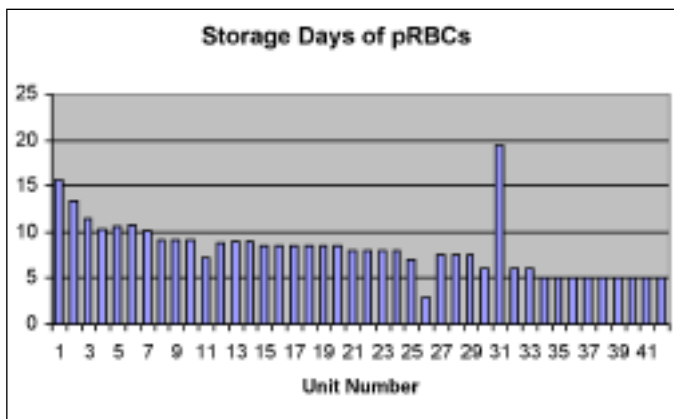


Figure 2. Number of storage days for packed red blood cell units (pRBCs) prior to transfusion in 115 trauma patients requiring emergency surgery at MetroHealth Medical Center between June 2003 and June 2004. A total of 2,595 units were transfused.

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/m¹⁸⁰ 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 × 10⁶ for hepatitis C, 1:30-200 × 10³ for hepatitis B, 1:1.5-4.7 × 10⁶ for human immunodeficiency virus, 1:2-8 × 10³ for bacterial contamination with platelet units, and 1:28-143 × 10³ 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).¹⁸³

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.¹⁸⁴ 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.¹⁷⁸

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

Parameter	Value
Mixed venous oxygen tension	>35 mm Hg
Mixed venous oxygen saturation (central venous or pulmonary artery)	>65%
Base deficit	> -3 mmol/L
Lactate	<2.5 mmol/L

Adapted from Ivatury RR, Simon RJ. Assessment of tissue oxygenation (evaluation of the adequacy of resuscitation). In: Ivatury RR, Cayten CGC, eds. *The Textbook of Penetrating Trauma*. Baltimore: Williams & Wilkins, 1996:927-938.

References

1. Stene J, Smith CE, Grande CM. Evaluation of the trauma patient, in Longnecker DE, Tinker JH, Morgan GE, eds. *Principles and Practice of Anesthesiology*, 2nd ed. Philadelphia: Mosby-Yearbook, 1998.
2. Grande CM, Smith CE, Stene J. Anesthesia for trauma, in Longnecker DE, Tinker JH, Morgan GE, eds. *Principles and Practice of Anesthesiology*, 2nd ed. Philadelphia: Mosby-Yearbook, 1998.
3. Stern SA, Dronen SC, Birrer P, Wang X. Effect of blood pressure on hemorrhage volume and survival in a near-fatal hemorrhage model incorporating a vascular injury. *Ann Emerg Med* 1993;22(2):155-63.
4. Holmes JF, Sakles JC, Lewis G, Wisner DH. Effects of delaying fluid resuscitation on an injury to the systemic arterial vasculature. *Acad Emerg Med* 2002;9(4):267-74.
5. Bickell WH, Wall MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994;331(17):1105-9.
6. Kwan I, Bunn F, Roberts I. WHO Pre-Hospital Trauma Care Steering Committee. Timing and volume of fluid administration for patients with bleeding. *Cochrane Database Syst Rev*. 2003;(3):CD002245. Update of: *Cochrane Database Syst Rev*. 2001;(1):CD002245.
7. Roberts K, Revell M, Youssef H, et al. Hypotensive resuscitation in patients with ruptured abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2006;31(4):339-44.
8. Krausz MM. Initial resuscitation of hemorrhagic shock. *World J Emerg Surg* 2006;1:14.
9. Lam AM, Winn HR, Cullen BF, Sundling N. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg* 1991;75(4):545-51.
10. Michaud LJ, Rivara FP, Longstreth WT Jr, Grady MS. Elevated initial blood glucose levels and poor outcome following severe brain injuries in children. *J Trauma* 1991;31(10):1356-62.
11. Vogelzang M, Nijboer JM, van der Horst IC, et al. Hyperglycemia has a stronger relation with outcome in trauma patients than in other critically ill patients. *J Trauma* 2006;60(4):873-9.
12. Conner TM, Flesner-Gurley KR, Barner JC. Hyperglycemia in the hospital setting: the case for improved control among non-diabetics. *Ann Pharmacother* 2005;39(3):492-501.
13. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;345(19):1359-67.
14. van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 2006;55(11):3151-9.
15. Ingels C, Debaveye Y, Milants I, et al. Strict blood glucose control with insulin during intensive care after cardiac surgery: impact on 4-years survival, dependency on medical care, and quality-of-life. *Eur Heart J* 2006;27(22):2716-24.
16. Hermans G, Wilmer A, Meersseman W, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. *Am J Respir Crit Care Med* 2007;175(5):480-9.
17. Shapira Y, Artru AA, Cotev S, et al. Brain edema and neurologic status following head trauma in the rat. No effect from large volumes of isotonic or hypertonic intravenous fluids, with or without glucose. *Anesthesiology* 1992;77(1):79-85.
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* 1998;86(6):1225-9.
19. Vink R, Golding EM, Williams JP, McIntosh TK. Blood glucose concentration does not affect outcome in brain trauma: a 3IP MRS study. *J Cereb Blood Flow Metab* 1997;17(1):50-3.
20. Ellger B, Debaveye Y, Vanhorebeek, I et al. Survival benefits of intensive insulin therapy in critical illness: impact of maintaining normoglycemia versus glycemia-independent actions of insulin. *Diabetes* 2006;55(4):1096-105.
21. Cull DL, Lally KP, Murphy KD. Compatibility of packed erythrocytes and Ringer's lactate solution. *Surg Gynecol Obstet* 1991;173(1):9-12.
22. Vincent JL, Berre J. Primer on medical management of severe brain injury. *Crit Care Med* 2005;33:1392-9.
23. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology* 1999;90(5):1265-70.
24. Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg* 2001;93(4):811-6.

25. Boldt J, Schöllhorn T, Münchbach J, Pabsdorf M. A total balanced volume replacement strategy using a new balanced hydroxyethyl starch preparation (6% HES 130/0.42) in patients undergoing major abdominal surgery. *Eur J Anaesthesiol* 2007;24(3):267-75.
26. Ruttman TG, Jamest MF, Lombard EH. Haemodilution-induced enhancement of coagulation is attenuated in vitro by restoring antithrombin III to pre-dilution concentrations. *Anaesth Intensive Care* 2001;29(5):489-93.
27. Ruttman TG, James MFM, Aronson I. In vivo investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation. *Br J Anaesth* 1998;80: 612-6.
28. Ruttman TG, James MFM, Finlayson J. Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery. *Br J Anaesth* 2002;89:226-30.
29. Roche AM, James MF, Bennett-Guerrero E, Mythen MG. A head-to-head comparison of the in vitro coagulation effects of saline-based and balanced electrolyte crystalloid and colloid intravenous fluids. *Anesth Analg* 2006;102(4):1274-9.
30. Kiraly LN, Differding JA, Enomoto TM, et al. Resuscitation with normal saline (NS) vs. lactated ringers (LR) modulates hypercoagulability and leads to increased blood loss in an uncontrolled hemorrhagic shock swine model. *J Trauma* 2006;61(1):57-65.
31. Waters JH, Gottlieb A, Schoenwald P, et al. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg* 2001;93(4):817-22.
32. Boldt J, Haisch G, Suttner S, Kumle B, Schellhase F. Are lactated Ringer's solution and normal saline solution equal with regard to coagulation? *Anesth Analg* 2002;94(2):378-84.
33. Boldt J. New light on intravascular volume replacement regimens: what did we learn from the past three years? *Anesth Analg* 2003;97:1595-604.
34. Gan TJ. Intraoperative fluid management and choice of fluids. In: ASA Annual Meeting *Refresher Course Lectures*, 2004;405:1-7
35. Boldt J, Suttner S. Plasma substitutes. *Minerva Anesthesiol* 2005;71(12):741-58.
36. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995;130:423-9.
37. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ* 1997;315(7113):909-12.
38. Wilkes NJ, Woolf RL, Powanda MC, et al. Hydroxyethyl starch in balanced electrolyte solution (Hextend)—pharmacokinetic and pharmacodynamic profiles in healthy volunteers. *Anesth Analg* 2002;94(3):538-44.
39. King DR, Cohn SM, Proctor KG. Changes in intracranial pressure, coagulation, and neurologic outcome after resuscitation from experimental traumatic brain injury with hetastarch. *Surgery* 2004;136:355-63.
40. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. *Crit Care Med* 2002;30:300-5.
41. Boldt J, Knothe C, Zickmann B, et al. Influence of different intravascular volume therapy on platelet function in patients undergoing cardiopulmonary bypass. *Anesth Analg* 1993;76:1185-90.
42. Sanfelippo MJ, Suberviola PD, Geimer NF. Development of a von Willebrand-like syndrome after prolonged use of hydroxyethyl starch. *Am J Clin Pharmacol* 1987;88:653-5.
43. Gan TJ, Bennett-Guerrero E, Phillips-Bute B, et al. Hextend, a physiologically balanced plasma expander for large volume use in major surgery: a randomized phase III clinical trial. Hextend Study Group. *Anesth Analg* 1999;88:992-8.
44. Martin G, Bennett-Guerrero E, Wakeling H, et al. A prospective, randomized comparison of thromboelastographic coagulation profile in patients receiving lactated Ringer's solution, 6% hetastarch in a balanced-saline vehicle, or 6% hetastarch in saline during major surgery. *J Cardiothorac Vasc Anesth* 2002;16:441-6.
45. Deusch E, Thaler U, Kozek-Langenecker SA. The effects of high molecular weight hydroxyethyl starch solutions on platelets. *Anesth Analg* 2004;99:665-8.
46. Finfer S, Bellomo R, Boyce N, et al. SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004;350(22):2247-56.
47. Lang K, Boldt J, Suttner S, Haisch G. Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. *Anesth Analg* 2001;93(2):405-9.
48. Boldt J, Ducke M, Kumle B, et al. Influence of different volume replacement strategies on inflammation and endothelial activation in the elderly undergoing major abdominal surgery. *Intensive Care Med* 2004;30(3):416-22.
49. London MJ. Colloids versus crystalloids in cardiopulmonary bypass. Pro: colloids should be added to the pump prime. *J Cardiothorac Anesth* 1990;4:401.
50. Wagner K, Smith CE, Avula R. Intraoperative Hextend administration in trauma patients requiring surgery. Poster presented at: TraumaCare 2007, the International Trauma Anesthesia and Critical Care Society (ITACCS) Annual Scientific Meeting; May 14-16, 2007; Las Vegas, Nevada.
51. Roberts I, Alderson P, Bunn F, et al. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2004 Oct 18;(4):CD000567. Update of: *Cochrane Database Syst Rev* 2000;(2):CD000567.
52. Boldt J. Fluid choice for resuscitation in trauma. *TraumaCare*. 2008;18(1):57-65.
53. Spittal MJ, Findlay GP. The seven year itch. *Anaesthesia* 1995;50:913-4
54. Cullen MJ, Singer M. Severe anaphylactoid reaction to hydroxyethyl starch. *Anaesthesia* 1990;45:1041-2.
55. Nearman HS, Herman ML. Toxic effects of colloids in the intensive care unit. *Crit Care Clin* 1991;7:713-23.
56. Barron ME, Wilkes MM, Navickis RJ. A systematic review of the comparative safety of colloids. *Arch Surg* 2004;139:552-63.
57. Boldt J. Fluid choice for resuscitation of the trauma patient: a review of the physiological, pharmacological, and clinical evidence *Can J Anesth* 2004;51:500-13.
58. Treib J, Baron JF, Grauer MT, Strauss RG. An international view of hydroxyethyl starches. *Intensive Care Med* 1999;25(3):258-68.
59. Huttner I, Boldt J, Haisch G, et al. Influence of different colloids on molecular markers of haemostasis and platelet function in patients undergoing major abdominal surgery. *Br J Anaesth* 2000;85(3):417-23.
60. Wilson RF. Blood replacement. In: Wilson RF, Walt A, eds. *Management of Trauma. Pitfalls and Practice*, 2nd ed. Baltimore: Williams & Wilkins, 1996.
61. Knutson JE, Deering JA, Hall FW, et al. Does intraoperative hetastarch administration increase blood loss and transfusion requirements after cardiac surgery? *Anesth Analg* 2000;90(4):801-7.
62. Kozek-Langenecker SA. Effects of hydroxyethyl starch solutions on hemostasis. *Anesthesiology* 2005;103(3):654-60.
63. Sedrakyan A, Gondek K, Paltiel D, Elefteriades JA. Volume expansion with albumin decreases mortality after coronary artery bypass graft surgery. *Chest* 2003;123(6):1853-7.
64. Deusch E, Thaler U, Kozek-Langenecker SA. The effects of high molecular weight hydroxyethyl starch solutions on platelets. *Anesth Analg* 2004;99(3):665-8.
65. Nielsen VG. Effects of hydroxyethyl starch and calcium on platelet activation. *Anesth Analg* 2005;100(5):1538-9.
66. Margaron MP, Soni N. Serum albumin: touchstone or totem? *Anaesthesia* 1998;53:789-803.
67. Qiao R, Siflinger-Birnboim A, Lum H, Tirupathi C, Malik AN. Albumin and Ricinus communis agglutinin decrease endothelial permeability via interactions with matrix. *Am J Physiol* 1993;265:C439-446.
68. Weil MH, Henning RJ, Puri VK. Colloid oncotic pressure: clinical significance. *Crit Care Med* 1979;7:113-26.
69. Fleck A, Raines G, Hawker F, et al. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. *Lancet* 1985; i:781-4.
70. Rackow EC, Mecher C, Astiz ME, et al. Effects of pentastarch and albumin infusion on cardiorespiratory function and coagulation in patients with severe sepsis and systemic hypoperfusion. *Crit Care Med* 1989;17:394-8.
71. Drobin D, Hahn RG. Kinetics of isotonic and hypertonic plasma volume expanders. *Anesthesiology* 2002;96(6):1371-80.
72. Wade CE, Hannon JP, Bossone CA, Hunt MM. Superiority of hypertonic saline/dextran over hypertonic saline during the first 30 min of resuscitation following hemorrhagic hypotension in conscious swine. *Resuscitation* 1990;20(1):49-56.
73. Tølløfsrud S, Elgjo GI, Prough DS, et al. The dynamics of vascular volume and fluid shifts of lactated ringer's solution and hypertonic-saline-dextran solutions infused in normovolemic sheep. *Anesth Analg* 2001;92:823-31.
74. Askenasy N, Navon G. Continuous monitoring of intracellular volumes in isolated rat hearts during normothermic perfusion and ischemia. *J Magn Reson* 1997;124(1):42-50.
75. Nakayama S, Kramer GC, Carlsen RC, Holcroft JW. Infusion of very hypertonic saline to bleed rats: membrane potentials and fluid shifts. *J Surg Res* 1985;38(2):180-6.
76. Mazzoni MC, Borgstrom P, Intaglietta M, Arfors KE. Luminal narrowing and endothelial cell swelling in skeletal muscle capillaries during hemorrhagic shock. *Circ Shock* 1989;29(1):27-39.
77. Mazzoni MC, Borgstrom P, Intaglietta M, Arfors KE. Capillary narrowing in hemorrhagic shock is rectified by hyperosmotic saline-dextran reinfusion. *Circ Shock* 1990;31(4):407-18.
78. Toung TJ, Chang Y, Lin J, Bhardwaj A. Increases in lung and brain water following experimental stroke: effect of mannitol and hypertonic saline. *Crit Care Med* 2005;33(1):203-8.

79. Vassar MJ, Fischer RP, O'Brien PE, et al. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride. The effect of added dextran 70. The Multicenter Group for the Study of Hypertonic Saline in Trauma Patients. *Arch Surg* 1993;128(9):1003-13.
80. Kramer GC, Perron PR, Lindsey DC, et al. Small-volume resuscitation with hypertonic saline dextran solution. *Surgery* 1986;100:239-46.
81. Jarhult J, Hillman J, Mellander S. Circulatory effects evoked by 'physiological' increases of arterial osmolality. *Acta Physiol Scand* 1975;93(1):129-34.
82. Kien ND, Kramer GC, White DA. Acute hypotension caused by rapid hypertonic saline infusion in anesthetized dogs. *Anesth Analg* 1991;73:597-602.
83. Mouren S, Delayance S, Mion G, et al. Mechanisms of increased myocardial contractility with hypertonic saline solutions in isolated blood-perfused rabbit hearts. *Anesth Analg* 1995;81(4):777-82.
84. Matthew CB, Durkot MJ, Patterson DR. Fluid shifts induced by the administration of 7.5% sodium chloride in 6% dextran 70 (HSD) in dehydrated swine. *Circ Shock* 1993;41(3):150-5.
85. Ho HS, Sondeen JL, Dubick MA, et al. The renal effects of 7.5% NaCl-6% dextran-70 versus lactated Ringer's resuscitation of hemorrhage in dehydrated sheep. *Shock* 1996;5(4):289-97.
86. Harutjunyan L, Holz C, Rieger A, et al. Efficiency of 7.2% hypertonic saline hydroxyethyl starch 200/0.5 versus mannitol 15% in the treatment of increased intracranial pressure in neurosurgical patients: a randomized clinical trial. *Crit Care* 2005;9(5):R530-40.
87. Battison C, Andrews PJ, Graham C, Petty T. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% Saline/6% dextran solution on increased intracranial pressure after brain injury. *Crit Care Med* 2005;33(1):196-202.
88. Ming-Yuan Tseng, Al-Rawi PG, Pickard JD, et al. Effect of hypertonic saline on cerebral blood flow in poor-grade patients with subarachnoid hemorrhage. *Stroke* 2003;34:1389-96.
89. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. *Stroke* 2002;33(1):136-40. [Comment in: *Stroke* 2002 Apr;33(4):1166-7; author reply 1166-7.]
90. Bentsen G, Breivik H, Lunder T, Stubhaug A. Predictable reduction of intracranial hypertension with hypertonic saline hydroxyethyl starch: a prospective clinical trial in critically ill patients with subarachnoid haemorrhage. *Acta Anaesthesiol Scand* 2004;48(9):1089-95.
91. Viallet R, Albanese J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med* 2003;31(6):1683-7.
92. Ware ML, Nemani VM, Meeker M, et al. Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: a preliminary study. *Neurosurgery* 2005;57(4):727-36.
93. Khanna S, Davis D, Peterson B, et al. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. *Crit Care Med* 2000;28(4):1144-51.
94. Wade CE, Grady JJ, Kramer GC, et al. Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. *J Trauma* 1997;42;5(Suppl):61S-5S.
95. Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury. *JAMA* 2004;291:1350-7.
96. Rizoli SB, Rhind SG, Shek PN, et al. The immunomodulatory effects of hypertonic saline resuscitation in patients sustaining traumatic hemorrhagic shock: a randomized, controlled, double-blinded trial. *Ann Surg* 2006;243(1):47-57.
97. Bunn F, Roberts I, Tasker R, Akpa E. Hypertonic versus near isotonic crystalloid for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2004;(3):CD002045. Update of: *Cochrane Database Syst Rev* 2002;(1):CD002045.
98. Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion* 2002;42(7):812-8.
99. Licker M, Ellenberger C, Sierra J, et al. Cardiovascular response to acute normovolemic hemodilution in patients with coronary artery diseases: assessment with transesophageal echocardiography. *Crit Care Med* 2005;33(3):591-7.
100. Levy PS, Kim SJ, Eckel PK, et al. Limit to cardiac compensation during acute isovolemic hemodilution: influence of coronary stenosis. *Am J Physiol* 1993;265(1 Pt 2):H340-9.
101. Spahn DR, Smith LR, Veronee CD, et al. Acute isovolemic hemodilution and blood transfusion. Effects on regional function and metabolism in myocardium with compromised coronary blood flow. *J Thorac Cardiovasc Surg* 1993;105(4):694-704.
102. Hopf HW, Viele M, Watson JJ. Subcutaneous perfusion and oxygen during acute severe isovolemic hemodilution in healthy volunteers. *Arch Surg* 2000;135(12):1443-9.
103. Leung JM, Weiskopf RB, Feiner J, et al. Electrocardiographic ST-segment changes during acute, severe isovolemic hemodilution in humans. *Anesthesiology* 2000;93(4):1004-10.
104. Weiskopf RB, Toy P, Hopf HW, et al. Acute isovolemic anemia impairs central processing as determined by P300 latency. *Clin Neurophysiol* 2005;116(5):1028-32.
105. Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA* 1998;279(3):217-21.
106. Spahn DR, Zollinger A, Schlumpf RB, et al. Hemodilution tolerance in elderly patients without known cardiac disease. *Anesth Analg* 1996;82(4):681-6.
107. Mathru M, Kleinman B, Blakeman B, et al. Cardiovascular adjustments and gas exchange during extreme hemodilution in humans. *Crit Care Med* 1991;19(5):700-4.
108. Ickx BE, Rigolet M, Van Der Linden PJ. Cardiovascular and metabolic response to acute normovolemic anemia. Effects of anesthesia. *Anesthesiology* 2000;93(4):1011-6.
109. Viele MK, Weiskopf RB. What can we learn about the need for transfusion from patients who refuse blood? The experience with Jehovah's Witnesses. *Transfusion* 1994;34(5):396-401.
110. Neff TA, Stocker R, Wight E, Spahn DR. Extreme intraoperative blood loss and hemodilution in a Jehovah's Witness: new aspects in postoperative management. *Anesthesiology* 1999;91(6):1949-51.
111. Zollinger A, Hager P, Singer T, et al. Extreme hemodilution due to massive blood loss in tumor surgery. *Anesthesiology* 1997;87(4):985-7.
112. Fang WC, Helm RE, Krieger KH, et al. Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. *Circulation* 1997;96(9 Suppl):II-194-9.
113. Pape A, Meier J, Kertscho H, et al. Hyperoxic ventilation increases the tolerance of acute normovolemic anemia in anesthetized pigs. *Crit Care Med* 2006;34(5):1475-82.
114. Meier J, Kemming G, Meisner F, et al. Hyperoxic ventilation enables hemodilution beyond the critical myocardial hemoglobin concentration. *Eur J Med Res* 2005;10(11):462-8.
115. Meier J, Kemming GI, Kisch-Wedel H, et al. Hyperoxic ventilation reduces six-hour mortality after partial fluid resuscitation from hemorrhagic shock. *Shock* 2004;22(3):240-7.
116. Meier J, Kemming GI, Kisch-Wedel H, et al. Hyperoxic ventilation reduces 6-hour mortality at the critical hemoglobin concentration. *Anesthesiology* 2004;100(1):70-6.
117. Weiskopf RB, Feiner J, Hopf HW, et al. Oxygen reverses deficits of cognitive function and memory and increased heart rate induced by acute severe isovolemic anemia. *Anesthesiology* 2002;96(4):871-7.
118. Suttner S, Piper SN, Kumble B, et al. The influence of allogenic red blood cell transfusion compared with 100% oxygen ventilation on systemic oxygen transport and skeletal muscle oxygen tension after cardiac surgery. *Anesth Analg* 2004;40:457-60.
119. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993;269(23):3024-9.
120. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340(6):409-17.
121. McIntyre L, Hebert PC, Wells G, et al. Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? *J Trauma* 2004;57(3):563-8.
122. Hebert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001;29(2):227-34.
123. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004;292(13):1555-62.
124. Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;345(17):1230-6.
125. Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies (Approved by the House of Delegates on October 22, 1995 and last amended on October 25, 2005) *An Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies*. <http://www.asahq.org/publicationsAndServices/BCTGuidesFinal.pdf>. Accessed June 2007.
126. Gervin AS, Fischer RP. Resuscitation of trauma patient with type-specific uncrossmatched blood. *J Trauma* 1984;24:327-31.
127. Murray OJ, Pennell BJ, Weinstein SL, Olson JD. Packed red cells in acute blood loss: dilutional coagulopathy as a cause of surgical bleeding. *Anesth Analg* 1995;80:336-42.

128. Murray OJ, Olson JD, Strauss R, Tinker JH. Coagulation changes during packed red cell replacement of major blood loss. *Anesthesiology* 1988;69:839.
129. Leslie SD, Toy PT. Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. *Am J Clin Pathol* 1991;96:770-3.
130. Soher PR, Scott RL. Massive transfusion. *Clin Lab Med* 1982;2:21-34.
131. Haan J, Scalea T. A Jehovah's Witness with complex abdominal trauma and coagulopathy: use of factor VII and a review of the literature. *Am Surg* 2005;71(5):414-5.
132. Klitgaard T, Tabanera y Palacios R, Boffard KD, et al. NovoSeven Trauma Study Group. Pharmacokinetics of recombinant activated factor VII in trauma patients with severe bleeding. *Crit Care* 2006;10(4):R104.
133. Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 1879;354(9193):1999-27.
134. Boffard KD, Riou B, Warren B, et al. NovoSeven Trauma Study Group. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma* 2005;59(1):8-15.
135. Rizoli SB, Boffard KD, Riou B, et al. NovoSeven Trauma Study Group. Recombinant activated factor VII as an adjunctive therapy for bleeding control in severe trauma patients with coagulopathy: subgroup analysis from two randomized trials. *Crit Care* 2006;10(6):R178.
136. Stein DM, Dutton RP, O'Connor J, Alexander M, Scalea TM. Determinants of futility of administration of recombinant factor VIIa in trauma. *J Trauma* 2005;59(3):609-15.
137. Dutton RP, McCunn M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2004;57(4):709-19.
138. Thomas GO, Dutton RP, Hemlock B, et al. Thromboembolic complications associated with factor VIIa administration. *J Trauma* 2007;62(3):564-9.
139. Mayer SA, Brun NC, Begtrup K, et al. Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005;352(8):777-85.
140. Malone DL, Hess JR, Fingerhut A. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *J Trauma* 2006;60(6 Suppl):S91-6.
141. Forestner JE. Massive transfusion protocols in trauma care. In: Smith CE, ed. *Trauma Anesthesia: Basic and Clinical Aspects*. In press, 2008.
142. Hirshberg A, Dugas M, Banez EI, et al. Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation. *J Trauma* 2003;54:454-63.
143. Armand R, Hess JR. Treating coagulopathy in trauma patients. *Transfus Med Rev* 2003;17:223-31.
144. MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. *J Trauma* 2003;55(1):39-44.
145. Gonzalez EA, Moore FA, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma* 2007;62(1):112-9.
146. Maegele M, Lefering R, Yucel N, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. *Injury* 2007;38(3):298-304.
147. Brohi K, Cohen MJ, Ganter MT, et al. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg* 2007;245(5):812-8.
148. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma* 2006;60:S3-11.
149. Kauvar DS, Holcomb JB, Norris GC, Hess JR. Fresh whole blood transfusion: a controversial military practice. *J Trauma* 2006;61(1):181-4.
150. Repine TB, Perkins JG, Kauvar DS, Blackborne L. The use of fresh whole blood in massive transfusion. *J Trauma* 2006;60(6 Suppl):S59-69.
151. Malone DL, Dunne J, Tracy JK, et al. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma* 2003;54(5):898-907.
152. Mostafa G, Gunter OL, Norton HJ, et al. Age, blood transfusion, and survival after trauma. *Am Surg* 2004;70(4):357-63.
153. Opelz G, Vanrenterghem Y, Kirste G, et al. Prospective evaluation of pretransplant blood transfusions in cadaver kidney recipients. *Transplantation* 1997;63(7):964-7.
154. Tartter PI, Steinberg B, Barron DM, Martinelli G. Transfusion history, T cell subsets and natural killer cytotoxicity in patients with colorectal cancer. *Vox Sang* 1989;56(2):80-4.
155. Jensen LS, Andersen AJ, Christiansen PM, et al. Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. *Br J Surg* 1992;79(6):513-6.
156. Weber EW, Slappendel R, Prins MH, et al. Perioperative blood transfusions and delayed wound healing after hip replacement surgery: effects on duration of hospitalization. *Anesth Analg* 2005;100(5):1416-21.
157. Ohwada S, Sato Y, Sato N, et al. Effects of transfusion on gastrointestinal anastomotic wound healing and leukocyte function in rats. *Eur Surg Res* 2000;32(6):353-8.
158. Ciesla DJ, Moore EE, Johnson JL, et al. Multiple organ dysfunction during resuscitation is not postinjury multiple organ failure. *Arch Surg* 2004;139(6):590-4.
159. Zallen G, Offner PJ, Moore EE, et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. *Am J Surg* 1999;178(6):570-2.
160. Gould S, Cimino MJ, Gerber DR. Packed red blood cell transfusion in the intensive care unit: limitations and consequences. *Am J Crit Care* 2007;16(1):39-48.
161. Utter GH, Nathens AB, Lee TH, et al. Leukoreduction of blood transfusions does not diminish transfusion-associated microchimerism in trauma patients. *Transfusion* 2006;46(11):1863-9.
162. Jensen LS, Hokland M, Nielsen HJ. A randomized controlled study of the effect of bedside leukocyte depletion on the immunosuppressive effect of whole blood transfusion in patients undergoing elective colorectal surgery. *Br J Surg* 1996;83(7):973-7.
163. Hebert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA* 2003;289(15):1941-9.
164. Taylor RW, O'Brien J, Trotter SJ, et al. Red blood cell transfusions and nosocomial infections in critically ill patients. *Crit Care Med* 2006;34(9):2302-8.
165. Blumberg N, Fine L, Gettings KF, Heal JM. Decreased sepsis related to indwelling venous access devices coincident with implementation of universal leukoreduction of blood transfusions. *Transfusion* 2005;45(10):1632-9.
166. Swanson K, Dwyre DM, Krochmal J, Raife TJ. Transfusion-related acute lung injury (TRALI): current clinical and pathophysiologic considerations. *Lung* 2006;184(3):177-85.
167. Bux J, Sachs UJ. The pathogenesis of transfusion-related acute lung injury (TRALI). *Br J Haematol* 2007;136(6):788-99.
168. Sessler DI. Perioperative thermoregulation and heat balance in humans. *FASEB J* 1993;7:638-44.
169. Smith CE, Patel N. Hypothermia in adult trauma patients: anesthetic considerations. Part I: Etiology and pathophysiology. *Am J Anesthesiol* 1996;23:283-90.
170. Smith CE, Patel N. Hypothermia in adult trauma patients: anesthetic considerations. Part II: prevention and treatment. *Am J Anesthesiol* 1997;24:29-36.
171. Reed RL 2nd, Johnston TO, Hudson D, Fischer RP. The disparity between hypothermic coagulopathy and clotting studies. *J Trauma* 1992;33:465-70.
172. Reed RL 2nd, Bracey AW Jr, Hudson JO, et al. Hypothermia and blood coagulation: dissociation between enzyme activity and clotting factor levels. *Circ Shock* 1990;32:141-52.
173. Valeri CR, MacGregor H, Cassidy G, et al. Effects of temperature on bleeding time and dotting time in normal male and female volunteers. *Crit Care Med* 1995;23:698-704.
174. Jurkovich GJ, Greiser WB, Luteran A, et al. Hypothermia in trauma victims: an ominous predictor of survival. *J Trauma* 1987;27:1019-24.
175. Novikov M, Avula R, Smith CE, Jernigan JR. Does hypothermia predict mortality in trauma patients? A hypothesis revisited. Poster presented at: TraumaCare 2007, the International Trauma Anesthesia and Critical Care Society (ITACCS) Annual Scientific Meeting; May 14-16, 2007; Las Vegas, Nevada.
176. Gentilello LM, Moujaes S. Treatment of hypothermia in trauma victims: thermodynamic considerations. *J Intensive Care Med* 1995;10:5-14.
177. Mendlowitz M. The specific heat of human blood. *Science* 1948;107:97.
178. Patel N, Knapke D, Smith CE, et al. Simulated clinical evaluation of conventional and newer fluid warming devices. *Anesth Analg* 1996;82:517-24.
179. Kahn RC, Jaseo HD, Carlon GC, et al. Massive blood replacement: correlation of ionized calcium, citrate, and hydrogen ion concentration. *Anesth Analg* 1979;58:274-8.
180. Insalaco SJ. Massive transfusion. *Lab ME* 1984;15:325.
181. Arrington P, McNamara JJ. Mechanism of microaggregate formation in stored blood. *Ann Surg* 1974;179:146-8.
182. Marcucci C, Madjdpour C, Spahn DR. Allogeneic blood transfusions: benefit, risks and clinical indications in countries with a low or high human development index. *Br Med Bull* 2004;70:15-28.
183. Scalea TM, Hartnett RW, Duncan AO, et al. Central venous oxygen saturation: a useful clinical tool in trauma patients. *J Trauma* 1990;30:1539-43.
184. Patel N, Smith CE, Pinchak AC. Clinical comparison of blood warmer performance during simulated clinical conditions. *Can J Anaesth* 1995;42:636-42.