Variation in Neonatal Transfusion Practice

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Objective To estimate the incidence of blood product transfusion, including red blood cells, platelets, and plasma, and characterize pretransfusion hematologic values for infants during their initial hospitalization after birth.

Study design Retrospective cohort study using data from 7 geographically diverse US academic and community hospitals that participated in the National Heart Lung and Blood Institute Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) from 2013 to 2016. Pretransfusion hematologic values were evaluated closest to each transfusion and no more than 24 hours beforehand.

Results Data from 60 243 infants were evaluated. The incidence of any transfusion differed by gestational age ($P < .0001$), with 80% (95% CI 76%-84%) transfused at <27 weeks of gestation (n = 329) and 0.5% (95% CI 0.5%-0.6%) transfused at ≥37 weeks of gestation (n = 53 919). The median pretransfusion hemoglobin was 11.2 g/dL (10th-90th percentile 8.8-14.1) for the entire cohort, ranging from 10.5 g/dL (8.8-12.3) for infants born extremely preterm at <27 weeks of gestation to 13.0 g/dL (10.5-15.5) for infants born at term. The median pretransfusion platelet count ($\times 10^9$/L) was 71 (10th-90th percentile 26-135) for the entire cohort, and was >45 for all gestational age groups examined. The median pretransfusion international normalized ratio for the entire cohort was 1.7 (10th-90th percentile 1.2-2.8).

Conclusions There is wide variability in pretransfusion hemoglobin, platelet count, and international normalized ratio values for neonatal transfusions. Our findings suggest that a large proportion of neonatal transfusions in the US are administered at thresholds greater than supported by the best-available evidence and highlight an opportunity for improved patient blood management. *(J Pediatr 2021;235:92-9).*

Anemia and thrombocytopenia are common in newborn infants and are often treated with red blood cell (RBC) and platelet transfusions. There are limited data describing neonatal transfusion practices in the US, with most studies in infants born extremely preterm and fewer data in more mature infants. One study estimated that RBC transfusion occurs in 0.43% of US neonatal admissions, although this incidence varied substantially between complicated vs uncomplicated births.[1]

In a 2012 international survey, almost one-half of the neonatal intensive care units (NICUs) surveyed did not have specific RBC transfusion guidelines, and clinicians reported wide variation in hemoglobin (Hb) transfusion thresholds used for infants born extremely preterm.[2] Similar variability was reported in a survey of platelet transfusion practices among US and Canadian neonatologists,[3] with most clinicians reporting the use of pretransfusion platelet count thresholds ≥50 × 10^9/L in the majority of clinical scenarios presented, despite this practice

ECMO	Extracorporeal membrane oxygenation
Hb	Hemoglobin
ICD	*International Classification of Diseases*
ICU	Intensive care unit
INR	International normalized ratio
NICU	Neonatal intensive care unit
RBC	Red blood cell
REDS-III	Recipient Epidemiology and Donor Evaluation Study-III

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not being supported by the best available evidence at the time.[4] Although surveys may not reflect actual transfusion practices, a retrospective multicenter cohort study among infants born preterm also found a wide range of pretransfusion platelet counts, with 65% being >50 × 10^9/L.[5] Data regarding plasma transfusion practices in newborn infants are sparse,[6] and evidence is lacking to support prophylactic plasma transfusions.[7] Italian centers reported that more than one-half of plasma transfusions given to patients in the NICU were not evidence-based.[8] However, a comprehensive evaluation of neonatal transfusion practices in the US, including thresholds used for transfusion, is currently lacking.

This study characterizes the epidemiology of neonatal transfusion practices in 7 US hospitals, which included infants admitted after birth and cared for in the NICU, as well as other hospital areas during the initial birth hospitalization. Our primary aim was to estimate the incidence of RBC, platelet, and plasma transfusions among newborn infants and to characterize pretransfusion hematologic thresholds by gestational age, postnatal age, and the presence of major neonatal comorbidities. We hypothesized, based on evidence from studies in infants born preterm, that there would be significant variability in transfusion incidence and in pretransfusion hematologic values among infants with different gestational ages and morbidities.

Methods

The National Heart, Lung, and Blood Institute Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) data are available as a public use dataset through BioLINCC. REDS-III involved 12 academic and community hospitals from 4 geographic regions of the US, of which 7 included newborn infants. Hospitals included both tertiary and quaternary centers, some of which performed cardiac and noncardiac surgery as well as extracorporeal membrane oxygenation (ECMO). The database, which covers a 4-year period beginning on January 1, 2013, has previously been described.[9] This dataset has been used to evaluate adult transfusion practices,[10,11] but this is the first report on neonatal transfusions. Approval for data collection was obtained from the institutional review board at each participating institution.

Study Population and Definitions

Infants born at participating REDS-III hospitals were followed from birth until hospital discharge, death, or 1 year of age if they remained hospitalized for that period (whichever occurred first) and included infants admitted to the NICU as well as to any other hospital area such as the pediatric ward or pediatric intensive care unit in the course of the birth admission. However, infants re-admitted after discharge home were not included. Gestational age (completed weeks), birth weight, and select diagnoses were determined from the *International Classification of Diseases* (ICD) *9/10* coding (codes available upon request). Laboratory values (Hb, platelet count, and international normalized ratio [INR]) closest in time to each transfusion and no more than 24 hours beforehand) were identified using a previously described approach[12] to capture pretransfusion values temporally relevant to transfusion. As the deidentified analysis dataset did not contain dates, we estimated the day of birth by using a common index medication administered at birth (vitamin K) in combination with a "Live-born" ICD 9/10 diagnosis code. This estimation was only used for analyses evaluating pretransfusion hematologic values by postnatal age.

Transfusion Exposures

A transfusion event was defined as the issuance of a blood product from the transfusion service. Data captured on the issued product included issue time, issue location (intensive care unit [ICU], operating room, procedure suite, or elsewhere), and a barcode (Codabar or ISBT 128) from which the product type was extracted.

Statistical Analyses

The sample size was fixed based on the REDS-III dataset. Transfusion incidence was calculated as a binomial proportion (% of infants) among birth admissions, and imprecision in estimates for this cohort were provided using corresponding 95% CIs. We estimated the incidence of any transfusion and of specific product types and compared the incidence by demographics, gestational age, and selected diagnoses. Density estimation plots were used to show the distribution of pretransfusion hematologic values by gestational age and diagnosis. *P* values comparing median pretransfusion hematologic values by gestational age, diagnosis, and postnatal age were calculated using the Kruskal–Wallis test, but pairwise comparisons were not performed to reduce type I error from multiple hypothesis testing. To determine the impact of center and case-mix, we tested whether there were differences in pretransfusion hematologic values among the study centers, after adjusting for gestational age group and whether an infant underwent any surgery during hospitalization using tests of Type III effects in a multivariable linear regression. We also evaluated whether location of surgery (operating room vs nonoperating room) was associated with pretransfusion hematologic values after adjusting for gestational age group and surgery. All analyses were conducted with SAS, version 9.4 (SAS Institute, Inc) and density estimation plots were generated with R version 4.1.0 (R Foundation for Statistical Computing).

Results

We evaluated a total of 60 243 infants, comprising all birth admissions at participating hospitals during the years of study. The cohort was 49% female and 10.5% preterm (<37 weeks of gestation), with 1.6% of infants being very low birth weight (<1500 g at birth) (**Table I**). Among the full cohort, the incidence of any blood product transfusion

Table I. Incidence of blood product transfusion, including specific components

Groups	Encounters	Any transfusion*	Any RBC	Any platelet	Any plasma
All	60 243	1.6 (1.5-1.7)	1.3 (1.2-1.4)	0.7 (0.6-0.7)	0.7 (0.6-0.7)
Sex					
Female	29 635	1.6 (1.4-1.7)	1.3 (1.2-1.4)	0.6 (0.5-0.7)	0.7 (0.6-0.7)
Male	30 608	1.7 (1.5-1.8)	1.4 (1.3-1.5)	0.7 (0.6-0.8)	0.7 (0.6-0.7)
Gestational age, wk†					
<27	329	80 (76-84)	70 (65-75)	34 (29-39)	24 (20-29)
27-28	288	49 (43-54)	44 (39-50)	12 (8-16)	11 (7-14)
29-32	996	16 (14-18)	13 (11-15)	5.8 (4.4-7.3)	4.7 (3.4-6.0)
33-36	4693	2.8 (2.3-3.2)	2.1 (1.7-2.5)	1.1 (0.8-1.4)	1.3 (1.0-1.6)
37+ weeks	53 919	0.5 (0.5-0.6)	0.4 (0.3-0.5)	0.3 (0.2-0.3)	0.3 (0.3-0.4)
Hospital stay >3 d					
<27 wk	295	81 (76-85)	71 (66-76)	34 (28-39)	23 (18-27)
27-28 wk	277	48 (42-54)	45 (39-51)	11 (7-14)	10 (7-14)
29-32 wk	987	16 (14-18)	13 (11-15)	5.8 (4.3-7.2)	4.6 (3.3-5.9)
33-36 wk	3063	4.1 (3.4-4.8)	3.1 (2.5-3.7)	1.6 (1.2-2.0)	1.8 (1.3-2.3)
37+ wk	8199	3.2 (2.8-3.6)	2.5 (2.2-2.8)	1.7 (1.4-2.0)	2.0 (1.7-2.3)
Birth weight, g‡					
<1000	443	74 (70-78)	64 (60-69)	31 (27-35)	19 (16-23)
1000 to <1500	518	26 (22-29)	22 (18-25)	7.9 (5.6-10.2)	6.2 (4.1-8.3)
1500 to <2500	3987	3.6 (3.0-4.2)	2.8 (2.3-3.3)	1.4 (1.0-1.7)	1.4 (1.0-1.7)
≥2500	55 285	0.7 (0.6-0.7)	0.5 (0.5-0.6)	0.3 (0.3-0.3)	0.4 (0.3-0.5)
Race§					
White	26 441	1.6 (1.4-1.7)	1.3 (1.2-1.4)	0.6 (0.5-0.7)	0.6 (0.5-0.7)
Black	10 109	2.0 (1.7-2.2)	1.6 (1.4-1.9)	0.9 (0.7-1.1)	0.7 (0.6-0.9)
Asian	3257	1.6 (1.2-2.0)	1.4 (1.0-1.8)	0.6 (0.3-0.8)	0.8 (0.5-1.1)
Not specified/other	20 436	1.5 (1.4-1.7)	1.3 (1.1-1.4)	0.7 (0.6-0.8)	0.6 (0.5-0.8)
Ethnicity					
Hispanic	9685	2.2 (1.9-2.5)	2.0 (1.7-2.2)	0.9 (0.7-1.1)	0.9 (0.7-1.1)
Non-Hispanic	41 511	1.7 (1.6-1.9)	1.4 (1.3-1.6)	0.7 (0.6-0.8)	0.7 (0.6-0.8)
Unknown	9047	0.5 (0.4-0.7)	0.2 (0.1-0.3)	0.3 (0.2-0.4)	0.1 (0.1-0.2)

All data are reported as % (95% CI), such that numbers in the table can be considered per 100 infants.
*Includes 1 infant who received cryoprecipitate without RBC, platelet, or plasma transfusion.
†Data not shown for 18 infants born preterm for whom gestational age was unknown.
‡Babies born at term who are missing a birth weight are assumed to be normal birth weight. Ten subjects have a premature diagnosis but no birth weight–related diagnosis or birth weight; thus, they are excluded from this stratification.
§Includes 324 patients of American Indian/Alaska Native descent, 62 of Native Hawaiian/Pacific Islander descent, 93 patients of more than 1 race, 9307 identified as other race, and 10 650 of unknown race.

was 1.6% (95% CI 1.5%-1.7%), with RBCs being the most common component transfused (1.3%; 95% CI 1.2%-1.4%), followed by platelets and plasma (each 0.7%; 95% CI 0.6%-0.7%). Among the most immature infants (<27 weeks of gestation), 80% (95% CI 76%-84%) had at least 1 transfusion exposure to any blood product, with 70% (95% CI 65%-75%) receiving RBCs, 34% (95% CI 29%-39%) platelets, and 24% (95% CI 20%-29%) plasma. The incidence of transfusion for all products decreased with increasing gestational age and was 0.5% (95% CI 0.5%-0.6%) among infants born full term at ≥37 weeks of gestation.

Next, we evaluated the incidence of transfusion among infants whose birth hospitalization was greater than 3 days (Table I), which excluded healthy newborns with a typical hospitalization duration as well as neonates with early death or transfer. Among this subset of infants born full term at ≥37 weeks of gestation with length of stay >3 days (n = 8199), 3.2% (95% CI 2.8%-3.6%) were exposed to transfusion (any blood product), with 2.5% (95% CI 2.2%-2.8%) receiving RBCs, 1.7% (95% CI 1.4%-2.0%) platelets, and 2% (1.7%-2.0%) plasma. By contrast, the incidence of any transfusion among the infants <27 weeks of gestation (n = 329) was 80%, which was numerically similar to the 81% among the subset of <27 weeks of gestation infants with length of stay >3 days (n = 295).

Incidence of Transfusion by Comorbidities

We estimated transfusion exposure among infants with various neonatal comorbidities (Table II). The incidence of any transfusion exposure ranged from 3.5% (95% CI 2.6%-4.4%) among infants with hemolytic disease of the fetus and newborn to 100% among infants undergoing cardiac surgery with cardiopulmonary bypass or ECMO, with similar variation in the use of specific blood components. In most diagnostic subgroups, RBCs were the most frequently transfused product, followed by platelets and plasma.

Pretransfusion Hematologic Values

In the entire cohort, a pretransfusion Hb within 24 hours before transfusion was available for 76% (2639) of RBC transfusions, which included multiple transfusions for some infants. The median pretransfusion Hb was 11.2 g/dL (10th-90th percentile 8.8-14.1). For those who received multiple transfusions, the pretransfusion Hb was 10.5 g/dL for the first transfusion and 11.4 g/dL for subsequent transfusions. Pretransfusion Hb values differed significantly by

Table II. Incidence of blood product transfusion, including specific components, among infants with specific diagnoses

Diagnoses	Encounters	Any transfusion*	Any RBC	Any platelet	Any plasma
NEC†	111	77 (70-85)	71 (63-80)	40 (31-49)	38 (29-47)
Chronic lung disease of prematurity or BPD	344	70 (65-75)	63 (58-68)	21 (17-26)	15 (11-19)
Intraventricular hemorrhage	415	54 (49-59)	45 (40-50)	23 (19-27)	20 (17-24)
Moderate or severe intraventricular hemorrhage	75	87 (79-94)	64 (53-75)	49 (38-61)	36 (25-47)
Sepsis	402	41 (36-46)	34 (29-38)	23 (19-27)	20 (16-24)
Retinopathy of prematurity	314	64 (58-69)	57 (52-63)	22 (17-27)	16 (12-20)
Hemolytic disease of the fetus and newborn	1526	3.5 (2.6-4.4)	3.3 (2.4-4.2)	1.4 (0.8-2.0)	1.4 (0.8-2.0)
Meconium aspiration	422	5.5 (3.3-7.6)	1.9 (0.6-3.2)	2.8 (1.3-4.4)	4.3 (2.3-6.2)
Hypoxic–ischemic encephalopathy	71	49 (38-61)	17 (8-26)	21 (12-31)	42 (31-54)
Congenital diaphragmatic hernia	77	77 (67-86)	70 (60-80)	30 (20-40)	53 (42-64)
Congenital diaphragmatic hernia, with ECMO	16	100 (100-100)	100 (100-100)	69 (46-91)	100 (100-100)
Congenital diaphragmatic hernia, without ECMO	61	70 (59-82)	62 (50-74)	20 (9.7-30)	41 (29-53)
Persistent pulmonary HTN‡	203	53 (46-60)	42 (36-49)	23 (17-29)	35 (28-42)
Persistent pulmonary HTN, with ECMO	18	100 (100-100)	100 (100-100)	78 (59-97)	94 (84-100)
Persistent pulmonary HTN, without ECMO	185	49 (41-56)	37 (30-44)	18 (12-23)	29 (23-36)
Acute renal failure	95	79 (71-87)	71 (61-80)	41 (31-51)	51 (40-61)
Cardiac surgery with bypass	93	100 (100-100)	99 (97-100)	83 (75-90)	94 (89-99)
Surgery without bypass	114	33 (25-42)	32 (24-41)	7.9 (2.9-12.8)	12 (6-18)
Without congenital heart disease	65	15 (7-24)	14 (5-22)	4.6 (0.0-9.7)	3.1 (0.0-7.3)
With congenital heart disease	49	57 (43-71)	57 (43-71)	12 (3-21)	24 (12-37)
Congenital heart disease, no surgery	1342	28 (25-30)	23 (21-26)	9 (8-11)	11 (10-13)
ECMO§	32	100 (100-100)	100 (100-100)	75 (60-90)	94 (85-100)

BPD, bronchopulmonary dysplasia; *HTN*, hypertension; *NEC*, necrotizing enterocolitis.
All data are reported as % (95% CI), such that numbers in the table can be considered per 100 infants.
*Includes 1 infant who received cryoprecipitate without RBC, platelet, or plasma transfusion.
†Includes 9 infants born at term (≥37 weeks of gestation) with NEC.
‡Includes 76 infants born preterm (<37 weeks of gestation) with a diagnosis of persistent pulmonary HTN.
§Includes the aforementioned patients with congenital diaphragmatic hernia and persistent pulmonary HTN.

gestational age ($P < .001$): Among infants <27 weeks of gestation, the median pretransfusion Hb was 10.5 g/dL (10-90th percentile 8.8-12.3), compared with 13.0 g/dL (10.5-15.5) among infants born full term (**Figure 1** and **Table III** [available at www.jpeds.com]). Pretransfusion Hb also varied by comorbid condition, with the greatest values found among infants with congenital diaphragmatic hernia (with or without ECMO), undergoing cardiopulmonary bypass, or on ECMO (**Figure 2** and **Table IV** [available at www.jpeds.com]).

Among the entire cohort, 93% (1162) of platelet transfusions had a pretransfusion platelet count, with a median of 71×10^9/L (10-90th percentile 26-135 $\times 10^9$/L). For those who received multiple transfusions, the pretransfusion platelet count was 70×10^9/L for the first transfusion and 71×10^9/L for subsequent transfusions. Pretransfusion platelet counts varied significantly by gestational age ($P < .001$), with a median pretransfusion platelet count of 70×10^9/L (33-100) among infants <27 weeks of gestation and a median platelet count of 85×10^9/L (17-185) among term infants (**Figure 1** and **Table V** [available at www.jpeds.com]). Among infants with different comorbidities, the greatest median pretransfusion platelet counts (>100×10^9/L) were found among infants on ECMO for congenital diaphragmatic hernia and/or persistent pulmonary hypertension of the newborn (**Figure 2** and **Table VI** [available at www.jpeds.com]). The median pretransfusion platelet count was >50×10^9/L for all diagnoses examined and all gestational age groups, with the exception of infants born at 33-36 weeks of gestation.

For plasma transfusions, a pretransfusion INR was available in 79% (895) of transfusions, and the median pretransfusion INR was 1.7 (10-90th percentile 1.2-2.8) among the entire cohort, which was 1.8 for the first transfusion and 1.7 for subsequent transfusions. When assessed based on gestational age, all gestational age subgroups had a median pretransfusion INR <2 except for infants born at 27-28 weeks of gestation, who had a median INR of 2.0 (**Figure 1** and **Table VII** [available at www.jpeds.com]). Similarly, infants in all diagnostic groups had median pretransfusion INR values <2, with the exception of meconium aspiration syndrome (2.0), hypoxic–ischemic encephalopathy (2.0), and surgery without cardiopulmonary bypass without congenital heart disease (2.4) (**Figure 2** and **Table VIII** [available at www.jpeds.com]).

Postnatal Age and Pretransfusion Hematologic Values

Next, we investigated whether pretransfusion Hb, platelet count, and INR values differed by postnatal age (**Tables III**, **V**, and **VII**). Overall, pretransfusion Hb values varied significantly by postnatal week of life in all gestational age groups, although they were not statistically significant for infants at 27-28 weeks of gestation (**Table III**). Significant differences in pretransfusion platelet count by week of life were observed among infants of all gestational ages except <27 weeks (**Table V**). Mean pretransfusion INR varied significantly with postnatal age in all gestational age groups except 29-32 and 33-36 weeks

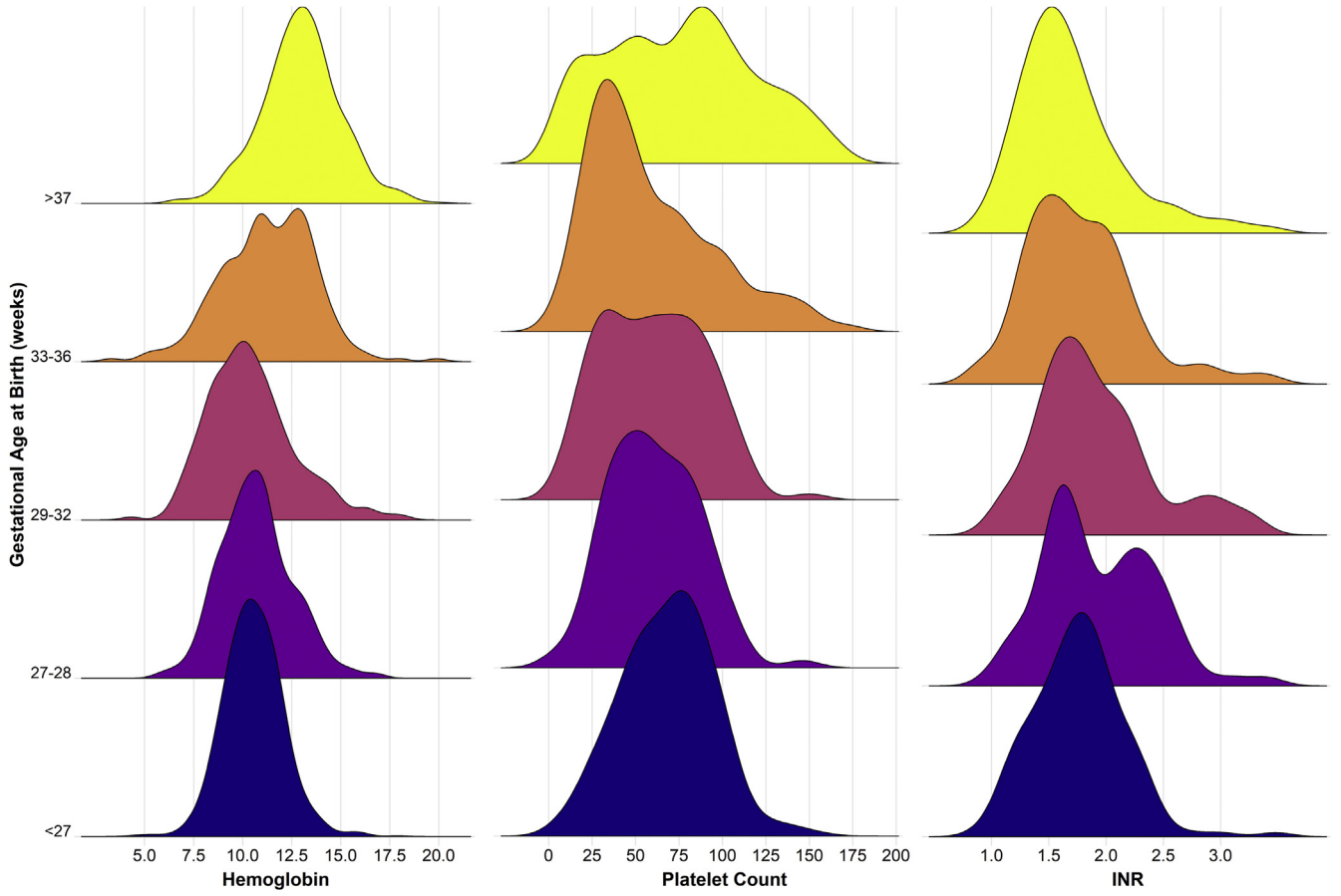

Figure 1. Pretransfusion hematologic values, stratified by gestational age. Density plots show the distribution of pretransfusion hematologic values for Hb (g/dL), platelet count ($\times 10^9$/L), and INR ($P < .001$ for testing for differences in median value by gestational age strata using Kruskal–Wallis test for each hematologic parameter).

(**Table VII**). The majority of pretransfusion hematologic values were observed within the first 4 months of life, although infants undergoing surgery comprised a larger proportion of transfusions evaluated after this period (**Table IX**; available at www.jpeds.com).

Differences in Pretransfusion Hematologic Values by Center and Location

In multivariable analyses adjusted for gestational age and surgical diagnosis, pretransfusion Hb ($P < .001$) and platelet counts ($P < .001$) differed among study centers but pretransfusion INR did not ($P = .17$). Most transfusions were administered in the ICU (62%), followed by non-ICU general ward (24%) and operating room (8%). Pretransfusion hematologic values differed between infants transfused in the operating room, compared with non- operating room setting, for Hb ($P < .001$) and platelet count ($P < .001$) but not INR ($P = .20$), after adjustment for surgical diagnosis and gestational age.

Number of Transfusions

The mean number of transfusions per patient (among infants receiving each product type) was 4.7 for RBCs, 3.3 for platelets, and 2.9 for plasma (**Table X**; available at www.jpeds.com).

Discussion

This study found marked variation in neonatal transfusion practices among a cohort of infants born and cared for in 7 US hospitals. Our findings suggested that many transfusions are administered at thresholds greater than supported by the best available evidence.

Our study cohort was unique in that it included newborn infants of all gestational ages admitted to the NICU as well as other hospital areas. Infants in this cohort were born at participating hospitals between 2013 and 2016, and thus our findings likely reflect contemporary transfusion practices. The incidence of any transfusion in our study was 1.6% (1.5-1.7), compared with 1.1% in another population-based study of neonatal and pediatric patients.[1] However, these overall population-based estimates for newborns mask the large variation in transfusion incidence among newborn infants of different gestational ages. In our study, the most immature infants born preterm had the greatest incidence of transfusion for all blood products.

Before 2013-2016, there were 2 randomized trials to guide RBC transfusion in infants born preterm. The multicenter Canadian Premature Infants in Need of Transfusion

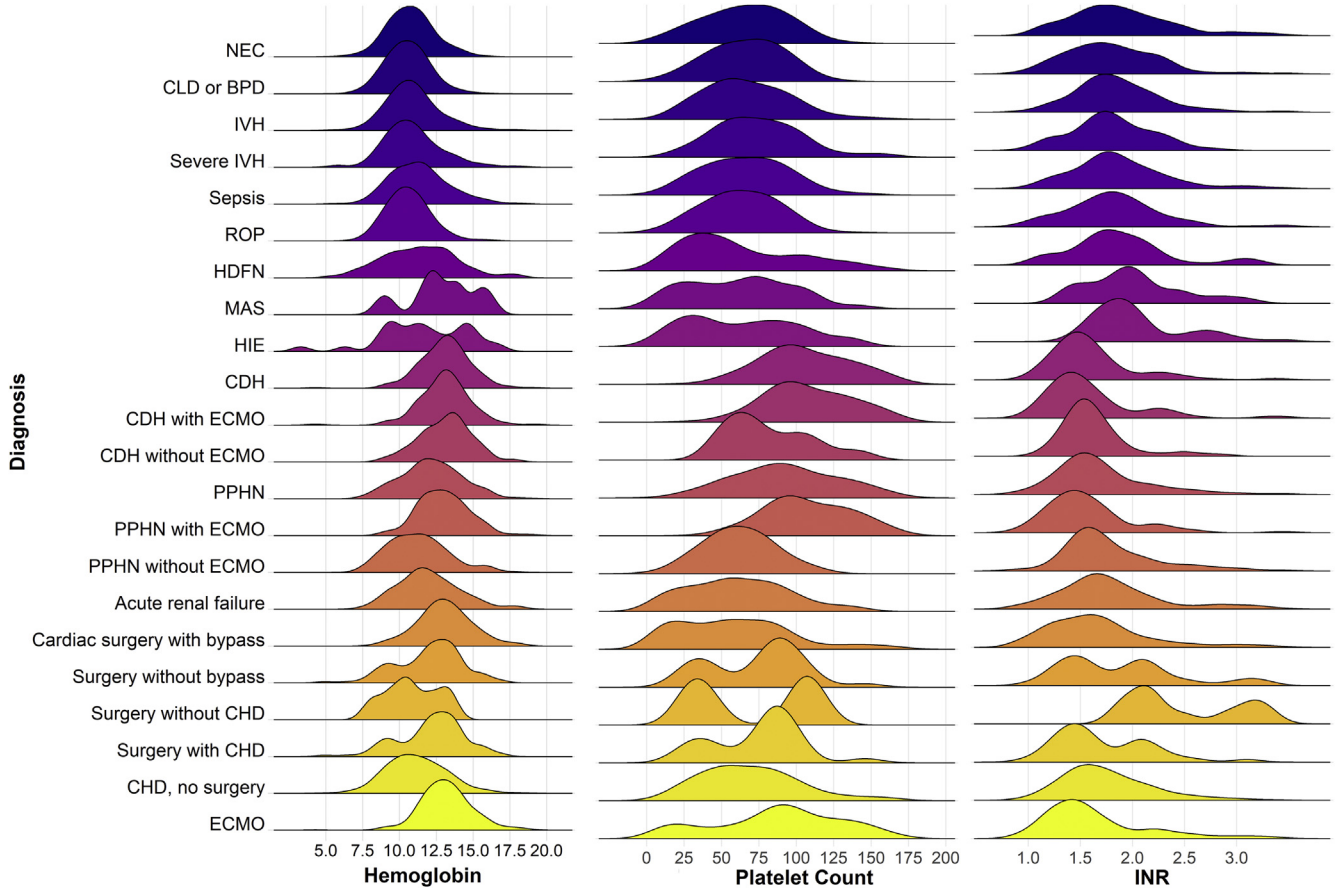

Figure 2. Pretransfusion hematologic values, stratified by diagnoses. Density plots shows the distribution of pretransfusion hematologic values for Hb (g/dL), platelet count ($\times 10^9$/L), and INR. Due to the skewed distribution of platelet data, the density estimation curves may span negative values. $P < .0001$ for test for difference in median values among groups using Kruskal–Wallis test. *BPD*, bronchopulmonary dysplasia; *CDH*, congenital diaphragmatic hernia; *CHD*, congenital heart disease; *CLD*, chronic lung disease; *HDFN*, hemolytic disease of the fetus and newborn; *HIE*, hypoxic–ischemic encephalopathy; *IVH*, intraventricular hemorrhage; *MAS*, meconium aspiration syndrome; *NEC*, necrotizing enterocolitis; *PPHN*, persistent pulmonary hypertension of the newborn; *ROP*, retinopathy of prematurity.

(PINT) trial, which enrolled 451 infants with extremely low birth weights (weighing <1000 g at birth), did not find a significant difference in mortality or short-term morbidity with the use of more liberal, compared with conservative, RBC transfusion thresholds.[13] In this trial, the greatest transfusion threshold in the restrictive/lower arm was a Hb of 11.5 g/dL. In our study, approximately one-quarter of infants ≤28 weeks of gestation had pretransfusion Hb values greater than this threshold, suggesting that a substantial proportion of infants in this cohort received RBC transfusions using a liberal Hb threshold. Long-term follow-up of the PINT trial suggested the possibility of worse cognitive outcomes among infants in the more restrictive transfusion arm,[14] and other studies have raised concerns regarding the risks of severe anemia on necrotizing enterocolitis.[15,16] In another single-center randomized trial, there was some evidence of worse short-term brain injury among infants born preterm randomized to a conservative, compared with a liberal, transfusion threshold,[17] although long-term brain growth and neurodevelopment were paradoxically worse in infants randomized to the liberal Hb threshold.[18] These conflicting findings highlight the historical uncertainty regarding optimal RBC transfusion thresholds in infants born preterm and may potentially explain the wide variation in Hb transfusion thresholds observed in our cohort.

The Effects of Liberal vs Restrictive Transfusion Thresholds on Survival and Neurocognitive Outcomes in Extremely Low-Birth-Weight Infants (ETTNO) trial enrolled 1013 infants with a birth weight <1000 g from 36 neonatal units in Europe and found no difference in either short-term morbidity or long-term survival without neurodevelopmental impairment among infants randomized to higher vs lower Hb transfusion thresholds.[19] Another recently published multicenter trial conducted by the National Institute of Child Health and Human Development Neonatal Research Network randomized 1824 infants born extremely preterm to higher vs lower Hb thresholds and reported no significant difference in survival without

neurodevelopmental impairment between study arms.[20] Both of these more recent trials, published after REDS-III was completed, are likely to support the use of lower Hb transfusion thresholds for infants born preterm, given the lack of benefit observed with use of greater transfusion thresholds.

For platelet transfusions, the incidence was greatest among the infants born most preterm (34% among <27 weeks of gestation). There have been a limited number of trials investigating platelet transfusion practices in infants born preterm, and none conducted in the US. A multicenter Canadian trial published in 1993 found no benefit in the use of platelet transfusion thresholds >50 × 10^9/L to prevent the incidence or progression of intracranial bleeding in infants born preterm.[4] In our study, however, more than one-half of infants born preterm received platelet transfusions at thresholds >50 × 10^9/L. More recently, a multicenter randomized trial conducted in Europe (PlaNeT-2) found evidence of harm, with an increased risk of death or serious bleeding associated with the use of a platelet transfusion threshold of 50 × 10^9/L, compared with 25 × 10^9/L, among infants <34 weeks of gestation.[21] Although 39% of infants in that trial received platelet transfusions before enrollment, these data generally support more conservative platelet transfusion practices and suggest that platelet transfusion exposure could be decreased substantially among US infants with the adoption of the lower threshold of 25 × 10^9/L. However, it is important to note that our study included a more heterogeneous population of infants born at term and preterm than was studied in the PlaNeT-2 trial, and therefore pretransfusion thresholds may not be directly comparable.

Trial data to guide prophylactic plasma transfusion thresholds in infants born at term and preterm are lacking. There are limited data in this population to identify INR values above which bleeding risk increases, with 2 studies reporting that INR and fibrinogen were associated with bleeding risk among infants with hypoxic–ischemic encephalopathy[22,23] and one suggesting that maintaining an INR <2 could prevent bleeding in this population. In our study, we found large variation in pretransfusion INR among infants with hypoxic–ischemic encephalopathy, with the 10th to 90th percentile ranging from 1.6 to 3.8.

We believe our study supports the application of patient blood management to the neonatal population. Increased efforts to support the translation of evidence into practice may be needed to promote evidence-based neonatal transfusion practices. One past study highlighted the importance of monitoring compliance with transfusion guidelines and reported improvements in outcomes following such efforts.[24] Patient blood management could be particularly useful in the preterm population, where a sufficient body of evidence is available to guide practice. However, data for term infants, including those undergoing surgery or ECMO, are limited and largely derived from observational studies. One study suggested that the use of a hematocrit of 35% (corresponding to a Hb of ~11.7 g/dL), instead of 40% (corresponding to a Hb of 13.3 g/dL), for transfusion during ECMO could reduce RBC transfusions without worse outcomes.[25] In our study, the median pretransfusion Hb among infants on ECMO was 13.1 g/dL, suggesting that evaluation of the safety and efficacy of more conservative thresholds is warranted, although we were unable to differentiate thresholds for blood products used to prime an ECMO circuit with those used for transfusion once an infant was on ECMO. Another study noted a higher risk of mortality among infants on ECMO with greater RBC and platelet transfusion exposure, even after controlling for illness severity,[26] and similar findings regarding the adverse effects of platelet transfusion were reported in a recent multicenter study of pediatric patients receiving ECMO.[27] By contrast, among infants undergoing surgery, one study found that a preoperative hematocrit <40% (corresponding to a Hb of 13.3 g/dl) was associated with greater odds of postoperative mortality,[28] although residual confounding may have led to bias.[29] In addition to infants on ECMO, newborn infants undergoing cardiac surgery with cardiopulmonary bypass had the greatest incidence of transfusions and highest transfusion thresholds in our study. Recent studies have described an association between RBC transfusions after stage 1 palliation and worse clinical outcomes[30] and between platelet transfusions during bypass rewarming and improved neonatal outcomes.[31] Taken together, these findings highlight the need for additional studies to guide transfusion decisions in the term, surgical and ECMO populations of infants, who are currently transfused at the greatest Hb and platelet count thresholds.

Our study has several limitations. Our goal was to estimate neonatal transfusion practices and not how they relate to specific outcomes; therefore, we were unable to determine the benefits or harms from the various pretransfusion hematologic values. We believe randomized trials are better suited for such evaluations. In addition, we could not determine whether transfusions were administered prophylactically or in response to bleeding or other circumstances that may explain the variation we observed in pretransfusion hematologic values. Finally, we relied on ICD 9/10 determination of gestational age, birth weight and comorbid conditions, and some misclassification is possible. Although outside the scope of this study, we also recognize that there is substantial center-to-center variability in the characteristics and modifications of the blood products transfused, such as the type of anticoagulant preservative solution for RBCs, the storage duration, the use and timing of irradiation, the use of pathogen inactivation technology for platelets, and ABO matching, among others. Additional studies are needed to investigate this product variability and the potential effects of these variables on neonatal outcomes. Finally, the centers that comprised this cohort may not be generalizable to all types of settings in which newborn infants are cared.

In conclusion, our study demonstrated wide variability in neonatal transfusion practices and suggests that a high percentage of transfusions given to infants in the US may be administered at thresholds greater than supported by the best available evidence. Our findings highlight the need to translate the existing evidence into patient blood

management in the neonatal population, to reduce unnecessary transfusion exposures and associated risks while potentially improving short- and long-term outcomes. ■

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Table III. Hb measured within 24 hours before RBC transfusion, by gestational and postnatal age

Gestational and postnatal ages*	n	10th %tile	25th %tile	50th %tile	75th %tile	90th %tile	P†
All	2639	8.8	9.8	11.2	12.7	14.1	
<27 wk	1020	8.8	9.6	10.5	11.5	12.3	<.0001
Week 1 of life	325	8.9	9.9	10.8	11.8	12.8	
Week 2 of life	185	9.0	9.8	10.8	11.6	12.4	
Week 3 of life	117	9.2	9.6	10.4	11.4	12.2	
Week 4 or more of life	393	8.5	9.3	10.1	11.1	11.9	
27-28 wk	328	8.4	9.5	10.6	11.8	13.2	.05
Week 1 of life	93	9.0	10.0	11.0	11.7	13.1	
Week 2 of life	51	9.0	9.6	10.7	11.6	12.4	
Week 3 of life	43	8.4	8.8	9.9	11.1	13.0	
Week 4 or more of life	141	8.2	9.1	10.5	12.3	13.3	
29-32 wk	249	7.9	8.8	10.2	11.6	13.5	.004
Week 1 of life	73	8.4	9.8	10.6	12.4	14.7	
Week 2 of life	19	7.0	8.6	9.3	10.7	12.5	
Week 3 of life	26	7.4	8.2	9.8	10.5	11.7	
Week 4 or more of life	131	7.9	8.6	10.0	11.7	13.3	
33-36 wk	234	8.2	9.6	11.3	13.0	14.0	.004
Week 1 of life	65	7.9	9.3	11.0	12.7	13.9	
Week 2 of life	37	9.6	11.0	12.3	13.8	14.7	
Week 3 of life	28	8.5	10.5	12.2	13.0	14.0	
Week 4 or more of life	104	8.1	9.3	11.1	12.8	13.5	
37+ wk	801	10.5	11.8	13.0	14.1	15.5	.002
Week 1 of life	210	10.3	11.9	13.2	14.9	15.9	
Week 2 of life	171	11.1	12.0	13.3	14.3	15.4	
Week 3 of life	90	10.8	11.8	12.8	14.0	15.7	
Week 4 or more of life	330	9.9	11.5	12.7	13.9	15.0	

Hb values are reported in g/dL.

*Seven infants born preterm with unspecified gestational age not shown.

†*P* values report tests for differences in median values by week of life using the Kruskal–Wallis test.

Table IV. Hb measured within 24 hours before RBC transfusion, by diagnosis

Diagnoses	n	10th %tile	25th %tile	50th %tile	75th %tile	90th %tile
All	2639	8.8	9.8	11.2	12.7	14.1
NEC	453	8.9	9.6	10.7	11.7	12.9
Chronic lung disease of prematurity or BPD	917	8.7	9.6	10.5	11.5	12.4
Intraventricular hemorrhage	735	8.8	9.7	10.8	11.8	13.3
Moderate or severe intraventricular hemorrhage	227	8.8	9.6	10.7	12.1	13.6
Sepsis	633	9	9.9	11.2	12.5	14.1
Retinopathy of prematurity	830	8.8	9.6	10.5	11.5	12.4
Hemolytic disease of the fetus and newborn	143	8.2	9.5	11.4	13.1	14.6
Meconium aspiration	13	9.3	11.7	12.5	14.1	15.7
Hypoxic–ischemic encephalopathy	30	8.65	9.5	11.55	14.5	15.15
Congenital diaphragmatic hernia	199	11.1	12	13.2	14.1	15.3
Congenital diaphragmatic hernia, with ECMO	144	11.1	12	13.1	14	15.1
Congenital diaphragmatic hernia, without ECMO	55	10.6	11.9	13.2	14.1	15.3
Persistent pulmonary hypertension	325	9.4	11	12.1	13.6	15
Persistent pulmonary hypertension, with ECMO	172	11.1	11.8	12.9	14.1	15.3
Persistent pulmonary hypertension, without ECMO	153	8.8	9.8	11.1	12.5	13.9
Acute renal failure	496	9.3	10.6	11.8	13.3	14.9
Cardiac surgery, with cardiopulmonary bypass	551	10.8	12	13.1	14.1	15.4
Surgery, without cardiopulmonary bypass	118	9	10.6	12.4	13.5	14.5
Without congenital heart disease	13	8.4	9.5	10.7	12.2	13.3
With congenital heart disease	105	9	11.2	12.4	13.7	14.6
Congenital heart disease	871	8.7	9.7	11	12.5	13.8
ECMO*	421	11.3	12.1	13.1	14.1	15.4

Hb values are reported in g/dL.
BPD, bronchopulmonary dysplasia; *NEC*, necrotizing enterocolitis.
*Includes the aforementioned patients with congenital diaphragmatic hernia and persistent pulmonary hypertension.

Table V. Platelet values measured within 24 hours before platelet transfusion, by gestational and postnatal age

Gestational and postnatal ages*	n	10th %tile	25th %tile	50th %tile	75th %tile	90th %tile	*P*†
All	1162	26	44	71	96	135	
<27 wk	373	33	50	70	86	100	.0007
Week 1 of life	137	44	60	77	92	105	
Week 2 of life	72	33	50	67	85	96	
Week 3 of life	37	34	53	66	77	98	
Week 4 or more of life	127	26	43	64	82	98	
27-28 wk	95	30	40	58	81	93	.03
Week 1 of life	45	33	47	64	82	94	
Week 2 of life	15	41	56	69	94	108	
Week 3 of life	8	20	27	56	77	90	
Week 4 or more of life	27	30	38	49	59	84	
29-32 wk	124	22	35	62	84	102	.01
Week 1 of life	62	22	32	53	82	94	
Week 2 of life	6	22	23	75	87	150	
Week 3 of life	10	9	17	39	74	89	
Week 4 or more of life	46	31	52	74	96	114	
33-36 wk	119	23	30	47	88	129	0.21
Week 1 of life	66	19	30	46	74	99	
Week 2 of life	22	25	27	63	124	129	
Week 3 of life	13	26	33	99	143	148	
Week 4 or more of life	18	25	35	51	65	79	
37+ wk	450	17	47	85	124	185	<0.0001
Week 1 of life	189	25	50	90	134	206	
Week 2 of life	121	38	73	98	132	191	
Week 3 of life	47	9	17	83	125	180	
Week 4 or more of life	93	13	29	58	85	113	

Platelet values are reported as $\times 10^9$/L.
*Two infants born preterm with unspecified gestational age not shown.
†*P* values report tests for differences in median values by week of life using the Kruskal–Wallis test.

Table VI. Platelet values measured within 24 hours before platelet transfusion, by diagnosis

Diagnoses	n	10th %tile	25th %tile	50th %tile	75th %tile	90th %tile
All	1162	26	44	71	96	135
NEC	228	29	47	69	87	105
Chronic lung disease of prematurity or BPD	292	32	49	69	85	98
Intraventricular hemorrhage	287	30	47	64	87	105
Moderate or severe intraventricular hemorrhage	84	42	55	76	97	107
Sepsis	413	29	45	67	86	104
Retinopathy of prematurity	281	29	45	63	81	97
Hemolytic disease of the fetus and newborn	87	17	32	54	99	134
Meconium aspiration	34	15	34	68	93	109
Hypoxic-ischemic encephalopathy	40	18	32	64	94	113
Congenital diaphragmatic hernia	163	72	87	106	135	166
Congenital diaphragmatic hernia, with ECMO	151	74	89	108	138	170
Congenital diaphragmatic hernia, without ECMO	12	49	61	74	103	116
Persistent pulmonary hypertension	270	51	71	95	125	155
Persistent pulmonary hypertension, with ECMO	188	75	89	108	136	166
Persistent pulmonary hypertension, without ECMO	82	32	47	63	78	95
Acute renal failure	243	16	33	60	86	114
Cardiac surgery, with cardiopulmonary bypass	192	14	33	70	129	273
Surgery, without cardiopulmonary bypass	34	30	43	85	97	114
Without congenital heart disease	6	27	33	72	107	114
With congenital heart disease	28	30	51	85	95	146
Congenital heart disease	441	30	46	68	92	121
ECMO*	302	23	65	95	126	157

Platelet values are reported as $\times 10^9$/L.
*Includes the aforementioned patients with congenital diaphragmatic hernia and persistent pulmonary hypertension.

Table VII. INR values measured within 24 hours before plasma transfusion, by gestational and postnatal age

Gestational and postnatal age*	n	10th %tile	25th %tile	50th %tile	75th %tile	90th %tile	*P*†
All	895	1.2	1.5	1.7	2.1	2.8	
<27 wk	152	1.2	1.5	1.8	2.0	2.3	.0002
Week 1 of life	77	1.5	1.7	1.9	2.2	2.4	
Week 2 of life	39	1.3	1.6	1.8	1.9	2.2	
Week 3 of life	5	1.2	1.5	1.6	1.8	3.7	
Week 4 or more of life	31	1.1	1.2	1.4	1.7	2.2	
27-28 wk	81	1.5	1.6	2.0	2.4	3.4	.03
Week 1 of life	52	1.5	1.6	1.9	2.3	2.6	
Week 2 of life	11	1.6	2.1	2.5	3.8	6.6	
Week 3 of life	3	1.5	1.5	2.3	2.6	2.6	
Week 4 or more of life	15	1.2	1.2	1.6	2.6	3.5	
29-32 wk	106	1.4	1.6	1.8	2.2	2.9	.62
Week 1 of life	56	1.5	1.6	1.9	2.2	2.8	
Week 2 of life	9	1.2	1.4	1.8	1.9	12.1	
Week 3 of life	6	1.4	1.5	1.8	3.0	4.0	
Week 4 or more of life	35	1.2	1.5	1.8	2.2	2.9	
33-36 wk	115	1.3	1.5	1.8	2.1	3.4	.04
Week 1 of life	79	1.4	1.5	1.8	2.3	3.8	
Week 2 of life	18	1.2	1.4	1.6	1.9	2.4	
Week 3 of life	7	1.2	1.2	1.3	2.0	2.1	
Week 4 or more of life	11	0.9	0.9	1.9	2.3	2.4	
37+ wk	438	1.2	1.4	1.6	2.0	2.6	.0006
Week 1 of life	241	1.3	1.5	1.7	2.1	2.7	
Week 2 of life	84	1.2	1.3	1.5	1.8	2.1	
Week 3 of life	37	1.2	1.3	1.5	1.9	2.6	
Week 4 or more of life	76	1.1	1.4	1.6	2.0	3.2	

*Two values for infants born preterm with unspecified gestational age not shown.
†*P* values report tests for differences in median values by week of life using the Kruskal–Wallis test.

Table VIII. INR values measured within 24 hours before plasma transfusion, by diagnosis

Diagnoses	n	10th %tile	25th %tile	50th %tile	75th %tile	90th %tile
All	895	1.2	1.5	1.7	2.1	2.8
NEC	123	1.3	1.6	1.9	2.3	3.1
Chronic lung disease of prematurity or BPD	116	1.2	1.5	1.7	2.1	2.3
Intraventricular hemorrhage	196	1.4	1.6	1.9	2.2	3.0
Moderate or severe intraventricular hemorrhage	69	1.3	1.6	1.8	2.2	2.6
Sepsis	263	1.4	1.6	1.8	2.2	2.7
Retinopathy of prematurity	120	1.2	1.6	1.8	2.1	3.3
Hemolytic disease of the fetus and newborn	60	1.3	1.6	1.8	2.1	3.0
Meconium aspiration	43	1.5	1.8	2.0	2.8	3.8
Hypoxic–ischemic encephalopathy	64	1.6	1.8	2.0	2.6	3.8
Congenital diaphragmatic hernia	136	1.2	1.4	1.5	1.7	2.2
Congenital diaphragmatic hernia, with ECMO	90	1.2	1.3	1.5	1.7	2.2
Congenital diaphragmatic hernia, without ECMO	46	1.3	1.5	1.6	1.7	2.0
Persistent pulmonary hypertension	217	1.3	1.4	1.6	1.9	2.4
Persistent pulmonary hypertension, with ECMO	90	1.2	1.3	1.5	1.7	2.2
Persistent pulmonary hypertension, without ECMO	127	1.4	1.5	1.7	2.1	2.7
Acute renal failure	184	1.2	1.5	1.7	2.1	3.0
Cardiac surgery, with cardiopulmonary bypass	190	1.2	1.3	1.6	1.9	2.6
Surgery, without cardiopulmonary bypass	52	1.3	1.5	1.9	2.2	3.1
Without congenital heart disease	12	1.9	2.1	2.4	3.2	3.3
With congenital heart disease	40	1.3	1.4	1.6	2.1	2.5
Congenital heart disease	383	1.3	1.5	1.7	2.1	2.6
ECMO*	180	1.2	1.3	1.5	1.9	2.6

*Includes the aforementioned patients with congenital diaphragmatic hernia and persistent pulmonary hypertension.

Table IX. Pretransfusion hematologic values by postnatal age among infants with and without surgery

	Hb		Platelet count		INR	
Postnatal ages	N	Median	N	Median	N	Median
<4 wk						
All infants	1800	11.3	934	73	766	1.7
Surgery	502	13.1	306	103	246	1.6
No surgery	1298	10.8	628	61	520	1.8
≥4 wk						
All infants	839	10.9	228	63	129	1.60
Surgery	319	12.7	96	75	85	1.6
No surgery	520	10	132	55	44	1.5
<4 mo						
All infants	2529	11.1	1119	70	867	1.7
Surgery	736	13.1	361	97	303	1.6
No surgery	1793	10.5	758	60	564	1.8
≥4 mo						
All infants	110	11.8	43	81	28	1.4
Surgery	85	12.4	41	81	28	1.4
No surgery	25	9.6	2	97	0	—

Hb values are in g/dL and platelet values are reported as $\times 10^9$/L.
Surgery includes infants who had cardiac and noncardiac surgery and ECMO.

Table X. Number of blood product transfusions and duration of birth hospitalization by product type and birth weight

		No. transfusions		Length of stay, d	
Products and birth weights	N	Mean	Median	Mean	Median
RBCs	808	4.7	3	64	55
<1000 g	284	5.3	4	81	82
1000 to <1500 g	113	2.4	2	59	55
1500 to <2500 g	111	3.2	2	52	37
≥2500 g	300	5.7	3	55	41
Plasma	393	2.9	2	54	29
<1000 g	85	2.3	1	71	54
1000 to <1500 g	32	2.9	2	44	33
1500 to <2500 g	55	2.5	2	52	28
≥2500 g	221	3.3	2	49	28
Platelets	400	3.3	1	58	32
<1000 g	138	3.4	2	75	65
1000 to <1500 g	41	2.2	1	44	38
1500 to <2500 g	55	2.7	1	52	28
≥2500 g	166	3.6	1	50	27
Missing	22	3.1	2	68	73