Red Blood Cell Transfusions are Independently Associated with Intra-Hospital Mortality in Very Low Birth Weight Preterm Infants

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Objective To test the hypothesis that red blood cell (RBC) transfusions in preterm infants are associated with increased intra-hospital mortality.

Study design Variables associated with death were studied with Cox regression analysis in a prospective cohort of preterm infants with birth weight <1500 g in the Brazilian Network on Neonatal Research. Intra-hospital death and death after 28 days of life were analyzed as dependent variables. Independent variables were infant demographic and clinical characteristics and RBC transfusions.

Results Of 1077 infants, 574 (53.3%) received at least one RBC transfusion during the hospital stay. The mean number of transfusions per infant was 3.3 ± 3.4, with 2.1 ± 2.1 in the first 28 days of life. Intra-hospital death occurred in 299 neonates (27.8%), and 60 infants (5.6%) died after 28 days of life. After adjusting for confounders, the relative risk of death during hospital stay was 1.49 in infants who received at least one RBC transfusion in the first 28 days of life, compared with infants who did not receive a transfusion. The risk of death after 28 days of life was 1.89 times higher in infants who received more than two RBC transfusions during their hospital stay, compared with infants who received one or two transfusions.

Conclusion Transfusion was associated with increased death, and transfusion guidelines should consider risks and benefits of transfusion. *(J Pediatr 2011;159:371-6)*.

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Despite recent efforts to decrease allogeneic red blood cell (RBC) transfusion thresholds, they remain an important supportive and life-saving intervention for neonatal intensive care patients.[1-6]

Concerns about the harm of RBC transfusions are traditionally focused on infections, but these risks have been progressively reduced.[7] Currently, lung injury, organ dysfunction, or both, hemolytic transfusion reactions, and transfusion related-sepsis are considered the most frequent causes of morbidity and mortality in adults.[8] In the neonatal setting, these effects are rarely suspected, and their effect on infant clinical condition and mortality rate is not fully understood.[9,10]

There is a growing body of evidence that RBC transfusions are independently associated with short- and long-term mortality, on the basis of observational studies in adults[11,12] and several plausible biological models of how transfusions may be harmful.[13] In adult patients who underwent cardiac surgery, RBC transfusions were strongly associated with a wide range of postoperative morbidity and with increased mortality rates as long as 5 years after surgery.[14] Kamper-Jorgensen et al reported higher short- and long-term mortality rates in 1 118 261 transfusion recipients than in the general population. The mortality ratio was 17.6 times higher during the first 3 months after the first transfusion and remained higher for transfusions recipients 1 to 4 years after the first transfusion (2.1 times) and even 17 years after (1.3 times).[11] Kneyber et al reported a higher mortality rate in children who received a transfusion compared with children and adolescents who did not receive a transfusion.[15] However, in the neonatal setting, especially in very low birthweight preterm infants who frequently receive multiple RBC transfusions, the association between RBC transfusions and mortality rate is unknown. Therefore, the objective of this study was to test the hypothesis that RBC transfusions in very low birth weight preterm infants are independently associated with an increase in intra-hospital mortality rates.

IVH	Intraventricular hemorrhage
RBC	Red blood cell
SNAPPE II	Score for Neonatal Acute Physiology–Perinatal Extension

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Methods

This multicenter study enrolled a cohort of preterm infants with birth weight <1500 g born in 8 centers of the Brazilian Network on Neonatal Research. It was a retrospective study, but the clinical data were prospectively entered in the database. The network 8 units were referral centers for high-risk pregnancies, treating patients of the Brazilian National Health System almost exclusively. The 8 centers had 282 intensive and intermediate care beds, varying from 20 to 48 beds per unit, with similar equipment and human resources in the units.

Neonates included in the study underwent transfusion according to 8 independent guidelines for allogeneic RBC transfusions defined by each neonatal intensive care unit (**Table I**; available at www.jpeds.com).[16] All RBC units were collected from volunteers in citrate-phosphate-dextrose-adenine-1 anticoagulant which were gamma irradiated and depleted of leukocytes before storage. To avoid hyperkalemia, irradiated RBC units stored for as long as 28 days were transfused in small aliquots of 15 mL/kg, slowly in 4 hours.[17]

Preterm infants born with gestational ages of 23.0 to 36.9 weeks of and birth weights of 400 to 1495 g in the 8 centers from January 2006 to December 2007 were included. Infants with major congenital anomalies were excluded.

These data were recorded: number of births in each center, neonatal demographic and clinical characteristics, intra-hospital deaths (death at any time during hospital stay and death after 28 days of life), percentage of neonates receiving at least one RBC transfusion during the first 28 days and during hospital stay, and number of RBC transfusions performed from 1 to 14 days, 15 to 28 days, and after 28 days of life until discharge from the hospital.

For clinical data, these neonatal characteristics were analyzed: gestational age (weeks); birthweight (g); Apgar score in the first and fifth minutes of life (categorized as <7 and 7-10); SNAPPE II[18] (Score for Neonatal Acute Physiology–Perinatal Extension, scored during the first 12 hours of life and stratified in <45 and ≥45); small for gestational age (birthweight <10th percentile for gestational age according to Alexander et al[19]); presence of respiratory distress syndrome; any grade of intraventricular hemorrhage (IVH) identified with intracranial ultrasound in the first week of life; and early- and late-onset sepsis (clinical sepsis diagnosed in the first 48 hours and after 48 hours of life, respectively).

Comparisons in groups were done with the two-tailed χ^2 test for categorical variables and t tests for continuous variables. To analyze the hazard of death, univariate and multivariate Cox regression analyses were applied. Differences were considered significant when P values were <.05. SPSS software for Windows version 17.0 (SPSS Inc, Chicago, Illinois) was used for all statistical procedures.

This study was approved by the ethical committee of each center and by the ethical committee of the Universidade Federal de São Paulo, Brazil, the lead center for this study.

Results

During the studied period, 1226 infants were born at 23.0 to 36.9 weeks of gestation with birth weight of 400 to 1495 g. Of these infants, 149 (12.2%) with congenital anomalies were excluded.

The main demographic characteristics of the 1077 remaining patients were: gestational age of 29.0 ± 2.8 weeks (30.2% <28 weeks), birth weight of 1046 ± 288 g (42.3% <1000 g), 40.7% (438/1076) were small for gestational age, 17.5% (188/1075) had a 5-minute Apgar score <7, and 16.4% (172/1046) had a SNAPPE II score ≥45. For morbidity, respiratory distress syndrome was present in 56.0% of patients (593/1058), any grade of IVH was present in 35.2% of patients (324/920), early-onset clinical sepsis was present in 41.9% of patients (448/1068), clinical late-onset sepsis was present in 41.9% of patients (447/1068), and necrotizing enterocolitis was present in 7.5% of patients (79/1058). The frequency of infants with gestational age <28 weeks ($P = .003$), 1-minute Apgar score <7 ($P < .001$), 5-minute Apgar score <7 ($P = .004$), SNAPPE II score ≥45 ($P < .001$), respiratory distress syndrome ($P < .001$), IVH ($P < .001$), early-onset sepsis ($P < .001$), late-onset sepsis ($P < .001$), and necrotizing enterocolitis ($P = .007$) were different in the centers.

Intra-hospital death occurred in 299 infants (27.8%), 29.1%, 25.4%, 36.5%, 28.4%, 22.5%, 25.0%, 27.9% and 25.5% in centers 1, 2, 3, 4, 5, 6, 7 and 8, respectively (χ^2 test for differences between centers, $P = .363$). Of the patients studied, 201 (18.7%) died before 14 days of life, 38 (3.5%) died in 15 to 28 days, and 60 (5.6%) died after 28 days.

Of the 1077 infants, 574 (53.3%) received at least one RBC transfusion during the hospital stay, 501 (46.5%) received at least one transfusion in the first 28 postnatal days, and 365 (33.9%) received more than one transfusion during their hospital stay. The frequency of infants who received at least one RBC transfusion during hospital stay varied in the centers (χ^2 test, $P < .001$): center 1, 46.6% (48/103); center 2, 53.1% (69/130); center 3, 48.9% (67/137); center 4, 59.3% (96/162); center 5, 46.5% (33/71); center 6, 47.4% (74/156); center 7, 72.7% (120/165); and center 8, 43.8% (67/153).

Of the 1908 transfusions performed, 738 (38.7%) were in the first 14 days of life, 495 (25.9%) were in 15 to 28 days of life, and 675 (35.4%) were after 28 days of life. The mean number of transfusions per infant during hospital stay was 3.3 ± 3.4, with a median of 2 (quartile range, 1 to 4). The mean number of transfusions per infant was 1.3 ± 1.5 in the first 14 days of life; 0.9 ± 1.1 in 15 to 28 days; and 1.2 ± 2.1 after 28 days until discharge from the hospital.

The number of RBC transfusions was higher in infants with these characteristics: 1-minute Apgar score <7 (2.1 ± 3.3 versus 1.3 ± 2.5, $P < .001$), 5-minute Apgar score <7 (2.4 ± 3.8 versus 1.7 ± 2.8, $P = .003$), SNAPPE II ≥45 (2.8 ± 4.2 versus 1.6 ± 2.7, $P < .001$), respiratory distress syndrome (2.1 ± 2.9 versus 1.5 ± 3.1, $P = .001$), IVH (2.9 ± 3.9 versus 1.4 ± 2.5, $P < .001$), early-onset sepsis (2.5 ± 3.6

Table II. Demographic and clinical characteristics of the neonates who died at any time during hospital stay and neonates who were discharged from the hospital alive

	Death at any time during hospital stay (n = 299)	Discharged alive (n = 778)	*P* value
Gestational age (weeks)	26.8 ± 2.5	29.8 ± 2.5	<.001
Gestational age <28 weeks	63.5%	17.4%	<.001
Birth weight (g)	800 ± 244	1141 ± 244	<.001
Birth weight <1000 g	79.9%	27.9%	<.001
Small for gestational age	34.6%	43.1%	.011
1-minute Apgar <7	78.0%	47.6%	<.001
5-minute Apgar <7	39.6%	9.0%	<.001
SNAPPE II ≥45	48.0%	5.5%	<.001
Respiratory distress syndrome	82.1%	46.7%	<.001
Early-onset sepsis	55.2%	37.0%	<.001
Late–onset sepsis	44.1%	41.0%	.356
Necrotizing enterocolitis	15.7%	4.5%	<.001
IVH*	55.5%	30.5%	<.001
Days of hospital stay	18 ± 30	60 ± 35	<.001
At least 1 RBC transfusion during hospital stay	65.9%	48.5%	<.001
Number of RBC transfusions during hospital stay†	2.2 ± 3.3	1.6 ± 0.3	.003
>2 RBC transfusions during hospital stay†	26.8%	21.6%	.072
At least 1 RBC transfusion before 14 days of life	56.9%	26.7%	<.001
Number of RBC transfusions before 14 days of life†	1.2 ± 1.7	0.5 ± 1.0	<.001
1-2 transfusions before 14 days of life†	41.1%	22.1%	<.001
>2RBC transfusions before 14 days†	15.5%	4.6%	<.001
At least 1 RBC transfusion before 28 days of life	63.9%	39.8%	<.001
Number of RBC transfusions up to 28 days of life†	1.7 ± 2.3	0.9 ± 1.6	<.001
At least 1 RBC transfusion after 28 days of life	14.4%	33.4%	<.001
Number of RBC transfusions after 28 days of life†	0.5 ± 1.6	0.7 ± 1.6	.233

*n = 920.
†Number of transfusions per studied infants.

versus 1.2 ± 2.2, $P < .001$), late-onset sepsis (3.3 ± 3.8 versus 0.7 ± 1.5, $P < .001$), and necrotizing enterocolitis (5.2 ± 5.8 versus 1.5 ± 2.5, $P < .001$).

Mortality rate during hospital stay was higher in neonates who underwent transfusion, compared with infants who did not (34.3% versus 20.3%, $P < .001$). The characteristics of the patients who died during hospital stay or were discharged from the hospital alive are shown in Table II. To test the hypothesis that mortality risk was independently associated with RBC transfusions, two models of Cox regression analysis were applied. The first model was a means of analyzing the risk of death at any time during hospital stay, and the second model was a means of determining the risk of death after 28 days of life. For both models, the univariate Cox regression analysis is shown in Table III.

For the multivariate Cox regression analysis, death during hospital stay was considered to be the dependent variable, and the independent variables included were those associated with higher mortality rates in the univariate analyses, such as gestational age (≥28 weeks; <28 weeks), 1- and 5-minute Apgar scores (<7; 7-10), SNAPPE II (<45; ≥45), presence of respiratory distress syndrome, IVH, early- and late-onset clinical sepsis, and necrotizing enterocolitis. Also, the model was adjusted for receiving any RBC transfusion during the first 28 days of life. Compared with infants who did not receive any transfusion before 28 days of life and adjusted for clinical

Table III. Univariate Cox regression analysis for variables associated with intra-hospital death or death after 28 days of life

Variables*	Death at any time during hospital stay†	Death after 28 days of life†
Gestational age <28 weeks	4.00 (1.88-2.14)	1.31 (1.03-1.53)
Birth weight <1000 grams	3.00 (2.51-3.33)	1.45 (1.03-1.90)
Small for gestational age	0.86 (0.85-0.88)	0.99 (0.79-1.16)
1-minute Apgar <7	2.10 (1.79-2.41)	1.44 (1.01-1.93)
5-minute Apgar <7	1.44 (1.39-1.48)	1.32 (1.20-1.41)
SNAPPE II ≥45	1.66 (1.61-1.70)	1.33 (1.21-1.41)
Respiratory distress syndrome	2.58 (2.16-3.01)	1.11 (0.77-1.48)
IVH	1.40 (1.24-1.55)	1.32 (1.01-1.62)
Early-onset sepsis	1.30 (1.18-1.55)	1.44 (1.08-1.78)
Late-onset sepsis	0.89 (0.79-1.01)	21.42 (4.30-47.49)
Necrotizing enterocolitis	1.38 (1.20-1.55)	1.49 (1.39-1.56)
At least 1 transfusion within 28 days of life	1.46 (1.20-1.53)	4.17 (1.83-6.91)
>2 RBC transfusions during hospital stay	0.96 (0.88-1.03)	2.63 (1.91-3.30)

*Entered as single variables in proportional hazards Cox regression models.
†Relative risk (95% CI).

Table IV. Final model of the multivariate Cox regression analysis for clinical variables associated with death at any time during hospital stay in the 1077 infants studied

Variables	RR	95% CI	*P* value
Gestational age <28 weeks	1.42	1.18-1.66	.001
SNAPPE II ≥45	1.53	1.35-1.63	<.001
Respiratory distress syndrome	1.76	1.32-2.26	<.001
Early-onset sepsis	1.23	1.01-1.44	.043
Necrotizing enterocolitis	1.23	1.01-2.25	.043
Any transfusion before 28 days of life	1.49	1.17-1.78	.001

RR, relative risk.
Co-variates entered simultaneously in proportional hazards regression model: gestational age, 1-minute Apgar (<7; 7-10), 5-minute Apgar (<7; 7-10), SNAPPE II score (<45; ≥45), presence of IVH, early-onset clinical sepsis, late-onset clinical sepsis, necrotizing enterocolitis, any number of RBC transfusions before 28 days of life (without transfusion, ≥1 transfusion).

Table V. Final model of the multivariate Cox regression analysis for clinical variables associated with death after 28 days of life in 839 very low birth weight preterm infants

Variables	RR	95% CI	*P* value
5-minute Apgar <7	1.52	1.05-2.02	.027
Late-onset sepsis	12.17	2.00-38.80	.008
Necrotizing enterocolitis	1.40	1.26-1.51	<.001
>2 RBC transfusions	1.89	1.19-2.69	.010

Covariates entered simultaneously in proportional hazards regression model: gestational age (≤28 weeks; >28 weeks), 1-minute Apgar (<7; 7-10), 5-minute Apgar (<7; 7-10), SNAPPE II score (<45; ≥45), presence of respiratory distress syndrome, IVH, early-onset clinical sepsis, late-onset clinical sepsis, necrotizing enterocolitis, and number of RBC transfusions during hospital stay (≤2; >2).

variables, the relative risk of death during hospital stay increased 49% (95% CI, 17% to 78%) in infants who received at least one transfusion in the first 28 days of life (Table IV).

Death after 28 days of life was analyzed in the 839 infants who survived beyond the neonatal period. In this group of patients, the variables included in the Cox regression analysis were gestational age, small for gestational age, 1- and 5-minute Apgar scores (<7; 7-10), SNAPPE II (<45; ≥45), presence of respiratory distress syndrome, IVH, early- and late-onset clinical sepsis, necrotizing enterocolitis, and more than two transfusions during hospital stay. After adjustment, the relative risk of death increased 1.9 times (95% CI, 1.2 to 2.7) in infants who received more than two RBC transfusions during hospital stay (Table V).

The multivariate Cox regression curve adjusted for potential confounders showed that infants who received at least one RBC transfusion ($P = .001$) during the first 28 days of life had a greater risk of death during hospital stay, compared with infants who did not receive a transfusion (Figure 1; available at www.jpeds.com). Infants with more than two transfusions at any time during hospital stay had a higher hazard of death after 28 days of life ($P = .010$), compared with infants who received one or two RBC transfusions (Figure 2; available at www.jpeds.com).

Discussion

Prospective and retrospective observational studies in critically ill adults show that RBC transfusions are independently associated with increased morbidity and mortality rates, irrespective of disease severity.[11,12] This is a large observational multicenter study in the neonatal setting to evaluate mortality risk associated with RBC transfusions in very low birthweight preterm infants. Similar to adults, in preterm infants RBC transfusions were independently associated with intra-hospital mortality. In addition, a dose-related relationship between the number of RBC transfusions and intra-hospital mortality rates was observed.

Because variables associated with the need of RBC transfusions are similar to those that may contribute to neonatal intra-hospital mortality, a Cox regression analysis was done to test whether RBC transfusions could be independently associated with the risk of death. After adjusting for potential confounders, an association between RBC transfusions and intra-hospital mortality rate was observed. Compared with infants who did not receive a transfusion, infants who received any RBC transfusions in the first 28 days of life had an approximately 50% increased risk of intra-hospital mortality. Also, mortality after 28 days of life was almost two times higher in infants who received more than two transfusions during the hospital stay than in infants with a lower number of RBC transfusions.

The association between RBC transfusions and mortality risk observed in this study is in agreement with the results of Khorana et al, who found an increased risk of mortality in adult patients with cancer who received RBC transfusions (OR, 1.34; 95% CI, 1.29 to 1.38) in a retrospective cohort of 504 208 hospitalizations in 60 US medical centers.[20] In the pediatric setting, Kneyber et al showed that RBC transfusions were associated independently with increased mortality and morbidity rates in a heterogeneous group of critically ill children.[15] Similarly, in a systematic review of the literature to determine the association between RBC transfusions and morbidity and mortality in high-risk hospitalized adults, Marik and Corwin noted that RBC transfusions were independent predictors of death in 17 of 18 studies, with a pooled OR of 1.7 (95% CI, 1.4 to 1.9).[21] Szekely et al examined 657 consecutive pediatric patients undergoing open heart procedures and, after adjustment for disease severity, the total amount of transfused blood was independently associated with an increased risk for infections (OR, 1.01; 95% CI, 1.002 to 1.020).[22] They did not find a significant association between RBC transfusions given during surgery or during the first 24 post-operative hours and mortality. In sicker infants, the contribution of illness severity probably overcomes the influence of RBC transfusions on the risk of death.

Although there is an association between RBC transfusions and intra-hospital mortality rate, we could not ascertain causality, especially in the neonatal setting. In adult populations, transfusion-related acute lung injury, hemolytic reactions,

and transfusion-associated sepsis emerge as the leading causes of allogeneic blood transfusion-related deaths.[8] However, these complications are seldom recognized in neonates. Some authors suggest that RBC transfusions are associated with immunosuppressive effects and the development of multiple system organ failure.[13] Probably the leukocytes in the donor blood are responsible for immunomodulation; however, in our study, all centers transfused leukocyte-depleted blood. The effect of leukocyte-depleted preparations on patient outcomes is still not evidence-based,[13] except for some benefits in patients having cardiac surgery.[8,23] In preterm infants, leukocyte-depleted blood is used in many countries[24] on the basis of the possible cause-effect relationship between the implementation of universal white blood cell reduction and a lower incidence of bronchopulmonary dysplasia (OR, 0.42; 95% CI, 0.25 to 0.70), retinopathy of prematurity (OR, 0.56; 95% CI, 0.33 to 0.93), and necrotizing enterocolitis (OR, 0.39; 95% CI: 0.17 to 0.93).[25]

Observational studies in adults have reported the association between prolonged storage of transfused RBCs and higher risk of organ dysfunction, nosocomial infections, and mortality. However, van de Watering et al did not find associations between the prolonged storage time and mortality or length of stay in the intensive-care unit.[26] A double-blind, multicenter, randomized controlled trial aiming to evaluate the effectiveness of stored versus fresh RBCs in neonates requiring transfusion is underway.[27]

The main limitation of this study is that patients who received transfusions and patients who did not were compared for mortality with the inclusion of sicker patients in the transfused group, thus introducing a selection bias difficult to control with statistical methods. However, the variables related to illness severity were adjusted by using gestational age, Apgar score, SNAPPE II score, and the presence of the most frequent neonatal diseases, all well-known markers of morbidity and mortality in very low birth weight preterm infants.[18,28] In addition, with the Cox regression model, the effect of RBC transfusions on mortality was shown to be greater in patients who received transfusions in the first 28 days of life and in infants with more than two transfusions during hospital stay. Despite these findings, the association may not be related to the RBC blood transfusions per se, but with transfusion being a proxy for unknown factors, unmeasured factors, or both that increase the risk of death.

The association between the risk of dying and RBC transfusions in the neonatal setting must be interpreted in relation to the consistency, strength, and biological plausibility. Further studies are needed to better define this association. In the meantime, clinicians should strongly consider risks and benefits for morbidity and mortality of very low birth weight preterm infants. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Psychomotor Seizures in Childhood. A Study of 120 Cases

Holowach J, Renda YA, Wapner I. J Pediatr 1961;59:339-46

Fifty years after this paper by our group on "psychomotor seizures in childhood," challenges remain in the clinical recognition and treatment of this disorder. The terminology of "complex partial seizures" was introduced by the International League Alliance on Epilepsy (1981), 20 years after this paper, to replace the term psychomotor seizures. This Alliance and many other studies have echoed our observations from 1961, including: (1) this condition accounted for approximately 10% of childhood epilepsy; (2) there was a variety of psychological and motor symptoms, but repetitive mastication was the most common; (3) early febrile convulsions were associated with a higher risk for this form of epilepsy; (4) learning and behavioral challenges were common co-morbidities; (5) one-third of cases occurred in children <3 years of age, and there was often failure of recognition or misdiagnosis of the condition; (6) electroencephalographic background abnormalities were almost universally present; and (7) treatment was challenging. Fifty years later, these observations remain relevant. Although therapeutic approaches to complex partial seizures in childhood have improved, this condition remains under-diagnosed, difficult to treat, and accompanied by a repertoire of cognitive and behavioral manifestations that challenge families. The observations outlined in our clinical study of 120 children, published 50 years ago, remind us of this important form of childhood epilepsy, its symptoms and signs, and clinical course.

However, this report also highlights the importance of the art of careful clinical characterization of any pediatric condition after reviews of thorough history, including family history, clinical course, and investigations. Such artful clinical evaluation and description of a large patient series appears to have diminished in the last 50 years. Thus, may we continue to carefully observe clinical patterns that may contribute as much to our field as that of our study of psychomotor seizures. Finally, although complex partial epilepsy remains difficult to treat, may we strive to practice with empathy and understanding for our children and their families, as noted by Martin H. Fischer: "In the sick room, ten cents' worth of human understanding equals ten dollars' worth of medical science."

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Table I. Red blood cell transfusion guidelines adopted by each neonatal unit[16]

NICU	Htc <40%	Htc <35%	Htc <30%	Htc <25%	Htc <21-22%
1		Acute phase of disease MV: Pwa >8, FiO_2 >0.30.	FiO_2 <0.30		Asymptomatic
2	Symptomatic anemia	Symptomatic anemia	Symptomatic anemia	Symptomatic anemia.	Asymptomatic
3	First 2 weeks of life Hemodynamic instability, Severe cardiopulmonary diseases, sepsis, MV: Pwa >10, and FiO_2 >0.50	First 2 wks of life MV: Pwa 6-10 and FiO_2 0.35 to 0.45. After 2 weeks BPD and need of MV.	First 2 weeks of life Stable without any symptoms of anemia After 2 weeks MV: Pwa <6, nasal CPAP; FiO_2 <0.35, 3 apnea spells and need of PPV, pre- or post-surgery tachycardia or tachypnea for >24 hours, poor weight gain in the previous 4 days		Asymptomatic with reticulocyte count <2%
4		Severe pulmonary diseases, Cyanotic heart disease, Heart failure.	Tachycardia with HR>180, Tachypnea with RR >80,3 apnea spells within 12 hours, weight gain <10 g/kg per day in the previous 4 days while receiving >120 kcal/kg/d in 4 days		Asymptomatic with reticulocyte count <1%
5	Cyanotic heart disease, heart failure, refractory shock	Pwa >8, Heart failure, Transport in MV, Major surgery.	Pwa ≤8, FiO_2 >0.35, Minor surgery.	FiO_2 ≤0.35, 6 apnea episodes in 2h or 2 in 24h, Tachycardia or tachypnea without any cause, Weight gain < 10g/kg/day over the previous 4 days while receiving >120 kcal/kg/d in 4 days.	Asymptomatic with reticulocyte count <2%, symptomatic anemia
6	Congenital heart disease, PDA with heart failure, BDP, sepsis	MV: Pwa 6-8, CPAP or Hood with FiO_2 >0.35.	MV: Pwa <6, CPAP or hood with FiO_2 <0.35.	Weight gain <10g/kg/day over the previous 4 days while receiving >120 kcal/kg/d in 4 days, More than 3 apnea spells, Surgery.	Asymptomatic
7	Acute blood loss with shock	MV: Pwa >8 and FiO_2 >0.5.	MV: Pwa 6-8 or FiO_2 >0.35.	MV: Pwa <6, CPAP FiO_2 0.25-0.35, oxygen by nasal catheter, Tachycardia with HR >180, Tachypnea with RR >80, Apnea/bradycardia >10 episodes with need of intervention, Weight gain <10g/kg/day over the previous 4 days while receiving >120 kcal/kg/d in 4 days	Asymptomatic with reticulocyte count <4%
8	Severe cardiopulmonary diseases, MV, acute blood loss (>10% volemia), cyanotic heart disease		Major surgery, FiO_2 >0.30.	Symptomatic anemia.	Symptomatic anemia

NICU, neonatal intensive care unit; *MV,* mechanical ventilation; *Pwa*, mean airway pressure expressed in cmH20; *FiO_2*, fraction of inspired oxygen; *PDA*, patent ductus arterious; *BDP,* bronchopulmonary dysplasia; *PPV*, positive pressure ventilation; *CPAP*, continuous positive airway pressure.

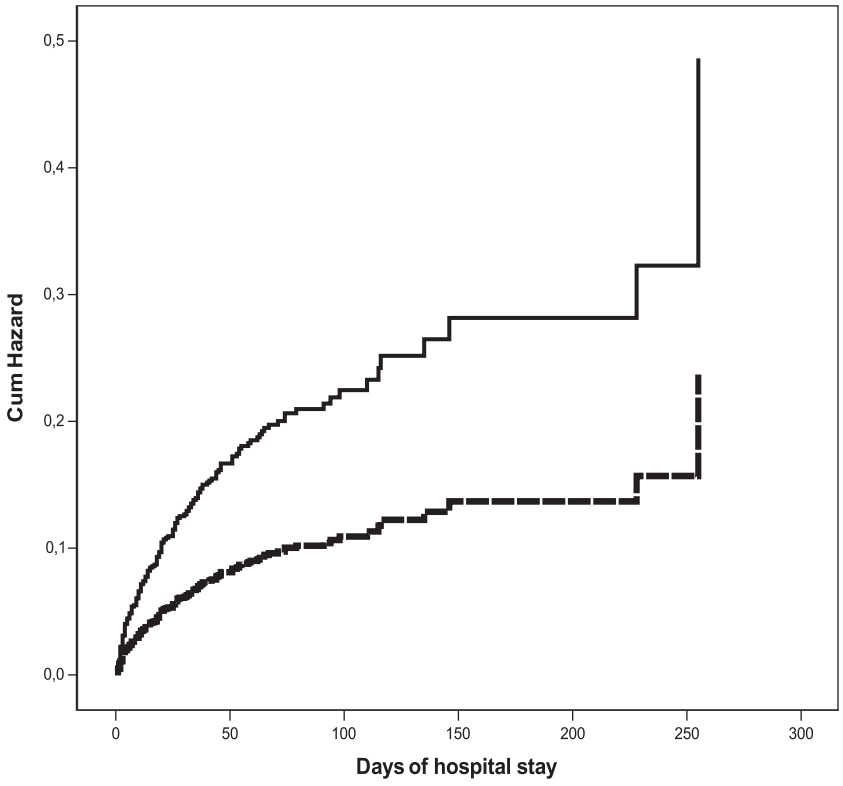

Figure 1. Intra-hospital death at any time during hospital stay in infants with at least one RBC transfusion in the first 28 days of life (*solid line*) and in infants who did not receive transfusion (*dotted line*).

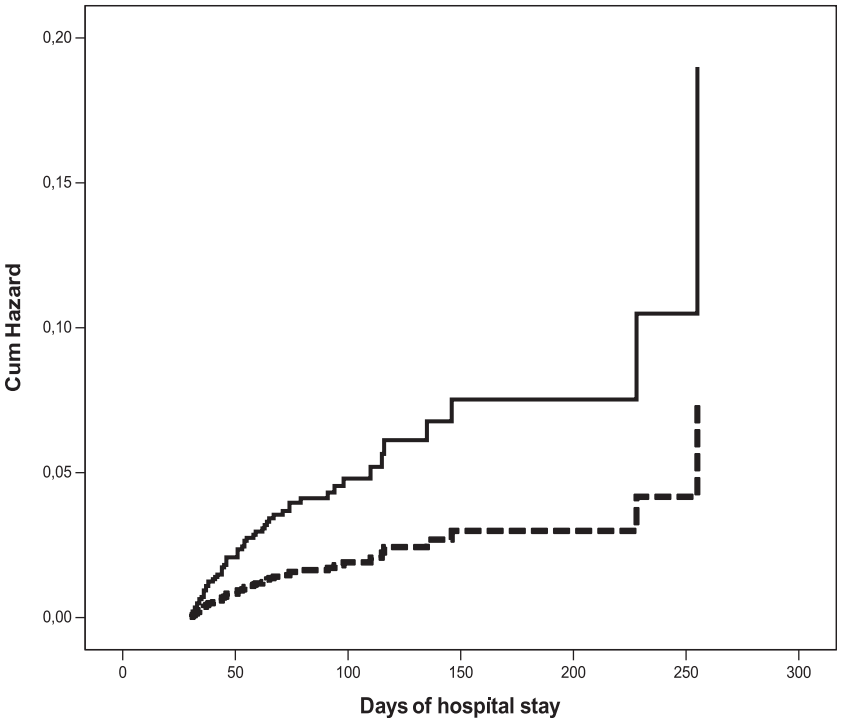

Figure 2. Intra-hospital death after 28 days of life for neonates who received more than two RBC transfusions (*solid line*), compared with neonates who received one or two transfusions during hospital stay (*dotted line*).

Appendix

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