CHAPTER 20

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Use of Blood Products

CHAPTER OUTLINE

LEARNING OBJECTIVES

After completing this chapter, the reader should have an understanding of:

- The indications for transfusion of various blood products.
- The current outcome data regarding red blood cell transfusions in the critically ill population.
- The indications for irradiated, filtered, and/or leukoreduced blood products.
- The types of transfusion reactions and their treatment.
- The risks associated with blood product transfusions.
- The complexities of transfusion therapy in special patient populations.

INTRODUCTION

Patients in the pediatric intensive care unit (PICU) frequently receive transfusions of blood products. While these therapies are often beneficial, they can be associated with significant, yet often overlooked, risks. Clinical guidelines for blood product transfusions must be well defined in order to prevent misuse of this limited resource. It is important for the intensivist to have a thorough understanding of the indications for specific blood products, and the transfusion needs of particular patient populations.

RED BLOOD CELL TRANSFUSIONS

Anemia is very common in the critically ill patient. The incidence of anemia is 30% in the adult ICU, with red blood cell (RBC) transfusion the most common treatment modality. Approximately 50% of adult ICU patients will receive at least one RBC transfusion, with that number rising to 85% for those spending more than 1 week in the ICU. In one large multicenter pediatric study, 33% of patients were anemic on admission to the PICU and another 41% developed anemia during the admission.

Pathophysiology

The goal of RBC transfusion is to maintain adequate tissue oxygen delivery (DO_2). Oxygen delivery is the product of cardiac output (CO) and arterial oxygen content (CaO_2).

The most common indication for RBC transfusion is "reduced physiologic reserve". Since anemia decreases the oxygen carrying capacity of the blood, and thereby oxygen delivery to the tissues, augmentation of oxygen delivery with RBC transfusion appears appropriate. The goal of RBC transfusion is to maintain adequate tissue oxygen delivery (DO_2). Oxygen delivery is the product of cardiac output (CO) and arterial oxygen content (CaO_2). Arterial oxygen content is a function of hemoglobin saturation, hemoglobin concentration, and the amount of oxygen dissolved in the arterial blood.

$$DO_2\,(\text{mL/min}) = CaO_2\,(\text{mL/dL}) \times CO\ (\text{L/min}) \times 10\ \text{dL/L},$$

where:

$$CaO_2\,(\text{mL/dL}) = 1.34\,(\text{mL/g}) \times Hgb\,(\text{g/dL}) \times SaO_2 + 0.003\,(\text{mL/dL/mm Hg}) \times PaO_2\,(\text{mm Hg})$$

The optimal red blood cell concentration is that which allows the greatest oxygen delivery at the lowest energy cost. Higher RBC concentrations will increase blood viscosity and inhibit microvascular perfusion while lower RBC concentrations will decrease oxygen carrying capacity.

Significant blood loss results in hypovolemia and anemia. Acute or uncompensated anemia causes tissue hypoxia not only as a result of reduced oxygen-carrying capacity, but also as a result of decreased cardiac output from deficient preload. In order to maintain oxygen delivery, tissues will compensate for reductions in oxygen carrying capacity by increasing regional blood flow. Most tissues are also able to increase oxygen extraction in response to decreased oxygen delivery. While the cardiac circulation has extremely high oxygen extraction ratio at rest (60–77%), its vasodilatory capacity in response to increased demand is limited. Under normal physiologic conditions, the heart relies on sympathetic discharge, increasing myocardial contractility, heart rate, and systemic vascular tone to further compensate for decreased oxygen delivery. When there is left ventricular dysfunction and/or coronary artery disease, the ability of the heart to increase cardiac output and coronary artery blood flow in response to severe anemia is compromised. Thus, anemia is poorly tolerated in the setting of cardiovascular disease.

Red blood cell transfusion would be expected to increase oxygen delivery and thereby prevent the tissue hypoxia and organ failure associated with anemia. However, oxygen delivery by transfused RBCs is not equivalent to that of native red blood cells and oxygen consumption does not reliably increase following RBC transfusion. In critically ill adults, RBC transfusion results in an increase in oxygen consumption *calculated* by the Fick equation, but no increase in oxygen *utilization* measured by indirect calorimetry. In all, transfusion of stored RBCs may not consistently increase tissue oxygen availability.

Indications and Outcomes

Recent studies have attempted to determine the "optimal" hemoglobin concentration in critically ill adults. The Canadian Critical Care Trials group (TRICC trial) reported that maintaining hemoglobin concentration between 7 and 9 or 10 and 12 g/dL in the critically ill adult patient resulted in comparable mortality rates. Patients <55 years of age, and those that were

less severely ill, were half as likely to die if they were treated with the restrictive regimen. The CRIT study found that RBC transfusions were independently associated with longer ICU stays, hospitalizations, and increased mortality even after controlling for severity of illness. Comparable results were found in another adult study in which worse outcomes were associated with higher numbers of transfused RBC units in a dose dependent manner.

As described above, patients with ischemic cardiovascular disease have been thought to be unable to compensate for anemia. Historically, hemoglobin levels are typically maintained >10 g/dL in these patients. However, there is conflicting evidence as to whether these patients actually benefit from this higher hemoglobin level. Subgroup analysis of patients with severe ischemic heart disease in the TRICC trial found no statistically significant difference in mortality between the restrictive versus the liberal transfusion groups. In contrast, a more recent retrospective study in elderly patients admitted for acute myocardial infarction, found a lower mortality rate in patients who were transfused for a low hemoglobin (<10 g/dL) compared to those who were not.

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In children, data regarding the hemoglobin level or clinical diagnosis for which the benefits of RBC transfusion outweigh the risks in critically ill pediatric patients is beginning to accumulate. A survey of pediatric intensivists revealed that transfusions were recommended for a hemoglobin concentration ranging from 7 to 13 g/dL, with hemodynamic instability or end organ insufficiency prompting the need for transfusion. An observational study of critically ill children examined those with hemoglobin levels <9 g/dL and found that, after controlling for severity of illness, transfusions were associated with increased days of oxygen use, mechanical ventilation, vasoactive agent infusions, and length of stay. In the TRIPICU study, 637 stable, critically ill children were randomized to a hemoglobin concentration threshold of 7 or 9.5 g/dL for red blood cell transfusion, demonstrating decreased transfusion requirements in the lower threshold group without an increase in adverse outcomes.

Our current, mostly empiric, approach has been to reserve red blood cell transfusion for those children with one of the following: (1) acute hemorrhage or chronic blood loss resulting in hemodynamic instability; (2) clinical evidence for hypovolemia paired with a low hemoglobin; (3) a cyanotic cardiac condition (where arterial blood is not fully oxygentated), compounded by an acute cardiopulmonary insult and low hemoglobin; or (4) hypoxic respiratory failure paired with a low hemoglobin.

RBC transfusions should be reserved for children with (1) acute hemorrhage or chronic blood loss resulting in hemodynamic instability, (2) clinical evidence for hypovolemia paired with a low hemoglobin, (3) a cardiac "mixing" lesion where deoxygenated blood perfuses the tissues, compounded by an acute cardiopulmonary insult, or (4) hypoxic respiratory failure paired with a low hemoglobin.

Types of RBC Units

Whole blood contains RBCs, plasma, white blood cells (WBCs) and platelets and is given to increase both red blood cell mass and plasma volume. Whole blood is rarely indicated except for acute, massive hemorrhage. "Packed" RBCs (pRBC) are produced by the removal of plasma from whole blood. Packed RBC units are most commonly utilized in the treatment of anemia as they deliver increased RBC mass in smaller volumes. The "packed" RBC component contains contaminating WBCs, platelets, cellular components, and "bioactive substances". Contaminating white blood cells may incite hemolysis resulting in leakage of potassium, toxic oxygen radicals, and destructive enzymes into the storage media. White blood cells have also been implicated in immunosuppression and postoperative infections. High levels of cytokines (IL-1, IL-8, TNF) found in the storage media are thought responsible for febrile transfusion reactions. Leukoreduction and irradiation are covered below.

Alloimmunization

Alloimmunization occurs when disparities between red cell antigens in the blood donor and blood recipient exist, and antibodies to these antigens develop in the blood recipient. The patient (blood recipient) becomes alloimmunized, and immune-mediated hemolysis will occur following any later exposure to the sensitizing donor antigens. Alloimmunization is

estimated to complicate 2.6% of RBC transfusions in the general population, and can limit subsequent red blood cell transfusion therapy. Alloimmunization occurs more frequently in patients who receive multiple RBC transfusions throughout their life. Cross-matching blood for patient transfusions is more timely and difficult in alloimmunized patients, and can limit both the amount, and the speed, at which blood products are available for transfusion.

Storage

The need to support a wounded military gave rise to the creation of modern transfusion medicine. In 1914, the media used to store RBCs was citrate anticoagulant and dextrose. Today "cellular nutrients" are added, increasing the lifespan of the stored product from 15 to 35–42 days. Nonetheless, RBCs stored *ex vivo* still undergo biochemical and morphological changes (RBC storage lesion) that hinder RBC transport and oxygen delivery. During storage, the erythrocyte is deprived of energy and a series of morphological changes occur including the loss of the normal biconcave disc shape with crenation and spicule formation producing echinocytes. The swelling of echinocytes forms spheroechinocytes. Eventually, the cell sheds its spicules as lipid vesicles and spherocytes are formed. Spherocytes, with their low surface to volume ratio, are unable to deform and transverse the microcirculation, and their increased osmotic fragility results in hemolysis. In addition, endogenous antioxidants are lost resulting in damage to cytoskeletal proteins and membrane phospholipids. Hemoglobin is also converted to methemoglobin which cannot bind oxygen. Finally, stored erythrocytes are depleted of 2,3-diphosphoglyerate (2,3-DPG) increasing oxygen affinity, and thus, hindering offloading of oxygen to tissues.

Twenty percent of RBC units held in American blood banks and transfusion centers are 28 days old or older, with units of relatively rare blood types (i.e., O−) more consistently older. Multiple studies have found an association between increased mortality, increased length of stay, multiple organ system failure, increased infections, and impaired tissue oxygen utilization with the length of RBC storage. In an analytic cohort analysis of the TRIPICU study of critically ill pediatric patients, storage duration of greater than 14 days was independently associated with increased multiple organ dysfunction syndrome (MODS) and storage > 21 days was associated with higher mortality. Prospective randomized trials in critical ill adults and children examining the effect of storage duration on clinical outcomes are currently being undertaken. Their results will guide future recommendations regarding the age of blood cells transfused.

Administration

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In adults, the average blood volume is 60–66 mL/kg; with one unit of packed RBCs generally raising the hemoglobin by 1 g/dL. Pediatric blood volume is approximately 70–75 mL/kg, and a 3 mL/kg pRBC transfusion generally increases the hemoglobin of a child by 1 g/dL. Adult patients typically receive 1–2 units of pRBCs with each transfusion; pediatric patients are usually transfused with 5–15 mL/kg of pRBCs. Our protocol is to give each pRBC transfusion over 3–4 h to the stable adult or pediatric patient. In the hypotensive patient, our practice is generally to infuse half of the volume rapidly as a bolus and the remainder over an hour if the patient is responding clinically.

Although general guidelines have been discussed, appropriate treatment of the critically ill child demands a careful, individualized approach. It is important to note that the volumes as well as the hematocrits of units of pRBCs may vary significantly within and between institutions. It is also important to take into account the average hematocrit of a particular unit and to be aware of the actual volume that will be given when transfusing a "unit". At our institution, the volume of one unit of filtered pRBCs is typically between 330 and 420 mL with a hematocrit between 50% and 55%. A unit of washed filtered red cells is between 200 and 250 mL with the hematocrit approximately 75–80%. Some blood banks concentrate pRBCs for neonates, a process that raises the hematocrit of the volume transfused. Our blood bank automatically utilizes volume-depleted pRBC units (hematocrit of 70–75%) for

transfusions in children less than 3 years of age. Only upon special request, and if specific criteria are met, will volume-depleted units be utilized for those over 3 years.

There are a number of formulas available to predict the volume of transfused red cells needed to achieve a particular hemoglobin or hematocrit. The traditional formula for RBC replacement is:

The traditional formula for RBC replacement is: volume of pRBC (mL) = EBV (mL) × (Desired Hct (%) − Actual Hct (%))/Hct of pRBCs (%).

$$\text{Volume of pRBCs (mL)} = \text{EBV (mL)} \times \frac{\text{Desired Hct (\%)} - \text{Actual Hct (\%)}}{\text{Hct of pRBCs (\%)}}$$

Where the EBV = estimated blood volume, Hct = hematocrit and the Hct of pRBCs is usually 55–70%.

A recent study found that some formulas underestimate the required volume. The authors proposed the following:

$$\text{Volume of packed cells to transfuse (mL)} = 4.8 \times \text{weight (kg)} \times \text{desired rise in hemoglobin (g/dL)}$$

$$\text{Volume of packed cells to transfuse (mL)} = 1.6 \times \text{weight (kg)} \times \text{desired rise in Hct (\%)}.$$

Of note, the above formulas apply to red cell units with a median hematocrit of 70% (hemoglobin of 23 g/dL). Depending upon the average hematocrit of the pRBC units at a given institution, the appropriate formula can be used to calculate the volume of pRBCs to be transfused.

Practitioners should always keep in mind that RBC transfusions are not without risk. Infection, transfusion reactions, acute lung injury, and alloimmunization are among the associated complications and will be discussed later in the chapter.

PLATELET TRANSFUSIONS

Indications

Primary hemostasis is dependent upon platelets. Platelet transfusions are indicated for patients who are compromised by decreased platelet production, increased platelet destruction, and/or platelet dysfunction. General indications for platelet transfusions include: (1) acute hemorrhage associated with thrombocytopenia, (2) prophylaxis in non-bleeding patients with severe thrombocytopenia and, (3) prophylaxis in thrombocytopenic patients requiring surgical interventions. Platelet transfusion should also be used in children with normal platelet counts who experience (1) bleeding in association with a qualitative platelet defect or (2) excessive bleeding while undergoing cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO). Children undergoing ECMO are typically maintained with a platelet count greater than 100×10^9/L (or 100,000/μL), even if they are not bleeding. In contrast, children undergoing cardiopulmonary bypass are not generally given platelet transfusions unless there is active bleeding and a platelet count less than 100,000/μL.

General indications for platelet transfusions include: (1) acute hemorrhage associated with thrombocytopenia, (2) prophylaxis in non-bleeding patients with severe thrombocytopenia, and (3) prophylaxis in thrombocytopenic patients requiring surgical interventions.

Platelet transfusion is generally not indicated in children with idiopathic thrombocytopenic purpura (ITP) unless there is life-threatening hemorrhage since transfused platelets will, like endogenous platelets, also be destroyed by immune mechanisms. Other treatment modalities are used. Platelet transfusions are contraindicated in thrombotic thrombocytopenic purpura (TTP) where the infused platelets may contribute to ongoing thrombosis.

The risk of spontaneous hemorrhage is highest at platelet counts below 5.0×10^3/μL, and platelets are generally transfused for this level of thrombocytopenia whether or not the patient is bleeding. Platelet counts between 5 and 10×10^3/μL are often associated with hemorrhage secondary to trauma, invasive procedures, or ulceration. Bleeding tendency is variable with platelet counts between 10 and 50×10^3/μL. In the absence of bleeding, but in anticipation of a surgical procedure, the typically accepted threshold for platelet transfusion is 100×10^3/μL. A study of

thrombocytopenia in patients with acute leukemia used a threshold of $10 \times 10^3/\mu L$ for prophylactic transfusions instead of $20 \times 10^3/\mu L$; this approach resulted in fewer transfusions overall and no difference in rates of severe bleeding, remission, or mortality. Therefore, using $10 \times 10^3/\mu L$ of platelets as a guideline for prophylactic transfusions in such children appears appropriate. For life-threatening bleeding in any patient, the platelet count should be maintained above $100 \times 10^3/\mu L$.

Types of Platelet Units and Storage Procedures

Difficulties with platelet clumping, bacterial contamination, and storage conditions made platelet transfusions unavailable until the late 1960s except when given in fresh whole blood. It was the development of gas-permeable plastic that allowed platelets to be safely separated from whole blood and then be stored at room temperature (20–24°C) for up to 5 days under constant agitation to prevent clumping. The shorter shelf life of platelets is due to their storage at room temperature, which increases the risk of bacterial growth. Platelets cannot be refrigerated as this severely compromises post-transfusion platelet survival due to platelet activation and clumping.

Platelet units are available as platelet concentrates, typically obtained from 5 to 7 whole blood donations, or single donor platelets collected from platelet apheresis. To produce platelet concentrates, red cells are separated from whole blood using a "soft-spin" technique; the platelets then undergo a "hard-spin" separating them out of the plasma forming a platelet concentrate suspended in approximately 50 mL of plasma. Each unit contains approximately $0.55–0.8 \times 10^{11}$ platelets. With platelet apheresis, multiple units of platelets can be collected from a single donor, thereby reducing the alloimmunization that can result from multiple donor exposures. Single donor platelets are more expensive than platelet concentrates and are typically reserved for patients requiring HLA-matched units.

Like RBC transfusions, platelet transfusions also carry risks of infection and alloimmunization. In December 2002, the College of American Pathologists mandated that platelet products be inspected for bacterial contamination. The accepted standard for testing is by culturing the platelet components and waiting 24 h for the results before releasing the platelets for transfusion. Platelet components also contain white blood cells which may cause allergic reactions. With the advent of universal leukoreduction, the incidence of these effects following platelet transfusions has greatly decreased (see below). Approximately one-half of patients receiving platelet concentrates develop alloimmunization. Alloimmunization occurs when antibodies in the recipient serum react with HLA class I antigens on donor platelet membranes, decreasing platelet survival and function. The patient's history of immunogenic stimuli (blood products and pregnancies) and genetic characteristics appear to determine whether alloimmunization will occur. Leukoreduction of platelet products has also significantly reduced the occurrence of alloimmunization from approximately 13% to 3% (see below). If a patient is alloimmunized, the current standard of care is to utilize either HLA-matched or cross-matched single donor platelets (SDP) for future platelet transfusions.

Administration

Typically, one unit of platelets is transfused per 10 kg body weight. For infants and children, this will raise the platelet count by approximately 50,000/μL. Six units of platelets in the "standard" adult patient should raise the platelet count by about 30,000/μL 1 h after the infusion. Each unit of platelets typically raises the platelet count by approximately 5,000–10,000/μL in adults. Platelet transfusions are considered successful if they stop bleeding, and if a post-transfusion corrected count increment of greater than 10,000/μL of platelets is achieved.

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Refractoriness to platelet transfusions, demonstrated by a lack of significant increase in platelet count following transfusion, is a major concern for patients with hematological diseases requiring continued platelet support. Both immune (alloimmunization) and non-immune processes contribute to platelet refractoriness. Non-immune causes of platelet refractoriness include infection, fever, consumption (disseminated intravascular coagulation), splenomegaly, cytotoxic drugs, antifungals (amphotericin), and antibiotics. Approximately one-third of transfused platelets are sequestered by the spleen, which may compound a poor response to platelet transfusions.

FRESH-FROZEN PLASMA

Clotting factor deficiencies occur commonly in the pediatric critical care patient. Coagulation proteins are often diminished in the setting of trauma, secondary to dilution following massive blood transfusion and the trauma itself. Tissue thromboplastins and plasminogen activators are released when tissue is devitalized, triggering the coagulation cascade and the consumption of coagulation factors. Trauma and burn patients with extensive tissue injury often develop disseminated intravascular coagulation (DIC) during which their coagulation proteins are consumed. Hypothermia, which often develops in these patients, inhibits serine protease activity leading to decreased activation of coagulation factors and prolongation of the PT and PTT. Severe sepsis may also activate the coagulation cascade causing a consumptive coagulopathy and/or DIC.

Replacement of coagulation proteins can be accomplished by infusion of fresh frozen plasma (FFP). Fresh frozen plasma is derived from whole blood donations placed at or below −18°C within 8 h of collection, and is viable for up to 12 months. Fresh frozen plasma contains all the coagulation factors (1 mL = 1 unit of factor activity) and naturally occurring inhibitors. The volume of one bag of FFP is about 200–250 mL. Larger volumes (400–600 mL) are collected via single donor plasmapheresis. In older children, single donor units are preferred over the use of two bags of FFP since this approach limits donor exposure.

Indications for the use of FFP in children include: (1) support during episodes of DIC, (2) factor replacement when concentrates are not available, (3) therapeutic plasma exchange in circumstances such as TTP, and (4) warfarin reversal to stop active bleeding or before surgery. FFP should not be used as a volume expander. If the prothrombin time (PT) >1.5 times the midpoint of the normal range, or the activated partial thromboplastin time (aPTT) >1.5 times the upper limit of the normal range, FFP should be considered if bleeding is present, or prior to an invasive procedure. (It is important to recognize that reference ranges for coagulation factors vary with age, and adult standards do not apply for pediatric patients). For the pediatric patient, the typical dose of FFP is 10–15 mL/kg. Of note, every 5–6 units of platelets contain a plasma protein volume equivalent to one bag of FFP, so that when platelets are also administered, a smaller volume of FFP is needed.

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CRYOPRECIPITATE

Cryoprecipitate is the cold precipitable protein fraction obtained from FFP thawed at 1–6°C. It is re-suspended in 9–16 mL of residual plasma supernatant, refrozen, and stored at −18°C for up to 1 year. Cryoprecipitate contains Factor VIII, von Willebrand factor (vWF), fibrinogen, Factor XIII, and fibronectin and is used as replacement therapy when these proteins are low in the setting of active bleeding or in preparation for an invasive or surgical procedure. Hypofibrinogenemia may be secondary to dilution after a massive transfusion, or may occur in the setting of DIC. Fibrinogen levels >100 mg/dL are adequate for hemostasis, and cryoprecipitate should only be given if the hypofibrinogenemia is associated with bleeding or bleeding risk. Dysfibrinogenemia, also in the context of bleeding or surgery, is another indication for cryoprecipitate. Cryoprecipitate can be similarly used in Factor XIII deficiency if Factor XIII is unavailable. Cryoprecipitate can also be used for patients with von Willebrand disease refractory to deamino-D-arginine vasopressin (DDAVP), when DDAVP is not indicated, and/or virally inactivated plasma-derived Factor VIII concentrate is not available. Cryoprecipitate is no longer used for children with Factor VIII deficiency because Factor VIII concentrates are widely available.

Cryoprecipitate contains Factor VIII, von Willebrand factor vWF, fibrinogen, Factor XIII, and fibronectin and is used as replacement therapy when these proteins are low in the setting of active bleeding or in preparation for an invasive or surgical procedure.

The amount of cryoprecipitate necessary to correct a deficit of fibrinogen can be calculated according to the formula: Desired increment in g/L = (0.2 × Number of Bags)/Plasma volume in L. A good rule of thumb is to transfuse one bag of cryoprecipitate for every 5 kg of body weight. The half-life of fibrinogen is 3–5 days with about a 50% recovery of transfused product. The specific content of vWF in a single bag of cryoprecipitate is unknown; the standard dose of cryoprecipitate to treat von Willebrand disease is one bag per 10 kg of body weight.

GRANULOCYTE TRANSFUSIONS

For over 70 years, there has been great interest in polymorphonuclear leukocyte (PMN) transfusions for the treatment and prevention of life-threatening infections in neutropenic patients. Initially, the inability to obtain adequate numbers of PMNs and limited leukapheresis techniques hindered the use of PMN transfusions. However, treating donors with granulocyte colony-stimulating factor (G-CSF) and corticosteroids prior to leukapheresis has been shown to elevate donor PMN counts and to increases PMN collection yields. The most cost-effective regimen for increasing PMN mobilization in donors appears to be a single dose of G-CSF, 450 μg subcutaneously, plus dexamethasone 8 mg po 12 h prior to leukapheresis. Most transfusion centers rely on continuous-flow centrifugation leukapheresis for granulocyte collection. The current goal is to transfuse the PMNs immediately after leukapheresis; yet there is some evidence to suggest that granulocytes can be safely stored for up to 24 h. At this time, there are no controlled trials to guide optimal storage duration.

The transfusion of PMNs has been found to restore peripheral blood PMN counts to the normal range in neutropenic recipients. The transfused granulocytes also demonstrate normal function, as evidenced by their ability to migrate to tissue sites *in vivo* (as measured by the buccal PMN response). The effectiveness of granulocyte transfusion therapy in treating infections in severely neutropenic patients remains in question. The literature is composed of uncontrolled studies with small sample sizes, variable dose and quality of PMNs, and variable underlying diseases, treatments, and types of infections. Taking these limitations into account, one meta-analysis concluded that 62% of subjects with bacterial sepsis benefited from granulocyte therapy; 71% of patients with fungal infections responded. A prospective phase I/II study of patients with severe neutropenia receiving granulocyte transfusions for uncontrolled sepsis found that infections cleared in 19 of 30 patients. Fourteen of seventeen patients with bacteremia recovered, but only 5 of 13 patients with fungemia cleared their infection. In all, recent evidence suggests that granulocyte transfusion therapy may be effective in neutropenic patients with life-threatening bacterial and fungal infections, but large controlled trials are necessary before recommendations can be made.

Most transfusion reactions secondary to granulocyte transfusions are similar to those associated with other blood products. Severe reactions (hypotension, pulmonary infiltrates, and respiratory distress) occur in 1–5% of transfusions, especially when granulocytes are given concomitantly with amphotericin B. As with RBC and platelet transfusions, alloimmunization is also a concern. The testing for antibodies to ABO antigens and for leukoagglutination, as well as the irradiation of PMN products prior to transfusion, has decreased the incidence of these problems.

ALBUMIN

Albumin is generally given in the emergency treatment of shock with hypovolemia, and in the acute management of burns. Other indications include: (1) acute hypotension with acute or chronic liver failure or following paracentesis for ascites, (2) maintenance of blood volume during plasma exchange procedures or therapeutic phlebotomy for polycythemia, (3) in combination with diuretics to induce diuresis in fluid-overload and protein-losing enteropathy or nephropathy, or acute-on-chronic liver failure, (4) to elevate protein levels in select patients with ARDS, and (5) cardiovascular collapse secondary to hypovolemia during extracorporeal circulation.

Albumin is derived from pooled human plasma and is indicated for volume expansion and colloid replacement. Albumin solutions are generally given in the emergency treatment of shock with hypovolemia, and in the acute management of burns. Other indications include: (1) acute hypotension with acute or chronic liver failure, or following paracentesis for ascites; (2) maintenance of blood volume during plasma exchange procedures or therapeutic phlebotomy for polycythemia; (3) in combination with diuretics to induce diuresis in fluid overload and protein-losing enteropathy or nephropathy, or acute-on-chronic liver failure; (4) to elevate protein levels in select patients with acute respiratory distress syndrome (ARDS); and (5) cardiovascular collapse secondary to hypovolemia during extracorporeal circulation.

The use of albumin for fluid resuscitation of critically ill patients with non-hemorrhagic hypovolemia has been subject to debate. The Cochrane Database of Systemic Review (2004) examined the effect of colloid versus crystalloid solutions on patient survival, specifically examining studies of critically ill patients with hypovolemia, burns, or hypoalbuminemia. There was an increased risk of death in the albumin-treated group for each patient category, suggesting that albumin may increase mortality in critically ill patients. The saline versus

albumin fluid evaluation (SAFE) trial randomized patients to receive either 4% albumin or normal saline for fluid resuscitation with death as the primary outcome. No significant differences in new single organ or multiorgan system failure, number of days in the ICU, number of total hospital days, days of mechanical ventilation, or days requiring renal replacement therapy were found. There was insufficient power to detect a difference between predefined groups such as traumatic brain injury or trauma patients. Results of the SAFE trial indicate that albumin and saline are clinically equivalent for intravascular volume replacement for the critically ill patient. In light of the fact that the cost of albumin is approximately 30 times greater that of crystalloid fluids and is in short supply, the use of albumin over crystalloid fluid to increase intravascular volume in the non-bleeding patient without hypoproteinemia or burns is not supported by the literature.

INTRAVENOUS IMMUNE GLOBULIN

Intravenous immune globulin (IVIG) is most commonly administered as replacement therapy in immune globulin deficient patients, or to suppress an autoimmune or inflammatory process in an immunologically competent individual. For treatment of immune deficiency, IVIG replaces missing antibodies. For immunomodulation, IVIG binds to mononuclear phagocyte Fc receptors and competitively inhibits Fc receptor binding to cell associated antibodies, preventing phagocytosis. IVIG is composed of 4 subclasses of IgG, with IgG1 being the major component. IgG1 is involved in virus inactivation, complement activation and tissue protection. Other postulated actions of IVIG include increased complement absorption, down regulation of immunoglobulin production, neutralization of viruses, enhancement of suppressor cells, inhibition of lymphocyte proliferation, and decreased production and activity of IL-1.

IVIG is most commonly administered as replacement therapy in immune globulin deficient patients, or to suppress an autoimmune or inflammatory process in an immunologically competent individual.

IVIG is derived from pooled human plasma (hundreds to thousands of donors) that has been isolated by the Cohn-Oncley process (cold ethanol fractionation). The manufacture of IVIG entails sequential precipitation and fractionation to isolate IgG from plasma proteins, although traces of IgA, IgM, IgD and IgE persist. In most IVIG products, ethanol is then removed by freeze-drying, producing stable intermediates and insoluble IgG aggregates that require further processing. Each IVIG preparation has different properties depending upon the approach to processing (i.e. solvent detergent, pasteurization, nanofiltration, ultrafiltration, etc.), but each is considered equivalent in efficacy. All products undergo virus inactivation or removal, but the potential for viral transmission still exists. Seven polyclonal IVIG preparations have FDA approval and are available in the US. Additionally, four hyperimmune products are indicated for the treatment of cytomegalovirus, hepatitis B (HBIG), and respiratory syncytial virus (RSV-IVIG) and for Rh prophylaxis (Rhogham).

The most common uses for IVIG in children are: (1) primary or secondary humoral immunodeficiency states; (2) hematologic diseases such as ITP or steroid-resistant autoimmune hemolytic anemia; (3) opportunistic infection prophylaxis in bone marrow transplant recipients; (4) neonatal alloimmune thrombocytopenia or neonatal sepsis (by providing immature infants with antibodies); (5) Kawasaki disease; or (6) Guillain-Barre syndrome. Diseases with less clear indications include: intractable seizures, myasthenia gravis, inflammatory myopathy, systemic lupus erythematosis, antiphospholipid antibody syndrome, rheumatoid arthritis, inflammatory bowel disease, systemic vasculitis, chronic idiopathic urticaria, asthma and bullous pemphigoid. Use of IVIG as an immunomodulator in septic states has generated great interest. It is speculated that IVIG may inactivate toxins, stimulate leukocyte and serum bactericidal activity, interfere with cytokine effects, and prevent excessive complement activation though there is no proven efficacy.

Headaches, myalgias, nausea, vomiting and facial flushing occur during 10% of IVIG infusions and may be alleviated by slowing or stopping the infusion. Acetaminophen, diphenhydramine and/or hydrocortisone prior to the infusion may lessen these reactions. Aseptic meningitis, transient hemiplegia, acute and chronic renal failure (with pre-existing renal disease), and anaphylaxis (with selective IgA deficiency) have been reported. For

treating immunodeficiency, 400–600 mg/kg IV Q3–4 weeks is the typical maintenance dose, with a goal trough serum IgG level >500 mg/dL. ITP is treated with higher doses of IVIG, generally 1 g/kg IV. Some of the complications noted above are more frequent with therapy at this dose. The rate of infusion depends upon the preparation and the patient's tolerance of the infusion, with rates ranging from 0.03 to 0.13 mL/kg/min. Preparations with a higher osmolality or sucrose concentration are infused more slowly. IgA deficient patients may have anti-IgA antibodies, and as such, can have a severe reaction to IVIG. Therefore, all persons receiving IVIG should have serum levels of IgA measured, and if they are IgA deficient, they should receive an IVIG product with the lowest IgA content possible.

ACTIVATED PROTEIN C

Protein C is a vitamin K-dependent glycoprotein synthesized by hepatocytes. Protein C circulates in its inactive form until it is activated by the thrombin-thrombomodulin complex on vascular endothelial cells. Activated Protein C has three main effects: (1) antithrombosis by inactivation of Factors Va and VIIIa; (2) anti-inflammatory effects secondary to a variety of mechanisms (blockage of cytokine formation, selectin activity, and NF-κB translocation); and (3) enhances fibrinolysis by the inactivation of plasminogen activator inhibitor-1, (PAI-1) and inhibition of thrombin-activated fibrinolysis inhibitor (TAFI). Severe sepsis is known to cause acquired protein C deficiency and lower levels have been associated with an increased morbidity and mortality in septic patients. Severe sepsis may also impair the conversion of Protein C to its activated form.

Knowledge of the role activated Protein C plays in sepsis prompted trials in which recombinant human activated Protein C (rhAPC), also known as activated drotrecogin alfa, was infused into septic patients. An adult study, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, demonstrated a decrease in 28 day all cause mortality in patients who received rhAPC. An open label study of pediatric patients with purpura-fulminans-associated meningococcemia demonstrated decreased morbidity and mortality in rhAPC treated patients. In view of these promising studies, a randomized, double blind, placebo controlled trial of rhAPC in pediatric patients with sepsis was performed. This investigation was stopped after interim analysis revealed treatment futility and an increase in CNS hemorrhage in treated subjects. The PROWESS-SHOCK trial, follow up to the original study, also did not find a mortality benefit in treated subjects. Since no benefit can be established, and later trials demonstrated increased risk of serious bleeding and death, activated drotrecogin alfa (Xigris) was taken off the worldwide market in October 2011 and all clinical trials involving the drug have been discontinued.

LEUKOREDUCTION

Generally accepted indications for leukoreduction of blood products include: (1) reduction of HLA alloimmunization risk in patients who require long term platelet support, or for potential organ transplant recipients, (2) reduction of CMV transmission in at-risk patients, and (3) reduction of the rate of recurrent febrile non-hemolytic transfusion reactions.

At most centers, red blood cell components are filtered shortly after collection, eliminating leukocytes in a process called prestorage leukoreduction. Leukoreduced red blood components contain $<1.0 \times 10^6$ leukocytes/unit. Platelet components are filtered or undergo specific apheresis collection protocols that reduce the number of leukocytes. Leukoreduced platelet components contain $<5.0 \times 10^6$ leukocytes/unit. Generally accepted indications for leukoreduction of blood products include: (1) reduction of HLA alloimmunization risk in patients who require long term platelet support, or for potential organ transplant recipients; (2) reduction of CMV transmission in at-risk patients; and (3) reduction of the rate of recurrent febrile, non-hemolytic transfusion reactions. Controversial indications include: (1) prevention of prion or viral reactivation; (2) prevention of post-operative infections; (3) reduction of tumor recurrence; (4) prevention of bacterial infection; (5) reduction in transfusion-related lung injury; and (6) reduction in transfusion-associated graft versus host disease.

A reduction of in-hospital mortality and serious nosocomial infections followed the adoption of leukoreduction of blood products in Canada. However, cost effectiveness of universal

leukoreduction remains controversial. In addition to the financial burden, there is considerable loss of blood elements with filtration. Leukocyte-depleted RBC units deliver a statistically smaller total RBC mass than non-leukoreduced units. Despite the debate, in January 2001, the US Department of Health and Human Services (DHHS) Advisory Committee on Blood Safety and Availability (ACBSA) recommended universal leukoreduction of cellular blood products in the United States.

IRRADIATED BLOOD PRODUCTS

As noted previously, blood filtration decreases, but does not eliminate WBC contamination. When viable T-lymphocytes in any blood product are transfused into an immunosuppressed patient, they can proliferate and cause transfusion-associated graft-versus-host disease (TA-GVHD). TA-GVHD is characterized by skin, gastrointestinal, hepatic and/or hematologic damage, occurring 10–28 days following a transfusion. It is associated with a high mortality. 2500 Gy of radiation applied to cellular blood components will prevent donor T-lymphocytes from dividing and thereby prevent GVHD in the recipient. FFP and cryoprecipitate do not require irradiation, as neither contain viable WBC and cannot cause TA-GVHD. Irradiation decreases RBC viability and causes potassium leakage, thus limiting storage duration to <28 days. For this reason, blood products are irradiated just prior transfusion.

Indications for irradiated blood products include: (1) mismatch of HLA haplotype between donor and recipient; (2) patients immunocompromised by chemotherapeutic regimens; (3) hematopoietic transplant patients; (4) neonates; and (5) patients with congenital cell-mediated immunodeficiencies. At some institutions, patients receiving solid organ transplants also receive irradiated blood products. At our institution, all blood products are irradiated. The clinician must remember that irradiation does not eliminate viruses.

Indications for irradiated blood products include: (1) mismatch of HLA haplotype between donor and recipient, (2) patients immunocompromised by chemotherapeutic regimens, (3) hematopoietic transplant patients, (4) neonates, (5) patients with congenital cell-mediated immunodeficiencies.

WASHED BLOOD PRODUCTS

RBC products also contain small amounts of residual plasma proteins. These proteins may produce allergic or other reactions in the transfusion recipient. "Washing" eliminates proteins from the RBC product and is indicated for patients with: (1) history of severe or recurrent allergic reactions associated with RBC transfusions; (2) IgA deficiency, when IgA deficient blood is unavailable (host anti-IgA antibodies react with IgA in donor transfusion product); (3) red-cell T activation. (In pediatrics, this is most commonly appreciated with necrotizing enterocolitis and invasive pneumococcal infections that cause the T antigen to be exposed on the RBC surface. Anti-T antibodies in donor plasma may cause hemolysis); and (4) complement-dependent autoimmune hemolytic anemia (washing prevents the infusion of complement).

IMMUNOMODULATION

Transfusions contain large quantities of cellular and soluble antigens (alloantigens) and bioactive substances with proinflammatory and/or immunosuppressive properties. As a consequence, allogenic blood transfusions induce a clinically significant alteration in the recipient immune function, termed transfusion-related-immune modulation (TRIM). A decreased helper-to-suppressor T-lymphocyte ratio, decreased natural killer cell function, defective antigen presentation, and reduced cell-mediated immunity occur secondary to TRIM.

Immunomodulation secondary to RBC transfusion was first suspected after an increase in renal allograft survival was noted after RBC transfusion. The suspicion was confirmed by performance of a prospective, randomized, controlled study that illustrated an increase in allograft survival following RBC transfusion. The increased allograft survival following RBC transfusion raised the question whether TRIM might also increase cancer recurrence

via down-regulation of host immune surveillance targeting malignant cells. Randomized, controlled trials have not supported an increase in cancer recurrence or post-operative infections secondary to perioperative allogeneic blood transfusion. However, difficulties with observational bias and patient selection make it difficult to exclude confounding variables in these studies. Further investigation is necessary to determine whether leukoreduction will limit immune-modulation from RBC transfusions.

TRANSFUSION REACTIONS

Transfusion reactions can be classified as (1) hemolytic reactions, (2) febrile non-hemolytic reactions, (3) allergic or anaphylactic reactions, and (4) non-immune transfusion reactions.

The United States blood supply is remarkably safe, however, the most frequent risk associated with blood transfusion is transfusion of an incorrect blood component. The risk of incorrect blood product transfusion is cited to be approximately 1 in 25,000 units transfused, and can be associated with death or major morbidity. The overall incidence of transfusion-related complications is 4% with the most common manifestations being: fever (1.9%); fluid overload (1.7%); and hypotension (1%). Transfusion reactions can be classified as: (1) hemolytic reactions, (2) febrile non-hemolytic reactions, (3) allergic or anaphylactic reactions, and (4) non-immune transfusion reactions.

Hemolytic Reactions

Most hemolytic reactions result from ABO incompatibility, but acquired alloantibodies (anti-Rh or anti-Jka), can also cause hemolytic reactions. In hemolytic reactions, donor red blood cell antigens form complexes with recipient antibodies leading to cell death. ABO mismatch carries the most significant risk of morbidity and mortality from blood transfusions, causing hemolysis (1 in 60,000) and death (1 in 600,000). During hemolysis, cellular products are released that damage renal tubular cells and may lead to hemoglobinuria, acute tubular necrosis, and renal failure. The immunologic response generated by antigen-antibody complexes may trigger a systemic consumptive coagulopathy or DIC.

A severe hemolytic transfusion reaction is manifested by fever, chills, rigors, hypotension, tachycardia, respiratory distress, hemoglobinuria and/or bleeding. When a hemolytic transfusion reaction is suspected, the transfusion must be stopped immediately. Treatment involves volume support with isotonic fluids to prevent hypotension and to ensure urine output of 100 mL/h in the adult patient and 2 mL/kg/h in the pediatric patient. Inotropic support should be considered in the setting of poor urinary output despite adequate volume resuscitation. Supportive care is often necessary to prevent cardiopulmonary complications, and DIC should be treated appropriately.

Febrile Non-hemolytic Reactions

Febrile non-hemolytic transfusion reactions (FNHTRs) occur in approximately 0.5% of RBC transfusions. Febrile non-hemolytic transfusion reactions are defined as an increase in the temperature of at least 1°C during a transfusion in the absence of another cause. These reactions are generally mild and resolve spontaneously, but can cause significant discomfort. Febrile non-hemolytic transfusion reactions may be characterized by fevers, chills, and dyspnea occurring within 6 h of the transfusion. These reactions are cytokine mediated and are usually prevented with use of leukocyte-reduced blood products. Since hemolytic reactions are also manifested by fever, management includes stopping the transfusion and evaluating for other possible transfusion reactions. Febrile non-hemolytic transfusion reactions often can be successfully treated with antipyretics, antihistamines, and/or meperidine (for rigors).

Allergic/Anaphylactic Reactions

The incidence of anaphylactic transfusion reactions is 1 per 18,000 transfusions, with platelet components and FFP responsible for the highest rates of reaction. Most allergic/

anaphylactic transfusion reactions are presumed to be secondary to plasma proteins. Clinically, the reaction is similar to anaphylaxis from other causes and is manifested as a rapid progression of hypotension, shock, angioedema, and respiratory distress. Management includes stopping the transfusion, the administration of subcutaneous or intramuscular epinephrine, airway management, oxygenation, volume and inotropic/vasopressor support.

Other Transfusion Complications

Other transfusion reactions include volume overload, hypothermia, citrate toxicity, hyperkalemia and transfusion related acute lung injury. Careful assessment and continued monitoring of the vascular volume status, pulmonary and renal function, and electrolyte balance is necessary before and during infusion of blood products. The intensivist must be prepared to provide oxygen, ventilator support and diuretics as necessary.

Neonates and infants are at greatest risk for volume overload and hypothermia from the transfusion of refrigerated blood. Standard practice is to transfuse 10–15 mL/kg of RBCs at a rate of 2–4 mL/kg/h. Slower rates of transfusion should be considered in children in whom anemia is severe, but developed in an indolent nature. A classic example occurs in infants who are fed iron poor cow's milk. The cow's milk causes occult intestinal blood loss that can lead to a slowly progressive and profound anemia with presenting hemoglobin values often less than 5 g/dL. Rapid transfusions may be appropriate for acute volume resuscitation. The risk of hypothermia increases when large volumes are transfused, especially through a central catheter. Hypothermia can be avoided by the use of a blood warmer.

Citrate, which binds to calcium, is an anticoagulant in RBC and plasma storage media. In large volume transfusions, citrate can lead to hypocalcemia. Citrate is metabolized in the liver to bicarbonate, and as a consequence, liver failure may increase the risk of citrate toxicity. In addition, simultaneously infusing calcium in tubing containing the blood product, or directly into the unit, may cause microemboli to form. The co-administration of Lactated Ringer's solution with blood is also contraindicated due to its high calcium content.

Red cells lyse during prolonged storage causing increased extracellular potassium to be present in the unit. It has been estimated that potassium levels may rise in the RBC unit by as much as 1 mEq/L/day during the first few weeks of storage. This potassium load is particularly dangerous to neonates and patients with renal insufficiency.

Pulmonary complications from blood transfusion comprise a spectrum of disease ranging in severity from mild pulmonary edema to transfusion related acute lung injury (TRALI). Transfusion related acute lung injury is defined as acute respiratory compromise with the onset of dyspnea, hypoxia, and non-cardiogenic pulmonary edema within 6 h of transfusion. All plasma-containing blood products (whole blood, RBC, platelets, FFP, cryoprecipitate and IVIG) have the potential to cause TRALI, and the incidence is cited as 1 in 5,000 transfusions. It has been postulated that TRALI results from an immunogenic response that leads to pulmonary capillary endothelial damage, capillary leak and edema formation. It is thought that donor antibodies react with the antigens on the recipient WBCs resulting in complement activation. Granulocyte chemotaxin (C5a) attracts leukocytes to the pulmonary circulation and neutrophil lysosomal enzymes damage the capillary endothelium resulting in capillary leak of fluid into pulmonary alveoli.

The diagnosis of TRALI is based on clinical criteria and is made primarily after excluding other possible conditions. Proposed clinical criteria for the diagnosis of TRALI include: (1) the acute onset of pulmonary insufficiency (within 6 h); (2) hypoxemia, specifically $PaO_2/FiO_2 < 300$ mm Hg; (3) bilateral fluffy infiltrates on chest radiography; (4) pulmonary artery wedge pressure ≤ 18 mm Hg; and (5) the absence of left atrial hypertension. Laboratory analysis of donor and recipient blood samples may further support the diagnosis.

If acute respiratory distress occurs during the transfusion, the transfusion should be stopped immediately. The treatment is primarily supportive; oxygenation and ventilation must be maintained and mechanical ventilation implemented as necessary. There is no supporting evidence for the use of corticosteroids or other anti-inflammatory medications in the treatment of TRALI. TRALI typically resolves after 48–96 h and does not cause permanent pulmonary damage. Although rare, this is a potentially severe complication of blood product transfusions.

Although TRALI should be considered in any pediatric patient with the onset of acute pulmonary disease within 6 h following transfusion, the clinician should remember that other conditions may mimic TRALI. The diagnosis of acute intravascular volume overload (TACO: transfusion-associated circulatory overload) should be considered in any child with underlying cardiac insufficiency. Hemolytic transfusion reactions, or anaphylaxis due to the transfusion of IgA-containing products to a recipient with IgA deficiency may also produce pulmonary manifestations. Several diagnoses, specific to the pediatric hematology-oncology population, may be confused with TRALI and include acute chest syndrome in transfused patients with sickle cell anemia, diffuse alveolar hemorrhage during bone marrow recovery in a bone marrow transplant patient, and acute respiratory distress occurring during granulocyte transfusions.

Platelet-Specific Transfusion Reactions

Five percent of platelet transfusions are associated with transfusion reactions. Sixty percent of these are febrile non-hemolytic reactions. Since platelet units contain few RBCs, the incidence of hemolytic reactions following platelet transfusions is very low. Febrile and/or allergic reactions following platelet transfusions are not uncommon. Patients with a history of an allergic response following platelet transfusions are commonly premedicated with acetaminophen and/or diphenhydramine. The efficacy of this practice has not been demonstrated in the literature. Prestorage leukoreduction and platelet washing have been found to reduce the incidence of allergic reactions from platelet transfusions. With the advent of universal leukoreduction of blood products in the United States, the incidence of febrile non-hemolytic transfusion reactions has decreased, and allergic reactions are becoming the most common type of transfusion reaction.

Bacterial infections transmitted by platelet products can be divided into two categories: (1) those that arise from contamination of stored platelet products and, (2) those that occur from occult donor infections causing septic platelet transfusion reactions (SPTR). Stored platelet products carry a high risk of bacterial contamination, as they provide excellent growth media for bacteria while being stored at 20–24°C for up to 5 days. Bacterial contamination occurs in 1 out of every 1,000–2,000 units of platelets. Transfusion-associated bacterial sepsis occurs in one-fourth to one-sixth of contaminated platelet transfusions. Currently, platelet products are routinely cultured in order to identify bacterial contamination, and thereby, reduce infection transmission. Attempts to eliminate bacterial contamination from platelet products include the use of ultraviolet light and psoralens. Both methods kill not only bacteria, but also viruses and white blood cells.

Septic platelet transfusion reactions (SPTR) are attributed to the contamination of platelet units from donor skin flora or asymptomatic bacteremia in the donor. SPTR have an approximate incidence of 1 in 5,000–15,000 transfusions, and a mortality of 17.4%. There has been a decline in SPTR since the adoption of single donor platelet transfusions; SPTR occur five times more often in patients receiving platelet concentrates compared to those receiving single donor platelets. Increased donor exposure and the number of phlebotomies necessary to obtain pooled platelet concentrates likely contribute to the higher risk of bacterial contamination in pooled concentrates.

INFECTIOUS RISKS

Identifying Risk

Since the AIDS epidemic of the late 1980s, there has been heightened awareness and public concern regarding the spread of infectious diseases through transfused blood products. The American Red Cross has responded by implementing more stringent donor history screening and improved donor testing. These approaches have dramatically reduced blood product related transmission of infectious diseases. The recent development and implementation of

molecular testing (polymerase chain reaction (PCR) based nucleic acid testing (NAT)) has greatly increased the sensitivity of infectious agent identification and has reduced the window period (the period of time during which a donor is potentially infectious, but will have negative serological tests). The existence of this window period prevents complete identification of infected blood products by either serologic or molecular screening tests.

The recent development and implementation of molecular testing (PCR based NAT) has greatly increased the sensitivity of infectious agent identification and has reduced the window period. However, the window period prevents complete identification of infected blood products by either serologic or molecular screening tests.

Human Immunodeficiency Virus (HIV)

The American Red Cross has implemented PCR nucleic acid testing (NAT) for Human Immunodeficiency virus (HIV). Most blood centers perform NAT assays for HIV as a mini-pool with 14–16 donors per pool. Some centers perform single-donor NAT that is associated with greater cost, but has an increased detection sensitivity of <50 HIV RNA copies/mL. With the implementation of mini-pool NAT, the estimated risk of transfusion-transmitted HIV is 1:4,000,000 with a window period of 11 days.

Hepatitis

Hepatitis B virus (HBV) detection is more difficult due to the transient nature of HBsAg detection in the plasma. Current donor screening is performed by testing HbsAg and anti-HBc serologies, and by obtaining donor history. Nucleic acid testing for HBV has been developed, but has not been implemented in the United States or Europe as the cost effectiveness has yet to be determined. The risk of transfusion-transmitted HBV is 1:205,000 with an estimated window period of 59 days. PCR-based NAT testing for Hepatitis C virus (HCV) was implemented in 1990. This approach has reduced the HCV window period to 10 days. The current transfusion-transmitted risk of HCV is 1:1,935,000. Hepatitis A and E do not have chronic phases; the viruses are transmitted during the acute viremic phase and should be identified on donor screening. Therefore, specific serologic or molecular screening assays are not used.

Cytomegalovirus

Cytomegalovirus (CMV), a herpes virus, is transmitted by leukocytes and therefore is associated only with *cellular* blood product transfusions. Any immunosuppressed patient is at risk of acquiring transfusion-related systemic CMV infection, and CMV is a significant cause of mortality in the hematopoietic stem cell transplant patient. The transfusion of CMV-seronegative blood products to CMV-negative patients, or the filtration of cellular blood products with third-generation leukocyte-reduction filters, has been found to prevent CMV transmission. Debate exists as to whether CMV-seronegatiave blood components are superior to filtered, leukoreduced components in the prevention of transfusion-transmitted CMV. In some institutions. leukoreduced blood products are used only if CMV-seronegative blood products are unavailable. At our institution, filtered leukoreduced blood products are used for immunocompromised or bone marrow transplant patients.

West Nile Virus

A seasonal flavivirus, the West Nile virus is transmitted by mosquitoes and 4,156 cases including 284 deaths were reported in the United States in 2002. In 2003, PCR NAT was introduced for the West Nile virus. Currently, testing is being performed regionally. Federal Drug agency approval of NAT for the viral genome is expected shortly. It is estimated that the virus may be present in the blood of 1:1,000 donors in endemic areas.

Adult T-cell Lymphoma/Leukemia

Adult T-cell lymphoma/leukemia (ATLL) is a peripheral T-cell neoplasm associated with infection by human T-lymphotrophic virus, type 1 (HTLV-I). These patients are primarily

TABLE 20-1

BLOOD COMPONENTS AND PLASMA DERIVATIVES

COMPONENT/PRODUCT	COMPOSITION	APPROXIMATE VOLUME	INDICATION
Whole blood	RBCs, Plasma, WBCs, Platelets	500 mL	Increase RBC mass and plasma volume (WBCs/platelets not functional) Deficient in FV and FVIII
Red blood cells	RBCs (Reduced plasma), WBCs, Platelets	250 mL	Increase RBC mass in symptomatic anemia (WBCs/platelets not functional)
Red blood cells + symptomatic Adenine-Saline	RBCs (Reduced plasma), WBCs, Platelets	330 mL, 100 mL additive solution	Increase RBC mass in symptomatic anemia (WBCs/platelets not functional)
RBC Leukocyte-Reduced (filtered)	Eighty five percent original volume of RBCs $<5\times10^6$ WBC, Few platelets, Minimal plasma	225 mL	Increase RBC mass; $<5\times10^6$ WBC Decreased febrile reactions, alloimmunization to WBC (HLA antigens) or CMV transmission
RBCs Washed	RBCs, $<5\times10^6$ WBC, No plasma	180 mL	Increase RBC mass; reduced risk of allergic reactions to plasma proteins
Granulocytes	Granulocytes ($>1.0\times10^{10}$ PMN/unit), Lymphocytes, Platelets ($>2.0\times10^{11}$/unit) Some RBCs (<500 PMN/μL)	220 mL	Provide granulocytes for selected patients with sepsis and neutropenia
Platelets	Platelets ($>5.5\times10^{10}$/unit), RBCs, WBCs, Plasma	50 mL	Bleeding due to thrombocytopenia or thrombocytopathy
Platelets Pheresis	Platelets ($>3.0\times10^{11}$/unit), RBCs, WBCs, Plasma	300 mL	Same as platelets; sometimes HLA matched
Platelets Leukocyte-Reduced	Platelets ($>3.0\times10^{11}$/unit), $<5\times10^6$ WBC per final dose of pooled platelets	300 mL	Same as platelets; $<5\times10^6$ WBC to limit febrile reactions to leukocytes (HLA antigens) or CMV transmission
FFP	FFP, Donor retested plasma has all coagulation factors, Thawed plasma has reduced FV and FVIII	220 mL	Treatment of some coagulation disorders
Cryoprecipitate	Fibrinogen, FVIII, FXIII, Von Willebrand factor	15 mL	Deficiency of fibrinogen or FXIII; second choice for treatment of hemophilia A, von Willebrand disease
Human Factor VIII Recombinant or plasma derived	Factor VIII plasma-derived has trace plasma proteins	25 mL	Hemophilia A (Factor VIII deficiency)
Human Factor IX Recombinant or plasma derived	Factor IX plasma-derived has trace plasma proteins	25 mL	Hemophilia B (Factor IX deficiency)
Albumin	Albumin, Some α–, β–globulins	(5% or 25%)	Volume expansion
Immune globulin	IgG antibodies	Varies	Hypo- or agammaglobulinemia; ITP
Rh Immune Globulin	IgG anti-D	1 mL	Prevention of hemolytic disease of the newborn due to D antigen; ITP
Antithrombin	Antithrombin	10 mL	Antithrombin deficiency
Recombinant Factor VIIa	Factor VIIa	2.2 mL(1.2 mg) 8.5 mL(4.8 mg)	Bleeding episodes for hemophilia A or B with inhibitors Bleeding episodes in patients with acquired hemophilia Bleeding episodes in patients with congenital factor VII deficiency

TABLE 20-2

COMPLICATIONS OF BLOOD PRODUCT TRANSFUSIONS

Hemolytic reactions
– Hemoglobinuria, hemoglobinemia, fever, dyspnea, hypotension
Febrile non-hemolytic reactions
– Fever, chills, tachycardia, headache, urticaria, rash, dyspnea
Generalized allergic/anaphylactic reactions
– Angioedema, wheezing, upper airway edema, hypotension, shock, arrhythmias, death
Coagulopathy
– Dilutional
Transfusion-transmitted infection
– CMV, HIV, HBV, HCV, HTLV
– Bacteremia
Graft-versus-Host Disease
Alloimmunization
Transfusion-related acute lung injury
– Acute onset, bilateral infiltrates on chest radiograph, PaO_2/FiO_2 ratio <300
Circulatory overload
– Dyspnea, pulmonary edema, congestive heart failure
Hypothermia
Metabolic Abnormalities
– Hypocalcemia, hyperkalemia

adults with antibodies to HTLV-I. The virus is endemic in the islands in southern Japan, the Caribbean basin (Jamaica), Trinidad, Africa and in the Southeastern portion of the United States. The virus may be transmitted through sexual contact, breast milk or through blood products. Current testing for human T-cell leukemia virus (HTLV) I/II is serologically based. Transfusion-transmitted HTLV-I/II is estimated to occur in 1: 2,993,000 transfusions, with a 51 day window period.

Other

Many other infectious agents have the potential to be transmitted through blood product transfusions. The availability of specific serologic and molecular tests for many agents is lacking, and in such circumstances, positive donor history leading to deferment is relied upon to prevent transmission.

Severe acute respiratory syndrome (SARS) was first identified in the Guangdong province of China in November 2002. The exact pathogenesis is unknown, but SARS is thought to be the result of a mutated coronavirus or paramyxovirus. SARS has been isolated from the blood of an infected patient, but it is unknown whether it can be transmitted through transfusions. The FDA has published recommendations on donor suitability for the prevention of transfusion-transmitted SARS; donors are deferred for 2 weeks following any possible exposure to SARS, or travel to a SARS-affected community.

Parvovirus B19 is potentially transmissible through blood product transfusions. Parvovirus B19 associated illness is rarely clinically significant except in pregnant women (where it can cause hydrous fetalis), in those with hemolytic anemia (where it can cause aplastic crisis), and in immunocompromised persons. It is estimated that parvovirus B19 viremia is present in approximately 0.025% of donors, yet there have only been rare reports of its transmission in plasma-derived blood products. No specific donor testing for parvovirus B19 exists. Nanofiltration and/or heat inactivation of plasma products is currently undertaken to prevent its transmission.

The spirochete *Treponema pallidum* causes syphilis and can be transmitted through sexual contact and blood transfusions. No cases of transfusion-transmitted syphilis have been reported since 1968, but serologic screening of donors using automated treponemal-based testing continues to be mandatory in the United States.

Malaria can also be transmitted through the blood stream. In the United States, there is currently no FDA-approved serologic test to screen blood donors for malaria. The prevention of transfusion-transmitted malaria has been accomplished by donor deferral based on

travel history. Despite this, 2–3 cases of transfusion-transmitted malaria occur each year in the United States with an incidence of 1:4,000,000 units.

An outbreak of Variant Creutzfeldt-Jacob disease (vCJD), a prion linked to bovine spongiform encephalopathy, occurred in the United Kingdom (U.K.) in 1996 raising the question of whether vCJD can be transmitted in humans via blood transfusions. The answer remains unknown. In the United States, blood donors are deferred if they have spent >3 months in the United Kingdom between 1980 and 1996, have spent >6 months in Northern Europe during this time period, have lived >5 years total in Europe, or have received a blood transfusion while in the United Kingdom.

Recent concern over bioterrorism has raised questions as to whether orthopoxviruses (smallpox, vaccinia, monkeypox) can be transmitted through blood transfusions. The last natural case of smallpox occurred in 1977 in Somalia. There are no FDA-approved serologic studies to screen for orthopoxviruses in the United States, and research in this regard is ongoing.

TRANSFUSIONS IN SPECIAL PATIENT POPULATIONS

Neonates

Premature infants receive RBC transfusions for a variety of clinical conditions associated with anemia (respiratory disease, apnea, tachycardia and poor weight gain). More than 50% of infants whose birth weights are <1,250 g receive RBC transfusions in the neonatal intensive care unit (NICU). Physiologic anemia with an inadequate bone marrow response, low levels of erythropoietin, poor nutritional status, iron deficiency, shorter RBC life span, and frequent blood sampling, contribute to anemia. Blood group incompatibility, hemoglobinopathies, and/or sepsis, if present, may compound the anemia associated with prematurity.

Recommendations are to maintain a hemoglobin of 13 g/dL in infants with severe cardiac or pulmonary disease, and a hemoglobin of 8.0–10.5 g/dL in those with anemia of prematurity and compromised oxygen delivery.

Red cell transfusion practices vary greatly among intensive care units across the United States. Information regarding the neonatal response to RBC transfusion is lacking, so that evidence based transfusion guidelines do not exist and expert opinion has primarily driven transfusion practices. Transfusion recommendations for neonates were published in the early 1990s by the American Association of Blood Banks, the British Committee for Standards in Haematology, and the Canadian Pediatric Society. Each of these bodies supported maintaining a hemoglobin of 13 g/dL in infants with severe cardiac or pulmonary disease, and a hemoglobin of 8.0–10.5 g/dL in those with anemia of prematurity and compromised oxygen delivery. Refer to Table 20-3 for more detailed neonatal RBC transfusion recommendations.

In an effort to limit donor exposure, transfusions are given in small aliquots from a single dedicated RBC unit dedicated for the life span of that unit. Red cell preservatives (mannitol, glucose, sodium chloride, phosphate, adenine) are manipulated in order to lengthen the unit's

TABLE 20-3

INDICATIONS FOR NEONATAL RED BLOOD CELL TRANSFUSION

- Transfuse all neonates with hemodynamic instability in the setting of blood loss
- Transfuse for hemoglobin <12 g/dL:
  - If mechanical ventilation and a FiO_2 >40% or MAwP >8 cm H_2O
- Transfuse for hemoglobin <9 g/dL:
  - If mechanical ventilation and a FiO_2 <40% or a MAwP <8 cm H_2O
  - If weaned off ventilation, but persistent FiO_2 requirement (>40%) and major surgery
  - If any of the following signs of anemia are present:
    - >15 episodes of unexplained apnea per day
    - An apneic episode requiring bag-valve-mask ventilation
    - Unexplained persistent tachycardia (>165 bpm)
    - Unexplained persistent tachypnea (>80 breaths/min)
    - Unexplained poor weight gain
- Transfuse for hemoglobin <6.5 g/dL

storage duration to 42 days. As previously described, prolonged storage can increase potassium, adenine and mannitol content. A solute load of such magnitude may lead to an osmotic diuresis, altered cerebral microcirculation, and renal toxicity in the small infant. Therefore, alternative RBC preservatives have been developed for use in neonates. AS-1 (750 mg/100 mL mannitol and 27 mg/100 mL adenine) and AS-3, (30 mg per 100 mL of adenine, but no mannitol) are safe for small volume (5–15 mL/kg) transfusions in neonates.

Congenital Heart Disease

Very few studies have examined transfusion thresholds for children with congenital heart disease either pre- or post-palliative or reparative surgical procedures. The optimal hemoglobin concentration for these children remains unknown. Subgroup analysis of patients in the TRIPICU study with congenital heart disease following cardiac surgery found similar results in those treated with a restrictive versus a liberal transfusion strategy. It appears that children undergoing biventricular repairs, once adequate hemostasis has been achieved, can tolerate anemia like their non-cardiac counterparts.

However, children with single ventricle physiology and mixing cardiac lesions causing cyanosis were excluded from this analysis. In children with cyanotic cardiac lesions secondary to intracardiac right to left shunts, chronic hypoxia promotes increased erythropoiesis to maintain tissue oxygen delivery. Postoperatively, these children have been managed historically with the goal of maintaining higher hemoglobin concentrations in order to ensure adequate tissue oxygen delivery. This practice is now being questioned as the risks of RBC transfusions are increasingly recognized. Adult and pediatric studies have found independent association between increased number of RBC transfusions and worse clinical outcomes following cardiac surgery with cardiopulmonary bypass. Additionally, over-correction should be avoided since polycythemia may actually decrease oxygen delivery. Polycythemia may result in "sludging" of the red cell mass at the capillary level thereby impeding blood flow to distal tissues. The only prospective study exploring RBC transfusion strategies in children with single ventricle physiology undergoing palliative procedures focused on infants and children undergoing bi-directional Glenn and Fontan procedures. Children managed with a restrictive transfusion strategy appeared no different from those maintained at higher hemoglobin levels. Larger prospective studies, and those including neonates undergoing stage 1 palliations are needed.

Anemia in cyanotic children should be prevented, but not overcorrected as polycythemia may actually decrease oxygen delivery by "sludging" of the red cell mass at the capillary level, and impede blood flow to distal tissues.

Patients with congenital cardiac disease often have associated chromosomal abnormalities (including chromosome 22 deletions of Di George syndrome), and thus, may be at increased risk of T-lymphocyte deficits. Consequently, it is our standard practice to transfuse this population with filtered and irradiated blood products. Two pRBC units are prepared by our blood bank for all congenital cardiac pediatric patients requiring cardiopulmonary bypass. One unit, a "fresh" pRBC unit (<5 days old) that is post-storage washed, is used first to prime the bypass circuit, with the residual volume available for additional transfusion as required. FFP is not given routinely on cardiopulmonary bypass nor used in the pump prime. The second pRBC unit is irradiated and leukoreduced, and patients are maintained on a filtered and irradiated protocol for the remainder of their hospitalization until their genetic profile is known.

During cardiopulmonary bypass, the balance between bleeding and thrombosis is deranged. Thrombocytopenia results from platelet consumption and hemodilution. In addition, platelets are rendered dysfunctional secondary to hypothermia and following their activation and release of mediators. The process of traversing the bypass circuit promotes thrombosis, so heparin and fibrinolytic agents are used intra-operatively and levels are monitored with activated clotting times (ACT). There is also a concomitant risk of bleeding secondary to hemodilution of coagulant proteins and a cytokine-driven inflammatory response to the bypass circuit. Individual physiology, the degree of cyanosis, and post-operative hemodynamic instability may further contribute to the coagulopathy experienced by these children. Thrombosis of surgical grafts, artificial valves, and conduits are often incompatible with life. Therefore, infusions of pro-coagulant blood products should be used only after careful considerations of the associated risks and benefits.

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a bypass circuit that channels blood through an oxygenator using a mechanical pump. Systemic venous blood (typically from a right atrial venous cannula) is drained from the patient and travels through a membrane oxygenator. A nonpulsatile roller pump then returns oxygenated, re-warmed blood to the patient via an arterial or venous cannula. Much like cardiopulmonary bypass, maintaining a balance between hemorrhagic complications and circuit thrombosis remains a challenge while providing ECMO support. Patients on ECMO are maintained on a heparin infusion to prevent clotting of the circuit and activated clotting time (ACT) is followed closely with a goal between 180 and 220 s. Despite anticoagulation with a heparin infusion, careful replacement of coagulation proteins with FFP and cryoprecipitate is essential, as the bypass circuit incites a consumptive coagulopathy which can be predictive of intracranial hemorrhage. Intracranial hemorrhage can occur in children on ECMO despite careful attention to coagulation parameters and is a common reason for cessation of treatment.

ECMO relies upon the use of large numbers of RBCs, FFP and platelet units, as well as careful attention to, and correction of, the electrolyte imbalances that may arise following large volume transfusions (hypocalcemia, hyperkalemia). It is our protocol to wash all RBC units given on ECMO to prevent hyperkalemia secondary to large volume RBC transfusions. One early study estimated that approximately 250 mL of pRBC, 80 mL FFP and two units of platelets are transfused each day to neonates on ECMO. Studies have shown that there is no benefit in keeping the hematocrit >35%. Typically, platelets are given daily to maintain a platelet count >100,000/μL, and FFP or cryoprecipitate is given to maintain normal coagulation proteins.

Uremic Patients

The association between renal disease and bleeding is well recognized. Renal failure is often complicated by mucocutaneous bleeding secondary to impaired hemostasis. The use of hemodialysis or peritoneal dialysis has greatly decreased the occurrence of hemorrhagic complications, but clinicians must remain aware of the hemorrhagic tendency of the uremic patient. The hemostatic defect associated with renal failure is multifactorial. Alterations in platelet metabolism, vascular and smooth muscle endothelial cells, and abnormal interactions between platelets and the vessel wall have been found in the uremic patient. The management of bleeding in the uremic patient includes increasing von Willebrand factor (vWF) to improve platelet dysfunction. Historically, the use of cryoprecipitate for this indication has been replaced by intravenous DDAVP which stimulates the release of Factor VIII and vWF from endothelial cells. Regarding the use of pRBCs, current practice is to adjust dialysis and transfuse patients with renal failure to maintain a hematocrit above 30%. Recombinant human erythropoietin therapy is standard treatment for anemia of renal insufficiency, and its use generally decreases the number of RBC transfusions.

As described previously, the concentration of extracellular potassium increases as RBC storage duration increases. Renal failure patients requiring RBC transfusions should receive blood less than 5 days “old” to prevent hyperkalemia. If such blood is unavailable, “older” blood can be washed immediately prior to transfusion to reduce its potassium content.

Patients with Inherited Bleeding Disorders

Patients with classic hemophilia (hemophilia A) have insufficient Factor VIII levels. Factor VIII (FVIII) concentrate is therefore the preferred replacement modality in these patients. Indications for FVIII infusions in children with this form of hemophilia include preparation for an invasive or surgical procedure, bleeding, or prophylaxis to prevent further joint disease. Children with severe hemophilia often receive routine infusions for the primary or secondary prevention of bleeding episodes. The Medical and Scientific Advisory Council of the National Hemophilia Foundation recommends recombinant FVIII as the first-line treatment of these patients. Plasma-derived virally inactivated FVIII concentrates are also available. Patients with hemophilia B (Christmas disease) have insufficient Factor IX levels

(FIX), and FIX is the preferred replacement for these patients. There are three types of FIX available: recombinant FIX (which is preferred); plasma-derived FIX; and prothrombin complex concentrates. Each can be used for treatment of acute bleeding or for prophylaxis. For both Factor VIII and Factor IX deficiency, if there is severe bleeding or if specific factor replacement is unavailable, FFP should be given.

Oncology/Transplant Patients

Anemia is quite common in patients with malignancies. Its origins are multifactorial: (1) ineffective or suppressed erythropoiesis secondary to chronic disease, marrow infiltration, or myelosuppressive therapy; (2) peripheral destruction from alloimmune and/or autoimmune hemolysis; and (3) hemorrhage secondary to acquired coagulopathies and thrombocytopenia, anatomic lesions, or surgical procedures. Transfusion therapy for these patients is complicated by persistent cytopenias and immunosuppression, but as for other groups, the use of hematopoietic growth factors have decreased the need for transfusions.

At our institution, patients with malignancies are placed on a blood bank protocol consisting of irradiated, filtered, and leukoreduced blood products. At some institutions, CMV-negative blood products are utilized until the CMV serostatus of the individual is known. Hematopoietic stem cell transplant (HSCT) patients receiving myeloablative therapy are particularly susceptible to bleeding complications. Both HSCT and solid organ transplant recipients are immunosuppressed and at risk for persistent cytopenias, infections, and transfusion-associated infectious and immunologic complications. Immunosuppressed oncology and transplant patients are at risk for developing TA-GVHD as described previously.

ALTERNATIVE THERAPY

Erythropoietin

In critically ill patients, endogenous erythopoietin levels are low despite the presence of anemia. However, research has demonstrated that the bone marrow of the ICU patient is extremely responsive to exogenous erythropoietin. Consequently, it has been postulated that administering exogenous erythropoietin to these patients would reduce anemia and the necessity of transfusion support. The main drawback to using erythropoietin therapy in the critically ill patient is the length of time between administration and the resultant marrow response (weeks). In fact, a recent, multicenter study demonstrated that the widespread use of erythropoietin would have little impact on the transfusion requirements of children admitted to the PICU. It is difficult to determine prospectively which PICU patients will have an extended length of stay, will require multiple RBC transfusions, and would therefore benefit from erythropoietin therapy. Use of erythropoietin as a blood conservation therapy for patients with chronic anemia, i.e., secondary to chronic renal failure, cancer etc., has been well supported.

Other Agents

A variety of agents are now available to decrease bleeding, promote hemostasis, and decrease the number of required blood product transfusions. Agents used to increase concentrations of clotting factors include desmopressin acetate (DDAVP), estrogens, recombinant Factor VIIa, and vitamin K. Agents to increase platelet concentrations and activity include recombinant thrombopoietin and recombinant human interleukin-11. Antifibrinolytics include transexamic acid, aminocaproic acid and aprotinin; aprotinin has been pulled off the market secondary to increased risk of complications and death. Hemostatic sealants and dressings are also available. Review of the mechanisms of action and clinical indications for these agents is beyond the scope of this chapter. However, the intensivist should be aware that these agents exist, and that they may be of great benefit to patients in certain situations.

SUMMARY

Understanding the role of blood products in the management of critically ill patients is extremely important. Blood product transfusions are exceedingly common, and likely to increase as medical advances in the care of critically ill patients continue. The decision to administer a blood product must be based on a clear understanding of the benefits and risks of the transfusion and made in the context of the clinical condition of the patient. It is of paramount importance that the clinician is familiar with the types of blood products available, the indications for their use, and the associated potential risks.

REVIEW QUESTIONS

1. **During morning rounds, the medical student suggests transfusing a 3 year old patient with idiopathic cardiomyopathy since her hemoglobin is 9.0 g/dL. She is tachycardic with a heart rate of 178 beats per minute and has a blood pressure of 81/44 mm Hg and a central venous pressure of 2 mm Hg. The most correct response to her suggestion is:**
   - **A.** No, do not transfuse because her hemoglobin is > 8.0 g/dL.
   - **B.** No, do not transfuse because she has a cardiomyopathy and is at risk of congestive heart failure.
   - **C.** No, do not transfuse because she is normotensive.
   - **D.** Yes, transfuse because her hemoglobin is < 10.0 g/dL and she has a cardiomyopathy.
   - **E.** Yes, transfuse because her hemoglobin is 9.0 g/dL and she is symptomatic.

2. **A ten year old 24 kg girl with relapsed leukemia develops pallor, tachycardia to 129 beats per minute and is found to have a hemoglobin of 6.7 g/dL. She has a history of doxorubicin-induced cardiac dysfunction and currently has a left ventricular ejection fraction of 50%. The most appropriate dose and duration of a packed red blood cell transfusion is:**
   - **A.** 3–5 mL/kg over 3 hours
   - **B.** 10 mL/kg over 1 hour
   - **C.** 15 mL/kg over 3 hours
   - **D.** Two units over 1 hour
   - **E.** Two unit over 2 hours

3. **A 4 year old male with multiple trauma develops symptomatic anemia. Prior to administering a packed red blood cell transfusion, the child's parents ask about the risk of HIV transmission. You answer that the risk is:**
   - **A.** <1 in 10,000
   - **B.** <1 in 100,000
   - **C.** <1 in 1 million
   - **D.** <1 in 2 million
   - **E.** <1 in 4 million

4. **Transfusion related acute lung injury is best defined as:**
   - **A.** acute onset of chest pain within 1 h of transfusion, hypoxemia, ($PaO_2/FiO_2 < 300$ mm Hg), bilateral infiltrates on chest radiography and absence of left heart failure
   - **B.** acute onset of chest pain within 6 h of transfusion, hypoxemia, ($PaO_2/FiO_2 < 300$ mm Hg), bilateral infiltrates on chest radiography and absence of left heart failure
   - **C.** acute onset of pulmonary insufficiency within 1 h of transfusion, hypoxemia, ($PaO_2/FiO_2 < 300$ mm Hg), bilateral infiltrates on chest radiography and absence of left heart failure
   - **D.** acute onset of pulmonary insufficiency within 6 h of transfusion, hypoxemia, ($PaO_2/FiO_2 < 300$ mm Hg), bilateral infiltrates on chest radiography and absence of left heart failure
   - **E.** acute onset of pulmonary insufficiency within 6 h of transfusion, hypoxemia, ($PaO_2/FiO_2 < 300$ mm Hg), hypercarbia ($PaCO_2 > 50$ mm Hg), bilateral infiltrates on chest radiography and absence of left heart failure

5. **The most correct statement regarding anemia and red blood cell transfusion is:**
   - **A.** Maintaining hemoglobin levels >9 g/dL in critically ill children is an appropriate therapeutic target as it reduces ICU morbidity.
   - **B.** Oxygen delivery by transfused red blood cells is comparable to that of native red blood cells and consistently increases tissue oxygen availability.
   - **C.** Packed red blood cells are produced by the removal of plasma and all cellular components other than red blood cells.
   - **D.** The ability of the heart to increase cardiac output and coronary artery blood flow in response to severe anemia is compromised. Symptomatic patients with underlying cardiovascular disease benefit from red blood cell transfusion.
   - **E.** Whole blood is an acceptable alternative to packed red blood cells when transfusing infants with cyanotic heart disease.

6. **Storage techniques that lengthen RBC lifespan may result in detrimental physiologic changes that include:**
   - **A.** Depletion of 2,3-diphosphoglyerate (2,3-DPG) with resultant decreased oxygen affinity and decreased oxygen-hemoglobin binding.
   - **B.** Increase in 2,3-diphosphoglyerate (2,3-DPG) with resultant decreased oxygen affinity and decreased oxygen-hemoglobin binding.
   - **C.** Increase in endogenous antioxidants resulting in damage to cytoskeletal proteins and membrane phospholipids.
   - **D.** Morphological changes including the loss of the normal biconcave disc shape ultimately leading to schistocyte formation.
   - **E.** Morphological changes including the loss of the normal biconcave disc shape ultimately leading to spherocyte formation.

7. A 10 year old girl with acute lymphocytic leukemia is in the PICU recovering from sepsis. She is extubated and off hemodynamic support. Her most current cell counts are white blood cell count 3,500/μL, hemoglobin 9.1 g/dL and platelets 11,000/μL. Her PT/PTT and INR are within normal limits. She has oozing around her broviac catheter. A transfusion of platelets is ordered. The most correct statement regarding the impending transfusion is:

A. One unit of platelets typically raises the platelet count by approximately 25,000–30,000/μL

B. Platelet apheresis allows multiple units of platelets to be collected from a single donor, thereby reducing the risk of alloimmunization.

C. Unlike packed red cell transfusions, platelets transfusions do not produce transfusion-related allergic reactions.

D. Refrigeration of platelets allows for safe serial transfusion from the same unit.

E. Spleen sequestration of transfused platelets rarely occurs and is not a cause of a poor response to platelet transfusion.

ANSWERS

1. E
2. C
3. E
4. D
5. D
6. E
7. B

SUGGESTED READINGS

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