Hemoglobin as a trigger for RBC transfusion in preterm infants: Maybe Not!

September 13, 2022

Cassandra D. Josephson, MD
Director, Cancer and Blood Disorders Institute (CBDI)
Clinical Division Director, Hematology/Oncology
Medical Director, Blood Bank/Transfusion Medicine
Johns Hopkins All Children's Hospital
Professor (PAR), Oncology
Johns Hopkins University School of Medicine
email: cjosep22@jhu.edu

JOHNS HOPKINS All Children's Hospital

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Faculty Disclosure

- Immucor- consultant
- Octapharma – unrestricted, research investigator
- Medtronics – unrestricted, research investigator
- Cellphine – consultant
- Sysmex – unrestricted, research investigator
- NHLBI – Co-chair for Recipient Epidemiology and Donor Evaluation Study-IV- Pediatric (REDS-IV-P)

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Objectives

- Discuss limitations of hemoglobin as a surrogate for tissue oxygenation and trigger for RBC transfusion.
- Explore consequences of permissive severe anemia; and what may occur when below those critical levels.
- Examine donor RBC variability and the potential impact on recipient morbidity and mortality.

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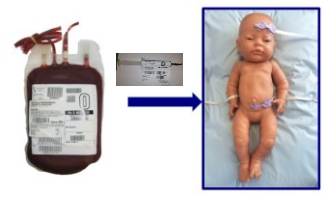
Limitations of infant's hemoglobin as a surrogate for tissue oxygenation and trigger for RBC transfusion

Infant considerations



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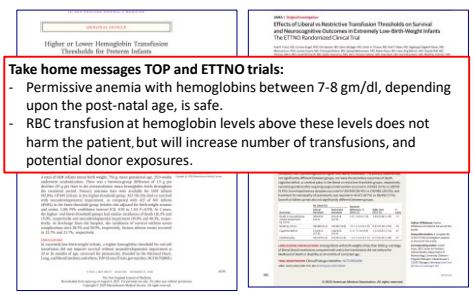
Transfusion Thresholds



Take home messages TOP and ETTNO trials:

- Permissive anemia with hemoglobins between 7-8 gm/dl, depending upon the post-natal age, is safe.
- RBC transfusion at hemoglobin levels above these levels does not harm the patient, but will increase number of transfusions, and potential donor exposures.

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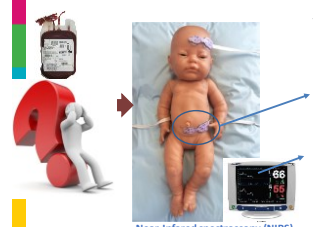
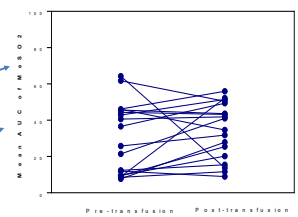
Variability in clinical and physiologic response to RBC transfusion



Near-Infared spectroscopy (NIRS)

18 RBC transfusions (N=14 infants, mean GA 28 wks)



Mes-S02= mesenteric regional saturation of oxygen
AUC=area under the curve

Guo et al. *Stat Methods Med Res.* 2018

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Hemoglobin: imprecise surrogate marker for oxygen delivery to tissues and as a trigger for RBC transfusion

Transfusion decision making requires consideration of the following:

- Anemia tolerance – linked to active pathology and physiologic reserve
- Relative risk from anemia attributable oxygen delivery failure vs. inherent hazards of transfusion
- Difference in donor RBC physiology from that of patient RBCs

Current approaches to transfusion decision making (e.g. hemoglobin thresholds) DO NOT :

- Differentiate between patients with similar anemia, but dissimilar pathology/physiology
- Guide transfusion timing and amount (volume) to efficacy-based goals (other than resolution of hemoglobin thresholds)

Markham C et al. Pediatric Clinics of North America, 2017-10-01, Volume 64, Issue 5, Pages 991-1015

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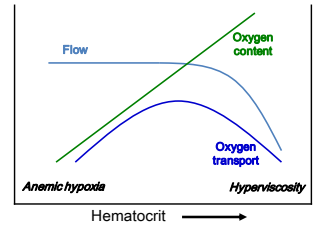
Impact of Hematocrit on Systemic Oxygen Transport



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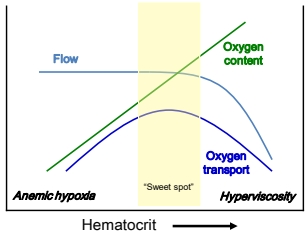
Impact of Hematocrit on Systemic Oxygen Transport



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Arterial Oxygen Content

$$O_2 \text{ delivery} = \text{cardiac output} \times CaO_2$$

$$CaO_2 = (1.34 \times [Hb] \times SpO_2) + (0.003 \times PaO_2)$$

primary determinant

https://rk.md/2017/oxygen-delivery-equation/

Potential role of transfusion approaches or tolerance of anemia

Potential role of oxygen saturation targets

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https://rk.md/2017/oxygen-delivery-equation/

Potential role of oxygen saturation targets

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Oxygen targeting and outcomes

Figure 3. Effect of Oxygen Saturation as Measured by Pulse Oximetry (Spo_2) Target Levels on Secondary Outcomes

Dichotomous Outcomes	No. of Infants With Event/Total No. (%)[a] Lower Spo_2 Target	Higher Spo_2 Target	Risk Difference (95% CI), %	Relative Risk (95% CI)	Favors Lower Spo_2 Target / Favors Higher Spo_2 Target	P Value	I^2, %
Death before postmenstrual age of 36 wk	415/2478 (17)	354/2481 (14)	2.5 (0.5 to 4.5)	1.18 (1.03 to 1.34)		.01	0
Death before discharge from hospital	460/2478 (19)	397/2481 (16)	2.6 (0.5 to 4.7)	1.17 (1.03 to 1.32)		.01	0
Patent ductus arteriosus[b]							
Treated medically or surgically	1139/2456 (46)	1127/2463 (46)	0.5 (-2.3 to 3.3)	1.01 (0.95 to 1.07)		.71	0
Treated surgically	281/2462 (11)	240/2464 (10)	1.7 (0 to 3.4)	1.18 (1.00 to 1.39)		.046	13
Treated retinopathy of prematurity before corrected age of 18-24 mo	220/2020 (11)	308/2065 (15)	-4.0 (-6.1 to -2.0)	0.74 (0.63 to 0.86)		<.001	80
Severe necrotizing enterocolitis[c]	227/2464 (9)	170/2465 (7)	2.3 (0.8 to 3.8)	1.33 (1.10 to 1.61)		.003	0
Supplemental oxygen at postmenstrual age of 36 wk	459/1846 (25)	578/1910 (30)	-5.6 (-8.5 to -2.7)	0.81 (0.74 to 0.90)		<.001	0
≥1 Readmission to hospital	942/1754 (54)	967/1819 (53)	0.6 (-2.6 to 3.9)	1.01 (0.96 to 1.07)		.64	0

0.5 1.0 2.0
Relative Risk (95% CI)

Askie et al. NeOProM collaboration. *JAMA.* 2018

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https://rk.md/2017/oxygen-delivery-equation/

Potential role of transfusion approaches or tolerance of anemia (permissive anemia)

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Randomized Trials of Transfusion Thresholds

TABLE 82.1 Red Blood Cell Transfusion Thresholds for Preterm Infants in Randomized Trials[a]

		Iowa Trial (Bell et al., 2005)	PINT Trial (Kirpalani et al., 2006)	TOP Trial	ETTNO Trial
Liberal	Upper	15.3	13.5	13.0	13.7
	Lower	10.0	8.5	10.0	9.3
Restrictive	Upper	11.3	11.5	11.0	11.3
	Lower	7.3	7.5	7.0	7.0

Patel and Josephson. *Neonatal Transfusion*. Avery's Disease of Newborn. 10th ed.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Higher or Lower Hemoglobin Transfusion Thresholds for Preterm Infants

H. Kirpalani, E.F. Bell, S.R. Hintz, S. Tan, B. Schmidt, A.S. Chaudhary, K.J. Johnson, M.M. Crawford, J.E. Newman, B.R. Vohr, W.A. Carlo, C.T. D'Angio, K.A. Kennedy, R.K. Ohls, B.B. Poindexter, K. Schibler, R.K. Whyte, J.A. Widness, J.A.F. Zupancic, M.H. Wyckoff, W.E. Truog, M.C. Walsh, V.Y. Chock, A.R. Laptook, G.M. Sokol, B.A. Yoder, R.M. Patel, C.M. Cotten, M.F. Carmen, U. Devaskar, S. Chawla, R. Seabrook, R.D. Higgins, and A. Das, for the Eunice Kennedy Shriver NICHD Neonatal Research Network*

22 to 28 weeks' gestation or birth weight ≤ 1000g

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TOP Trial

Randomized 1824 infants

Age	High Threshold		Low Threshold	
Week of life	Resp. Support	No Support	Resp. Support	No Support
1	13.0 / 38	12.0 / 35	11.0 / 32	10.0 / 29
2	12.5 / 37	11.0 / 32	10.0 / 29	8.5 / 25
≥ 3	11.0 / 32	10.0 / 29	8.5 / 25	7.0 / 21

Hemoglobin (g/dl) / Hematocrit (%)

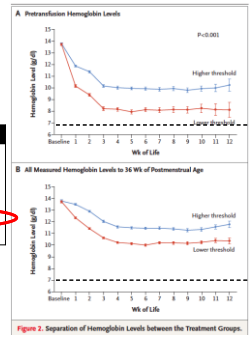

Figure 2. Separation of Hemoglobin Levels between the Treatment Groups.

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TOP Trial - Primary Outcome

Outcome	Higher Hemoglobin Threshold (N=845)	Lower Hemoglobin Threshold (N=847)	Adjusted Relative Risk (95% CI)	P Value
	no. of infants/total no. (%)			
Primary outcome: death or neurodevelopmental impairment	423/845 (50.1)	422/847 (49.8)	1.00 (0.92–1.10)	0.93
Components of primary outcome				
Death†	146/903 (16.2)	135/901 (15.0)	1.07 (0.87–1.32)	
Neurodevelopmental impairment	277/699 (39.6)	287/712 (40.3)	1.00 (0.88–1.13)	
Cognitive delay‡	269/695 (38.7)	270/712 (37.9)	1.04 (0.91–1.18)	
Moderate or severe cerebral palsy§	48/711 (6.8)	55/720 (7.6)	0.87 (0.60–1.26)	
Severe vision impairment	5/713 (0.7)	6/720 (0.8)	0.83 (0.25–2.76)¶	
Severe hearing impairment	14/710 (2.0)	25/715 (3.5)	0.56 (0.29–1.07)¶	

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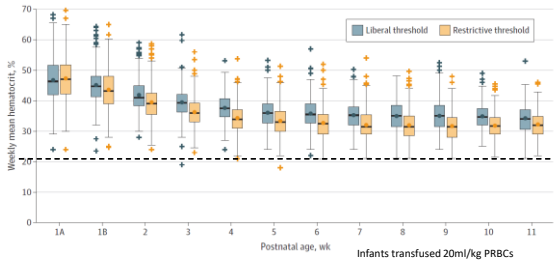
ETTNO Trial



Infants transfused 20ml/kg PRBCs

Franz et al. *JAMA*. 2020

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ETTNO Trial - Primary Outcome

Outcomes	No./total (%) Liberal threshold	Restrictive threshold	Absolute difference, % (95% CI)	Odds ratio (95% CI)	*P* value
Death or neurodevelop-mental impairment by 24 mo	200/450 (44.4)	205/478 (42.9)	1.6 (−4.8 to 7.9)	1.05 (0.80-1.39)	.72
Death by 24 mo	38/460 (8.3)	44/491 (9.0)	−0.7 (−4.3 to 2.9)	0.91 (0.58-1.45)	.70
Cognitive deficit	154/410 (37.6)	148/430 (34.4)	3.1 (−3.3 to 9.6)	1.12 (0.83-1.51)	.47
Cerebral palsy	18/419 (4.3)	25/443 (5.6)	−1.3 (−4.2 to 1.5)	0.75 (0.40-1.40)	.37

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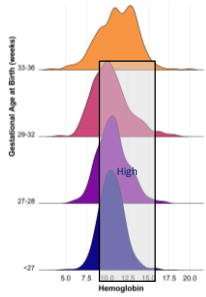
Transfusion thresholds in US centers



From NHLBI REDS-III study: 2013-2016
N=60,243 infants from 7 US centers

Patel et al. *J Pediatr. 2021*

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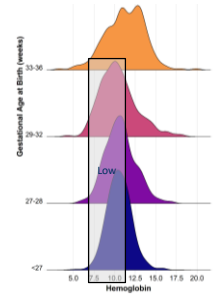
Transfusion thresholds in US centers



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Patel et al. *J Pediatr. 2021*

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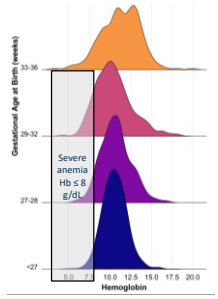

From NHLBI REDS-III study: 2013-2016
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Patel et al. *J Pediatr. 2021*

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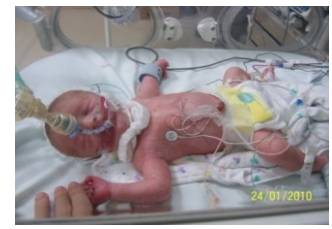
Potential consequences of permissive severe anemia: what may occur when below those critical levels?



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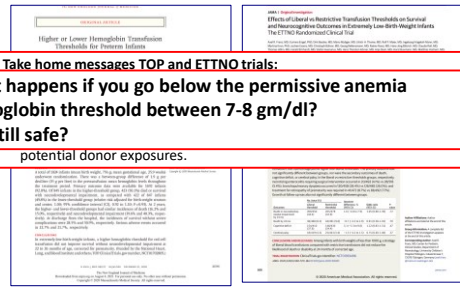
Transfusion Thresholds



Take home messages TOP and ETTNO trials:

- What happens if you go below the permissive anemia hemoglobin threshold between 7-8 gm/dl?
- Is it still safe?

potential donor exposures.

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RBC Transfusion and Necrotizing Enterocolitis (NEC) in VLBW infants

- Patel *et al*. JAMA 2016 published a prospective, multi-center birth cohort study, of VLBW infants (≤1500g), identified the severity of anemia prior to RBC transfusion as being an independent risk factor for NEC.
- Further, a sub-group analysis of a 2017 case-crossover study also found that infants with anemia were at higher risk of NEC than infants who were not anemic.

Garg P. J Perinat Med. 2018.
Hay S, Zupancic JA, et al. Semin Perinatol. 2017
Le VT et al. PLoS One 2017

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Severe anemia associated with NEC

Risk Factors	NEC Cause-Specific HR (95% CI)[b]	*P* Value	% Reliability[c]
Model 1—Primary Analysis (N = 598)			
Received RBC transfusion in a given week[c]	0.44 (0.17-1.12)	.09	45
Severe anemia in a given week (hemoglobin ≤8 g/dL)	5.99 (2.00-18.0)	.001	70

- 4565 longitudinal measurements of Hb (median 7 per infant), the rate of NEC was significantly increased among VLBW infants with severe anemia in a given week compared with those who did not have severe anemia.
- Estimates adjusted for birth weight, SNAP score, breastfeeding, antibiotic exposure, and center
- Findings consistent in additional analyses controlling for early respiratory illness severity and in propensity score analyses (covariate adjustment and inverse probability of treatment weighting)

Patel RM et al. *JAMA*. 2016

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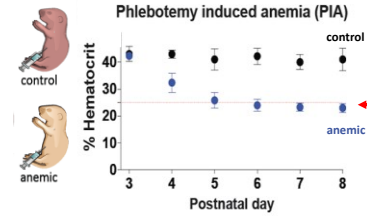
Effect of anemia on intestinal hypoxia



Arthur *et al. Transfusion*. 2019

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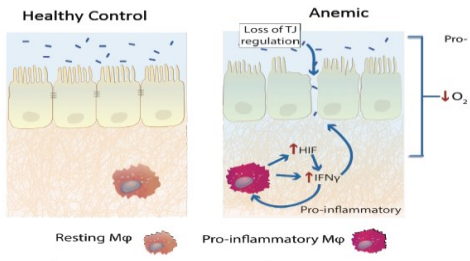
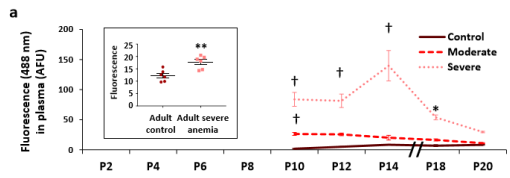
Macrophages mediate barrier alterations



Arthur *et al. Transfusion*. 2019

29

Severity of anemia and gut permeability



MohanKumar *et al. AJP Gastro*. 2020

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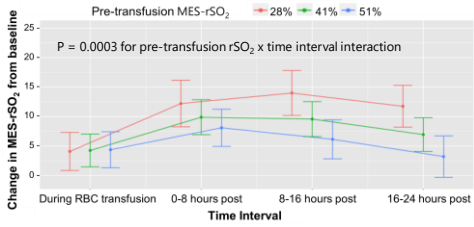
Change in gut oxygenation by baseline MES-rSO$_2$



- Pre-transfusion baseline oxygenation is associated with response to RBC transfusion
- The lower the baseline oxygenation is the greater the response to transfusion

Patel *et al.* PAS 2021

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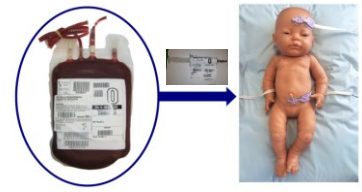
Donor RBC variability and the potential impact on recipient morbidity and mortality

Donor RBC considerations



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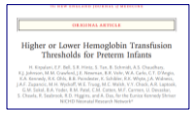
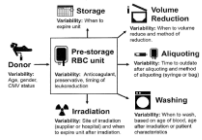
Variation in donor RBCs





Variation in neonatal RBC product modification survey results

Survey population	RBC anticoagulant or preservative products[a]	RBC washing procedures	Irradiation	Dedication of donor units
47 blood banks at academic medical centers part of the University Health Consortium in the United States [45]	6%—CPD or CP2D only 15%—CPDA-1 allowed 60%—at least one type of AS[b] 45%—all 3 forms of AS[b]	82%—no policy 18%—policy addressing risk of hyperkalemia 9%—policy specifying number of days after irradiation or storage	Not asked	N/A
29 NICUs participating in the TOP trial in the United States [46]	38%—CPD/CPDA only 21%—AS[c] only 41%—combination	34%—policy for large-volume transfusions 17%—policy specifying number of days after irradiation or storage	93% irradiate (88% performed on site, 34% by off-site donor center)	77%—aliquot from unit until expiration date 21%—do not dedicate unit[c]

Abbreviations: AS, additive solution; CP2D, citrate phosphate double dextrose; CPD, citrate phosphate dextrose; CPDA-1, citrate phosphate dextrose adenine; N/A, not applicable; NICU, neonatal intensive care unit; TOP, Transfusion of Prematures.
[a] Blood banks often maintain a varied inventory of RBC products.
[b] AS-1, AS-3, AS-5 units.
[c] These sites will switch to another unit when the RBC unit ages to a certain point (age range to switch ranges from 5 to 28 days of RBC age).

Patel RM, *et al. Trans Med Rev.* 2016

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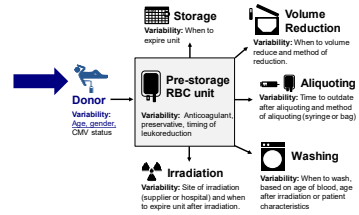
Variation in donor RBCs



Patel RM, et al. *Trans Med Rev.* 2016

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Effect of RBC donor characteristics in Adults

Donor Group	HR per Unit Transfused (95% CI)[a]
KPNC (n = 34 662)	
Female	0.99 (0.96-1.03)
Previously pregnant[b]	1.00 (1.00-1.01)
Sex-discordant	1.02 (0.99-1.05)
REDS-III (n = 93 724)	
Female	1.00 (0.99-1.01)
Previously pregnant[b]	1.01 (0.98-1.03)
Sex-discordant	0.99 (0.98-1.00)
SCANDAT (n = 918 996)	
Female	1.00 (0.99-1.00)
Parous	1.00 (1.00-1.01)
Sex-discordant	1.00 (0.99-1.00)

[a] KPNC indicates Kaiser Permanente Northern California; REDS-III, Recipient Epidemiology and Donor Evaluation Study III; SCANDAT, Scandinavian Donations and Transfusions

Edgren et al. *JAMA.* 2019

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RBC donor sex in preterm infants

Table II. Regression models to predict BPD, any neonatal morbidity, and length of stay

	BPD*			Any major morbidity		
Predictors	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Maternal age	0.99	0.94-1.05	.8144	0.99	0.94-1.04	.6251
Antenatal steroids	1.10	0.37-3.24	.8699	0.80	0.29-2.24	.6711
Gestational age	0.69	0.57-0.83	.0001	0.61	0.51-0.74	.0001
Female ± male donor blood	1.95	0.90-4.21	.0917	2.35	1.11-4.95	.0251
Adjusting for total number of transfusions:						
Maternal age	0.99	0.94-1.05	.7628	0.98	0.93-1.04	.5027
Antenatal steroids	1.03	0.33-3.19	.9644	0.61	0.20-1.88	.3869
Gestational age	0.78	0.64-0.96	.0158	0.71	0.58-0.88	.0017
Female ± male donor blood	1.44	0.64-3.25	.3804	1.50	0.65-3.45	.3385
Number of transfusions	1.21	1.08-1.35	.0009	1.53	1.28-1.84	.0001

Any major morbidity: death, BPD, IVH, PVL, ROP, SIP, or NEC

Murphy et al. *J Pediatr.* 2018

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Interaction between RBC donor sex and number of transfusions

Predictors	BPD OR	BPD 95% CI	BPD P	Any major morbidity OR	Any major morbidity 95% CI	Any major morbidity P
Maternal age	0.96	0.90-1.03	.2315	0.98	0.91-1.04	.4774
Antenatal steroids	0.62	0.19-2.00	.4201	0.54	0.17-1.76	.3069
Gestational age	0.84	0.66-1.05	.1273	0.66	0.51-0.86	.0018
Donor sex						
Female only vs male[†]	1.48	0.53-4.11	.4521	1.56	0.58-4.17	.3743
Number of transfusions[‡]	1.34	1.06-1.69	.0143	1.30	1.01-1.67	.0417
Female donor × number of transfusions	0.85	0.64-1.12	.2448	2.63	1.21-5.70	.0146

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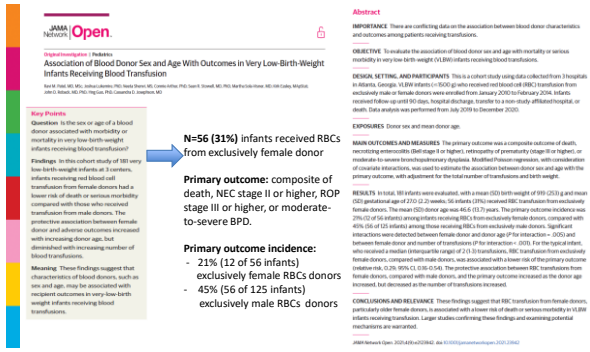
JAMA Network Open.

Original Investigation | Pediatrics

Association of Blood Donor Sex and Age With Outcomes in Very Low-Birth-Weight Infants Receiving Blood Transfusion

Key Points

Question Is the sex or age of a blood donor associated with morbidity or mortality in very low birth-weight infants receiving blood transfusion?

Findings In this cohort study of 181 very low birth-weight infants at 3 centers, infants receiving red blood cell transfusion from female donors had a lower risk of death or serious morbidity compared with those who received transfusion from male donors. The protective association between female donor and adverse outcomes increased with increasing donor age, but diminished with increasing number of blood transfusions.

Meaning These findings suggest that characteristics of blood donors, such as sex and age, may be associated with recipient outcomes in very-low-birth weight infants receiving blood transfusions.

Abstract

IMPORTANCE There are conflicting data on the association between blood donor characteristics and outcomes among patients receiving transfusions.

OBJECTIVE To evaluate the association of blood donor sex and age with mortality or serious morbidity in very low birth weight (VLBW) infants receiving blood transfusions.

DESIGN, SETTING, AND PARTICIPANTS This is a cohort study using data collected from 3 hospitals in Atlanta, Georgia. VLBW infants (<1500 g) who received red blood cell (RBC) transfusion from exclusively male or female donors were enrolled from January 2010 to February 2014. Infants received follow-up until 90 days, hospital discharge, transfer to a non-study-affiliated hospital, or death. Data analysis was performed from July 2019 to December 2020.

EXPOSURES Donor sex and mean donor age.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite outcome of death, necrotizing enterocolitis (Bell stage II or higher), retinopathy of prematurity (stage III or higher), or moderate-to-severe bronchopulmonary dysplasia. Modified Poisson regression, with consideration of covariate interactions, was used to estimate the association between donor sex and age with the primary outcome, with adjustment for the total number of transfusions and birth weight.

RESULTS In total, 181 infants were evaluated, with a mean (SD) birth weight of 999 (253) g and mean (SD) gestational age of 27.0 (2.2) weeks; 56 infants (31%) received RBC transfusion from exclusively female donors. The mean (SD) donor age was 46.6 (13.7) years. The primary outcome incidence was 21% (12 of 56 infants) among infants receiving RBCs from exclusively female donors, compared with 45% (56 of 125 infants) among those receiving RBCs from exclusively male donors. Significant interactions were detected between female donor and donor age (P for interaction = .005) and between female donor and number of transfusions (P for interaction = .003). For the typical infant, who received a median (interquartile range) of 2 (1-3) transfusions, RBC transfusion from exclusively female donors, compared with male donors, was associated with a lower risk of the primary outcome (relative risk, 0.29; 95% CI, 0.16-0.54). The protective association between RBC transfusions from female donors, compared with male donors, and the primary outcome increased as the donor age increased, but decreased as the number of transfusions increased.

CONCLUSIONS AND RELEVANCE These findings suggest that RBC transfusion from female donors, particularly older female donors, is associated with a lower risk of death or serious morbidity in VLBW infants receiving transfusion. Larger studies confirming these findings and examining potential mechanisms are warranted.

N=56 (31%) infants received RBCs from exclusively female donor

Primary outcome: composite of death, NEC stage II or higher, ROP stage III or higher, or moderate-to-severe BPD.

Primary outcome incidence:
- 21% (12 of 56 infants) exclusively female RBCs donors
- 45% (56 of 125 infants) exclusively male RBCs donors

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Primary results

Table 2. Estimates of Association of Exposures with Primary Outcome

Variable	Relative risk of primary outcome (95% CI)[a]
Female vs male donor (overall)[b]	0.29 (0.16-0.54)
By different mean donor ages[c]	
38.6 y (25th percentile)	0.41 (0.21-0.77)
48.6 y (50th percentile)	0.27 (0.14-0.50)
57.6 y (75th percentile)	0.18 (0.09-0.38)
Birth weight per 100 g increase[d]	0.89 (0.82-0.98)

[a] Multivariable model was used to derive estimates and included the following main effects: female donor sex, mean donor age (centered at the mean for all transfusions an infant received), total number of transfusions, and birth weight (in grams). In addition, the following interaction terms were included: total number of transfusions by female donor sex, total number of transfusions by birth weight, and mean donor age (centered) by female donor sex. Parameter estimates are reported in eTable 1 in the Supplement.

[b] Refers to estimate at the median number of transfusions of 2 per infant and mean donor age.

[c] Refers to estimate of female vs male donor sex at the median number of transfusions of 2 per infant and the listed mean donor age.

[d] Refers to estimate at the median number of transfusions of 2 per infant and same donor sex.

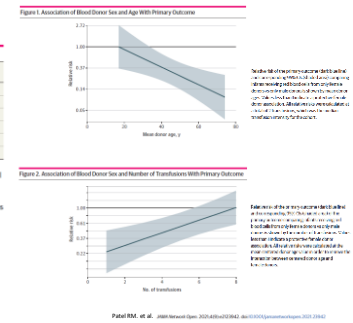
Figure 1. Association of Blood Donor Sex and Age With Primary Outcome

Figure 2. Association of Blood Donor Sex and Number of Transfusions With Primary Outcome

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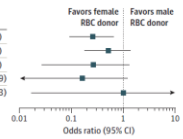
Individual Components

Figure 3. Risk of Individual Components of the Composite Outcome by Donor Exposure

	Risk of infant outcome by donor exposure, n/N (%) Female donor	Male donor	Adjusted odds ratio (95% CI)
Composite	12/56 (21.4%)	56/125 (44.8%)	0.26 (0.09-0.65)
BPD	9/56 (16.1%)	35/125 (28.0%)	0.52 (0.18-1.35)
Death	2/56 (3.6%)	15/125 (12.0%)	0.27 (0.03-1.29)
NEC	1/56 (1.8%)	12/125 (9.6%)	0.17 (0.004-1.19)
ROP	1/56 (1.8%)	3/125 (2.4%)	1.00 (0.02-18.33)



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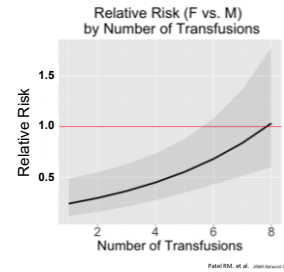
Donor sex and adverse outcomes



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Donor age and adverse outcomes

Patel RM. et al. JAMA Network Open. 2021;4(9):e2139842. doi:10.1001/jamanetworkopen.2021.39842

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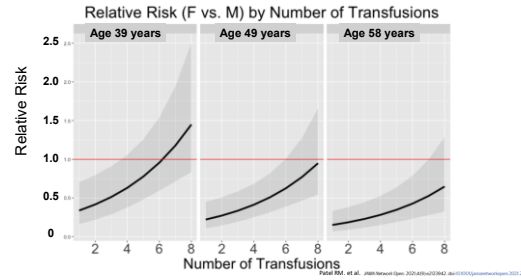
Donor sex, age and adverse outcomes



Patel RM. et al. JAMA Network Open. 2021;4(9):e2139842. doi:10.1001/jamanetworkopen.2021.39842

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Conclusions

- RBCs from female donors, compared to male donors, associated with a lower risk of adverse outcomes
- Lowest risk with older, female donors, but effect diminishes with increasing number of transfusions

Patel RM. et al. JAMA Network Open. 2021;4(9):e2139842. doi:10.1001/jamanetworkopen.2021.39842

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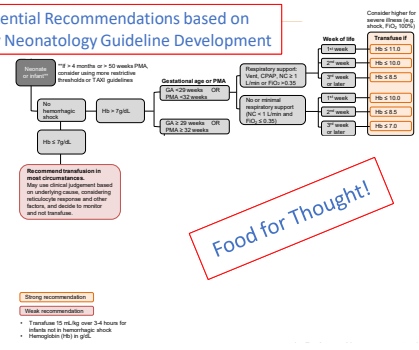
Potential Recommendations based on Emory Neonatology Guideline Development



Food for Thought!

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Conclusions: Fact or Fiction?

- At this moment in time it is both a "home run" and "loud foul", for RBC transfusion in preterm infants in the 21st century, just need to continue to "play ball".
- An amazing accomplishment: 2 RCTs conducted & Level 1 evidence-based, lower hemoglobin thresholds defined in preterm infants, that do not harm neurodevelopment or cause death & decrease the number of transfusions.
- Still, there is much to learn and understand, as using hemoglobin alone isn't a good correlative biomarker to predict regional saturation of oxygen in different tissue beds.
- Caution must be applied when using lower transfusion thresholds, below those studied in RCTs, as consequences of severe anemia may lead to increased morbidity and mortality.
- Characteristics of RBCs transfused (donor and special processing post- donation) may play a role in patient outcomes (either protective or harmful), more research required.

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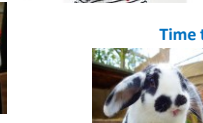
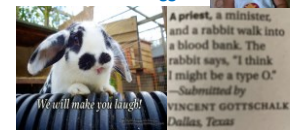
Any questions?

Time to Giggle!!

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