Pathophysiology, Diagnosis, and Prevention of Neonatal Anemia
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John A. Widness, MD*

OBJECTIVES
After completing this article, readers should be able to:

1. Describe the best methods of evaluating neonatal anemia.
2. Delineate the most important mechanism of anemia among critically ill term and preterm infants.
3. List the mechanisms of anemia of prematurity.
4. Describe how safe and efficacious criteria for blood transfusion are established.
5. Describe the role of clinical and laboratory postdischarge evaluation with regard to neonatal anemia.

Causes of Neonatal Anemia
Evaluating the etiology of neonatal anemia can be a daunting task. The numerous and diverse causes of this condition can be grouped into three broad pathogenetic categories: 1) decreased erythrocyte production, 2) increased erythrocyte destruction, and 3) blood loss (Table 1). The importance of obtaining a complete and accurate history and performing a physical examination for diagnosing anemia cannot be overemphasized. In particular, the infant’s family history and the mother’s obstetric history often are of critical importance in narrowing down the etiologic possibilities.

The decision of whether a particular hemoglobin (Hb) value is sufficiently low to meet the criteria for neonatal anemia must be based on the infant’s birthweight, postnatal age, and the site of blood sampling. Failure to consider these factors adequately can lead to errors in diagnosis and unnecessary laboratory tests. At birth and for the first 2 to 3 months of life, healthy preterm infants have lower Hb levels than term infants. Normative data for postnatal Hb levels are readily available in standard neonatology and pediatric textbooks. Values below two standard deviations of the mean are diagnostic of anemia. It is also important to appreciate that Hb determinations performed on capillary blood samples, especially in the first days of life, are higher than those obtained from venous or arterial samples because of red blood cell (RBC) sludging in low-flow capillaries with resultant transudation of plasma.

At any age, the presence of anemia may provide an important indication of a specific underlying disease process in need of immediate attention. When recognized immediately after birth, the diagnosis and treatment of anemia is a matter of urgency. There is one circumstance where transfusion is indicated without regard to the Hb concentration—the occurrence of acute, severe, life-threatening hemorrhage. The diagnosis of acute blood loss should be considered immediately in a pale infant who shows signs of acute hypovolemic shock. Rapid replacement of the intravascular volume—even before a Hb level is determined—can be lifesaving. Under these circumstances, diagnostic considerations include fetal-to-maternal hemorrhage, twin-to-twin transfusion, fetal or placental hemorrhage (often iatrogenic), rupture of the umbilical cord or other placental vessels, and internal hemorrhage. At delivery, the placenta should be examined for evidence of hemorrhage, pallor, and abnormally inserted blood vessels that may have been torn in the delivery process. Although usually indicative of maternal hemorrhage, maternal vaginal bleeding may result from torn fetal placental or umbilical vessels and lead to sudden, massive fetal blood loss.

An important initial consideration in the evaluation of anemia is whether it can be explained solely by iatrogenic laboratory testing (see next section). If this can be excluded and the cause of anemia remains uncertain, a systematic laboratory evaluation usually leads to the correct diagnosis (Fig. 1). The initial laboratory evaluation of anemia includes a complete blood count with red blood cell indices and peripheral blood smear, a reticulocyte count, RBC antibody by direct antiglobulin test and RBC antibody screen, and measurement of serum or plasma bilirubin. Additional neonatal blood testing may be helpful in identifying specific diagnoses, such as serologic tests to identify viral infection, blood cultures to identify bacterial and fungal infections, plasma ferritin to define iron status, blood smears and special stains for Heinz bodies and for nonimmune hemolytic anemias, and quantitative assays for specific erythrocyte enzyme deficiencies. Kleihauer-Betke testing of maternal blood can provide quantitative evidence of fetal-to-maternal hemorrhage.

Laboratory Blood Loss and Neonatal Anemia
An estimated 60% to 80% of very low-birthweight (VLBW) infants (ie, those whose birthweights are <1,200 g) currently receive one or more RBC transfusions prior to hospital discharge as treatment for clini-
TABLE 1. Pathophysiologic Classification of Neonatal Anemia

<table>
<thead>
<tr>
<th>Decreased Erythrocyte Production</th>
<th>Increased Erythrocyte Destruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow failure syndromes</td>
<td>Immune hemolytic anemia</td>
</tr>
<tr>
<td>—Erythroid cell line only—eg, congenital red cell aplasia (Diamond-Blackfan anemia), transient erythrocytopenia of childhood, congenital dyserythropoietic anemias</td>
<td>—Rh, ABO, or minor group incompatibility</td>
</tr>
<tr>
<td>—Pancytopenias—eg, reticulocytosis, refractory sideroblastosis syndrome (“Pearson syndrome”), Fanconi anemia</td>
<td>—Maternal infantile autoimmune hemolytic anemia, including those associated with maternal collagen-vascular diseases</td>
</tr>
<tr>
<td>Infection</td>
<td>Drug-induced hemolytic anemia—eg, penicillin, cephalothin, alpha-methylidopa, valproic acid</td>
</tr>
<tr>
<td>—Acquired bacterial or viral sepsis</td>
<td>—Vitamin E deficiency, particularly in the presence of oxidants—eg, iron</td>
</tr>
<tr>
<td>—Congenital viral—eg, rubella, parvovirus</td>
<td>—Red cell membrane disorders</td>
</tr>
<tr>
<td>Nutritional deficiencies—eg, protein, iron, folate, B₁₂</td>
<td>Hereditary spherocytosis</td>
</tr>
<tr>
<td>Transcobalamin II deficiency</td>
<td>Hereditary elliptocytosis</td>
</tr>
<tr>
<td>Congenital leukemia</td>
<td>Other rare hereditary disorders—eg, stomatocytosis, pyropoikilocytosis</td>
</tr>
</tbody>
</table>

Blood Loss
- Iatrogenic blood loss due to laboratory testing
- Obstetric accidents—eg, traumatic bleeding into umbilical cord, placenta, or amniotic fluid due to cordocentesis or amniocentesis; rupture of umbilical cord; surgical incision through the placenta at cesarean section; tight nuchal cord; prolonged positioning of the infant above placenta after birth but before clamping cord
- Malformations of the placenta or cord—eg, velamentous insertion of the umbilical cord, vasa previa rupture
- Occult hemorrhage prior to birth or during delivery
  —Fetal-to-maternal
  —Twin-to-twin (only with monozygotic, monochorionic twinning)
- Internal hemorrhage (including due to trauma or clotting disorders)—eg, intracranial, intrahepatic, cephalohematoma, subgaleal hemorrhage
- Diffuse intravascular coagulation with external or internal blood loss
NEONATAL ANEMIA
Pathophysiology and Diagnosis

Even in the absence of iatrogenic laboratory phlebotomy loss, preterm infants experience more rapid and severe decreases in Hb levels than term infants (often to 7 to 8 g/dL), with the lowest levels observed among the smallest, least mature infants. It is a physiologic condition that does not result in signs of illness and does not require any treatment. Evidence suggesting laboratory phlebotomy loss as an important contributor to neonatal anemia is the close relationship reported between the blood removed for laboratory testing and the volume of blood transfused. Estimates of laboratory phlebotomy loss among infants in the neonatal intensive care unit (NICU) during the first 6 weeks of life range from 11 to 22 mL/kg per week, with nearly identical volumes of packed RBCs transfused over these same time periods (Table 2). In these and other studies, highly significant direct correlations have been observed between the volume of blood removed and that transfused (ie, correlation coefficients of 0.8 to 0.9). Because hidden blood loss (eg, blood adherent to sampling syringes, gauze pads, bedding, tubing) is inevitable and because accurate assessment of the volume of blood removed for laboratory testing is imprecise, reported data may have underestimated laboratory losses by 10% to 30%.

A reduction in iatrogenic blood loss for laboratory testing almost certainly would decrease the need for RBC transfusions among critically ill neonates. There are several approaches to address this issue. One is to limit testing to only those blood tests absolutely necessary. Although convincing evidence for the success of this approach has yet to be documented, this may be an important explanation for the seemingly lower RBC transfusion needs of VLBW infants in several European centers. An alternative approach is to reduce the sample volume required by laboratory instruments. Recent improvements in the miniaturization of biosensing devices and computerization have led to the development and implementation of point-of-care testing devices that are capable of performing laboratory measurements accurately and reliably on ever smaller blood volumes with a rapid turnaround time and less preanalytic error. Most recently, in vivo and ex vivo point-of-care monitors attached to intravascular catheters have been shown to operate with blood loss that is one order of magnitude less than that needed for benchtop analyzers and 50% of that with near patient point-of-care analyzers.

Pathophysiology of Anemia of Prematurity

In the 8- to 10-week period immediately following birth, there is a gradual and progressive decline in Hb concentration in both term and preterm infants. In term infants, the decline reaches a nadir of approximately 11 to 12 g/dL (6.82 to 7.44 mmol/L) and is referred to as early anemia. This normal process does not result in signs of illness and does not require any treatment. It is a physiologic condition believed to be related to several factors, foremost of which may be the increase in tissue oxygenation experienced at birth when switching from dependency on the placenta to dependency on the lungs for oxygen exchange. This transition occurs in the context of a lower tissue oxygenation set point for fetuses relative to adults (ie, a lower responsiveness to hypoxia). Other factors thought to contribute to the postnatal decline in Hb include rapid body growth, shortened RBC lifespan, and low blood erythropoietin (EPO) levels.

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Prematurity (neonatal anemia) is merely an exaggerated, albeit physiologic, form of the early anemia observed among term infants or a pathologic condition (eg, inadequate protein, iron, and vitamin intakes). Likely the anemia of prematurity represents several mechanisms occurring simultaneously, with some being physiologic and others pathologic. Some preterm infants seem to tolerate Hb levels of 6 to 7 g/dL (3.72 to 4.34 mmol/L) without apparent difficulty; others do not. Because the consequences of anemia on tissue oxygenation are so diverse, it can be difficult to document such effects definitively as pathologic. Some studies have reported that Hb levels of 6 to 8 g/dL (3.72 to 4.96 mmol/L) in preterm infants are associated with reduced weight gain, apnea, pathologically increased heart and respiratory rates, and increased oxygen consumption, but this has not been confirmed in other studies. Definitively determining whether anemia of prematurity is a pathologic process is confounded further by the complicated hospital course that critically ill, immature infants experience as a result of lung disease, infection, and other common neonatal morbidities. Thus, it is not surprising that considerable controversy surrounds the need to treat neonatal anemia with RBC transfusions (see next section).

With the approval of recombinant human EPO (r-HuEPO) for the treatment of adults who have anemia due to chronic renal insufficiency in the late 1980s came intense interest in using r-HuEPO to prevent and treat anemia of prematurity. Although both chronic renal disease in adults and anemia in preterm infants are associated with low plasma EPO levels, the mechanism for the low EPO levels may differ. Low levels in adults who have chronic renal disease likely reflect pathologically low endogenous EPO production. In contrast, low plasma EPO levels in infants may reflect three- to fourfold greater EPO clearance rates in infants relative to adults, despite increased endogenous EPO production rates. Because of its nonlinear pharmacokinetic behavior, accurate quantitative determinations of EPO production rates are assessed best in studies in which tracer doses of labeled r-HuEPO are administered. Unfortunately, no non-radiolabeled r-HuEPO tracers are available for this purpose. Thus, the issue of whether EPO production is pathologically low in neonates has yet to be resolved unequivocally.

In considering the potential efficacy of r-HuEPO for correcting anemia of prematurity, it is important to recognize that the low EPO plasma levels manifested by healthy and anemic infants also are observed in normal and anemic human fetuses. This finding is consistent with rapid clearance of EPO in the fetus, and it suggests that factors other than EPO (eg, specific nutrients and hormones) are important in facilitating the 25% rise in Hb levels experienced by healthy fetuses from 18 to 40 weeks’ gestation. During the second half of pregnancy, the healthy fetus’ daily rate of RBC production is approximately six times that of maximally stimulated erythropoiesis in adults, but it still is less than that

<table>
<thead>
<tr>
<th>INVESTIGATORS</th>
<th>NO. OF INFANTS</th>
<th>GROUP STUDIED</th>
<th>POSTNATAL AGE (wk)</th>
<th>MEAN BIRTH-WEIGHT (g)</th>
<th>WEEKLY PHLEBOTOMY LOSS (mL/kg*)</th>
<th>WEEKLY TRANSFUSION VOLUME (mL/kg*)</th>
<th>CORRELATION COEFFICIENT (r†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kakaiya et al (1979)</td>
<td>18</td>
<td>All NICU infants</td>
<td>Birth to 1.1 wk</td>
<td>1,822</td>
<td>21.7</td>
<td>12.3</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blanchette and Zipursky (1984)</td>
<td>57</td>
<td>Infants &lt;1,500 g</td>
<td>Birth to 6 wk</td>
<td>Not reported</td>
<td>11.1</td>
<td>6.7</td>
<td>0.82</td>
</tr>
<tr>
<td>Obladen et al (1988)</td>
<td>60</td>
<td>Infants &lt;1,500 g</td>
<td>Birth to 4 wk</td>
<td>1,161</td>
<td>12.7</td>
<td>10.6</td>
<td>0.91</td>
</tr>
<tr>
<td>Ringer et al (1998)</td>
<td>270</td>
<td>Hospital A: Infants &lt;1,500 g</td>
<td>Birth to 2 wk</td>
<td>1,073</td>
<td>8.2</td>
<td>15.7</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hospital B: Infants &lt;1,500 g</td>
<td></td>
<td></td>
<td></td>
<td>978</td>
<td>21.4</td>
<td>16.8</td>
<td>Not reported</td>
</tr>
<tr>
<td>Alagappan et al (1998)</td>
<td>80</td>
<td>Infants &lt;1,250 g</td>
<td>Birth to 2 wk</td>
<td>948</td>
<td>20.7</td>
<td>21.7</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mean</td>
<td>1,196</td>
<td>15.9</td>
<td>14.0</td>
<td>0.87</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>360</td>
<td>6.0</td>
<td>5.2</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on birthweight.
†Phlebotomy versus transfusion.
NICU = neonatal intensive care unit.
attributed to iatrogenic laboratory phlebotomy loss experienced by critically ill preterm infants.

There is increasing recognition that inadequate protein intake is an important contributor to anemia in preterm infants. This has been documented in VLBW infants treated with or without r-HuEPO, although protein supplementation appears to assume even greater importance among r-HuEPO-treated infants than among those not treated with it. Rönnholm and Siimes were the first to demonstrate that the "normal" postnatal fall in Hb levels can be attenuated by 1.0 to 1.5 g/dL (0.62 to 0.93 mmol/L) in VLBW infants receiving 3.5 to 3.6 g/kg of protein per day compared with those receiving only 1.8 to 1.9 g/kg per day (Fig. 2). The implication is that the lower protein intakes are inadequate for optimal production of EPO and RBCs. These and other data indicate that the amount of protein intake needed for optimal body growth is related to body size and the level of maturity, with the smallest infants requiring the greatest daily protein intakes per kilogram of body weight (Table 3).

FIGURE 2. The effect of human protein milk supplementation on hemoglobin levels in VLBW infants treated with 3.5 to 3.6 g/kg per day of protein (closed circles) compared with infants treated with 1.8 to 1.9 g/kg per day of protein (open circles). Reprinted with permission from Rönnholm and Siimes, 1985.

Transfusions for Neonatal Anemia

USE OF CLINICAL SIGNS AS A TRIGGER

The fundamental basis for erythrocyte transfusion is a decrease in oxygen transport capacity to the extent that cardiorespiratory status becomes impaired. Although the risks associated with RBC transfusion are well described, far less is known about the benefits of transfusing anemic infants at specific Hb levels or infants who exhibit a variety of signs and symptoms believed to be related causally to neonatal anemia. Because of this uncertainty, neonatal transfusion practices have varied widely over time and place.

The establishment of sound, experimentally based criteria to guide decisions for administering RBC transfusions to anemic infants is an important, unmet need. Although a growing body of literature indicates that moderately low levels of Hb (ie, 7 to 9 g/dL [4.34 to 5.58 mmol/L]) are well tolerated in critically ill adults, sound scientific studies have yet to be reported in neonates. Nonetheless, increasingly restrictive transfusion criteria are being reported in many, if not most, neonatal centers in North America. Not surprisingly, this change in practice has been associated with declining numbers of RBC transfusions being administered to VLBW infants.

UNCERTAINTY IN TRANSFUSION TARGET

Safety, efficacy, and cost-related issues must be considered when deciding on an appropriate post-transfusion Hb target. What is too high a level for infants of different gestational ages and different clinical conditions with respect to past and present oxygenation and type of feeding to avoid developing polycythemia/hyperviscosity complications such as necrotizing enterocolitis? What is too low a level to avoid the risks and costs of too frequent repeated transfusions? Although not typical, consideration of transfusing to a specified Hb level would seem more appropriate than transfusing a specified volume if this can be achieved without jeopardizing the infant’s acute cardiovascular status. Infants who experience late cord clamping tolerate placental transfusions of one third to one half their blood volume at birth without apparent adverse effects.

One small study of infants who had gestational ages of 28 to 32 weeks demonstrated a benefit to delaying cord clamping for more than 30 seconds while the infant was held 20 cm below the level of the placenta.

SUGGESTED TRANSFUSION CRITERIA

Guidelines similar to those recommended by the American College of Pathologists have been adopted by a number of nurseries in North America (Table 4). These transfusion criteria are among the most restrictive recommended by any professional group and represent a marked departure from practices in North America in the past as well as in other countries. Results of recent long-term neurodevelopmental outcome studies of severe immune-mediated fetal anemia are reassuring, but the important issue of long-term developmental outcomes of neonatal anemia has not been studied.

Although determination of a transfusion trigger that can be applied to newborns is a formidable task, a number of parameters have been suggested. These include blood lactate, plasma EPO, total body RBC mass, gut pH, Pco2 by tonometry, and peripheral mixed venous oxygen saturation by near-infrared spectroscopy. The failure of previous efforts to demonstrate conclusively the merit of some of these parameters (eg, blood lactate and plasma EPO) as clinically useful indicators of the need for RBC transfusion could be the result of studying infants who are only modestly anemic and in whom tissue oxygenation is adequate. To avoid overzealous reductions in neonatal RBC transfusion criteria, careful
clinical and preclinical studies are needed to establish safe and efficacious standards. The merits of evolving restrictive RBC transfusion practices have yet to be documented.

**Postdischarge Care of Anemic Infants**

**ANEMIA OF PREMATURITY**

Although anemia of prematurity is by far the most prevalent anemia encountered at discharge, it is usually not a problem of major clinical significance. Recent studies indicate that all but the sickest, most immature infants are discharged at postconceptional ages ranging from 35 to 37 weeks. Applying the RBC transfusion criteria presently used in many nurseries in North America for infants who have anemia of prematurity and are free of clinical signs of anemia (i.e., a hematocrit >0.20 [≥20%] or Hb >7.0 g/dL [≥4.34 mmol/L]), simple “top-up” transfusions are necessary only rarely at or near the time of discharge.

Hb levels in most infants who have anemia of prematurity have reached their nadir and are rising by the time discharge is considered. For those few infants whose Hb levels have not yet begun to rise, weekly evaluation of the infant’s clinical condition and Hb levels until the expected rise in Hb levels occurs is prudent. In these situations, reticulocyte counts are highly informative in predicting when a sustained rise in Hb levels is imminent (Fig. 3). If the infant has been treated with r-HuEPO, this therapy should be discontinued 1 or more weeks prior to discharge. Such cessation has not been shown to exacerbate clinically significant anemia among VLBW infants who do not have renal disease. Postdischarge cardiorespiratory monitoring of infants who have only anemia of prematurity is not indicated.

**IMMUNE HEMOLYTIC ANEMIA**

Infants who have immune hemolytic disease should be followed at regular intervals after discharge. Clinically significant anemia may persist in this group of predominantly term infants for up to 2 to 3 months following birth, with an occasional infant remaining anemic for up to 5 months. Anemia in this group can become so severe that congestive heart failure occurs. This condition

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**TABLE 3. Protein Accretion, Loss, and Suggested Intake for Low-birthweight Infants**

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Tissue Protein Accretion (g/d)</th>
<th>Protein Loss via Urine and Skin (g/d)</th>
<th>Suggested Protein Intake (g/kg per day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>700 TO 1,000 g</td>
<td>1.8</td>
<td>0.9</td>
<td>4.0</td>
</tr>
<tr>
<td>1,000 TO 1,500 g</td>
<td>2.5</td>
<td>1.4</td>
<td>3.8</td>
</tr>
<tr>
<td>1,500 TO 2,000 g</td>
<td>3.3</td>
<td>1.9</td>
<td>3.5</td>
</tr>
<tr>
<td>2,000 TO 2,700 g</td>
<td>4.1</td>
<td>2.6</td>
<td>3.2</td>
</tr>
</tbody>
</table>

*Based on estimated gastrointestinal protein absorption of 80% to 90%.

Modified from Ziegler EE, 1994, with permission.


- Hematocrit ≤0.20 (≤20%) or hemoglobin ≤7 g/dL (≤4.34 mmol/L) and reticulocyte count <4% (or absolute reticulocyte count <100,000/mcL).

- Hematocrit ≤0.25 (≤25%) or hemoglobin ≤8 g/dL (≤4.96 mmol/L) and any of the following conditions:
  - Apnea/bradycardia ≥10 episodes/24 h or ≥2 episodes requiring bag-mask ventilation
  - Sustained tachycardia >180 beats/min or sustained tachypnea >80 breaths/min over 24 h by averaging 4 h measurements
  - Cessation of adequate weight gain × 4 days (≤10 g/d despite ≥420 kJ/kg per day)
  - Mild RDS with FiO₂ 0.25 to 0.35 or nasal cannula ≤ 8 cm H₂O
  - Cessation of adequate weight gain ≥ 3 days (≤10 g/d despite ≥420 kJ/kg per day)

- Hematocrit ≤0.30 (≤30%) or hemoglobin ≤10 g/dL (≤6.2 mmol/L) with moderate RDS + FiO₂ >35 or nasal cannula O₂ or intermittent mandatory ventilation with Psw 6 to 8 cm H₂O

- Acute blood loss with shock: blood replacement to re-establish adequate blood volume and hematocrit of 0.40 (40%) without other indications.

- Do not transfuse to replace blood removed for laboratory tests or low hematocrit alone unless above criteria are met.

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identifying a suitably cross-matched donor may be difficult, it is essential. To increase the interval between transfusions and thereby minimize the number of transfusions administered, post-transfusion Hb levels should be increased to 8.06 to 8.68 mmol/L (13 to 14 g/dL). This may necessitate administration of several 10 to 20 mL/kg transfusions several hours apart. The use of r-HuEPO to treat anemia resulting from immune hemolytic disease cannot be recommended at present because there are no adequately powered, masked, controlled trials to support treatment of a condition whose mechanism appears to be unrelated to decreased EPO production.

PREVENTION OF LATE NUTRITIONAL ANEMIA

Both term and preterm infants should be discharged from the hospital on supplemental iron, either as iron-fortified formulas or as an oral supplement of 2 to 3 mg/kg per day elemental iron for breastfed infants. These supplements should be continued for the first year of life. Although only limited supportive data are available, it appears to be prudent to screen for iron deficiency between 6 and 12 months of age by measuring Hb concentration. Because of their small size, limited iron endowment at birth, and rapid rate of growth, iron deficiency (ie, ferritin levels <12 mcg/L) is common among preterm infants in the first year of life. This is particularly true for breastfed VLBW infants.

Because of their limited body supplies of the water-soluble vitamins and higher protein requirements, it is also prudent to supplement breastfed preterm infants at discharge with a multivitamin supplement containing B₁₂ and folate.

PERSISTENT HEMOLYTIC AND HYPOPLASTIC ANEMIAS

For the minority of infants discharged with diagnoses other than anemia of prematurity or immune hemolytic anemia, follow-up and treatment should be directed at the underlying cause of the anemia. This includes the occasional infant whose anemia is due to persistent, ongoing underproduction of erythrocytes or hemolysis. These infants should be comanaged by a pediatric hematologist and a pediatrician or family practitioner.

FIGURE 3. Relationship of hemoglobin to reticulocyte index (Hb in g/dL x reticulocyte count in percent) during the first 12 weeks of life. The shaded region represents the reticulocyte index for 60 untransfused infants whose birthweights were 800 to 1,500 g. The filled circles represent values observed in 12 infants who had similar birthweights and received exchange transfusions at birth for nonhemolytic anemia. Reprinted with permission from Oski FA, Stockman JA III. Anemia in early infancy. Br J Haematol. 1974;27:193–200.

almost certainly is due to the persistence of maternal anterythrocyte antibody in the infant’s circulation, leading to continued hemolysis, as indicated by modestly elevated plasma bilirubin levels and the persistence of anemia. Hb levels, reticulocyte counts, and clinical signs of anemia (eg, fatigue with feedings, a fall in weight gain, tachycardia, tachypnea) should be monitored at least weekly until laboratory indicators improve. As with anemia of prematurity, an increase in reticulocyte count is the first indicator that anemia is nearing resolution. Consultation with a pediatric hematologist is advisable if anemia does not follow the expected course.

The mainstay of treatment for symptomatic anemia due to immune hemolytic disease prior to and following discharge consists of allogeneic RBC transfusion. Although...
1. A 4-day-old infant, whose birth-weight was 1,100 g and estimated gestational age at birth was 31 weeks, is being ventilated with a fraction of inspired oxygen of 0.40, mean airway pressure of 6 cm H₂O, and ventilator rate of 12 breaths/min. She has a soft systolic murmur, blood pressure of 42/28 mm Hg, and resting heart rate of 148 beats/min. Her arterial blood gas values are: PaO₂, 68 mm Hg; PaCO₂, 42 mm Hg; and pH, 7.36. Her central hematocrit is 0.28 (28%). Of the following, the most appropriate plan of management is to:

A. Administer intravenous indomethacin.
B. Infuse plasma expander.
C. Instill intratracheal surfactant.
D. Provide recombinant erythropoietin.
E. Transfuse packed red blood cells.
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