Chapter 6
Adverse Reactions

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Abbreviations

2,3-DPG	2,3-Diphosphoglycerate
AHTRs	Acute hemolytic transfusion reactions
ARDs	Acute respiratory distress syndrome
BRMs	Biologic response modifiers
CMV	*Cytomegalovirus*
DIC	Disseminated intravascular coagulation
ECMO	Extracorporeal membrane oxygenation
ESAs	Erythropoiesis-stimulating agents
FNHTRs	Febrile nonhemolytic transfusion reactions
G6PD	Glucose-6-phosphate dehydrogenase
HLA	Human leukocyte antigens
HNAs	Human neutrophil antigens
HTRs	Hemolytic transfusion reactions
IgG	Immunoglobulin G
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
RBCs	Red blood cells
TACO	Transfusion-associated circulatory overload
TA-GVHD	Transfusion-associated graft-versus-host disease
TANEC	Transfusion-associated necrotizing enterocolitis
TRALI	Transfusion-related acute lung injury

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Red Cell Storage Lesions and Metabolic Imbalances

When red blood cells are stored, they undergo a variety of physiologic changes known as red cell storage lesions. Changes associated with red cell storage lesions include increased extracellular potassium, decreased 2,3-diphophoglycerate (2,3-DPG), and increased plasma hemoglobin. These lesions are accelerated with irradiation. While not considered to be true transfusion reactions, red cell storage lesions can cause harmful side effects to neonatal patients undergoing transfusions. Given their small blood volumes, neonates are at an increased risk of developing metabolic imbalances following transfusion secondary to red cell storage lesions. This is due, in part, to the inability of their immature liver to effectively metabolize citrate and the reduced glomerular filtration rate associated with kidney immaturity that causes slower excretion of excess potassium, acid, and calcium. Hypocalcemia may occur after rapid transfusion of citrate, and alkalosis may develop after metabolism of large amounts of citrate. Because of this, infants less than 4 months of age may develop hyperkalemia, acid–base imbalances, or hypocalcemia following large-volume transfusions. In addition, the preservative solutions used to increase the shelf life of blood products can contain solutes causing diuresis, altered blood volume, and potentially altered cerebral blood flow leading to increased risk of intraventricular hemorrhage [40, 46].

Hyperkalemia

The increase in storage-related extracellular potassium along with the impaired renal function in neonates due to disease or prematurity can put them at increased risk for transfusion-associated hyperkalemia. This occurs primarily during large-volume rapid transfusions such as occur with extracorporeal membrane oxygenation (ECMO), exchange transfusions, or during surgery. Small-volume transfusions administered at a slow rate have been shown to have little effect on serum potassium concentrations on neonates.

For example, a typical unit of red blood cells (RBCs) contains a starting extracellular potassium concentration of 5–10 mEq/L. Sometimes due to donor issues, the unit may start out with higher levels of potassium. During refrigerated storage, the intracellular potassium within RBCs continues to be released into the extracellular space due to reduction in the activity of the Na–K ATPase pump. The type of anticoagulant-preservative solution used in the storage of RBCs influences the amount of potassium leak. For example, after 35 days, the concentration of extracellular potassium within a unit of red blood cells preserved with CPDA-1 can reach 70–80 mEq/L. In contrast, after 42 days the concentration of extracellular potassium within a unit of red blood cells preserved with AS-1, AS-3, or AS-5 reaches approximately half of that amount at 40–50 mEq/L. Increases in extracellular potassium secondary to hemolysis can also occur due to excessive heating or freezing of the unit, the use of hypo-osmotic solutions during RBC transfusion, bacterial contamination, mechanical hemolysis from transfusion

through small-gauge needles, and exposure to UV light in patients undergoing phototherapy.

Life-threatening effects of hyperkalemia, especially when administered through a central or intracardiac line where high concentrations of potassium are being rapidly delivered to the heart without first being filtered through the kidneys, include cardiac arrest and death. In order to reduce the risk of hyperkalemia in neonatal patients, transfusion with fresh RBCs is recommended. Washing a red cell unit can also be an effective means of removing extracellular potassium, especially for units that have been stored for >24 h or have been irradiated >24 h before transfusion as irradiation potentiates potassium release. However, this effect is only temporary with extracellular potassium rising again following washing (up to 5 mEq/L in non-irradiated and 12 mEq/L in irradiated units after 24 h).

Irradiation of blood products accelerates the rate of red cell storage lesions, especially the extracellular leakage of potassium >12 h after irradiation. Therefore, it is recommended that red blood cells be irradiated as close to the time of transfusion as possible, especially for large-volume transfusions (>20 mL/kg) in order to minimize the accumulation of extracellular potassium. In neonates receiving aliquots, it is preferable to irradiate only the aliquot being transfused instead of the entire parent unit. This is only possible if a hospital has an irradiator on site, which is preferable for institutions who routinely administer large-volume transfusions to neonatal patients. If hospitals do not have an irradiator and must receive irradiated blood from an outside source, hyperkalemia may be a concern if the irradiated unit is not transfused immediately (within 12 h of irradiation). There have been case reports and anecdotal reports of infant deaths caused by infusions of high concentrations of extracellular potassium in as little as 24 h after irradiation [23]. If the unit cannot be used in a neonatal patient within 12 h of irradiation, then the irradiated unit should be assigned to a larger child or adult patient instead.

Because of these time constraints, communication between the clinical team and the blood bank is essential to coordinate the time of transfusion in order to help reduce the risk of hyperkalemia. Ideally, procedures should be in place to rapidly irradiate and dispense such units. If irradiation cannot be performed fast enough for the patient's transfusion needs, policies should be in place to evaluate the risk of transfusion-associated hyperkalemia, transfusion-associated graft-versus-host disease, and transfusion delays. Alternatively, if a neonate requires large-volume transfusion, it may be helpful for the transfusing provider to preemptively treat the infant for hyperkalemia. Calcium boluses can be given up front. In some instances, albumin or glucose could also be utilized.

2,3-Diphosphoglycerate

2,3-DPG is a molecule that is essential for red blood cell metabolism. It normally works to shift the hemoglobin–oxygen dissociation curve to the right, increasing the ability of red blood cells to release oxygen into tissue. During storage, the amount

of 2,3-DPG diminishes rapidly which shifts the hemoglobin–oxygen dissociation curve to the left, thereby reducing the ability of red blood cells to release oxygen into tissue. By storage day 21, the amount of 2,3-DPG is completely depleted from the red blood cell unit. Studies in adults have shown that it takes between 3 and 8 h for 2,3-DPG to be regenerated after one unit of RBCs has been transfused and that older patients are able to compensate for the resulting hypoxia by increasing their heart rate. However, infants younger than 4 months old are not able to compensate as effectively. In addition, sick neonates with respiratory distress syndrome or sepsis may have even lower levels of intracellular 2,3-DPG. Because of this, it has been suggested that fresh blood products be used for neonates undergoing large-volume transfusions in order to increase the amount of 2,3-DPG that they receive. As with hyperkalemia, the need for fresh blood products in small-volume transfusions is unnecessary as the decreased amount of 2,3-DPG is unlikely to reduce the amount of oxygen available to tissues.

Special Processing of Blood Components

Neonates comprise a special patient population that requires additional manipulation of blood products (i.e., washing, irradiation, bedside filtration, or concentration) which can extend the preparation time, shorten the shelf life, and alter the composition of the blood product (i.e., hyperkalemia) being transfused. This special processing of blood products is primarily performed in order to reduce the risk of the infant's immature immune system from exposure to many infectious and noninfectious complications of transfusion. Much of an infant's humoral (antibody-mediated) immunity is provided by the mother through the placental transfer of immunoglobulins in utero, which consist predominantly of the immunoglobulin G (IgG) class of molecules. After delivery, the mother is no longer able to provide these antibodies to the infant for immune protection. In addition, an infant's cellular immunity is incompletely developed at birth, making them especially susceptible to transfusion-associated graft-versus-host disease.

Irradiation

The irradiation of blood is performed on cellular products in order to prevent transfusion-associated graft-versus-host disease (TA-GVHD). It is recommended that cellular blood products be irradiated for the following patients: premature infants weighing <1200 g at birth, any patient with a known or suspected cellular immune deficiency, any patient with significant immunosuppression related to chemotherapy or radiation treatment, and any patient receiving HLA-matched or crossmatched platelet components. In addition, parents or other blood relatives who wish to be a direct blood donor for an infant must have the donated units irradiated. For practical

purposes, many institutions choose to set an age in which all neonates under the set age will receive irradiated blood. The irradiation of blood products may generate increased operational costs, time delays, and damage to red blood cells.

Washing

The washing of RBCs is most commonly performed in order to remove excess extracellular potassium or preservative solutions in large-volume transfusions. This process also reduces the number of leukocytes, although not enough to label the washed product as leukocyte reduced. Unfortunately, when a unit of RBCs is washed, up to 20 % of the red cell mass can be lost. In addition, because washing usually occurs in an open system, the expiration date of washed RBCs decreases to 24 h. The reduction in shelf life of washed products is in part due to the increased possibility of external contamination or other technical errors, and also because the preservative solution has been removed, thereby affecting the viability of the red blood cells. Because the amount of potassium and adenine in aliquot transfusions of <20 mL/kg have not been shown to be detrimental, the benefits of washing the blood product in small-volume transfusions must be weighed against the potential risks. In many cases, washing is unnecessary and may inadvertently expose the patient to increased risk. If, however, the patient requires a large-volume transfusion, the transfusion is being administered through a central or intracardiac line, the blood product is greater than 7–14 days old, or the blood product has been irradiated >12 h before the transfusion, then washing could be considered in order to reduce the amount of extracellular potassium. In addition, it is strongly encouraged that any RBCs or platelets which were donated by the mother be washed in order to remove maternal plasma and reduce the risk of hemolytic disease of the fetus and newborn, neonatal alloimmune cytopenia, and transfusion-related acute lung injury (TRALI).

In neonates, the most common indication for washing platelets is to remove ABO-incompatible antibodies. For example, infants with neonatal alloimmune thrombocytopenia must receive transfusions from a donor who lacks the particular antigen, which is often the mother. However, the donors who lack the antigen will have the corresponding antibody to that antigen. Because of this, it is necessary to wash the donor platelets prior to transfusion in order to remove the offending antibody. Platelets should also be washed prior to being transfused in patients with severe allergic transfusion reactions, IgA deficiency, and anti-IgA antibodies. However, the washing of platelets can result in a loss of up to 50–75 % of platelets with an associated loss in activation and function. One study has suggested that washing platelets with ACD-A buffered saline helps retain platelet function when compared to washing platelets with saline [53, 61]. In addition, washing platelets with an automated method via cell processor may provide a loss of only 8 % of platelets with more consistent results. Washing platelets reduces the shelf life to 4 h. If, as often occurs in the neonatal population, the volume of washed platelets exceeds the transfusion need, the remaining unused washed platelets will be wasted.

Leukocyte Reduction

The risk of acquiring *Cytomegalovirus* (CMV) by transfusion is between 1 and 3%. Signs and symptoms of CMV infection in neonates are highly variable and can range from asymptomatic seroconversion to death. At high risk of transfusion-transmitted CMV infection are low-birth-weight infants (<1200 g) who are born to seronegative mothers. Because of this, it is recommended that low-birth-weight infants who are born to seronegative mothers receive CMV-reduced-risk blood. While deglycerolized, washed RBCs and blood from seronegative donors have been shown to reduce the risk of transfusion-transmitted CMV infection; the most common approach utilized today to reduce the risk of CMV transmission is leukocyte reduction.

Photochemical Pathogen Inactivation Treatment

A photochemical treatment process has been developed and approved for use in Europe since 2002 and has been shown to inactivate viruses, bacteria, protozoa, and leukocytes that may contaminate blood products. This technique uses amotosalen, a synthetic psoralen that penetrates cellular and nuclear membranes and covalently crosslinks to the nucleic acid–base pairs upon exposure to low-energy UVA light to block DNA and RNA replication [74]. This process renders leukocytes and pathogens unable to cause disease while maintaining the function of the plasma or platelet components, which do not require nucleic acid replication for therapeutic effect. Extensive preclinical safety programs demonstrated the absence of any relevant toxic effects in juvenile or adult animals. No amotosalen-related effects on clinical signs, body weight, hematology, clinical chemistry, urinalysis, gross pathology, or histopathology were noted despite administration of amotosalen concentrations as high as 48 times the standard exposure in adult patients [8]. An active hemovigilance program was implemented in order to prospectively examine adverse events associated with the transfusion of photochemically treated platelets [50, 51]. A prospective study over 7 years examined 4067 patients who received 19,175 platelet transfusions containing the photochemical treatment process and found a similar safety profile as conventional platelet components [50, 51] with a lower rate of acute transfusion reactions (9.5% of patients transfused with platelets in plasma plus photochemical additive solution vs. 15.5% of patients transfused with conventional platelets suspended in plasma). No cases of TRALI, TA-GVHD, transfusion-transmitted infection, or death were attributed to the transfusion of photochemical treatment-processed platelets [34].

Transmission of Infectious Disease

Despite improvements in donor screening and testing of blood components, every transfusion is associated with a risk of infectious disease transmission. For example, current testing is unreliable during the window period between donor infections and

seroconversion. In addition, the risk of transfusion-transmitted infectious diseases increases with exposure. Given their small size, neonates are often transfused with small-volume aliquots, which are often collected from the original unit of blood via an opened port system. When an open collection system is used, the primary unit of blood expires 24 h after the initial aliquot is produced. Any subsequent transfusion requirements occurring after 24 h require an aliquot to be produced from a new primary unit. Because of this, over the course of a hospital stay, a neonatal patient could be exposed to multiple donors, thereby putting them at increased risk for disease transmission or other transfusion-related complications. On average, premature infants weighing <1 kg are exposed to more than five donors during a single hospital stay if an opened port system is utilized for aliquot production. When a sterile collecting device is used, blood products are able to be stored for longer periods of time, and the neonate is able to receive multiple aliquots from the same primary unit. This decreases their exposure to multiple blood donors and the associated complications. In addition, this minimizes the wastage of blood components. However, sometimes there may be concern for continually exposing a patient to the same donor. For example, if the dedicated donor blood contains a previously undetected infectious disease or a harmful substance, this can introduce an increased dose of a life-threatening or toxic substance.

Several measures have been adopted in order to prevent or eliminate the potential infectious risk from the transfusion of blood products including solvent/detergents used in viral reduction of pooled plasma and methylene blue used in single-donor plasma. While these methods are very effective in eliminating lipid-enveloped viruses, they have little to no effect on nonenveloped pathogens. These methods are also not licensed for use in the United States. As previously mentioned, new photochemical pathogen inactivation treatments have been shown to be effective at inactivating bacteria, viruses, protozoa, and donor leukocyte contaminants within plasma and platelet units while preserving to therapeutic effectiveness of the blood component. While potential hazards of introducing amotosalen and UVA light (the components used in photochemical pathogen inactivation treatments) include genotoxicity, carcinogenicity, and phototoxicity, no specific target organ toxicity, phototoxicity, or reproductive toxicity has been observed [9, 10].

The use of recombinant human erythropoietin has been shown to reduce donor exposures in neonatal patients while minimizing the severity of their anemia. Erythropoietin stimulates the bone marrow to produce red blood cells with relatively small side effects, therefore reducing transfusion requirements. Studies evaluating the non-hematopoietic effects of erythropoiesis-stimulating agents (ESAs) have suggested that they may also be neuroprotective by promoting oligodendrogenesis, decreasing inflammation, decreasing oxidative injury, and decreasing apoptosis. One study found that the weekly administration of ESAs in preterm infants resulted in higher cognitive and object permanence scores with a lower incidence of cerebral palsy at 18–22 months corrected age [48]. Therefore, ESAs may not only be a beneficial therapy in preterm infants at risk for anemia but may also act as a neuroprotective agent which can improve neurodevelopmental outcomes.

Sepsis

Bacterial infections are more frequently associated with the transfusion of platelets than any other blood product. Despite extensive donor screening and testing, transfusion-transmitted infections continue to occur. Fever, chills, and hypotension are the most common symptoms of sepsis that occur during or shortly after the transfusion. These symptoms may overlap with other transfusion-associated reactions, including acute hemolytic transfusion reactions (AHTR) or febrile nonhemolytic transfusion reactions (FNHTRs). In cases of suspected posttransfusion sepsis, visual examination of the returned blood component should be conducted in order to detect changes in color along with any bubbles or frothiness. In addition, a Gram stain should be performed on the returned blood component along with cultures of both the returned blood component and a posttransfusion blood sample from the patient. The key to diagnosing transfusion-associated sepsis is to culture the same organism from both the patient and the remainder of the blood component. Any intravenous solutions that were administered concomitantly should be cultured as well. Supportive measures including broad-spectrum antibiotics may be started to help treat the patient.

Febrile Nonhemolytic Transfusion Reactions

A febrile nonhemolytic transfusion reaction (FNHTR) is defined as a greater than 1 C increase in temperature above 37 C which is associated with transfusion and for which no other cause of fever is identifiable. It is important to note that a preexisting fever may mask a FNHTR in febrile patients. FNHTRs are caused by leukocyte antibodies and/or accumulated cytokines within a cellular blood component. It is thought that the rise in temperature is a result of recipient HLA antibodies reacting with antigens present on transfused lymphocytes, granulocytes, or platelets that incite an antigen–antibody reaction and a release in cytokines.

Associated symptoms may include shaking, chills, increased respiratory rate, change in blood pressure, and feelings of anxiety. The onset of symptoms usually occurs while the blood product is being transfused but may occur up to 2 h after the transfusion has been completed. Although they may cause discomfort and changes in hemodynamics and respiration, FNHTRs are benign. However, it is important to distinguish symptoms of a FNHTR from those that may overlap with other more serious transfusion reactions such as hemolytic transfusion reactions (HTRs), sepsis, and TRALI. Other signs and symptoms along with laboratory data can be used to help determine which transfusion reaction occurred, with FNHTR being a diagnosis of exclusion.

When FNHTR is suspected, the transfusion should be stopped immediately and a transfusion reaction workup initiated. Antipyretics should be administered, and

once symptoms subside, the patient may once again be safely transfused. In order to help prevent FNHTR, prestorage leukocyte reduction can be used in order to reduce the number of residual leukocytes to less than 5 × 10^6 in red blood cells and apheresis platelets. Antipyretics and leukocyte reduction have been shown to decrease the frequency of FNHTR without compromising the ability to detect serious transfusion complications.

Acute Hemolytic Transfusion Reactions

While a relatively uncommon complication of blood product transfusions (estimated to occur in 1 per 76,000 transfusions) [73], acute hemolytic transfusion reactions (AHTRs) occur due to the transfusion of ABO-incompatible blood products. Symptoms are a result of preformed antigens within the recipient that interact with donor antigens present in the blood component being transfused. The most severe AHTRs occur in red cell transfusions that are ABO incompatible with the recipient's isohemagglutinins. Preformed IgM or IgG antibodies recognize the corresponding donor red cell antigens leading to acute intravascular destruction of the transfused cells resulting in hemolysis, hemoglobinemia, and hemoglobinuria. IgM and, when present in high enough concentrations, IgG antibodies can activate complement leading to the production of C3a, C3b, and C5a which are anaphylatoxins that coat the donor red blood cells, assemble a membrane attack complex, and lead to intravascular hemolysis. C3a and C5a also promote the release of histamine and serotonin from mast cells resulting in vasodilation and smooth muscle contraction predominantly within the respiratory and gastrointestinal tracts. C3a and C5a also stimulate monocytes, macrophages, endothelial cells, and platelets to release cytokines, leukotrienes, free radicals, nitric oxide, interleukin-8 (IL-8), tumor necrosis factor alpha (TNFα), IL-1β, IL-6, and monocyte chemoattractant protein-1 into the bloodstream. The antigen–antibody complex itself stimulates the release of bradykinin and norepinephrine, and phagocytosis of IgG-coated red blood cells leads to additional cytokine release [16].

ABO-incompatible plasma found in apheresis platelets has also been shown to cause hemolysis of the recipient's red blood cells. This scenario typically occurs when group O platelets from donors with high anti-A antibody titers are transfused to group A patients [28, 60]. Unlike AHTRs associated with red blood cell transfusions, AHTRs associated with platelet transfusions tend to be less clinically significant. In the presence of non-ABO antibodies, complement activation does not proceed to completion, leading to extravascular hemolysis with red blood cells that are coated in C3b or IgG being rapidly removed from circulation by phagocytosis. Figure 6.1 is a compatibility chart for red blood cells, whole blood, and plasma products (platelets, plasma, and cryoprecipitate).

Blood type	Compatible red blood cells	Compatible whole blood	Compatible platelets and plasma
O positive	O+, O–	O+, O–	All types
O negative	O–	O–	All types
B positive	B+, B–, O+, O–	B+, B–	Any B or AB
B negative	B–,O–	B–	Any B or AB
A positive	A+, A–, O+, O–	A+, A–	Any B or AB
A negative	A–, O–	A–,	Any B or AB
AB positive	All types	AB+, AB–	Any AB
AB negative	All types	AB–	Any AB

Fig. 6.1 Compatibility chart for red blood cells, whole blood, and plasma products (platelets, plasma, and cryoprecipitate)

The most common symptoms associated with AHTRs include fever, chills, rigors, abdominal pain, chest pain, back pain, and flank pain. In severe cases, one can see hypotension, dyspnea, and dark urine due to intravascular hemolysis which can progress to shock or even disseminated intravascular coagulation (DIC) in some cases. In neonates, a relatively large amount of incompatible blood may have been transfused before acute hemolysis is recognized. However, as soon as an AHTR is suspected, immediate cessation of the transfusion is critical. The unit of blood being transfused should be returned to the blood bank for investigation and root-cause analysis. If a large amount of incompatible blood has been transfused, red cell exchange transfusions may be considered using antigen-negative blood.

Saline should be administered to the patient in order to help treat hypotension and to ensure adequate renal blood flow. Urine output should be closely monitored, with a goal urine flow rate of greater than 1 mL/kg/h. Low-dose dopamine hydrochloric acid may also be administered in order to provide an inotropic cardiac effect while selectively improving renal blood flow, and furosemide can further enhance renal cortical blood flow and urine output. If urine output remains low after infusion of 1 L of saline, this may indicate that acute tubular necrosis of the kidneys has occurred, and the patient may be at risk for developing pulmonary edema. A nephrologist should be consulted as oliguric renal failure may lead to hyperkalemia with subsequent cardiac arrest. The presence of metabolic acidosis and uremia may indicate the need for dialysis.

Disseminated intravascular coagulation (DIC) is another potentially life-threatening complication of AHTR. The antigen–antibody interaction may active the intrinsic pathway of the clotting cascade, resulting in the activation of Factor XII. This can result in hypotension, vascular permeability, and vasodilation. Activation of complement, interleukin-1, and tumor necrosis factor-α can increase the expression of tissue factor, which results in activation of the extrinsic pathway of the clotting cascade that is associated with the development of DIC. DIC characteristically results in microvascular thrombi formation, ischemic damage to tissue and organs, consumption of platelets, fibrinogen and coagulation factors, and activation of fibrinolysis [57]. Patients may experience symptoms ranging from generalized oozing to uncontrollable bleeding. Patients in DIC may require transfusion support with platelets, fresh frozen plasma, cryoprecipitate, and activated protein C. The use of heparin in treating DIC is controversial.

The severity of symptoms correlates with the amount of incompatible blood transfused. Therefore, prompt recognition and immediate cessation of the transfusion can help to prevent progression of AHTRs. Many of the signs and symptoms of AHTRs may overlap with other acute transfusion reactions. Fever, chills, and hypotension may also be seen in sepsis and TRALI. In addition, a patient's underlying condition may present with symptoms similar to an AHTR. For example, patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency may experience hemolysis following a transfusion, and patients with autoimmune hemolytic anemia or sickle cell disease may experience fever and hypotension as a result of their condition. It is also important to differentiate between immune and nonimmune causes of hemolysis. For example, transfusion-associated hemolysis can occur as a result of the improper shipment conditions, inappropriate storage temperature, or incomplete deglycerolization of frozen red blood cells. As often occurs in the neonatal population, mechanical hemolysis can occur by using inappropriately small needle core sizes, employing rapid pressure infusers, the improper use of blood warmers, or the simultaneous transfusion of red blood cells with hypotonic solutions. Although these symptoms may not represent a true AHTR, it is always best to immediately stop a transfusion whenever a transfusion reaction is suspected as an AHTR can occur rapidly with the transfusion of as little as 10 mL of ABO-incompatible blood.

Prevention is crucial in AHTRs due to the fact that the most common cause is transfusing blood components to the wrong patient due to clerical and human errors. Identifying the wrong patient, patient sample, and blood unit have been cited as the most common causes of mistransfusion. Institutional policies and procedures should be in place to identify, correct, and minimize such errors. In addition, concentrating or volume reduction helps to minimize transfusion-incompatible plasma.

Transfusion-Associated Allergic Reactions

Transfusion-associated allergic reactions are common, occurring in approximately 1–3 % of all transfusions and accounting for 13–33 % of all transfusion reactions [17, 72]. Allergic reactions occur most commonly with the transfusion of plasma or platelets. Transfusion-associated allergic reactions can range from more common mild urticaria to less common life-threatening anaphylaxis. Urticaria, or hives, is a pruritic red, raised, and swollen wheals on the skin which can occur anywhere on the body and can vary in size. While urticaria can last hours to several days after the transfusion has been stopped, they tend to respond quickly to antihistamines. In more severe cases, urticaria may be associated with angioedema. Angioedema is an accumulation of fluid beneath the skin that commonly occurs around the eyes and lips. Angioedema occurring around the throat, tongue, or lungs can cause respiratory distress. A more serious complication is an anaphylactoid transfusion reaction, which can include urticaria and angioedema with additional cardiovascular symptoms including hypotension, tachycardia, arrhythmia, shock, loss of consciousness,

or cardiac arrest. When the respiratory system is often involved, wheezing, stridor, and dyspnea can be seen. Approximately 30 % of these patients will also experience gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal cramps.

Transfusion-associated allergic reactions that are more severe and progress beyond urticaria may be seen in IgA-deficient patients and are caused by the reaction of anti-IgA antibodies in the recipient to IgA in the donated blood component. While IgA deficiency is estimated to occur in up to 1 in 700 people of European ancestry, only a small percentage of people go on to create antibodies to IgA. This may reflect the difference between patients with an absolute IgA deficiency and those with decreased but detectable amounts of IgA but form subclass-specific antibodies (i.e., anti-IgA1, anti-IgA2) depending on which component they are lacking. While it is important to recognize an IgA deficiency in patients receiving a blood transfusion, it is important to note that that the majority of anaphylactoid reactions are caused by allergens other than IgA [59]. Other known triggers of anaphylactoid reactions include antibodies against haptoglobin [63], penicillin, ethylene oxide, and C4 complement [37].

Transfusion-associated allergic reactions most commonly occur in response to allergens within the blood component being transfused and less commonly by antibodies from an allergic donor. Preformed IgE antibodies in the recipient interact with allergens present within the blood component, usually a plasma protein. Mast cells are activated by the binding of IgE on their surface to antigens in a type I hypersensitivity reaction [25]. This reaction causes degranulation of the mast cells including release of histamine, chemotactic factors, proteases, and proteoglycans. Secondary mediators such as cytokines, arachidonic acid metabolites, leukotrienes, prostaglandin D2, and platelet-activating factor are also released in response to mast cell activation [14].

Symptoms generally occur within seconds to minutes of starting the transfusion. On rare occasions, symptoms may take several hours to develop. It is important to distinguish symptoms associated with a transfusion-associated allergic reaction from a vasovagal response that can manifest with hypotension diaphoresis, nausea, vomiting, weakness, bradycardia, and occasionally loss of consciousness. In addition, patients who are taking angiotensin-converting enzyme (ACE) inhibitors may develop an isolated hypotension. This is thought to occur due to the dual actions on bradykinin caused both by the inhibition of catabolism by the ACE inhibitor and the activation of prekallikrein activity in the plasma protein fraction.

Premedication with antihistamines, approximately 30 min before transfusion, may help to prevent allergic reactions. If antihistamines are not sufficient, premedicating with prednisone or parenteral steroids may be useful. If premedication does not work, washing red cells or platelets prior to transfusion may be of some benefit. In patients who develop urticaria, the transfusion should be paused in order to administer diphenhydramine. A mild allergic reaction is the only transfusion reaction scenario in which administration of the remainder of the blood component may be resumed after treatment, and no laboratory investigation is required. Severe urticarial reactions may require treatment with methylprednisolone. If, however,

symptoms do not subside or are accompanied by more severe symptoms such as hypotension or dyspnea, the transfusion must then be stopped. The patient's hypotension can be treated by placing them in the Trendelenburg position and infusing them with crystalloids. In cases of suspected anaphylaxis, prompt efforts should be made to maintain the airway and provide oxygenation. Epinephrine may be used in this case, with doses being repeated every 5–15 min up to three times unless palpitations, anxiousness, or tremors develop. If bronchospasm does not respond to epinephrine, the addition of a beta II agonist or aminophylline may be required. Patients who are unresponsive due to an ACE inhibitor or beta-adrenergic blocker may respond to intravenous glucagon [4]. In addition, patients with anaphylaxis should be tested for antibodies against immunoglobulin A (anti-IgA), and quantitative IgA levels should be assessed. In patients who are found to have an IgA deficiency, they should subsequently be transfused with components from IgA-deficient donors or after cellular components have been washed.

Hypothermia

Neonates are particularly susceptible to the life-threatening side effects of hypothermia, due to their decreased body fat, an immature epidermal barrier, and higher surface area to weight ratio [26, 38]. Complications of hypothermia can include alterations in pulmonary vasomotor tone, acid–base imbalances, an increased metabolic rate, hypoglycemia, and apnea leading to cardiac arrest. This is especially true during massive transfusions such as ECMO, exchange transfusions, cardiac surgery, and trauma. Even blood products at room temperature have been shown to decrease an infant's core body temperature by 0.7–2.5 C. Therefore, in-line blood warmers are required for all neonatal RBC exchange transfusions. It is important to remember, however, that heating blood products to elevated temperatures can cause red cell damage with associated increases in lactate dehydrogenase, extracellular potassium, and plasma hemoglobin due to hemolysis. Because of this, only FDA-approved devices that can accurately measure and maintain the temperate of the blood product should be used.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is estimated to occur in 1 of every 1300–5000 transfusions and is the leading cause of transfusion-related mortality. All plasma-containing blood components, including whole blood, red blood cells, platelets, cryoprecipitate, and fresh frozen plasma, have been implicated in TRALI reactions with as little as 15 mL transfusion volumes. The symptoms of TRALI typically include fever, chills, dyspnea, cyanosis, hypotension, and the new onset of bilateral pulmonary edema [54]. Symptoms generally occur within hours of

transfusion and can be fatal. The lung injury that occurs with TRALI is defined as hypoxemia with a PaO2/FiO2 ratio of 300 mmHg, radiographic evidence of bilateral pulmonary edema, no preexisting acute lung injury present before the transfusion occurred, onset of symptoms within 6 h of transfusion, and no temporal relationship to alternative risk factors for acute lung injury. TRALI can often be confused with acute respiratory distress syndrome (ARDS). However, where ARDS is often irreversible, TRALI is often transient. The majority of patients will show improvement after 48–96 h despite the need for mechanical ventilation and oxygen supplementation. Most commonly, TRALI is confused with transfusion-associated circulatory overload (TACO), where pulmonary edema is seen but is a result of cardiogenic factors. Unfortunately, up to 20 % of patients with TRALI will experience either a prolonged clinical course or even death.

While the exact mechanism is unknown, TRALI has been associated with antibodies to leukocyte antigens and the transfusion of biologic response modifiers (BRMs) [55, 64] that initiate a sequence of events resulting in cellular activation, basement membrane damage, and leakage of protein-rich fluid into alveolar spaces leading to pulmonary edema. A two-event model has been proposed as the mechanism of TRALI [65]. The first event occurs when biologically active compounds activate pulmonary vascular endothelial cells and prime neutrophils resulting in the sequestration of neutrophils within the pulmonary vasculature. In addition to transfusion, this first event can occur in sepsis and after surgery, therefore predisposing the patient to developing TRALI. The second event occurs when BRMs or antibodies are transfused into the recipient's circulation and activate the primed neutrophils within the pulmonary microvasculature. This results in pulmonary endothelial damage, capillary leakage, and pulmonary edema. In the majority of cases, the source of the antibodies is the donor rather than the recipient. Specifically, antibodies to HLA class I antigens, HLA class II antigens, and human neutrophil antigens (HNAs) have been implicated in TRALI which can form after exposure to foreign antigens during pregnancy, prior transfusions, or transplantation.

In patients with TRALI, treatment consists of respiratory and circulatory support including oxygen supplementation, possible mechanical ventilation, and pressors to support blood pressure. Unlike TACO, diuretics are unnecessary in TRALI because the associated pulmonary edema is not a result of circulatory overload. In addition, corticosteroids have been shown to improve clinical outcomes [68].

Methods to help prevent TRALI reactions include the use of male-donor or nulliparous female-donor plasma exclusively for transfusions while diverting multiparous female-donor plasma for fractionation as the prevalence of HLA antibodies increases with each subsequent pregnancy and testing female-plasma donors for the presence of HLA antibodies. These measures do not address this issue of antibodies to HNAs, however. Directed donations from blood relatives, particularly the mother, should also be discouraged as TRALI has been reported in this donor population [5, 7, 18, 75]. In cases of suspected TRALI, a sample of the donor's serum should be tested for the presence of HLA and HNA antibodies. Also, HLA typing the patient will help confirm TRALI cases, if in fact the donor has the corresponding HLA antibody to the patient's HLA antigens.

Transfusion-Associated Circulatory Overload

Transfusion-associated circulatory overload (TACO) has been estimated to occur in approximately 1 in 700 red blood cell recipients, with up to 20 % of these patients having received only a single unit. TACO also accounts for 8 % of transfusion-associated fatalities. TACO generally occurs within 1–2 h of transfusion and is associated with jugular venous distension, gallop, elevated central venous pressure, dyspnea, orthopnea, new ST segment or T wave changes on electrocardiogram, elevated serum troponins, and increased blood pressure with a widening of the pulse pressure. Imaging often shows a widened cardiothoracic ratio. While large transfusion volumes and high flow rates are frequently implicated in TACO, volume overload has been seen even with modest transfusion volumes.

TACO is often confused for TRALI due to the fact that they both present with pulmonary edema. It is, of course, possible for a patient to develop both TACO and TRALI after a transfusion. However, TACO can be differentiated based on the presence of hypertension and rapid improvement with either diuretics or inotropic agents. In addition, laboratory studies showing a pre-transfusion to post-transfusion brain natriuretic peptide ratio of 1.5 with a posttransfusion level of greater than 100 pg/mL have an 80 % sensitivity and specificity level for TACO.

As soon as TACO is suspected, the transfusion should be stopped, and the patient should be placed in the seated position. Supplemental oxygen should be administered as needed, and the patient should be placed on diuretics in order to reduce the intravascular volume. If symptoms persist in confirmed TACO, additional diuretics of therapeutic phlebotomy may be utilized. While the majority of neonates do not benefit from volume reduction due to platelet loss during centrifugation, concentrating or volume-reducing platelets helps to minimize the risk of volume overload. Patients at risk for volume overload include infants with cardiac diseases and oliguric renal failure. However, concentration performed using an open system procedure limits the shelf life to 4 h. Also, concentration can activate platelets during centrifugation, and the pH of concentrated platelets stored in a syringe rapidly declines and should therefore be transfused as soon as possible.

Transfusion-Associated Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a common yet devastating condition in neonates which carries significant morbidity and mortality and very few treatment options. NEC is estimated to effect between 6 and 10 % of very-low-birth-weight (<1500 g) infants and leads to an increased length of hospital stay [45]. The etiology of NEC is multifactorial with risk factors including prematurity, small for gestational age, hypoxic-ischemic events, early and rapid advancements of enteral feeds, formula feeds, bacterial overgrowth, and even exposure to platelet-activating factor acetylhydrolase present in platelet suspensions [20]. The prevalence of NEC is estimated to be 5 %.

While some studies did not find recent red blood cell transfusion to be a risk factor for developing NEC [32, 62], others have suggested the potential role of red blood cell transfusions in causing what is known as transfusion-associated NEC (TANEC) [21]. Although the exact mechanism is unclear, some have proposed theories include an underlying medical condition; extreme anemia with impaired blood flow to the gastrointestinal system; altered blood flow during feeding; exposure to biologically active mediators such as free hemoglobin, increased cytokines, and broken red cell fragments within the transfused blood which triggers an immunologic response within the intestinal mucosa; altered angiogenesis within the intestine; and reperfusion associated with transfusion [2, 52]. Studies have shown that infants who develop TANEC tend to be younger, lower birth weight, have higher illness severity scores, have a patent ductus arteriosus with intestinal "steal" [22], be receiving ventilator support [42], and have exposure to transfusion within 48 h when compared to infants with NEC not associated with transfusion [70]. While the risk factors may differ, some studies have shown that there are little differences in morbidity or mortality between infants with TANEC and those with NEC not associated with transfusion [70]. In contrast, other studies suggest that TANEC is associated with an increased need for surgical intervention [52], prolonged hospitalization [30], and increased mortality [6, 41] than those with NEC not associated with transfusion. It is important to note that the factors that place neonates at increased risk for TANEC (i.e., prematurity, low birth weight, etc.) are all independently associated with adverse outcomes and may be confounding.

Some proposed suggestions in reducing the occurrence of TANEC include withholding feeds during the transfusion in order to counteract postprandial alterations in blood flow. In addition, bacteria from the gastrointestinal tract release sialidases which are enzymes that cleave sialic acid residues creating neonatigens. Naturally occurring complement-dependent antibodies can cause lysis of the neoantigen-labeled red blood cells. T activation in infants is common (approximately 13 % of infants in NICU), while hemolysis is less common. Therefore, it is controversial as to whether it is necessary to provide washed red cells to all neonates with necrotizing enterocolitis or only those with evidence of hemolysis.

T Activation and Positive Lectins

Several case reports have identified hemolysis after the transfusion of blood products in infants, generally occurring in association with NEC. It has been suggested that this hemolysis occurs as a result of T activation, which refers to alterations in RBC membrane glycoprotein structure generally by microbial enzymatic action. The T antigen, an exposed RBC cryptantigen, binds to the IgM anti-T [56] which

leads to the removal of N-acetylneuraminic acid (also known as sialic acid) from the RBC by neuraminidase [27]. Anti-T is present in the plasma of most adults but is generally absent in early infancy [43]. It is believed that many bacteria and viruses contain a substance that is identical to the T antigen [67]. Because of this, antibodies are formed as a result of antigenic stimulation by intestinal flora in a manner similar to the development of ABO antibodies. Neuraminidase is produced by many microbiologic agents including bacteria, viruses, and protozoa. In addition, neuraminidase-producing organisms are known to produce hemolytic toxins as well [43]. T antigen activation has also been reported in association with anaerobic, especially clostridial, sepsis, and other severe infections. Animal studies have suggested that hemolysis of T-activated RBCs is due to the enhanced clearance of RBCs containing decreased N-acetylneuraminic acid rather than immunologic-mediated mechanisms [15, 19].

Variants of T activation, including Th and Tx activation, occur less commonly and are thought to be incomplete forms of T activation [27, 56]. Tk and Tn activation, however, are different and distinct from T activation. Tk activation occurs due to exposure to N-acetylglucosamine by the bacterial enzyme β-galactosidase which cleaves the terminal galactose residue from the RBC. In contrast, Tn is not induced by microbial action but rather results from a clonal RBC mutation that is persistent rather than transient [3]. In order to distinguish between the various types of polyagglutinable RBCs, testing can be performed with a panel of lectins. Table 6.1 identifies the major lectins and their reactions with different erythrocyte cryptoantigens involved in polyagglutination.

Because of the severe hemolysis that can occur following the transfusion of blood products in infants with T-activated RBCs, many clinicians avoid or delay the transfusion of plasma-containing blood components to neonates who are at high risk of T activations, particularly those with NEC [33, 47]. Therefore, the routine screening of infant RBCs for T activation, ensuring the availability of low-titer anti-T blood com-

Table 6.1 Major lectins and reactivity with erythrocyte crypoantigens

	Erythrocyte cryptoantigens				
Lectins	T	Tk	Tn	Cad	Tx
Arachis hypogaea	+	+	–	–	+
Dolichos biflorus	–	–	+	+	–
Glycine soja	+	–	+	+	–
Salvia sclarea	–	–	+	–	–
Salvia horminum	–	–	+w	+	–
Bandeiraea simplicifolia	–	+	–	–	–
Salvia farinacea	–	–	+w	+	–
Leonurus cardiaca	–	–	–	+	–
Vicia cretica	+	–	–	–	–
Medicago disciformis	+	–	–	–	–

ponents, and washing plasma-containing blood components in lectin-positive patients has been considered. However, one study found that although infants with T and T variant-activated RBCs had a higher rate of hemolysis and mortality, the use of low-titer anti-T blood products did not reduce the rate of mortality [49]. In addition, the washing of blood products could lead to a delay in appropriate treatment, thereby putting the patient at risk. Currently, there is no expert consensus, and additional studies are warranted to implement changes in clinical practice.

Transfusion-Associated Graft-Versus-Host Disease

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare complication of blood transfusion. TA-GVHD occurs when donor lymphocytes from transfused blood mount an immune response against the recipient. A key mechanism in TA-GVHD is the inability of the host's immune system to recognize or fight off the donor cells transferred via transfusion. TA-GVHD most frequently occurs in immunocompromised patients. Given their immature immune system, neonatal patients are at particular risk for developing TA-GVHD. However, TA-GVHD can also occur in immunocompetent patients with no underlying diagnosis known to cause immune compromise. This may occur with shared HLA antigens when the donor lymphocytes are able to evade the host immune response. Rarely, TA-GVHD has been associated with extreme prematurity, neonatal alloimmune thrombocytopenia, and extracorporeal membrane oxygenation (ECMO).

One study found that the majority of cases of TA-GVHD occurred after transfusion of cellular components less than 10 days old that were not leukoreduced and not irradiated [36]. The number of lymphocytes present within a donor sample may also play a role in TA-GVHD, with a significant reduction in the risk of developing TA-GVHD occurring after leukoreduction. Neonatal patients with TA-GVHD typically present with fever, rash, gastrointestinal symptoms, liver injury, and hypoproliferative pancytopenia. The diagnosis of TA-GVHD can be made based on a combination of characteristic clinical findings, tissue biopsy, and leukocyte chimerism (the presence of donor lymphocytes in recipient tissue) occurring between 2 days to 6 weeks after receiving a transfusion. It is recommended that any patient exhibiting signs and symptoms of TA-GVHD receives a thorough evaluation and workup including investigation of HLA antigens.

Unfortunately, TA-GVHD is associated with >90% mortality and has limited treatment options. However, TA-GVHD can be prevented with pre-transfusion irradiation of blood products. As previously mentioned, new photochemical pathogen inactivation treatments have been shown to be effective at inactivating bacteria, viruses, protozoa, and donor leukocyte contaminants within plasma and platelet units while preserving to therapeutic effectiveness of the blood component and may also help to prevent TA-GVHD.

References

1. Andreu G, Morel P, Forestier F, et al. Hemovigilance network in France: organization and analysis of immediate transfusion incidence reports from 1994 to 1998. Transfusion. 2002;42:1356–64.
2. Blau J, Calo JM, Dozor D, et al. Transfusion-related acute gut injury: necrotizing enterocolitis in very low birth weight neonates after packed red blood cell transfusion. J Pediatr. 2011;158(3):403–9.
3. Boralessa H, Modi N, Cockburn H, et al. RBC T activation and hemolysis in a neonatal intensive care population: implications for transfusion practice. Transfusion. 2002;42:1428–34.
4. Brown SGA, Mullins RJ, Gold MS. Anaphylaxis: diagnosis and management. Med J Aust. 2006;185:283–9.
5. Campbell Jr DA, Swartz RD, Waskerwitz JA, et al. Leukoagglutiniation with interstitial pulmonary edema. A complication of donor-specific transfusion. Transplantation. 1982;34:300–1.
6. Christensen RD, Lambert DK, Henry E, et al. Is "transfusion-associated necrotizing enterocolitis" an authentic pathogenic entity? Transfusion. 2010;31(3):183–7.
7. Church GD, Price C, Sanchez R, et al. Transfusion-related acute lung injury in the paediatric patient: two case reports and a review of the literature. Transfus Med. 2006;16:343–8.
8. Ciaravino V, Hanover J, Lin L, Sullivan T, Corash L. Assessment of safety in neonates for transfusion of platelets and plasma prepared with amotosalen photochemical pathogen inactivation treatment by a 1-month intravenous toxicity study in neonatal rats. Transfusion. 2009;49:985–94.
9. Ciaravino V, McCullough T, Cimino G, Sullivan T, et al. Preclinical safety profile of plasma prepared using the INTERCEPT blood system. Vox Sang. 2003;85:171–82.
10. Ciaravino V, McCullough T, Cimino G. The role of toxicology assessment in transfusion medicine. Transfusion. 2003;43:1481–92.
11. Collard KJ. Is there a causal relationship between the receipt of blood transfusions and and the development of chronic lung disease of prematurity? Med Hypotheses. 2006;66:355–64.
12. Cooke RWI, Clark D, Hickey-Dwyer M, et al. The apparent role of blood transfusions in the development of retinopathy of prematurity. Eur J Pediatr. 1993;152:833–6.
13. Cooke RW, Drury JA, Yoxall CW, et al. Blood transfusion and chronic lung disease in preterm infants. Eur J Pediatr. 1997;156:47–50.
14. Cotran RS, editor. Robbins pathologic basis of disease. 9th ed. Philipdelphia: WB Saunders; 2014. p. 178.
15. Crookston KP, Reiner AP, Cooper LJN, et al. RBC T-activation and hemolysis: implications for pediatric transfusion management. Transfusion. 2000;40:801–12.
16. Davenport RD. Hemolytic transfusion reactions. In: Popovsky MA, editor. Transfusion reactions. 3rd ed. Bethesda: AABB Press; 2007. p. 1–55.
17. Domen RE, Hoeltge GA. Allergic transfusion reactions: an evaluation of 273 consecutive reactions. Arch Pathol Lab Med. 2003;127:316–20.
18. Dunbar N, Cooke M, Diab M, Toy P. Transfusion-related acute lung injury after transfusion of maternal blood: a case–control study. Spine. 2010;35(23):1322–7.
19. Durocher JR, Payne RC, Conrad ME. Role of sialic acid in erythrocyte survival. Blood. 1975;45:11–20.
20. Furukawa M, Lee EL, Johnston JM. Platelet-activating factor-induced ischemic bowel necrosis: the effect of platelet-activating factor acetylhydrolase. Pediatr Res. 1993;34:237–41.
21. Garg PM, Ravisankar S, Bian H, Macgilvray S, Shekhawat P. Relationship between packed red blood cell transfusion and severe form of necrotizing enterocolitis: a case control study. Indian Pediatr. 2015;52:1041–5.
22. Gupta S, Wylie J, and Plews D. Hemodynamic effects of packed red blood cell transfusion volume in premature infants: results of a randomized controlled trial. E-PAS. 2007;5899.6

23. Hall TL, Barnes A, Miller JR, et al. Neonatal mortality following transfusion of red cells with high plasma potassium levels. Transfusion. 1993;33:606–9.
24. Hebert PC, Wells G, Tweeddale M, et al. Does transfusion practice affect mortality in critically ill patients? Transfusion requirements in critical care (TRICC) investigators and the Canadian critical care trials group. Am J Respir Crit Care Med. 1997;155:1618–23.
25. Hennino A, Berard F, Guillot I, et al. Pathophysiology of urticaria. Clin Rev Allergy Immunol. 2006;30:3–11.
26. Horan M, Edwards AD, Firmin RK, et al. The effect of temperature on the QTc interval in the newborn infant receiving extracorporeal membrane oxygenation (ECMO). Early Hum Dev. 2007;83:217–23.
27. Horn KD. The classification, recognition and significance of polyagglutination in transfusion medicine. Blood Rev. 1999;13:36–44.
28. Josephson CD, Mullis NC, Van Demark C, et al. Significant numbers of apheresis-derived group O platelet units have "high-titer" anti-A/A, B: implications for transfusion policy. Transfusion. 2004;44:805–8.
29. Josephson CD, Su LL, et al. Platelet transfusion practice among neonatologists in the United States and Canada: results of a survey. Pediatrics. 2009;123:278–85.
30. Josephson CD, Wesolowski A, Bao G, et al. Do red cell transfusions increase the risk of necrotizing enterocolitis in premature infants? J Pediatr. 2010;157(6):972–8, e1–e3.
31. Kahn DJ, Richardson DK, Billett HH. Associated of thrombocytopenia and delivery method with intraventricular hemorrhage among very-low-birth-weight infants. Am K Obstet Gynecol. 2002;186(1):109–16.
32. Kirpalani H, Zupancic JA. Do transfusions cause necrotizing enterocolitis? The complementary role of randomized trials and observational studies. Semin Perinatol. 2012;36:269–76.
33. Klein RL, Novak RW, Novak PE. T-cryptantigen exposure in neonatal necrotizing enterocolitis. J Pediatr Surg. 1986;21:1155–8.
34. Knutson F, Osselaer J, Pierelli L, et al. A prospective, active haemovigilance study with combined cohort analysis of 19,175 transfusions of platelet components prepared with amotosalen-UVA photochemical treatment. Vox Sang. 2015;12287:1–10.
35. Kohn DJ, Richardson DK, Billett HH. Inter-NICU variation in rates and management of thrombocytopenia among very low birth-weight infants. J Perinatol. 2003;23(4):312–6.
36. Kopolovic I, Ostro J, Tsubota H, et al. A systematic review of transfusion-associated graft-versus-host disease. Blood. 2015;126:406–14.
37. Lambin P, Pennec L, Hauptmann G, et al. Adverse transfusion reactions associated with a precipitating anti-C4 antibody of anti-Rogers specificity. Vox Sang. 1984;47:242–9.
38. Laptook AR, Salhab W, Bhaskar B. Admission temperature of low birth weight infants: predictors and associated morbidities. Pediatrics. 2007;119:e643–9.
39. Levy G, Strauss R, Hume H, et al. National survey of neonatal transfusion practices: I. Red blood cell therapy. Pediatrics. 1993;91:523–9.
40. Luban N. Neonatal red blood cell transfusions. Cur Opin Hematol. 2002;9:533–6.
41. Mally P, Golombek SG, Mishra R, et al. Association of necrotizing enterocolitis with elective packed red blood cell transfusions in stable, growing, premature neonates. Am J Perinatol. 2006;23(8):451–8.
42. Mohamed A, Shah PS. Transfusion associated necrotizing enterocolitis: a meta-analysis of observational data. Pediatrics. 2012;129:529–40.
43. Mollison PL, Engelfriet CP, Contreras M, editors. Blood transfusion in clinical medicine. 10th ed. Oxford: Blackwell Scientific; 1997. p. 233–6.
44. Neonatal Transfusion Guidance. American Association of Blood Bankers. Revised 2012.
45. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med. 2011;364:255–64.
46. New HV. Pediatric transfusion. Vox Sang. 2006;90:1–9.
47. Novak RW, Abbott AE, Klein RL. T-cryptantigen determination affects mortality in necrotizing enterocolitis. Surg Gynecol Obstet. 1993;176:368–70.
48. Ohls RK, Kamath-Rayne BD, et al. Cognitive outcomes of preterm infants randomized to darbepoetin, erythropoietin, or placebo. Pediatrics. 2014;133:1023–30.

49. Osborn DA, Lui K, Pussell P, et al. T and Tk antigen activation in necrotizing enterocolitis: manifestations, severity of illness, and effectiveness of testing. Arch Dis Child Fetal Neonatal Ed. 1999;80:F192–7.
50. Osselaer JC, Cazenave JP, Lambermont M, et al. An active hemovigilance program characterizing the safety profile of 7437 platelet transfusions prepared with amotosalen photochemical treatment. Vox Sang. 2008;94(4):315–23.
51. Osselaer JC, Messe N, Hervig T, et al. A prospective observational cohort safety study of 5106 platelet transfusions with components prepared with photochemical pathogen inactivation treatment. Transfusion. 2008;48(6):1061–71.
52. Paul DA, Mackley A, Novitsky A, et al. Increased odds of necrotizing enterocolitis after transfusions or red blood cells in premature infants. Pediatrics. 2011;127(4):635–41.
53. Pineda AA, Zylstra VW, Clare DE, et al. Viability and functional integrity of washed platelets. Transfusion. 1989;29:524–7.
54. Popovsky MA, Haley NR. Further characterization of transfusion-related acute lung injury: demographics, clinical and laboratory features and morbidity. Immunohematology. 2000;16:157–9.
55. Popovsky MA, Moore SB. Diagnostic and pathogenic considerations in transfusion-related acute lung injury. Transfusion. 1985;25:573–7.
56. Ramasethu J, Luban N. T-activation. Br J Haematol. 2001;112:259–63.
57. Roback JD, Grossman BJ, Harris T, Hillyer CD, editors. AABB Technical manual. 17th ed. Bethesda: AABB; 2011.
58. Sacks LM, Schaffer D, Anday EK, et al. Retrolental fibroplasia and blood transfusion in very low-birthweight infants. Pediatrics. 1981;68:770–4.
59. Sandler SG, Mallory D, Malamut D, et al. IgA anaphylactic transfusion reactions. Transfus Med Rev. 1995;9:1–8.
60. Sapatnekar S, Sharma G, Downes KA, et al. AHTR in a pediatric patient following transfusion of apheresis platelets. J Clin Apher. 2005;20:225–9.
61. Schoenfeld H, Muhm M, Doepfmer U, et al. Platelet activity in washed platelet concentrations. Anesth Analg. 2004;99:17–20.
62. Sharma R, Kraemer DF, Torrazza RM, Mai V, et al. Packed red blood cell transfusion is not associated with increased risk of necrotizing enterocolitis in premature infants. J Perinatol. 2014;34:858–62.
63. Shimada E, Odagiri M, Chaiwong K, et al. Detection of Hp(del) among Thais, a deleted allele of the haptoglobin gene that causes congenital haptoglobin deficiency. Transfusion. 2007;47:2315–21.
64. Silliman CC, Ambruso DR, Boshkov LK. Transfusion-related acute lung injury. Blood. 2005;105:2266–73.
65. Silliman CC, Boshkov LK, Mehdizadehkashi Z, et al. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. Blood. 2003;101:452–62.
66. Slonim AD, Joseph JG, Turenne WM, et al. Blood transfusions in children: a multi-institutional analysis of practices and complications. Transfusion. 2008;48:73–80.
67. Springer GF, Tegtmeyer H. Origin of anti-Thomsen-Friedenreich (T) and Tn agglutinins in man and in White Leghorn chicks. Br J Haematol. 1981;47:453–60.
68. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006;354:1671–84.
69. Strauss RG. Transfusion therapy in neonates. Am J Dis Child. 1991;145:904–11.
70. Stritzke AI, Smyth J, Synnes A, et al. Transfusion-associated necrotizing enterocolitis in neonates. Arch Dis Child Fetal Neonatal Ed. 2012. doi:10.1136/fetalneonatal-2011-301282.
71. Sullivan MT, McCullough J, Schreiber GB, et al. Blood collection and transfusion in the United States in 1997. Transfusion. 2002;42:1253–60.
72. Vamvakas EC. Allergic and anaphylactic reactions. In: Popovsky MA, editor. Transfusion reactions. 3rd ed. Bethesda: AABB Press; 2007. p. 105–56.
73. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. Blood. 2009;113:3406–17.

74. Wollowitz S. Fundamentals of the psoralen-based Helinx technology for inactivation of infectious pathogens and leukocytes in platelets and plasma. Semin Hematol. 2001;38 Suppl 11:4–11.
75. Yang X, Ahmed S, Chandrasekaran V. Transfusion-related acute lung injury resulting from designated blood transfusion between mother and child: a report of two cases. Am J Clin Pathol. 2004;121:590–2.