CHEST Postgraduate Education Corner
CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Complications of Massive Transfusion

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Massive transfusion (MT) is a lifesaving treatment of hemorrhagic shock, but can be associated with significant complications. The lethal triad of acidosis, hypothermia, and coagulopathy associated with MT is associated with a high mortality rate. Other complications include hypothermia, acid/base derangements, electrolyte abnormalities (hypocalcemia, hypomagnesemia, hypokalemia, hyperkalemia), citrate toxicity, and transfusion-associated acute lung injury. Blood transfusion in trauma, surgery, and critical care has been identified as an independent predictor of multiple organ failure, systemic inflammatory response syndrome, increased infection, and increased mortality in multiple studies. Once definitive control of hemorrhage has been established, a restrictive approach to blood transfusion should be implemented to minimize further complications.

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Abbreviations: ALI = acute lung injury; FFP = fresh frozen plasma; GCS = Glasgow Coma Scale; ISS = injury severity score; LOS = length of stay; MOF = multiple organ failure; MT = massive transfusion; OR = odds ratio; PRBC = packed red blood cell; SIRS = systemic inflammatory response syndrome; TACO = transfusion-associated circulatory overload; TA-MC = transfusion-associated microchimerism; TRALI = transfusion-related acute lung injury; TRIM = transfusion-related immunomodulation

Massive transfusion (MT) is a lifesaving treatment of hemorrhagic shock but can be associated with numerous and significant complications. We review possible complications and their management, particularly as they pertain to MT in the trauma patient.

Complications of MT

There are numerous problems associated with MT, including infectious, immunologic, and physiologic complications related to the collection, testing, preservation, and storage of blood products (Table 1). Clinicians must be fully aware of these complications and strategies to both prevent and treat them. The cumulative risks of blood transfusion have been related to the number of units of packed red blood cells (PRBCs) transfused, increased storage time of transfused blood, and possibly donor leukocytes. A number of potential mechanisms that may mediate adverse affects associated with blood transfusion in trauma have been proposed.[1-3] These data have led some to conclude that blood transfusion should be minimized whenever possible.[4]

Lethal Triad of Acidosis, Hypothermia, and Coagulopathy

Uncontrolled hemorrhage may ultimately result in the development of hypothermia, coagulopathy, and acidosis.[5] Each of these life-threatening abnormalities exacerbates the others, contributing to a spiraling cycle, sometimes called the "bloody vicious cycle," that rapidly results in death unless hemorrhage is stopped and the abnormalities reversed.[6-8] A number of strategies, including early definitive control of hemorrhage, improved blood resuscitation, and more aggressive treatment of coagulopathy and hemostatic defects, have all been implemented in attempts to improve survival with MT.

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Table 1—*Complications Associated With Massive Blood Transfusion*

Acute
Acute hemolytic transfusion reactions
Febrile nonhemolytic transfusion reactions
TRALI
TACO
Allergic reactions
Bacterial sepsis
Hypocalcemia
Hypokalemia, hyperkalemia
Acidosis
Hypothermia
Dilutional coagulopathy
Dilutional thrombocytopenia
Delayed
Delayed hemolytic transfusion reactions
TRIM
Microchimerism
Transfusion-transmitted diseases
Posttransfusion graft-vs-host disease
Posttransfusion purpura

TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury; TRIM = transfusion-related immunomodulation.

Hypothermia and MT

Hypothermia occurs frequently in patients with hemorrhagic shock requiring MT. In trauma patients there are multiple factors that contribute to hypothermia, including exposure, infusion of cold fluids and blood products, opening of body cavities, decreased heat production, and impaired thermoregulatory control. Infusion of unwarmed or inadequately warmed IV fluids and cold blood products is a well-known cause of hypothermia and may contribute to the multiple adverse consequences of hypothermia, such as peripheral vasoconstriction, metabolic acidosis, coagulopathy, infection, and cardiac and other morbidities. Blood products are normally stored between 1°C and 6°C, and rapid transfusion of large quantities will lead to hypothermia. Hypothermia is associated with a number of serious complications including, but not limited to:

1. Decreased citrate metabolism
2. Decreased hepatic metabolism
3. Decreased drug clearance
4. Decreased synthesis of acute phase proteins
5. Decreased production of clotting factors

Hypothermia has a significant effect on the coagulation cascade. There is a 10% reduction in coagulation factor activity for each 1°C drop in temperature,[9] which prolongs clotting times at temperatures below 33°C.[10] Hypothermia results in a decreased ability to form stable clots, which is critically important in trauma patients with hemorrhage. However, clinicians may underestimate the effect of hypothermia on coagulation factor activity *in vivo* because prothrombin time and activated partial thromboplastin time assays are performed at 37°C.[11,12] Hypothermia can be avoided in patients requiring MT by:

- Elevating the room temperature
- Surface warming the patient with heating blankets, heating lamps
- Using heated and humidified inspired gases for ventilators
- Using blood and fluid warmers for all fluids administered[13]

Coagulopathy and Thrombocytopenia Associated With MT

A number of hemostatic abnormalities develop in patients requiring massive PRBC transfusion, including dilutional and consumptive coagulopathy and thrombocytopenia.[14] Impaired hemostasis in these patients is often caused by a combination of dilution and consumption of clotting factors and hyperfibrinolysis. Coagulation defects are related to the total volume of blood transfused, preexisting hemostatic abnormalities, and therapeutic maneuvers for cessation of hemorrhage. A number of screening tests have been used to examine the coagulation and hemostasis defects seen with MT, including prothrombin time/partial thromboplastin time, thrombin time, platelet count, fibrinogen, and serum haptoglobin to determine evidence of hemolysis.

We know that 25% to 30% of severely injured patients are coagulopathic upon arrival in the ED.[15,16] Early coagulopathy is associated with increased mortality in trauma.[17,18] A landmark study[19] confirmed that 75% of patients who had received 20 or more RBC-containing products of any kind (PRBCs, cell-saver units, or whole blood) had dilutional thrombocytopenia with platelet counts less than 50×10^9/L compared with no patients who had received less than 20 units of blood ($P < .001$). After transfusion of 12 units of relatively plasma-free red cell products (PRBCs or cell-saver units), 100% of patients had prothrombin time prolonged by more than 1.5 times normal, compared with only 36% in patients given less than 12 units ($P = .012$). Although prothrombin time is a poor indicator of bleeding propensity and coagulation factor deficiency, these data confirmed that MT patients receiving RBCs alone developed significant thrombocytopenia and coagulopathy and required coagulation factor and platelet replacement.

It is clearly recognized that the labile clotting factors V and VIII deteriorate with blood storage time. Furthermore, MT with PRBCs alone causes a dilutional coagulopathy, whereas massive hemorrhage causes a consumptive coagulopathy. Underlying hemostatic

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disorders also contribute to coagulation abnormalities, including liver disease, warfarin and antiplatelet drug use, and disseminated intravascular coagulation, which often occurs in trauma patients either due to tissue crush injury or a septic focus.

The ability of transfusion to maintain normal concentrations of RBCs, platelets, and coagulation factors disappears as bleeding progresses.[20] This occurs because the standard process of making components (separate units of PRBCs, platelets, and fresh frozen plasma [FFP]) out of whole blood results in a loss of platelets and dilution of all components with preservative. Therefore, recombining the components (1 unit each of PRBCs, platelets, and FFP) does not result in a product equivalent to whole blood. The mean hematocrit of a mixture of 1 unit PRBCs, 1 unit platelets, and 1 unit of plasma is 29% (200 mL of PRBCs in 680 mL), whereas the mean platelet count is about 85,000/μL (5.5×10^{10} platelets in 680 mL), and the mean coagulation factor activity is 62% of normal (300 mL of plasma in 480 mL of acellular fluid). Nonviable cells, blood cell and plasma losses in making leukoreduced products, ongoing blood loss, clotting factor and platelet consumption, and other isotonic crystalloid fluid administration only worsen the situation regarding dilutional coagulopathy and thrombocytopenia.

Hemodilution is inevitable when giving specific blood component therapy, even in the commonly used 1:1:1 ratio of PRBC:plasma:platelets. Table 2 compares whole blood (500 mL) with component therapy with PRBCs, platelets, and FFP (660 mL), documenting significantly reduced hemoglobin concentration and decreased platelet count and coagulation activity compared with whole blood.

Thus, massive bleeding is potentiated by hemotherapy-induced hemodilution and coagulopathy. This is part of the reason that the number (increasing hemodilution) and age (increasing numbers of nonviable cells) of PRBC units transfused correlates with mortality.[21] It is also why better methods for hemorrhage control are viewed as so important for further reductions in mortality for trauma patients. Management of coagulopathy after MT is largely driven by expert opinion. A recent international survey of clinical practice in the management of coagulopathy in trauma identified significant regional as well as institutional variability and very few MT protocols specifically addressed the issue of early treatment of coagulopathy.[22]

Early Coagulopathy of Trauma and Mechanisms

In the past, coagulopathy associated with trauma was viewed largely as a dilutional event.[23] Today, post-

Table 2—*Whole Blood Composition Compared With Component Therapy*

Whole Blood (500 mL)	Component Therapy (660 mL)
Hematocrit 38%-50%	1 unit PRBC = 335 mL with hematocrit 55%
Platelets 150-400 K/μL	1 unit platelets = 50 mL with 5.5×10^{10} platelets
Plasma coagulation factors = 100%	1 unit plasma = 275 mL with 80% of the coagulation activity compared with whole blood

Thus, 1 unit PRBCs + 1 unit platelets + 1 unit FFP = 660 mL with hematocrit 29%, platelets 88 K/μL, and coagulation activity 65% compared with whole blood. PRBC = packed red blood cells.

traumatic coagulopathy appears to be the sum of the effects of injury severity, blood loss, factor depletion, fibrinolysis, hypothermia, hypocalcemia, acidosis, and the patient's individual biologic response to both traumatic injury and treatment.[24-26] The early identification and management of coagulopathy may help to better control hemorrhage and may represent a key step in reducing mortality associated with traumatic injury.[27]

Recent evidence suggests that an acute endogenous coagulopathy (before clotting factor depletion) is present shortly after injury (Fig 1).[25,28] This acute coagulopathy of trauma is associated with systemic hypoperfusion and is characterized by anticoagulation and hyperfibrinolysis.[29] It has recently been identified that early traumatic coagulopathy occurs only in the presence of tissue hypoperfusion and appears to occur without significant consumption of coagulation factors. Alterations in the thrombomodulin-protein C pathway are consistent with activated protein C activation and systemic anticoagulation.

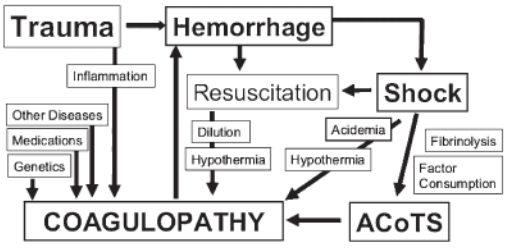

Figure 1. A diagram showing some of the mechanisms leading to coagulopathy in the injured. Trauma can lead to hemorrhage, which can lead to resuscitation, which in turn leads to dilution and hypothermia causing coagulopathy and further hemorrhage. This is classic dilutional coagulopathy. Hemorrhage can also cause shock, which causes acidosis and hypothermia, which in turn lead to coagulopathy, the fatal triad. Trauma and shock can also cause the ACoTS associated with factor consumption and fibrinolysis. Coagulopathy is further associated with trauma-induced inflammation and modified by genetics, medications, and acquired diseases. ACoTS = acute coagulopathy of trauma-shock. (Reprinted with permission from Hess et al.[28])

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Admission plasma thrombomodulin and protein C levels are predictive of clinical outcomes following major trauma.[25,30]

This new information has important implications, since currently the management of traumatic coagulopathy is almost entirely directed at augmenting thrombin generation with blood component therapy or recombinant factor VIIa. However, if the primary derangement in early coagulopathy is related to hypoperfusion resulting in anticoagulation from activation of the thrombomodulin-protein C pathway, augmentation of thrombin generation in the presence of hyperperfusion may cause further activation of anticoagulant and fibrinolytic pathways. Subsequently, once protein C is exhausted, increasing thrombin generation further may result in clot formation in hypoperfused tissues, microvascular thrombosis, and subsequent organ dysfunction and failure.

Electrolyte Abnormalities

Hypokalemia, Hyperkalemia

The potassium concentration of plasma increases in stored blood. Potassium concentrations in PRBCs can range from 7 to 77 mEq/L with higher concentrations seen with increased duration of PRBC storage.[31] This is in part due to red blood cell membrane ATPase pump inactivation. Potassium concentrations of units of PRBCs are increased by irradiation and reduced by washing. After infusion of stored blood, the ATPase pump is restored, and red cells begin active metabolism and intracellular potassium uptake.

Clinical problems associated with hyperkalemia due to MT are less common in adults than in children and neonates. Interestingly, 38.5% of transfused trauma (noncrush) patients had a serum potassium >5.5 mEq/L with maximum 7.7 mEq/L compared with 2.9% of nontransfused patients. Transfusion of >7 units PRBCs was independently associated with hyperkalemia. No clinical sequelae of hyperkalemia were reported.[32] Another study documented that the prevalence of hyperkalemia 12 h after ICU admission for trauma was 29% and was independently associated with a serum potassium >4.0 mEq/L in the ED and with blood transfusion.[33]

Hyperkalemia is usually associated with patients who have underlying renal insufficiency or renal failure or severe tissue injury, including rhabdomyolysis and myonecrosis. When rates of blood transfusion exceed 100 to 150 mL/min, transient hyperkalemia is much more common. Rapid transfusion through a central venous catheter has been associated with hyperkalemic cardiac arrest in vulnerable populations, including critically ill adults.[31] Hypokalemia has been seen with MT in more than 50% of patients in two studies of surgical patients.[34,35] Additionally, hypokalemia was seen in 72% of pediatric liver transplant patients and was associated with large-volume FFP administration and normal renal function.[36] However, the phenomenon has not been studied in the trauma population. Hypokalemia occurs secondary to multiple mechanisms:

- Restoration of red cell membrane ATPase pump thus allowing potassium to re-enter the red cells[37]
- Release of aldosterone, antidiuretic hormone, catecholamines
- Metabolic alkalosis (resulting from citrate administration, lowers serum potassium)
- Co-infusion of potassium-poor solutions, including crystalloid, platelets, and FFP

Plasma potassium concentrations should be carefully monitored in patients who require MT.

Hypocalcemia, Hypomagnesemia

Stored blood is anticoagulated with citrate, which binds calcium. Each unit of PRBCs contains approximately 3 g of citrate. The healthy adult liver metabolizes 3 g of citrate every 5 min.[38] Transfusion rates higher than 1 unit every 5 min or impaired hepatic function, such as from hypothermia or preexisting liver disease,[39] may lead to hypocalcemia related to citrate toxicity, with citrate concentrations 40 to 140 times normal.[40] It is therefore critically important to frequently monitor arterial blood ionized calcium concentrations and keep them in the normal range. Total serum calcium concentrations are not useful in patients requiring MT due to the hemodilution that occurs with massive resuscitation.

Signs of citrate toxicity include tetany, prolonged QT interval, decreased myocardial contractility, hypotension, narrow pulse pressure, elevated end-diastolic left ventricular pressures, and elevated central venous pressures.[41] These patients may develop severe hypocalcemia resulting in clinical signs, such as:

- Prolonged QT intervals on electrocardiogram
- Circulatory depression due to decreased ventricular contractility
- Hypotension due to decreased peripheral vascular resistance
- Muscle tremors
- Pulseless electrical activity, ventricular fibrillation may ensue

Intravenous calcium administration is the appropriate treatment of clinical signs and symptoms of hypocalcemia or documented ionized hypocalcemia.

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Table 3—*Elemental Calcium Concentrations in Calcium Chloride and Calcium Gluconate*

Solution	Elemental Calcium	Unit Volume	Total Elemental Calcium	Osmolarity
10% Calcium chloride	27 mg (1.36 mEq)/mL	10 mL Ampule	270 mg/ 10 mL	2000 mOsm/L
10% Calcium gluconate	9 mg (0.46 mEq)/mL	10 mL Ampule	90 mg/ 10 mL	680 mOsm/L
10% Calcium chloride continuous infusion	2.45 mg/mL	5 Amps/500 mL NS	1,350 mg/ 550 mL	200 mOsm/L
10% Calcium gluconate continuous infusion	0.82 mg/mL	5 Amps/500 mL NS	450 mg/ 550 mL	200 mOsm/L

Amps = ampules; NS = normal saline. (Adapted with permission from Stratta et al.[42])

It is important to recognize the differences in elemental calcium that calcium chloride and calcium gluconate provide (Table 3).[42] As elemental calcium is replaced intravenously, it is important to continue to monitor serial arterial ionized calcium concentrations.

Prolonged QT interval during MT may also be related to hypomagnesemia, and therefore both blood calcium and magnesium concentrations must be monitored during MT. Low levels of magnesium during MT can be due to the infusion of large volumes of magnesium-poor fluids as well as the binding of magnesium to citrate.[43]

Acidosis and Alkalosis

The storage of blood in citrate phosphate dextrose adenine solution leads to a pH of 7.0 of most fresh PRBC units. Blood pH decreases to 6.6 to 6.8 with storage for 21 to 35 days, in part related to an increased CO_2 concentration.[44] As citrate is metabolized to bicarbonate, it is common that patients who require MT frequently develop a metabolic alkalosis. Therefore the presence of a metabolic acidosis in patients who require MT is an indicator of tissue hypoperfusion and is not related to blood product administration. Aggressive resuscitative measures should be continued in these patients. The reversal of acidosis with alkalinizing agents (sodium bicarbonate, tromethamine) in these patients should be used as a temporizing measure in patients with severe metabolic acidosis and hemodynamic instability or with renal dysfunction or renal failure, and therefore an inability to compensate for the metabolic acidosis. Restoration of adequate tissue perfusion is paramount to reverse any underlying lactic acidosis.

Acidosis, however, may exacerbate coagulopathy. Clotting factors are enzymes whose activity is impaired by acidemia; for example, a decrease of pH from 7.4 to 7.0 reduces the activity of factor VIIa by more than 90%, factor VIIa/tissue factor complex by 55%, and the factor Xa/factor Va (prothrombinase) complex by 70%.[45] Thrombin generation, the primary engine of hemostasis, is thus profoundly inhibited by acidosis.[46] The effect of acidosis on coagulation has been measured by thromboelastography, which reveals progressive impairments up to 168% of control levels in the rate of clot formation and polymerization with a decrease in pH from 7.4 to 6.8.[47]

A notable impairment of hemostasis arises with severe metabolic acidosis. Thus, in cases of severe hemorrhage, buffering toward physiologic pH values (arterial pH $\geq$7.2) is recommended, especially with massive transfusion of older RBCs displaying exhausted RBC buffer systems.[5] Patients with liver failure who require massive transfusion may manifest a metabolic acidosis that is more severe and difficult to treat as they do not metabolize lactate, nor do they convert the citrate in blood products to bicarbonate. The impaired liver may also produce lactate, thus compounding the problem.[48]

Blood Transfusion and Postinjury Multiple Organ Failure

Blood transfusion was first identified as an independent risk factor for multiple organ failure (MOF) in a 3-year single-institution study (n = 394) aimed at finding a predictive model for postinjury MOF.[49] Trauma patients (n = 394) with an injury severity score (ISS) > 15 and survival > 24 h were examined. The following variables were identified as early independent predictors of MOF: age > 55 years, ISS $\geq$ 25, and > 6 units PRBCs in the first 12 h postinjury. Additionally, a base deficit > 8 mEq/L (0-12 h) and lactate > 2.5 mmol/L (12-24 h) were independent predictors of MOF.

A subsequent prospective study by this group confirmed that blood transfusion was an independent risk factor of postinjury MOF (513 trauma patients with ISS > 15 admitted to the ICU who survived > 48 h), controlling for other indices of shock, including base deficit and lactate.[50] A dose-response relationship between early blood transfusion and postinjury MOF was identified and blood transfusion was confirmed as an independent risk factor for MOF in multiple logistic regression analysis.

Blood Transfusion and Systemic Inflammatory Response Syndrome

Blood transfusion in trauma was associated with an increased incidence of systemic inflammatory response syndrome (SIRS) (defined as SIRS score $\geq$ 2[51]) in a

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single-institution study (n = 7,602).[52] Blood transfusion and increased total volume of blood transfusion were associated with SIRS, ICU admission, and mortality in trauma patients by multinomial logistic regression analysis, after stratification for ISS, Glasgow Coma Scale (GCS) score, and age. Transfused trauma patients had a twofold to nearly sixfold increase in SIRS and more than a fourfold increase in ICU admission (odds ratio [OR], 4.62; 95% CI, 3.84-5.55) and mortality (OR, 4.23; 95% CI, 3.07-5.84) compared with nontransfused patients. Transfused patients had significantly longer hospital length of stay (LOS) (16.8 vs 9.9 days) and ICU LOS (14.5 vs 2.5 days) compared with nontransfused patients.

Another prospective observational study confirmed by logistic regression analysis that transfusion of >4 units blood was an independent risk factor for SIRS in critically injured patients and recommended strategies to limit blood transfusions in this population.[53] A consequence of posttraumatic SIRS is the induction of posttraumatic anemia.[54] Trauma-induced hyperinflammation causes impaired bone marrow function by means of blunted erythropoietin response and impaired erythropoiesis, reduced iron availability, suppression and egress of erythroid progenitor cells, and reduced RBC survival. Thus, a worsening of SIRS by a "second hit" through blood transfusion should be avoided if possible.[55]

Blood Transfusion and Mortality

Blood transfusion within the first 24 h postinjury has been associated with increased mortality. One large study examined 15,534 patients over 3 years and controlled for all potential confounding shock variables (including base deficit, serum lactate, and shock index [heart rate/systolic blood pressure]) on admission, as well as stratification by age, gender, race, GCS, and ISS.[56] Blood transfusion was a strong independent predictor of mortality (OR, 2.83; 95% CI, 1.82-4.40; $P < .001$), ICU admission (OR, 3.27; 95% CI, 2.69-3.99; $P < .001$), ICU LOS ($P < .001$), and hospital LOS ($P < .001$) when stratified by indices of shock (base deficit, serum lactate, shock index, and anemia). Admission anemia (hematocrit <36%) was an independent predictor of ICU admission ($P = .008$), ICU LOS ($P = 012$), and hospital LOS ($P < .001$). A subsequent study by this group confirmed the trauma registry data with blood bank data and delineated that the association of blood transfusion and mortality was higher (OR, 4.13 vs OR, 3.10) when patients were transfused early (<24 h) after injury compared with >24 h postinjury.[57]

A retrospective 4-year single-institution review of all adults with blunt hepatic and/or splenic injuries admitted to a level I trauma center[58] documented that transfusion was an independent predictor of mortality in all patients (OR, 4.75; 95% CI, 1.37-16.4; $P = .014$) and in those managed nonoperatively (OR, 8.45; 95% CI, 1.95-36.53; $P = .0043$) after controlling for indices of shock and injury severity. The risk of death increased with each unit of PRBCs transfused (OR per unit, 1.16; 95% CI, 1.10-1.24). Transfusion-associated mortality risk was highest in the patients managed nonoperatively.

Another single-institution retrospective study examined the interaction between patient age, PRBC transfusion volume, and mortality after injury in a 6-year retrospective review of 1,312 patients who received PRBCs postinjury (1,028 [78%] ≤55 years of age and 284 [22%] >55 years of age).[59] Overall mortality was 21.2%. Age, ISS, GCS, and PRBC transfusion volume were independent predictors of mortality. Mean PRBC transfusion volume for elderly survivors (4.6 units) was significantly less than that of younger survivors (6.7 units). No patient older than 75 years with a PRBC transfusion volume >12 units survived. This study documented that age and PRBC transfusion volume were associated with increased mortality following injury. A 5-year single-institution study confirmed that low hemoglobin, abnormal prothrombin and partial thromboplastin time, and physiologic signs of shock (low systolic blood pressure and elevated base deficit) were independent predictors of mortality in trauma.[60] Currently, the only treatment available for hemorrhagic shock in trauma patients is the transfusion of stored red blood cells.

Blood transfusions were also associated with increased mortality in other critically ill patients in two large prospective multicenter studies quantifying the incidence of anemia and use of RBC transfusions in the ICU.[61,62] A recent systematic review of the efficacy of PRBC transfusion in the critically ill identified 45 observational studies comprising 272,596 patients. In 42 of the 45 studies, the risks of PRBC transfusion outweighed the benefits; the risk was neutral in two studies with the benefits outweighing the risks in a subgroup of a single study (elderly patients with an acute myocardial infarction and a hematocrit <30%). These authors concluded that the risks and benefits of PRBC transfusion should be assessed in every patient before transfusion.[63]

Blood Transfusion and Infection

Immunosuppression is a consequence of allogeneic blood transfusion in humans.[64] The precise mechanisms underlying transfusion-related immunomodulation (TRIM) remain uncertain, but include transfusion-associated microchimerism (TA-MC), wherein small populations of donor allogeneic leukocytes from the blood donor engraft in the transfusion recipient and

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persist for years and decades.[65] There is engraftment of the donor's hematopoietic stem cells in transfusion-recipient patients who then develop microchimerism. TA-MC seems to be common (affecting approximately 10% of transfused injured patients), enduring (lasting years to decades), and pronounced (involving up to 5% of circulating leukocytes and multiple immunophenotypic lineages suggestive of hematopoietic engraftment). Further study of TA-MC may reveal important information regarding potential clinical consequences of TA-MC, as well as basic hematologic and immunologic processes. TRIM may manifest as a potentially increased risk of cancer recurrence after potentially curative surgery[66] as well as an increase in the frequency of postoperative bacterial infections.[67]

A metaanalysis examined the relationship of transfusion to postoperative bacterial infection.[68] Twenty peer-reviewed articles (n = 13,152 with 5,215 transfused patients) published from 1986 to 2000 were included, and a separate metaanalysis was performed for the subgroup of trauma patients. The common odds ratio for the risk of postoperative bacterial infection for transfused vs nontransfused patients was 3.45 (range, 1.43-15.15). The common odds ratio of the subgroup of trauma patients was 5.263 (range, 5.03-5.43), with all studies showing a value of $P < .05$. These results provide strong support that transfusion is associated with a significantly increased risk of postoperative bacterial infection in surgical patients, and that transfusion is associated with an even greater risk of infection in trauma patients.

A number of single-institution studies document that blood transfusions correlate with infections in trauma patients in a dose-dependent manner.[69-71] In a prospective study of 1,172 trauma patients admitted to the ICU over a 2-year period, blood product transfusion was associated with a significantly greater infection rate (34 vs 9%; $P < .001$) and mortality (19 vs 8.3%; $P < .001$). Multivariate analysis (risk-adjusted for severity of injury by ISS, age, sex, and race and stratified by blood product type) confirmed that risk of infection increased by 5% for each unit of PRBCs transfused. This study concluded that there is a dose-dependent correlation between blood product transfusion and adverse outcome (increased mortality and infection) in trauma patients.[72] Similarly, studies in critically ill patients have documented increased rates of nosocomial infection in transfused patients compared with nontransfused patients, after stratification of severity of illness and age.[73-75]

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is defined as acute lung injury (ALI) that occurs within 6 h of transfusion and is clearly not related to other risk factors for ALI or ARDS.[76,77] ALI and ARDS were defined by the North American-European Consensus Conference in 1994 as acute hypoxemia ($PaO_2/FIO_2 \leq 300$ mm Hg for ALI or < 200 for ARDS or saturations $\leq 90\%$ on room air), bilateral pulmonary infiltrates on chest radiograph, and no evidence of left atrial hypertension.[78]

Recently Marik and Corwin have proposed expanding the definition to include the syndrome of delayed TRALI, which occurs 6 to 72 h after transfusion. These patients often have additional risk factors for ALI/ARDS, such as sepsis, trauma, or burns.[79] The risk of TRALI varies by the type of blood product used and ranges from 1 case per 5,000 units PRBCs to 1 per 2,000 units FFP to 1 per 400 units platelets.[80-82] However, a more recent study in a medical ICU population found that 8% of transfused patients developed TRALI and that the risk was increased almost threefold for patients who got either FFP or platelets.[83] Another study by the same group showed that the odds ratio of acquiring TRALI was 1.39 for any PRBC transfusion, 2.48 for FFP transfusion, and 3.89 for platelet transfusion.[84]

The lungs of a critically ill patient are exquisitely sensitive to the effects of transfusion, such that even small amounts of blood products can result in lung injury.[85] PRBC transfusion after the development of ALI/ARDS was associated with increased mortality risk.[86] Multiple PRBC transfusions have long been considered a risk factor for ALI and ARDS.[87,88] Blood transfusion has been associated with an increased development of and increased mortality in ARDS.[89-96] These findings further support restrictive transfusion practices after hemorrhage is controlled. Treatment is largely supportive with the use of lung-protective strategies for mechanically ventilated patients as well as minimizing fluid administration when possible to reduce the amount of fluid crossing the damaged pulmonary endothelium and epithelium.

TRALI can be difficult to distinguish from transfusion-associated circulatory overload (TACO). TRALI is a phenomenon of increased permeability, whereas TACO is hydrostatic pulmonary edema—a pressure phenomenon. Differentiating the two can be difficult, although measures of diastolic dysfunction or cardiac stretch (such as B-type natriuretic peptide) may be helpful.[97]

Potential Mechanisms for Transfusion-Associated Adverse Outcome

A number of potential mechanisms have been delineated regarding adverse effects of blood transfusion, including increased storage time of blood,[98-106] decreased RBC deformability resulting in reduced

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microcirculatory perfusion,[107-111] increased inflammatory response, immunosuppression and microchimerism, and increased free hemoglobin with nitric oxide binding.

Bioreactive substances, including cytokines and lipids, accumulate during storage of RBCs, but their clinical importance is uncertain. However, a study comparing PRBCs with polymerized human hemoglobin showed lower levels of markers of inflammation with the polymerized hemoglobin, showing that transfusions can induce a profound inflammatory reaction.[112] RBC transfusion has been shown to result in neutrophil priming and activation.[113,114] This effect increases with duration of PRBC storage and is diminished by washing.[114-116]

Free hemoglobin (related to hemolysis) and polymorphonuclear leukocyte elastase concentrations also increase with longer blood storage time.[117] Increasing concentrations of elastase may lead to further increased RBC hemolysis. Histamine, eosinophil cationic protein, eosinophilic protein X, and myeloperoxidase concentrations increase threefold to 35-fold in the supernatant fluid of RBC components between days 0 and 35 of storage, and may affect the integrity of the red cell membrane.[118] Trauma patients who sustained significant injury and received massive blood transfusion have evidence of hemolysis, with decreased serum haptoglobin concentration and positive urine hemoglobin in 84% of patients.[119] Furthermore, another study identified that after blood transfusion during surgery for trauma, serum haptoglobin concentration decreased with transfusion of 1,000 mL or more of whole blood.[120]

Free hemoglobin in units of stored RBCs can therefore bind nitric oxide and cause vasoconstriction.[121] It has further been identified that erythrocytes contain the majority of intravascular nitrite in whole blood.[122] Upon deoxygenation of erythrocytes, resident nitrite may be catalytically reduced to produce nitric oxide, putatively providing a mechanism for matching local blood flow to oxygen demand *in vivo*. This may, in part, explain the splanchnic vasoconstriction that occurs with transfusion of aged stored blood.

For TRALI there are two postulated mechanisms, which are likely not mutually exclusive. The first is that donor antibodies interact with recipient leukocytes via anti-HLA class 1, anti-HLA class 2, and antigranulocyte antibodies.[123] In testing of 308 units of a variety of blood products, 22% had antileukocyte antibodies.[124] These antibody interactions activate complement, leading to pulmonary sequestration and activation of neutrophils, endothelial cell damage, and capillary leak in the lungs.[125] These antibodies appear to be more prevalent in blood products from multiparous women. A retrospective study showed a significant reduction in Pa_{O_2}/F_{IO_2} ratio after FFP or platelet transfusion from female donors compared with similar transfusions from male donors.[126] In a randomized controlled crossover trial with 105 ICU patients lower oxygen saturations and higher recipient serum tumor necrosis factor-α levels were measured after transfusion of FFP from multiparous women than after transfusion of FFP from a nonimmunized donor.[127]

The second theory is a two-hit model where the pulmonary epithelium is activated, resulting in local sequestration of polymorphonuclear lymphocytes. Biologic response modifiers in the transfused blood component then activate these polymorphonuclear lymphocytes, resulting in endothelial damage, capillary leak, and the clinical manifestations of ALI.[128]

Table 4—*Strategies to Reduce the Complications Associated With Massive Transfusion*

Complication	Strategies to Reduce Risk
Hypothermia	Warm the room
	Surface warm the patient with heating blankets, heating lamps
	Heat and humidify inspired gases for ventilators
	Warm all IV fluids and blood products when administered
Coagulopathy and thrombocytopenia	Transfuse PRBC:FFP:platelets in 1:1:1 ratio
	Recombinant factor VIIa as indicated (see text)
Electrolyte abnormalities	Monitor potassium, calcium, and magnesium serum concentrations closely and correct as needed
Acid-base disorders	Sodium bicarbonate or tromethamine for severe metabolic acidosis with hemodynamic instability or renal failure
Multiple organ failure	Supportive care
SIRS	Supportive care, minimize transfusions once hemorrhage is controlled
Infection	Maintain high index of suspicion to allow for early diagnosis and appropriate treatment (antimicrobial therapy ± debridement)
TRALI	Minimize transfusions once hemorrhage is controlled
	Consider using PRBCs with a shorter storage time and FFP from men and or nulliparous women

FFP = fresh frozen plasma; SIRS = systemic inflammatory response syndrome. See Tables 1 and 2 for expansion of other abbreviations.

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This may explain the cases of TRALI in which there are no antibodies present. A minority of cases of TRALI (< 10%) are due to recipient antibodies to donor leukocytes.[129]

Preventive Strategies to Reduce Complications of Transfusion Therapy

It is critically important to be aware of all clinical strategies to reduce complications related to transfusion therapy (Table 4). Some of these strategies should be standardized in MT protocols, such as warming of all blood and blood products transfused. Other strategies, such as the prevention and treatment of coagulopathy and thrombocytopenia, will need to be modified depending on the patient population (surgery, trauma, medical), the cause of the hemorrhage, and the ability to obtain prompt hemorrhage control.

Transfusion After Hemorrhage Control

In light of the adverse effects of transfusions, once definitive control of hemorrhage has been established a restrictive approach to blood transfusion should be implemented.[130,131] A number of published transfusion guidelines advocate for a restrictive transfusion practice (transfuse for hemoglobin < 7 g/dL or hematocrit < 21%) once acute hemorrhage has been controlled and initial resuscitation has been completed and the patient is stable in the ICU with no evidence of ongoing bleeding.[132,133]

Conclusion

Massive transfusion is a necessary treatment of severe hemorrhagic shock. However, it remains fraught with complications, and clinicians need to be aware of its implications. Complications include hypothermia, coagulopathy, acid/base and electrolyte disturbances, increased risk of infection, SIRS, TRALI, and MOF. Some of these can be attenuated by careful attention during MT and by following hemostatic resuscitation principles. Once hemorrhage is controlled, a restrictive transfusion practice should be implemented to minimize further adverse effects of transfusion.

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[no notes on this page]