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Anaemia of Prematurity: Pathophysiology & Treatment

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Abstract

Most infants with birth weight <1.0 kg are given multiple red blood cell (RBC) transfusions within the first few weeks of life. The anaemia of prematurity is caused by untimely birth occuring before placental iron transport and fetal erythropoiesis are complete, by phlebotomy blood losses taken for laboratory testing, by low plasma levels of erythropoietin due to both diminished production and accelerated catabolism, by rapid body growth and need for commensurate increase in red cell volume/mass, and by disorders causing RBC losses due to bleeding and/or hemolysis. RBC transfusions are the mainstay of therapy with recombinant human erythropoietin largely unused because it fails to substantially diminish RBC transfusion needs — despite exerting substantial erythropoietic effects on neonatal marrow.

Introduction

Preterm infants with birth weight <1.0 kg (commonly designated as *extremely low birth weight*, or ELBW, infants) have completed ≤29 weeks of gestation, and nearly all will need red blood cell (RBC) transfusions during the first weeks of life. Every week in the United States, approximately 10,000 infants are born prematurely (ie, <37 weeks of gestation), with 600 (6%) of these preterm infants being ELBW.(1) Approximately 90% of ELBW neonates will receive at least one RBC transfusion.(2,3) Physiologic and nonphysiologic factors related to prematurity are responsible for the anaemia of prematurity and this high transfusion rate, with phlebotomy blood loss for laboratory testing as, perhaps, the biggest contributor.(4) Because of efforts to minimize the amounts of blood drawn from neonates for laboratory testing (5) and to transfuse more conservatively (ie, to accept lower pretransfusion hematocrit values), the number of RBC transfusions given to preterm infants has dropped over the years.(2,6) At the University of Iowa Hospitals & Clinics, the mean value during years 2000 to 2005 of RBC transfusions given to each transfused ELBW infant was 5.4/infant, compared to 1.1/infant for premature infants with higher birth weights from 1001 to 1500 g.

Pathophysiology of the Anaemia of Prematurity

All neonates experience a decline in circulating RBCs during the first weeks of life. This decline results both from multiple physiological factors and, in sick preterm infants, from several additional factors — the major one being phlebotomy blood losses for laboratory testing. In

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healthy term infants, the nadir hemoglobin value rarely falls below 10 g/dL at an age of 10 to 12 weeks. Because this postnatal drop in hemoglobin level in term infants is well tolerated and requires no therapy, it is commonly referred to as the "physiological anaemia of infancy." In contrast, this decline is more rapid (ie, nadir at 4–6 weeks of age) and the blood hemoglobin concentration falls to lower levels in infants born prematurely — to approximately 8 g/dL in infants with birth weights of 1.0 to 1.5 kg and to approximately 7 g/dL in infants with birth weights <1 kg. Consequently, because the pronounced decline in hemoglobin concentration that occurs in many ELBW infants is associated with abnormal clinical signs and need for allogeneic RBC transfusions, the "anaemia of prematurity" is not accepted to be a physiological and benign event.(7)

Physiological factors play a role in the pathogenesis of the anaemia of prematurity. Because ELBW infants are born before the 3rd trimester of gestation, they are deprived of most of the iron transported from the mother and a great deal of *in utero* fetal erythropoiesis. Extrauterine body growth is extremely rapid during the first months of life, and RBC production by neonatal marrow must increase commensurately. It is widely accepted that the circulating life span of neonatal RBCs in the bloodstream is shorter than that of adult RBCs due to several developmental differences in metabolic and membrane characteristics of neonatal RBCs compared to RBCs from adults. However, this is difficult to measure accurately because studies of transfused autologous (neonatal or placental) RBCs labeled with biotin or radioactive chromium may underestimate RBC survival in the infant's bloodstream for technical reasons.(8) In healthy adults — where body size is stable so that blood and RBC volumes are constant (ie, not increasing with growth), when no RBC transfusions are given, and when large volumes of blood (RBCs) are not being taken for laboratory studies — the gradual disappearance of transfused labeled RBCs, caused by dilution with RBCs produced by the bone marrow, accurately reflects RBC survival in the bloodstream. In contrast, one or more of these confounding factors (ie, growth and increasing blood volume, RBC transfusions, phlebotomy RBC losses) exists in infants — particularly, sick preterms — to introduce errors into the calculations performed when determining RBC survival.

A key reason that the hemoglobin nadir is lower in preterm than in term infants is the former group's diminished plasma erythropoietin (EPO) level in response to anaemia.(9) Although anaemia provokes EPO production in premature infants, the plasma levels achieved in anemic infants, at any given hematocrit value, are lower than those observed in comparably anemic older persons.(10) Erythroid progenitor cells of newborn infants are quite responsive to EPO in vitro — a finding suggesting that inadequate production EPO is, at least, one major cause of neonatal anaemia, *not* marrow unresponsiveness.(11)

All of the mechanisms responsible for the low plasma EPO levels, as seen in preterm neonates, are only partially defined and, likely, they are multiple. One mechanism is that the primary site of EPO production in preterm infants is in the liver, rather than kidney.(12) This dependency on hepatic EPO is important because the liver is less sensitive to anaemia and tissue hypoxia — hence, there is a relatively sluggish EPO response (ie, production) to the infant's falling hematocrit (HCT) level. The timing of the switch from liver to kidney as the primary site for EPO production is set at conception and is not accelerated to compensate for preterm birth. Viewed from a teleological perspective, decreased hepatic production of EPO under *in utero* conditions of relative tissue hypoxia may offer an advantage to the fetus. If this were not the case, normal levels of fetal hypoxia *in utero* could trigger high levels of EPO production and lead to extreme erythrocytosis and consequent hyperviscosity. Following birth, however, diminished EPO responsiveness to tissue hypoxia is disadvantageous to the infant and leads to anaemia because it impairs compensation for low HCT levels caused by rapid growth, RBC losses due to phlebotomy, clinical bleeding, hemolysis, etc.

Diminished EPO production cannot entirely explain low plasma EPO levels in anemic infants because extraordinarily high plasma levels of EPO have been reported in some fetuses and infants.(13,14) Moreover, macrophages from human cord blood produce normal quantities of EPO messenger RNA and protein.(15) Thus, additional mechanisms beyond low production must contribute to diminished EPO plasma levels. For example, plasma levels of EPO are influenced by rapid metabolism (clearance) as well as by production. Data in human infants (16) 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 — when compared to values in adults. Thus, accelerated catabolism compounds the problem of diminished EPO production, so that the low plasma EPO levels are a *combined effect* of decreased synthesis plus increased metabolism.

Phlebotomy blood losses play a key role in the anaemia of prematurity and in the need for RBC transfusions — particularly, during the first few weeks of life. The modern practice of neonatology requires critically ill neonates to be monitored closely with serial laboratory studies such as blood gases, electrolytes, blood counts and cultures. 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. In the past, the mean volume of blood removed for sampling has been reported to range from 0.8 to 3.1 mL/kg per day during the first few weeks of life for preterm infants requiring intensive care.(17) Promising “in-line” devices that withdraw blood, measure multiple analytes and then reinfuse most of the sampled blood have been reported.(18,19) They have decreased the need for RBC transfusions. However, until these devices are proven more extensively to be feasible, cost-effective, clinically efficacious and safe, replacement of blood losses due to phlebotomy will remain a key factor responsible for RBC transfusions given to critically ill neonates — particularly, transfusions given during the first four weeks of life. Meanwhile, it is critical to limit testing to only those tests absolutely needed for optimal care and to avoid overdraw (ie, taking more infant blood than actually needed).(5)

RBC Transfusions to Treat the Anaemia of Prematurity

Guidelines for transfusing RBCs to preterm neonates are controversial, and practices vary greatly.(20–24) This lack of a universal approach stems from limited knowledge of the cellular and molecular biology of erythropoiesis during the perinatal period, an incomplete understanding of infant physiological/adaptive responses to anaemia, and contrary/controversial transfusion practice guidelines as based on results of randomized clinical trials and expert opinions. Generally, RBC transfusions are given to maintain a level of blood hemoglobin or HCT believed to be optimal for each neonate's clinical condition. Guidelines for RBC transfusions, judged to be reasonable by most neonatologists to treat the anaemia of prematurity, are listed by Table I. These guidelines are very general, and it is important that terms such as “severe” and “symptomatic” be defined to fit local transfusion practices/policies. Importantly, guidelines are not mandates for RBC transfusions that must be followed; they simply suggest situations when an RBC transfusion would be judged to be reasonable/acceptable.

An important controversy that is still unresolved is the wisdom — or lack, thereof — of prescribing RBC transfusions to neonates using restrictive (RES) guidelines (ie, permitting relatively low pretransfusion HCT values before giving an RBC transfusion) versus liberal (LIB) guidelines (ie, relatively high pretransfusion HCT values). Two randomized, controlled trials have been published 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 RES guidelines.(25,26) In both trials, preterm infants were randomly allocated to receive all small-volume RBC transfusions per either RES or LIB

guidelines — with guidelines based on a combination of the pretransfusion HCT or hemoglobin level, age of the neonate, and clinical condition (ie, need for ventilation, oxygen, etc) at the time each transfusion was given.

Both studies found that neonates in the RES group received fewer RBC transfusions, without an increase in mortality or in morbidity as assessed by several clinical outcomes. However, one critical discrepancy was present. Bell et al(25) found increases in apnea, severe intraventricular bleeding and brain leukomalacia in infants transfused per RES guidelines, whereas, Kirpalani et al(26) found no differences in serious outcomes between infants in the RES versus LIB groups. However, rates of serious outcomes were fairly high in both groups of the Kirpalani study — perhaps, due to the extreme prematurity of the infants.(26) Although it is tempting to speculate that the higher blood HCT levels, in some way, protected the LIB group infants of Bell et al, it must be noted that the poor neurological outcome reported by Bell et al was a *post hoc* composite endpoint.(25) Although the combination of severe apnea, intraventricular bleeding and brain leukomalacia was statistically significantly more frequent in RES infants, the trial was not designed to study this endpoint *a priori*. Thus, the finding cannot be accepted as proven at this time, nor has a cause-and-effect relationship between RBC transfusion practices and neurological damage been established.

It is important to note that a follow-up study of infants enrolled in the trial of Kirpalani et al (26) was completed when the infants reached the age of 18–24 months.(27) There was no statistically significant difference found between RES and LIB groups when assessed by the primary outcome, stated *a priori*, as a composite of either death or survival with one or more findings of cognitive delay (Bayley II MDI <70), cerebral palsy, blindness or deafness. However, in a *post hoc* analysis using a higher Bayley II MDI score of <85, subjects in the RES group did significantly worse — suggesting some agreement with the finding of Bell et al(25) that RBC transfusions given per RES guidelines may place preterm infants at risk of neurological injury. Obviously, additional studies are needed to establish optimal transfusion practices, but until more information is available, it seems wise to transfuse preterm neonates using conventional, not greatly restrictive guidelines (ie, do not place infants at possible risks of under-transfusion).

The vast majority of RBC transfusions given to ELBW infants are “small volume” and consist of 10 to 20 mL per Kg (infant’s weight on the day of transfusion) of allogeneic RBCs stored in preservative solution at an hematocrit (HCT) of ~60% (42-day storage permitted in modern “additive” AS-1, AS-3, AS-5 solutions) or ~70% (35-day storage permitted in older CPDA solution). Other than personal bias, there are no demonstrated advantages for transfusing CPDA RBCs or disadvantages for AS-1, AS-3 or AS-5 RBCs when used for small volume transfusions.(28–31) Moreover, the quantities of “additives” transfused with small volumes of AS-1, AS-3 or AS-5 RBCs are extremely small compared to estimated toxic doses (Table 2) and, importantly, multiple clinical trials have documented both efficacy and safety of RBCs stored in additive solutions when transfused into infants.(28,30) Accordingly, the remainder of this discussion will deal with RBCs stored in additive solutions.

Most RBC transfusions given to infants are prescribed to treat the anaemia of prematurity and consist of 15 ± 5 mL/Kg RBCs infused over 2–4 hours. Because of the small quantity of extracellular fluid (RBC additive storage media) that is infused very slowly with small-volume transfusions, the type of anticoagulant and preservative solution in which the RBCs are suspended poses no apparent risk for most premature infants. Accordingly, the historical practice to transfuse only fresh RBCs (<7 days of storage) has been replaced in most centers by the practice of transfusing aliquots of RBCs from a dedicated unit of RBCs stored up to 42 days, as a means to diminish the high donor exposure rates among infants who undergo numerous transfusions.(30) Neonatologists who insist on transfusing fresh RBCs generally

raise the following four objections to prescribing stored RBCs: (a) the progressive increase in the concentration of potassium in the plasma (ie, RBC storage/supernatant fluid) during storage; (b) the decrease in the level of RBC 2,3-DPG; (c) the possible risks of individual additives such as mannitol and adenine and the relatively large amounts of glucose (dextrose) and phosphate present in additive solutions; and (d) the changes in RBC shape and deformability that develop during storage and, consequently, may lead to poor flow through the microvasculature. Although these concerns are legitimate for large-volume (≥25 mL/Kg) transfusions, particularly when infusion is rapid, they do not apply to small-volume transfusions for the following four reasons.

First, after 42 days of storage in additive solutions (AS-1, AS-3, AS-5) at a HCT of approximately 60%, extracellular ("plasma") potassium concentrations in RBC units approximate 50 mEq/L (0.05 mEq/mL), a level that at first glance seems alarmingly high. Simple calculations, however, show that the actual dose of ionic potassium transfused in the extracellular "plasma" fluid is small. An infant weighing 1 Kg given a 15-mL/Kg transfusion of RBCs stored 42 days in extended storage medium at a HCT of 60% receives only 0.3 mEq K^+ — a dose quite small when compared to the usual daily K+ requirement of 2 to 3 mEq/Kg — and one that has been shown in several clinical studies not to cause clinically significant hyperkalemia following RBC transfusions.(28,30,32)

Second, by 21 days of storage, 2,3-DPG is totally depleted from RBCs, as reflected by a P_{50} value — [defined simply as the pressure of oxygen needed to keep the hemoglobin 50% saturated with oxygen; the lower the P_{50} value, the more tightly oxygen is held by hemoglobin with lesser quantities of oxygen released to the tissues] — that decreases from approximately 27 mm Hg in fresh blood to 18 mm Hg in stored RBCs at the time of outdate. Owing to the effects of high fetal hemoglobin levels in neonatal RBCs, the 18 mm Hg value of RBCs transfused after maximum storage is quite similar to the expectedly low P_{50} value present in endogenous RBCs produced by the marrow of healthy preterm infants at birth. Thus, both older stored RBCs and endogenous RBCs from neonates have a similarly reduced ability to off-load oxygen compared with fresh adult RBCs. However, older adult RBCs in units of blood bank provide an advantage over the infant's own RBCs because 2,3-DPG and the P_{50} values of transfused adult RBCs (but not endogenous infant RBCs) increase rapidly after transfusion. When infant blood samples were studied serially in the setting of small-volume (15 mL/Kg) RBC transfusions, RBC 2,3-DPG levels were maintained in infants given stored RBCs.(33)

Third, 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). Regardless of the type of additive storage solution, the quantity of additives is quite small in the clinical setting in which a neonate would receive a small-volume transfusion of RBCs infused over 2 to 4 hours (Table 2). Moreover, efficacy and safety have been proven in clinical studies in which infants received one or more RBC transfusions.(28,30,32,33)

Fourth, during storage in all conventional preservative solutions, RBCs sustain progressive decreases in 2,3-DPG and adenosine triphosphate, and they undergo membrane and cytoskeletal changes that lead to the formation of echinocytes and microvescicles and to decreased deformability. The last changes may lead to diminished perfusion of the microvasculature and, consequently, to tissue/organ dysfunction. For the last few years, the argument has raged over whether critically-ill adult patients are harmed by receiving "old" RBCs (usually defined as stored ≥15 days), and whether mortality, multi-organ failure, infections, need for mechanical ventilation, length of stay in intensive care units and in the hospital, etc could be diminished by transfusing only fresh RBCs. The argument is unresolved, with a recent meta-analyses actually finding poorer outcomes in some patients given *fresh* RBC transfusions.(34)

The situation is similar in the setting of neonatal RBC transfusions (ie, neonates are often critically-ill and questions about morbidity due to transfusing stored RBCs have been raised). However, well-designed trials 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, (28,30,32,33) Moreover, the intravascular recovery 24 hours after transfusion and long-term survival of stored allogeneic donor RBCs is normal, when measured in human infants using biotinylated RBCs.(8) Because the risks of multiple donor exposure can be nearly eliminated by transfusing infants with RBCs taken from dedicated, stored units and the fact that speculated increased risks of transfusing stored RBCs versus fresh have not been convincingly demonstrated, it seems prudent at present to continue transfusing RBCs stored in additive solutions up to 42 days for small volume transfusions.

Recombinant Erythropoietin to Treat the Anaemia of Prematurity

Recognition of low plasma EPO levels and normally responsive RBC progenitor cells in preterm infants provides a rational basis to consider recombinant human erythropoietin (r-HuEPO) as treatment for the anaemia of prematurity. Because the inadequate quantity of plasma EPO is the major cause of anaemia — not a subnormal response of marrow erythroid progenitors to EPO — it is logical to assume that r-HuEPO will correct EPO deficiency and will effectively treat the anaemia of prematurity. Regardless of the assumed logic, r-HuEPO has not been widely accepted in clinical neonatology practice because its efficacy is incomplete. On one hand, clonogenic erythroid progenitors from neonates respond well to r-HuEPO *in vitro* and r-HuEPO and iron effectively stimulate erythropoiesis *in vivo* as evidenced by increased blood reticulocyte and RBC counts in recipient infants (ie, efficacy successful at the marrow level). On the other hand, when the primary goal of r-HuEPO therapy is to eliminate RBC transfusions, r-HuEPO often fails to do so (ie, efficacy at the clinical level has not been consistently successful).(20,35)

By the end of 1999, over 20 controlled clinical trials assessing the efficacy of r-HuEPO to eliminate RBC transfusions in the anaemia 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 thru 1999. Two major conclusions emerged from the meta-analysis.(35) First, the controlled trials of r-HuEPO to treat the anaemia 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 premature to make firm recommendations regarding use of r-HuEPO in clinical practice to treat the anaemia of prematurity. Second, when the four studies with highly desired characteristics were analyzed separately, r-HuEPO was found to be efficacious in significantly reducing RBC transfusion needs. However, the magnitude of the effect of r-HuEPO on reducing the total RBC transfusions given to infants throughout their initial hospitalization was, in fact, relatively modest and of questionable clinical importance.(35)

Because meta-analysis of reports through 1999 did not give firm guidelines for the use of r-HuEPO, neonatologists must determine if reports published after 2000 have provided useful information. Donato et al(36) randomized 114 neonates with birth weight <1.25 kg to receive either r-HuEPO or placebo during the first two weeks of life, followed by a six week treatment period during which all infants (ie, both groups) were given r-HuEPO, iron and folic acid. During the first three weeks of life, r-HuEPO increased reticulocytes and hematocrit values, but there was no difference in RBC transfusions between groups. However, at the end of all treatment (eight weeks), a subgroup of infants with birth weight <0.8 kg and phlebotomy losses >30 mL/kg, given r-HuEPO 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 et al(37) found a modest advantage for a subgroup of very low birth weight infants given r-HuEPO. Infants

with birth weight 0.8 to 0.99 kg were given fewer RBC transfusions with r-HuEPO than control infants not given r-HuEPO (2.1 ± 1.9 vs 3.5 ± 1.6, p<0.04).

A randomized, blinded trial by Meyer et al(38) found an advantage for r-HuEPO. Neonates with birth weight <1.7 kg, plus fulfilling criteria that predicted a likely need for RBC transfusions, were randomized either to receive r-HuEPO beginning shortly after birth or to experience a sham treatment simulating placebo injections. Iron was given to all infants, but at two different doses (unfortunately) — a much lower dose was given to control infants not given r-HuEPO and a higher dose was given to infants given r-HuEPO — thus, creating two experimental variables/differences that might affect erythropoiesis and need for RBC transfusions (r-HuEPO and iron dose, rather than just r-HuEPO) in treated vs control infants. Overall, there was no overall difference found in RBC transfusions, but in a subset of infants with birth weight <1.0 kg, RBC transfusions given late (ie, after 30 days of age) were reduced by r-HuEPO vs controls (0.5 ± 0.7 vs 1.6 ± 1.1, p=0.01).

Two reports defined r-HuEPO "success" as maintaining a hematocrit of ≥30% without need for any RBC transfusions. Maier et al(39) randomized 219 neonates with birth weights 0.5 to 0.99 kg to receive either early r-HuEPO (from the first week of life for nine weeks), late r-HuEPO (from the fourth week of life for six weeks), or no r-HuEPO. "Success" rates were modest (13% with early r-HuEPO, 11% with late r-HuEPO, and 4% with no r-HuEPO). Only early r-HuEPO infants were significantly superior to no r-HuEPO (p=0.026). Avent et al(40) randomized 93 neonates with birth weight 0.9 to 1.5 kg to receive either low dose r-HuEPO (250 units/kg), high dose r-HuEPO (400 units/kg), or no r-HuEPO. Treatment began within 7 days of life and continued until discharge (median 32 days and maximum 74 days). "Success" at maintaining a reasonable hematocrit without RBC transfusions was met by 75% of low dose r-HuEPO infants, 71% of high dose r-HuEPO and 40% of no r-HuEPO infants (p<0.001). Interestingly, the total number of RBC transfusions given to all infants treated with r-HuEPO vs those given no r-HuEPO was not significantly different! On further analysis, the authors concluded that r-HuEPO did not significantly decrease RBC transfusions in infants, birth weight 0.9 to 1.5 kg, when phlebotomy losses were small and when RBC transfusions were given per stringent transfusion guidelines.(40)

The observation by Avent et al(40) that the benefits of r-HuEPO in reducing the number of RBC transfusions given can be equalled by stringent/conservative transfusion guidelines has been made by others. Franz and Pohlandt(41) assessed both the number of RBC transfusions given the and RBC transfusion guidelines followed in four prospective, randomized trials of r-HuEPO given to preterm neonates. To be selected for analysis, the clinical trials had to include ventilated infants (ie, sick infants likely to receive RBC transfusions). The authors found that, when restrictive transfusion guidelines were followed, the number of RBC transfusions and the volume of RBCs transfused were similarly low in infants either given or not given r-HuEPO. (41) Similarly, Amin(42) found no difference in the number of RBC transfusions given; whether or not r-HuEPO was prescribed to preterm infants with birth weight ≥1.0 kg, when RBC transfusions were given per strict transfusion guidelines.

Practice Points

- RBC transfusions are the key treatment modality for the anaemia of prematurity.
- RBCs stored up to 42 days since donation are efficacious and safe for small volume transfusions (15 ± 5 mL/kg).
- Vigorous attempts must be made to limit volumes of blood drawn for laboratory testing.

- Recombinant human erythropoietin, although clearly stimulating erythropoiesis in infant marrow, has very limited use, currently, to treat the anaemia of prematurity.

Research Agenda

- Define optimal (ie, efficacy and toxicity) pretransfusion blood hematocrit/hemoglobin levels that "trigger" red blood cell transfusions in preterm infants.
- Explore biology/pharmacology of recombinant human erythropoietin in neonatal/infant erythropoiesis to establish the basis for possible future therapy of the anaemia of prematurity.
- Determine long-term outcomes of RBC transfusions given to neonates/infants on the basis of restrictive vs liberal transfusion guidelines and of red blood cell units stored briefly since donation vs long-term storage (eg, stored <14 days vs stored >14 days) to define optimal RBC transfusion practices.

Acknowledgments

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Table I

Allogeneic RBC Transfusions for the Anaemia of Prematurity

Transfuse to maintain the blood HCT per each clinical situation:
> 40% (35 to 45% *) for severe cardiopulmonary disease
> 30% for moderate cardiopulmonary disease
> 30% for major surgery
>25% (20 to 25% *) for symptomatic anemia
> 20% for asymptomatic anemia

* Reflects practices that vary among neonatologists. Thus, any value within range is acceptable for local practices.

Table 2

Quantity of additives transfused (mg/kg infant body weight) with a 15/mL/Kg RBC transfusion*

Additive	AS-1	AS-3	AS-5	Toxic Dose
Mannitol	45	None	32	360 mg/Kg/day
Adenine	1.6	1.8	1.8	15 mg/Kg/dose
Phosphate	Trace	17	Trace	>60 mg/Kg/day
Citrate	Trace	38	Trace	180 mg/Kg/hour
Dextrose	132	66	54	240 mg/Kg/hour
NaCl	54	25	53	137 mg/Kg/day

*Modified from data in reference [28].