Transfusion practice for the neonatal and pediatric population requires an understanding of the physiologic changes that accompany the transition from fetus to neonate, neonate to infant, and throughout childhood. Hematologic values, blood volume, and physiologic responses to stresses such as hypovolemia and hypoxia exhibit wide variations and affect transfusion practice. The most dynamic change occurs during the perinatal period and early infancy. Consequently, pediatric transfusion concerns are usually divided into two time periods: from birth through 4 months, and older infants (>4 months) and children.

Advances in medical care now permit the survival of extremely premature neonates. Blood providers must be capable of furnishing components tailored to satisfy the specific needs of very low-birth-weight (VLBW < 1500 g) and extremely low-birth-weight (ELBW < 1000 g) patients, whose small blood volumes and impaired organ functions provide little margin for safety. Ill neonates are more likely than hospitalized patients of any other age group to receive red cell transfusions.

Advances in critical-care neonatology, such as surfactant therapy, use of high-frequency ventilators, and adherence to transfusion practice guidelines, have diminished the number of transfusions given; most are now given to infants with birth weights less than 1000 g.

Fetal and Neonatal Erythropoiesis

The predominant sites of hematopoiesis in the developing embryo shift from the wall of the yolk sac to the liver to the bone marrow in the first 24 weeks. Hematopoiesis is regulated by gradually increasing erythropoietin (EPO) levels stimulated by low oxygen tensions during intrauterine life. Fetal red cells, rich in hemoglobin F, are well-adapted to low intrauterine oxygen tensions. The high oxygen affinity of fetal hemoglobin enhances transfer of oxygen exchange from
maternal erythrocytes to fetal erythrocytes throughout pregnancy.

The “switch” from fetal to adult hemoglobin begins about 32 weeks’ gestation; at birth, hemoglobin F constitutes 60-80% of the total hemoglobin. The time of conception appears to determine the time of the shift. Gestational age at the time of birth does not affect it, so that preterm neonates are born with higher levels of fetal hemoglobin than those born at term. The mean cord hemoglobin of healthy term neonates is 16.9 ± 1.6 g/dL, and that of preterm neonates is 15.9 ± 2.4 g/dL. Hemoglobin concentration gradually falls in the first few weeks of life. This has been called “physiologic anemia of infancy” in term newborns and “physiologic anemia of prematurity” in preterm newborns. It is considered physiologic because it is self-limited, is usually well tolerated, and is not associated with any abnormalities in the infant. Erythropoietic activity diminishes secondary to an increase in pulmonary blood flow and rise in arterial pO2, as well as the increase in red cell content of 2,3-diphosphoglycerate (2,3-DPG) and of hemoglobin A, that enhance the release of oxygen to the tissues. As tissue oxygenation improves, levels of EPO decline and erythropoiesis diminishes. This, along with decreased survival of fetal red cells and expansion of the blood volume due to rapid growth, causes the hemoglobin concentration to decline. The rate of decline is dependent on gestational age at birth; hemoglobin may drop to as low as 8.0 g/dL at 4-8 weeks of age in preterm infants weighing less than 1500 g.

Despite hemoglobin levels that would indicate anemia in older children and adults, the normally developing infant usually maintains adequate tissue oxygenation. Physiologic anemia requires treatment if the degree or timing of the anemia causes symptoms in the patient, a frequent problem in very low-birthweight preterm infants who are ill and require extensive laboratory monitoring.

Unique Aspects of Neonatal Physiology

Infant Size and Blood Volume

Full-term newborns have a blood volume of approximately 85 mL/kg; preterm low-birth-weight newborns have an average blood volume of 100 mL/kg. As survival rates continue to improve for infants weighing 1000 g or less at birth, blood banks will increasingly be asked to provide blood components for patients whose total blood volume is less than 100 mL. The need for frequent laboratory tests has made replacement of iatrogenic blood loss the most common indication for transfusion of low-birth-weight preterm neonates. However, the previous practice of replacing blood mL for mL is now giving way to replacement as needed to maintain a target hematocrit in certain clinical situations.

Newborns do not compensate for hypovolemia as well as adults. After a 10% volume depletion, a newborn diminishes the left ventricular stroke volume, without increasing the heart rate. To maintain systemic blood pressure, peripheral vascular resistance increases and this, combined with the diminished cardiac output, results in poor tissue perfusion, low tissue oxygenation, and metabolic acidosis.

Erythropoietin Response

Erythropoietin response in newborns differs from that of adults and older children. In older children and adults, oxygen sensors in the kidney recognize diminished oxygen delivery and release EPO into the circulation. In the fetus, the oxygen sensor that stimulates EPO
production is believed to be the liver, which appears to be programmed for the hypoxic intrauterine environment. This hyporesponsiveness to hypoxia protects the fetus from becoming polycythemic. Eventually, EPO production shifts from the liver to the kidneys, a developmental change thought to be regulated by time of conception, not birth, and possibly not beginning until term. After birth, it is the most immature infants who produce the least amount of EPO for any degree of anemia; this may reflect the absence of the developmental shift of erythropoietin production from the liver to the kidneys. Sick preterm neonates who receive many transfusions shortly after birth have reduced circulating levels of fetal hemoglobin. Circulating EPO levels are lower, for a given hematocrit, in preterm neonates with higher proportions of hemoglobin A (which favors release of oxygen to the tissues) relative to hemoglobin F. Erythroid progenitor cells in the hypoproliferative bone marrow of these preterm infants show normal intrinsic sensitivity to EPO; clinical trials are in progress to evaluate treatment of the anemia of prematurity with recombinant human erythropoietin.

**Cold Stress**

Hypothermia in the newborn causes exaggerated effects, including increased metabolic rate, hypoglycemia, metabolic acidosis, and a tendency toward apneic episodes that may lead to hypoxia, hypotension, and cardiac arrest. Because exchange transfusion with blood at room temperature may decrease a newborn’s rectal temperature by 0.7-2.5 °C, blood for exchange transfusion should be warmed. The usual method is to use an in-line warmer. Blood should not be warmed under a radiant heater (either large or small volumes), but small volumes of blood are sometimes placed in a temperature-controlled incubator, where there are safeguards against excessive warming. When transfusions are given to infants in phototherapy unit, the tubing should be introduced through the side port, because red cells in tubing that enters the top port may be hemolyzed.

**Immunologic Status**

Infants have an immature humoral immune system, and any antibodies present derive almost entirely from the maternal circulation. Transplacental transfer of immunoglobulin and other proteins is independent of molecular size; IgG (150 kDa) is transferred much more readily than albumin (64 kDa). In humans, maternal IgM does not reach the fetus and IgA is not readily transferred, although low levels have been found in the newborn.

All four subclasses of IgG are transported across the placenta, but the rate varies between individual mother-fetus pairs. Early in pregnancy, IgG probably passes from mother to fetus by diffusion, and concentration in fetal serum is low for all subgroups. Between 20 and 33 weeks of gestation, fetal IgG levels rise markedly, apparently due to maturation of a selective transport system that involves, in part, specific protein receptors on the membrane of placental cells. IgG1, the predominant subclass in maternal blood, crosses the placenta first and is transported in greatest quantity. Cord blood has higher antibody concentrations than maternal blood. Catabolism of IgG occurs more slowly in the fetus than in the mother, so that transplacental maternal antibody is conserved during the neonatal period.

A fetus exposed to an infectious process in utero or an infant exposed shortly after birth may produce small amounts of IgM detectable by sensitive techniques, but unexpected red cell alloantibodies of either
IgG or IgM class are rarely formed during the neonatal period.\textsuperscript{10}

The cellular immune system of neonates is also immature. Graft-vs-host disease (GVHD) has been reported in newborns, most often in infants who had confirmed or suspected congenital immunodeficiency. It has, however, occurred in infants who received intrauterine transfusion followed by postnatal exchange transfusion.\textsuperscript{11} A proposed explanation is that lymphocytes given during intrauterine transfusion could induce host tolerance, impairing rejection of lymphocytes given in the subsequent exchange transfusions. GVHD is not considered a significant clinical problem in exchange transfusions in immunologically normal newborns, and irradiation of blood to prevent GVHD is probably unnecessary. However, some neonatal nursery units provide irradiated blood for low-birth-weight, low-gestational-age, or septic preterm neonates, based on the belief, not yet universally accepted, that such infants are immunologically more vulnerable to GVHD.\textsuperscript{11} Irradiation should be performed on blood for intrauterine transfusion and on all subsequent transfusions that this infant receives; directed-donor units should be irradiated.\textsuperscript{12}

\section*{Metabolic Problems}

Acidosis or hypocalcemia may occur after large-volume transfusion because the immature liver of the newborn metabolizes citrate inefficiently. Immature kidneys have reduced glomerular filtration rate and concentrating ability, and newborns may have difficulty excreting excess potassium, acid, and/or calcium.

\section*{Potassium}

Although potassium levels increase rapidly in the plasma of stored red cells, small-volume, simple transfusions have little effect on serum potassium concentration in newborns. It has been calculated that transfusion of 10 mL/kg of red cells (hematocrit 80\%) obtained from a unit of blood stored for 42 days in extended storage medium, would deliver 0.1 mEq of potassium if transfused slowly to a 1 kg neonate.\textsuperscript{13} This is much less than the daily potassium requirement of 2-3 mEq/kg. Serum potassium may, however, rise rapidly after infusion of large volumes of red cells in such circumstances as surgery, exchange transfusion, or extracorporeal circulation, depending upon the plasma potassium levels in the blood and manipulation of the blood component.

In stored, irradiated blood, the problem of potassium leak is potentiated; it may be desirable, for selected patients, to wash irradiated cells if they have subsequently been stored.\textsuperscript{14} It is preferable to perform irradiation as close to the time of administration as possible.

\section*{2,3-Diphosphoglycerate}

Neonates with respiratory distress syndrome or septic shock have decreased levels of 2,3-diphosphoglycerate (2,3-DPG). Alkalosis and hypothermia may further increase the oxygen affinity of hemoglobin, shifting the dissociation curve to the left and making oxygen even less available to the tissues. Arterial oxygenation may be further compromised by respiratory distress syndrome or other pulmonary disease. Mechanisms that compensate for hypoxia in adults, such as increased heart rate, are limited in newborns. If a large proportion of an infant’s blood volume has come from transfusion, transfusion of 2,3-DPG-depleted blood may cause problems that would not affect older children or adults. Since 2,3-DPG levels decrease in stored blood, exchange transfusion in newborns should use the freshest blood con-
veniently available. For small-volume transfusions, the medical necessity for fresh blood has never been demonstrated and arguments have been raised to suggest it is unnecessary.

Cytomegalovirus Infection

Perinatal infection by cytomegalovirus (CMV) may occur, acquired either in utero or during the birth process, and neonates can be infected during breast feeding or by close contact with mothers or nursery personnel. CMV can be transmitted by transfusion, but current transfusion practice has made this uncommon.

Infection in newborns has extremely variable manifestations, ranging from asymptomatic seroconversion to death. Studies of CMV in neonatal transfusion recipients reveal the following observations:

1. The overall risk of symptomatic posttransfusion CMV infection seems to be inversely related to the seropositivity rate in the community. Where many adults are positive for CMV antibodies, the rate of symptomatic CMV infection in newborns is low.

2. Symptomatic CMV infection during the neonatal period is uncommon in children born to seropositive mothers.

3. The risk of symptomatic posttransfusion infection is high in multitransfused preterm infants weighing less than 1200 g who are born of seronegative mothers.

4. The risk of acquiring CMV infection is directly proportional to the cumulative number of different donor exposures incurred during transfusion.

5. Cytomegalovirus in blood is associated with leukocytes. The risk of viral transmission can be reduced by transfusion of blood from seronegative donors or of components that have been processed to eliminate viable CMV-containing leukocytes. Deglycerolized red cells, both seronegative and seropositive, have been used successfully. The use of washed red cells may have some effect, but the use of washed cells for this indication remains controversial.

Leukocyte reduction with highly efficient leukocyte-reduction filters also appears to be an effective way of reducing CMV infection. AABB Standards for Blood Banks and Transfusion Services states that cellular components with minimal risk of transmitting CMV should be used for newborns who weigh less than 1200 g, and are born to mothers who lack CMV antibodies or whose antibody status is unknown. The level of leukocyte reduction necessary to prevent CMV transmission is given as less than $5 \times 10^6$ leukocytes in the final component. To avoid intrauterine infection of the fetus, components with minimal risk of transmitting CMV should also be used for intravascular or intrauterine transfusions in the pregnant woman who lacks CMV antibody or whose antibody status is unknown.

Red Cell Transfusions in Infants Less Than 4 Months of Age

Red Blood Cells (RBCs) are the component most often transfused during the neonatal period. Many of the physiologic considerations mentioned affect decisions about indications for transfusion selection and administration of red cell components, and the extent of compatibility testing.
Compatibility Testing

Because the neonate and young infant are immunologically immature, alloimmunization to red blood cell antigens is rare during the neonatal period. A study of 90 neonates who received 1269 transfusions from different donors found no instances of antibody production even with use of very sensitive detection techniques. Other investigators confirm the relative infrequency of alloantibodies directed against red cell antigens as well as HLA antigens.

Because alloimmunization is extremely rare and repeated testing increases iatrogenic blood loss, AABB Standards requires only limited pretransfusion serologic testing for infants under 4 months old. Initial testing must include ABO and Rh typing of red cells and a screen for red cell antibodies; the antibody detection test may be done on either serum or plasma, from either the infant or the mother.

During any one hospitalization, compatibility testing and repeat ABO and Rh typing may be omitted, provided that the screen for red cell antibodies is negative; that all red cells transfused are group O or ABO-identical or ABO-compatible; and that red cells are either Rh-negative or the same Rh type as the patient. If an unexpected red cell antibody is detected in the infant’s specimen or the mother’s serum contains a clinically significant red cell antibody, the infant should be given either red cell units tested and found to lack the corresponding antigen(s) or units compatible by antiglobulin crossmatch; this should continue for as long as maternal antibody persists in the infant’s blood. The institution’s policy will determine how frequently to perform a screen for red cell antibodies; once a negative result is obtained, subsequent crossmatches and/or provision of blood lacking the target antigen are unnecessary. It is important to avoid transfusion of any component that may transfer unexpected antibody to the infant.

It is unnecessary to test the infant’s serum for anti-A and/or anti-B unless there will be transfusion of non-group O cells. If there will be non-group O transfusion, testing for anti-A and/or anti-B must include the antiglobulin phase. If antibody is detected and for as long as it remains present, transfused cells must lack the corresponding antigen, but need not be crossmatched.

Indications for Red Cell Transfusion

Certain events in the perinatal period cause anemia for which the benefits of red cell transfusion are unquestioned. These include spontaneous fetomaternal or fetoplacental hemorrhage, twin-twin transfusion, obstetric accidents, and internal hemorrhage. A venous hemoglobin of less than 13 g/dL in the first 24 hours of life indicates severe anemia. For severely anemic neonates with congestive heart failure, it may be necessary to remove aliquots of their dilute blood and transfuse concentrated red cells, a “partial exchange” transfusion. Most red cell transfusions in the neonatal period, however, are given either to treat iatrogenic blood loss or to treat clinical problems that complicate the physiologic decline in hemoglobin (anemia of prematurity).

Because tissue need for oxygen cannot be measured directly and because so many variables determine oxygen availability, no universally accepted criteria exist for transfusion of preterm or term neonates. Despite the widespread use of micromethods for laboratory tests and beginning use of in-situ monitoring devices, infants sustain significant cumulative blood loss for laboratory sampling. In a sick neonate, red cell replacement is usually considered when approximately 10% of the blood volume has been re-
moved. The decision to transfuse a newborn for anemia should include evaluation of the hemoglobin levels expected for age and of the patient’s clinical status and amount of blood loss over time. Transfusion may be more aggressive in the infant in respiratory distress who is hypoxic and more vulnerable to cerebral hemorrhage.

Considerable controversy surrounds the correlation of the “signs of anemia” in the preterm infant (tachycardia, tachypnea, recurrent apnea, decreased vigor, and poor weight gain of unexplained origin) with response to RBC transfusions. When red cells are transfused, they are usually given in small volumes. A transfusion of 10 mL/kg of red cells at a hematocrit greater than 80% should raise the hemoglobin concentration by approximately 3 g/dL.

Red Cell Components Used for Neonatal Transfusion

The small-volume requirements of transfusion to neonatal recipients make it possible to prepare several aliquots from a single donor unit, thus limiting donor exposure and decreasing donor-related risks. Several technical approaches are available to realize this advantage and to minimize wastage.

Multiple Packs

A multiple-pack system is the most common technique for providing small-volume red cell transfusions. If a single unit of whole blood is apportioned into four integrally attached containers (“quad packs”) of 125 mL, the original seal remains intact and, until entered, each container has the expiration date of the original unit. Aliquots from an individual quad pack can be transferred to smaller containers, each with a 24-hour shelf life.

The hematocrit can be adjusted at either division step. For example, plasma can be removed shortly after phlebotomy, for storage as fresh frozen plasma (FFP), and the remaining red cells can be divided into each of the three attached bags. If the contents of each quad pack are apportioned, at the time of use, into four small-volume transfer packs, a single donation can provide a dozen 20-mL aliquots of red cells and a unit of FFP. Alternatively, the original whole blood can be expressed into satellite bags, each of which can be entered for subsequent removal of plasma or subdivision into smaller aliquots.

Each aliquot must be fully labeled as it is prepared, including the time it outdates, and the origin and disposition of each aliquot must be recorded. Sterile connecting devices have made it much easier to prepare aliquots without decreasing shelf life; with this technique, a recipient can receive multiple small-volume transfusions from a single donation until the expiration of the unit, thereby reducing donor exposure.

Multi-Portion System

A multi-portion system is useful in settings where syringe pumps are used for small-volume transfusions for large numbers of patients. Blood is collected into either single or multiple packs. If triple or quadruple bag sets are used, the hematocrit can be adjusted initially and FFP may be prepared. Alternatively, red cells can be concentrated by gravity sedimentation for 12 hours, resulting in a hematocrit of approximately 65%. Bags are hung in an inverted position in the refrigerator so that sedimented cells can be carefully drawn through one of the access ports into a syringe.

A resealable sampling or injection site coupler inserted into the access port permits repeated entry. Once the coupler is inserted, the contents of a bag stored at 1-6 C have a 24-hour shelf life. The precise volume of blood requested
can be aspirated into a syringe through a large-bore needle inserted through the sampling site coupler. The packed or sedimented red cells can be drawn into the syringe through an in-line filter. If blood is not filtered during loading, a filter is required in the infusion set. Aseptic technique should be used and the sampling site coupler covered with sterile gauze when not in use.

The filled syringe should be protected with a sterile cap, and must be appropriately labeled for the recipient. The distribution of aliquots to individual recipients as filled syringes must be recorded. Use of syringes for multi-portion distribution allows precise measurement of components and efficient use of donor resources, but enlarges the dissemination of any transmissible organisms that the unit might contain.

**Deglycerolized Red Cells**

After glycerolization and before freezing, a unit of red cells can be divided into three or four aliquots. A single unit may be designated for repeated transfusion to a single recipient, thereby minimizing donor exposure, or aliquots can be assigned to different patients. Each aliquot can be thawed as needed, with the usual 24-hour shelf life after thawing and deglycerolization. This is an expensive system, but it provides a component with the 2,3-DPG level of freshly drawn blood and, after the postthaw wash, with much reduced content of plasma proteins, electrolytes, anticoagulant, white cells, and platelets. Alternatively, entire group O units can be thawed and deglycerolized, and aliquots removed as needed during the permitted 24-hour shelf life.

**Individual Small Units**

It is permissible to draw less than 450 ± 45 mL of blood, provided the proportions of blood and anticoagulant are correct (see Table 4-1) and the unit is labeled properly. After unneeded anticoagulant has been expressed into one satellite bag of a triple pack, approximately 225 mL of blood can be collected, and the plasma expressed into the same satellite bag, which is then discarded. The remaining red cells can be apportioned between the primary container and the remaining satellite bag; this provides two units of red cells of approximately 60 mL volume.

Units containing approximately 30-60 mL of whole blood can be obtained by collecting blood into a system with an extra satellite bag. A unit intended for use as whole blood would be collected in a double bag; a unit intended for division into red cells, platelets, and FFP would be collected in a quadruple set instead of a triple set. Collection sets have enough anticoagulant-preservative for 450 mL ± 45 mL of blood, and donors of suitable size may give up to 525 mL. If the volume drawn can be measured accurately, it is permissible to draw 495 mL of whole blood into the primary bag. Expressing 30-60 mL into the extra satellite bag leaves a satisfactory volume in the primary bag and provides an extra small-volume unit with normal shelf life. The hematocrit of these small units can be adjusted by removing plasma prior to transfusion. Alternatively, a sterile connection device can be used to transform units of any size into pediatric units without having to change the expiration date.

**Red Cells with Additive Solution**

Most red cells used for pediatric transfusions have been stored in CPDA-1. Additive solutions (AS) used as anticoagulant-preservatives contain additional adenine and dextrose and some contain mannitol. There has been concern about the potential side effects of these additives, particularly when units are fresh.
The metabolites of adenine are known to be nephrotoxic in animals and man, but there is little information about its effects in preterm infants. With mannitol infusion, there is concern about renal toxicity and about the diuretic effect, which may cause unacceptable fluctuations in cerebral blood flow. Table 22-1 lists differences between CPDA-1 and one of the additive solutions (AS-1), in total quantities and in the small-volume transfusion usual for VLBW infants. When the dose of transfused red cells is approximately 10 mL/kg, the recipient is exposed to relatively small amounts of constituents. A clinical comparison of red cells stored in these two preservatives showed transfusion of cells prepared in the extended-storage additive solution to have no apparent detrimental effects and, after adjustment for the lower hematocrit of the component, to be as effective as CPDA-1 cells in increasing hemoglobin.

A review based on theoretical calculations also suggests that red cells preserved in extended-storage media present no substantive risks when used for small-volume transfusions. For preterm infants with severe hepatic or renal insufficiency, however, removing the additive-containing plasma is recommended, particularly if there will be multiple transfusions that could have a cumulative effect. The use of red cells stored with additives should be avoided for massive transfusion settings, such as cardiac surgery or exchange transfusions.

### Transfusion Administration

Vascular access is often difficult in the tiny newborn and in any infant requiring long-term or repeated intravenous infusions. Within a short time after birth, the umbilical artery may be cannulated. Thereafter, a vein large enough to accommodate a 23- or 25-gauge needle or a 22- or 24-gauge vascular catheter should be chosen for blood administration.

#### Table 22-1. Constituents of AS-1 and CPDA-1

<table>
<thead>
<tr>
<th></th>
<th>AS-1</th>
<th>CPDA-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant solution per 100 mL</td>
<td>Dextrose, 2.2 g</td>
<td>Dextrose, 3.2 g</td>
</tr>
<tr>
<td></td>
<td>Sodium chloride, 900 mg</td>
<td>Trisodium citrate, 2.6 g</td>
</tr>
<tr>
<td></td>
<td>Mannitol, 750 mg</td>
<td>Citric acid, 327 mg</td>
</tr>
<tr>
<td></td>
<td>Adenine, 27 mg</td>
<td>Monobasic sodium phosphate, 222 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adenine, 27.5 mg</td>
</tr>
<tr>
<td>Transfused products (hematocrit = 60%)</td>
<td>Dextrose, 76 mg</td>
<td>Dextrose, 17 mg</td>
</tr>
<tr>
<td></td>
<td>Sodium chloride, 33 mg</td>
<td>Trisodium citrate, 14 mg</td>
</tr>
<tr>
<td></td>
<td>Citrate, 8.5 mg</td>
<td>Citric acid, 1.8 mg</td>
</tr>
<tr>
<td></td>
<td>Phosphate, 3.2 mg</td>
<td>Phosphate, 1.2 mg</td>
</tr>
<tr>
<td></td>
<td>Adenine, 0.9 mg</td>
<td>Adenine, 0.1 mg</td>
</tr>
<tr>
<td></td>
<td>Mannitol, 25 mg</td>
<td></td>
</tr>
</tbody>
</table>

Transfused products have been calculated for a 1 kg neonate receiving a transfusion of 10 mL/kg. All calculations are based on the volume of plasma constituents and the red cell mass. (Reproduced with permission from Goodstein data adapted from Luban.

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It is not usually necessary to warm small-volume transfusions that are given slowly, but it is important to be able to control the volume and rate of infusion. Constant-rate electromechanical syringe delivery pumps provide this control and cause minimal hemolysis, even when used with in-line third-generation filters.

The length of the plastic tubing used can add significantly to the volume required for a transfusion. Infusion sets identified as suitable for platelets or components have less dead space than standard sets because they have short tubing and a small 170-micron filter. Pediatric microaggregate filters (20- or 40-micron) are useful for their small priming volume, not for the removal of microaggregates, which do not accumulate significantly in blood stored less than 1 week. Hemolysis occurs when stored blood is given by negative pressure filtration through these filters.

Third-generation leukocyte-reduction filters are not recommended for routine use in the neonatal period. Leukocyte reduction by filtration does, however, appear to be effective in reducing the risk of transfusion-transmitted CMV.

Exchange Transfusion

Exchange transfusion, originally used almost exclusively to treat hemolytic disease of the newborn, is infrequently performed today. With the use of surfactant replacement therapy for respiratory distress syndrome and the ongoing evaluation of intravenous gammaglobulin in treating sepsis, exchange transfusion is rarely considered as adjunctive therapy for these disorders. While exchange transfusion may be performed empirically for disseminated intravascular coagulation (DIC) or to remove toxins, the most common current indication for exchange transfusion in newborns is unconjugated hyperbilirubinemia.

Exchange transfusion carries risk both from the transfused blood and from the procedure itself. Overall mortality from the procedure, to which only sick, high-risk, and often low-birth-weight infants are subjected, is estimated at 2-3 deaths per 1000 procedures, when the operators are experienced. As fewer procedures are performed and clinical experience diminishes, morbidity and mortality rates may increase. Exchange transfusions equivalent to one or two volumes of the neonatal blood volume may be performed. A two-volume exchange removes approximately 80-90% of the infant’s original circulating blood.

Hyperbilirubinemia

Hyperbilirubinemia is one of the most frequent problems in the newborn period. The fetal liver has limited capacity to conjugate bilirubin. When the fetus is in utero, unconjugated bilirubin crosses the placenta for excretion through the mother’s hepatobiliary system. After birth, transient hyperbilirubinemia occurs during the first week of life referred to as “physiologic jaundice.” Normal newborns rarely develop dangerous hyperbilirubinemia. However, when the level of unconjugated bilirubin in serum exceeds the level for crossing the blood-brain barrier, bilirubin may concentrate in the basal ganglia and cerebellum; the resulting damage to the central nervous system (CNS) is called kernicterus.

Causes

Mechanisms that affect bilirubin levels include:

1. An increase in the bilirubin load in the liver due to an increased red cell volume, shortened life span of fetal red cells or increased enterohepatic circulation of bilirubin.
2. Poor hepatic uptake of bilirubin, sometimes reflecting low levels of albumin, which functions as a bilirubin carrier protein.
3. Transient deficiency of uridine diphosphoglucuronyl transferase, the hepatic microsomal enzyme, that converts unconjugated lipid-soluble bilirubin to the water-soluble glucuronide conjugate that is excreted without damage to the CNS.
4. Metabolic or mechanical defects in bilirubin excretion.

Prematurity exaggerates all of the processes listed above, and preterm infants may also have one or more of the following pathologic processes:
1. Hemolysis secondary to maternal alloantibody.
2. Hemolysis secondary to:
   a. inherited deficiencies of red cell enzymes, most commonly glucose-6-phosphate dehydrogenase or, less often, pyruvate kinase
   b. congenital red blood cell membrane defects, such as hereditary spherocytosis
   c. hemoglobinopathies, associated with shortened red cell survival
3. Destruction of extravascular red cells, due to hemorrhage into an enclosed space, especially likely in prolonged labor or difficult delivery.
4. Increased enterohepatic circulation due to any form of intestinal obstruction or delay in bowel transit time, allowing deconjugation and reabsorption.
5. Displacement of bound bilirubin from albumin by competing substances, usually drugs given to the mother or neonate, such as sulfonamides, vitamin K, or salicylates.

Initial Treatment

Phototherapy with fluorescent blue lights is the most common treatment for hyperbilirubinemia; exchange transfusion is reserved for phototherapy failures. In neonates with nonhemolytic jaundice, phototherapy is more effective than exchange transfusion in achieving prolonged reduction of bilirubin levels. When bilirubin near the surface of the skin is exposed to light it undergoes photoisomerization to form “photobilirubin.” These isomers of bilirubin are transported in the plasma to the liver where they are rapidly excreted in bile without the need for conjugation.

Effects of Exchange

Exchange transfusion removes unconjugated bilirubin and provides additional albumin to bind residual bilirubin. If the problem is antibody-mediated hemolysis, exchange transfusion is additionally beneficial in removing free antibody and antibody-coated red cells and providing red cells that will survive normally.

Exchange transfusion should be done before bilirubin rises to levels at which CNS damage occurs. Several factors affect the threshold for toxicity. CNS damage occurs at lower levels if there is prematurity, decreased albumin binding capacity, or the presence of such complicating conditions as sepsis, hypoxia, acidosis, hypothermia, or hypoglycemia. In full-term infants, kernicterus usually does not develop at bilirubin levels less than 20 mg/dL but in sick, VLBW infants, kernicterus has occurred at bilirubin levels as low as 10 mg/dL.

The magnitude of the hyperbilirubinemia, not its cause, influences the decision to perform exchange transfusion, but the rate at which bilirubin rises is a better predictor of imminent need for exchange transfusion than any single value. Neonates in whom bilirubin is rising faster than 1 mg/dL/hour and/or who have significant anemia may require exchange transfusion. A two-volume ex-
change transfusion decreases the serum bilirubin to 45-50% of its preexchange value. This observed efficiency of bilirubin removal is less than the theoretical predicted efficiency because of reequilibration between bilirubin in plasma and in extravascular tissues even while the exchange is taking place. Also, in the subsequent few hours, more extravascular bilirubin enters the circulation to equilibrate with lowered serum levels. Although phototherapy is usually instituted after the initial exchange, the rebound rise in bilirubin, combined with continued bilirubin production, may so elevate the serum level that a repeat exchange is needed. Indications for repeat exchange are similar to those for the initial exchange.

**Disseminated Intravascular Coagulation**

In the neonatal period, DIC occurs secondary to many conditions, including shock, sepsis, asphyxia, and necrotizing enterocolitis. The diagnosis is based on the clinical features as well as age-corrected results of coagulation screening tests, low levels of platelets and fibrinogen, and presence of fibrin degradation products. Transfusion of plasma and platelet components may improve hemostasis, but the most important therapy for neonatal DIC is to treat the underlying disease. Exchange transfusion has given variable results, perhaps because only the sickest infants have been selected to receive this therapy.

**Other Toxins**

Exchange transfusion is occasionally used to remove other toxins, such as drugs or chemicals given to the mother near the time of delivery, drugs given in toxic doses to the neonate/infant, or substances such as ammonia that accumulate in the newborn because of prematurity or inherited metabolic diseases.

**Partial Exchange (Erythrocytapheresis) for Polycythemia**

Red cells can be removed while blood volume is maintained by manual erythrocytapheresis. A venous hematocrit greater than 65% or hemoglobin in excess of 22 g/dL any time in the first week of life defines polycythemia, a condition that occurs in approximately 5% of all newborns; groups at special risk are small-for-gestational-age infants and infants of diabetic mothers. As the hematocrit rises above 50% the viscosity of blood increases exponentially and oxygen transport decreases. The infant has limited ability to compensate for hyperviscosity by increasing cardiac output and may develop congestive heart failure. Impairment of blood flow can cause CNS abnormalities, pulmonary and renal failure, and necrotizing enterocolitis. Partial exchange is intended to normalize the hematocrit to 55-60% and improve tissue perfusion, while maintaining the blood volume.

Whole blood is removed and the volume replaced with 5% albumin or crystalloid, the choice being based on the quantity needed and on the infant’s clinical condition. Plasma is not recommended because, if coagulation problems are present, the volume given is insufficient to correct them and because necrotizing enterocolitis has been reported with its use in this procedure. A formula for the volume of colloid replacement required for the exchange is:

\[
\text{Volume of replacement fluid} = \frac{\text{blood volume} \times (\text{observed hemoglobin} - \text{desired hemoglobin})}{\text{observed hemoglobin}}
\]
**Technique of Exchange Transfusion**

**Choice of Components**

Many different combinations of blood components have provided safe and effective exchange transfusion; no single component or combination is unequivocally best. Most frequently used are red cells in CPDA-1, which can be used alone, with 5% albumin, or with FFP if coagulation factors are required. Whole blood collected in CPDA-1 has given satisfactory results in term neonates. The red blood cells used for exchange transfusion should lack hemoglobin S, to avoid any possibility of intravascular sickling.

If the blood is anticoagulated with citrate, calcium has traditionally been administered to offset its calcium-binding effects. This practice does not appear to have any significant effects on ionized calcium levels and, despite low serum levels of ionized calcium, clinical tetany is rarely seen during exchange transfusion. Calcium should never be infused through the same infusion line as transfused blood because it can precipitate clotting.

**Glucose.** The glucose load administered during exchange transfusion can be extremely high. This stimulates the infant to secrete insulin, which leads to rebound hypoglycemia. It is important to monitor blood glucose levels for the first few hours after the procedure.

**Albumin.** Unconjugated bilirubin binds to albumin. Increased intravascular binding is thought to enhance diffusion of extravascular bilirubin into the circulation, thereby increasing the total quantity of bilirubin removed during the exchange. Some physicians give 25% serum albumin, either 1 g/kg 1 hour before the exchange or at 100-mL intervals during exchanges intended to reduce hyperbilirubinemia. A study that compared 15 hyperbilirubinemic neonates given albu-

**Volume and Hematocrit**

An exchange transfusion equal to twice the patient’s blood volume is typically recommended for newborns. Rarely is more than one full unit of donor blood appropriate during an exchange transfusion, since bilirubin, antibody, sensitized red cells, and/or toxins are removed with progressively less efficiency in the late stages of the procedure. In practice, the calculated volume for exchange is an estimate; the actual volume exchanged is one unit of whole blood or one unit of red cells reconstituted with one unit of compatible FFP. The final hematocrit of transfused material is approximately 40-50% and sufficient plasma will be present to provide clotting factors and enhance the efficiency of exchange. In the unusual event that the infant’s condition demands a high postexchange hematocrit, a small-volume transfusion of red blood cells can also be given. It is important to keep the donor blood mixed during the exchange; if it settles in the container, the final aliquots will not have the intended hematocrit. The infant’s hematocrit and bilirubin level should be measured on the last aliquot removed in the exchange.

**Vascular Access**

Exchange transfusions in the newborn period are usually accomplished via...
catheters in the umbilical vessels. Catheterization is easiest within hours of birth, but it may be possible to achieve vascular access at this site for several days. The catheters should be radiopaque to facilitate radiographic monitoring during and after placement. If umbilical catheters are not available for exchange transfusion, small central venous or saphenous catheters may be used.

**Methods Used**

Two methods of exchange transfusion are in common use. In the isovolumetric method, there is vascular access through two catheters of identical size and withdrawal and infusion occur simultaneously, regulated by a single peristaltic pump. The umbilical artery is usually used for withdrawal, and the umbilical vein for infusion.

The push-pull technique can be accomplished through a single vascular access if necessary. A three-way stopcock joins the unit of blood, the patient, and an extension tube that leads to the graduated discard container. An in-line blood warmer and a standard blood filter should be incorporated in the administration set. The maximum volume of each withdrawal and infusion will depend on the infant's size and hemodynamic status. The rate at which exchange transfusion occurs may alter the infant's hemodynamic status. The procedure should take place over 1 to 1.5 hours.

**Transfusion of Other Components**

While approximately 80% of VLBW infants can be expected to receive multiple red cell transfusions, only 15-20% will also receive other components. Platelet Transfusion

The normal platelet count in newborns is similar to that in adults. A platelet count less than 150,000/µL in a full-term or premature infant is abnormal. Approximately 20% of infants in neonatal intensive care units have mild to moderate thrombocytopenia, which is the most common hemostatic abnormality in the sick infant. Neonatal thrombocytopenia may result from impaired production or increased destruction of platelets, abnormal distribution, or a dilutional effect secondary to massive transfusion such as exchange transfusion. Increased destruction is the most usual cause; it may be associated with a multitude of conditions and is usually transient. Alloimmune thrombocytopenia is discussed in Chapter 21.

**Indications**

Platelet transfusion is indicated in neonates and young infants with platelet counts below 50,000/µL who are experiencing bleeding. The issue of prophylactic platelet transfusions in the newborn remains controversial. Bleeding is rare in older patients with thrombocytopenia unless the platelet count is less than 10,000/µL, but preterm neonates and infants with other complicating illnesses may bleed at higher platelet counts. Factors that may contribute to bleeding at higher platelet counts include: immaturity of the coagulation system; circulation of an anticoagulant that enhances inhibition of thrombin; intrinsic or extrinsic platelet dysfunction; and altered vascular elements that may increase vascular fragility. Of major concern is intraventricular hemorrhage, which occurs in up to 40% of preterm neonates in the first 72 hours. While prophylactic platelet transfusions increase platelet counts and shorten the bleeding time in these infants, the inci-
dence or extent of intraventricular hemorrhage are not reduced. After a platelet transfusion, a 1-hour posttransfusion platelet count can evaluate survival in the circulation, but may not predict hemostatic efficacy.

**Platelet Components**

A platelet unit prepared from a single donation of whole blood contains approximately $5.5 \times 10^{10}$ platelets and should raise the platelet count of an average full-term newborn by 50,000-100,000/µL if given in a dose of 5-10 mL/kg. The same dose taken as an aliquot from a unit of apheresis platelets will produce a similar increment. The platelet component should be group-specific, if possible, and should not contain clinically significant unexpected red cell antibodies. Transfusion of incompatible plasma is more dangerous in infants, with their very small blood volume, than in adults. If it is necessary to give a platelet unit of which the plasma is incompatible (due to antibodies in the ABO or other blood groups), plasma can be removed (see Method 9.13), and the platelets resuspended in saline or albumin. FFP can be administered if the patient requires clotting factors. Routine centrifugation of platelets to reduce the volume of transfusion is not necessary unless severe restriction of all intravenous fluids is required. When platelets have been volume-reduced and placed in a syringe, which is then laid in the isolette, the pH declines rapidly, a potential problem for an already ill, acidic patient.

**Granulocyte Transfusion**

Neonates are more susceptible than older children to severe bacterial infection due to both quantitative and qualitative defects of neutrophil function and, in the absence of pathogen-specific maternal antibody, to deficiency of humoral immunity. Group B streptococcus is the most frequent cause of early-onset neonatal sepsis and, despite improvement in antimicrobial therapy and intensive care, it is still associated with a high mortality rate. Controversy surrounds several issues in granulocyte transfusions for neonates, including dose, neutrophil level at which to transfuse, type of component to use, and efficacy as compared to other forms of therapy. There have been encouraging observations on the use of intravenous immunoglobulin (IVIG) in the treatment of early neonatal sepsis as well as preliminary studies of hematopoietic growth factors in the treatment of overwhelming bacterial infection in the newborn.

**Indications**

While the precise role of granulocyte transfusion for neonatal sepsis is unclear, certain clinical situations exist in which granulocyte transfusion may be considered as supplemental treatment to antibiotic therapy. Candidates for possible Granulocyte transfusion are infants with strong evidence of bacterial septicemia, an absolute neutrophil count below 3000/µL, and a diminished bone marrow storage pool, such that less than 7% of nucleated cells in the marrow are granulocytes at the stage of metamyelocytes or more mature forms. Once the decision is made to treat a septic newborn with granulocyte transfusion, the dose of granulocytes should be at an adequate level.

**Granulocyte Components**

The component of choice is a granulocyte concentrate harvested by standard apheresis techniques. Smaller quantities of granulocytes can be harvested, by gravity sedimentation or by an automated method, from the buffy coat of
units of freshly donated whole blood. However, the efficacy of buffy coat transfusions has not been proven. 42,43 The dose currently recommended is $1 \times 10^9$ neutrophils/kg body weight, in a volume of 15 mL/kg. 1,23 Because granulocyte concentrates contain large numbers of lymphocytes, many workers think it desirable to irradiate granulocyte concentrates for neonatal transfusion to prevent GVHD. For granulocyte transfusions to neonates, donors are usually selected who are CMV seronegative and ABO- and Rh-compatible with the infant.

Transfusion to Enhance Hemostasis

Serious bleeding may occur in the first week of life, especially in the sick premature infant, as a result of acquired disorders of hemostasis. Elements of the hemostatic system of the newborn are similar to those of older children and adults, but the concentration of many proteins is decreased. Coagulation factors do not cross the placenta, but are independently synthesized by the fetus, progressively increasing with gestational age. At birth, the infant's prothrombin time and partial thromboplastin time are prolonged, compared to times for children and adults, due to physiologically low levels of the vitamin K-dependent factors (II, VII, IX, and X), and contact factors (XI, XII, prekallikrein), and high-molecular-weight kininogen. 44 Proteins C and S and antithrombin inhibitors of coagulation are also at low levels. 44 These two systems usually balance each other, so that spontaneous bleeding and thrombosis in the healthy newborn are rare, but very little reserve capacity exists for responding to pathologic insults.

Neonates not only have physiologically low levels of the vitamin K-dependent factors; they also may become vitamin K-deficient during the first 2-5 days of life, placing them at risk of bleeding. Hemorrhagic disease of the newborn, as this has been referred to, is now rare because intramuscular vitamin K is routinely given at birth. If vitamin K therapy is omitted or especially if the neonate is breast fed, life-threatening hemorrhage may occur, which should be treated with FFP. 45

Although hereditary deficiencies of coagulation factors may be apparent in the newborn, significant bleeding is rare. Coagulopathy more often results from an acquired defect such as liver disease or DIC. Component replacement may temporarily correct the hemostatic problem, but lasting therapy must treat the underlying disease.

Newborns who are heterozygous for deficiencies of inhibitory proteins rarely experience complications in the absence of another pathologic insult. The homozygous form of protein C deficiency has, however, caused life-threatening thrombotic complications in the newborn period; initial treatment has included plasma infusions. 45

Fresh Frozen Plasma

Fresh frozen plasma is often used to replace coagulation factors in newborns, particularly if multiple factors are involved, such as in vitamin K deficiency. The usual dose is 10-15 mL/kg, which should increase factor activity by 10-20% unless there is marked consumptive coagulopathy. 45 As with red cell transfusions, there are several methods to provide small-volume FFP infusion with minimal donor exposure and wastage of components. Collection of blood into a multiple pack allows three or four aliquots to be prepared for freezing. Once thawed, these aliquots can be further divided and used for several patients within a 24-hour period. The FFP used must be ABO-compatible with the neonate and lack clinically significant unex-
expected antibodies. Group AB FFP is often used because a single unit provides aliquots that are compatible with the red cells of all recipients.

**Cryoprecipitate**

Cryoprecipitate is rich in fibrinogen and coagulation Factors VIII and XIII. This component is often used in conjunction with platelet transfusions to treat DIC in the newborn, especially when volume overload is a concern. In DIC, fibrinogen and platelets are the elements most often severely depleted. The plasma in which the platelets are suspended is a source of stable coagulation factors. Cryoprecipitate provides concentrated levels of fibrinogen and Factor VIII, which is also consumed readily in DIC. One 10-15 mL unit contains at least 80 units of Factor VIII and 150 mg of fibrinogen. A single unit, therefore, would be sufficient to achieve hemostatic levels in the newborn. As with FFP and platelets, the cryoprecipitate should be ABO-compatible with the recipient.

**Extracorporeal Membrane Oxygenation**

Extracorporeal membrane oxygenation (ECMO) is a modified cardiopulmonary bypass technique that has been used for short-term support for respiratory failure. The use of ECMO in patients other than neonates is not widespread. It is performed in specialized centers and only for patients in whom conventional medical therapy has failed and survival with aggressive therapy is limited. It is more successful in infants, whose small blood volume allows for total cardiorespiratory support, and whose primary respiratory problem often resolves after 1-2 weeks of support by ECMO. ECMO provides gas exchange independent of the patient’s lungs, allowing them time to improve or heal without exposure to aggressive ventilator support and the secondary lung damage this may cause.

ECMO is used most commonly for term or near-term infants with meconium aspiration, congenital diaphragmatic hernia, persistent pulmonary hypertension, pneumonia with sepsis, and hyaline membrane disease. Individual ECMO centers establish their own specific criteria for patient selection. Because systemic heparinization is necessary, ECMO is not used in patients with a significant coagulopathy or bleeding complications. The ECMO team should be in close communication with the blood bank or transfusion service staff and there should be mutual agreement on protocols to ensure consistency of care. Many infants requiring ECMO have been transferred from other hospitals, where they may already have received numerous transfusions. Personnel at the ECMO center should obtain a complete transfusion history from the referring hospital. It is often desirable to crossmatch the red cells used in the ECMO circuit because previous transfusions will have modified the infant’s initial serologic status. The amount of red cell, platelet, and FFP support required to maintain hematologic and hemodynamic equilibrium will vary depending on the clinical situation.

**Transfusion Practices in Older Infants and Children**

The indications for transfusion of red cells and other components in older infants (>4 months) and children are similar to those for adults, considering differences in blood volume and ability to tolerate blood loss, and age-appropriate hemoglobin and hematocrit levels. As in
adults, the most common indication for red cell transfusion in children is to
reverse or prevent tissue hypoxia resulting from decreased red cell mass. It
is important to remember that normal hemoglobin and hematocrit levels are
lower in children than adults. Pediatric patients may remain asymptomatic
despite extremely low levels of hemoglobin, if the anemia develops slowly,
such as may occur with iron deficiency anemia.

The decision to transfuse should be based not only on the hemoglobin level
but also on the presence or absence of symptoms, the functional capacity of the
child, the etiology of the anemia, the possibility of using alternative therapies,
and the presence or absence of additional clinical conditions that increase
the risk for developing hypoxia. If small-volume transfusions are required, many
of the methods described in the discussion of neonates can be applied.

Hemoglobin Disorders

In certain childhood conditions, chronic red cell transfusions are given not only
to treat tissue hypoxia but to suppress endogenous hemoglobin production.

Sickle Cell Diseases

Approximately 6-10% of children with sickle cell disease suffer a stroke; two-
thirds of these children experience recurrent stroke in the absence of transfu-
sion therapy. The goal of transfusion is to reduce the percentage of circulating red
cells capable of sickling, without altering blood viscosity. The rate of recur-
rent stroke has been reduced to 0-10% by maintaining a pretransfusion hemoglo-
bin level of 8-9 g/dL with a hemoglobin S level less than 30%, in children
who have had a cerebrovascular accident. This can usually be achieved with
a simple or partial exchange transfusion every 3-4 weeks. There are no definite
criteria for when it is safe to discontinue transfusion therapy; therefore, it is often
continued indefinitely. Because of concern about iron overload, some workers
follow several uneventful years of transfusions to keep hemoglobin S below 30%
with a less aggressive protocol that maintains hemoglobin S between 40% and 50%.

Red cell transfusions are used to treat acute complications associated with the
sickle cell diseases, such as splenic sequestration, aplastic crisis, overwhelming pneumonia, or pulmonary in-
farction. An area that remains unresolved is the necessity of preopera-
tive transfusion and the optimal levels of total hemoglobin and hemoglobin S that
should be achieved in preparation for inhalation anesthesia.

Thalassemias

Transfusions are given to children with severe anemia due to thalassemia, not
only to improve tissue oxygenation but to suppress erythropoiesis, because the characteristically brisk, ineffective
erthropoiesis causes many of the comp-
llications associated with thalassemia.

Hypertransfusion protocols maintain a minimum pretransfusion hemoglobin
concentration between 8 and 9 g/dL, which allows normal growth and devel-

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Antibody Production

The frequency of red cell alloimmunization in chronically transfused children varies with the disease, the number of transfusions given, and the ethnic background of donors and recipients. Antibodies to the common antigens of the Rh, Kell, Duffy, and Kidd systems are often involved. It may be desirable, therefore, to phenotype the patient’s red cell antigens as completely as possible before beginning transfusion therapy, and maintain a permanent record of the results. This can be helpful in selecting compatible blood if alloimmunization occurs. The practice of transfusing only phenotypically matched units is controversial. In patients who have already become immunized and are at high risk of developing additional antibodies, use of phenotypically matched units may be a reasonable approach. Leukocyte-reduced blood components should be considered for these chronically transfused patients, to diminish development of alloimmunization to HLA antigens and prevent febrile transfusion reactions.

Platelets and Plasma

The indications for FFP and platelet transfusions in older infants and children parallel those for adults. Platelet transfusions are most often given as prophylaxis to children receiving chemotherapy. Prophylactic platelet transfusions are seldom given when platelet counts are above 20,000/µL, but as for red cell transfusion, the threshold for platelet transfusion should not simply be number of platelets. When such risk factors as fever, sepsis, DIC, or other severe clotting abnormalities are present, the level may need to be raised; in the absence of such factors a much lower level may be appropriate.

References


