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How I transfuse red blood cells and platelets to infants with the anemia and thrombocytopenia of prematurity

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Abstract

Many aspects of hematopoiesis are either incompletely developed in preterm infants or still functioning to serve the fetus (i.e., the intrauterine counterpart to a liveborn preterm neonate). This delayed development and/or slow adaptation to extrauterine life diminishes the capacity of the neonate to produce red blood cells (RBCs), platelets (PLTs), and neutrophils—particularly during the stress of life-threatening illnesses encountered after preterm birth such as sepsis, severe pulmonary dysfunction, necrotizing enterocolitis, and immune cytopenias. The serious medical and/or surgical problems of preterm birth can be further complicated by phlebotomy blood losses, bleeding, hemolysis, and consumptive coagulopathy. To illustrate, some preterm infants, especially those with birth weight less than 1.0 kg and respiratory distress, are given numerous RBC transfusions early in life owing to several interacting factors. Neonates delivered before 28 weeks of gestation (birth weight, <1.0 kg) are born before the bulk of iron transport has occurred from mother to fetus via the placenta and before the onset of marked erythropoietic activity of fetal marrow during the third trimester. Soon after preterm birth, severe respiratory disease can lead to repeated blood sampling for laboratory studies and, consequently, to replacement RBC transfusions. Additionally, preterm infants are unable to mount an effective erythropoietin (EPO) response to decreasing numbers of RBCs, and this factor contributes to the diminished ability to compensate for anemia—thus enhancing need for RBC transfusions.

PATHOPHYSIOLOGY OF ANEMIA OF PREMATURITY

During the first weeks of life, all infants experience a decline in the number of circulating RBCs. In healthy term infants, the nadir blood hemoglobin (Hb) value rarely decreases to less than 9 g per dL (mean, 11–12 g/dL) at an age of approximately 10 to 12 weeks.[1] Because this postnatal decrease in Hb level is universal and is well tolerated by term infants, it is commonly called the physiologic anemia of infancy. Among preterm infants, this decline occurs at an earlier age and is more pronounced in severity. Mean Hb concentration decreases to approximately 8 g per dL in infants of 1.0 to 1.5 kg birth weight and to 7 g per dL in infants weighing less than 1.0 kg.2 This marked decline in Hb frequently is exacerbated by phlebotomy blood losses and may be associated with symptomatic anemia that necessitates RBC transfusions—making the anemia of prematurity an illness rather than a “physiologic” event.

Physiologic factors that influence erythropoiesis and the biologic characteristics of EPO are critical in the pathogenesis of the anemia of prematurity. Growth is extremely rapid during the first weeks of life, and RBC production by neonatal marrow must increase commensurately to avoid a decreasing hematocrit (Hct) caused by an insufficient number of circulating RBCs being diluted within the expanding blood volume. It is widely accepted that the circulating life

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span of neonatal RBCs in the bloodstream is shorter than that of adult RBCs—although the precision of measuring RBC survival in an infant with rapid growth is problematic. Another clinical factor is the need for repeated blood sampling to monitor the condition of critically ill neonates. Small preterm infants are the most critically ill, require the most frequent blood sampling, and suffer the greatest proportional loss of RBCs because their circulating RBC volumes are smallest. Promising "in-line" devices that withdraw blood, measure multiple analytes, and then reinfuse the sampled blood have been reported to decrease RBC transfusions.[3,4] Until these devices are proven more extensively to be practical, effective, and safe, however, replacement of blood losses due to phlebotomy will remain a critical factor responsible for RBC transfusions given to critically ill neonates.

A key reason that the nadir Hb values of preterm infants are lower than those of term infants is that preterm infants have a relatively diminished EPO plasma level in response to anemia.[5] Although anemia provokes EPO production in premature infants, the plasma levels achieved in anemic infants, at any given Hct, are lower than those observed in comparably anemic older persons.[6] Erythroid progenitor cells of preterm infants are quite responsive to EPO in vitro—suggesting that inadequate production EPO is the major cause of physiological anemia, not marrow unresponsiveness.[7]

The mechanisms responsible for the diminished EPO plasma levels in preterm neonates are only partially defined and, likely, are multiple. One mechanism is that the primary site of EPO production in preterm infants is in the liver, rather than kidney.[8] This dependency on hepatic EPO is important because the liver is less sensitive to anemia and tissue hypoxia—hence, a relatively sluggish EPO response to the decreasing Hct. The timing of the switch from liver to kidney is set at conception and is not accelerated by preterm birth. The decreased hepatic production of EPO under in utero conditions of tissue hypoxia may be an advantage for the fetus to prevent very high levels of EPO that could lead to erythrocytosis and, consequently, hyperviscosity. After birth, however, diminished EPO responsiveness to tissue hypoxia is disadvantageous for the neonate and leads to anemia because it impairs compensation for low Hct levels caused by rapid growth and RBC losses due to phlebotomy, clinical bleeding, hemolysis, and so forth.

Diminished EPO production cannot entirely explain low plasma EPO levels in preterm infants because extraordinarily high plasma levels of EPO have been reported in some fetuses and infants.[9,10] Moreover, macrophages from human cord blood produce normal quantities of EPO messenger RNA and protein.[11] Thus, additional mechanisms contribute to diminished EPO plasma levels. For example, plasma levels of EPO are influenced by metabolism (clearance) as well as by production. Data in human infants[12] have demonstrated low plasma EPO levels due to increased plasma clearance, increased volume of distribution, more rapid fractional elimination, and shorter mean plasma residence times than comparative values in adults. Thus, accelerated catabolism accentuates the problem of diminished EPO production, so that the low plasma EPO levels are a combined effect of decreased synthesis plus increased metabolism.

RBC TRANSFUSIONS FOR THE ANEMIA OF PREMATURITY

RBC transfusions are given to maintain the Hct at a level judged best for the clinical condition of the infant.[13] General guidelines acceptable to most neonatologists are listed in Table 1. Many aspects of neonatal RBC transfusion therapy are controversial, however, and vary from center to center. This lack of consistency stems from incomplete knowledge of the cellular and molecular biology of erythropoiesis during the perinatal period, of the pathophysiologic effects of neonatal anemia, and of the infant's response to RBC transfusions. Although well-designed clinical trials have been reported,[14,15] they are not mutually supportive and questions remain.

Therefore, it is important that physicians critically evaluate the guidelines in Table 1 and apply and/or adjust them in light of neonatal practice at their respective institutions.

An important current controversy is the wisdom—or lack thereof—of prescribing RBC transfusions to neonates with restrictive guidelines (i.e., low pretransfusion Hct values) versus liberal guidelines (i.e., conventional, relatively high pretransfusion Hct values). Two randomized, controlled trials have been published[14,15] and, although many of their results agree, they disagree in one extremely important way—specifically, whether preterm infants are at increased risk of brain injury when given RBC transfusions per restrictive guidelines (i.e., due to undertransfusion). In both trials, preterm infants were randomly allocated to receive all small-volume RBC transfusions per either restrictive or liberal guidelines—with guidelines based on a combination of the pretransfusion Hct or Hb level, age of the neonate, and clinical condition at the time each transfusion was given. Both studies found that neonates in the restrictive transfusions group received fewer RBC transfusions, without an increase in mortality or in morbidity based on several clinical outcomes. One critical discrepancy was present, however. Bell and coworkers[14] found increases in apnea, intraventricular bleeding, and brain leukomalacia in infants transfused per restrictive guidelines, whereas Kirpalani and colleagues[15] found no differences between infants in the restrictive versus liberal groups. Rates of serious outcomes were fairly high in both groups of the Kirpalani study, however,—perhaps, due to the extreme prematurity of the infants—making it difficult to detect possible differences. Moreover, because neonates in the liberal RBC transfusion group of Bell and colleagues had substantially higher blood Hct and/or Hb levels than neonates in the liberal group of Kirpalani and colleagues (a mean of 6 Hct points or 2 g/dL Hb higher), it is reasonable to speculate that the higher blood Hct levels, in some way, protected liberally transfused infants in the study by Bell.[14,15] These studies have been critically analyzed with the recommendation that until more information is available, it seems wise to transfuse preterm neonates with conventional, relatively liberal guidelines (i.e., do not place infants at possible risks of under transfusion by strict conservative practices).[16]

Maintain Hct level higher than 40 to 45 percent for severe cardiopulmonary disease

In neonates with severe respiratory disease, such as those requiring high volumes of oxygen with ventilator support, it is customary to maintain the Hct level higher than 40 to 45 percent (Hb concentration, >13–14 g/dL). Presumably, transfused donor RBCs, containing adult Hb with its superior interaction with 2,3-DPG compared to fetal Hb, will provide optimal oxygen delivery throughout the period of diminished pulmonary function. Similarly, it seems logical to maintain the Hct level higher than 40 percent in infants with congenital heart disease that is severe enough to cause either cyanosis or congestive heart failure and higher than 30 to 35 percent for moderate cardiopulmonary disease (Table 1).

Maintain Hct level higher than 30 percent for major surgery

Definitive studies are not available to establish the optimal Hct level for neonates facing major surgery. It seems reasonable, however, to maintain the Hct level higher than 30 percent because of limited ability of the neonate's heart, lungs, and vasculature to compensate for anemia and the inferior off-loading of oxygen to tissues by neonatal RBCs owing to the diminished interaction between fetal Hb and 2,3-DPG. This transfusion guideline must be applied with flexibility to individual infants facing surgical procedures of varying complexity (i.e., minor surgery may not require a Hct level >30%), and the amount of anticipated blood loss must be strongly considered (i.e., with a likelihood of large blood loss, some physicians might like the preoperative Hct level to be relatively high).

Maintain Hct level higher than 20 to 25 percent for stable infants with symptomatic anemia

In general, infants who are clinically stable with modest anemia do not require RBC transfusions, unless they exhibit significant clinical problems that are ascribed to the presence of anemia or are predicted to be corrected by donor RBCs.17 As an example, proponents of RBC transfusions to treat disturbances of cardiopulmonary rhythms believe that a low blood level of RBCs contributes to tachypnea, dyspnea, apnea, and tachycardia or bradycardia because of decreased oxygen delivery to the respiratory center of the brain. Transfusions of RBCs might decrease the number of apneic spells by improving oxygen delivery to the brain. Results of clinical studies have been contradictory, however.14,16,[17] Another controversial clinical indication for RBC transfusions is to treat unexplained growth failure. Some neonatologists transfuse RBCs for weight gain—particularly if the Hct level is less than 25 percent and if other signs of distress are evident (e.g., tachycardia, respiratory difficulty, weak suck and cry, diminished activity).[18] In this setting, growth failure has been ascribed to the increase in metabolic expenditure required to support the work of labored breathing. Results of clinical studies, however, have not supported this practice.17 Thus, little rationale exists to justify maintaining any predetermined Hct level by prophylactic, small-volume RBC transfusions in stable, growing infants who seem to be otherwise healthy.

In day-to-day practice, the decision of whether or not to transfuse RBCs is based on the desire to maintain the Hct concentration at a level judged to be most beneficial for the infant's clinical condition (Table 1). Investigators who believe this "clinical" approach is too imprecise have suggested the use of "physiologic" criteria such as RBC mass,[19] available oxygen,[20] mixed venous oxygen saturation, and measurements of oxygen delivery and utilization[21] to develop guidelines for transfusion decisions. Another physiologic factor, considered in transfusion decisions, is use of the circulating RBC volume and/or mass rather than the blood Hct or Hb level. Although circulating RBC volume and/or mass is a potentially useful index of the blood's oxygen-carrying capacity, it cannot be predicted accurately from blood Hct or Hb concentration levels; hence, it must be measured directly.[22] Unfortunately, circulating RBC volume and/or mass measurements and the other physiologic criteria for RBC transfusions mentioned are not widely available for clinical use and, consequently, are impractical.

RBC PRODUCTS TO TRANSFUSE

Most RBC transfusions are given to preterm infants as small-volume transfusions (10–20 mL/kg body weight) of RBCs suspended in extended storage medium (additive solution AS-1, AS-3, AS-5) at a Hct level of approximately 55 to 60 percent. Although some neonatologists prefer citrate-phosphate-dextrose-adenine (CPDA) solution with RBCs at a Hct level of approximately 70 percent, the superiority of this last solution over extended storage media has not been shown by comparative trials. Some centers prefer to centrifuge RBC aliquots before transfusion to prepare a uniformly packed RBC concentrate (Hct > 80%).23 Because of the small quantity of extracellular fluid (RBC storage media) infused very slowly (usually over 2–4 hr), the type of anticoagulant and preservative solution in which the RBCs are suspended poses no risk for most premature infants receiving small-volume transfusions.24,25 Accordingly, the traditional use of relatively fresh RBCs (<7 days of storage) has been largely replaced by the practice of transfusing aliquots of RBCs from a dedicated unit (or part of a unit) of RBCs stored up to 42 days, as a means to diminish the high donor exposure rates among infants who undergo numerous transfusions. 23,25 Neonatologists who object to prescribing stored RBCs and insist on transfusing fresh RBCs generally raise four objections: 1) the increase in "plasma" potassium (i.e., RBC supernatant fluid) during storage; 2) the decrease in RBC 2,3-DPG during storage; 3) the possible risks of additives such as mannitol and the relatively large amounts of glucose (dextrose) and phosphate present in extended-storage

preservative solutions; and 4) that stored RBCs may increase morbidity or mortality due to RBC "storage" lesions. Although these concerns are, in some cases, legitimate for large-volume (≥25 mL/kg) transfusions, particularly when infusion is rapid, they do not apply to small-volume transfusions for the following reasons.

After 42 days of storage in extended storage medium (AS-1, AS-3, AS-5) at a Hct level of approximately 60 percent, extracellular (plasma) potassium levels in RBC units approximate 50 mEq/L (0.05 mEq/mL), a concentration that at first glance seems alarmingly high. Simple calculations, however, show the actual dose of ionic potassium transfused in the extracellular plasma fluid is very small. An infant weighing 1 kg given a 15 mL per kg transfusion of RBCs stored 42 days in AS-1, AS-3, or AS-5 storage medium at a Hct level of 55 to 60 percent receives only 0.3 mEq K^+. The potassium concentration of RBCs stored in CPDA solution at a Hct level of 70 percent increases to 70 to 80 mEq per L after the 35 days of permitted storage, and the dose of potassium infused with a 15 mL per kg transfusion to an infant weighing 1 kg is 0.3 to 0.4 mEq. These doses are quite small when compared to the usual daily K^+ requirement of 2 to 3 mEq per kg and have been shown in several clinical studies not to cause hyperkalemia.[25]

By 21 days of storage, 2,3-DPG is totally depleted from RBCs as reflected by a P_{50} value that decreases from approximately 27 mmHg in fresh blood to 18 mmHg in stored RBCs at the time of outdate. Because of high fetal Hb levels in endogenous neonatal RBCs, the 18 mmHg value of RBCs transfused after maximum storage corresponds to the expectedly low P_{50} value of RBCs produced by many healthy preterm infants at birth. Thus, both older stored RBCs and endogenous RBCs from neonates have a similarly reduced ability to offload oxygen compared with fresh adult RBCs. Older adult RBCs in units of blood bank RBCs, however, provide an advantage over the infant's own RBCs because 2,3-DPG and the P_{50} of transfused adult RBCs (but not endogenous infant RBCs) increase rapidly after transfusion. When studied after small-volume (15 mL/kg) RBC transfusions, 2,3-DPG levels were maintained in infants given stored RBCs.[26]

The quantity of additives present in RBCs stored in extended storage media is unlikely to be dangerous for neonates given small-volume transfusions (15 mL/kg).[24,25] With AS-1 and AS-3 RBCs as examples (Table 2), the dose of extended storage medium additives transfused during a typical small-volume RBC transfusion is estimated to be far less than levels believed to be toxic.[24] This assumption was proved correct in clinical studies in which infants received one or more transfusions of RBCs stored in AS-1 or AS-3.[25,26]

During storage in conventional preservative solutions, RBCs sustain decreases in 2,3-DPG and adenosine triphosphate, and they undergo membrane and cytoskeletal changes that lead to the formation of echinocytes and microvesicles and to decreased deformability. The last changes may lead to diminished perfusion of the microvasculature and, consequently, to tissue and/or organ dysfunction. For the past few years, the argument has raged over whether critically ill adult patients are harmed by receiving "old" RBCs (usually defined as stored ≥15 or ≥21 days) and whether mortality, multiorgan failure, infections, need for mechanical ventilation, length of stay in intensive care units and in the hospital, and so forth, could be diminished by transfusing only fresh RBCs. Older, largely observational, studies generally support the idea that old RBCs put critically ill patients at risk, particularly if they receive multiple transfusions. Several more recent studies have challenged this concept and have cautioned against insisting on transfusions of fresh RBCs.[27,28] Well-designed, clinical trials are needed to resolve this question.

The situation is similar for neonatal RBC transfusions (i.e., neonates are often critically ill and questions about morbidity due to transfusing stored RBCs have been raised).Well-designed

trials, however, have addressed efficacy and safety and, within the limits of the number of infants studied, fresh and stored RBCs have been documented to be equivalent.[14,25,26] Moreover, the intravascular recovery 24 hours after transfusion and long-term survival of stored RBCs is normal, when measured in human infants with biotinylated RBCs.29 Because the risks of multiple donor exposure can be nearly eliminated by transfusing in infants with RBCs taken from dedicated, stored units and increased risks of transfusing stored RBCs versus fresh have not been demonstrated, it seems prudent to continue transfusing stored RBCs for small volume transfusions.

APPROACH TO THE ANEMIA OF PREMATURITY

For many infants with a birth weight less than 1.0 kg, the anemia of prematurity is severe and necessitates therapy with RBC transfusions and/or the administration of recombinant human EPO (rHuEPO) plus iron. For decades, RBC transfusion has been the standard of care, and in my view, continues to be so. A key principle is that allogeneic donor exposure be minimized by transfusing RBCs from dedicated units stored as long as permitted (e.g., 42 days for extended-storage anticoagulant-preservative solutions).

At the University of Iowa, DeGowin Blood Center, preterm infants who need RBC transfusions are assigned to dedicated units of RBCs suspended in extended-storage (42-day) solutions. At the time the first RBC transfusion is ordered, one-half of a freshly collected unit (stored ≤ 7 days) is dedicated to a preterm infant with a birth weight of not more than 1.0 kg. The rest of the unit can be assigned to another infant, so that 1 unit can serve two infants simultaneously. When RBC transfusions are ordered, aliquots are removed sterilely and issued.[23] Once an infant is assigned to a unit, it is used throughout 42 days of storage. If a unit has been stored 14 days without an infant being assigned, however, it has become relatively aged (14 of its 42 storage days have lapsed), and it enters the general inventory to be used for older patients. This plan has been demonstrated to be cost-effective.30

Recognition of low plasma EPO levels and adequate erythropoietic activity in preterm infants provides a rational basis to consider rHuEPO as treatment for the anemia of prematurity. Because the inadequate quantity of EPO is the major cause of anemia—not a subnormal response of erythroid progenitors to EPO—it is logical to assume that rHuEPO will correct EPO deficiency and will effectively treat the anemia of prematurity. Unfortunately, rHuEPO has not been widely accepted in clinical neonatology practice because its efficacy is incomplete. On the one hand, clonogenic erythroid progenitors from neonates respond well to rHuEPO in vitro, and rHuEPO and iron effectively stimulate erythropoiesis in vivo as evidenced by increased blood reticulocyte and RBC counts in recipient infants (i.e., efficacy successful at the marrow level). On the other hand, when the primary goal of rHuEPO therapy is to eliminate RBC transfusions, rHuEPO often fails (i.e., efficacy at the clinical level has not been consistently successful).[13,31]

By 2000, more than 20 controlled clinical trials assessing the efficacy of rHuEPO to eliminate RBC transfusions in the anemia of prematurity were published with inconsistent results. To investigate the extent and reasons for the inconsistencies, a meta-analysis was conducted of the controlled clinical studies published between 1990 through 1999.[31] Two major conclusions emerged from the meta-analysis. First, the controlled trials of rHuEPO to treat the anemia of prematurity differed from one another in multiple ways and, consequently, produced markedly variable results that could not be adequately explained. Hence, it was judged impossible to make firm recommendations regarding use of rHuEPO in clinical practice to treat the anemia of prematurity. Second, even when rHuEPO was found to be efficacious in significantly reducing RBC transfusion needs, the effect was relatively modest and of questionable clinical importance.[31]

Although the meta-analysis was unable to recommend how to use rHuEPO in clinical practices, it was apparent that: 1) relatively large or stable preterm infants are given relatively few RBC transfusions with today's conservative transfusion practices and, accordingly, have little need for rHuEPO when the goal is to avoid RBC transfusions; and 2) extremely small preterm infants, who are critically ill and unstable, have not consistently responded to rHuEPO plus iron when the outcome measure is to reduce need for RBC transfusions. Several reports published after 2000 have little altered the findings of the meta-analysis, but have provided useful information. Donato and coworkers[32] randomly assigned 114 neonates to receive either rHuEPO or placebo during the first 2 weeks of life, followed by a 6-week treatment period during which *all infants* were given rHuEPO, iron, and folic acid. At the end of all treatment (8 weeks), a subgroup of infants with birth weight of less than 0.8 kg and phlebotomy losses of more than 30 mL per kg, given rHuEPO shortly after birth, received fewer total RBC transfusions than infants initially given placebo (3.4 ± 1.1 vs. 5.4 ± 3.7; $p < 0.05$). Similarly, Yeo and coworkers[33] found a modest advantage for a subgroup of infants with birth weight 0.8 to 0.99 kg who were given fewer RBC transfusions with rHuEPO than control infants not given rHuEPO (2.1 ± 1.9 vs. 3.5 ± 1.6; $p < 0.04$). A randomized, blinded trial by Meyer and colleagues34 found an advantage for a subset of infants of less than 1.0 kg given rHuEPO.

Two reports claimed modest "success" for rHuEPO, defined as maintaining a Hct level of at least 30 percent without need for any RBC transfusions.[35,36] Finally, two studies found that, when restrictive transfusion guidelines were followed (i.e., transfusions given at relatively low pretransfusion Hct level), the number of RBC transfusions and the volume of RBCs transfused were similarly low in infants either given or not given rHuEPO.[37,38] Thus, the routine use of rHuEPO to treat all preterm neonates is not supported by evidence-based medicine.

PATHOPHYSIOLOGY OF NEONATAL THROMBOCYTOPENIA

Blood PLT counts of at least 150×10^9 per L are present in normal fetuses (as early as 17 weeks of gestation) and in normal neonates. Thus, PLT counts are in the normal range, regardless of gestational age at birth. Low PLT counts indicate potential problems. Preterm neonates commonly have thrombocytopenia (e.g., in one neonatal intensive care unit, 22% of infants had PLT counts $<150 \times 10^9$/L).[39] In contrast, thrombocytopenia is documented in less than 1 percent of term neonates.[40] Blood PLT counts of less than 100×10^9 per L may pose significant clinical risks—likely for unstable preterm infants. In one study, neonates with birth weights less than 1.5 kg and a PLT count of less than 100×10^9 per L were compared with neonates of similar size who did not have thrombocytopenia.[41] The bleeding time was prolonged when PLT counts were less than 100×10^9 per L, and PLT dysfunction was suggested by bleeding times disproportionately long for the degree of thrombocytopenia present. The incidence of intracranial hemorrhage was 78 percent among thrombocytopenic neonates with a birth weight less than 1.5 kg versus 48 percent for similar neonates without thrombocytopenia. In addition, the extent of hemorrhage and neurologic morbidity was greater among infants with thrombocytopenia.[41]

Although multiple pathogenetic mechanisms underlying thrombocytopenia likely are involved in these sick neonates, accelerated PLT destruction frequently is implicated by shortened PLT survival time, increased level of PLT-associated immunoglobulin G, increased PLT volume, normal number of marrow megakaryocytes, and an inadequate response to PLT transfusions.[39,42] Another mechanism that contributes to neonatal thrombocytopenia is diminished PLT production. This is evidenced by neonatal megakaryocytes that are smaller and of lower ploidy than those of adults.[43] In addition, some investigators have reported decreased numbers of megakaryocyte progenitors,[44] whereas others have not.[43] The response to thrombocytopenia in adults is to increase megakaryocyte number, volume, and ploidy—mediated primarily by thrombopoietin—all of which leads to increased PLT production. Thrombocytopenic neonates

either fail to increase megakaryocyte number, volume, and ploidy or the increases are inadequate when compared to adults and, consequently, they cannot raise PLT counts sufficiently to correct thrombocytopenia.[43,45] Moreover, thrombopoietin seems to increase neonatal megakaryocyte proliferation, but to inhibit endoreduplication;[46] in contrast, both are increased in adults.

As is reminiscent of neonatal RBC and neutrophil production, where basal erythropoiesis and myelopoiesis are adequate, basal PLT production and thrombopoiesis are adequate. Under the stress of cytopenia, however, none of the three cell lines is capable of increasing production to completely and promptly correct low blood counts (i.e., they lack sufficient hematopoietic reserve).

PLT TRANSFUSIONS FOR THE THROMBOCYTOPENIA OF PREMATURITY

The relative risks of different degrees of thrombocytopenia in various clinical settings during infancy remain largely unanswered. Prophylactic PLT transfusions to prevent bleeding in preterm neonates were studied systematically several years ago, and the results still seem relevant.[47] No randomized clinical trials of therapeutic PLT transfusions have been reported for bleeding thrombocytopenic neonates. Recognizing the need for more data, it seems logical in the interim to transfuse thrombocytopenic neonates per the guidelines presented in Table 3.

Two firm indications for PLT transfusions are either to control hemorrhage that has already occurred or to prevent it from complicating an invasive procedure. No disagreement exists over a pretransfusion blood PLT count of 50×10^9 per L as a minimum transfusion trigger in these instances. However, PLT transfusions are given at blood PLT counts of more than 50×10^9 per L by some physicians to neonates to control bleeding or in hopes of reducing either the threat of, or the worsening of, intracranial hemorrhage in high-risk preterm neonates.[41] No data exist to definitively establish the efficacy of PLT transfusions at these relatively high blood PLT levels—particularly in stable preterm neonates.[47]

Conventional prophylactic PLT transfusions are given to prevent bleeding when severe thrombocytopenia poses a likely risk of spontaneous hemorrhage. Prophylactic PLT transfusions are given by some physicians to maintain the presence of a normal PLT count in hopes of preventing the neonate from slipping into high-risk situations that might lead to spontaneous bleeding. Regarding the first circumstance, most experts agree that it is reasonable to give PLTs to any infant with a blood PLT count of less than 20×10^9 per L because spontaneous hemorrhage is a likely risk at this PLT count. Severe thrombocytopenia occurs most commonly among sick infants who, because of the underlying illness, often receive medications that can compromise the function of their already diminished number of PLTs. Because these factors are more pronounced in extremely preterm infants, who are clinically unstable, some neonatologists favor prophylactic PLT transfusion whenever the PLT count decreases to less than 50×10^9 per L or even to less than 100×10^9 per L, in critically ill infants.[41]

The need to maintain a completely normal PLT count ($\geq 150 \times 10^9$/L) in stable preterm neonates without bleeding has been shown not to be efficacious.[47] Moreover, such a practice can place infants at increased risk due to more PLT donor exposures. Intracranial hemorrhage occurs commonly among sick preterm infants. Although neither a causative role for thrombocytopenia nor a therapeutic benefit for PLT transfusion has been established in this disorder, it seems logical to presume thrombocytopenia might be a risk factor.[48] Accordingly, in a randomized trial designed to address this issue, transfusion of PLTs whenever the blood PLT count decreased below the normal value of 150×10^9 per L (which maintained the mean daily PLT count $>200 \times 10^9$/L) was compared with transfusion of PLTs only when the PLT count decreased below50×10^9 per L.[47] There was no difference in the incidence of intracranial

hemorrhage (28% vs. 26%) in the two groups. Thus, there is no documented benefit to transfusing "prophylactic PLTs" to maintain a completely normal PLT count in stable preterm neonates versus transfusing of "therapeutic PLTs" to treat thrombocytopenia when it actually occurs.

PLT PRODUCTS TO TRANSFUSE

The ideal goal of PLT transfusions for many thrombocytopenic neonates is to increase the low pretransfusion PLT count to a posttransfusion count of more than 50×10^9 per L and for sick unstable preterm infants to more than 100×10^9 per L. This can be achieved consistently by transfusing 5 to 10 mL per kg *unmodified* PLT concentrates (withdrawn from a unit of PLTs collected either by centrifugation of fresh units of whole blood or by platelet-pheresis and transfused directly).[47] PLT concentrates should be transfused as rapidly as the neonate's condition allows, certainly within 2 hours.

Routinely reducing the volume of PLT concentrates for infants by means of additional centrifugation steps is both unnecessary and unwise—unless a specific reason exists to do so. To illustrate, transfusion of 10 mL per kg PLT concentrate, taken directly from the unit and transfused, provides approximately 10×10^9 PLTs. If the blood volume of an infant is 70 mL per kg body weight and the plasma volume is 40 mL per kg, the PLT dose of 10 mL per kg increases the PLT count 100×10^9 to 150×10^9 per L above the pretransfusion baseline—assuming a posttransfusion PLT recovery of 60 percent. This calculated increment is consistent with the increment actually achieved after transfusing this dose as observed at our center (unreported data) and as reported in clinical studies.[47] With modest thrombocytopenia, a 5 mL per kg dose may be sufficient. In general, 5 to 10 mL per kg is not an excessive transfusion volume even for sick neonates, as long as the intake of other intravenous fluids, medications, and nutrients is adjusted. If volume reduction is to be done, the method of reduction *and* the efficacy of PLT transfusions after reduction must be validated *locally* to ensure the quantity and quality of PLTs (both ex vivo and in vivo) remaining after modification.

In the selection of PLT units for transfusion, it is desirable that the infant and the PLT donor be of the same ABO blood group. It is important to minimize repeated transfusions of group O PLTs to group A or B recipients, because large quantities of passive anti-A or anti-B in the plasma can lead to hemolysis. This should be easily avoided, with the exception of a directed-donor situation in which the infant is forced—usually by an emotional rather than medical decision—to receive PLT transfusions from an out-of-group donor. Hopefully, sound medical sense will prevail and ABO-identical PLTs from the general inventory will be selected. Proven methods exist to reduce the volume of PLT concentrates when truly warranted (e.g., multiple transfusions anticipated in which several doses of passive anti-A or anti-B may lead to hemolysis, or documented failure to respond to a transfusion of 10 mL/kg unmodified PLT concentrate). Additional processing should be performed with great care, however—with a method well-validated *locally*—because of probable PLT loss, clumping, and dysfunction caused by the additional handling.

APPROACH TO THE THROMBOCYTOPENIA OF PREMATURITY

Thrombocytopenia exists wherever the blood PLT count is less than 150×10^9 per L. Every infant with thrombocytopenia needs an evaluation—if nothing more than a repeated complete blood count, a review of the medical history, and a physical examination. Definitive management of thrombocytopenia depends on the underlying disorder. Correction of the thrombocytopenia per se by means of PLT transfusions is based on maintaining a blood PLT count deemed appropriate for the infant's clinical condition (Table 3).

There are no alternatives, established by evidence-based medicine, to PLT transfusion in the care of neonates with thrombocytopenia. Recombinant thrombopoietin (c-Mpl ligand or megakaryocyte growth and differentiation factor) and interleukin-11 (IL-11) are promising agents in older patients. Neither is recommended for use during infancy, however, and both have potential toxicities that can preclude their use in the care of sick preterm infants. Thrombopoietin has broad actions on the early precursors of all three major lineages in the marrow and may produce effects in excess of those expected on megakaryocytes and PLTs. Moreover, its interactions with fetal and/or neonatal megakaryocytes may be quite different than with adults.[46] IL-11 may cause anemia. Clearly, they must not be prescribed in the treatment of infants, except in experimental settings with parental consent and institutional oversight. Recombinant activated Factor VII has been used successfully "off-label" to treat life-threatening bleeding during infancy,49 but the clinical situations in which benefits are likely and its potential toxicity—particularly thrombosis—remain unknown. Although ε-aminocaproic acid and aprotinin may diminish bleeding in settings of thrombocytopenia and/or PLT dysfunction, their efficacy and potential toxicity in preterm infants have not been established.

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TABLE 1

RBC transfusions for the anemia of prematurity*

Maintain > 40%–45% Hct for *severe* cardiopulmonary disease
Maintain > 30%–35% Hct for *moderate* cardiopulmonary disease
Maintain > 30%–35% Hct for *major* surgery
Maintain > 20%–25% Hct for infants with *stable* anemia, especially if:
Unexplained breathing disorders
Unexplained tachycardia
Unexplained poor growth

* Words in italics must be defined locally. For example, “severe” pulmonary disease may be defined as requiring mechanical ventilation with >0.35 FiO_2 and “moderate” as less intensive ventilation.

TABLE 2

Quantity (total mg/kg) of additives infused during a transfusion of 15 mL per kg AS-1 or AS-3 RBCs at a Hct level of 60%

Additive	AS-1	AS-3	Toxic dose*
Sodium chloride	42	7.5	137 mg/kg/day
Dextrose	129	23	240 mg/kg/hr
Adenine	0.6	0.6	15 mg/kg/dose
Citrate	9.8	12.6	180 mg/kg/hr
Phosphate	2.0	5.6	>60 mg/kg/day
Mannitol	33	0	360 mg/kg/day

* The accuracy of toxic dose is difficult to predict because RBC infusion rates are slow, allowing metabolism and distribution of additives into extravascular sites. In addition, dextrose, adenine, and phosphate enter RBCs and are somewhat sequestered and not immediately “available” in the extracellular solution. Potential toxic doses from Luban et al.[24]

TABLE 3

PLT transfusions for the thrombocytopenia of prematurity*

Maintain > 50×10^9 to 100×10^9/L PLTs for *significant* bleeding
Maintain > 50×10^9/L PLTs for invasive procedures
Maintain > 20×10^9/L PLTs prophylactically for *clinically stable* neonates
Maintain > 50×10^9 to > 100×10^9/L PLTs prophylactically for *clinically unstable* neonates

* Words in italics must be defined locally. For example, consider bleeding site and extent, degree of prematurity, and underlying medical condition.