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EM Critical Care

UNDERSTANDING AND CARING FOR CRITICAL ILLNESS IN EMERGENCY MEDICINE

The Use Of Blood Products In The Critically Ill Patient: Indications And Risks

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Abstract

It is imperative that emergency physicians have a basic understanding of blood products and the indications and risks associated with their use. Evidence-based, restricted use of blood components in critically ill patients can lead to decreased mortality while avoiding unnecessary morbidity and complications. Recognition of the need for irradiated or leukoreduced components in special populations further reduces adverse events. This issue reviews the preparation of blood components and indications for their use, infusion of products, and the determination of stability after infusion. Infectious and immunologic risks associated with transfusion are reviewed, with special attention given to pulmonary complications, as well as guidelines for comprehensive informed consent. Massive transfusion protocols and the use of oxygen-carrying substitutes are also discussed.

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CME Objectives

Upon completion of this article, you should be able to:

1. Describe the indications for PRBCs, plasma, and platelet transfusion.
2. Identify the techniques and equipment required for transfusion.
3. Recognize patients who may have unique requirements for blood products.
4. Summarize the current evidence relating to transfusion in critically ill patients.
5. Provide accurate informed consent to patients and/or family members of those receiving blood products.

Prior to beginning this activity, see "Physician CME Information" on the back page.

Case Presentations

No sooner have you hung up your coat in the ED than an announcement comes on: "Attention ED staff, medic 19 is en route with a trauma. A 78-year-old male, victim of a MVC…vital signs unstable…" Your team quickly gathers to receive a report from EMS:

> *"Mr. Smith is a 78-year-old male who was the restrained front-seat driver involved in a roll-over motor vehicle crash. The vehicle slid on ice and collided with the median. We noted significant damage to the vehicle with intrusion of 14 inches into the compartment. The patient was extricated from the car and immediately placed on a backboard with cervical-spine immobilization. Vital signs en route were notable for a heart rate of 110 and a systolic blood pressure of 100."*

The patient is moved onto the stretcher and you initiate the primary survey. The patient is mentating and has bilateral breath sounds but a rapid, thready pulse. Vital signs are as follows: temperature, 36.8°C; heart rate, 136 beats/min; respiration rate, 26 breaths/min; blood pressure 80/30 mm Hg; oxygen saturation, 90% by nonrebreather mask. He is awake, but confused. There is no trauma to the face, chest, or extremities. His pelvis is unstable, however, and he groans when you press on his abdomen. The nurses announce that 16-gauge IVs have been placed in each arm and they ask you what combination of fluids and blood products you want to use to resuscitate the patient. Just then, you're pulled aside by your charge nurse…

"There is a gentleman we just brought back to Room 3. He doesn't look well and says he's been throwing up blood." You walk into room 3 and see a young man in his 30s clutching a basin half full of coffee-ground emesis. As your nurse is placing 2 18-gauge IVs in him, a set of vital signs is also obtained: temperature, 35.6°C; heart rate, 130 beats/min; blood pressure, 90/65 mm Hg; respiration rate, 32 breaths/min; and oxygen saturation, 98% on room air. After an antiemetic is given, the patient notes that he had been taking large amounts of ibuprofen over the past 10 days due to a recent ankle injury. He complains of feeling lightheaded, with associated palpitations and shortness of breath. He also mentions his stool has been dark black, and frequent. He has no other medical problems. You ask the nurse to send a type and screen, CBC, complete metabolic panel, and coagulation panel.

You have 2 unstable patients in your ED who are actively bleeding. Both potentially need blood products, but who needs them now and who can wait?

Introduction

Since the first complete description of the circulatory system by William Harvey in 1628,[1] physicians have recognized the potential of blood products as a means of curing disease and saving lives. Most early attempts at blood transfusion were met with complications, likely due to unrecognized reactions of the immune system.[2,3] The discovery of the major blood groups by Karl Landsteiner at the turn of the 20th century, and the development of technology to fractionate and store blood and plasma gave rise to the modern era of transfusion.[4] With the onset of World War II, the administration of blood products became a vital component of medical care.[5]

While the first half of the 20th century was characterized by technological advancements in transfusion medicine, the second half was largely dominated by the emergence of previously unrecognized risks associated with this new practice. The appearance of transfusion-associated hepatitis in World War II survivors was, perhaps, the first sign this intervention may not always be beneficial for the recipient. A period of several decades passed before the responsible agent, the hepatitis B virus, was identified and adequate screening was developed.[6] While the blood supply of industrialized countries is increasingly safe, the administration of blood products is not risk free. New infectious pathogens have emerged, and noninfectious hazards such as transfusion-related acute lung injury (TRALI) are now recognized.[7,8]

In the 21st century, the emergency department (ED) has become the front line of transfusion medicine. Critically ill patients with life-threatening hemorrhage, anemia, thrombocytopenia, and coagulopathy are encountered on a daily basis. By understanding the best available evidence and implementing appropriate transfusion practices, emergency physicians can utilize blood products to decrease morbidity and mortality while minimizing risk to critically ill patients.

Note: a list of abbreviations used in this issue is included on page 19.

Critical Appraisal Of The Literature

A literature search was performed using Ovid MEDLINE® and PubMed for articles from 1950 to the present related to the use of blood products in critically ill patients. The search included only English-language publications and primarily focused on human studies, but it did not specifically exclude applicable animal studies. Search terms included *blood transfusion, critical illness, erythrocyte transfusion, blood component transfusion, blood coagulation factors, blood group incompatibility, acute lung injury, informed consent, hemorrhage,* and *hemorrhagic shock.* Clinical guidelines relevant to the use of blood products from the American Association of Blood Banks, the United States Food and Drug Administration (FDA), the American Red Cross, and the Cochrane Database of Systematic Reviews were reviewed. Additional articles were identified using cited reference searches and by reviewing the bibliographies of the articles

found in the primary search. This search strategy returned over 5000 articles and reports. Articles were examined with regard to study design and relevance to topics being covered in this review. The most weight was given to randomized controlled and aggregate studies including meta-analyses of clinical trials. Retrospective studies, case-controlled studies, panel consensus, and case reports were also considered in areas lacking stronger evidence. In total, we reviewed and incorporated 128 articles.

Going Deeper: How Red Blood Cell, Plasma, And Platelet Transfusions Work

Blood typing and screening should be performed in all patients and preferably before transfusion if the patient is stable. Typing involves identifying the patient's ABO blood group and Rh status. Apart from ABO and Rh, there are many other human blood groups that are potentially antigenic, but these only rarely cause transfusion reactions. As a result, a preliminary "screen" is all that is needed to exclude the presence of antibodies to these less-common blood groups. A type and screen is typically ordered when there is a chance that a transfusion will be required. The blood bank will not set aside units for a patient or crossmatch them (a process in which donor red blood cells [RBCs] are directly mixed with the recipient's blood), until it is known that a transfusion will be performed. The entire process of type and screen compatibility testing typically takes 1 hour, but the final step – the crossmatch – can be performed in as little as 10 to 15 minutes, assuming the type and screen is already complete. Of note, if the patient's screen is positive, the blood bank must identify which atypical antibody (or antibodies) the recipient carries; finding compatible units of donor blood can be a lengthy and complex process.

In the event that the patient is unstable and hemorrhaging, uncrossmatched blood can be utilized. In this case, group O RBCs are administered, making it unlikely that the recipient will have a hemolytic transfusion reaction. Multiple studies from the trauma literature have not reported evidence of transfusion reactions with the use of uncrossmatched blood, suggesting that this practice is safe in this setting.[9,10] However, in a retrospective review of 265 patients who received group O RBCs, Goodell et al identified at least 1 patient who had laboratory evidence of non-ABO antibody-mediated hemolysis. They noted that the symptoms of hemolytic transfusion reaction may be difficult to identify in critically ill trauma patients.[11] (For more information on the symptoms of these reactions, see the section "Complications Of Blood Product Administration," page 7.)

Blood components are separated from whole blood donations by centrifugation or they are collected individually by apheresis techniques. Whole blood has limited availability and is rarely used in the civilian setting. **Table 1 (see page 4)** lists characteristics of the commonly used blood products.[12]

Packed Red Blood Cells

Erythrocyte concentrates are most commonly prepared from whole blood donations via centrifugation. Packed red blood cells (PRBCs) are stored in a solution of citrate, phosphate, and dextrose anticoagulant. Sodium adenine glucose mannitol (SAGM), a preservative solution that maintains adenosine triphosphate (ATP) levels, supports RBC metabolism, and reduces hemolysis is added to prolong RBC viability. PRBCs are stored for up to 42 days at 1°C to 6°C. During storage, several biochemical and physiologic changes occur, including increased fragility of the cell membrane, a decrease in 2,3-bisphosphoglycerate and ATP levels, and an increase in potassium levels. These changes are collectively referred to as the "storage lesion" and, theoretically, lead to decreased viability and functionality of transfused cells.[13,14] While several retrospective and prospective studies have suggested an increase in morbidity and mortality with the use of PRBCs stored for prolonged periods of time,[15-21] other studies have failed to reproduce these results and expert opinion is conflicting regarding the clinical significance of the storage lesion.[22-28] In a small trial of ventilated critically ill patients, Walsh et al measured multiple indices of tissue oxygenation in 22 anemic patients randomized to receive 2 units of PRBCs ≤ 5 days old or ≥ 20 days old. Arterial pH, base excess, and lactate levels were not significantly different between the 2 groups.[29] The Age of Blood Evaluation (ABLE) trial, a large double-blind multicenter randomized controlled trial, will compare the use of PRBCs ≤ 7 days old versus 15 to 20 days old, and may provide a more definitive answer to this controversy.[30,31]

Prior to storage, RBC concentrates and other blood products may be filtered to remove white blood cells in a process called leukodepletion or leukoreduction. Alternatively, blood products may be "gamma irradiated," a process in which they are exposed to high levels (eg, 25 Gy) of radiation in order to deactivate and destroy donor lymphocytes. Both of these procedures are aimed at preventing complications of blood product administration and will be discussed in greater detail in the section, "Complications Of Blood Product Administration" on page 7.

Plasma Components

Plasma is separated from whole blood or collected via apheresis and then frozen at -18°C to -30°C. If this occurs within 8 hours of collection, it is referred to as fresh-frozen plasma (FFP). If it is frozen within 24 hours, the plasma becomes frozen plasma 24

(FP24). While FP24 has slightly decreased levels of several coagulation factors, these differences are not thought to be of clinical significance. Both FFP and FP24 can be stored for up to 1 year, but once they are thawed, degradation of labile coagulation factors (particularly factor V and factor VIII) ensues, such that units must be stored at 1°C to 6°C and used within 5 days.[32]

When FFP is thawed, some of the coagulation factors precipitate and can be collected by centrifugation. The resulting product, cryoprecipitate, has a much lower volume (15 mL/unit) than FFP, and contains higher concentrations of factor VIII, fibrinogen, factor XIII, and von Willebrand factor (vWF). The product can be stored for up to 1 year at -18°C. Due to the factor VIII content, cryoprecipitate was used frequently in the treatment of patients with hemophilia A until factor concentrates became available. The use of cryoprecipitate is now almost exclusively restricted to patients with fibrinogen deficiency and active bleeding (as can occur in disseminated intravascular coagulopathy or thrombotic thrombocytopenic purpura). As noted previously, a unit of cryoprecipitate actually contains less fibrinogen than a unit of FFP, although its concentration is much higher.

In certain rare circumstances, cryodepleted plasma, which is deficient in factor VIII, fibrinogen, factor XIII, and vWF may be utilized. Cryodepleted plasma contains all the vitamin K-dependent coagulation factors, so it can be used for the reversal of warfarin-induced coagulopathy (although FFP is typically administered). The one setting in which cryodepleted plasma has traditionally been preferred to FFP is for patients with thrombotic thrombocytopenic purpura, but recent studies have shown no significant benefit.[33,34]

Platelets

Platelet preparations are either pooled from multiple units of donated blood or collected via apheresis. A single unit of platelets is collected from each unit of blood and 4 to 6 units are then pooled together for a single transfusion unit. Pooled platelets are

Table 1. Overview Of Blood Products[12]

Product	Contents	Physiologic Components and Volume	Storage Temperature	Shelf Life	Expected Response	Physiologic Effects
Packed red blood cells	Erythrocytes Citrate Phosphate Dextrose Saline Adenine	Hgb 42.5-80 g/unit Hct 55%-80%/unit Total volume of 300-400 mL/unit	1°C -6°C	42 days	High increase of 1 g/dL/unit Hct of 3%/unit within 15 minutes (if no bleeding or hemolysis)	Increased oxygen-carrying capacity
Fresh-frozen plasma/frozen plasma 24	All coagulation factors Citrate Dextrose Phosphate	Volume of single unit varies (average 250 mL) Standard dose: 10-20 mL/kg	(-)18°C - (-)30°C	1 y (frozen) 5 days (thawed)	Decrease in PTT and PT	Repletion of coagulation factors towards hemostatic levels (not likely to improve INR to < 1.4)
Cryoprecipitate	Factor VIII Fibrinogen Factor XIII Fibronectin von Willebrand factor	150-200 mg fibrinogen 80-100 unit factor VIII 10-20 mL/unit 5 units/pool	(-)18°C - (-)30°C	1 y (frozen) 4-6 h (thawed)	1 pool should raise fibrinogen level by ~50 mg/dL	Correction of bleeding as a result of von Willebrand factor, fibrinogen, factor XIII or factor VIII deficiency
Random-donor platelets (RDP)	Platelets (from multiple donors) Citrate Dextrose Phosphate	7-8.5 x 10^{10} platelets/RDP in 40-70 mL plasma 3-4 x 10^{11} platelets/ 4-6 pooled units	20°C-24°C	5 days	Increase of 5-10 x 10^3/mcL/RDP given (within 10-60 min)	Hemostasis in the setting of thrombocytopenia or platelet dysfunction
Single-donor platelets (SDP)	Platelets (from a single donor) Citrate Dextrose Phosphate	3.5 x 10^{11} platelets in 100-500 mL plasma	20°C-24°C	5 days	Increase of 50-100 x 10^3/mcL/RDP given (within 10-60 min)	Hemostasis in the setting of thrombocytopenia or platelet dysfunction

Hct, hematocrit; Hgb, hemoglobin; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; RDP, random donor platelets.

cheaper and easier to collect, but they also expose the recipient to multiple donors. Apheresis involves removing whole blood from the donor. The blood is then separated into its components and, in the case of platelet apheresis, platelets are kept and the remaining components are transfused back into the donor. Single-donor platelets allow for matching donor blood type and human leukocyte antigen type to recipients.

All platelet concentrates are stored in a small amount of plasma at room temperature (typically 20°C-24°C). The warmer temperature, in addition to constant gentle agitation, prevents clumping of platelets, which leads to reduced survivability when transfused.[35] Nutrient-rich plasma and warmer temperatures also contribute to an increased risk bacterial growth.[36] Platelet concentrates can be stored for up to 5 days, although it should be noted that platelet concentrates stored for 5 days have been shown to have a higher incidence of contamination on Gram stain when compared to those stored for < 4 days, which suggests a greater possibility of bloodstream infection.[37] The risk of bacterial contamination also appears to be higher with pooled platelets, likely due to the additional phlebotomy involved. A recent study done by the American Red Cross supported this notion, indicating that the risk of bacterial contamination was approximately 5 times greater for platelets pooled from 5 donors than those collected, through apheresis, of a single donor.[38]

What Patients Need: Packed Red Blood Cells, Plasma, Or Platelet Transfusions?

When considering the administration of any blood product, the provider must evaluate the risks and benefits with the ultimate goal of maximizing clinical outcomes and minimizing unnecessary transfusions.[39] While transfusion thresholds for PRBCs have been thoroughly investigated through clinical trials, there is still no clear consensus. Similarly, plasma and platelet transfusion thresholds are not as well established.[40]

Packed Red Blood Cell Indications

PRBCs are transfused when there is hypovolemia secondary to hemorrhage or critical anemia. In the past, a transfusion trigger of hemoglobin (Hgb) < 10 g/dL had been used; however, this has been widely replaced with a lower transfusion threshold.[41] Following publication of the Transfusion in Critical Care (TRICC) trial results in 1999, a transfusion threshold of Hgb < 7 g/dL has been adopted. The multicenter TRICC trial randomly assigned critically ill patients to either a restrictive transfusion strategy (< 7 g/dL) or a liberal transfusion strategy (< 10 g/dL) and found decreased hospital mortality among patients in the restrictive transfusion arm.[42] Additionally, this hypothesis has been recently confirmed in a subset of patients with acute upper gastrointestinal bleeding. Villanueva et al randomized 921 patients with acute upper gastrointestinal bleeding to either a transfusion threshold < 7 g/dL or < 9 g/dL. Patients in the restrictive transfusion arm had a higher probability of survival at 6 weeks, fewer complications, and decreased bleeding when compared to the liberal transfusion arm.[43]

One clinical scenario where a more liberal transfusion strategy may offer a benefit is in a patient with acute myocardial ischemia.[44] A subset analysis of patients in the TRICC trial with acute ischemic cardiovascular disease had a trend towards improved outcomes when following a more liberal transfusion threshold of Hgb < 10 g/dL.[45]
In addition to following transfusion thresholds, the physician must consider the clinical condition of the patient with anemia when deciding whether or not to transfuse PRBCs. Transfusion of PRBCs is typically not indicated for Hgb > 10 g/dL except in extraordinary circumstances, such as massive hemorrhage. Published transfusion thresholds for PRBCs range from Hgb < 6 g/dL to 8 g/dL.[44,46-49] **(See Table 2.)** For more information on transfusion thresholds, please see the November 2013 issue of *Emergency Medicine Practice*, "Anemia In The Emergency Department: Evaluation And Treatment."

Plasma Indications

The transfusion of plasma products should occur in patients when there is insufficient coagulation and there is a clinical concern for ongoing bleeding that outweighs the risk of the transfusion. Clinical conditions that may benefit from plasma transfusion include exsanguination requiring massive transfusion,

Table 2. Packed Red Blood Cell Transfusion Recommendations[49]

Hemoglobin Level	Transfusion Recommendations
Hgb < 6 g/dL	Transfusion is recommended except in exceptional circumstances.
Hgb 6-7 g/dL	Transfusion is generally likely to be indicated.
Hgb 7-8 g/dL	Transfusion should be considered in postoperative surgical patients, including those with stable cardiovascular disease, after evaluating the patient's clinical status.
Hgb 8-10 g/dL	Transfusion is generally not indicated, but should be considered for some populations (eg, those with symptomatic anemia, ongoing bleeding, acute coronary syndromes with ischemia).
Hgb > 10 g/dL	Transfusion is generally not indicated except in exceptional circumstances.

Abbreviation: Hgb, hemoglobin.

patients requiring an invasive procedure with a high risk of bleeding complications, or patients requiring an invasive procedure with a low risk of bleeding but with abnormal baseline coagulation studies.[40,50] It is important to note that plasma products have a short duration of action and should not be used to correct an elevated international normalized ratio (INR) without clinical concern for bleeding, especially when considering that INR is unlikely to be improved to any value < 1.4.[51]

Platelet Indications

Platelet transfusions can be given prophylactically or they can be given based on the clinical status of the patient.[52,53] It is important to consider the cause of thrombocytopenia when deciding whether or not to administer prophylactic platelets to prevent spontaneous bleeding. Prophylactic platelets are given to patients with a platelet count < 10×10^3/mcL.[54] Although there are limited data to predict which thrombocytopenic patients will spontaneously bleed, patients with an acute infectious process, mucosal bleeding, or history of bleeding at specific platelet levels are generally at higher risk for spontaneous hemorrhage.[55] Patients with acute promyelocytic leukemia have an associated coagulopathy and should receive prophylactic platelets at a higher threshold < 30×10^3/mcL to 50×10^3/mcL.[56]

Patients with consumptive platelet disorders such as immune thrombocytopenia and disseminated intravascular coagulation generally require platelet transfusion in the setting of active bleeding rather than a specific platelet threshold. Platelet transfusion should only be considered in thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia in the setting of life-threatening bleeding. Of note, concern for transfusion-associated thrombosis should not prevent platelet transfusion in patients with life-threatening bleeding.[57]

Patients with a platelet count < 20×10^3/mcL requiring a central line placement should receive prophylactic platelet transfusion.[58] Thrombocytopenic patients requiring a lumbar puncture may have a higher threshold, ie, < 30×10^3/mcL for prophylactic platelet transfusion.[59]

Patients with a platelet count < 50×10^3/mcL who are actively bleeding should receive therapeutic platelet transfusion. Similarly, patients with a low platelet count < 100×10^3/mcL who have sustained a central nervous system injury or multisystem trauma will likely benefit from platelet transfusion.[50] Exsanguinating patients will also require platelet transfusion in conjunction with PRBCs and plasma via a massive transfusion protocol.

Cryoprecipitate Indications

The only absolute indication for cryoprecipitate use is in the setting of hemorrhage associated with low fibrinogen levels, such as in disseminated intravascular coagulopathy. The administration of cryoprecipitate may also be considered when specific factor concentrates are not available.

Tools And Techniques: Practical Considerations For Transfusions

Blood delivered in a cooler from the blood bank is viable for up to 4 hours, although different coolers that allow for longer storage time exist. Please refer to your own institution's protocol. Product verification is mandatory, including identifying the patient with 2 unique identifiers, as well as the unit of blood product for ABO/Rh type, expiration date, and any compatibility testing. Emergent transfusion of uncrossmatched blood may be necessary in critical situations; however, there would not be compatibility testing in this situation.

Infusion Considerations

A peripheral large-bore intravenous (IV) line is preferred for transfusion; however, a 22-gauge line can be used in stable patients being transfused in the setting of symptomatic anemia. In the setting of large-volume transfusions, if a rapid transfuser is being used, an IV catheter larger than 18 gauge should be used, as this will allow for faster infusion rates.[60] It is also important to note that triple-lumen central catheters and peripherally inserted central catheter lines allow for slower infusion rates, as they have greater resistance due to their length and diameter.

Infusion rates range from 2 to 4 hours for PRBCs. The blood is transfused through a blood filter administration set, which can be used for a set period of time or amount of blood. These numbers will vary based on the institution's infuser; please refer to your institution's protocol. In the ED and intensive care unit, blood can be transfused more rapidly using a gravity blood filtration system with pressure bags. **(See Figure 1, page 7.)**

Normal saline is used to prime tubing prior to the administration of blood; however, it is not administered in conjunction with transfusion. Dextrose-containing solutions, if given in conjunction with blood, can cause hemolysis and should be avoided. Similarly, medications should not be administered through the blood product transfusion either directly or via piggyback.

FFP is administered over 15 min/unit (approximately 250 mL). Cryoprecipitate is typically infused at 200 mL/h to 300 mL/h for a typical infusion time of 30 minutes for a 10-unit pool (10 mL for each unit). Platelets are typically infused in < 1 hour; volume depends on the amount ordered.

The use of a rapid infuser is indicated when > 2 L of fluid or 3 units of PRBCs are required over 1 hour and when patients are coagulopathic and/or

hypothermic. The use of rapid transfusion systems have demonstrated a lower incidence of hypothermia, coagulopathy, and the use of less total fluids and blood products in resuscitation of the hypovolemic trauma patient.[60]

Blood warmers should be used to help prevent hypothermia that is often induced by rapid transfusion of large volumes of refrigerated blood. Clinical situations indicating the possible use of a warmer include the following: trauma, surgery, neonatal exchange transfusion, plasma exchange, cold agglutinin disease, and intraperitoneal infusions of fluids for warming of hypothermic patients.

Autotransfusion

Autotransfusion is the collection and filtration of blood from an active bleeding site and reinfusion of that blood into the same patient for the maintenance of blood volume. Autotransfusion is commonly used for trauma patients and for patients undergoing invasive procedures, reducing the need for banked blood transfusions and the risk of transfusion reactions and disease transmission.[61]

Indications for autotransfusion in the appropriate patient populations include active bleeding (> 100 mL/h) and the accumulation of > 300 mL of drainage in the collection chamber. Blood salvaged through autotransfusion undergoes damage and should be limited to a total volume of 10 L to 15 L.

Figure 1. Manual Pressure Bag

This image was published in *Emergency Nursing Procedures.* Proehl JA, ed. Bowman AJ. Blood and fluid pressure infusers. St. Louis: Saunders; 372-377. Copyright Elsevier (2009).

Complications Of Blood Product Administration

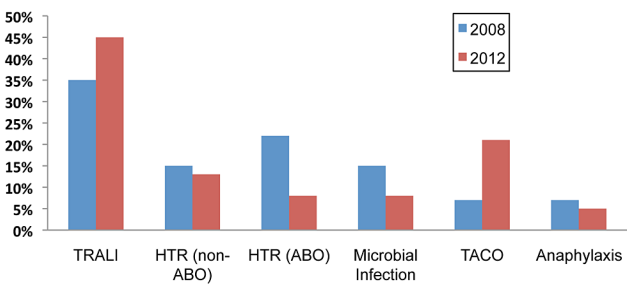
Transfusion of blood products is not without risk. According to the Annual Summary of the FDA for 2012, there were 38 transfusion-related fatalities in the United States, as opposed to 46 in 2008.[62] Since the number of adverse outcomes is small in comparison to the overall number of transfusions (an estimated 24 million in 2008), many emergency physicians are unfamiliar with the potential complications of blood product administration. As an example, TRALI is unfamiliar to many physicians and not universally discussed with patients during the consent process,[63] despite the fact that it was the leading cause of transfusion-related fatality in both 2008 and 2012.[62] **(See Figure 2.)**

This section covers the most common and dangerous transfusion reactions, situations in which they may arise, and measures for their prevention and treatment. Less-severe adverse events, such as febrile nonhemolytic transfusion reactions, are also discussed, as well as strategies for distinguishing major and minor transfusion reactions.

Transfusion-Related Acute Lung Injury

As early as the 1950s, noncardiogenic pulmonary edema was recognized as a potential complication of blood transfusion, although it was not until 1983 that

Figure 2. Etiology Of Transfusion-Related Fatalities[62]



Abbreviations: HTR, hemolytic transfusion reaction; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

Popovsky and colleagues coined the term "transfusion-related acute lung injury."[64] These investigators reported that transfusion of whole blood, RBCs, and plasma from multiparous women was found to be associated with the rapid onset of hypoxemia and pulmonary infiltrates, either during transfusion or within several hours of administration. The association with multiparous donors suggested as the mechanism of lung injury the passive transfer of antibodies in the transfused blood product, with subsequent activation of recipient white blood cells. Just as pregnant women can become immunized to Rh antigen present on the RBCs of the fetus during periods of feto-maternal hemorrhage, exposure to fetal white blood cells can give rise to antileukocyte antibodies. This idea has been supported by the identification of antileukocyte antibodies in transfused blood products derived from multiparous women.[8] Although other factors may contribute to the pathogenesis of TRALI,[65] exposure to plasma or plasma-containing blood products containing antileukocyte antibodies is still believed to be the primary mechanism for this transfusion-related syndrome.

Both the American Association of Blood Banks and the American Red Cross have implemented changes to reduce this risk, including the preferential use of male plasma, especially in high-plasma-content products (FFP and platelets).[66,67] A national survey in 2008 revealed that > 90% of blood banks had instituted collection of male-only, male-predominant, or never-pregnant female plasma.[68] Retrospective studies support these practices, confirming a significant reduction in rates of TRALI following their adoption.[67] Unified definitions of TRALI have been proposed by the National Institutes of Health (NIH) and a Canadian Consensus Panel.[69,70] The Consensus Panel defined 4 criteria, as well as a separate diagnostic category, "possible TRALI," for patients in which the development of acute lung injury is temporally related to both transfusion and another potential cause of acute lung injury (eg, sepsis). **(See Table 3.)**

Table 3. Canadian Consensus Criteria For Transfusion-Related Acute Lung Injury[69,70]

TRALI
1. Acute onset during or within 6 hours of transfusion
2. Hypoxemia
3. Bilateral infiltrates on chest x-ray
4. No evidence of volume overload
5. No preexisting lung injury
6. No alternative risk factor for ALI
Possible TRALI
1. Criteria for TRALI, as stated above in criteria 1-5
2. Alternative risk factor for ALI identified (ie, sepsis)

Abbreviations: ALI, acute lung injury; TRALI, transfusion-related acute lung injury.

Acute Hemolytic Transfusion Reactions

Other than transfusion-associated graft-versus-host disease (TA-GVHD), acute hemolytic transfusion reaction (AHTR) is the most-feared complication of blood transfusion. AHTRs are typically due to ABO mismatch and represent a life-threatening medical emergency. Incompatible erythrocytes are rapidly coated with preformed antibodies to a foreign blood group(s), resulting in clearance of RBCs by the reticuloendothelial system, activation of the complement cascade, and intravascular hemolysis. The latter can result in hemoglobinuria, renal failure, disseminated intravascular coagulation, and even death.[71] Onset is typically immediate, although it can be as late as 1 to 2 hours after transfusion. Symptoms may include patient anxiety (feeling of impending doom), pain at the site of transfusion, fever, dyspnea, chills, back pain, altered mental status, and hypotension.[72] That said, AHTR can be overlooked in critically ill patients with altered level of consciousness or preexisting hemodynamic instability.[73] Emergency physicians and nurses must be particularly vigilant in these patients and have a high degree of suspicion if hemolysis is suspected. In extreme cases (in which a patient is already intubated, sedated, and receiving vasoactive medications) hemoglobinuria or frank bleeding from disseminated intravascular coagulopathy may be the only signs of an AHTR.

Once AHTR is suspected, the emergency physician must immediately stop transfusion, as the severity of the reaction depends on the volume of incompatible blood transfused, with most fatalities associated with transfusion of 200 mL of blood or more.[74] Implicated PRBCs and all associated tubing should be sent to the blood bank. Patient samples should be drawn and sent to the laboratory for repeat crossmatch and typing, as well as Coombs tests, complete blood count (CBC), serum haptoglobin, serum bilirubin, coagulation tests, and markers of disseminated intravascular coagulopathy (fibrinogen and D-dimer). A urine sample should also be collected to test for hemoglobinuria. Supportive care should be initiated, including crystalloid to maintain a urine output of 100 mL/hr to 200 mL/hr. Furosemide or urinary alkalization are of unclear benefit and can be considered in consultation with nephrology. Emergency hemodialysis may be necessary due to massive hemolysis and resultant hyperkalemia.

Delayed Hemolytic Transfusion Reaction

Delayed hemolytic transfusion reactions (DHTRs) typically occur 2 to 10 days after transfusion and are less severe than AHTRs. The etiology is usually a mismatch in a minor (non-ABO) blood group, most commonly the Kidd antigen. Patients are often asymptomatic and may only present with an unexplained decrease in hematocrit. No intervention is typically required. One notable exception is DHTR

in patients with sickle cell disease, which can be a life-threatening event, as discussed in the "Special Circumstances" section on page 11.

Transfusion-Associated Circulatory Overload

In contrast to TRALI, transfusion-associated circulatory overload (TACO) is cardiogenic pulmonary edema due to the infusion of blood products. While rapid infusion is the most common cause of TACO, the ability of the patient to handle expansion of intravascular volume is a key factor and may precipitate this complication even when blood products are administered slowly and judiciously. The incidence of TACO is not well defined. In a single-center retrospective study, circulatory overload was identified in only 0.1% of patients receiving PRBCs.[75] In contrast, an analysis of Medicare patients undergoing hip arthroplasty found an order of magnitude greater incidence (approximately 1%), despite a relatively modest transfusion requirement of 1 to 2 units. Not surprisingly, patients at the extremes of age were at higher risk for this complication, presumably due to diminished cardiac reserve. One interesting finding from this study was that patients already had a mean positive fluid balance of 2.5 L before the transfusion triggered the reaction.[76] While these data were collected in patients undergoing orthopedic surgery, this is certainly a scenario that could develop in the ED (eg, elderly patients with a gastrointestinal bleed, where crystalloid has been administered prior to PRBCs and/or FFP). Emergency physicians should be aware of the risk of circulatory overload and should consider both reduced rates of administration (2-4 mL/min of PRBCs) and the prophylactic use of diuretics in susceptible patients.

Since other complications of blood product administration (eg, hemolytic transfusion reactions) can manifest with dyspnea, a chest radiograph should be part of the initial workup of patients who develop respiratory symptoms in the aftermath of transfusion, especially if there is associated hypoxemia. The presence of bilateral infiltrates strongly suggests TRALI or TACO, although it does not help to distinguish these entities. Likewise, caution should be exercised in diagnosing TRALI versus TACO based on the type of blood product administered. While the risk of TRALI is greater following the administration of platelets, cryoprecipitate, and FFP, PRBCs contain small amounts of plasma and TRALI is associated with erythrocyte transfusion.[77] A case-control study from the mid-1990s suggested that brain natriuretic peptide may have some utility in making this distinction. In particular, the authors found that a post- to pretransfusion B-type natriuretic peptide (BNP) ratio of > 1.5 had a specificity of nearly 90% for diagnosing TACO.[78] Unfortunately, recent studies have been less optimistic, suggesting that differentiating between these syndromes (as well as other causes of acute lung injury) may be difficult for emergency physicians and intensivists alike.[79]

Emergency physicians should be aware of TRALI and TACO and in what situations they are most likely to arise. In the case of TRALI, physicians should understand its association with plasma-containing blood products and have a sense of its typical natural history, which tends to be one of rapid onset and resolution.[70] If TRALI is suspected, the blood bank should be notified and appropriate work-up initiated. In patients at risk for volume overload, TACO should be suspected and a therapeutic trial of diuresis considered. In either case, positive pressure ventilation may be of benefit, although there have been no randomized, controlled trials to support this assertion. As with all lung injury patients, physicians should avoid concomitant barotrauma through use of a low-tidal-volume strategy, as outlined by The Acute Respiratory Distress Syndrome Network.[80]

Transfusion-Transmitted Bacterial Infections

With the implementation of product and donor screening, bacterial contamination of blood products has overtaken the transmission of viral infection as the leading infectious risk of transfusion.[81] Platelets are stored at room temperature and are the most prone to bacterial growth. Increased length of storage correlates with a higher incidence of contaminated product.[37] Skin flora, *Staphylococcus epidermidis* and *Staphylococcus aureas*, are the most common contaminants.[82]

If a patient develops a fever with associated rigors, tachycardia, and change in blood pressure, a transfusion transmitted bacterial infection must be considered and the transfusion must be stopped. Send the donor blood and additional samples to the blood bank as with any other transfusion reaction. In addition, send a blood culture from the patient. A transfusion-transmitted bacterial infection is confirmed when the patient blood and donor blood grow the same organism. Broad-spectrum antibiotics should be started, and they should be monitored closely for hemodynamic instability leading to septic shock.

Urticarial Transfusion Reaction And Anaphylactic Transfusion Reactions

Type I hypersensitivity reactions can occur with the transfusion of any blood product. These reactions are caused by preformed immunoglobulin E (IgE) in the recipient's blood, which reacts to donor protein(s). As with any other type I hypersensitivity reaction, a spectrum of severity is seen, ranging from simple urticaria to anaphylaxis. In the event of

an allergic transfusion reaction, administration of the blood product should be stopped and antihistamines (eg, diphenhydramine 25-50 mg) should be given. In patients with rash but no other symptoms, suggesting a more severe reaction or anaphylaxis (eg, airway compromise, wheezing, gastrointestinal upset, hypotension), the transfusion may be restarted under close observation once the rash clears, although this decision should be made in consultation with the blood bank.

If signs of anaphylaxis develop, epinephrine should be administered as first-line treatment. As always, the adult patient should be given an intramuscular dose of 0.2 mg to 0.5 mg, or 0.2 mL to 0.5 mL of a 1:1000 preparation. The recommended pediatric dose is 0.01 mg/kg. The transfusion should be stopped immediately and the airway secured, if necessary. If hemodynamic instability persists, a continuous infusion of epinephrine may be started. An epinephrine drip can be prepared at the bedside by mixing a 1 mg (1:10,000) dose with 500 mL of normal saline and infusing at a rate of 1 mL/min to 5 mL/min, for a dose of 2 mcg/min to 10 mcg/min.[83]

Febrile Nonhemolytic Transfusion Reactions

Febrile nonhemolytic transfusion reactions (FNHTRs) are the most common type of transfusion reaction and also the most benign. A FNHTR is defined as a temperature of 38ºC or higher that occurs either during or within 6 hours of the transfusion of blood products.[84] FNHTRs were originally attributed to the presence of human leukocyte antigen-incompatible leukocytes in platelet and red cell concentrates, although there is increasing evidence that interleukins and other cytokines present in the plasma portions of these blood products may contribute as well. While FNHTRs pose little risk to the recipient in and of themselves, they are of some concern because the primary manifestation, fever, can be mistakenly attributed to infection or more serious complications of transfusion (eg, hemolysis, septic contamination of blood products, or TRALI). This can lead to increased antibiotic usage, changing of indwelling catheters, discarding of valuable blood products, and excessive cost.[85]

The optimal management of a FNHTR is controversial and typically dictated by hospital policy. There is no consensus regarding the routine pretreatment of patients with antipyretics (most commonly acetaminophen). Although there is little evidence that dangerous transfusion reactions (eg, hemolysis) are masked by antipyretic prophylaxis, the cost-benefit implications of this practice are unknown.[85] If a patient develops a fever during transfusion, administration should be stopped and hospital policy consulted. Typically, the implicated unit is returned to the blood bank for evaluation and the patient is treated with acetaminophen. If there is no further evidence of a more serious reaction, and the product is not expired, the transfusion may be restarted under close observation.

Since donor leukocytes are believed to be responsible for the majority of FNHTRs, leukoreduction of blood products has been proposed as a means for reducing rates of this adverse reaction.[86] This process typically involves passing blood components through a polyester or polyurethane filter to which leukocytes (but not RBCs or platelets), adhere.[87] According to the American Association of Blood Banks, blood products must be 99% depleted, or contain $< 1 \times 10^4$ leukocytes/mL to be considered leukoreduced.[88] Universal leukodepletion has been adopted in Canada and a variety of European nations but not in the United States.[89]

Transfusion-Related Immunomodulation

Transfusion-related immunomodulation (TRIM) describes the clinical syndrome of immunosuppression secondary to allogenic blood transfusions. This reaction has been shown to have beneficial clinical effects through improved renal allograft survival as well as deleterious clinical effects (increased cancer recurrence and postoperative bacterial infections).[90-92] The exact mechanism of TRIM is not well understood and the magnitude of its deleterious effects has been widely debated.[93] Despite this dispute, several studies have investigated the use of leukoreduced PRBCs to avoid deleterious effects of TRIM. It has been shown through randomized controlled trials that the use of leukoreduced PRBCs reduced short-term mortality in a subset of patients undergoing cardiac surgery.[94] Leukoreduction is further discussed in the "Special Circumstances" section on page 11.

Transfusion-Associated Graft-Versus-Host Disease

TA-GVHD is, by far, the most serious transfusion reaction, with a mortality of 80% to 90%, and it is likely to be unfamiliar to most emergency physicians.[91] TA-GVHD is caused by donor T-cells passively transferred during blood product administration. If the recipient is unable to reject these lymphocytes, they engraft and mount an immune response to the recipient's healthy tissues. As with other forms of GVHD, the result is multiorgan dysfunction. The skin, liver, gastrointestinal tract, and bone marrow are the most affected organ systems, and death is, typically, the result of infection or hemorrhage from pancytopenia and hepatic dysfunction.[92] Onset is typically within a few days after transfusion, with death occurring a median of 21 days after transfusion.[91] Treatment is entirely supportive, and patients with suspected TA-GVHD should be admitted to the hospital, with consultation of appropriate specialty services (eg, pathology, hematology, etc.).

From the standpoint of the emergency physi-

cian, awareness and avoidance of this rare (but deadly) condition are perhaps more important than recognition or diagnosis. There are 2 situations in which patients are at risk for TA-GVHD, each of which is characterized by an inability of the recipient to reject donor lymphocytes: In the first situation, the recipient has impaired cellular immunity, either due to congenital T-cell immunodeficiency (DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency syndrome, etc.), hematologic malignancy, chemotherapy, or bone marrow transplant. The second situation involves patients receiving blood products from first-degree relatives who may share similar human leukocyte antigen haplotypes.[93]

Since treatment for TA-GVHD is almost always ineffective, efforts are primarily directed at prevention. In immunocompetent patients, the strict avoidance of blood product administration from first-degree relatives is typically adequate. For patients with impaired cellular immunity, or in the event that human leukocyte antigen-matched blood products must be administered, gamma irradiation has been found to be a highly effective means of preventing TA-GVHD via the deactivation and/or destruction of donor lymphocytes. Blood products are placed in a dedicated irradiator, which contains a long-half-life gamma emitter, and exposed to high doses (eg, 25 Gy) of radiation. Surprisingly, this process appears to have little effect on erythrocytes or platelets. **Table 4** indicates patients for whom TA-GVHD may be a risk and for whom gamma-irradiated blood products should be a consideration.[95]

Distinguishing Major From Minor Transfusion Reactions

One question that often arises in the discussion of transfusion reactions is how physicians can distinguish potentially life-threatening syndromes (such as AHTR and bacterial contamination) from relatively minor complications (such as a FNHTR), given that a fever may be the only initial presenting symptom. There is no single recommended approach to distinguishing a major from a minor transfusion reaction.

The majority of approaches to the patient with a suspected transfusion reaction are institution-specific. We recommend that any transfusion be stopped in the setting of a new subjective or objective change in the patient. Isolated urticarial rash, without other associated symptoms or changes in vital signs, suggests a minor allergic reaction. The patient should be treated with antihistamines. If laboratory results do not suggest a more serious reaction and products are not expired, the transfusion may be restarted under close observation. We recommend the same approach in the patient who develops a fever. If there are no other associated symptoms or changes in vital signs and no evidence of a more serious reaction, a FNHTR has occurred. An antipyretic should be administered and the transfusion may be restarted, with close monitoring, if the product has not expired.

Table 4. Patients For Whom Gamma Irradiated Blood Products Should Be Considered

- Patients with known or suspected congenital immunodeficiency syndromes
- Patients with hematologic malignancies (leukemia, lymphoma)
- Patients with solid tumors receiving chemotherapy
- Patients after bone marrow transplant
- Patients receiving human leukocyte antigen-matched donations or directed blood prodcuts from first-degree relatives

Measuring Response

Repeat cell counts or coagulation profiles can be sent to quantify a patient's response to transfusion. The time at which these studies should be sent can be determined from **Table 1 (see page 4)**.[12] Patients may have inadequate responses to RBC transfusion because of ongoing bleeding, hemolysis, or blood volume expansion due infusion of crystalloid or colloid-containing solutions. Determining the cause of inadequate response to platelet transfusion can be even more challenging. Considerations include: (1) "platelet refractoriness," a condition in which recipients destroy transfused platelets due to ABO incompatibility or other immune mechanisms; (2) consumptive processes such as disseminated intravascular coagulopathy, sepsis, or uncontrolled bleeding; (3) splenomegaly; or (4) certain medications (most importantly heparin), that can induce thrombocytopenia via several distinct mechanisms. In addition to laboratory testing, attention should be paid to clinical findings that suggest improvement or continued deterioration.

Special Circumstances

Leukoreduced And Irradiated Blood Products

Donor leukocytes are implicated as the major causative agents of numerous transfusion reactions, including TA-GVHD, FNHTRs, human leukocyte antigen alloimmunization, and (potentially) immunosuppression of the recipient, which can increase the risk of infection.[96] As discussed previously, depletion of leukocytes using a filter has been pro-

posed as a means of eliminating some of these transfusion reactions. While leukoreduction of cellular blood components is controversial,[49] approximately 75% of blood components in the United States are leukoreduced prior to storage. In 2001, The University Health System Consortium performed a systematic review of the literature and provided a list of indications for the use of leukoreduced blood components.[97] **(See Table 5.)** Leukoreduction is not effective in preventing TA-GVHD, and patients at risk for this complication should be given only gamma-irradiated blood products.

Erythrocyte Alloimmunization And Delayed Hemolytic Transfusion Reaction In Sickle Cell Disease

Patients receiving frequent PRBC transfusions (such as those with hemolytic anemia), are at risk for non-ABO erythrocyte alloimmunization. These patients develop antibodies to less-common red blood cell antigens, such as those from the MNS, Kell, Duffy, and Kidd groups. Patients with sickle cell disease appear to be at particular risk in the United States, most likely because of antigenic differences between the sickle cell disease population (predominantly black) and the majority of blood donors in this country.[98] This notion is supported by significant differences in the rate of alloimmunization in sickle cell disease patients in the United States and Uganda.[99] Matching additional (non-ABO) erythrocyte antigens in chronically transfused sickle cell disease patients has been shown to reduce rates of RBC alloimmunization and has become the standard of care in the United States.[100] Apart from being aware of the expected delays in obtaining cross matched blood for these patients, emergency physicians should be aware of erythrocyte alloimmunization and the potential for life-threatening DHTRs in patients with sickle cell disease. Also referred to as hyperhemolytic delayed transfusion reactions (HDTRs), these events typically occur several days after transfusion and can mimic vaso-occlusive crisis, with severe pain and a drop in hemoglobin. A high index of suspicion for DHTR/HDTR should be used in any patient with sickle cell disease presenting with acute pain and worsened anemia in the context of a recent transfusion.[101]

Table 5. Patients For Whom Leukoreduced Blood Products Should Be Considered[97]

- Patients who are non-hepatic solid organ transplant candidates
- Patients who have had 1 or more documented FNHTR
- Patients requiring long-term platelet support (eg, aplastic anemia, ITP)
- Patients at risk for clinically significant CMV infection (eg, bone marrow transplant recipients, etc.)

Abbreviations: CMV, cytomegalovirus; FNHTR, febrile nonhemolytic reaction; ITP, idiopathic thrombocytopenic purpura.

Informing Patients And Obtaining Consent

Although transfusion of blood products is frequently performed in the ED, several recent studies indicate that physicians often fail to effectively communicate the associated risks and benefits. Although the majority of these studies are fairly small and rely on patient and physician surveys, they conclude that many patients receiving blood transfusions are either not given or cannot recall sufficient information to make an informed decision regarding consent to transfusion.[63,102] Most hospitals in the United States utilize "consent forms" that patients are given and asked to sign, but which may be written at a reading level far beyond the comprehension level of the average patient.[103] While trials comparing different strategies for consenting patients are rare, common sense dictates that a combination of written materials and a conversation with a well-informed physician are likely to result in the best-informed consent.

Emergency physicians should consider several pitfalls in the consent process. First, providers appear to be more likely to discuss the benefits of transfusion than the risks.[63] With some risks (such as TRALI), this is likely due to a lack of familiarity with the subject, or an inability to describe it concisely in layman's terms. Physicians are encouraged to develop a brief script regarding these less-familiar complications. In the case of TRALI, the reaction can be described as a rare (but potentially life-threatening) allergic reaction of the patient's lungs to the donor's blood plasma. Patients can be informed that steps have been taken to reduce the risk (eg, male-predominant plasma) and statistics can be quoted from the hospital's consent form (or a risk of approximately 1:500,000 units of PRBCs or 1:250,000 units of FFP, from hemovigilance data from the American Red Cross).[67]

Providers may also be hesitant to discuss the transmission of infectious agents, as this is undoubtedly the issue that provokes the greatest concern in the general public. Rather than dismissing this concern as unwarranted, physicians should have some knowledge of the historical events responsible for suspicion on the part of the lay public.[104] On several occasions in the past 50 years, such as the emergence of posttransfusion hepatitis in the 1970s and early 1980s, a lack of knowledge on the part of the medical profession led to misinformation and put patients at substantial risk. Indeed, with the appearance of each new transfusion-transmissible infectious disease (HIV, Creutzfeldt-Jakob disease, West Nile virus, etc.), physicians have faced difficulties in providing patients with the information necessary for informed consent.[106]

Physicians are encouraged to develop a script regarding the major transfusion-transmissible

diseases to supplement the information provided on written consent forms. Physicians should be aware that the FDA mandates that all blood components are tested for hepatitis B virus (HBV), hepatitis C virus (HCV), HIV types 1 and 2, human T-lymphotropic virus Types 1 and 2, syphilis, Trypanosoma cruzi, and West Nile virus. Blood is not currently tested for other transfusion-transmissible agents (such as babesiosis, malaria, and variant Creutzfeldt-Jakob [prion] disease), because of extremely low rates of infection and, in some cases, donor screening and exclusion based on travel to endemic areas.[105] In the case of transfusion-transmissible viruses (eg, HBV, HCV, HIV, etc.), testing is done via sensitive amplification of viral genetic material (nucleic acid testing), which helps to eliminate the "window" period in which donors may be infected but not yet antibody positive.[106] With the addition of nucleic acid testing to donor screening and serologic testing, the risk of receiving HCV or HIV positive blood in the United States is now significantly < 1:1,000,000 units transfused.[107]

Cutting Edge: Use Of Oxygen-Carrying Substitutes

Given concerns over limited supply, risks of infectious and noninfectious complications, and storage difficulties, it is no surprise that there has been interest in developing alternatives to human donor-derived blood products. Foremost among these has been the hemoglobin-based oxygen carriers. This topic is complex and reviewed in-depth elsewhere.[108,109] As a brief summary, infusion of free hemoglobin is laden with toxicities, notably renal tubular toxicity (leading to kidney failure) and scavenging of intravascular and perivascular nitric oxide, (leading to vasoconstriction and profound systemic and pulmonary hypertension).[110] Numerous attempts have been made to avoid these toxicities by genetic modification, chemical crosslinking, and polymerization of Hgb. Several high profile products, including HBOC-201 and PolyHeme®, reduced the need for PRBC transfusion in phase 3 randomized controlled trials but increased the risk of adverse events like hypertension, myocardial infarction, and stroke.[111] To date, no product has gained FDA approval.[112,113]

Massive Transfusion/Exsanguination Protocols

Massive transfusion is defined as the replacement of > 50% of a patient's blood volume within a 12- to 24-hour period or as transfusion of > 10 units PRBCs within 24 hours or 4 units PRBCs within 1 hour. Traumatic injuries are the most common situation where massive transfusion is required, although the majority of trauma patients do not ever meet these high levels of transfusion. Trauma patients may have a further disruption of normal coagulation secondary to tissue damage, acidosis, and hypoxia. Massive transfusions may also be required in gastrointestinal bleeding, aortic aneurysm rupture, obstetric hemorrhage, and organ transplant surgery. When giving large amounts of PRBCs, there is a dilutional effect on platelets and coagulation factors that will lead to coagulopathy.[113,114] Retrospective and observational studies suggest that patients should be given platelets and plasma early in their treatment, in addition to erythrocyte concentrates, in order to achieve hemostasis.[115]

There are no completed randomized controlled trials, but several retrospective and prospective studies suggest improved survival when giving component replacement in high plasma:RBCs and/or platelet:RBC ratios.[115-124] The Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial is currently recruiting and will be comparing survival in trauma patients who received either a 1:1:1 or 1:1:2 ratio of plasma:platelet:PRBCs. Based on the current available data and knowledge of the dilutional effect with massive transfusion, we recommend transfusing in either a 1:1:1 or 1:1:2 ratio of plasma:platelet:PRBCs. Other considerations in massive transfusion include patients being at risk for hypothermia, hypocalcemia, metabolic alkalosis, and hyperkalemia.[125]

Hypothermia can occur in massive transfusion if blood products are not warmed; therefore, we recommend warming blood in massive transfusion. A 70 kg patient who receives 4 units of chilled PRBCs will decrease their body temperature by 1ºC .[1]

Risk is increased when patients undergo surgery after massive transfusion. Citrate is a common anticoagulant in PRBCs and can contribute to complications when instituting massive transfusion protocols, specifically with metabolic alkalosis and hypocalcemia. In a healthy individual, these complications arise after infusion of extremely large volumes of blood products. For example, a 50-kg patient with normal hepatic function would have to receive > 8.9 units whole blood or > 26.7 units PRBCs in 1 hour before citrate toxicity would occur. It should be noted, though, that the risk for citrate toxicity is much higher in patients with underlying liver disease. If a patient requires large amounts of product or has underlying liver dysfunction, the emergency physician should consider calcium repletion with calcium gluconate or calcium chloride.

Hyperkalemia is another complication that can occur with massive transfusion. This risk can be reduced by selecting recently donated blood (within the last 5-10 days prior to transfusion) and PRBCs washed in isotonic saline prior to transfusion, when possible. In the setting of massive transfusion, we

recommend frequent monitoring of temperature, pH, ionized calcium, electrolytes, prothrombin time/INR, partial thromboplastin time, and fibrinogen levels.

Of note, several studies suggest increased survival in patients requiring massive transfusion when a protocol has been implemented. The decrease in mortality is thought to be the result of having blood products available early in resuscitation.[126-128] We advocate the implementation of a pathway that expedites access to blood products in the setting of massive hemorrhage.

Disposition

Most patients requiring transfusion will be admitted to the hospital; however, some institutions have transfusion protocols that allow for observation placement in chronic conditions requiring transfusion.

Summary

The transfusion of blood products occurs commonly in EDs. Careful attention should be given to providing the patient with appropriate informed consent for all blood products, when possible. Understanding hospital policies, equipment, and turnover time for blood products facilitates seamless transfusion in critical situations. Guidelines for transfusion of PRBCs are outlined in **Table 2 (page 5)** and should be considered prior to transfusion. Plasma and platelet transfusion guidelines are not as well established; however, general recommendations are detailed in the section, "Must-Do Markers Of Quality Emergency Department Critical Care."

Case Conclusions

Mr. Smith continued to be alert. Given the concern for pelvic fracture, the team wrapped a sheet around his waist and tied it securely. Uncrossmatched blood was available in the ED because the trauma system had been activated, and 2 units were hung and rapidly infused using a warmer, given the patient's mild hypothermia. Your primary and secondary surveys revealed no other obvious injuries, and you noted a moderate amount of free fluid on the pelvic view of the focused assessment with sonography for trauma (FAST) exam. The chest x-ray was normal, but the pelvic x-ray revealed a severe lateral compression fracture with a "windswept" appearance (internal rotation on one side and external rotation with diastasis of the pubic symphysis on the other). Mr. Smith's repeat vital signs showed a heart rate of 110 beats/min with a blood pressure of 105/60 mm Hg. His oxygen saturation improved slightly to 94% on the nonrebreather mask, but his mental status remained tenuous. You performed rapid sequence endotracheal intubation and tube placement was confirmed by auscultation and repeat portable chest x-ray. Additional blood was hung and the hospital's massive transfusion protocol was initiated, as Mr. Smith received 4 units in the ED. He was transported to the interventional radiology suite for chemoembolization with platelets and FFP given in addition to PRBCs, in a 1:1:1 ratio.

In your second case, with the young man vomiting blood, you suspected a bleeding ulcer as the cause of the patient's hematemesis, given his ibuprofen use and lack of preexisting liver disease or esophageal varices. A rectal exam revealed black, tarry, and heme-positive stool. You started a PPI drip and 2 L of saline. He stopped vomiting after antiemetics and his hemoglobin came back at 8.2 mg/dL. You notified the gastrointestinal doctor, who was at home, of the likely need for emergent endoscopy and alerted the intensivist that the patient would be admitted to the ICU. Heart rate was 107 beats/min and his blood pressure was 101/74 mm Hg. You decided to defer blood product transfusion, given the patient's age, lack of cardiac disease, and Hgb > 7.0 mg/dL.

Must-Do Markers Of Quality Emergency Department Critical Care

- Promptly initiate PRBC transfusion in patients with acute hemorrhage or Hgb < 7 g/dL.
- Consider a transfusion of plasma in critically ill patients with suspected coagulation abnormalities or patients who are undergoing a procedure with a high likelihood of bleeding.
- Initiate prophylactic platelet transfusion in patients with platelet count < 10×10^3/mcL, or < 100×10^3/mcL in patients undergoing invasive procedure.
- Initiate therapeutic platelet transfusion in patients with active bleeding and platelet count < 50×10^3/mcL or < 100×10^3/mcL with central nervous system injury or multisystem trauma.
- Provide thorough and accurate informed consent to patients prior to blood product transfusion.
- Transfuse a ratio of 1:1:1 or 1:1:2 warmed plasma, platelets, and PRBCs when transfusing > 4 units of PRBC in 1 hour.

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Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following

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1. There is clear evidence that the storage lesion of PRBCs increases morbidity and mortality.
a. True
b. False

2. Cryoprecipitate contains which of the following components?
a. Fibrinogen
b. Factors VIII and XIII
c. von Willebrand factor
d. A and B
e. All of the above

3. In which circumstances is a plasma transfusion NOT indicated?
a. To correct an elevated INR without clinical concern for bleeding
b. In massive PRBC transfusion
c. In patients requiring an invasive procedure with high-risk bleeding complications
d. In patients requiring an invasive procedure with low-risk bleeding complications but known coagulopathy

4. The incidence of TRALI has declined in recent years due to:
a. The use of plasma from female donors only
b. The use of plasma from male donors only
c. A decline in cases of sepsis
d. The use of whole blood instead of plasma

5. **When does TRALI usually occur?**
   a. Within the first 15 minutes of the beginning of the transfusion
   b. Within 4 hours
   c. During or within 6 hours
   d. Within a few days

6. **The risk factor for developing TRALI after receiving plasma versus PRBCs is:**
   a. Lower
   b. Same
   c. Higher

7. **If a patient develops volume overload following administration of blood products, what condition should be suspected?**
   a. TRALI
   b. TACO
   c. DHTR
   d. TA-GVHD

8. **What is the risk for developing TRALI after receiving PRBCs?**
   a. 1:100,000
   b. 1:250,000
   c. 1:400,000
   d. 1:500,000

9. **What best describes the risk rate of receiving blood with HCV or HIV?**
   a. < 1:100,000
   b. < 1:500,000
   c. < 1:1,000,000
   d. < 1:10,000,000

Abbreviations Used In This Issue

AHTR: Acute hemolytic transfusion reaction
DHTR: Delayed hemolytic transfusion reaction
FFP: Fresh-frozen plasma
FNHTR: Febrile nonhemolytic transfusion reaction
FP24: Frozen plasma 24
GVHD: Graft-versus-host disease
HDTR: Hyperhemolytic delayed transfusion
TACO: Transfusion-associated circulatory overload
TA-GVHD: Transfusion-associated graft-versus-host disease
TRALI: Transfusion-related acute lung injury
TRIM: Transfusion-related immunomodulation
vFW: von Willebrand factor

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