Essentials of emergency transfusion—The complement to stop the bleed

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ABSTRACT: Over the past decade, the shift toward damage control surgery for bleeding trauma patients has come with an increased emphasis on optimal resuscitation. Two lifesaving priorities predominate: to quickly stop the bleed and effectively resuscitate the hemorrhagic shock. Blood is separated into components for efficient storage and distribution; however, bleeding patients require all components in a balanced ratio. A variety of blood products are available to surgeons, and these products have evolved over time. This review article describes the current standards for resuscitation of bleeding patients, including characteristics of all available products. The relevant details of blood donation and collection, blood banking, blood components, and future therapies are discussed, with the goal of guiding surgeons in their emergency transfusion practice. (*J Trauma Acute Care Surg.* 2019;87: 420–429. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Transfusion; trauma.

Optimizing resuscitation has been a key priority in the delivery of trauma care over the past decade. High-quality evidence has demonstrated the benefit of damage control resuscitation during the critical first hours of trauma care. This includes the rapid diagnosis and control of hemorrhage, as well as aggressive resuscitation with blood products with the goal of normalization of hemodynamics, core body temperature, and acid-base status. Consequently, our contemporary resuscitation strategy has shifted from being reactive, with volume expansion followed by correction of laboratory derangements, to a more proactive approach, focusing on early balanced resuscitation with packed red blood cells, plasma, and platelets.[1,2]

There is no accurate way to measure the profound impact of blood transfusion in terms of lives saved; literally thousands of injured patients benefit from this lifesaving therapy each day. Yet this does not come without a cost. There is a significant financial burden associated with transfusion. Even a single unit of blood product has cost estimates in the hundreds of dollars range.[3] Moreover, the additional costs of collection, storage, and administration are difficult to quantify, and likely greatly exceed that estimate.

A staggering 16 to 17 million blood components are transfused annually in the United States alone.[4] Everyday, approximately 32,000 units of red blood cells, nearly 6,000 units of platelets, and 8,000 units of plasma are utilized nationwide.[4] Despite this widespread use, blood components are a limited resource. Blood has a defined shelf life and must be continually replaced. Episodic shortages exist in this country and worldwide. As recently as 2016, the American Red Cross issued an emergency appeal for blood and platelet donation, reporting 39,000 fewer donations than needed. Another nationwide platelet shortage occurred in the winter of 2017 to 2018, due to severe flu season.[5] Globally, only 40% of blood is collected in developing countries, where more than 80% of the population lives, resulting in frequent shortages of blood available to those who need it.[6]

To meet the significant demand for blood, blood banks often separate blood into its component parts, to maximize the efficiency of use.[6] While resuscitation with whole blood is being utilized in some centers, standard transfusion practices in the United States rely heavily on component therapy.[7] Consequently, it is essential that trauma surgeons have a clear understanding of what these component products are and how they should be optimally utilized.

BLOOD COLLECTION AND DONATION

In the United States, blood is collected by either national or regional organizations, including individual hospitals. National organizations include the American Red Cross, America's Blood Centers, United Blood Services, and the Armed Services Blood Program. In addition to this, over 100 regional organizations are also in operation. These organizations are all regulated by the US Food and Drug Association (FDA), which has standardized the collection and donation of blood products.

The process for obtaining blood to be transfused begins with a donor health assessment, a critical step that is designed to protect both the donor and the recipient.[8] The health assessment typically includes a questionnaire evaluating risk factors for transmissible infectious agents and screening minimum physiologic criteria (e.g., hemoglobin or hematocrit, platelet count, vital signs). As a precaution, donors are also given instructions to call the blood center after donation if they develop an illness, or if they develop concerns that their blood may no longer be safe to give to another person.

Blood can be collected as whole blood, or via apheresis technology, which involves extraction of a single component from the donor's blood, with the remaining components reinfused into the donor. Blood and blood components are collected into an anticoagulant/nutrient solution.

After the blood is collected from the donor, routine testing is performed. This includes testing for HIV 1, HIV 2, HTLV 1, HTLV 2, hepatitis B, hepatitis C, West Nile virus, Zika virus, and syphilis. Blood is also tested for *Trypanosoma cruzi*, the organism responsible for Chagas disease, but this test is sometimes omitted if the donor has previously tested negative for the organism and has not subsequently lived in an area endemic for the disease. American Red Cross blood may also be tested for Babesiosis if the donor is from an endemic area, per an FDA investigational protocol.[9] A portion of the donated blood inventory is tested for cytomegalovirus (CMV) for use on a case by case basis. Currently, all apheresis platelets are also cultured to detect bacterial contamination before shipment to hospitals for transfusion. Newer technologies have been developed to inactivate blood transmissible pathogens in platelets, and one system is now FDA approved.[10] These technologies, though costly, eliminate the need to culture platelets before they are used by patients, and are therefore becoming increasingly popular.

BLOOD BANKING

Blood products must be maintained in a temperature-controlled environment and stored under specific conditions that vary by type of product. Understanding the storage conditions of each product is critical for the trauma surgeon, as it directly impacts access to these products.

Aseptic technique must always be utilized during the preparation and administration process. If the sealed container is breached, the component expires 4 hours after entry if maintained at room temperature (20°C–24°C), or 24 hours after entry if refrigerated (1°C–6°C). Prior to transfusion, visual inspection should be performed to ensure that the container is intact and the appearance is normal (e.g., normal color with no cloudy appearance to suggest excessive hemolysis).

All components should be transfused through a filter designed to remove clots and microaggregates. Standard blood filters have a pore size between 170 and 20 microns. Microaggregate filters with pore size as low as 0 microns were previously developed for patients receiving greater than 4 units to 6 units of blood, in attempt to prevent the development of Acute Respiratory Distress Syndrome (ARDS). However, it has since become clear that these do not prevent ARDS, nor do they achieve substantial leukocyte reduction. In some institutions, these filters may still be used at bedside; however, their use is not recommended if leukocyte reduced products are used.[11] No medications or solutions may be added to, or infused through the same tubing simultaneously with blood or blood components, with the exception of 0.9% sodium chloride, or other isotonic solutions that have been FDA-approved or documented to be safe, such as morphine.[12]

Periodic observation and recording of vital signs should occur before, during, and after transfusion. Blood products should be warmed before administration, whenever clinically appropriate. The World Health Organization standard transfusion rate for a unit of red blood cells (RBCs) is to transfuse over 2 hours to 4 hours (100–150 mL/h).[13] Platelets, plasma, and cryoprecipitate are recommended to run over 1 hour to 2 hours (150–300 mL/h). In emergency situations, blood can be infused more rapidly, with no maximum rate of infusion. Rapid infusion systems are available that incorporate warming with the rapid transfusion of blood, including the Belmont Rapid Infuser (Belmont Instrument Corporation, Billerica, MA) and the Smiths Medical Level I Fast Flow Fluid Warmer (Smiths Medical, Minneapolis, MN). These devices have the capability to infuse fluids at rates up to 60 L/h. The flow rate is limited by the size and resistance of the intravenous cannula used; therefore, rapid infusers should be connected to large bore intravenous cannulas, typically 16 gauge or larger. Importantly, volume status should be continually monitored, and blood should be sufficiently warmed if infused rapidly. Rapid infusion of large volumes of blood products carries the potential for overtransfusion, or overinfusion of fluids. Also, it can depress body temperature, and the danger is compounded in patients experiencing shock or surgical or anesthetic manipulations that disrupt temperature regulation. Hypothermia carries a risk of cardiac arrhythmia or cardiac arrest and exacerbation of coagulopathy. All blood products can safely be warmed provided the warming is accomplished using an FDA-cleared blood warming device so as not to cause hemolysis.[14] The American Association of Blood Banks standards set the maximum temperature for blood products at 42°C.[13] Rapid infusers use electromagnetic induction heating to warm fluids as rapidly as they are transfused. The length of transit tubing from the infuser to the patient should be minimized, or tubing with continual countercurrent should be used to prevent fluids from cooling before entering the body.

In addition to the risk of hypothermia, rapid transfusion of either RBCs or fresh-frozen plasma (FFP) can lead to excessive citrate in circulation. Citrate binds ionized (free) calcium and results in clinical hypocalcemia. Ionized calcium levels should therefore be checked regularly during rapid transfusion and intravenous calcium should be administered as needed.

Multiple processes have been developed to improve blood product safety. Leukocyte reduction is the process of removing white blood cells from blood components. This is performed with a filter or apheresis technology during blood collection, after collection via filtration prior to storage, or at the bedside at the time of infusion after the product is dispensed from the blood bank. The goal of leukocyte reduction is to decrease the frequency of recurrent febrile nonhemolytic transfusion reactions, as well as to reduce the risk of transmitting leukotropic viral infections. Leukocyte reduction has been shown to reduce the risk of transmission of CMV and to reduce the incidence of human leukocyte antigen (HLA) alloimmunization, thereby decreasing the probability of platelet transfusion refractoriness. This process is most important for CMV-negative immunocompromised or pregnant patients, chronically transfused patients, and patients with a history of recurrent febrile transfusion reactions. However, it has become increasingly common place for all patients to receive leukocyte reduced blood products. Leukocyte reduction is now universal in most developed countries, however, in the United States, controversy over the cost and benefit has delayed universal implementation. Several randomized controlled trials have evaluated the benefit of leukocyte reduction, but have had inconsistent conclusions.[15,16] This may be due to the intention-to-treat methodology where patients who did not receive transfusion diluted the treatment effect. A recent meta-analysis including only patients who received blood transfusion demonstrated a significant reduction in postoperative infections in patients who received leukocyte reduced blood.[17] Leukocyte-reduced blood products have rarely been reported to cause severe hypotension in patients taking ACE inhibitors. The mechanism for this reaction is not clear, but it is suspected to be related to bradykinin-mediated vasodilation.

Irradiation of blood products is a treatment which prevents proliferation of T lymphocytes, which is the cause of transfusion-associated graft-versus-host disease (TA-GVHD). Irradiation is performed by exposing the component to 2,500 cGy of gamma irradiation targeted to the center of the container. Recently, psoralen-treated Ultraviolet A (UVA) irradiation of platelets has also been shown to be effective in preventing TA-GVHD.[10,18] Irradiated products should be used for patients at high risk for GVHD, as listed in Table 1.

Irradiation causes erythrocyte membrane damage and decreases the shelf life from 42 days to 28 days or less, depending on the preirradiation shelf life. The irradiation also causes supernatant potassium levels to increase.

Washing is a specialized process performed to prevent anaphylactic or recurrent severe allergic reactions to transfusions. It involves flushing the blood component with 0.9% sodium chloride, and occasionally, small amounts of dextrose. This process removes unwanted plasma proteins, which is performed to reduce antigen exposure to recipients with a history of recurrent severe allergic transfusion reactions or anaphylaxis related to absolute IgA deficiency. For example, removing plasma-containing IgA from components being transfused to an absolute IgA-deficient recipient who has anti-IgA, or removing

TABLE 1. Indications for Irradiated Blood Products

IUT and Infants Who Have Received IUTs
Pediatric patients: infants and children with or suspected to have an immune deficiency, e.g., SCID or DiGeorge syndrome
Leukemia/lymphoma (e.g., Hodgkin disease)
Granulocyte transfusions
Blood product from a related donor (any degree relation), regardless of the patient's immune status
Blood product from an HLA-selected or crossmatched donor, regardless of patient's immune status
Patient receiving T-cell suppression therapy. Current lists include purine nucleoside analogs and antagonists (e.g., fludarabine, bendamustine, azathioprine, alemtuzumab, antithymocyte globulin).

Products for allogeneic or autologous HPC transplants must *not* be irradiated.
HPC, hematopoietic progenitor cell; IUT, intrauterine transfusion; SCID, severe combined immunodeficiency.

plasma-containing haptoglobin from components being transfused to a haptoglobin-deficient recipient with antihaptoglobin antibodies.[19,20] The shelf life of washed components is reduced to 24 hours if refrigerated or 4 hours if maintained at room temperature after washing.

A CMV-seronegative blood is obtained by testing frequent donors for CMV antibodies. This specification is indicated for cellular components only, and is used for transfusion to at-risk groups, such as pregnant women and their fetuses, low birth weight infants, transplant recipients, and certain immunocompromised recipients.

Blood Components

Red Blood Cells

Red blood cells consist of erythrocytes that have been prepared from whole blood donation or apheresis. Red blood cells are anticoagulated by a preservative solution containing citrate. Red blood cells prepared with additive solutions (AS) exhibit lower viscosity, allowing the RBCs to flow through administration systems in a manner more comparable to that of whole blood. The specific preservative or AS are selected by the blood bank. Depending on the preservative-anticoagulant, the hematocrit of RBCs is approximately 55% to 65% for AS-1, AS-3, AS-5, and AS-7, and about 65% to 80% for citrate-phosphate-dextrose-adenine solutions CPDA-1, CPD, and CP2D. RBCs contain 20 mL to 100 mL of donor plasma in addition to preservative and anticoagulant. The typical volume of AS RBCs, including AS, is 300 mL to 400 mL, but volumes vary with the amount that was collected from the donor. Each unit contains 160 mL to 275 mL of red cells, which is 50 g to 80 g of hemoglobin. Other physical properties, such as electrolyte concentrations and pH, vary based on AS used and the time, during its lifetime, it is tested.

The transfusion of RBCs increases oxygen carrying capacity. Typically, the transfusion of one unit of RBCs would be expected to increase the hemoglobin concentration of an average-sized adult by approximately 1 g/dL (3% hematocrit increase), although this will vary with the volume of the transfused unit.

There are several products available for transfusion of red blood cells, with the vast majority utilized in the U.S. being RBCs and Leukocyte Reduced RBCs (Table 2).

Transfused RBCs must be compatible with ABO antibodies in the recipient's plasma. Serologic compatibility between recipient and donor is established by performing ABO/Rh typing, antibody screening, and crossmatching, which takes approximately 1 hour in total (although longer times are often required when any of the testing is outside normal limits). Once a blood sample is collected from the patient, ABO/Rh typing is performed in two parts:

1. Forward typing: the patient's RBCs are mixed with reagent antisera to assess the antigens on red cells.
2. Reverse typing: the patient's plasma or serum is mixed with known group/type RBCs to assess for the presence of antibodies.

From this point, the ABO group has been determined, and ABO group specific blood can be used when necessary. The

TABLE 2. RBC Products

Product Type	*Description*
RBCs	
Leukocyte-reduced RBCs	
Washed RBCs	–Indicated for patients with absolute IgA deficiency resulting in anaphylactic or recurrent severe allergic reactions to red cells
Deglycerolized RBCs	–Previously frozen red cells made available for infusion (RBCs are stored frozen for patients with rare red cell phenotypes and rare antibodies. Glycerol is added prior to freezing for cryoprotection. Once frozen, the RBCs can be stored for longer than 10 years. Glycerol is then removed by washing the cells with successively lower concentrations of sodium chloride.) –In addition to the side effects and hazards of RBC transfusion, deglycerolized RBCs carry a risk of intravascular hemolysis if deglycerolization has been inadequate.
Rejuvenated RBCs	–Prepared from RBCs stored in CPD, CPDA-1, and AS-1 storage solutions up to 3 days after expiration –An FDA-approved solution is added, and cells are washed to remove toxins prior to transfusion. –Rejuvenation of units may be indicated for patients with many antibodies, who therefore have a difficult crossmatch. –After rejuvenation, they should be transfused within 24 hours or frozen.
Whole blood	–Must be ABO-identical –Can be transfused for patients with both symptomatic anemia and volume deficits –Can be stored at 1–6°C for 21–35 days, depending on the solution –Autologous whole blood or RBCs can also be collected from patients who anticipate requiring blood transfusions.

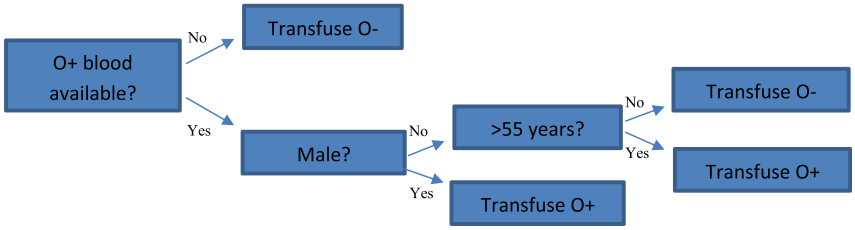

Figure 1. Group O algorithm.

next step is an antibody screen, which is performed by mixing the patient's plasma with reagent RBCs of a known phenotype and antihuman globulin reagent, incubating, and spinning down to check for agglutination. If this antibody screen is positive, panels containing additional reagent red cells are used to identify the specific antibody. The 18 most common antigens in the United States include D, C, E, c, e, K, k, Fy ^{a}, Fy ^{b}, Jk ^{a}, Jk ^{b}, Le ^{a}, Le ^{b}, P1, M, N, S, and s. The final step is crossmatching recipient and potential donor. If the antibody screen was positive, an antihuman globulin crossmatch must be performed to ensure compatibility for the previously determined antibodies. If the antibody screen was negative, the crossmatch can be performed as either an immediate spin crossmatch or an electronic crossmatch. In an immediate spin crossmatch, a small number of RBCs from the potential donor unit is combined with a small amount of the recipient's plasma or serum, and the sample is checked for agglutination and/or hemolysis (which would indicate ABO incompatibility). In laboratories with a validated computer system following the FDA approved guidance, the immediate spin crossmatch can be replaced by a computer matching procedure (also called electronic crossmatch).[21]

Uncrossmatched group O RBCs can be transfused if the patient's ABO group is unknown and lifesaving transfusion is needed urgently. Group O erythrocytes do not express A or B antigens, and therefore will not cause an ABO incompatibility hemolytic transfusion reaction. These group O "Emergency Release" RBCs are frequently utilized in trauma. Alternatively, uncrossmatched ABO group specific RBCs can be used as soon as the patient's ABO blood type has been determined, even if there is insufficient time to complete the other steps of routine pretransfusion testing. As a patient safety measure, some institutions require that ABO group determination be performed on two separate samples of the patient's blood for initial presentations, before issuing ABO group specific RBCs. In emergency situations where uncrossmatched group O or ABO group specific blood is used, there remains a risk for hemolytic transfusion reaction if the recipient has a preexisting red cell antibody to another antigen on the donor cells. This can cause hemolysis of the donor unit(s) and potential organ injury in the recipient. However, this is rare, and occurs at an incidence of less than 1%.[22]

Overall, the trauma surgeon should consider several tiers of patients requiring emergent RBC transfusion (Figs. 1 and 2):

1. All males and females above childbearing age (commonly >55 years old but determined by the hospital transfusion service) can be preferentially transfused with group O Rh type positive RBCs (to preserve group O Rh type negative units).
2. If no group O Rh type positive RBCs are available, or if the patient is a female of childbearing age, group O Rh type negative RBCs should be transfused. Transfusing females of childbearing age with only Rh type negative RBCs prevents Rh sensitization and anti–D-mediated hemolytic disease of the newborn in future pregnancies. If an Rh type negative female does inadvertently receive emergency release Rh type positive blood, the potential for harm is small. Routine prenatal care includes drawing multiple blood samples to identify and treat for the presence of such antibodies.
3. As soon as the patient's ABO group is determined, patients should be transitioned to ABO group matched RBCs.

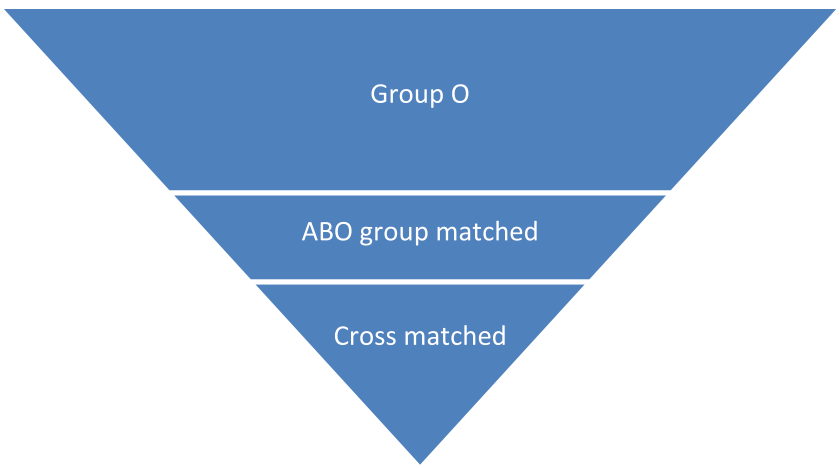

Figure 2. Algorithm for matched RBCs.

4. Patients should receive crossmatched blood as soon as the process has been completed. However, if an actively bleeding patient has a negative antibody screen and has received more than 10 RBC units in a short time period, the crossmatch test is waived by many hospital transfusion services, so that group O or ABO group specific RBCs can be transfused without delaying for crossmatching.

RBCs are maintained in liquid form refrigerated up to 42 days, or if necessary, at room temperature for up to 4 hours. RBCs can be returned to the blood bank only if blood that has been removed from storage controlled by a licensed blood bank/transfusion service has been stored continuously at 1°C to 6°C, and/or has been shipped between 1°C and 10°C.[4,23]

RBCs can be stored in validated coolers to be dispensed to the trauma bay or operating room. Blood coolers are not required to have a specific premarket qualification, for example, a cooler purchased from a grocery store can be used. However, when used as a blood cooler, they are required to follow Current Good Manufacturing Practice (CGMP) enforced by the US Food and Drug Administration (FDA). CGMP assures proper design, monitoring, and control of manufacturing processes and facilities. The physical cooler and the "ice" must be validated by placing discarded blood into the cooler to determine how long it takes for the temperature of the blood to exceed storage (6°C) and transport (10°C) temperatures. This is performed with multiple units for each cooler, and the length of time determined is the time the units in that cooler can be outside of the blood bank control and still be returned to the blood bank inventory. After this validation, the blood bank has established that the units in that cooler will remain between 1°C and 6°C (for storage) or between 1°C and 10°C (for transport) for that validated period of time, which is equivalent to the storage and transport temperatures used in the blood bank.

RBCs can also be stored frozen for up to 10 years as described previously, but this is not routine. The shelf life of refrigerated RBCs depends on the anticoagulant/preservative system used, but most blood banks choose to use preservative systems that permit 42 days of storage. RBCs that have been stored for a shorter period of time may be superior, due to the potential for cellular changes and the accumulation of bioactive materials during storage. Older age RBCs transfused in early trauma resuscitation have been demonstrated in retrospective studies to be an independent risk factor for post injury multiple organ failure.[24] However, prospective studies, including a recent multicenter, randomized, blinded trial of 4,995 patients, have failed to demonstrate decreased mortality with "fresh blood" (mean, 11 days vs. 22 days).[25]

There is great variability in the length of time RBCs can be expected to survive in circulation after transfusion. According to FDA guidelines, up to 25% of transfused RBCs may not survive beyond 24 hours.[26] Conversely, the maximum survival post transfusion is 135 days.[27,28]

The immediate immunologic consequences of transfusion of RBCs can occur acutely within seconds of initiating transfusion, to as much as hours after initiation. An acute hemolytic transfusion reaction typically occurs within minutes to hours of initiating a transfusion, and involves the intravascular destruction of donor red cells by the interaction between host antibodies and complement proteins. The most severe example is ABO group incompatibility, which can be fatal. Two deaths were reported due to ABO group incompatibility in the U.S. in 2015. Transfusion-related acute lung injury (TRALI) is another acute immunologic cause of death after transfusion. It is generally caused by the transfusion of donor antibodies that react with recipient white blood cells. In susceptible individuals, the interaction of donor antibodies with host white cells triggers a pulmonary reaction that presents as hypoxemia and noncardiogenic pulmonary edema, typically during or within 6 hours of transfusion. Anaphylactoid or anaphylactic reactions are also a rare cause of transfusion fatality. They present with hypotension, tachycardia, GI symptoms, pulmonary or laryngeal edema, and bronchospasm and/or laryngospasm. Less severe immediate immunologic consequences include febrile nonhemolytic reactions, which occur during or shortly after transfusion. These are attributed to either the action of host antibodies against donor white blood cells, or the action of cytokines generated by transfusion. Finally, mild allergic reactions present as urticaria or wheezing, and usually respond to antihistamines.

Delayed immunologic reactions occur in the days to weeks following transfusion. Delayed hemolytic reactions are typically due to extravascular hemolysis, and cause mild anemia, slight fever, and hyperbilirubinemia. Occasionally, delayed intravascular hemolysis can occur. Alloimmunization is an immune response from exposure to antigens that are different from the host. Alloimmunization can occur to red blood cells, white blood cells, or platelets. If alloimmunization occurs, there is a risk for systemic response with subsequent transfusions, or accelerated removal of the cells transfused. Another delayed reaction, post transfusion purpura, occurs when the body produces alloantibodies to the donor's platelets' antigens. This causes a precipitous thrombocytopenia that occurs days after transfusion. Finally, TA-GVHD can occur if T lymphocytes from the donor component react against recipient HLA class I and II antigens. Transfusion-associated graft-versus-host disease usually occurs in immunocompromised patients, and manifests with fever, skin rash, anorexia, nausea and emesis, watery or bloody diarrhea, and sometimes hyperbilirubinemia or elevated liver enzymes. Transfusion-associated graft-versus-host disease can occur in immunocompetent patients who are transfused with directed RBCs from related family donors or from HLA-matched or crossmatched platelet products.

Nonimmunologic reactions include transmission of CMV or other infectious diseases, bacterial sepsis, hypothermia, metabolic complications, transfusion-associated circulatory overload, or pain reactions.

Due to the potential for adverse events, it is essential to consider all strategies for minimizing transfusion. A full description of such strategies is outside the scope of this review; however, this must begin with aggressive hemorrhage control, as well as consideration given to intraoperative blood salvage, pharmacologic therapies to promote hemostasis, and meticulous fluid and temperature management to minimize the impact on their coagulopathy.

Plasma

Similar to red blood cells, plasma is manufactured from the fractionation of whole blood or collected directly by

TABLE 3. Plasma Products

Product Type	Description
FFP	–Frozen within 6–8 hours of collection, and then stored at minus 18°C or colder until thawed for use –Contains physiological quantities of all coagulation factors
PF24	–Frozen within 24 hours of collection, and then stored at minus 18°C or colder until thawed for use –Contains physiological quantities of all coagulation factors.
PF24RT24	–Prepared from apheresis collections –Contains physiological quantities of all coagulation factors
Thawed plasma	–FFP, PF24, or PF24RT24 can be relabeled as Thawed Plasma when stored at 1°C to 6°C, for up to a total of 5 days, including the initial 24-hour postthaw period
Thawed plasma cryoprecipitate reduced	–Prepared from whole blood-derived FFP after thawing, centrifugation, and removal of the cryoprecipitate –Use is essentially limited to treatment of thrombotic thrombocytopenic purpura
Liquid plasma	–Separated no later than 5 days after the expiration date of the corresponding whole blood unit, is never frozen and is stored at 1–6°C for up to 26 days[26] –Can be used for initial treatment of patients requiring massive transfusion because of life-threatening trauma or hemorrhage and who have clinically significant coagulation deficiencies
Octaplas (pooled plasma (human), solvent/detergent treated solution for intravenous infusion)	–Approved by the FDA for use in the United States in January 2013 –Produced in pools of plasma from 630 to 1,520 donors, undergoes 1 μM filtration, solvent-detergent reagent treatment, and affinity column filtration to bind prion proteins –Units are supplied in ABO-specific 200-mL volumes.
Pathogen-reduced plasma	–Treated with an agent that inactivates most infectious agents –Eliminates the need to culture the plasma prior to administration.

PF24, plasma frozen within 24 hours after phlebotomy; PF24RT24, plasma frozen within 24 hours after phlebotomy held at room temperature up to 24 hours after phlebotomy.

apheresis. It is composed of albumin, coagulation factors, fibrinolytic proteins, immunoglobulin, and other proteins. Labile coagulation factor levels vary based on several factors, including ABO group and storage conditions. The average volume of a unit is 200 mL to 250 mL, but apheresis-derived units may contain as much as 400 mL to 600 mL. The volume of a unit is determined by the quantity obtained from an individual donor, and there is no standard or minimum volume. Plasma is utilized to correct global factor deficiencies and should not be used when a specific factor replacement is available.

There are many different categories of plasma used in the United States in support of trauma resuscitation (Table 3).

Regardless of the plasma product used, plasma should be ABO group compatible with the recipient's red blood cells. However, in emergencies, group AB plasma can be transfused to recipients whose blood group is unknown, because it does not contain anti-A or anti-B antibodies to potentially react with a recipient's ABO red cell antigens. Unfortunately, group AB plasma is often in short supply, and with the shift to early and aggressive transfusion of RBCs and plasma in a 1:1 ratio for massive transfusion, there is extreme pressure on blood donor collection programs to provide an increased amount of this universal donor plasma. As a result, many centers have begun utilizing group A plasma for initial emergency transfusions. In such cases, there is a small risk of hemolytic transfusion reaction if the recipient has group B or group AB red cells.[29,30] Since the majority of the population is group O or group A, only a minority of patients with unknown blood type are at risk for reacting to anti-B antibodies if group A plasma is used for their trauma resuscitation. If group A plasma is to be utilized for emergencies in this way, as a precaution, the units can be prescreened for titers of anti-B antibodies, and those with high titers of anti-B reserved for known group O or group A patient only. Prescreening for titers is not FDA-mandated, and no maximum titer threshold has been validated or universally accepted, but it may decrease the chance of transfusion reaction when group A plasma is utilized for emergencies. Many trauma centers have developed tiered transfusion plans which keep group A plasma thawed and available for the initial transfusion, group AB units are then thawed upon trauma activation, and ABO-identical plasma is ultimately used as soon as the patient's native ABO group is determined.

Liquid (never frozen) plasma has not been routinely used in the United States, but this is likely to change, as availability

TABLE 4. Platelet Products

Product Type	Description
Platelet concentrates	–Random platelet concentrates that are prepared from whole blood donation
Pooled platelets	–Concentrates combined from multiple donors
Leukocytes reduced platelets	
Leukocytes reduced pooled platelets	–Prepared by pooling platelets from multiple donors and filtering
Apheresis platelets (platelets pheresis)	–One unit of apheresis platelets is equivalent to 4–6 units of platelets from whole blood
Leukocytes reduced apheresis platelets (platelets pheresis leukocytes reduced)	
Apheresis platelets with platelet AS added and leukocytes reduced	–Collected by apheresis then suspended in plasma and an approved platelet AS
Pathogen reduced apheresis platelets	

has increased with demand by trauma centers. Recent studies indicate that liquid plasma may have superior hemostatic potential when compared to FFP, plasma frozen within 24 hours after phlebotomy, and thawed plasma.[31,32] A large cohort study demonstrated improved short-term mortality associated with the use of liquid plasma in comparison to fresh frozen plasma.[31]

If a frozen plasma product is used, it must be thawed in a water bath at 30°C to 37°C or in an FDA-cleared microwave device. This takes approximately 15 minutes. After thawing, plasma should be used immediately, or it can be stored at 1°C to 6°C for up to 24 hours. After 24 hours, it must be relabeled as "thawed plasma" and used within the next 4 days or discarded.

Another plasma product that is becoming increasingly popular is freeze dried plasma. This dehydrated plasma product does not require refrigeration or thawing. It has been in use for several years in Europe, as well as by the US military forces overseas. It has not yet gained FDA approval for use in the United States; however, in 2018, the FDA and Department of Defense issued a joint statement committing to fast-track approval.[33]

The most common reactions associated with plasma transfusion include TRALI; transfusion-associated circulatory overload, and allergic or anaphylactic reactions.[34] Infection transmission, febrile nonhemolytic reactions, RBC alloimmunization, and hemolytic transfusion reactions are also possible, though less common.

Platelets

Platelets are a critical part of the hemostatic process and are often underutilized during damage control resuscitation. They function specifically in the formation of a primary hemostatic plug. They are indicated for patients with thrombocytopenia or dysfunctional platelets who are bleeding or at high risk for bleeding.

Platelets are manufactured from whole blood separation to prepare random or pooled platelet concentrates or, more commonly, are collected directly by apheresis. They are suspended in a small volume of the original plasma and stored at room temperature (20–24°C) in an oxygen-permeable container, gently agitated. They typically have a shelf life of 5 days (although the FDA now permits platelets to be stored for 7 days under stringent conditions) and should not be refrigerated. Current research is ongoing as to the effectiveness of cold platelet storage and has shown promise in the resuscitation of bleeding patients. One unit of platelets from whole blood usually contains at least 55 billion platelets suspended in 40 mL to 70 mL of plasma. One such unit would be expected to increase the platelet count of a 70-kg adult by 5 to 10,000/μL. Platelet units contain small amounts of leukocytes and may contain trace amounts of red blood cells. In the United States, greater than 80% of platelets that are transfused are acquired by apheresis, and these products contain at least 300 billion platelets in about 300 mL of plasma and/or AS.[35]

There are several different categories of platelets available for use in the United States (Table 4).

Platelet transfusion should be along ABO-compatible lines; however, other compatibility testing is not necessary, unless dealing with a patient experiencing immune-mediated platelet transfusion refractoriness. Platelets can be irradiated by X-ray, gamma radiation or psoralen/UVA light, to prevent GVHD. Adverse effects associated with platelet transfusion include hemolytic transfusion reactions (if group O platelets are transfused to non–group O recipients), febrile nonhemolytic reactions, allergic reactions, sepsis, TRALI, circulatory overload, GVHD, and posttransfusion purpura. Also, similar to ABO incompatibility of red blood cells, immune-mediated platelet destruction can occur due to alloantibodies in the recipient to Human Leukocyte Antigen (HLA) or (HPA) antigens on transfused platelets. This can cause patients to be refractory to platelet transfusion.

Similar to RBCs, the lifespan of transfused platelets varies. While native platelets survive in circulation an average of 10 days, transfused platelets more frequently circulate for 5 days to 7 days.[36] Cold storage of platelets was abandoned in the 1970s due to the shortened lifespan of cold platelets in circulation post transfusion. However, several studies have suggested that refrigerated platelets may have superior hemostatic function.[37] In addition, cold storage increases the shelf life and decreases the risk for bacterial contamination. For these reasons, cold-stored platelets are now being reconsidered for resuscitation of bleeding patients.

Cryoprecipitate

Cryoprecipitate functions as a source of fibrinogen, Factor VIII, Factor XIII, von Willebrand factor (vWF), and fibronectin. These products can be used to control bleeding associated with congenital or acquired fibrinogen deficiency with lower volume infusion than FFP. They can also be used as second-line therapy for von Willebrand disease, Factor VIII deficiency, or Factor XIII deficiency.

Cryoprecipitate is prepared by thawing FFP between 1°C and 6°C and recovering the precipitate. The cold-insoluble precipitate is placed in the freezer within 1 hour after removal from the refrigerated centrifuge. Units from several donors (usually five bags at a time) can be combined and labeled "pooled." If pooled, the precipitate should be mixed well with 10 mL to 15 mL of diluent (0.9% sodium chloride preferred) to ensure complete removal of all material from the container. The recovery of transfused fibrinogen is 50% to 60%. The dose for transfusion is o bag (one donor unit)/7-kg to 10-kg patient body weight to raise plasma fibrinogen levels 50 mg/dL to 75 mg/dL. The dose should be calculated based on the patient's fibrinogen level; however, a standard adult dose is often 5 or 10 bags.

The cryoprecipitate products available for transfusion are displayed in Table 5.

Compatibility testing is unnecessary for cryoprecipitate, because there is such a small amount of plasma contained in the product. However, ABO-compatible cryoprecipitate is preferred whenever available, to prevent the small chance of a

TABLE 5. Cryoprecipitate Products

Product Type	Description
Cryoprecipitate (single donor)	– Must contain at least 150 mg of fibrinogen, but usually contains 200–250 mg –Generally used for pediatrics
Pooled cryoprecipitate (5 donors)	–Contains at least 1–1.5 g of fibrinogen

transfusion reaction from donor antibodies contained in a cryoprecipitate unit. Cryoprecipitate is stored frozen and thawed in a protective plastic overwrap in a water bath at 30°C to 37°C. It should not be refrozen and should be maintained at room temperature and transfused within 6 hours of being thawed.

Adverse effects associated with cryoprecipitate transfusion include hemolytic transfusion reactions (if excessive amounts of group O cryoprecipitate are transfused to non–group O patients), febrile nonhemolytic reactions, allergic reactions, sepsis, TRALI, and circulatory overload.

Whole Blood

Whole blood can be transfused for patients with both symptomatic anemia and volume or clotting factor deficits. Whole blood must be ABO identical to the recipient. Autologous whole blood can be collected from patients who anticipate requiring blood transfusions. Whole blood can be stored at 1°C to 6°C for 21 days to 35 days, depending on the solution.

Despite the movement toward component therapy, fresh whole blood has remained an important resource for the military, especially in the form of "walking donors." Due to the successful military experience, some nonmilitary hospitals in the United States have recently returned to whole blood for transfusion of hemorrhaging patients.[38] Whole blood has been approved by the FDA for years. In contrast to type O RBCs, type O whole blood contains a significant volume of plasma that is not crossmatched to the blood of the recipient. For this reason, lower titer units are likely safer for transfusion, though no specific antibody titer requirements exist. Due to the limited supply of O-negative blood, O-positive whole blood is considered an alternate transfusion option, with potential Rh immunoglobulin (e.g., Rhogam, Winrho, Rhophylac) administration to females of childbearing age as needed.

Future Therapies

The high cost and limited availability of blood products underscores the importance of efficient transfusion practice by the trauma surgeon. The current trend is for massive transfusion in a balanced ratio to be followed by specific product transfusion, guided by coagulation assays, once available. A recent randomized controlled trial demonstrated improved survival with resuscitation guided by viscoelastic testing, when compared with conventional coagulation assay-guided resuscitation.[39] This technology has the potential to decrease the demand for blood products by optimizing the utilization and is consequently becoming more ubiquitous.

There is hope that artificial blood substitutes will someday replace allogeneic blood transfusions. Artificial blood substitutes have the potential advantages of unlimited availability, widespread compatibility, and longer storage capability. They also minimize the risk for transmission of infectious diseases. Indeed, several hemoglobin-based oxygen carriers have been developed. However, the FDA has not approved any of the current products due to short half-life and significant side effects.[40] Artificial blood substitutes remain an important area for ongoing research. However, at least for the foreseeable future, the world remains dependent on blood transfusions for the resuscitation of hemorrhage. It is critical then that trauma surgeons master the administration of this costly, scarce, and lifesaving resource.

AUTHORSHIP

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