

# Predictive factors and practice trends in red blood cell transfusions for very-low-birth-weight infants

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**BACKGROUND:** Red blood cell (RBC) transfusions in very-low-birth-weight (VLBW) infants, while common, carry risk. Our objective was to determine clinical predictors of and trends in RBC transfusions among VLBW infants.

**METHODS:** RBC transfusion practice and its clinical predictors in 1,750 VLBW ( $\leq 1,500$  g) infants were analyzed in a single-center cohort across sequential epochs: 2000–2004 (Epoch 1), 2005–2009 (Epoch 2), and 2010–2013 (Epoch 3).

**RESULTS:** Overall, 1,168 (67%) infants received  $\geq 1$  transfusions. The adjusted likelihood of  $\geq 1$  transfusions decreased for each 1-g/dl increment in initial hemoglobin concentration following birth, for females, and for each 100-g increment in birth weight. The adjusted likelihood of  $\geq 1$  transfusions increased with infants receiving mechanical ventilation, with increasing length of hospital stay, necrotizing enterocolitis, and nonlethal congenital anomalies requiring surgery. The adjusted mean (SEM) number of transfusions per patient was decreased in Epoch 3, compared with Epoch 1 and Epoch 2. For an initial hemoglobin of  $\geq 16.5$  g/dl, the predicted probability of being transfused was  $\leq 50\%$ .

**CONCLUSION:** Adjusted RBC transfusions declined and female sex conferred an unexplained protection over the study period. Modest increases in initial hemoglobin by placental transfusion at delivery may reduce the need for RBC transfusion.

Red blood cell (RBC) transfusion is the most common therapy for the treatment of anemia in very-low-birth-weight (VLBW) infants. An estimated 70% of VLBW infants receive at least one transfusion within the first 4 wk of life (1), with ~80% receiving  $\geq 1$  RBC transfusions during their hospital stay (2). RBC transfusions, although lifesaving, can lead to immediate and delayed adverse transfusion reaction (3) and have been associated with intraventricular hemorrhage (4), necrotizing enterocolitis (NEC) (5), retinopathy of prematurity (6), and bronchopulmonary dysplasia (7).

The practice of administering RBC transfusions is largely governed by the degree of prematurity and severity of illness of

the infant. Few studies have examined the clinical characteristics of VLBW infants that require RBC transfusions (8–10). These studies have either been in subsets of infants weighing less than 1,000 g or of small sample size. As the survival rate among VLBW infants continues to improve and clinicians become more cognizant of the risks associated with RBC transfusions, it is important to reexamine the clinical predictors and trends of RBC transfusions. We hypothesized that doing so would identify important, potentially modifiable factors that would enable reducing exposure to RBC transfusions among VLBW infants.

## RESULTS

Of the 1,825 VLBW infants who met inclusion criteria, 35 were excluded from the analysis because they had been enrolled in a research trial in which RBC transfusion criteria was prescribed (11). Seven infants were excluded because they had received an exchange blood transfusion, and 33 were excluded due to incomplete data (i.e., discrepant number of RBC transfusions, incomplete documentation of number of days on mechanical ventilation). Characteristics of the 1,750 VLBW infants available for analyses changed over epochs (Table 1). Birth weight (BW), gestational age (GA), length of stay and the incidence of NEC increased over time. During the study period, 66.7% of infants received  $\geq 1$  RBC transfusions (Table 2). There was no difference across epochs in the unadjusted number of RBC transfusions administered per infant.

To assess independent clinical predictors of  $\geq 1$  RBC transfusions, multivariable logistic regression analysis (Table 3) revealed that the likelihood of receiving  $\geq 1$  RBC transfusions decreased with each 1.0 g/dl increment of initial hemoglobin concentration (Hgb) after birth (aOR 0.70, CI 0.65–0.75), female sex (aOR 0.64, CI 0.47–0.87), and with 100-g BW increments (aOR 0.71, CI 0.65–0.76). The clinical factors that independently increased the likelihood of any transfusion included nonlethal congenital anomaly requiring surgery (aOR 6.97, CI 1.57–30.89), time spent mechanically ventilated, (1–7 d [aOR 1.79, CI 1.25–2.57], 7–28 d [aOR 8.33, CI 4.78–14.51], and  $\geq 28$  d [aOR 67.41 CI 8.79–517.00]), and each incremental

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**Table 1.** Study population clinical characteristics by epoch

Characteristic	All epochs	Epoch 1 (2000–2004, N = 562)	Epoch 2 (2005–2009, N = 685)	Epoch 3 (2010–2013, N = 503)	P <sup>a</sup>
Female, N (%)	873 (49.9)	279 (49.6)	334 (48.8)	260 (51.7)	0.52
Birth weight, g, mean (SD)	1026 (294)	1001 (292)	1042 (297)	1033 (290)	0.04
≤500, g, N (%)	61 (3.5)	21 (3.7)	24 (3.5)	16 (3.2)	
501–750, g, N (%)	299 (17.1)	104 (18.2)	111 (16.2)	84 (16.7)	
751–1,000, g, N (%)	441 (25.2)	154 (26.9)	161 (23.5)	126 (25.1)	0.008 <sup>b</sup>
1,001–1,250 g, N (%)	443 (25.3)	147 (25.7)	174 (25.4)	122 (24.3)	
1,251–1,500 g, N (%)	506 (28.9)	136 (23.8)	215 (31.4)	155 (30.8)	
Gestational age, weeks, mean (SD)	28.0 (2.8)	27.8 (2.8)	28.1 (2.7)	28 (2.9)	0.04
<26 wk, N (%)	355 (20.3)	136 (24.2)	121 (17.7)	98 (19.5)	
26–28 wk, N (%)	648 (37.0)	210 (37.4)	263 (38.4)	175 (34.8)	
29–30 wk, N (%)	435 (24.9)	124 (22.1)	179 (26.1)	132 (26.2)	0.004 <sup>b</sup>
>30 wk, N (%)	312 (17.8)	92 (16.4)	122 (17.8)	98 (19.5)	
Weight for gestational age					
Small for gestational age, N (%)	373 (21.31)	110 (19.6)	152 (22.2)	111 (22.1)	
Appropriate for gestational age, N (%)	1366 (78.06)	449 (79.9)	530 (77.4)	387 (76.9)	0.44 <sup>b</sup>
Large for gestational age, N (%)	11 (0.63)	3 (0.53)	3 (0.44)	5 (1.0)	
Mechanical ventilation days (%)					
None, N (%)	420 (24.0)	147 (26.2)	159 (23.2)	114 (22.7)	
1–7, N (%)	549 (31.4)	141 (25.1)	255 (37.2)	153 (30.4)	
8–27, N (%)	308 (17.6)	121 (21.5)	104 (15.2)	83 (16.5)	0.43 <sup>b</sup>
≥28, N (%)	473 (27.0)	153 (27.2)	167 (24.4)	153 (30.4)	
Intraventricular hemorrhage					
None, N (%)	1444 (82.5)	452 (80.4)	570 (83.2)	422 (83.9)	
Grade I, N (%)	113 (6.5)	40 (7.1)	46 (6.7)	27 (5.4)	
Grade II, N (%)	60 (3.4)	17 (3.0)	21 (3.1)	22 (4.4)	0.09 <sup>b</sup>
Grade III–IV, N (%)	133 (7.6)	53 (9.4)	48 (6.4)	32 (6.4)	
Non-lethal congenital anomaly requiring surgery, N (%)	25 (1.4)	9 (1.6)	8 (1.2)	11 (2.2)	0.38
Necrotizing enterocolitis, N, %	52 (2.97)	8 (1.4)	18 (2.63)	26 (5.17)	<0.001
Duration of any respiratory support, median (IQR)	12 (1–38)	13 (1–37)	11 (1–37)	12 (1–44)	0.85
Duration of supplemental O <sub>2</sub> , days, median (IQR)	42 (11–84)	46 (9–89)	40 (11–78)	43 (13–88)	0.29
Length of hospital stay, days, median (IQR)	63 (41–90)	64 (36–91)	61 (41–85)	65 (45–94)	0.03
Hemoglobin, g/dL mean (SD)	15.8 (2.7)	15.9 (2.7)	15.9 (2.8)	15.6 (2.6)	0.09
Died in NICU, N (%)	87 (5.0)	34 (6.1)	33 (4.8)	20 (4.0)	0.12

NICU, neonatal intensive care unit.

<sup>a</sup>P values across epochs. <sup>b</sup>P value across subcategories.

hospital day (aOR 1.04, CI 1.03–1.05). Every infant who developed NEC received at least one RBC transfusion. Inclusion of the nursery neurobiologic risk score (NBRS) as an additional predictor or a replacement for assisted ventilation duration in the multivariable logistic regression model did not improve the model fit; therefore, time spent on mechanical ventilation was utilized as a proxy for illness severity throughout the entire hospital stay.

In assessing RBC transfusion trends, compared with Epoch 3, the likelihood of receiving ≥1 RBC transfusions was greater in Epoch 1 (aOR 2.39, CI 1.56–3.65) and Epoch 2 (aOR 2.81, CI 1.90–4.15). The adjusted mean (SEM) number of RBC

transfusions per subject derived from the Poisson regression analysis was 2.05 (0.12) in Epoch 3, compared with 2.40 (0.14) in Epoch 1 and 2.58 (0.15) in Epoch 2.

The adjusted probability of receiving ≥1 transfusions for any initial Hgb decreased in Epoch 3 compared to Epoch 1 and Epoch 2 is shown in [Figure 1](#). The figure is an effect plot for the subgroup of males who were not ventilated, did not develop NEC and did not have surgery for congenital anomaly; the continuous variables of BW per 100 g and length of stay in days were held at their midpoints in the model. The predicted probability of receiving ≥1 RBC transfusions, as estimated by the effect probability plot, in the most recent epoch was 50% for an

**Table 2.** Univariate analysis of RBC transfusions in VLBW infants by epoch

	All	Epoch 1 (2000–2004, N = 562)	Epoch 2 (2005–2009, N = 685)	Epoch 3 (2010–2013, N = 503)	P <sup>a</sup>
Number per patient, median (IQR)	2 (0–5)	2 (0–5)	2 (0–5)	2 (0–5)	0.18
Number of red blood cell transfusions					
None, N (%)	582 (33.3)	178 (31.7)	218 (31.8)	186 (37.0)	
1, N (%)	228 (13.0)	62 (11.0)	110 (16.1)	56 (11.1)	
2, N (%)	213 (12.2)	97 (17.3)	70 (10.2)	46 (9.2)	
3–5, N (%)	360 (20.6)	95 (16.9)	150 (21.9)	115 (22.9)	0.32 <sup>b</sup>
6–10, N (%)	271 (15.5)	96 (17.1)	98 (14.3)	77 (15.3)	
11–15, N (%)	71 (4.1)	25 (4.5)	29 (4.2)	17 (3.4)	
>15, N (%)	25 (1.4)	9 (1.6)	10 (1.5)	6 (1.2)	

<sup>a</sup>P value across epochs. <sup>b</sup>P value across subcategories.

**Table 3.** Multivariable logistic regression analysis for the predictors of the outcome any RBC transfusion

Predictor	Odds ratio (95%CI)
Epoch	
Epoch 1 vs. Epoch 3	2.39 (1.56–3.65)
Epoch 2 vs. Epoch 3	2.81 (1.90–4.15)
Epoch 3	Reference
Female sex	0.64 (0.47–0.87)
Birth weight (per 100 g increment)	0.71 (0.65–0.76)
Ventilator duration, days	
None	Reference
1–7 d vs. none	1.79 (1.25–2.57)
8–27 d vs. none	8.33 (4.78–14.51)
≥28 d vs. none	67.41 (8.79–517.00)
Nonlethal congenital anomalies requiring surgery	6.97 (1.57–30.89)
Length of stay (per day increment)	1.04 (1.03–1.05)
Initial Hgb at birth (per g/dL increment)	0.7 (0.65–0.75)
(AGA or LGA) vs. SGA	1.37 (0.89–2.13)

Model includes necrotizing enterocolitis; all patients who had NEC were transfused, yielding an adjusted OR of infinity.

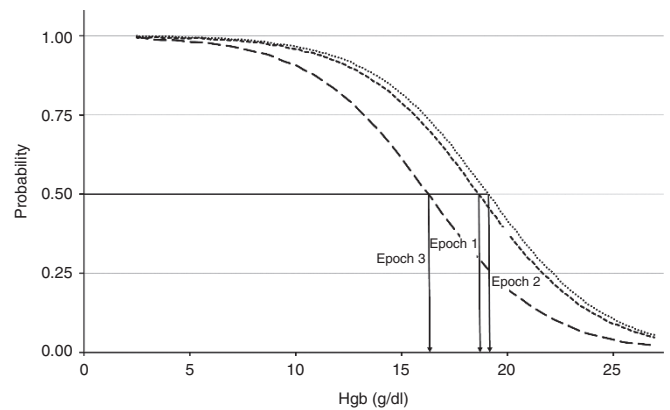
C statistic is 0.942.

SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; RBC, red blood cell; NEC, necrotizing enterocolitis; OR, odds ratio.

initial Hgb of ~16.5 g/dl and was less than 50% for higher initial Hgb values. In epoch 3, for any initial Hgb, the probability of requiring ≥1 RBC transfusions is less in females compared to males (Figure 2).

**DISCUSSION**

Of the examined clinical predictors of RBC transfusions in VLBW infants in this single-center retrospective study, initial Hgb following delivery was found to have a major effect on the likelihood of administering ≥1 RBC transfusions. Each 1 g/dl increment in initial Hgb decreased the adjusted likelihood of receiving ≥1 RBC transfusions by 30%. For an Hgb of ~16.5 g/dl, the predicted probability of being transfused was 50%, and this probability declined as the initial Hgb

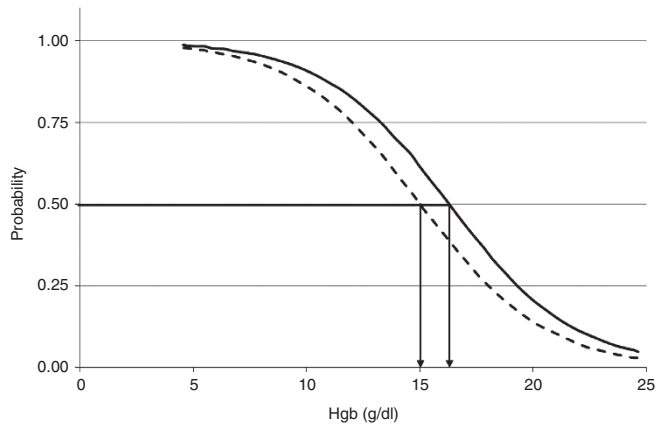


**Figure 1.** Probability of male infants being transfused based on initial hemoglobin concentration during 3 epochs. For any level of Hgb, the probability of ≥1 RBC transfusions is less in epoch 3, thick dashed curve, compared to epoch 1, light dotted curve and epoch 2 thick dotted curve. The arrows indicate the Hgb level which predict 50% probability of ≥1 RBC transfusion. Effect probability plot are for males who were not ventilated, did not develop NEC or have surgery for congenital anomaly. Continuous variables held at their midpoints included in the model are birthweight per 100 g and length of stay in days. Hgb, initial hemoglobin concentration following birth; RBC, red blood cell; NEC, necrotizing enterocolitis.

increased. These findings suggest that modest increments in initial Hgb achieved by placentofetal transfusion at birth might yield clinically meaningful reductions in the need for RBC transfusions.

Of the other clinical predictors, several have been reported previously and thus were expected. Also, given that ventilator support is included in our institutional RBC transfusion guideline, we expected it to be predictive. However, female sex was an unexpected independent predictor that decreased the adjusted likelihood of ≥1 RBC transfusions. Female sex was also associated with a reduced Hgb concentration that predicted a 50% likelihood of requiring an RBC transfusion when compared to males.

Three prior observational studies have reported a similar relationship between higher initial Hgb and reduced administration of RBC transfusions to preterm infants. However, two examined only extremely-low-birth-weight infants, the majority of whom received concurrent erythropoietin therapy, thus



**Figure 2.** Probability of male and female infants being transfused based on initial hemoglobin concentration during Epoch 3. For any level of Hgb, the probability of  $\geq 1$  RBC transfusion is less in females, dotted curve, compared to males, dashed curve, in epoch 3. The arrows indicate the Hgb level which predict 50% probability of  $\geq 1$  RBC transfusion. Effect probability plot are for males and females infants were not ventilated, did not develop NEC or have surgery for congenital anomaly. Continuous variables held at their midpoints included in the model are birthweight per 100 g and length of stay in days. Hgb, initial hemoglobin concentration following birth; RBC, red blood cell; NEC, necrotizing enterocolitis.

confounding direct comparison with this study (8,9). The third study reported only *P* values without effect size (10).

Randomized clinical trials on placentofetal transfusion in preterm infants have reported larger blood volumes (12), higher Hgb concentration after birth (13–15), and fewer overall RBC transfusions in infants exposed to delayed cord clamping or umbilical cord milking (16–18). In addition, improved neurodevelopmental status at 7 mo (19) and 4 y (20) have been reported in some longitudinal studies of term infants. A Cochrane review examining delayed cord clamping or cord milking vs. immediate cord clamping found fewer transfusions of packed RBCs, better circulatory stability, less intraventricular hemorrhage (all grades), decreased oxygen requirement at 36 wk corrected GA and lower risk for NEC with delayed cord clamping or cord milking (21).

However, disruption of timely resuscitation, the ideal duration of time to delay cord clamping, and whether umbilical cord milking is a safe and effective alternative to delayed cord clamping (22,23) remain concerns requiring further study. Also, there continues to be a need for clinical data on the long-term neurodevelopmental implications of these strategies in preterm infants (23,24).

To our knowledge, this is the first report to identify female sex as an independent protective factor for requiring RBC transfusions. In the reviewed literature, there does not appear to be any direct relationship between male sex and decreased red cell mass, erythropoietin production, impaired bone marrow function or increased RBC senescence. However, it has been suggested that when compared to females, males carry an unexplained intrinsic risk for adverse neonatal outcomes overall (25). Males have higher rates of neonatal mortality, respiratory morbidities, and adverse neurologic outcomes, even after adjusting for maternal factors, GA and BW (26).

The other observed factors in this study that contributed to the likelihood of RBC transfusions relate to the degree of prematurity and the severity of illness. Nonlethal congenital anomalies requiring surgery, time spent on mechanical ventilation, NEC and per day increments of length of hospital stay were all significantly associated with an increased likelihood of requiring  $\geq 1$  RBC transfusions. These factors are difficult to modify given current neonatal intensive care unit (NICU) therapies. Together and individually, they reflect the severity of illness of the infant. As such, they commonly necessitate frequent blood sampling for close clinical monitoring. It is common for the cumulative phlebotomy loss for laboratory analysis during the first weeks of life to equal or exceed the infant's total circulating blood volume (27); estimates of laboratory phlebotomy loss among preterm infants vary from 1.1 to 3.5 ml/kg/d in the first few weeks of life (28–30). Techniques for reducing phlebotomy losses, such as utilizing placental blood at birth for initial laboratory analyses (31) and inline analyzers/point-of care blood test analyzers have been shown to reduce phlebotomy losses in the first week of life by 25% and to reduce the exposure to RBC transfusion by 33–48% without any adverse short- or long-term outcomes (27,32).

The secondary aim of this study was to evaluate the temporal trend in RBC transfusions in VLBW infants over the 14-y study period. **Figure 1** depicts this trend clearly. Each curve represents the probability of being transfused by epoch based on the initial Hgb after birth. At any level of starting hemoglobin, the probability of being transfused was decreased in epoch 3 when compared to epoch 1 and 2. The adjusted likelihood of exposure to  $\geq 1$  RBC transfusions and the adjusted mean number of RBC transfusions both decreased in the most recent epoch compared with earlier epochs. This occurred despite the lack of change in institutional RBC transfusion guidelines.

From the same NICU, we previously reported a significant decrease in the unadjusted number of transfusions per infant compared at three different years: 1982, 1989, and 1993 (1). The percent of VLBW infants transfused during hospitalization in 1982 and 1993 were 88 and 62%, respectively. The unadjusted number of transfusions (mean  $\pm$  SD) per infant was  $7.0 \pm 7.4$  in 1982 and  $2.3 \pm 2.7$  in 1993. However, major changes occurred over the study period that influenced transfusion practice. These included the identification of human immunodeficiency virus, improved practice of administering maternal corticosteroids, administration of pulmonary surfactant to infants with respiratory distress syndrome, and adoption of stricter RBC transfusion criteria. In the current study timeframe, a comparable proportion of VLBW infants, 66.7%, received one or more RBC transfusions. There was no difference across epochs in the unadjusted number of RBC transfusions per infant, but the adjusted mean number of transfusions decreased.

We speculate that the reduced adjusted mean number of transfusions in the most recent epoch may be due to clinicians being more conservative in prescribing transfusions. They may not be following the transfusion guideline strictly but using clinical judgment to decide. In addition, and of minor effect, is the influence of the research trial in which RBC transfusion



criteria was prescribed (11), in which our institution became a part of in 2013. Infants not enrolled in the trial may be placed at a transfusion threshold closer to the restrictive threshold, thus reducing overall transfusions. However, compliance with institutional transfusion guideline was not available; therefore, we cannot ascertain if less stringent adherence to institutional transfusion guideline accounts for the reduced transfusion numbers in the most recent epoch.

It is important to recognize other strengths and weaknesses of the current study. Although the study includes a large and robust dataset, allowing for adjustment for many predictors of transfusion, we are limited by its observational nature. Thus, we may not have identified and studied all predictors. In addition, it is a single-center study, limiting its generalizability to other centers.

### Conclusions

In conclusion, a small decrease in the adjusted likelihood of being transfused was observed from 2000 to 2013, but 63% of VLBW required at least one RBC transfusion in the most recent epoch. Strategies aimed at optimizing Hgb at birth through placentofetal transfusion and limiting phlebotomy losses have the potential to reduce further the number of RBC transfusions VLBW infants receive.

### METHODS

We performed a cohort analysis of VLBW infants admitted to the NICU at the University of Iowa Children's Hospital from 2000 to 2013. Data were obtained from a prospectively collected NICU registry, a database of clinical information on patients admitted to the NICU. The NICU registry data were supplemented and validated by electronic medical chart review. We included all infants with BW  $\leq 1500$  g who were admitted within 72 h of birth and survived longer than 48 h. Infants were excluded if they had an exchange blood transfusion, had incomplete data or were subjects in a research trial in which RBC transfusion criteria were prescribed (11).

The study was approved by the University of Iowa Institutional Review Board. A waiver of parental consent was obtained as the study posed minimal risk. Also, it was impractical to consent each subject given the study period.

### RBC Transfusion Procedures and Guidelines

Throughout the entire study period, the NICU RBC transfusion guidelines developed in 1998 remained unchanged (33). Infants were transfused with 15 ml/kg of packed RBC (hematocrit 80–85%) when: (i) Hgb was  $< 13$  g/dl and the infant was mechanically ventilated with  $\text{FiO}_2 \geq 0.7$ , had sepsis or NEC; (ii) Hgb was  $< 11.5$  g/dl and the infant was mechanically ventilated with  $\text{FiO}_2 \leq 0.7$  or receiving nasopharyngeal continuous positive airway pressure with  $\text{FiO}_2 \geq 0.4$ ; (iii) Hgb was  $< 10$  g/dl, receiving nasopharyngeal continuous positive airway pressure with  $\text{FiO}_2 \leq 0.4$  or before a surgical procedure; (iv) Hgb was  $< 8$  g/dl without supplemental oxygen, but with clinical signs of anemia; or (v) Hgb was  $< 7$  g/dl without supplemental oxygen or clinical signs of anemia.

During the study period delayed cord transfusion was not implemented. This practice was instituted in 2014.

### Study Definitions

To assess the effect of time on transfusion practice, the cohort was grouped into three sequential epochs: 2000–2004 (Epoch 1), 2005–2009 (Epoch 2), and 2010–2013 (Epoch 3). Clinical predictors examined included BW, GA, appropriateness of BW for GA, sex, length of stay until discharge, transfer or death, initial Hgb recorded after birth, presence of nonlethal congenital anomalies requiring surgery (i.e., intestinal atresia, esophageal atresia, surgically corrected

patent ductus arteriosus), time receiving supplemental oxygen, time receiving mechanical ventilation, intraventricular hemorrhage severity (34), and NEC by the modified Bell classification stage IIA or higher (35). Severity of illness throughout hospitalization was estimated with the nursery neurobiologic risk score system (36). The nursery neurobiologic risk score incorporates subcategories of seven parameters: infection, blood pH, seizures, intraventricular hemorrhage, assisted ventilation, periventricular leukomalacia, and hypoglycemia.

### Statistical Analyses

To characterize and compare patient groups across epochs, means, medians, and variances of continuous variables and distributions of categorical variables were calculated and tested using analysis of variance,  $\chi^2$ , and Kruskal–Wallis tests. Cochran–Mantel–Haenszel and Cochran–Armitage tests were used to assess RBC transfusion trends across epochs. Multivariable logistic regression analysis was performed to identify independent clinical predictors for the outcome of  $\geq 1$  transfusions. A Poisson regression analysis for the outcome of adjusted mean number of transfusions by epoch was also performed. Adjusted effect plots of transfusion probability as a function of initial Hgb were calculated for each epoch. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc. Cary, NC).

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