Consultation with the Specialist: Red Blood Cell Transfusions

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CONSULTATION WITH THE SPECIALIST

Red Blood Cell Transfusions

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Objectives

After completing this article, readers should be able to:

1. Discuss the complications of a red blood cell transfusion for a child who has autoimmune hemolytic anemia.
2. Delineate the risk of transmitting infectious diseases during blood transfusions.
3. Describe the hemolytic, febrile, and urticarial reactions that may be associated with red blood cell transfusions.
4. Explain the role of red blood cell transfusions in the management of anemia.

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Introduction

Red blood cells (RBCs) carry hemoglobin-bound oxygen from the lungs to capillaries, where they release some of their oxygen for diffusion into surrounding tissues that have lower oxygen tension. The ability to increase cardiac output and to shift the oxygen dissociation curve of hemoglobin allows the body, in most instances, to compensate for loss of oxygen-carrying capacity, increased tissue need, or hypoxia. In some circumstances, however, the compensatory mechanisms are insufficient, and RBC transfusion may be beneficial.

The first reported blood transfusion took place between two dogs in 1666 at Oxford University in an experiment by Richard Lower. By the following year, French physician Jean Denys was transfusing blood from lambs and calves into patients afflicted with mental illness, hoping to balance their "humors" with those of the docile, domesticated animals. Many transfusion recipients had acute hemolytic reactions, and some died (Denys was tried for murder in one instance), essentially putting a halt to the use of blood transfusions for more than a century.

In 1818, British obstetrician James Blundell performed the first known human-to-human transfusions, reporting success in some women who had severe postpartum hemorrhage. By mid-century, the first transfusions in the United States were performed, but they remained rare until the 20th century.

The early 1900s brought major advances in transfusion medicine, starting with Karl Landesteiner's discovery and description of the ABO blood grouping system (he called it ABC) and, subsequently, the Rh antigen. Terminal sugars attached to the end of the universal H antigens on RBCs can change them to A or B antigens. Genes for the A and B transferases are codominant, so individuals can be of blood type A, B, AB, or O (all have the H antigen), with O and A being most common. The Rh system consists of more than one antigen, but the most important is the Rh (D) antigen, which is present in most people. Its presence ("positive") or absence ("negative") conventionally is annotated after the ABO type. Individuals develop antibodies to the nonself antigens (alloantibodies). As a result, type

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O-negative blood should be tolerated by any recipient and can be used in an emergency for recipients of unknown blood type, whereas AB-positive individuals are universal recipients because they should not have alloantibodies to major RBC antigens. Development of antibodies to Rh (D) requires prior exposure to the Rh antigen. This sensitization can occur in Rh-negative women during delivery of Rh-positive babies (from placental hemorrhage and fetal-maternal transfusion) or from therapeutic transfusion. Coombs' development of RBC antibody testing allowed for the discovery of a variety of minor RBC antigens that are not targets of alloantibodies in the normal state.

The development of safe anticoagulant and preservative solutions allowed donated blood to be stored for later transfusion and led to the creation of blood banks. Blood transfusions played an important role in the treatment of World War II battlefield injuries, and civilian medical use of blood transfusions increased until the mid-1980s, when the first reports of transfusion-associated human immunodeficiency virus (HIV) infection and hepatitis led to increased public concerns about the safety of blood transfusions and even the donation process. The resulting decrease in blood donations and transfusions was small, however; currently, more than 10 million units of blood are donated and transfused each year in the United States.

Indications for Blood Transfusion

The role of blood transfusion in the medical and surgical care of adults has been studied fairly well, and there is evidence that liberal blood transfusion guidelines for adults undergoing surgery or receiving intensive care may be harmful. Few pediatric data, however, are available to guide transfusion recommendations for children. There are few absolute indications for blood transfusion and no universal hemoglobin and hematocrit values below which transfusion is required. The healthier the child and more chronic the loss of oxygen-carrying capacity, the lower the hemoglobin concentration and hematocrit that can be tolerated without needing transfusion. Written guidelines have suggested transfusion thresholds that vary with age (newborns versus older children) and clinical setting. Blood transfusions are used frequently in the management of surgical or traumatic hemorrhage, in the care of preterm or sick newborns, and in the management of a variety of congenital and acquired anemias. Pediatric practitioners should consult with specialists when this need arises.

Acute severe blood loss can lead to hemorrhagic shock, organ dysfunction, and death. In traumatic hemorrhage, estimated blood loss of 25% or more or signs of hemorrhagic shock frequently are considered to be indications for blood transfusion following standard fluid resuscitation and control of bleeding. Estimated surgical blood loss of 15% commonly is considered a trigger for transfusion, but a variety of measures (eg, optimizing coagulation status, hemodilution, surgical techniques to minimize bleeding) can be used to reduce transfusion requirements during surgery. Hemoglobin values required preoperatively depend on the type of operation and the patient's underlying clinical state; transfusions may not be necessary in otherwise healthy children who have anemia and are undergoing minor operative procedures without significant anticipated blood loss.

Transfusions in Neonates

Physiologic anemia of the newborn rarely is symptomatic, but anemia of prematurity often requires transfusion because of its greater severity, the frequent presence of pulmonary or other disease states, and the newborn's higher concentration of fetal hemoglobin, which is a somewhat ineffective oxygen donor because of its high oxygen affinity. Minimizing the amount of blood drawn for laboratory testing may lessen the need for transfusions, and separation of single units of donated blood into small aliquots for use at different times by the same infant lessens the number of donors to whom each infant is exposed. The use of recombinant human erythropoietin (rHuEPO) has been shown to reduce the number of transfusions needed by very low-birthweight (VLBW) infants, but not the number of donor exposures. Also, there are concerns about adverse effects, including a possible increase in the incidence or severity of retinopathy of prematurity. Therefore, the use of rHuEPO for anemia of prematurity remains somewhat controversial.

Published transfusion guidelines vary in their recommendations, but most list varying thresholds, depending on the level of ventilatory and oxygen support as well as on cardiac and respiratory symptoms of anemia. One study that compared liberal and restrictive transfusion thresholds for VLBW infants showed fewer transfusions in the restrictive transfusion group but more adverse outcomes, such as intraparenchymal brain hemorrhage, periventricular leukomalacia, and apnea episodes. Although another study, using different transfusion thresholds, showed no statistically significant increase in adverse events by employing a restrictive transfusion regimen, the benefits of a more restrictive approach seem to be

sufficiently limited not to warrant the possible risks.

Exchange transfusion may be employed in neonates who have hyperbilirubinemia and are considered to be at risk for kernicterus and in severe cases of hemolytic disease of the newborn (HDN). In both cases, whole blood or reconstituted whole blood (packed RBCs [PRBC] + plasma) is used. Extracorporeal membrane oxygenation requires significant transfusion support and monitoring for neonates and older children. Infants who have uncorrected cyanotic heart disease require high hemoglobin concentrations to maintain adequate oxygen delivery to tissues.

Blood Transfusions in Older Children

Older children may be transfused for a variety of hypoproductive and hemolytic anemias. The decision to transfuse depends not only on clinical signs but on the nature and expected course of the anemia.

Deficiencies of iron, vitamin B12, or folate in children can result in severe anemia (the latter two causing megaloblastic anemia). Despite presenting hemoglobin concentrations that sometimes are lower than 5 g/dL (50 g/L), children suffering these deficiencies infrequently require transfusion because they usually have acclimated to gradually declining hemoglobin concentrations. Response to iron, vitamin B12, or folate supplementation should be rapid, and PRBC transfusions are necessary only if there is cardiac or respiratory compromise (more likely with more rapid hemoglobin decline). Some authors, however, recommend initial blood transfusions, even for clinically stable patients who have severe megaloblastic anemia, to mitigate the adverse metabolic consequences of the rapid erythropoiesis that follows vitamin B12 or folate replacement therapy.

Children who have inherited bone marrow failure syndromes such as Fanconi anemia, dyskeratosis congenita, and Pearson syndrome frequently require regular RBC and platelet transfusions, as do children afflicted with severe acquired aplastic anemia, although many eventually respond to medical therapy or hematopoietic stem cell transplantation. Diamond-Blackfan anemia (congenital hypoplastic anemia) often responds to corticosteroids, but nonresponders require regular PRBC transfusions simply to maintain a hemoglobin concentration of 6 g/dL (60 g/L), as do many children who have congenital dyserythropoietic anemias types I or II or sideroblastic anemias. Transient erythroblastopenia of childhood is, as its name implies, a self-limited disorder, but PRBC transfusion sometimes is required for severe anemia causing cardiorespiratory compromise.

Periodic RBC transfusions are required for many children receiving myelosuppressive cancer chemotherapy or radiation therapy (XRT), and most oncologists use a high transfusion threshold for children receiving XRT because adequate oxygen delivery to tissues is necessary for optimum radiation effect. The proper role of rHuEPO treatment in pediatric oncology patients still is being elucidated. Although studies suggest benefit in some patient groups, concerns exist about adverse effects, including thrombosis and possible stimulation of tumor growth. The use of rHuEPO has lessened the transfusion needs of children afflicted with anemia of chronic renal failure.

Children who have sickle cell disease (SCD) tolerate chronic hemoglobin concentrations of 6 to 8 g/dL (60 to 80 g/L) without apparent cardiac or respiratory compromise. However, they may need standard PRBC or exchange transfusions to lower the Hb S percentage and improve oxygen-carrying capacity during a variety of SCD-related complications, such as stroke, acute chest syndrome, and splenic sequestration, as well as preoperative transfusion to lessen the likelihood of peri- and postoperative sickling events. Transfusion may be necessary to treat profound anemia during aplastic crises caused by parvovirus B19 infection. Some complications of SCD, particularly stroke and abnormal transcranial Doppler testing results, are indications for chronic transfusion regimens to keep the Hb S concentration below 30% to 50% and reduce the risk of additional complications (in these instances, stroke).

For children afflicted with thalassemia major, regular monthly PRBC transfusions to maintain hemoglobin concentrations greater than 10 g/dL (100 g/L) can prevent many complications of the disease by suppressing ineffective medullary and extramedullary hematopoiesis. Chronic transfusion regimens lead to iron overload, however, which can cause liver and heart failure. Therefore, such patients also should receive iron chelation through nightly subcutaneous deferoxamine infusions or the newer oral iron chelator deferasirox. Chronically transfused patients also are more likely to develop alloantibodies to minor RBC antigens and to leukocyte antigens. They always should receive RBCs that have been matched phenotypically for minor blood group antigens and leukoreduced.

Most children born with hereditary spherocytosis (HS) have mild disease that is characterized by nonlife-threatening exacerbations, but some require periodic RBC transfusions during hemolytic or aplastic crises. Splenectomy is cura-

tive for children requiring frequent transfusion. The physiologic anemia of the newborn period is more pronounced in infants who have HS; many require RBC transfusions during the first few weeks after birth. Hereditary elliptocytosis, another RBC membrane disorder, typically is mild and does not result in transfusion requirements.

Acute hemolytic episodes caused by oxidative stress in children who have the Mediterranean form of glucose-6-phosphate dehydrogenase deficiency can be severe enough to require RBC transfusion, but can be largely avoided by not exposing the child to certain drugs as well as fava beans. Other RBC enzyme defects, including pyruvate kinase deficiency, may cause hemolytic anemia that requires transfusion.

Children who experience autoimmune hemolytic anemia (AIHA) can develop cardiac and respiratory compromise quickly from rapid destruction of RBCs. Although AIHA often responds to corticosteroids (for warm-reactive antibodies), plasmapheresis (for cold-reactive antibodies), or other treatments, improvement can take days, and transfusion may be needed in the interim. Patients who have warm AIHA often have autoantibodies that react with multiple common RBC antigens, making it impossible to find donated blood that can be completely crossmatched. In these cases, patients can be transfused with the least-incompatible RBCs. Although the donated red cells are destroyed, they usually last as long as the patient's own RBCs, which should allow patients to be stabilized while waiting for definitive therapy to take effect. Such transfusions should be started slowly and the patients monitored closely for signs of accelerated hemolysis. If a child who has cold-reactive antibodies requires transfusion, a blood warmer should be used.

Immune hemolytic anemia in newborns (HDN) results from placental transfer of maternal antibodies that are reactive with antigens on the babies' RBCs. HDN from ABO incompatibility is a common cause of neonatal jaundice, but rarely is severe enough to require exchange transfusion because the levels of A and B antigen expression on newborn RBCs are fairly low, the antigens are expressed on other cells, and anti-A and -B antibodies often are composed of immunoglobulin M (IgM), which does not cross the placenta.

Rh incompatibility, conversely, frequently causes fetal demise or severe HDN that requires exchange transfusion. In utero exchange transfusions have been performed to prevent hydrops fetalis. The incidence of Rh HDN has decreased with routine postpartum administration of Rh immune globulin to Rh-negative mothers of Rh-positive infants to prevent sensitization.

Safety and Potential Adverse Effects

Blood transfusion is safe compared with many other treatments but is not without risks. Life-threatening transfusion reactions are rare, with an estimated fatality rate in the United States of 1 in 18 million transfusions. Mistaken administration of ABO-mismatched blood (particularly type A blood given to a type O recipient) can result in profound hemolysis and is the most common cause of transfusion-related death in the United States. The incidence of this type of error has decreased, however, with the implementation of many safeguards. Transfusion-associated bacterial sepsis is less of a problem with RBC transfusions than with transfusions of platelet or plasma concentrates. Transfusion-related acute lung injury, an acute respiratory distress-like condition, is far more common in adults than children, in whom respiratory difficulty during transfusion is more likely to be due to fluid overload.

Febrile nonhemolytic transfusion reactions (FNHTR) occur in about 0.2% of transfusions and usually are caused by cytokine release from donor white blood cells (WBCs) due either to prolonged storage or to recipient antibodies against donor WBC antigens. Fever and chills also can result from bacterial contamination of blood products or immediate hemolytic transfusion reactions. The likelihood of FNHTR is minimized by the use of leukocyte-filtered blood (reducing WBCs by >99% and RBCs by <10%). Routine premedication with acetaminophen does not decrease the incidence of FNHTR any further, so it need not be employed.

Allergic reactions causing urticaria occur during about 0.4% of transfusions; in such cases, antihistamines should be administered and the transfusion held. If the urticaria resolves quickly, it may be safe to resume the transfusion. Anaphylaxis is far less common and is more of a concern in individuals who are IgA-deficient. Routine premedication of transfusion recipients with antihistamines has not been shown to decrease the incidence of allergic reactions and need not be used. Children who have a history of allergic reactions to blood products may benefit from the use of washed or plasma-reduced PRBCs, and premedication with a corticosteroid should be considered.

Immediate hemolytic transfusion reactions, caused by high-titer antibodies in the recipient's plasma, are rare, although severe. Such reactions often result from inadvertent administration of ABO-incompatible RBCs. Signs and symptoms include

fever, chills, nausea, abdominal or back pain, tachycardia, and hypotension. If an immediate hemolytic reaction is suspected, the transfusion must be stopped immediately and intensive supportive care given, including treatment of shock and disseminated intravascular coagulation, as well as maintenance of renal blood flow and urine output to prevent renal failure from hemoglobinuria.

Delayed hemolytic transfusion reactions can result from primary immunization during the transfusion or anamnestic responses by previously sensitized recipients whose low-titer alloantibodies were not detected by pretransfusion antibody screen. Primary immunization causes very mild hemolysis and may be evident only as a slight decrease in hemoglobin concentrations 2 to 3 weeks after transfusion. Delayed hemolytic transfusions from anamnestic responses can cause many of the same effects as immediate hemolytic reactions, albeit considerably milder, and occur 3 to 7 days after transfusion. In addition to supportive care, affected patients may develop sufficiently severe anemia to require additional RBC transfusion.

Although transmission of HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) remains a primary concern of many patients and parents, advances in donor screening and in the testing of donated blood over the past 2 decades have lessened significantly the risks of acquiring these infections via transfusion. The "window period" between the time of transmissibility of infection in a prospective donor and the ability to detect the infection on testing has been shortened considerably with the development of more sophisticated methods of detecting virus particles, including nucleic acid amplification testing (NAT), to replace antibody screening. For example, NAT has shortened the window period for HIV from about 22 days to 10 days and for HCV from 10 weeks to 10 days. Because of the rarity of transmission, risk estimates are based on mathematical models rather than on actual rates. One recent estimate of the risk of HIV transmission was 1 in 2,135,000, for HCV was 1 in 1,935,000, and for HBV was 1 in 205,000; these risks are expected to decrease further with advancement of NAT screening.

Thirty cases of transfusion-associated West Nile virus (WNV) infection were reported in the United States between 2002 and 2004. "Minipool" NAT screening of multiple units of blood together has been shown to be feasible and may lower the risk of transfusion-associated WNV infection to about 1 in 350,000.

Since variant Creutzfeld-Jacob disease (vCJD) was first described in England in 1996, more than 100 cases have been reported in that country, as well as a small number in France and Italy. The infectious agent is the same prion responsible for bovine spongiform encephalopathy ("mad cow disease"). vCJD has not been reported in the United States. Although no cases of transmission-acquired vCJD have been reported anywhere, prions have been transmitted via transfusion in animal models, and the long incubation period of spongiform encephalopathies suggests that the reported cases of vCJD represent only a small fraction of the total number of infections. Because of these theoretical risks, people who recently have been in Europe have been restricted from donating blood in the United States.

Cytomegalovirus (CMV) can cause life-threatening infection in immunocompromised patients and in neonates, and infection can be transmitted via transfusion from a CMV-positive donor to a CMV-negative recipient (or reactivated in a CMV-positive recipient). Because about 50% of all blood donors have been infected with CMV, only a fraction of donated units is tested for CMV antibodies, enough to create a supply of CMV-negative blood. CMV is harbored in white blood cells, so leukodepletion can render blood products "CMV-safe." Blood from CMV-negative donors should be reserved for CMV-negative recipients at highest risk for severe CMV infection, such as recipients of hematopoietic stem cell or solid organ transplants, children who have congenital or acquired immunodeficiency, and preterm infants. Patients at lower levels of risk should receive CMV-safe (leukodepleted) blood products, and many physicians use CMV-safe blood even for very high-risk patients. Because WBCs also can transmit other pathogens (Epstein-Barr virus, bacteria, and others) and cause febrile nonhemolytic transfusion reactions, sensitization to alloantigens on donated platelets, and possible immunosuppression, universal prestorage leukoreduction has gained favor and currently is practiced by most blood banks in the United States. After standard leukoreduction (via filtration), however, a small number of immunologically competent lymphocytes may remain. These lymphocytes can cause fatal transfusion-associated graft versus host disease (TA-GVHD) in neonates, immunosuppressed patients, and those receiving donor-directed transfusions from relatives. Children considered to be at risk for TA-GVHD, therefore, should receive blood products that have been gamma-irradiated to eradicate any remaining lymphocytes.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

Match the blood type to the clinical description.

5. Universal blood donor.

6. Universal blood recipient.

7. Most common blood type.

   A. B−.
   B. AB−.
   C. AB+.
   D. O−.
   E. O+.

8. The percentage of blood loss during surgery that typically is used to trigger transfusion in the absence of compensating measures is:

   A. 5%.
   B. 10%
   C. 15%.
   D. 20%.
   E. 25%.

9. A child who has which of the following conditions is *most* likely to require a "least-incompatible" red blood cell transfusion?

   A. Fanconi anemia.
   B. Hereditary spherocytosis.
   C. Iron deficiency anemia.
   D. Sickle cell disease.
   E. Warm autoimmune hemolytic anemia.

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