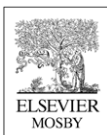Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

ADVANCES IN ANESTHESIA

Advances in Transfusion Medicine

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T ransfusion medicine has developed as a specialty by linking rapidly evolving knowledge in areas of physiology and immunology to the vastly expanded clinical requirements for blood products resulting from advances in medicine and surgery. This article covers major developments in transfusion medicine related to anesthesiology and surgery. It will familiarize the anesthesia practitioner with evolving concepts in basic science as they relate to innovations in clinical care in three areas: (1) red cell transfusion, (2) other blood components, and (3) recently introduced massive transfusion protocols.

RED BLOOD CELL TRANSFUSION

Blood component therapy is a limited resource that contributes to overall health care expense. In the United States, four million patients will receive 12 million units of packed red blood cells this year. The estimated hospital cost for a unit of autologous blood ranges from $250 to $750. Actual costs of transfusion therapy, alternatives to transfusion therapy, complications associated with transfusion therapy, and complications associated with anemia are unknown [1].

The Transfusion Requirement in Critical Care trial has shown that a conservative strategy of red blood cell transfusion (transfusion for a hemoglobin of less than 7 g/dL) is as effective, if not superior to, a liberal transfusion strategy (transfusion for a hemoglobin less than 9 g/dL) in normovolemic critically ill patients [2]. Following a conservative transfusion strategy, institutions may decrease costs by limiting perioperative erythrocyte transfusions and their complications [2]. Erythrocytes compose an estimated 25 trillion of the 100 trillion cells that are found in the human body [3]. The major function of the erythrocyte is to transport hemoglobin, which in turn carries oxygen from the lungs to the tissues. Along with oxygen transporting capacity, hemoglobin acts as an acid–base buffer. The buffering capacity of hemoglobin provides about 70% of the buffering capacity of whole blood. Red blood cells also remove carbon dioxide from the body by using carbonic anhydrase, an enzyme that catalyzes

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the reaction between carbonic acid and water. This reaction allows the red blood cell to transport carbon dioxide from the tissues to the lungs for elimination [4].

Each red blood cell contains 270 million hemoglobin molecules. Each molecule of hemoglobin carries four heme groups, and each heme group can bind with one molecule of oxygen. Four separate oxygen molecules bind to one molecule of hemoglobin, and each gram of hemoglobin carries 1.38 L of oxygen.

The formula for the oxygen delivery capacity of blood is: $DO_2 = CO * CaO_2$, where DO_2 is oxygen delivery; CO is cardiac output, and CaO_2 is the oxygen-carrying capacity of blood, and 10 changes volume % from O_2/dL to ml O_2/L.

Cardiac output (CO) is recognized as: $CO = HR * SV$, where HR is heart rate, and SV is stroke volume of the left ventricle.

CaO_2 is derived in the following way: $(1.38*hemoglobin* SaO_2) + (0.0031*PaO_2)$, where SaO_2 is the percent of hemoglobin saturated with oxygen in the arterial circuit; 0.0031 is the coefficient for oxygen solubility in blood. This equation illustrates PaO_2 as a minimal part of oxygen delivery at sea level unless the hemoglobin or arterial blood saturation is decreased severely [5]. The purpose of erythrocyte transfusion is to maintain or increase the oxygen carrying capacity of blood. There is almost no indication to transfuse a hemoglobin level greater than 10 g/dL but there is almost always an indication for hemoglobin less than 6 g/dL. Preoperative hematocrit and estimated blood volume can be used to predict transfusion requirements intraoperatively. One unit of packed red blood cells will increase the hematocrit by approximately 3% and the hemoglobin 1 g/dL in the average adult [6]. Estimated total blood volume is about 65 cc/kg of blood for women and 75 cc/kg of blood for men. The estimated total blood volume then is multiplied by the percent hematocrit ($\times$/100), which gives the estimated red blood cell volume.

The estimated red blood cell volume at a hematocrit of 30 (previously used as a hematocrit target for patients with cardiac disease) is the estimated total blood volume multiplied by 30/100. Subtracting the estimated blood volume at a hematocrit of 30 from the blood volume at the normal hematocrit gives the volume of blood the patient can lose to reach a hematocrit of 30 and gives a baseline at which to consider blood transfusion.

For example, a 70 kg man has 70 kg * 75 cc/kg of blood volume = 5250 cc of blood volume. If his hematocrit is 45, then 45% of his blood volume will be erythrocytes. His blood volume of 5250 cc multiplied by .45 will yield 2362.5 cc of erythrocytes. Using 30 as the previously targeted hemoglobin, his blood volume of 5250 *.30 will be 1575. Using these numbers, he will need to lose 2362.5 – 1575 = 787.5 cc before his hematocrit decreases to 30.

Red blood cell transfusions are indicated in symptomatic anemic patients to restore oxygen-carrying capacity and delivery. Blood viscosity is determined primarily by erythrocyte concentration. In anemia, blood viscosity can decrease severely, which, in turn, decreases the resistance to blood flow in peripheral blood vessels. The decrease in peripheral resistance returns larger than

normal quantities of blood from the tissues to the heart, which greatly increases cardiac output. Hypoxemia also results from the decreased transport of erythrocytes, which further decreases peripheral vascular resistance, allowing more blood return to the heart, further increasing CO and myocardial oxygen consumption. Not only does anemia decrease oxygen delivery, it also increases cardiac output, myocardial oxygen consumption, and possibly the risk of end organ ischemia [4].

The lowest limit of hemoglobin tolerated in people is not known, as critical limits for tissue oxygenation remain poorly defined [7]. Even with the detrimental effects of anemia, recent trials have indicated that transfusion is not necessarily the best treatment. Current opinion holds that a universal hemoglobin or hematocrit transfusion trigger is inappropriate for all patients or situations. Therefore, the historical transfusion triggers of hemoglobin of 10 and a hematocrit of 30 have fallen out of favor intraoperatively, postoperatively, and in ICU patients [2].

Blood loss should be replaced with crystalloid or colloid solutions to maintain normovolemia until the danger of anemia outweighs the risks of transfusion. Patients who have low hemoglobin levels before surgery are at higher risk of receiving allogeneic transfusion.

COMPATIBILITY TESTING

The ABO-Rh type, crossmatch, and antibody screen are compatibility tests. These tests were designed to demonstrate harmful antigen–antibody interactions in vitro so harmful in vivo interactions could be prevented [8]. Pretransfusion testing is performed to ensure ABO compatibility between the donor and the recipient. The ABO group remains the most important factor tested, because the most likely cause of death secondary to transfusion therapy is ABO incompatibility [9].

There are three common alleles present on the ABO locus on chromosome 9. ABO is based on inheritance of genes that encode for glycosyltransferases that add specific sugars to make an A or B antigen. The genes are codominant, so an individual inheriting both genes is designated as having AB blood type. Homozygous AA and heterozygous AO are both known as type A blood. The inheritance of O does not create a functional enzyme. Patients make antibodies to the antigens that they lack. Type O people lack A and B antigens on their red cells, so they will have anti-A and anti-B antibodies in their plasma. These naturally occurring antibodies occur in patients even with no prior blood exposure. The antibodies produced against ABO antigens are IgM and capable of causing intravascular hemolysis if incompatible blood is transfused.

In ABO testing, a sample of whole blood is centrifuged to separate red cells from serum. This process allows the red cells and serum to be tested separately and allows the type to be double-checked. The ABO group is determined by mixing the patient's red cells using anti-A and anti-B reagents and by reverse-typing the patient's serum against A and B reagent cells. If agglutination occurs with anti-A reagent, then the patient has type A blood. If agglutination

occurs with anti-B reagent, then it is type B blood. If both cause agglutination, it is type AB, and if there is no agglutination, then it is type O blood. The patient's serum is screened for the presence of unexpected antibodies by incubating it with selected reagent red cells (screen cells) using an antihuman globulin (AHG) technique (indirect antiglobulin or Coombs test.) (Table 1).

The type and screen test looks only for the ABO-Rh type and screens for any unexpected antibodies. The Rh system has more than 40 red blood cell (RBC) antigens, but D, C, E, c, and e are the most significant of these antigens. Clinically, the D antigen is the most immunogenic RBC antigen and is known as the Rh factor. The antibody screen consists of detecting abnormal red blood cell antibodies to clinically significant antigens. There are more than 600 antigens, but only a fraction of these are noted to be clinically significant [9].

If the antibody screen is negative, and the patient has no past history of unexpected antibodies, it can be predicted that more than 99.99% of ABO-compatible red blood cell units would be compatible with an AHG crossmatch. If the antibody screen is positive (approximately 1% of patients), the unexpected antibody or antibodies must be identified before antigen negative-compatible RBCs can be found. This process usually takes several hours [10].

The type and cross includes the ABO-Rh type and antibody, screen but it also includes mixing donor red blood cells and recipient serum to inspect for any reactions. The crossmatch takes between 45 to 60 minutes and is characterized by three phases, immediate, incubation, and antiglobulin phases. The two most important phases are the incubation and antiglobulin phases, because the antibodies that appear in these phases can cause severe hemolytic reactions. Once donor blood is crossmatched with recipient blood, that blood is made unavailable to anyone other than the crossmatched recipient by the blood bank for up to 48 hours [8].

Emergent blood supplies should be ABO type O, as this is the least antibody-inducing type of blood. Donor blood used for emergency transfusion of group-specific blood must be screened for both hemolytic anti-A or anti-B antibodies. The Rh factor should be negative, but Rh factor positive blood can be used in men, and postmenopausal women with a small risk of reaction. Rh factor

Table 1
ABO compatibility testing

| Blood group | Red cells tested with | | Serum tested with | |
	Anti-A	Anti-B	A cells	B cells
A	+	−	−	+
B	−	+	+	−
AB	+	+	−	−
O	−	−	+	+

Abbreviations: +, agglutination; −, no agglutination.
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positive blood should not be used in premenopausal women because of the risk of transfusing Rh-positive blood into an Rh-negative female and causing erythroblastosis fetalis in subsequent pregnancies [8].

Table 2 summarizes donor blood groups that patients may safely receive.

RISKS ASSOCIATED WITH CONVENTIONAL RED BLOOD CELL TRANSFUSIONS

There are many complications associated with blood transfusion. Transfused blood has been shown to cause immunomodulation, systemic inflammatory response, occlusion of microvasculature, and an increased risk of postoperative low-output heart failure when transfusion occurs during coronary artery bypass surgery [11].

Allogeneic red blood cell transfusions can induce immunomodulation in the recipient of the transfusion. Allogeneic donor leukocytes appear to mediate significant immunomodulating effects. Leukocyte depletion may reduce the immunomodulation. Immunomodulation caused by transfusion can increase the incidence of postoperative infections and increase the risk of tumor recurrence in patients who have resected malignancies [12]. There is a dose–response relationship showing immunomodulation increases with the increasing number of allogeneic erythrocyte transfusions administered [13].

Immunomodulation can be beneficial for transplant patients. Allogeneic blood transfusions have been shown to improve allograft survival in renal transplants [14]. The mechanism of immunomodulation is suspected to be caused by up-regulation of humoral immunity and down-regulation of cell mediated immunity [15].

TRANSFUSION REACTIONS

Three types of allergic reactions to erythrocyte transfusions are mild, moderate, and anaphylaxis. If any of these transfusion reactions are noted, the transfusion should be stopped, and a new sample of blood should be sent for retype and cross.

A mild allergic reaction will cause focal urticaria that occurs in approximately 3% of patients. It is characterized by well-circumscribed, localized, erythematous, raised, urticarial lesions or hives, and is not associated with other symptoms.

Table 2
Donor blood groups that patients can receive

Donor	Recipient
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

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The transfusion should be held to administer antihistamines and resumed if the reaction stops. A moderate allergic reaction is seen clinically as a more widespread skin rash and a respiratory component, including bronchospasm or stridor. The transfusion should be stopped, and the patient may require steroids and vasopressors [9].

Anaphylaxis is the most severe systemic allergic reaction and is a medical emergency. It occurs in 1 in 20,000 to 47,000 blood transfusions. It has multiple organ system involvement. The symptoms generally begin with hives, dyspnea, flushing, wheezing, and they progress to coughing, stridor, and cardiovascular collapse. The transfusion must be stopped immediately, and the patient should be treated with epinephrine, diphenhydramine, histamine 2 receptor antagonist, steroids, and intravenous fluids [9].

The febrile nonhemolytic transfusion reaction is one of the most common causes of temperature change during blood transfusions. The temperature must change by more than 1°C or 2° F. This reaction can be accompanied by chills or anxiety, and it is seen most often in patients who have multiple transfusions and in multiparous women. Once fever is detected, the transfusion should be stopped, and the patient should be treated with antipyretics [16]. Once the temperature begins to decrease and the suspicion of septic transfusion reaction or acute hemolytic transfusion reaction is eliminated, the transfusion may be started again.

Bacterial contamination of transfused RBCs can cause sepsis in the transfusion recipient. The most common organism associated with contamination is *Yersinia enterocolitica* and other gram-negative organisms. Bacterial contamination of RBC units is related directly to the length of storage [17].

Contamination with gram-negative organisms is the result of occult asymptomatic transient donor bacteremia occurring during collection. The growth of the cryophilic bacteria *Yersinia, Serratia,* and *Pseudomonas* is enhanced by the refrigerated storage conditions of RBCs. Endotoxin produced by these organisms also can induce fulminant sepsis in the recipient. Septic transfusion reactions caused by gram-negative rods can be rapidly fatal, with a mortality rate of 60% [9]. It can evolve over several hours and go unrecognized. Clinically, a temperature increase of greater than 2 or 3°C, severe hypotension, hypertension, disseminated intravascular coagulation, and shock are seen. These signs and symptoms may be absent in a cold surgical patient or a patient who has a postoperative fever. If these symptoms occur, the transfusion should be stopped and a sample of blood sent for culture from the patient and from the donor unit. If there is a high suspicion, treatment should be initiated immediately without waiting for cultures. Broad-spectrum antibiotics, treatment for shock, acute renal failure (ARF), and disseminated intravascular coagulation (DIC) should be initiated immediately. Although restricting the use of antibiotics and particularly broad-spectrum antibiotics is important for limiting superinfection and for decreasing the development of antibiotic-resistant pathogens, patients who have severe sepsis warrant empirical therapy until the causative organ is identified [18].

The acute hemolytic transfusion reaction is a frequent cause of a fatal transfusion reaction caused by ABO incompatibility. The incidence is 1 per 250,000 to 1,000,000 transfusions [17]. Half of all deaths from acute hemolytic transfusion reactions are secondary to administrative errors. The severity of this reaction is related to the amount of blood transfused. If acute hemolytic transfusion reaction is suspected, the transfusion must be stopped and the untransfused blood returned to the blood bank along with a sample of the patient's blood for retyping and crossmatching. Supportive care should ensue.

Transfusion-related acute lung injury, more commonly known as TRALI, is an acute severe respiratory distress syndrome with an incidence of 1 per 5000 units transfused [18]. It usually occurs within 4 hours after transfusion and is characterized by the acute onset of dyspnea and hypoxemia, and it progresses to noncardiogenic pulmonary edema requiring mechanical ventilation and ICU treatment. The PaO_2 to FIO_2 ratio will be less than 300, the SpO_2 less than 90% on room air, and the chest radiograph will show bilateral pulmonary infiltrates.

Donor leukoagglutinins and donor antibodies to human leukocyte antigens (HLA), which react with the recipient leukocytes and monocytes, are hypothesized to cause TRALI. This reaction activates complement, which in turn leads to neutrophil aggregation and increased permeability of the pulmonary microcirculation. Multiparous female donors typically carry these leukoagglutinins [19].

Treatment of TRALI includes supportive measures, supplemental oxygen, tracheal intubation, mechanical ventilation, and positive end-expiratory pressure (PEEP) as indicated. The reaction usually resolves within 48 hours, and 90% of patients experience a complete recovery. Most cases resolve within 4 days of transfusion, but there is a high (5 in 100) incidence of fatal reaction. The incidence of pulmonary edema and acute respiratory distress syndrome (ARDS) is higher in patients who are transfused liberally [20].

DELAYED TRANSFUSION REACTIONS

Delayed transfusion reactions consist of viral contamination, delayed hemolytic transfusion reactions, and graft versus host disease (GVHD). Viral risks include HIV, hepatitis viruses A, B, and C (HAV, HBV, HCV), and human T-cell lymphotrophic virus types I and II. Some new viruses include hepatitis G virus, Torque teno (TT) virus, and human herpes virus 8 (associated with Kaposi's sarcoma) [21]. For HIV transmission, there is an incidence of 1 in 676,000; for HCV, the incidence is 1 in 103,000, and for HBV the incidence is 1 in 63,000. Along with multiple viruses, there is the risk of transmission of bacteria, parasites, and malaria. To date, malaria, Chagas disease, severe acute respiratory syndrome, and variant Creuzfeldt Jakob disease cannot be detected by screening tests [22].

GVHD is a rare complication resulting from foreign lymphocytes, and 90% of patients die. GVHD is T-lymphocyte mediated and usually occurs within

2 weeks of the transfusion. GBHD targets the host endothelium and bone marrow, which results in an aplastic anemia and pancytopenia. It usually is seen in immunosuppressed patients. The only known prevention of this reaction is radiograph or gamma radiation of the donor RBCs to inactivate all donor T cells [16].

METABOLIC COMPLICATIONS OF TRANSFUSIONS

Hyperkalemia, hypocalcemia, and acid-base alterations are the most commonly noted metabolic complications induced by blood transfusion. Hyperkalemia usually is seen in massive transfusions with increased red cell lysis or in renal failure. When red cells are stored, they leak potassium into their storage fluid, but leakage is corrected with transfusion and replenishment of cell energy stores.

Hypocalcemia can occur, because citrate binds calcium and is used as an anticoagulant in stored blood products. Rapidly transfusing RBCs may decrease the level of ionized calcium in the recipient. The liver should metabolize the citrate, but in clinical scenarios with impaired liver function, liver transplantation, or hypothermia, citrate metabolism may be decreased. Ionized calcium levels should be followed, because total serum calcium measures the citrate-bound calcium and may not reflect free serum calcium accurately.

Alterations in acid–base status occur, because stored blood is becomes more acidic secondary to the accumulation of RBC metabolites. The acid load is minimal when transfused. Alkalosis following a massive transfusion is common secondary to metabolism of citrate to bicarbonate by the liver [6].

ALTERNATIVES TO ALLOGENEIC BLOOD TRANSFUSION

Reasons to seek alternatives to allogeneic blood transfusions are numerous, including infectious risks, short supply, rare blood phenotypes, massive transfusion settings, and patient refusal of allogeneic blood transfusion. Blood conservation strategies include autologous blood transfusion, acute normovolemic hemodilution, and intraoperative blood recycling. Future options may include artificial oxygen carriers.

BLOOD CONSERVATION STRATEGIES

There are several ways to perform autologous blood donation. The techniques include acute normovolemic hemodilution, preoperative blood donation, and intraoperative blood salvage. When considering perioperative autologous blood donation, it is mandatory to carefully select patients to reduce the rate of discarded autologous units. Autologous blood donation is one of the simplest, most economical ways to decrease the amount of allogenic blood transfusion used [23].

Acute normovolemic hemodilution uses intraoperative venous drainage of one or more units of blood, with intraoperative storage of this blood. The blood removed is replaced milliliter for milliliter with colloid or 3 cc of

crystalloid to 1 cc of blood removed. Blood replacement with dextran or hetastarch may result in coagulation defects. Crystalloid and colloid volume replacement also decreases the risk of anaphylaxis associated with dextran. The volume replacement allows the blood lost intraoperatively to have a lower hematocrit, with the idea that more dilute blood may be lost and then replaced with the more concentrated blood removed at the beginning of the case [24].

The amount of blood that can be removed during hemodilution is calculated using the formula $V = EBV \times Hi\text{-}Hf/Hav$, where V is the volume of blood expected to be removed; EBV is estimated blood volume (TBW(kg) * 60 cc/kg (female) or 70 cc/kg (male). Hi is the patient's initial hematocrit level before onset of hemodilution; Hf is the desired hematocrit at the end of hemodilution, and Hav is the average hematocrit level during hemodilution (Hi + Hf/2) [21].

Acute normovolemic hemodilution is useful and cost-effective in procedures where expected estimated blood loss is greater than 1000 mL. It is less expensive than perioperative autologous blood donation, and it eliminates the risk of administrative errors that may occur anytime blood is banked.

PREOPERATIVE AUTOLOGOUS BLOOD DONATION

The ability of the patient to donate sufficient blood depends on his or her total blood volume and ability to regenerate red blood cells. Autologous blood donation is something that can be performed in patients who are stable before donation and are having elective surgery known to require transfusion. Criteria for self-donation as outlined by the American Association of Blood Banks includes a donor hemoglobin of greater than or equal to 11 g/dL, or a hematocrit of 33%. There is no age or weight requirement. The amount a patient can donate for him/herself is 10.5 mL/kg body weight. The limitation includes no donation at least 72 hours before the procedure to allow the patient to recover his or her intravascular volume status before surgery and to allow the blood bank to process the donated blood [25].

Poor candidates for autologous blood donation include patients with significant heart disease or those with preoperative anemia. Autologous blood donation is not recommended in patients who are to undergo procedures where the incidence of blood transfusion is low. Contraindications to autologous blood donation include: evidence of infection, risk of bacteremia, surgery to correct aortic stenosis, unstable angina, acute seizure disorder, myocardial ischemia or cerebrovascular accident within 6 months of donation, patients with cardiac or pulmonary disease who have not been cleared for surgery by their primary physician, high-grade left main coronary artery disease, cyanotic heart disease, or uncontrolled hypertension [26].

Another form of autologous blood donation is intraoperative blood salvage (cell saver), which includes the retrieval of blood from the surgical patient and return of that blood to the patient. A suction device used by the surgeon aspirates shed blood that is anticoagulated with citrate or heparin and returned to a disposable sterile centrifugal bowl. The collected blood then is washed with

normal saline, concentrated to a hemoglobin of 50%, and returned to a second bag, which then is returned to the patient [27].

Cell salvage may cause a metabolic acidosis secondary to the loss of bicarbonate associated with a parallel increase in the chloride concentration (hyperchloremic acidosis), because the red blood cells recovered are washed with normal saline. Calcium and magnesium concentrations also may decrease with progressive cell salvage transfusions. The processed erythrocyte suspension never should be administered under pressure, as the bag contains air. If the bag is placed under pressure, the risk for venous air embolism is increased greatly, causing a potentially fatal complication. Because the washed blood is solely erythrocytes and may contain residual heparin, patients may develop a coagulopathy after a liter of transfused salvaged cells. RBC salvage should not be used in operations with nonsterile fields or during an oncologic surgery based on the risks of infusing bacteria or tumor cells into the patient [26].

Erythrocyte production is regulated by the secretion of erythropoietin by the kidney in response to renal hypoxia. If there are adequate supplies of folate, iron, and vitamin B12, erythropoietin will stimulate an increase in red cell production by marrow and an increase in oxygen-carrying capacity. Exogenous erythropoietin affects erythropoiesis in the same way. For elective postsurgical patients, erythropoietin will stimulate the rate of erythropoiesis to return RBC mass to a steady state. Exogenous erythropoietin will increase RBC mass in many anemic states and has been shown to do the same for preoperative surgical patients undergoing autologous blood transfusions. It has been demonstrated to decrease transfusion requirements in the postoperative period when patients are given erythropoietin preoperatively, provided there is iron available. It also can be given to anemic postoperative patients to increase the rate of recovery to normal hemoglobin levels. Perioperative erythropoietin is expensive but generally well tolerated, and with low doses costs may be comparable to preoperative autologous blood donation. This option increases the patient's red cell mass before surgery with exogenous erythropoietin. The efficacy of erythropoietin in reducing the volume of allogeneic blood transfused per patient and reducing the number of patients requiring transfusions is documented well in certain populations (renal insufficiency, anemia of chronic disease, refusal of transfusion) [1].

The combination of acute normovolemic hemodilution with preoperative erythropoietin has been found to be effective, because acute normovolemic hemodilution is more successful when there is a higher hemoglobin before beginning hemodilution. The use of recombinant human erythropoietin and/or iron therapy is effective for increasing RBC mass preoperatively.

Current research focuses on alternatives to blood transfusion, namely, blood substitutes. Blood substitutes are volume-expanding, oxygen-carrying solutions. The two types of blood substitutes in development are hemoglobin-based oxygen carriers and perfluorocarbon emulsions. Hemoglobin-based oxygen carriers have shown some promising results but must be modified in some way to prolong vascular retention, decrease renal toxicity, and decrease

vasoconstriction. Perfluorocarbon emulsions can increase the amount of oxygen carried in blood, but their particulate nature can lead to adverse effects including thrombocytopenia and influenza-like symptoms [28].

TRANSFUSION OF NON–RED BLOOD CELL COMPONENTS

During elective surgery, replacement of blood loss up to half the blood volume (equivalent to five units of packed red blood cells to restore red cell mass to control levels) will not substantially affect hemostasis in most patients, and clotting functions, platelet counts, and clotting factor assays will not reach to abnormal levels. Numerous studies suggest that between 6 and 10 units of blood loss, replaced with packed RBCs and crystalloid solution only, a gradual prolongation of the prothrombin time (PT) and partial thromboplastin time (PTT) can be detected, before signs of microvascular bleeding indicate the onset of early coagulopathy [29]. Factor assays at this time in elective cases, somewhere around one blood volume lost and replaced, will reveal significant decreases in fibrinogen, which may contribute to the generalized ooze on the surgical field [30]. In elective cases with significant ongoing blood loss, platelets decrease to abnormal levels relatively late. In trauma cases, however, thrombocytopenia may occur more rapidly, sometimes at less than one blood volume, so that defects in primary hemostasis (quantitative platelet function) may be the cause of the earliest microvascular bleeding. Maintenance of body temperature with fluid warming and forced air heating may prevent physiologic depression of clotting factor and platelet function, but in patients losing blood, a threshold eventually will be reached where blood components will be required, in addition to packed red cells and buffered salt solutions, to reverse the trend toward coagulopathy.

Although the primary focus of this discussion is on slow blood loss in elective surgical patients, it should be noted that the onset of coagulopathy occurs consistently earlier in the trauma patient, and that many of these cases show laboratory and clinical signs of ongoing coagulopathy on arrival in the emergency room. Therefore, there is a growing preference in trauma care favoring early prophylaxis for coagulopathy from the first units of blood given to emergency patients who have continuing blood loss [31]. With heavy blood loss, whether the situation is elective or emergent, it appears easier to control coagulopathy with early blood component use, rather than to regain control when coagulopathy is present.

Blood components used in massive transfusion situations are fresh-frozen plasma (FFP), platelets, cryoprecipitate, recombinant factor VIIa, and prothrombin complex concentrate (descending order of frequency of use). Component indications, major complications, and methods for monitoring hemostasis are essential knowledge for the anesthesiologist for managing the bleeding patient.

PLASMA—FRESH-FROZEN PLASMA, FRESH-THAWED PLASMA

Plasma is removed from centrifuged units of blood and frozen for later use. It contains albumin, immune globulins, and clotting factors, some of which retain

much of their activity after thawing and transfusion. In some hospitals where large amounts of plasma are used, units are thawed in advance of request, so that warm thawed plasma is ready at all times for use, hence the use of the term fresh-thawed rather than fresh-frozen in some centers. Because the indications and usages for both FTP and FFP are identical, the two terms are used interchangeably in this discussion.

Most cases of early coagulopathy can be corrected by transfusion of FFP, usually in a volume of 10 to 15 cc/kg [29]. Because most of the citrate added to blood during donation is removed with the plasma during preparation of Adsol packed red cells, transfusion of plasma rapidly often results in hypocalcemia and transient hypotension. Rapid infusion of FFP should be considered an indication for small bolus doses of calcium chloride, 3 to 5 mg/kg, infused slowly to antagonize the citrate in the plasma. Slow infusion of plasma should not affect the serum calcium.

FFP provides excellent colloid volume support, and is similar to albumin in its ability to acutely support intravascular volume. It contains some active clotting factors, but fibrinogen supplementation from a single unit is limited, so that when fibrinogen levels are inadequate, cryoprecipitate would be preferred to FFP for correction. The amount of fresh-thawed plasma (FTP) required to normalize the prothrombin time in patients taking coumadin may produce fluid overload in patients at risk of congestive heart failure. Standard FTP therapy in this situation should be avoided in high-risk patients, and correction in emergencies should be managed with prothrombin complex concentrate.

The labile clotting factors, VIII, IX, and vWF (von Willebrand factor), already may have decreased in plasma during processing before freezing, so deficiency in these factors should be corrected with specific factor concentrates, or in mild cases, treated with desmopressin. Noncellular factors in FFP also may be responsible for TRALI, which has been reported following single-unit FFP transfusions.

During rapid exsanguination in trauma, FTP may be indicated from the beginning of fluid resuscitation for prophylaxis or therapy of coagulopathy. The amount of FTP recommended ranges from 0.4 to 1 units of FTP for every unit of packed red cells, with some evidence favoring the higher dose based on computer simulation studies [32]. Such early FFP therapy is supported by reported observation in many trauma units, but no class I evidence supports this from randomized clinical trials, which would be difficult if not impossible to perform in the emergency setting [33].

PLATELETS

Murray and colleagues [29] noted that the rare patient with coagulopathy that was not corrected by FFP usually would have microvascular bleeding controlled after infusion of platelets. A platelet concentration target of 100,000/mm^3 usually is considered the threshold for thrombocytopenia and associated quantitative deficiency in primary hemostasis, in patients with ongoing blood loss requiring replacement with blood components. A lower threshold for coagulopathy, of half this level, 50,000/mm^3, generally is considered appropriate

for patients with more stable blood volumes who are assumed to be maintaining an equilibrium between platelet consumption and release from reservoirs in the reticuloendothelial system.

Platelets are supplied either in pooled packs separated from five or six units of whole blood during processing, or in apheresis units from single donors. A platelet pack from either source should increase the platelet count by 50,000/mm^3 in a nonbleeding and nonconsuming patient. Thrombocytopenia can result from dilution or consumption, and in clinical practice, the treatment is usually the same. If disseminated intravascular coagulation is suspected, however, the determination and treatment of the inciting cause should be a major focus of therapy.

Platelet sepsis and TRALI have been the two leading causes of death from blood component therapy for the last decade. Although the incidence of platelet-related sepsis is very low, from bacterial growth in the platelet packs during storage at room temperature, the mortality risk is significant. Both TRALI and platelet sepsis account for 35 to 50 deaths each per year in the United States, more than the mortality from incompatible blood transfusion.

CRYOPRECIPITATE

Cryoprecipitate is fractionated from cooled and thawed plasma, and it is given in pooled units from 10 separate donors, thawed and prepared for each patient in the blood bank. There may be some delay in preparation, and cryoprecipitate is relatively expensive. It must be given immediately when received, because it expires 4 hours after preparation. In addition to large amounts of fibrinogen in each pool, significant factor VIII, XIII, and von Willebrand factor are preserved in the processing, and are active on infusion. Cryoprecipitate is the best replacement for fibrinogen deficiency complicating moderate-to-severe blood loss, and it is included in most massive transfusion protocols.

RECOMBINANT FACTOR VIIA

Recombinant FVIIa (NovoSeven, Novo Nordisk Pharmaceuticals, Princeton, New Jersey) works through several points on the coagulation cascade to produce a thrombin burst to promote coagulation. It replaces endogenous FVII, which is the earliest clotting factor affected by dilution in vivo, and which also decreases most rapidly in vitro during storage of blood or plasma. It is very expensive, with the price of a 4.8 mg dose over $4000. Use of NovoSeven in trauma is off-label, because the factor is only approved for use in hemophilia A or B with FVIII or FIX inhibitors. The procoagulant activity of NovoSeven is inhibited by acidosis, but not by hypothermia. It requires adequate amounts of substrate to function properly, so prothrombin and other clotting factors must be present before it will slow or control coagulopathic bleeding. Loading of FFP and possibly cryoprecipitate is encouraged before its use, to provide adequate procoagulant concentrations in the circulation.

Enthusiasm for its procoagulant actions has been decreased by recent reports of possible thrombotic complications, as reported in the press, but not currently

documented in the medical literature in peer-reviewed publications [34]. As a result of anecdotal experience in several trauma centers, and the military experience in Iraq, use of Novoseven in initial care of bleeding trauma patients, which was being advocated until quite recently, has been stopped in many trauma centers, or has been restricted to a lower dose (2.4 mg dose) when used treating coagulopathy. If NovoSeven does promote thrombotic complications, whether dose restriction will prevent such problems has not been proven. Retrospective review of clinical experience in several medical centers, including the authors', has not confirmed any thrombotic complications in patients who have received FVIIa, although these are admittedly not carefully conducted prospective studies. Until the potential for thrombotic events following NovoSeven therapy is either confirmed or rejected, this expensive therapy is questionable in any dose range. The authors continue to use the high dose in their massive transfusion protocol for lack of any local evidence to substantiate complications associated with its use.

PROTHROMBIN COMPLEX CONCENTRATE

This new clotting factor preparation is derived from pooled plasma, and it includes very concentrated factor II, factor VII, factor IX, and factor X, all lipid-soluble factors that are decreased by the anticoagulant coumadin. It is used in reversal of coumadin effect with correction of the prothrombin time to normal, in clinical situations when rapid reversal of coumadin is needed such as emergent surgery or when internal bleeding in patients taking coumadin requires rapid control. Prothrombin complex concentrate (PCC) only recently has been supplied to transfusion medicine services, and experience with it has been limited. There are early indications that it occasionally may reverse coumadin inadequately, because the content of factor VII may be reduced during processing. When the prothrombin time does not return to normal following its use, a half dose of FVIIa (2.4 mg) may be administered intravenously to boost inadequate FVII activity in the PCC (Ravinder Sarode, MD, personal communication, 2007). A tendency toward arterial thrombosis in a very small percentage of patients (less than 10%) has been noted following PCC in some centers, but this has not been studied prospectively in a well-designed series, probably because the preparation is new and not widely used in any center at this time.

MASSIVE TRANSFUSION PROTOCOLS

As defined by the American Association of Blood Banks, massive transfusion is the replacement of one blood volume (10 units of blood) in any 24-hour period, or of one-half of the blood volume (five units of blood) in any 4-hour period. Hospitals with busy trauma services will treat injured patients whose transfusion needs exceed these limits on an almost daily basis. In addition, occasional elective surgery and other patients with coagulopathies also meet these simple

criteria. Most patients needing massive transfusion support have blunt or penetrating trauma, and already will be rapidly exsanguinating because of their injuries on arrival at the emergency room. Such patients who are hypovolemic and hypotensive on arrival usually have received large volumes of crystalloid (balanced salt solution) during initial stabilization and transport, and they may need transfusion immediately.

The decision for immediate transfusion and volume replacement with packed red cells is based on assessment of vital signs and acid–base status as reflected in arterial blood gas determinations. Blood loss may result in anemia and coagulation abnormalities, but specific coagulation assays, even performed at the bedside, may take too long to perform to reflect rapidly changing conditions in the trauma patient. Such testing will serve to confirm the effects of ongoing therapy, rather than to guide future therapy in the acute situation. Coagulation factor therapy therefore is based on empiric assumptions related to estimated blood volume loss.

Under these circumstances, trauma services in North America and Europe have set up massive transfusion protocols, designed to support rapid transfusion with regular shipments of blood products released automatically on a timed basis. These products are organized in five-unit increments of packed red cells, with varied other blood products as typically needed at that level of blood loss. Once triggered by the request of the anesthesiologist or surgeon, the blood shipments would continue uninterrupted under the protocol until the bleeding was controlled or the patient expired.

The massive transfusion protocol (MTP) at Parkland Memorial Hospital has been operational for 2.5 years (Fig. 1). During the first 10 units of blood loss, the primary need is for volume support with packed RBCs and crystalloid. Levels of specific clotting factors are maintained, but FTP usually is given to support blood volume and to attempt to control coagulopathy in its early phases. Between 10 and 15 units of blood loss, platelet levels and fibrinogen levels decrease rapidly, and replacement with platelet packs and cryoprecipitate may be necessary to support coagulation. By roughly one blood volume of blood loss, factor VII and other procoagulants may be reaching marginal levels, and early use of high-dose NovoSeven (4.8 mg) is included in the protocol at that time.

Early experience with the protocol has shown that blood products can be provided at a maximum rate of 20 units of packed red blood cells (PRBCs) per hour, with the various other components given on schedule. Under most circumstances, it has been possible to maintain blood volume and arterial pressure satisfactorily using the blood products delivered automatically according to schedule, and most patients on the protocol are maintaining their clotting functions at near normal values until their transfer to the ICU.

Patient survival does not seem to be improving using the protocol. In a group of 100 consecutive patients meeting MTP criteria, prior to beginning the protocol and treated with blood products at the direction of the anesthesiologist and trauma surgeon, patient survival at 30 days was 50%. In the first two years

Shipment	RBC	TP	5PLT/APH	CR	rFVIIa
1a	5 (O-Neg)	2 (AB)			
1b	5	2			
2	5	2	1		
3	5	2		10	rFVIIa
4	5	2	1		
5	5	2			
6	5	2	1	10	
7	5	2			
8	5	2	1		
9	5	2		10	
10	5	2	1		

Fig. 1. The current Parkland Hospital massive transfusion protocol. Each shipment takes roughly 30 minutes to prepare, and shipments may be doubled during massive transfusion as needed, to a maximum delivery rate of 20 units of PRBCs per hour. *Abbreviations:* CR: cryoprecipitate, pooled 10-unit bag (in cooler);PLT/APH, platelet pool (five-pack) or apheresis single-donor unit equivalent to five pooled transported at room temperature; RBC, packed Adsol-1 or Adsol-5 red cells (in cooler); rFVIIa, recombinant factor VIIa (lyophilized powder with diluent); TP, thawed fresh plasma (in cooler).

of the protocol, 30-day survival each year remained in the 50% range, which was no better than the control group. The amount of PRBC units transfused, as a marker of the number of blood shipments sent out on the protocol, appears to be reduced by 25% compared with the total PRBC units used for the control group. It would appear that patients are clotting better and bleeding less, assuming a homogeneous trauma population over the past 5 years. NovoSeven was introduced into wider clinical use after the control group was studied, however, so the reduction in total blood products might be due partly or solely to the use of rFVIIa, rather than to the greater use of procoagulants on schedule in the MTP. The number of patients on the MTP each year is roughly the size of the control group, (around 100), and ongoing analysis of variables within the survivor and nonsurvivor groups may yield further information (Ravinder Sarode, MD, personal communication, January 2007).

The implementation of the MTP has produced a general improvement in the delivery of blood products to operating rooms for trauma resuscitation. Relieving the anesthesia and nursing personnel of continual worry about blood supplies during urgent trauma surgery has been of great benefit in the opinion of most involved staff. Outcome data to prove that the MTP is of benefit to the patients will be more difficult to produce, and benefit in terms of better clotting functions and improved survival may be several years away. Just the savings in blood products could be cited as an advantage, if further data analysis suggests that the roughly 25% decrease in blood product usage in massive transfusion using the protocol actually persists in the future data. It appears that the MTP has proven its worth in more convenience to medical and nursing personnel, even if patient benefit and cost savings are not entirely proven benefits at this time.

References

[1] Lankin PN, Hanson CW, Manaker S. The intensive care unit manual. Philadelphia: WB Saunders; 2001. p. 185.

[2] Hebert PC, Wells G, Blaichman MA, et al. A multicenter randomized controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409–17.

[3] Stoelting RK, Hillier SC. Pharmacology and physiology in anesthetic practice. 4th edition. Philadelphia: Lippincott Williams and Wilkins; 2006. p. 849.

[4] Guyton AC, Hall J. Textbook of medical physiology. 11th edition. Philadelphia: W.B. Saunders; 2006.

[5] Marino PI. The ICU book. 2nd edition. Philadelphia: JB Lippincott; 1998. p. 22.

[6] Morgan GE Jr, Mikhail MS, Murray MJ, editors. Clinical anesthesiology. 3rd edition. New York: McGraw-Hill; 2002. p. 632, 639.

[7] Spahn D, Casutt M. Eliminating blood transfusion; new aspects and perspectives. Anesthesiology 2000;93:242–4.

[8] Miller R, Cucchiara R, Miller ED, editors. Miller's anesthesia. 6th edition. New York: Churchill Livingstone; 2002. p. 1801–2.

[9] Speiss BD, Spence RK, Shander A, editors. Perioperative transfusion medicine. 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2006.

[10] Benson K, Chapin J, Despotis G, et al. Q & A about transfusion practice. 3rd edition. Park Ridge (IL): American Society of Anesthesiologists; 1997.

[11] Surgenor SD, DeFoe GR, Fillinger MP, et al. Intraoperative red blood cell transfusion during coronary artery bypass grafting increases low output heart failure. Circulation 2006;114(Suppl):I43–8.

[12] Varmvakas EC. Transfusion-associated cancer recurrent and postoperative infection: meta-analysis of randomized, controlled clinical trials. Transfusion 1996;36: 175–86.

[13] Blumberg N, Heal JM. Immunomodulation in blood transfusion: an evolving scientific and clinical challenge. The science of medical care. Am J Med 1996;101:299–308.

[14] Opel G, Terasaki P. Improvement of kidney graft survival with increased number of transfusions. N Engl J Med 1978;299:799.

[15] Klein H. Immunomodulatory aspects of transfusion: a once and future risk? Anesthesiology 1999;91:861–5.

[16] Harmening DM. Modern blood banking and transfusion practices. 5th edition. Philadelphia: FA Davis; 2005. p. 340, 346.

[17] Goodnough LT, Brecher ME, Kanter MH, et al. Transfusion medicine, blood transfusion. N Engl J Med 1999;340:438–47.

[18] Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858–72.

[19] Murray M, Coursin D, Pearl R, et al. Critical care medicine: perioperative management. 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 569.

[20] Wall M, Surgenor S. Concepts of transfusion triggers. American Society of Anesthesiologists Newsletter 2006;70:17.

[21] Monk T. Acute normovolemic hemodilution. Anesthesiol Clin North America 2005;23: 271–81.

[22] Mungai M, Tegtmeier G, Chamberland M, et al. Transfusion transmitted malaria in the United States 1963–1999. N Engl J Med 2001;344:1973–8.

[23] Goodnough LT. Autologous blood donation. Anesthesiol Clin North America 2005;23: 263–70.

[24] Jones S, Whitten C, Despotis G, et al. The influence of crystalloid and colloid replacement solutions in acute normovolemic hemodilution: a preliminary survey of hemodynamic markers. Anesth Analg 2003;96:363–8.

[25] Standards for blood banks and transfusion services. American Association of Blood Banks, AABB Bulletin; 2002.

[26] Goodnough LT, Shander A, Spence R. Bloodless medicine: clinical care without allogeneic blood transfusion. Transfusion 2003;43:668–73.

[27] Handin RI, Lux SE, Stoessel TP. Blood—principles and practice of hematology. 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 2014–15.

[28] Winslow RM. Current status of blood substitute research: towards a new paradigm. J Intern Med 2003;253:508–17.

[29] Murray DJ, Pennell BJ, Weinstein SL, et al. Packed red cells in acute blood loss: dilutional coagulopathy as a cause of surgical bleeding. Anesth Analg 1995;80:336–42.

[30] Hiippala ST, Myllyla GJ, Bahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 1995;81:360–5.

[31] Ketchum L, Hess JR, Hiippala S. Indications for early fresh-frozen plasma, cryoprecipitate, and platelet transfusion in trauma. J Trauma 2006;60:S51–8.

[32] Hirshberg A, Dugas M, Banez EI, et al. Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation. J Trauma 2003;54:454–63.

[33] Malone DL, Hess JR, Fingerhut AF. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. J Trauma 2006;60:S91–6.

[34] Little R. Dangerous remedy. Military doctors in Iraq say that Factor VII saves wounded soldiers, but other doctors and medical research suggest that it can cause fatal clots. The Baltimore Sun. November 19, 2006.