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Anemia in the preterm infant: Erythropoietin versus erythrocyte transfusion — It's not that simple

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SYNOPSIS

Since the late 1980s recombinant human erythropoietin (r-Epo) has been studied as an alternative to packed red blood cell (RBC) transfusion for the treatment of anemia of prematurity in very low birth weight (VLBW, <1500 grams) infants. Initial trials and reports focused on r-Epo's ability to prevent or treat anemia of prematurity with the goal of eliminating RBC transfusion, but achieved limited success. Reduced volumes of blood sampling for laboratory tests and improved blood banking techniques have decreased the need for RBC transfusion. New concerns about the safety of r-Epo administration have emerged. Past cost-benefit analyses of r-Epo administration versus transfusion for the treatment of anemia of prematurity have been nearly balanced. Autologous transfusion, blood-sparing technologies, changes in RBC transfusion technique and safety, and further elucidation of the risk-benefit ratio of r-Epo therapy may change the cost-benefit analysis. The jury is still out with regard to the role of r-Epo therapy in the VLBW population.

Keywords

erythropoietin; transfusion; very low birth weight; infant; premature

INTRODUCTION

Since the late 1980s recombinant human erythropoietin (r-Epo) has been studied as an alternative to packed red blood cell (RBC) transfusion in the treatment of anemia of prematurity (AoP). Two decades later hematologists and neonatologists have not reached consensus on when r-Epo should be used in very low birth weight (VLBW, <1500 grams) infants. Initial trials and reports focused on r-Epo to prevent or treat AoP with the goal of eliminating RBC transfusion. Later studies found response to r-Epo was influenced by: 1) significant volumes of blood loss, especially in the smallest, sickest infants, 2) the physiology of r-Epo which requires days to weeks to increase hematocrit, and 3) need for supplementation of protein, iron,

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folate, and vitamin E. In addition, recent reports have raised the red flag of undesirable side-effects, including a possible increase in retinopathy of prematurity with early administration of r-Epo.

This paper reviews the history of AoP treatment, starting with the physiology of AoP and the development of specialized transfusion techniques for the VLBW population. We continue by describing the initial trials of r-Epo to prevent or treat AoP and the implementation of restrictive RBC transfusion criteria. Finally, we discuss recent concerns about the side effects of r-Epo administration and outline therapies that may limit the need for r-Epo administration, shifting the cost-benefit balance away from treatment with r-Epo to prevent or treat AoP.

PHYSIOLOGY OF ANEMIA OF PREMATURITY

During the third trimester of gestation, fetal red cell production transitions from hepatic to marrow erythropoiesis. The glycoprotein hormone erythropoietin (Epo) is the driving force behind red cell production, and fetal hematocrit rises in conjunction with fetal levels of Epo.[1] Epo production switches near term from liver to kidney; the “hypoxia sensor” of the liver is much less sensitive than the kidney. Nonetheless, fetal Epo production is responsive to decreased red cell mass and rises appropriately in response to pathologic conditions, for example, in the setting of erythroblastosis faetalis.[2]

After birth, infants display a physiologic drop in hematocrit accompanied by a fall in blood Epo levels. Although cord blood levels of Epo are high, little is found in full term neonatal blood from the second day of life until 6–8 weeks of age.[3] This decrease in Epo and subsequent lack of erythropoiesis after birth leads to the “physiologic nadir” of hematocrit around 3 months of life in the term infant. Oxygen delivery to tissues seems to be preserved in full term infants at the physiologic nadir, and symptoms of anemia are rarely seen without exacerbating factors.

Premature infants experience a lower nadir of hematocrit than full term infants resulting in a normocytic, normochromic anemia coincident with a low reticulocyte count and low Epo level. The nadir is inversely related to gestational age. This condition is termed AoP.[4] Some premature infants tolerate AoP well. Others, especially the smallest, sickest infants, develop signs and symptoms such as tachycardia, tachypnea, apnea and bradycardia, poor weight gain, oxygen requirement, diminished activity, pallor, and elevated serum lactate.[4,5] These symptoms can lead to increased length of stay in the hospital and infectious complications if indwelling lines are needed for nutritional support and hydration.

Physiologic studies of the preterm infant indicate that stimulation of endogenous Epo is governed by hypoxia and anemia, as it is in the adult population; however, preterm infants have been shown to have a relatively low Epo level for a given hematocrit as compared to adults.[6] Further investigation demonstrated the importance of factors other than hematocrit governing red cell production in the preterm infant. Stockman and colleagues in 1977 determined that oxygen unloading capacity influences erythropoiesis. He described that hemoglobin levels in premature infants with a right-shifted oxyhemoglobin dissociation curve, due to a lower proportion of fetal hemoglobin (HbF < 30%), fell 2–3 grams per deciliter lower than those infants with a left-shifted dissociation curve (HbF > 60%) before endogenous Epo production resumed.[7] In 1984 Stockman published data showing that endogenous Epo is also sensitive to dissolved oxygen; central venous oxygen tension varies inversely with Epo level in the premature infant.[8] Still, the most premature infants seem to display a much lower mean Epo level in the face of similar “available oxygen” when compared to adults.[9] Interestingly, these data about the physiology of AoP indicate that RBC transfusion, which increases the proportion of hemoglobin A in the preterm neonate, may contribute to a lower nadir of

hematocrit by improving oxygen availability to the tissues and lowering the stimulus for Epo production.[5]

The natural history of AoP is often exacerbated by iatrogenic factors such as low hematocrit at birth and postnatal phlebotomy as well as endogenous factors such as rapid infant growth, shortened RBC lifespan, and expansion of blood volume. Technological advances have decreased the volume of blood needed for neonatal laboratory studies. Despite these improvements many VLBW infants do not tolerate exacerbation of AoP and require treatment.

TREATING ANEMIA OF PREMATURITY

RBC Transfusion

The incidence of AoP has increased with the survival of VLBW infants, and treatment for symptomatic AoP has become common. For many years RBC transfusion was the only effective treatment for severe anemia. AoP is refractory to other therapies including supplementation with iron, vitamin E and folic acid. Early transfusion protocols called for infants to be transfused with “fresh” RBCs (less than 7 days old). The goal was to maximize the life of cells *in vivo* and minimize the risk of hyperkalemia and acidosis. At approximately 15 milliliters per kilogram body weight, tiny babies require relatively small volumes of blood per transfusion. To conserve a valuable resource, a procedure termed the “cow technique” was employed; multiple infants were cross-matched against a single RBC unit which was used to provide transfusions to multiple infants until depleted.[10] Since VLBW infants often received several transfusions to maintain adequate blood volume and hematocrit, exposure to multiple donors was common.

In the early 1990s blood banks serving neonatal units began to dedicate a single unit of blood to each infant. The unit is accessed and resealed under sterile conditions and can be used for multiple transfusions until the unit’s original expiration date, 35–42 days after collection. This method limits each neonate’s donor exposure.[11–15] Even with donor-sparing blood banking techniques, blood transfusion is not without risk. Blood-borne infection is a primary concern. The risk of hepatitis B, hepatitis C, human immunodeficiency virus, cytomegalovirus and Epstein-Barr virus transmission is as low as it has ever been, due to donor screening and post-collection testing and processing techniques. Still, emerging infections exist and are a risk.[16] Treatments for AoP that further limit or eliminate the need for blood transfusion are desirable.

Until the 1990s the only treatment for symptomatic AoP was RBC transfusion. Most infants born prematurely before 30 weeks gestation needed a RBC transfusion during their initial hospitalization. Early transfusions (in the first one to two weeks of life) were typically given for acute blood loss due to blood sampling during critical illness. Late transfusions were given after two weeks of life for symptomatic AoP. Criteria for transfusion for AoP were largely unstandardized, though, and transfusion practice varied widely.[17–20] A common indication for transfusion was “blood out,” or blood losses due to phlebotomy (most likely in the smallest, sickest infants). It was assumed that replacing losses routinely would be beneficial. Likewise, many clinicians transfused RBCs based on an absolute hemoglobin or hematocrit level. Evidence accumulated that there was no benefit to either practice.[20–22]

Erythropoietin to Limit RBC Transfusion

In 1987 the first clinical trial of r-Epo, in adults with end-stage renal disease, demonstrated that r-Epo treatment was associated with an increased hematocrit and reduction in RBC transfusions.[23] There was reason to believe that the synthetic hormone could help VLBW infants. Although the pathophysiology of AoP was incompletely understood, premature infants were known to have a low Epo level in the setting of low hematocrit.[8] In addition, *in vitro*

studies demonstrated that both circulating erythroid progenitor cells and those found in the bone marrow were highly sensitive to r-Epo.[24–26]

In 1990 the first pilot study of the effect of erythropoietin on AoP was published.[27] Many subsequent randomized, controlled trials attempted to elucidate the effect of r-Epo on AoP and to develop optimal patient selection, dosing, nutritional supplementation, and timing of therapy with the goal of limiting RBC transfusion in premature neonates.[28–42] Ohls summarized many of these studies in her excellent review in this Journal in 2000.[43]

The initial r-Epo trials in VLBW infants showed that administration of the drug resulted in reticulocytosis with subsequent increase in hematocrit.[30,33] Furthermore, most r-Epo-exposed infants received fewer and lower volumes of RBC transfusion during the study period.[29,30,32–34,36] This finding was strongest in stable, growing preterm infants, most of whom had received multiple blood transfusions prior to study entry.[30,33] The first study of r-Epo administration to extremely low birth weight (ELBW, < 1000 grams) infants indicated that the hormone also helped prevent transfusion in these smallest, sickest infants.[34] However, later randomized, controlled studies did not find a significant reduction in RBC transfusion in ELBW patients.[40,42]

Two different timing strategies were employed in the r-Epo trials. “Early” treatment (before 8 days of age) with r-Epo was employed to prevent AoP.[30,40] “Late” treatment (at or after 8 days of age) protocols were designed to treat AoP and decrease RBC transfusions during convalescence.[28,33] Both regimens were shown to reduce RBC transfusion.[29,30,32–34, 36] Despite hopes that early r-Epo administration would be superior to late administration in preventing RBC transfusion, subsequent studies comparing the two practices found no significant difference in this outcome.[39,41,44]

If r-Epo reduces RBC transfusion in VLBW infants, why, then, is its administration not routine? One answer lies in the magnitude of the drug’s effect. Although r-Epo administration did reduce RBC transfusion in many trials, questions persist about whether the absolute reduction in transfusion volume (milliliters per kilogram per patient) achieved is of clinical significance in this era of single-donor, dedicated RBC unit transfusion protocols.[41,45–47] Furthermore, a more pertinent question today is: Does r-Epo prevent multiple blood donor exposure? As of yet, no multicenter randomized, controlled studies have answered this question.[42]

The initial r-Epo studies also shed light on optimal dosing and nutritional supplementation. The very first r-Epo studies used doses roughly equivalent to adult dosing protocols. These doses were found to be insufficient for premature infants who require larger doses of the hormone per kilogram of bodyweight compared to adults due to higher volume of distribution and faster elimination.[48,49] Although infants require relatively high doses of r-Epo, a therapeutic threshold does seem to exist above which no further Epo response is obtained. Head-to-head comparison of “high dose” (1500 units/kg/week) versus “low dose” (750 units/kg/week) of r-Epo did not reduce RBC transfusion in ELBW infants.[38] Finally, it is well documented that infants receiving r-Epo have increased nutritional needs. Adequate protein and vitamin E administration, either enterally or parenterally is essential to achieve full benefit of r-Epo. Infants receiving r-Epo have lower ferritin levels and hypochromic red cells necessitating supplementation with iron.[31] Both intravenous and oral iron supplementation have been shown to maintain serum ferritin levels and support erythropoiesis.[33,35,37,50]

Restrictive Transfusion Criteria

Perhaps the most important finding of the first randomized control trials of r-Epo was the fact that implementing standard criteria for RBC transfusion alone safely reduced the number of transfusions administered, even to control patients.[20,29,32,33] Prior to the r-Epo trials,

investigators studied whether so-called liberal transfusion criteria would alleviate symptoms of AoP and reported mixed results. One study did not find a routine positive effect of red cell transfusion on tachypnea, tachycardia, or the incidence of apnea and bradycardia.[19] Another found a significant decrease in apnea and periodic breathing after RBC transfusion.[51]

In their multicenter study of r-Epo in growing preterm neonates, Shannon and colleagues chose restrictive transfusion guidelines when standardizing their transfusion protocol across participating institutions. These conservative, staged transfusion criteria were based on oxygen and ventilatory requirements as well as reticulocyte production and clinical symptoms (tachycardia, apnea and bradycardia, and somatic growth).[33] Subsequently, comparative trials tipped the balance from liberal transfusion protocols toward restrictive criteria.[20–22, 52,53] Bifano and colleagues found no benefit to maintaining a hematocrit > 32 as compared to a lower hematocrit (< 30) with regard to weight gain, days on a ventilator, total hospital days, one year weight gain and head growth, and neurodevelopmental outcome.[53] Kirpalani and colleagues found no difference in negative outcomes (death, retinopathy of prematurity, bronchopulmonary dysplasia, brain ultrasound) with restrictive transfusion criteria.[52] Although one study [54] did find more apnea, intraventricular hemorrhage and periventricular leukomalacia in a restrictive transfusion group, these risks have not been confirmed by others. [52,53,55] As compared to earlier liberal transfusion practices, these more restrictive criteria limit the number of transfusions (and, therefore, donor exposures) without apparent harm to the infant. (Table 1)

Since their introduction, restrictive transfusion criteria have become the norm in many major newborn intensive care units. Still, even with restrictive transfusion guidelines there may be over-transfusion.[56] A recent review of transfusion practices and guidelines for neonates recommends further studies of “need-based transfusions” via creation of a “transfusion marker” such as measurement of the adequacy of oxygen delivery, improvement in signs or symptoms of anemia, and resolution of cardiovascular impairment, possibly via echocardiographic measurement.[55] Such a marker would, ideally, simultaneously limit RBC transfusions and risks of anemia.

REFINING THE USE OF r-EPO

In the new millennium attempts to refine the patient population and timing of r-Epo use for optimal benefit have been tempered by increasing evidence of potential harm due to the drug. There are still no absolute indications for the use of r-Epo in the preterm population, and there are no data to suggest that r-Epo dramatically decreases or eliminates the need for RBC transfusions in preterm infants.[57] Some investigators have hypothesized that r-Epo will be of greatest benefit in the preterm population at highest risk for transfusion. Still, even in this select population, data suggest that r-Epo does not prevent a significant number or volume of transfusions.[4,42] In a sub-group analysis from Ohls’ 2001 report[40], r-Epo did prevent RBC transfusion in ELBW babies after one month of age, leading to the hypothesis that the drug might prevent second donor exposure in that population.[41]

Several meta-analyses have lent strength to this theory that r-Epo prevents late transfusion in preterm neonates, although the effect size is small.[45,47,58] One meta-analysis evaluated reduction in RBC transfusion in VLBW infants using late r-Epo. For this outcome 19 studies enrolling 912 infants were included. The composite number needed to treat for benefit was 5. The weighted mean reduction in number of transfusions was 0.78 transfusions, and the total weighted mean RBC volume reduction was 7 mL. Post hoc analysis of the highest quality studies showed a smaller effect size than seen in the primary analysis.[45] The clinical relevance of sparing this relatively small number and volume of late transfusions remains debatable, since most VLBW infants receive transfusions early in life.

RISKS OF r-EPO ADMINISTRATION

In the initial r-Epo trials a primary concern was whether administration of the hormone to premature infants would redirect hematopoiesis preferentially toward the erythrocyte line, resulting in neutropenia and increasing the rate of infection in exposed infants. Those studies found a decrease in circulating and myeloid neutrophils and precursors, but no increased rate of infection was reported.[27,28] These early results were confirmed by the randomized, controlled studies that found wide variation in the neutrophil counts of treated patients and did not show increased rates of infections in those receiving r-Epo.[33,36]

More recent studies in the adult literature have raised new concerns about r-Epo. In 2006 two studies published in the New England Journal of Medicine found that administration of r-Epo to patients with chronic kidney disease did not improve survival and might be harmful. The first trial, Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE), enrolled 603 patients with stage 3 or 4 chronic kidney disease in 94 different centers in 22 countries. 75% of intervention subjects and 83% of control subjects were followed for two years after enrollment. They found that administering r-Epo to achieve a target hemoglobin level of 13 to 15 grams per deciliter compared to 10.5 to 11.5 grams per deciliter did not reduce the incidence of first cardiovascular event, although those in the treatment group did report improved general health and physical function.[59]

The second trial, Correction of Hemogloblin and Outcomes in Renal Insufficiency (CHOIR), enrolled 1432 patients with chronic kidney disease at 130 United States centers. The investigators found an increased risk of the composite primary outcome, time to “death, myocardial infarction, hospitalization for congestive heart failure, or stroke” and no improvement in quality of life in the group that received r-Epo to achieve a higher hemoglobin level.[60] An editorial in the same issue of the Journal recommended caution with regard to normalization of red blood cell levels via r-Epo in patients with chronic kidney failure.[61] Extrapolating these results to VLBW infants, maintenance of high-normal hematocrit through r-Epo administration may not be warranted, since an evaluation of liberal transfusion criteria to maintain hematocrit high-normal did not show any benefit.[52,54]

Perhaps of more concern for neonates, r-Epo has been linked to neovascularization and tumor progression. Elucidation of the physiology of Epo indicates that its cellular pathways and targets result in angiogenesis.[62,63] Epo has been associated with pathologic blood vessel growth, for example, in proliferative diabetic retinopathy.[64] Furthermore, in at least three published adult trials, r-Epo has been linked to decreased survival for some patients with cancer due to tumor progression related to neovascularization.[65–68] Several clinical trials of darbepoetin (a modified r-Epo protein with a longer half life) were stopped when increased mortality was found in the treatment group.[68]

No studies have reported r-Epo-associated neoplasm in neonates, and, although a few studies have suggested that retinopathy of prematurity (ROP, a disorder of vascular proliferation) may be exacerbated by r-Epo, there are no definitive data demonstrating this outcome.[44,69,70] A meta-analysis of early r-Epo administration, and one comparing early versus late r-Epo, reported unpublished data regarding ROP.[39,41,44,46] Only one study included in the meta-analyses found a statistically significant increase in any ROP with early compared to late administration of r-Epo.[39] No study included in the meta-analysis found the rate of ROP stage >= 3 significantly different in infants treated early with r-Epo.[44] If there is a link between r-Epo and ROP, perhaps they are at most risk if the drug is continued past 34 weeks postmenstrual age when both the vascular phase of ROP and endogenous reticulocytosis begin.

COST-BENEFIT OF ERYTHROPOIETIN USE

Many studies in the 1990s attempted to capture the costs of erythropoietin versus RBC transfusion.[30,32,71–74] The results varied, and the relative benefit of r-Epo for AoP is related to the study design (early versus late treatment; liberal versus restrictive transfusion criteria), patient population, and value assigned to complex outcomes. Not all studies took into account the risk of infection transmission, exclusion of which would lower the cost of transfusion.[32] Studies evaluating the cost of treating stable, growing premature infants with r-Epo are more likely to favor RBC transfusion over r-Epo compared to studies focused on sicker premature infants at greater risk for RBC transfusion.[71,73] An up-to-date, comprehensive analysis could be helpful to clinicians and should include at least all of the items listed in Table 2.

One item that is perhaps most difficult to evaluate is the psychosocial burden imposed on family, patient, and caregivers by transfusion or the potential risk of transfusion-related infection, however rare transmission may be. Although most such infections can be now be cured (bacterial infection) or managed as chronic diseases (human immunodeficiency virus, hepatitis C), significant social stigma and psychological burden may be associated with acquisition. The value assigned to avoiding such infection is highly subjective and, therefore, difficult to model accurately.

FUTURE DIRECTIONS

Current use of r-Epo in the VLBW population varies widely in the United States, and the future use of the medication is not easy to predict. New technologies, improvements in transfusion practice, and further understanding of the side effects of r-Epo may change the equation. Longer-acting darbepoetin has become the drug of choice for adult patients requiring Epo replacement. There are no large multicenter, randomized, controlled trials yet to determine its safety and efficacy in the neonatal population. One study indicates that darbepoetin may increase reticulocytosis in convalescent VLBW infants. The cost savings achieved for adults treated with darbepoetin versus r-Epo may not hold true in the neonatal population since newborns may require larger per kg doses at more frequent intervals than children or adults.[75,76] Still, the possibility of reduced dosing, necessitating fewer needle sticks, is attractive in this population susceptible to infection.

Strategies to increase autologous blood volume would tip the balance away from r-Epo. Autologous transfusion with banked cord blood is a logical adjunct, although most institutions are not equipped to offer this therapy.[55] A related practice is delayed umbilical cord clamping. Delaying clamping (e.g.: by 30 seconds) has been shown to increase birth hematocrit and decrease RBC transfusion in VLBW infants. In a few recent studies delayed clamping has also been associated with lower rates of intraventricular hemorrhage and improved neurodevelopmental outcome.[77–79]

Reducing blood sampling through microanalytical techniques and more judicious use of blood tests reduced the need for RBC transfusions in the 1990s. Further minimizing phlebotomy through use of point of care technologies that use 0.1 mL of blood compared with 0.3–0.5 mL needed for most laboratory microassays, in-line monitors, or non-invasive testing would further reduce blood loss and transfusion requirements. Developments that would tip the balance toward use of r-Epo are emergence of new blood-borne infections or compromise of the blood supply, other increase in costs of RBC administration, or discovery of other beneficial effects of r-Epo.

CONCLUSION

The jury is still out with regard to the role of r-Epo therapy in the VLBW population, and therefore the use of r-Epo varies widely throughout the United States. At the Newborn Special Care Unit, Yale New Haven Children's Hospital VLBW infants are not routinely treated.

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Table 1

Transfusion Criteria: Then & Now

Typical RBC transfusion criteria for VLBW infants prior to 199010

Indications for transfusion:

* "When 5 to 10 percent of the infant's blood volume has been removed in a period of less than 48 hours it should be replaced with packed red blood cells.

* In infants who weigh less than 1500 grams, hemoglobin values should be maintained in excess of 13 g/dl during the first week of life."

* In convalescent infants (3–8 weeks of age), clinical symptoms or signs (persistent tachycardia or tachypnea, lethargy, easy fatigue with feedings, poor weight gain, central venous oxygen tension <25 mm Hg)

Example of current conservative RBC transfusion criteria for VLBW infants80

1 For infants requiring moderate or significant ventilation (defined as MAP >8 cm H_20 and FiO_2> 0.40)

Transfuse if: Hematocrit ≤35% (Hemoglobin ≤ 11 gms/dL)

2 For infants requiring minimal mechanical ventilation [defined as (a) all other infants requiring

PPV or (b) CPAP (ET or NCPAP) ≥ 6 cm H_2O and FiO_2> 0.40]

Transfuse if: Hematocrit ≤ 30% (Hemoglobin <10 gms/dL)

3 For infants on supplemental oxygen who are not requiring mechanical ventilation.

Transfuse if: Hematocrit ≤25% (Hemoglobin ≤ 8 gms/dL) and one or more of the following are present:

* >24 hours of tachycardia (heart rate >180) or tachypnea (RR >80)

* an increased oxygen requirement from the previous 48 hours, defined as:

a. ≥four-fold increase in nasal canula flow (ie: 1/4 L/min to 1 L/min) OR

b. an increase in NCPAP ≥ 20% from previous 48 hours (ie: 5 to 6 cm H_2O) OR

c. an absolute and sustained increase in FiO_2≥ 0.10 (via oxyhood, nasal CPAP or cannula)

* weight gain < 10 gm/kg/d over the previous 4 days while receiving ≥100 kcal/kg/d

* multiple episodes of apnea and bradycardia (≥10 episodes in a 24 hour period or ≥2 episodes in a 24 hour period requiring bag-mask ventilation) while receiving therapeutic doses of methylxanthines

* undergoing surgery

4 For infants without any symptoms

Transfuse if: Hematocrit ≤ 20% (Hemoglobin < 7 gms/dL) and the absolute reticulocyte count is < 100,000 cells/uL (<2%)

Table 2

Variables influencing cost-benefit studies of r-Epo treatment

- r-Epo units/kg/week
- Weeks of r-Epo therapy
- r-Epo price and administration costs (including waste of r-Epo)
- Adverse effects of r-Epo (immediate and long-term)
- Number and volume of transfusion with/without r-Epo (using restrictive transfusion criteria)
- Transfusion administration costs (type & crossmatch, blood products, blood screening and processing, set-up charges, nursing costs)
- Transfusion-related complications (infection, graft vs. host disease, NEC)
- Cost of technology to minimize transfusions