Treating Neonates with Anemia and Thrombocytopenia: Can current evidence drive the practices?

University of Toronto
Transfusion Medicine Rounds

1-25-2024

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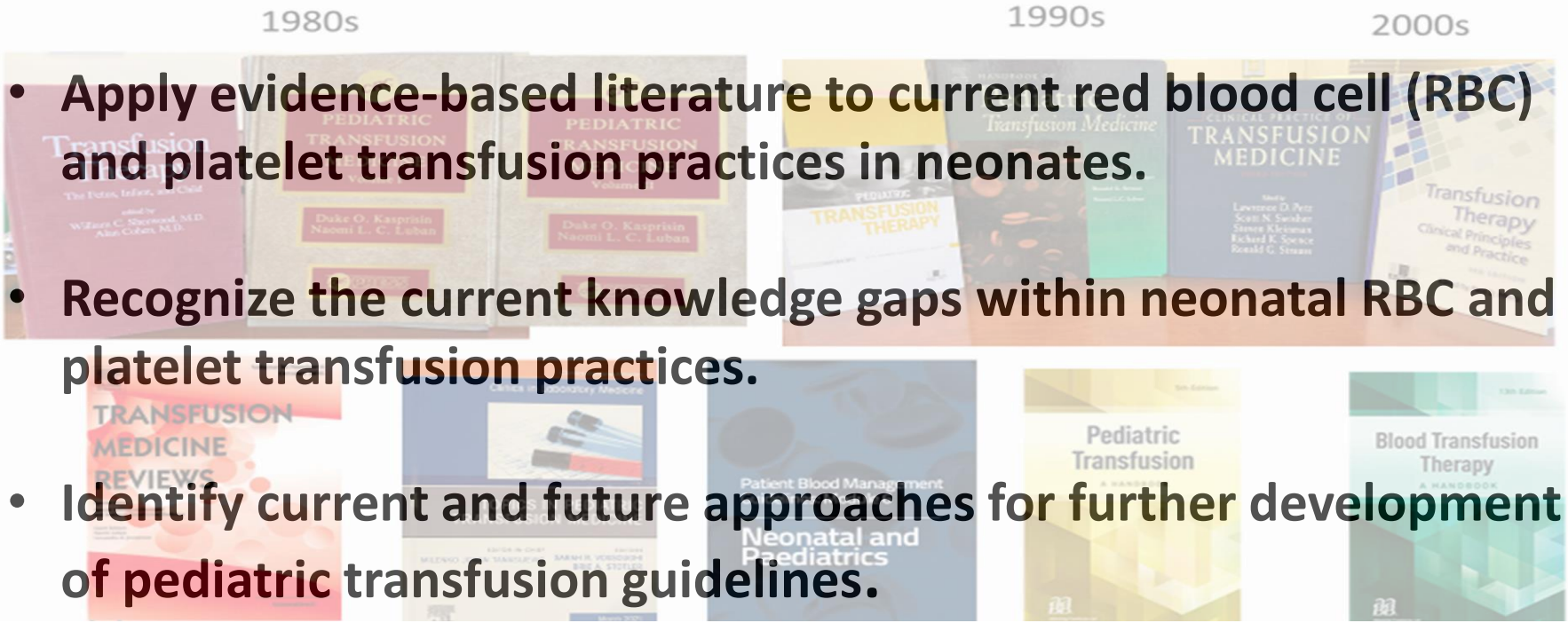
Faculty Disclosures

- Octapharma – unrestricted, research investigator
- Immucor - consultant
- Medtronics – unrestricted, research investigator
- Cellphire – consultant
- Sysmex – unrestricted, research investigator
- Westat – consultant for NHLBI REDS-IV-P

Learning Objectives

After participating in this educational activity, participants should be able to:



- **Apply evidence-based literature to current red blood cell (RBC) and platelet transfusion practices in neonates.**
- **Recognize the current knowledge gaps within neonatal RBC and platelet transfusion practices.**
- **Identify current and future approaches for further development of pediatric transfusion guidelines.**

Audience Participation Questions

1. **The PLaNeT-2 Study demonstrated all of the following except:**

a. Death or major bleeding occurred more often in patients in a lower platelet transfusion threshold group, OR 1.57 (1.06-2.32).
b. Death or major bleeding occurred more often in infants 26% vs. 19% in high platelet threshold group.
c. Nearly 40% of patients received a platelet transfusion prior to randomization.
d. Platelets transfused in the trial were only plasma-based, without platelet additive solutions or pathogen reduction technologies applied.
e. Harmful effects occurred in neonates regardless of a high or low baseline risk of death or bleeding.

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2. **The Age of Red Blood Cell Study (ARIPI) RCT in pre-term infants demonstrated that (< 7 days versus standard issue) may not be associated with increased morbidity in neonates (ie. Composite outcome NEC, ROP, BPD, IVH, death). Several caveats to the study were published: All of the following except are published caveats to the study:**

a. Hemoglobin threshold for the RBC transfusions were not specified or standardized during the study.
b. Age of RBCs of most of the units were greater than 23 days old, mean 14.6 days hence centers with conservative transfusion practices would be a challenge.
c. Anemia has been associated with an increased risk for NEC and not RBC transfusion therefore a liberal transfusion threshold may mask this outcomes.
d. The same additive solution was used for all RBC transfusions there for this is not generalizable.

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3. **All of the following were demonstrated in the TOP and ETTNO studies except:**

a. No difference in death/neurodevelopmental disability at 24 months between restrictive and liberal transfusion groups.
b. Most infants in both groups were transfused, just variable number of transfusions (6+/-4.3 vs 4.4+/-4.0 in TOP).
c. Permissive anemia with hemoglobins 7-8 gm/dL, depending upon the post-natal age, is safe, but will increase the number of transfusions, and potential donor exposures.
d. There is a limited ability to assess the detrimental effects associated with RBC transfusion since both arms of the study received transfusion.
e. Many patients in the TOP and ETTNO study were transfused for hemoglobin levels less than 7 gm/dl especially during the first week of life.

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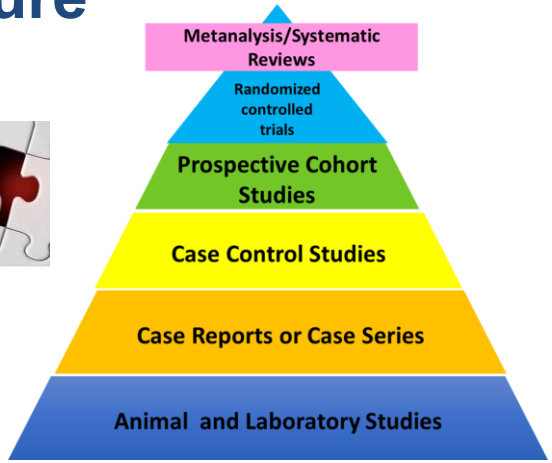
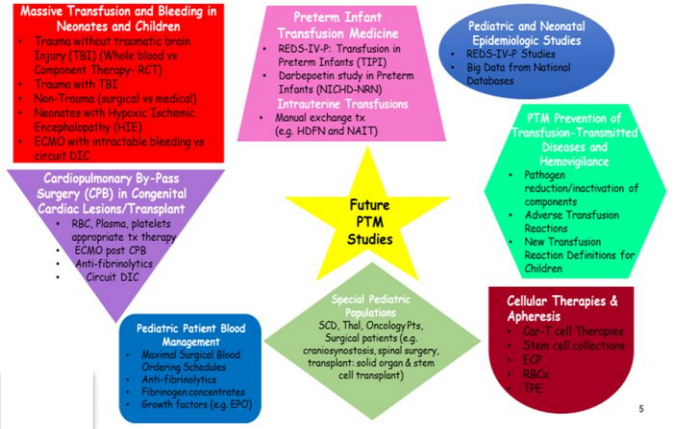
How/when do I treat neonates with anemia and thrombocytopenia?
Fact, "Fiction", and the Future

Definitions:

- **Fact:** RCT and high quality evidence to support practice recommendations



- **"Fiction":** Gaps in the evidence where expert opinion and consensus opinion is made due to little or no data to support evidenced based-practice recommendations.



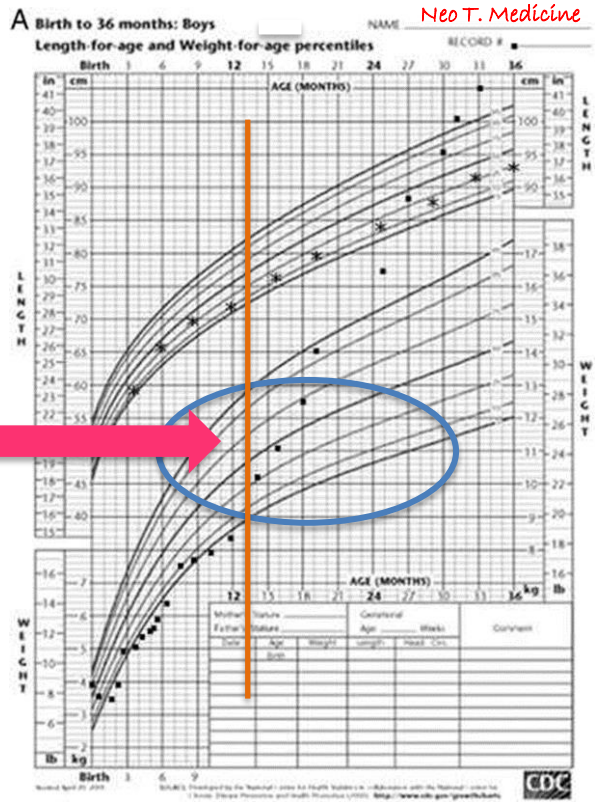
- **Future:** Where do we go from here?

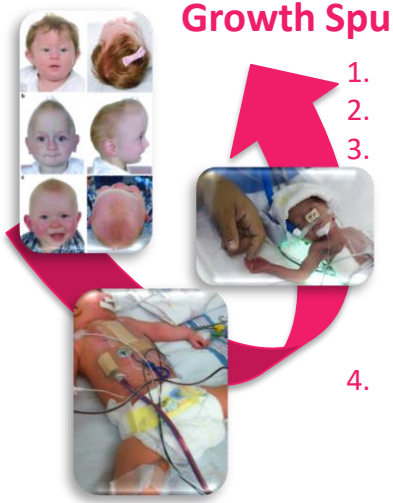
Impression: Recovery from Failure to Thrive

21ST CENTURY

Neonatal Transfusion Medicine

We are here





Neonatal Transfusion Medicine Growth Spurts (high velocity)

1. NIH-supported networks
2. Homogeneous populations
3. Neonatologists, Anesthesiologists, Ped Surgeons, Neurosurgeons, and Cardiac Surgeons - focused on sub-populations of infants
4. Almost all of these hospitalized patients receive blood products at some pt.

Crossmatch/Prepare RBC

Accept | Cancel

Priority: Routine | Routine | STAT

Frequency: ONE TIME

Starting: 5/19/2022 | Today | Tomorrow | At: 2151

First Occurrence: **Today 2151**

Show Scheduled Times

05/19/22 2151

When do I transfuse?

Last Resulted: Lab Test Results

Component	Time Elapsed	Value	Range	Status
Hemoglobin-Blood	12 days (05/07/22 1237)	10.0		
Hematocrit-Blood	12 days (05/07/22 1237)	29.7		

Transfusion Indications

☐ Acute Blood Loss ☐ Anticipated Surgical Blood Loss

☐ Symptomatic Anemia not from acute blood loss ☐ Hemoglobin <8 g/dL or Hematocrit <24%

☐ Complications of Sickle Cell Disease ☐ RBC Exchange ☐ Other (please indicate)

Volume in mL

Special Requirements

☐ CMV Negative ☐ Irradiated ☐ Hemoglobin S - Negative ☐ Fresh < 7 days ☐ Syringe

☐ Split Unit (please specify volume in 'Comment') ☐ Neonatal Protocol ☐ Other (please specify)

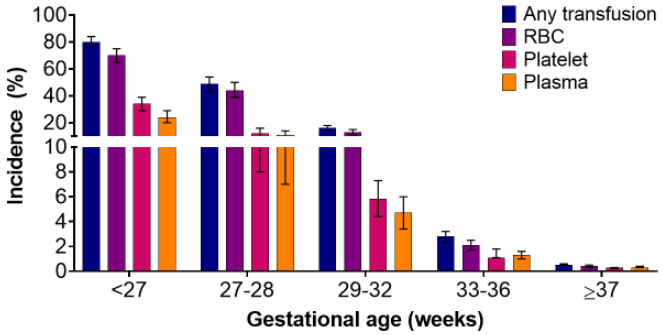
Which boxes do I check?

Neonatal RBC and Platelet Transfusions

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)

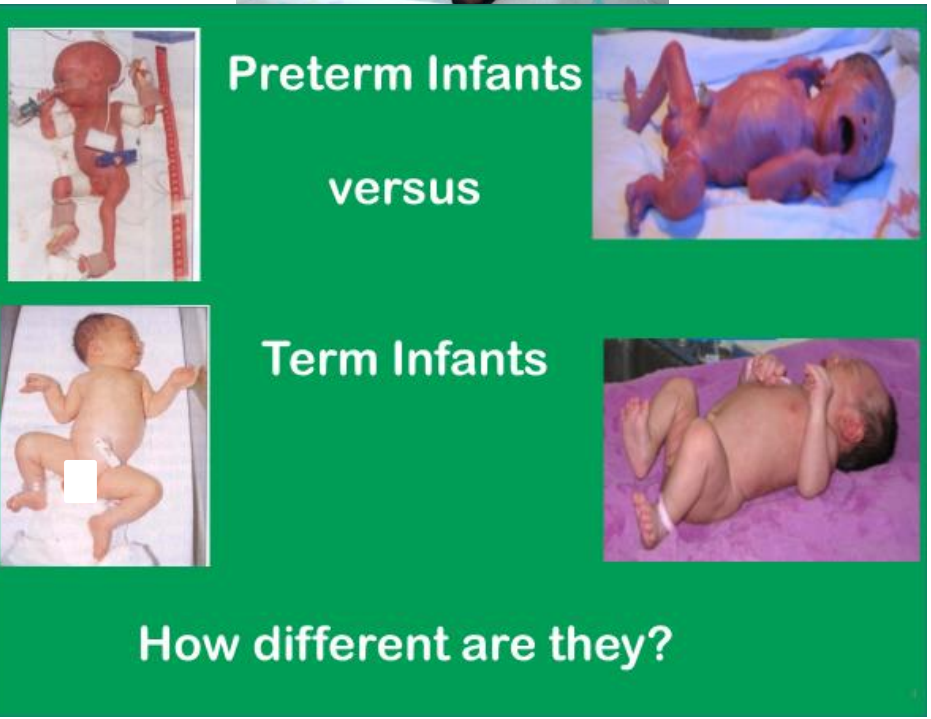
Incidence of transfusion by gestational age



From NHLBI REDS-III study
Vein-to-Vein Database
N=60,243 infants from 7 US centers

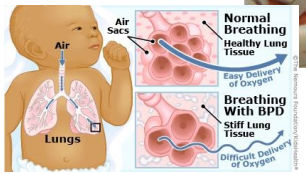
Patel et al., J Pediatr, 2021

Preterm Infants versus Term Infants



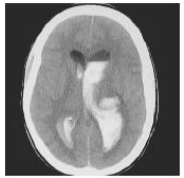
Prematurity: Definitions and Co-morbidities

Bronchopulmonary Dysplasia (BPD)

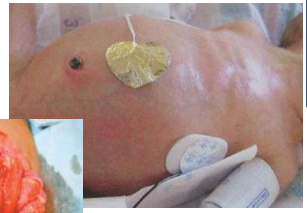


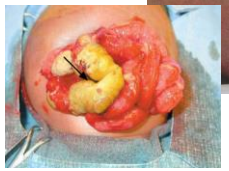
- **Extremely Low Birth Weight (ELBW) Infants: < 1,000 grams**
- **Very Low Birth Weight (VLBW) Infants: ≤ 1500 grams**

Intraventricular Hemorrhage (IVH)

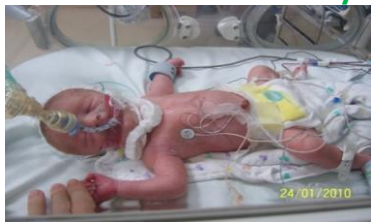


Necrotizing Enterocolitis (NEC)

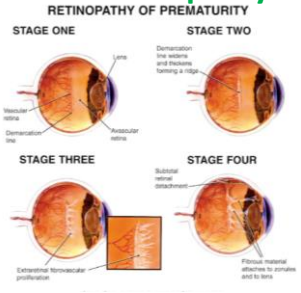




Anemia of Prematurity

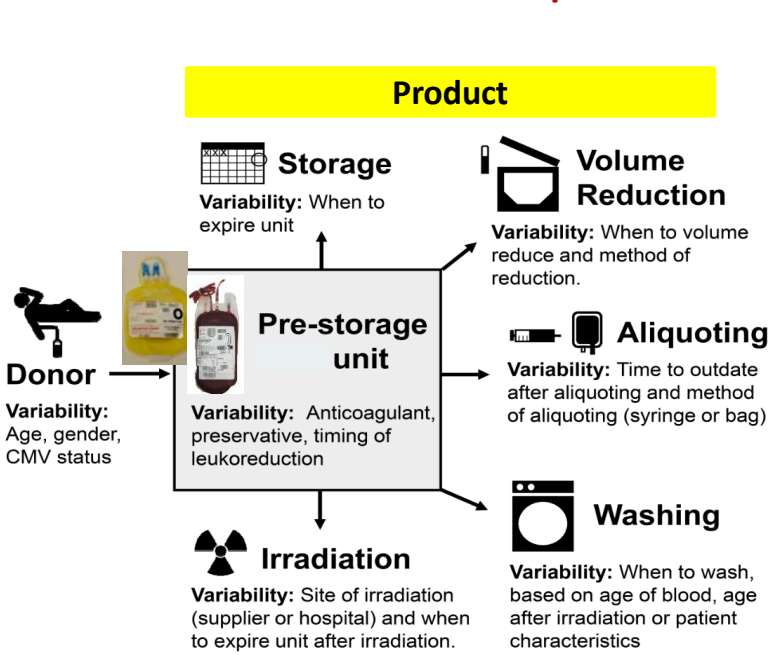


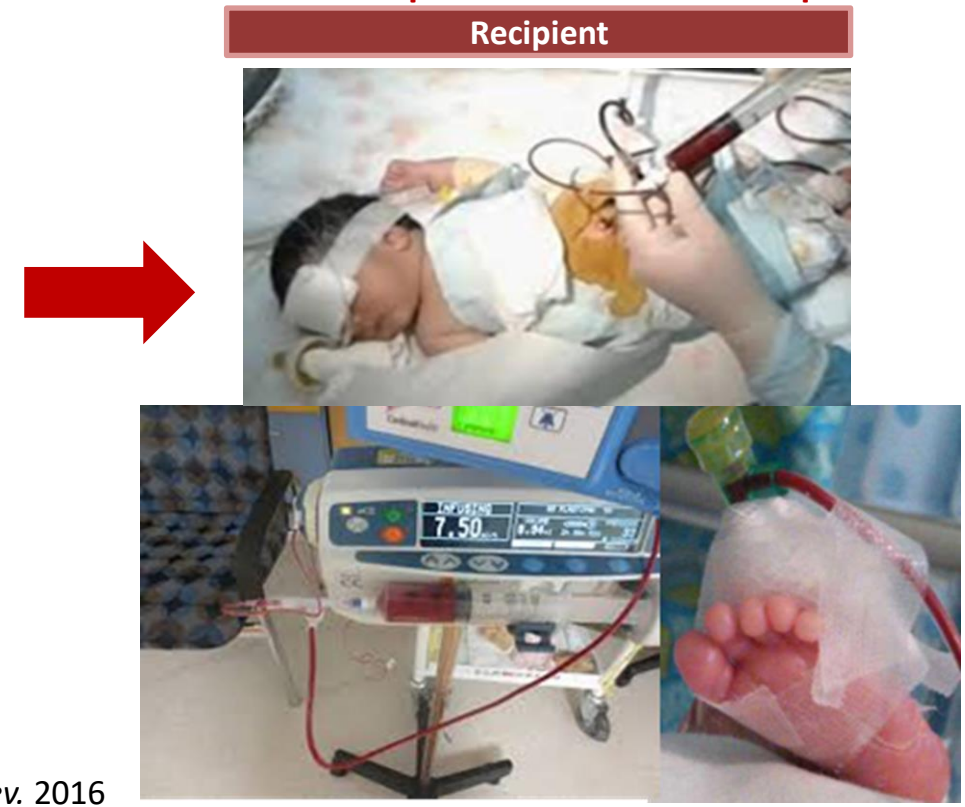
Retinopathy of Prematurity (ROP)



Cellular Blood Products (RBCs and Platelets) Variability of Donor and Products can Impact Recipients

Vein-2-Vein Databases Can Help Derive Evidence & All Pediatric Recipients Aren't Created Equal





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

Randomized Control Trials
Highest Level of Evidence for Recipient Population & Intervention Studied

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Higher or Lower Hemoglobin Transfusion Thresholds for Preterm Infants

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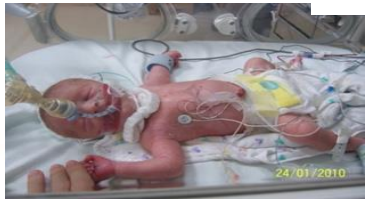
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Platelet-Transfusion Thresholds in Neonates

JAMA | Original Investigation

Effects of Liberal vs Restrictive Transfusion Thresholds on Survival and Neurocognitive Outcomes in Extremely Low-Birth-Weight Infants
The ETTNO Randomized Clinical Trial



blood

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

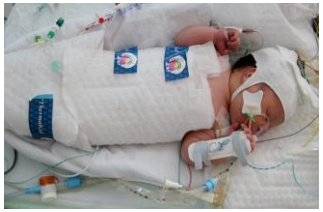
Preterm neonates benefit from low prophylactic platelet transfusion threshold despite varying risk of bleeding or death

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Erythropoietin for Neuroprotection in Preterm Infants

S.E. Juul, B.A. Comstock, R. Wadhawan, D.E. Mayock, S.E. Courtney, T. Robinson, K.A. Ahmad, E. Bendel-Stenzel, M. Baserga, E.F. LaGamma, L.C. Downey, R. Rao, N. Fahim, A. Lampland, I.D. Frantz III, J.Y. Khan, M. Weiss, M.M. Gilmore, R.K. Ohls, N. Srinivasan, J.E. Perez, V. McKay, P.T. Vu, J. Lowe, K. Kuban, T.M. O'Shea, A.L. Hartman, and P.J. Heagerty, for the PENUT Trial Consortium*



ONLINE FIRST

Effect of Fresh Red Blood Cell Transfusions on Clinical Outcomes in Premature, Very Low-Birth-Weight Infants
The ARIPI Randomized Trial

Trial Registration clinicaltrials.gov Identifier: NCT00326924; Current Controlled Trials Identifier: ISRCTN65939658

JAMA. 2012;308(14):1443-1451
Published online October 8, 2012. doi:10.1001/2012.jama.11953 www.jama.com

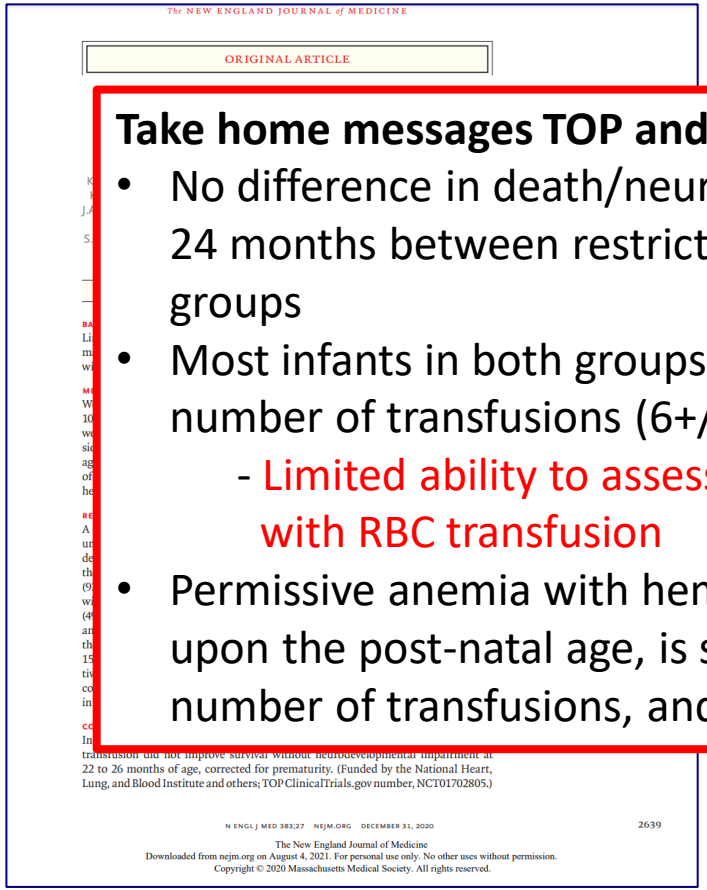
The NEW ENGLAND JOURNAL of MEDICINE

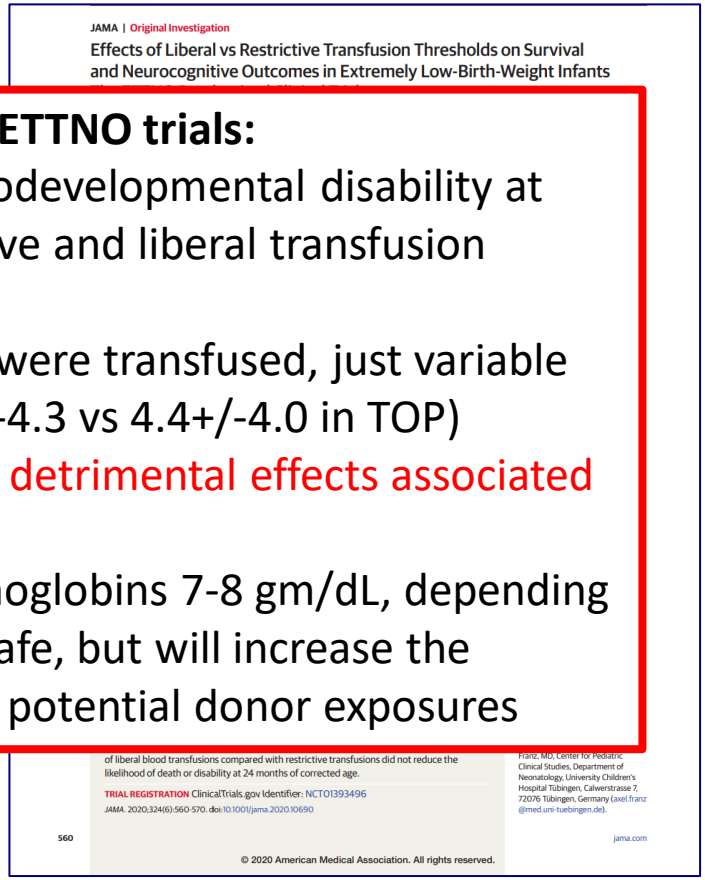
RESEARCH SUMMARY

Trial of Erythropoietin for Hypoxic–Ischemic Encephalopathy in Newborns

Wu YW et al. DOI: 10.1056/NEJMoa2119660

RBC Transfusion Thresholds





Take home messages TOP and ETTNO trials:

- No difference in death/neurodevelopmental disability at 24 months between restrictive and liberal transfusion groups
- Most infants in both groups were transfused, just variable number of transfusions (6+/-4.3 vs 4.4+/-4.0 in TOP)
  - Limited ability to assess detrimental effects associated with RBC transfusion
- Permissive anemia with hemoglobins 7-8 gm/dL, depending upon the post-natal age, is safe, but will increase the number of transfusions, and potential donor exposures

RBC: Beyond TOP and ETTNO

Key questions remain regarding RBC transfusions

- What are the mechanisms underlying the pro-inflammatory effects of RBC transfusions?
- Which cells are targeted by RBC transfusions in different organs (particularly brain and intestine)?
- How does the sex of the recipient impact inflammatory responses?
- Are there modifiable factors that attenuate or enhance the inflammatory response to RBC transfusions in neonates?
    - Donor sex, storage time, irradiation, washing

ONLINE FIRST

Effect of Fresh Red Blood Cell Transfusions on Clinical Outcomes in Premature, Very Low-
The ARIPI Rar

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Kuppuchipalayam Ramesh,
Stan Shapiro, PhD

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Age of RBCs in Premature Infants (ARIPI) Trial

- ARIPI (n= 377, BW≤ 1250 gm infants) age of RBCs (< 7 days versus standard issue) **may not be associated** with increased morbidity in neonates (ie. composite outcome NEC, ROP, BPD, IVH, death).
- **Caveat:** hgb thresholds for txn were not specified or standardized, nor was the age of RBCs of most units studied greater than 23 days old, mean 14.6 days. Therefore, generalizing the findings to centers with conservative transfusion practices would be a challenge.
- **Caveat:** anemia is associated with an increased risk for NEC and not RBC transfusion; therefore a liberal transfusion threshold might mask this outcome.
- **Caveat:** There was also no control for the additive/anticoagulant solution (e.g., SAG-M, AS-3, CPDA-1) used for RBC transfusion.
- **Conclusion:** For these and other reasons, further studies to definitively answer whether the age of RBCs is detrimental for certain neonatal pts

Fergusson DA, *et al.* JAMA. 2012
Patel RM. Josephson CD. JAMA (editorial) 2012

Storage Age of Red Blood Cells for Transfusion of Premature Infants

To the Editor: The Age of Red Blood Cells in Premature Infants (ARIPI) study by Dr Fergusson and colleagues[1] found no difference in the primary outcome between infants receiving red blood cells (RBCs) stored for less than 7 days (mean, 5.1 days) and those receiving older RBCs (mean, 14.6

is finding suggests
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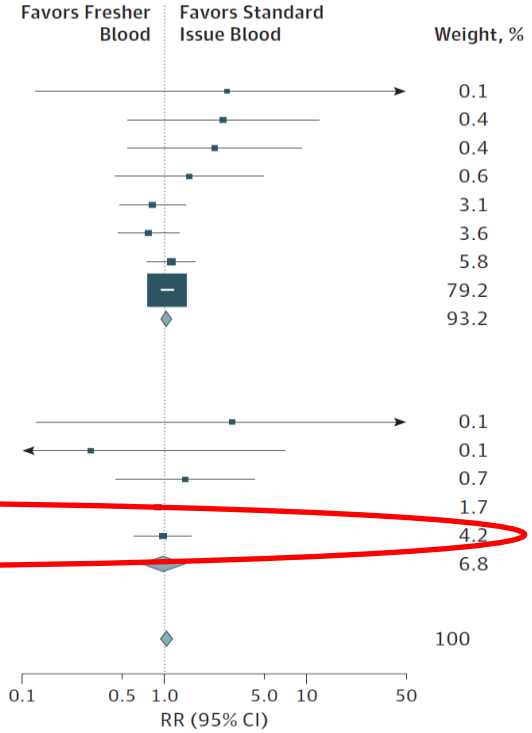
d 14 to 21 days.

edicine (Dr Patel), Depart-
ments of Pathology and Pediatrics (Dr Josephson; cjoseph@emory.edu), Emory University School of Medicine, Atlanta, Georgia.

Effect of storage of red cells on survival

Source	Fresher Blood: No. of Deaths	Fresher Blood: Total No.	Standard Issue Blood: No. of Deaths	Standard Issue Blood: Total No.	RR (95% CI)	Weight, %
Adults						
Bennett-Guerrero et al,[33] 2009	1	12	0	11	2.77 (0.12-61.65)	0.1
Aubron et al,[34] 2012	5	25	2	26	2.60 (0.55-12.19)	0.4
Schulman et al,[30] 2002	4	8	2	9	2.25 (0.55-9.17)	0.4
Hébert et al,[32] 2005	5	26	4	31	1.49 (0.45-4.98)	0.6
Steiner et al,[41] 2015	23	538	29	560	0.83 (0.48-1.41)	3.1
Kor et al,[37] 2012	17	50	22	50	0.77 (0.47-1.27)	3.6
Heddle et al,[36] 2012	35	309	61	601	1.12 (0.75-1.65)	5.8
Lacroix et al,[40] 2015	448	1211	430	1219	1.05 (0.94-1.17)	79.2
Subtotal	538	2179	550	2507	1.04 (0.95-1.15)	93.2
Heterogeneity: $\tau^2=0$; $\chi^2_7=5.47$; $P=.60$; $I^2=0\%$						
Tests for overall effect: z score = 0.85; $P=.40$						
Neonates, Infants, and Children						
Dhabangi et al,[38] 2013	1	37	0	37	3.00 (0.13-71.34)	0.1
Strauss et al,[29] 1996	0	21	1	19	0.30 (0.01-7.02)	0.1
Dhabangi et al,[39] 2015	7	143	5	143	1.40 (0.45-4.31)	0.7
Fernandes da Cunha et al,[31] 2005	3	26	10	26	0.90 (0.44-1.83)	1.7
Fergusson et al,[35] 2012	30	188	31	189	0.97 (0.61-1.54)	4.2
Subtotal	47	415	47	414	0.99 (0.69-1.42)	6.8
Heterogeneity: $\tau^2=0$; $\chi^2_4=1.46$; $P=.83$; $I^2=0\%$						
Tests for overall effect: z score = 0.06; $P=.96$						
Overall	585	2594	597	2921	1.04 (0.95-1.14)	100
Heterogeneity: $\tau^2=0$; $\chi^2_{12}=7.00$; $P=.86$; $I^2=0\%$						
Tests for overall effect: z score = 0.81; $P=.42$						
Tests for subgroup differences: $\chi^2_1=0.08$; $P=.78$; $I^2=0\%$						



Carson JL et al. *JAMA.* 2016

Questions of Patient Blood Management

Questions of RBC transfusion negatively impacting recipients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Erythropoietin for Neuroprotection in Preterm Infants

S.E. Juul, B.A. Comstock, R. Wadhawan, D.E. Mayock, S.E. Courtney, T. Robinson, K.A. Ahmad, E. Bendel-Stenzel, M. Baserga, E.F. LaGamma, L.C. Downey, R. Rao, N. Fahim, A. Lampland, I.D. Frantz III, J.Y. Khan, M. Weiss, M.M. Gilmore, R.K. Ohls, N. Srinivasan, J.E. Per... A.L. Hartman, an...

BACKGROUND

High-dose erythropoietin clinical models of neonat efficacy; however, the b infants have not been es

METHODS

In this multicenter, rand assigned 941 infants wh gestation to receive eryt ropoietin was administer weight every 48 hours fo 400 U per kilogram thr completed weeks of post saline followed by shan neurodevelopmental imp neurodevelopmental imp ite motor or composite o below the mean, with hi Scales of Infant and Tod

RESULTS

A total of 741 infants w ceived erythropoietin an ence between the erythr death or severe neurode [26%] vs. 94 children [2 1.32; P=0.80). There we rates of retinopathy of p enterocolitis, bronchopul adverse events.

CONCLUSIONS

High-dose erythropoieti from 24 hours after birt in a lower risk of severe age. (Funded by the Na PENUT ClinicalTrials.go

Pediatric RESEARCH

www.nature.com/pr

CLINICAL RESEARCH ARTICLE

Transfusions and neurodevelopmental outcomes in extremely low gestation neonates enrolled in the PENUT Trial: a randomized clinical trial

Phuong T. Vu[1,27], Robin K. Ohls[2], Dennis E. Mayock[3], Kendell R. German[3], Bryan A. Comstock[1], Patrick J. Heagerty[1], Sandra E. Juul[3] and for the PENUT Consortium

BACKGROUND: Outcomes of extremely low gestational age neonates (ELGANs) may be adversely impacted by packed red blood cell (pRBC) transfusions. We investigated the impact of transfusions on neurodevelopmental outcome in the Preterm Erythropoietin (Epo) Neuroprotection (PENUT) Trial population.

METHODS: This is a post hoc analysis of 936 infants 24-0/6 to 27-6/7 weeks' gestation enrolled in the PENUT Trial. Epo 1000 U/kg or placebo was given every 48 h × 6 doses, followed by 400 U/kg or sham injections 3 times a week through 32 weeks postmenstrual age. Six hundred and twenty-eight (315 placebo, 313 Epo) survived and were assessed at 2 years of age. We evaluated associations between BSID-III scores and the number and volume of pRBC transfusions.

RESULTS: Each transfusion was associated with a decrease in mean cognitive score of 0.96 (95% CI of [−1.34, −0.57]), a decrease in mean motor score of 1.51 (−1.91, −1.12), and a decrease in mean language score of 1.10 (−1.54, −0.66). Significant negative associations between BSID-III score and transfusion volume and donor exposure were observed in the placebo group but not in the Epo group.

CONCLUSIONS: Transfusions in ELGANs were associated with worse outcomes. We speculate that strategies to minimize the need for transfusions may improve outcomes.

Pediatric Research (2021) 90:109–116; https://doi.org/10.1038/s41390-020-01273-w

IMPACT:

- Transfusion number, volume, and donor exposure in the neonatal period are associated with worse neurodevelopmental (ND) outcome at 2 years of age, as assessed by the Bayley Infant Scales of Development, Third Edition (BSID-III).
- The impact of neonatal packed red blood cell transfusions on the neurodevelopmental outcome of preterm infants is unknown.
- We speculate that strategies to minimize the need for transfusions may improve neurodevelopmental outcomes.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Trial of Erythropoietin for Hypoxic–Ischemic Encephalopathy in Newborns

Wu YW et al. DOI: 10.1056/NEJMoa2119660

CLINICAL PROBLEM

Hypoxic–ischemic encephalopathy accounts for more than one fifth of neonatal deaths worldwide, and survivors face long-term disability. Therapeutic hypothermia is the only known treatment that improves neurodevelopmental outcomes in affected infants, but its benefits are limited. Erythropoietin has been proposed as a potential adjuvant therapy.

CLINICAL TRIAL

Design: A phase 3, double-blind, randomized, placebo-controlled trial examined the safety and efficacy of erythropoietin combined with therapeutic hypothermia in U.S. infants born at 36 weeks or more of gestation with moderate or severe hypoxic–ischemic encephalopathy.

Intervention: 500 infants who began standard therapeutic hypothermia within 6 hours after birth were assigned to receive intravenous erythropoietin (1000 U per kilogram of body weight) or saline placebo within 26 hours after birth and at 2, 3, 4, and 7 days of age. The primary outcome was death or neurodevelopmental impairment of any severity at 22 to 36 months of age.

RESULTS

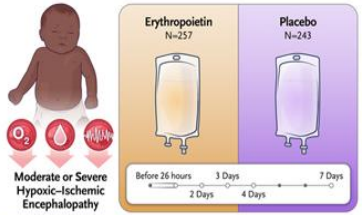
Efficacy: The incidence of death or neurodevelopmental impairment did not differ significantly between the erythropoietin and placebo groups.

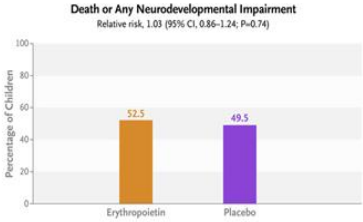
Safety: The mean number of serious adverse events per child was higher in the erythropoietin group, as was the percentage of children with at least one serious adverse event.

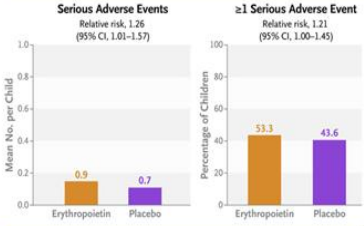
LIMITATIONS AND REMAINING QUESTIONS

- The usefulness of erythropoietin in settings where therapeutic hypothermia is unavailable or ineffective could not be assessed.
- The trial was limited to patients with moderate or severe hypoxic–ischemic encephalopathy; the effects of erythropoietin on milder illness were not evaluated.
- The trial was conducted in the United States, so the findings may not apply to infants in other countries.

Links: Full Article | NEJM Quick Take

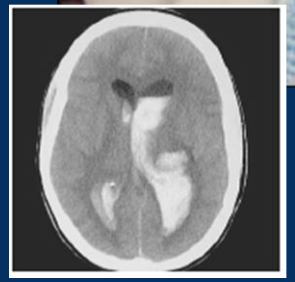






CONCLUSIONS

Among infants with moderate or severe hypoxic–ischemic encephalopathy receiving therapeutic hypothermia, multiple high doses of erythropoietin did not lower the risk of death or neurodevelopmental impairment and were associated with a greater number of serious adverse events than placebo.

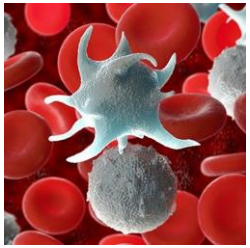


Platelets


Apheresis platelets psoralen-treated (APPT)
Untreated apheresis platelets in PAS-E
Untreated apheresis platelets in plasma
B
Rh POSITIVE
A
Rh POSITIVE
A
Rh POSITIVE

Platelet Variability of Donor and Products can Impact Recipients

Vein-2-Vein Databases Can Help Derive Evidence & All Pediatric Recipients Aren't Created Equal



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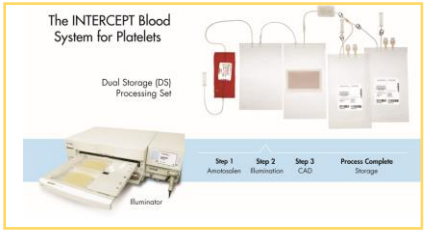
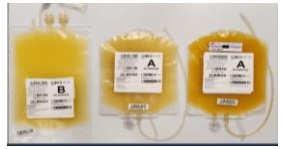


Product

Donor

Variability: Age, gender, CMV status



Whole blood derived/Buffy Coat, pathogen reduced, PAS, Apheresis Platelets Leukoreduced

Platelet Storage

Variability: When to expire unit

Irradiation

Variability: Site of irradiation (supplier or hospital) and when to expire unit after irradiation.

Volume Reduction

Variability: When to volume reduce and method of reduction.

Aliquoting

Variability: Time to outdate after aliquoting and method of aliquoting (syringe or bag)

Washing

Variability: When to wash, based on age of blood, age after irradiation or patient characteristics

Recipient

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

ORIGINAL ARTICLE

ıtelet-Transfusion
Neonates

PlaNeT-2 trial caveats

- 39% of randomized neonates received at least one (1-3) platelet transfusion prior to randomization
- Study required a head ultrasound within 6 hours prior to randomization
  - Patients with severe IVH were excluded for 72 hours

No. at Risk									
Low-threshold group	309	297	290	284	279	276	274	271	269
High-threshold group	308	298	282	270	264	256	252	247	243

Death or major bleeding: 26% vs. 19% in high- vs. low threshold group, OR 1.57 (1.06-2.32)

Effects consistent across subgroups

blood®
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Preterm neonates benefit from low prophylactic platelet transfusion threshold despite varying risk of bleeding or death

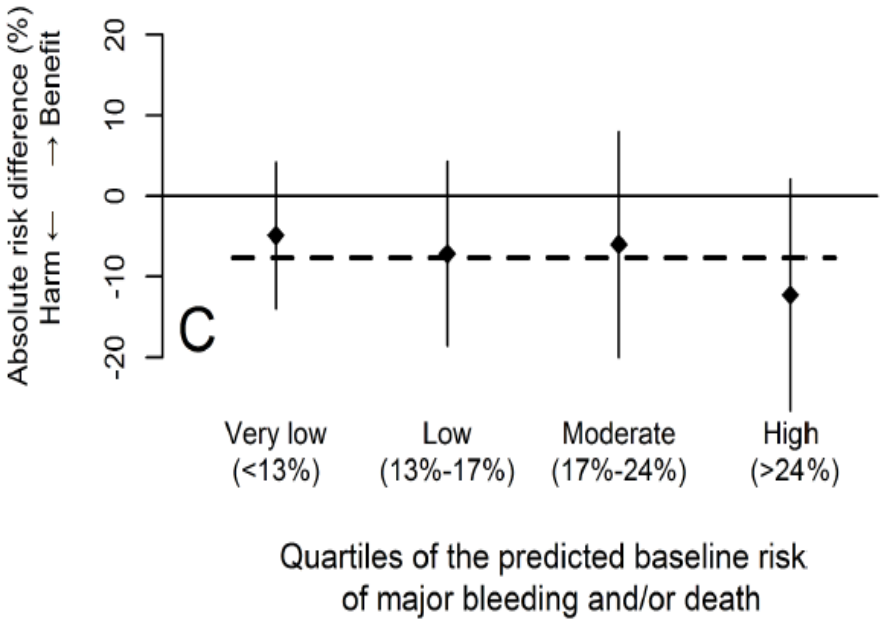
Susanna F. Fustolo-Gunnink,[1-3] Karin Fijnvandraat,[2,4] David van Klaveren,[5,6] Simon J. Stanworth,[7-9] Anna Curley,[10] Wes Onland,[11] Ewout W. Steyerberg,[12] Ellen de Kort,[13] Esther J. d'Haens,[14] Christian V. Hulzebos,[15] Elise J. Huisman,[16] Willem P. de Boode,[17] Enrico Lopriore,[18] and Johanna G. van der Bom,[1,3] for the PlaNeT-2 MATISSE Collaborators

[1]Center for Clinical Transfusion Research, Sanquin Research, Leiden, The Netherlands; [2]Pediatric Hematology, Emma Children's Hospital, Amsterdam University Medical Center (UMC), University of Amsterdam, The Netherlands; [3]Department of Epidemiology, Leiden University Medical Center, Leiden, The Netherlands; [4]Department of Molecular Cellular Hemostasis, Sanquin Research, Amsterdam, The Netherlands; [5]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands; [6]Predictive Analytics and Comparative Effectiveness Center, Tufts Medical Center, Boston, MA; [7]Transfusion Medicine, National Health Service (NHS) Blood and Transplant, Oxford, United Kingdom; [8]Department of Haematology, Oxford University Hospitals, NHS Foundation Trust, Oxford, United Kingdom; [9]Radcliffe Department of Medicine, Biomedical Research Centre (BRC) Haematology Theme, University of Oxford, Oxford, United Kingdom; [10]Department of Neonatology, National Maternity Hospital, Dublin, Ireland; [11]Department of Neonatology, Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands; [12]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands; [13]Department of Neonatology, Máxima Medical Center, Veldhoven, The Netherlands; [14]Department of Neonatology, Amalia Children's Center, Zwolle, The Netherlands; [15]Department of Neonatology, Beatrix Children's Hospital, University Medical Center Groningen, Groningen, The Netherlands; [16]Department of Pediatric Hematology, Erasmus Medical Center/Sophia Children's Hospital, Rotterdam, The Netherlands; [17]Department of Neonatology, Radboud University Medical Center, Nijmegen, The Netherlands; and [18]Division of Neonatology, Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands

KEY POINTS

- A recent trial showed increased risk of death or bleeding in neonates who received platelet transfusions for platelet counts above 25 × 10⁹/L.
- The current analysis reveals that these harmful effects occur in neonates with high, as well as low, baseline risk of death or bleeding.

The Platelets for Neonatal Thrombocytopenia (PlaNeT-2) trial reported an unexpected overall benefit of a prophylactic platelet transfusion threshold of 25 × 10⁹/L compared with 50 × 10⁹/L for major bleeding and/or mortality in preterm neonates (7% absolute-risk reduction). However, some neonates in the trial may have experienced little benefit or even harm from the 25 × 10⁹/L threshold. We wanted to assess this heterogeneity of treatment effect in the PlaNet-2 trial, to investigate whether all preterm neonates benefit from the low threshold. We developed a multivariate logistic regression model in the PlaNet-2 data to predict baseline risk of major bleeding and/or mortality for all 653 neonates. We then ranked the neonates based on their predicted baseline risk and categorized them into 4 risk quartiles. Within these quartiles, we assessed absolute-risk difference between the 50 × 10⁹/L- and 25 × 10⁹/L-threshold groups. A total of 146 neonates died or developed major bleeding. The internally validated C-statistic of the model was 0.63 (95% confidence interval, 0.58-0.68). The 25 × 10⁹/L threshold was associated with absolute-risk reduction in all risk groups, varying from 4.9% in the lowest risk group to 12.3% in the highest risk group. These results suggest that a 25 × 10⁹/L prophylactic platelet count threshold can be adopted in all preterm neonates, irrespective of predicted baseline outcome risk. Future studies are needed to improve the predictive accuracy of the baseline risk model. This trial was registered at www.isrctn.com as #ISRCTN87736839. (*Blood*. 2019;134(26):2354-2360)

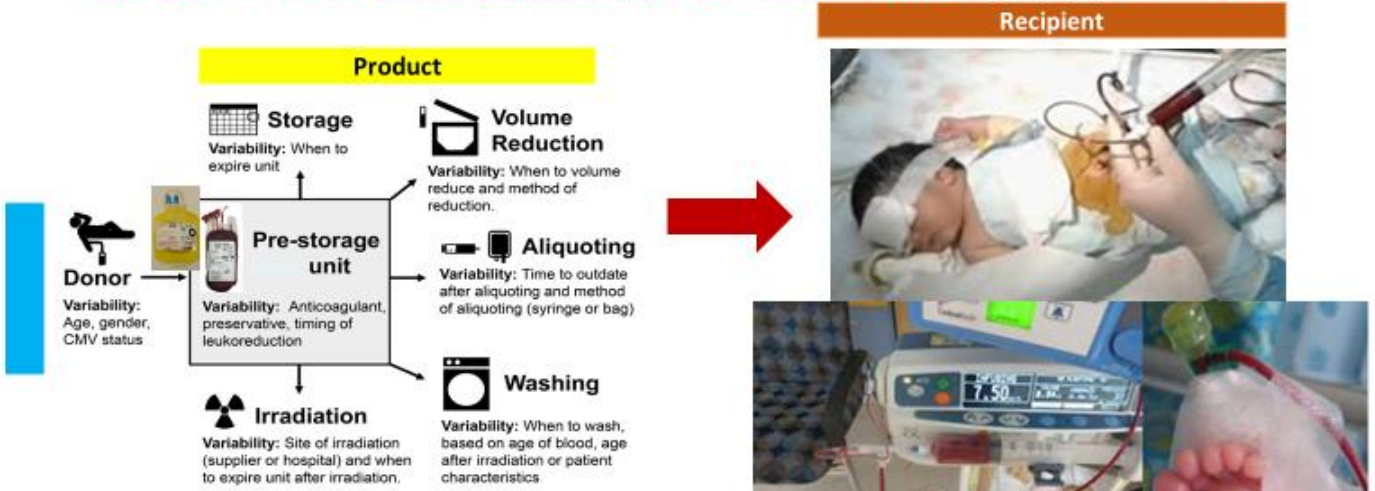


Fustolo-Gunnick et al. *Blood.* 2019

“Fiction”

Cellular Blood Products (RBCs and Platelets)
Variability of Donor and Products can Impact Recipients

Vein-2-Vein Databases Can Help Derive Evidence & All Pediatric Recipients Aren’t Created Equal



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

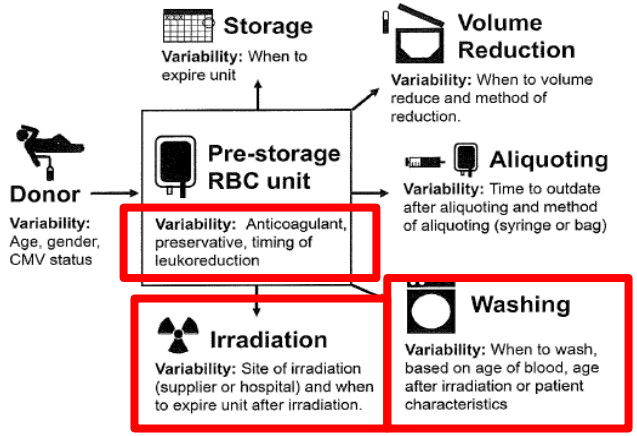
Variation in donor RBCs

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*



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[b] only 41%—combination	34%—policy for large-volume transfusions 17%—policy specifying number of days after irradiation or storage	93% irradiate (66% 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.

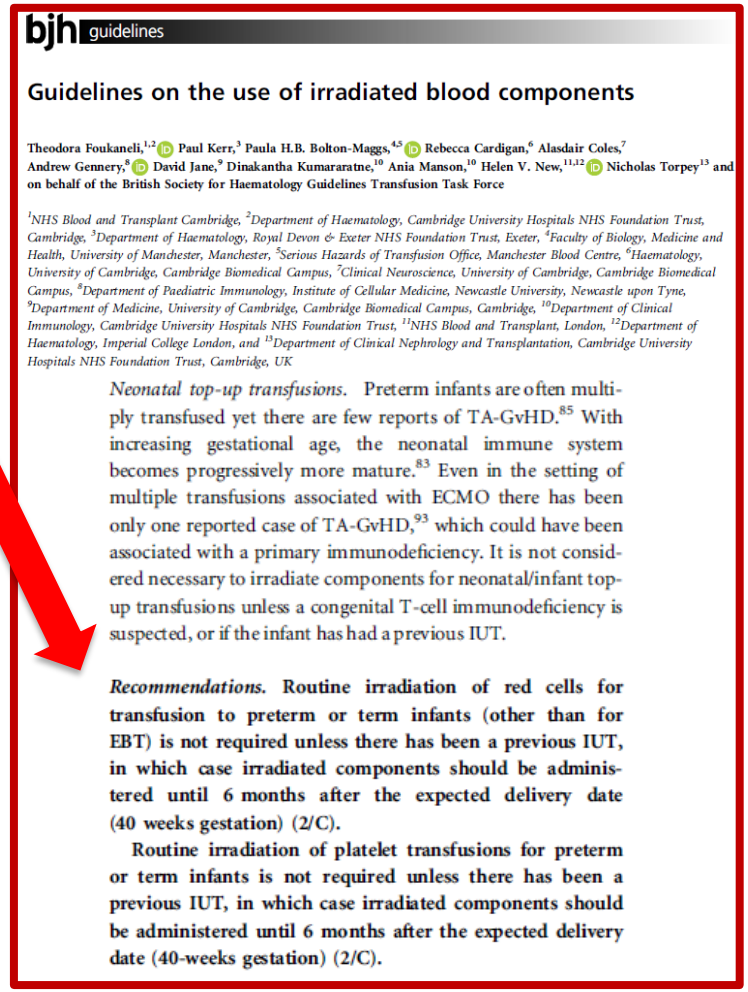
[b] AS-1, AS-3, AS-5 units.

[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

Irradiation of Cellular Blood Products, Prevention of TA-GVHAD

- Undiagnosed immunodeficiencies – out of caution some institutions irradiate all cellular products transfused to neonates and infants.
- Other institutions selectively irradiate products transfused to neonates weighing < 1200 g.
- The 2020 Guidelines on Irradiation from the British Society for Haematology Guidelines Transfusion Task Force state that routine irradiation is not required for cellular products transfused to preterm or term infants unless those infants received intra-uterine transfusions.
- Neonates or children with known or suspected cellular immunodeficiencies, undergoing BMT, and receiving directed donor products require irradiated cellular blood products.
- Impact of irradiation storage duration on outcomes in infants and children has not been studied in detail, though metabolomic changes are evident in the RBC unit.
- The British Society Guidelines recommend that irradiated RBCs are transfused within 24 hours of irradiation if the fetal/neonatal recipient is at risk for hyperkalemia (e.g. large volume transfusion, exchange transfusion, intra-uterine transfusion).



bjh guidelines

Guidelines on the use of irradiated blood components

Theodora Foukaneli,[1,2] Paul Kerr,[3] Paula H.B. Bolton-Maggs,[4,5] Rebecca Cardigan,[6] Alasdair Coles,[7] Andrew Gennery,[8] David Jane,[9] Dinakantha Kumararatne,[10] Ania Manson,[10] Helen V. New,[11,12] Nicholas Torpey[13] and on behalf of the British Society for Haematology Guidelines Transfusion Task Force

[1]NHS Blood and Transplant Cambridge, [2]Department of Haematology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, [3]Department of Haematology, Royal Devon & Exeter NHS Foundation Trust, Exeter, [4]Faculty of Biology, Medicine and Health, University of Manchester, Manchester, [5]Serious Hazards of Transfusion Office, Manchester Blood Centre, [6]Haematology, University of Cambridge, Cambridge Biomedical Campus, [7]Clinical Neuroscience, University of Cambridge, Cambridge Biomedical Campus, [8]Department of Paediatric Immunology, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, [9]Department of Medicine, University of Cambridge, Cambridge Biomedical Campus, Cambridge, [10]Department of Clinical Immunology, Cambridge University Hospitals NHS Foundation Trust, [11]NHS Blood and Transplant, London, [12]Department of Haematology, Imperial College London, and [13]Department of Clinical Nephrology and Transplantation, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Neonatal top-up transfusions. Preterm infants are often multiply transfused yet there are few reports of TA-GvHD.[85] With increasing gestational age, the neonatal immune system becomes progressively more mature.[83] Even in the setting of multiple transfusions associated with ECMO there has been only one reported case of TA-GvHD,[93] which could have been associated with a primary immunodeficiency. It is not considered necessary to irradiate components for neonatal/infant top-up transfusions unless a congenital T-cell immunodeficiency is suspected, or if the infant has had a previous IUT.

Recommendations. **Routine irradiation of red cells for transfusion to preterm or term infants (other than for EBT) is not required unless there has been a previous IUT, in which case irradiated components should be administered until 6 months after the expected delivery date (40 weeks gestation) (2/C).**

Routine irradiation of platelet transfusions for preterm or term infants is not required unless there has been a previous IUT, in which case irradiated components should be administered until 6 months after the expected delivery date (40-weeks gestation) (2/C).

Received: 22 February 2022 | Revised: 8 September 2022 | Accepted: 12 September 2022
DOI: 10.1111/trf.17135

TRANSFUSION COMPLICATIONS

TRANSFUSION

Transfusion-associated hyperkalemia in pediatric population: Analy

Chisa Yamada[1] | Mau
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Funding information
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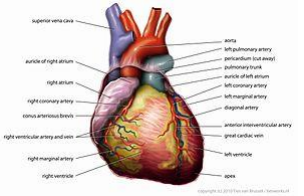
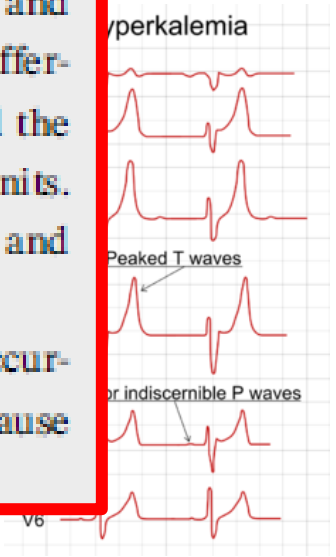
Results/Findings: Pre-transfusion creatinine, comorbidities of kidney and/or liver dysfunctions, and total transfused volume within 12 h (tV-12) per kg and per estimated total blood volume (eTBV) showed statistically significant differences between TAH and non-TAH groups. Multivariate analysis revealed the biggest factor in TAH occurrence was tV-12/kg followed by age of RBC units. The thresholds of risks were tV-12/kg of 30 ml/kg, tV-12/eTBV of 30%, and RBC unit age of 7.95 days.

Conclusions: The study findings suggest that the biggest factor on TAH occurrence is tV-12/kg. More importantly, 30% of eTBV transfusion could cause TAH in patients with multiple comorbidities.

Conclusions: The study findings suggest that the biggest factor on TAH occurrence is tV-12/kg. More importantly, 30% of eTBV transfusion could cause TAH in patients with multiple comorbidities.

- **Small patients receiving la**

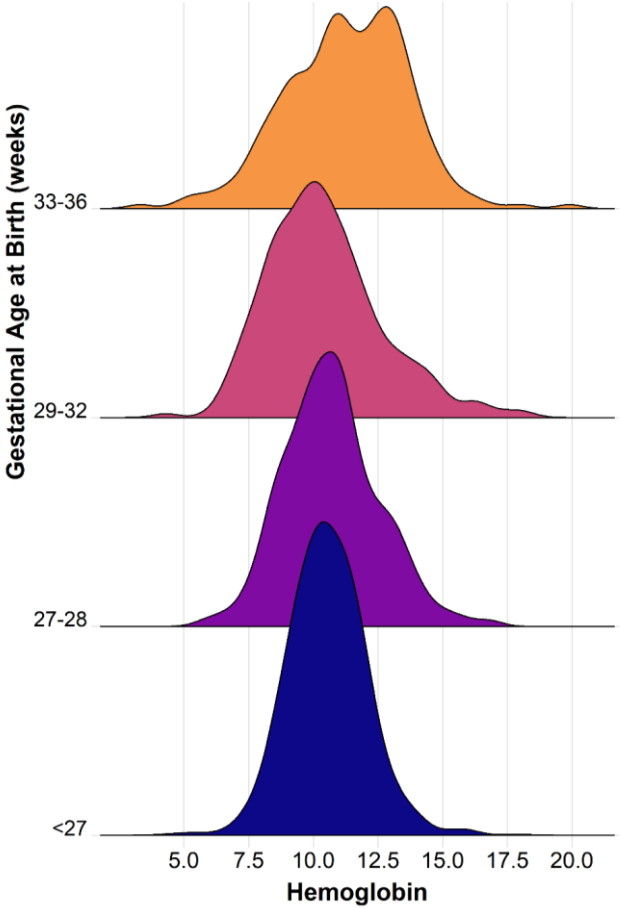




Hall, Transfusion, 1993 & Baz, Transfusion Medicine, 2002 & wikipedia images

Transfusion thresholds in US centers

What about infants 33-36 weeks GA?

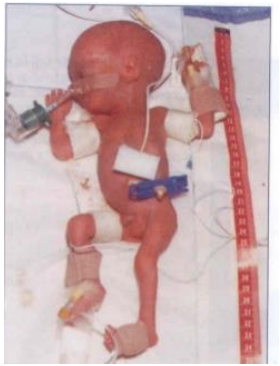


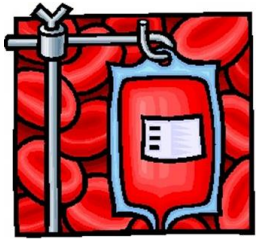
From NHLBI REDS-III study
N=60,243 infants from 7 US centers

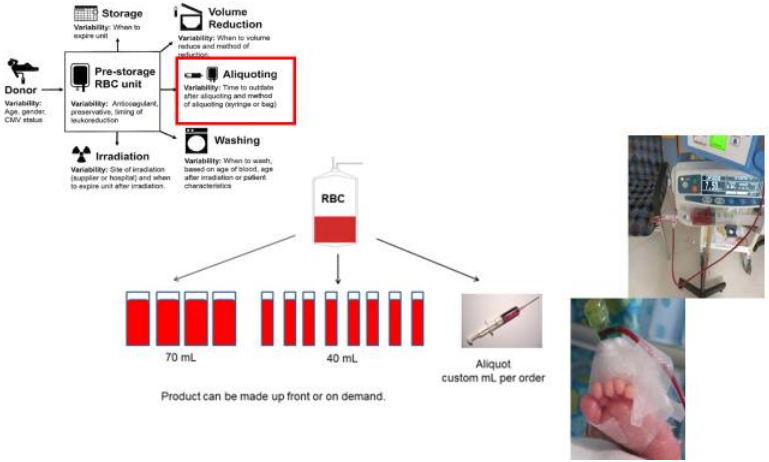
Patel et al. *J Pediatr. 2021*

Manufacturing RBCs Products= Aliquoting

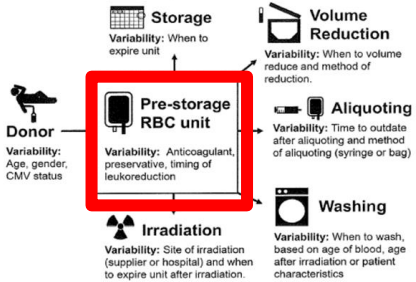
- Goals when approaching infant RBC transfusion
  - Minimize donor exposure
  - Minimize exposure to large doses of
    - Adenine and other solutes
    - Potassium
- Other “standard” targets
  - Minimize viral transmission
  - Minimize risk of transfusion-associated graft versus host disease
  - Concerns of age of blood and the “storage lesion” effects

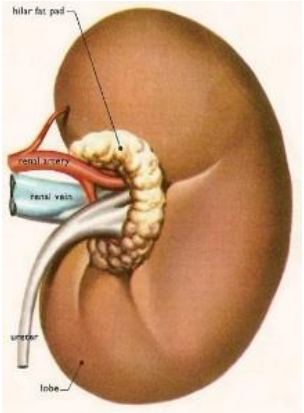






Adenine and other solutes in additive solutions





- **Adenine** → phosphoribosyl transferase → metabolizes 95% of adenine
- Adenine → xanthine oxidase →dihydroxyadenine (DOA) insoluble precipitate → **crystals can block renal tubules and cause liver toxicity**
- **Mannitol** is a large molecule that has high osmolality
  - Pulls water into vessels
  - Concern about causing osmotic diuresis and compromising cerebral blood flow in neonates
- **Hyperglycemia** can occur with transfusion of blood products
- Other risks
  - **Hypernatremia**: Sodium in the blood product
  - **Hypocalcemia:** Citrate & phosphate chelate patient's calcium

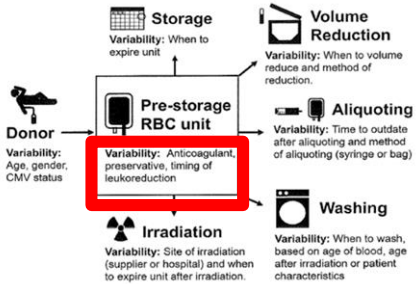
Clinical studies support low volume transfusions with additive RBC units

Table 3. Small-volume red blood cell transfusions given as stored red blood cells to limit donor exposure without causing apparent adverse effects

Reference	Solution	Storage	Dose	Hct* (%)	Transfusions	Donors
Liu [4]	CPDA-1	≤35 d	15 mL/kg	75	5.6	2.1
Lee [5]	CPDA-1	≤35 d	13 mL/kg	68–75	6.0	2.0
Wood [6]	NR	≤35 d	15 mL/kg	NR	5.6	4.9
Strauss [2]	AS-1	≤42 d	15 mL/kg	85	3.5	1.2
Strauss [3]	AS-3	≤42 d	15 mL/kg	85	3.6	1.3
van Straaten [14]	SAGM	≤35 d	15 mL/kg	NR	3.2	1.1 high risk
	SAGM	≤35 d	15 mL/kg	NR	0.4	1.1 low risk
Mangel [13]	AS-3	≤21 d	7 mL/kg	55–60	4.7	1.7

AS, adenine saline; CPDA, citrate phosphate dextrose adenine; NR, not recorded; SAGM, saline adenine glucose mannitol.

- Six studies
  - Different age of product, type of solution, dose transfused
  - No evidence of hyperglycemia, hypoglycemia, hypocalcemia, hyperkalemia, hyponatremia



Luban et al. Curr Op Hematol, 2002

Research

JAMA Pediatrics | Original Investigation

Association of Preoperative Anemia With Postoperative Mortality in Neonates

Susan M. Goobie, MD, FRCPC; David Faraoni, MD, PhD; David Zurakowski, PhD; James A. DiNardo, MD

IMPORTANCE Neonates undergoing noncardiac surgery are at risk for adverse outcomes. Preoperative anemia is a strong independent risk factor for postoperative mortality in adults. To our knowledge, this association has not been investigated in the neonatal population.

OBJECTIVE To assess the association between preoperative anemia and postoperative mortality in neonates undergoing noncardiac surgery in a large sample of US hospitals.

DESIGN, SETTING, AND PARTICIPANTS Using data from the 2012 and 2013 pediatric databases of the American College of Surgeons National Surgical Quality Improvement Program, we conducted a retrospective study of neonates undergoing noncardiac surgery. Analysis of the data took place between June 2015 and December 2015. All neonates (0-30 days old) with a recorded preoperative hematocrit value were included.

EXPOSURES Anemia defined as hematocrit level of less than 40%.

MAIN OUTCOMES AND MEASURES Receiver operating characteristics analysis was used to assess the association between preoperative hematocrit and mortality, and the Youden J Index was used to determine the specific hematocrit cutoff point to define anemia in the neonatal population. Demographic and postoperative outcomes variables were compared between anemic and nonanemic neonates. Univariate and multivariable logistic regression analyses were used to determine factors associated with postoperative neonatal mortality. An external validation was performed using the 2014 American College of Surgeons National Surgical Quality Improvement Program database.

RESULTS Neonates accounted for 2764 children (6%) in the 2012-2013 American College of Surgeons National Surgical Quality Improvement Program databases. Neonates inlcuded in the study were predominately male (64.5%), white (66.3%), and term (69.9% greater than 36 weeks' gestation) and weighed more than 2 kg (85.0%). Postoperative in-hospital mortality was 3.4% in neonates and 0.6% in all age groups (0-18 years). A preoperative hematocrit level of less than 40% was the optimal cutoff (Youden) to predict in-hospital mortality. Multivariable regression analysis demonstrated that preoperative anemia is an independent risk factor for mortality (OR, 2.62; 95% CI, 1.51-4.57) in neonates. The prevalence of postoperative in-hospital mortality was significantly higher in neonates with a preoperative hematocrit level less than 40%; being 7.5% (95% CI, 1%-10%) vs 1.4% (95% CI, 0%-4%) for preoperative hematocrit levels 40%, or greater. The relationship between anemia and in-hospital mortality was confirmed in our validation cohort (National Surgical Quality Improvement Program 2014).

CONCLUSIONS AND RELEVANCE To our knowledge, this is the first study to define the incidence of preoperative anemia in neonates, the incidence of postoperative in-hospital mortality in neonates, and the association between preoperative anemia and postoperative mortality in US hospitals. Timely diagnosis, prevention, and appropriate treatment of preoperative anemia in neonates might improve survival.

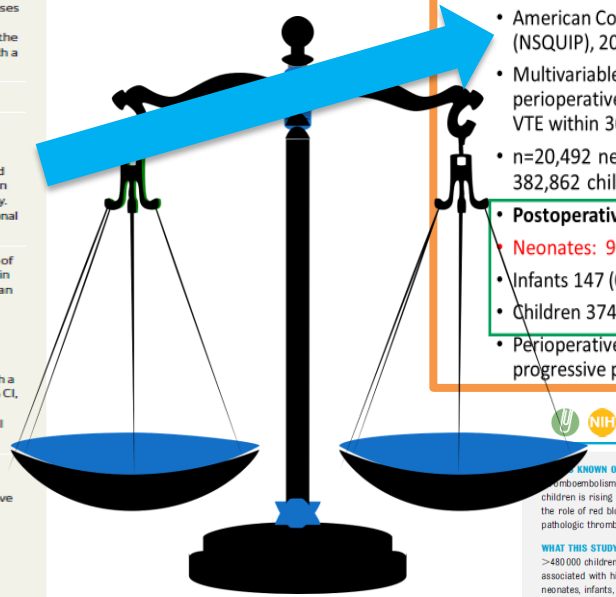
JAMA Pediatr. 2016;170(9):855-862. doi:10.1001/jamapediatrics.2016.1032
Published online July 18, 2016.

Perioperative Transfusions and Venous Thromboembolism

Ruchika Goel, MD, MPH,[a,b] Cassandra D. Josephson, MD,[c,d] Eshan U. Patel, MPH,[a] Molly R. Petersen, ScM,[a] Sarah Makhani, MS,[a] Steven M. Frank, MD,[f] Paul M. Ness, MD,[a] Evan M. Bloch, MD,[a] Eric A. Gehrie, MD,[a] Parvez M. Lokhandwala, MD, PhD,[a] Marianne M. Nellis, MD, MS,[g] Oliver Karam, MD, PhD,[h] Beth H. Shaz, MD,[i] Ravi M. Patel, MD, MSc,[c] Aaron A.R. Tobian, MD, PhD[a]

RBC and VTE a possible new Adverse Event

- American College of Surgeons' National Surgical Quality Improvement Project (NSQUIP), 2012- 2017.
- Multivariable logistic regression was used to examine the association between perioperative RBC transfusion status and the development of new or progressive VTE within 30 days of surgery.
- n=20,492 neonates (0-28 days), n= 79,744 infants (≥ 28 d-< 1 year), and, n= 382,862 children (≥ 1 year)
- **Postoperative development of VTE:**
  - Neonates: 99 (0.48%) — Neonates: aOR = 4.1, 95% [CI] = 2.5-6.7
  - Infants 147 (0.2%) — Infants: aOR = 2.4, 95% CI = 1.7-3.6
  - Children 374 (0.1%) — Children: aOR = 2.2, 95% CI = 1.7-2.9)
- Perioperative RBC txs are independently associated with development of new or progressive postoperative VTE in children, infants, and neonates.



WHAT IS KNOWN ON THIS SUBJECT: Annual incidence of venous thromboembolism (VTE) including postoperative VTE in hospitalized children is rising significantly. A growing body of evidence supports the role of red blood cells in physiologic hemostasis as well as pathologic thrombosis.

WHAT THIS STUDY ADDS: In this prospective registry study of >480 000 children, perioperative red blood cell transfusions were associated with higher odds of VTE within 30 days of a surgery in neonates, infants, and children, with a potential dose-response relationship among older children.

To cite: Goel R, Josephson CD, Patel EU, et al. Perioperative Transfusions and Venous Thromboembolism. *Pediatrics*. 2020;145(4):e20192351

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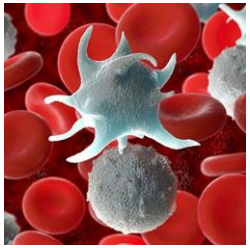
Drs Goel, Tobian, and Josephson and Mr Patel, Ms Petersen, and Ms Makhani conceptualized and designed the study, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Frank, Ness, Bloch, Gehrie, Lokhandwala, Nellis, Karam, Shaz, and Patel helped draft the manuscript, critically reviewed the manuscript for important intellectual content, and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Platelet Variability of Donor and Products can Impact Recipients

Vein-2-Vein Databases Can Help Derive Evidence & All Pediatric Recipients Aren't Created Equal



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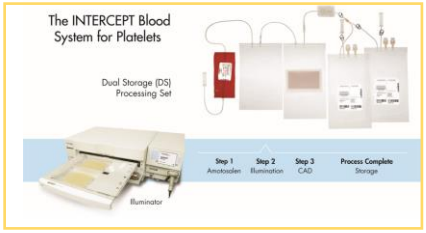


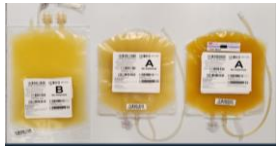
Donor

Variability: Age, gender, CMV status

Product

Platelet Storage

Variability: When to expire unit



Whole blood derived/Buffy Coat, pathogen reduced, PAS, Apheresis Platelets Leukoreduced

Irradiation

Variability: Site of irradiation (supplier or hospital) and when to expire unit after irradiation.

Volume Reduction

Variability: When to volume reduce and method of reduction.

Aliquoting

Variability: Time to outdate after aliquoting and method of aliquoting (syringe or bag)

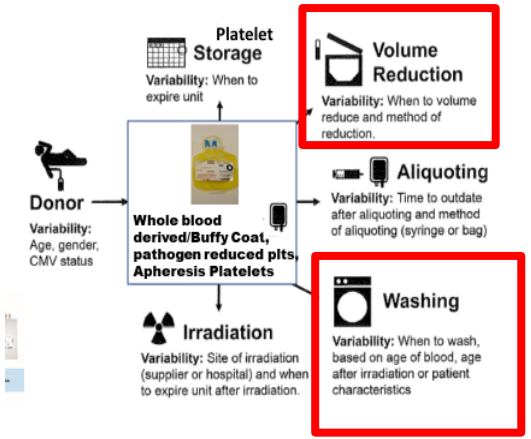
Washing

Variability: When to wash, based on age of blood, age after irradiation or patient characteristics

Recipient

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

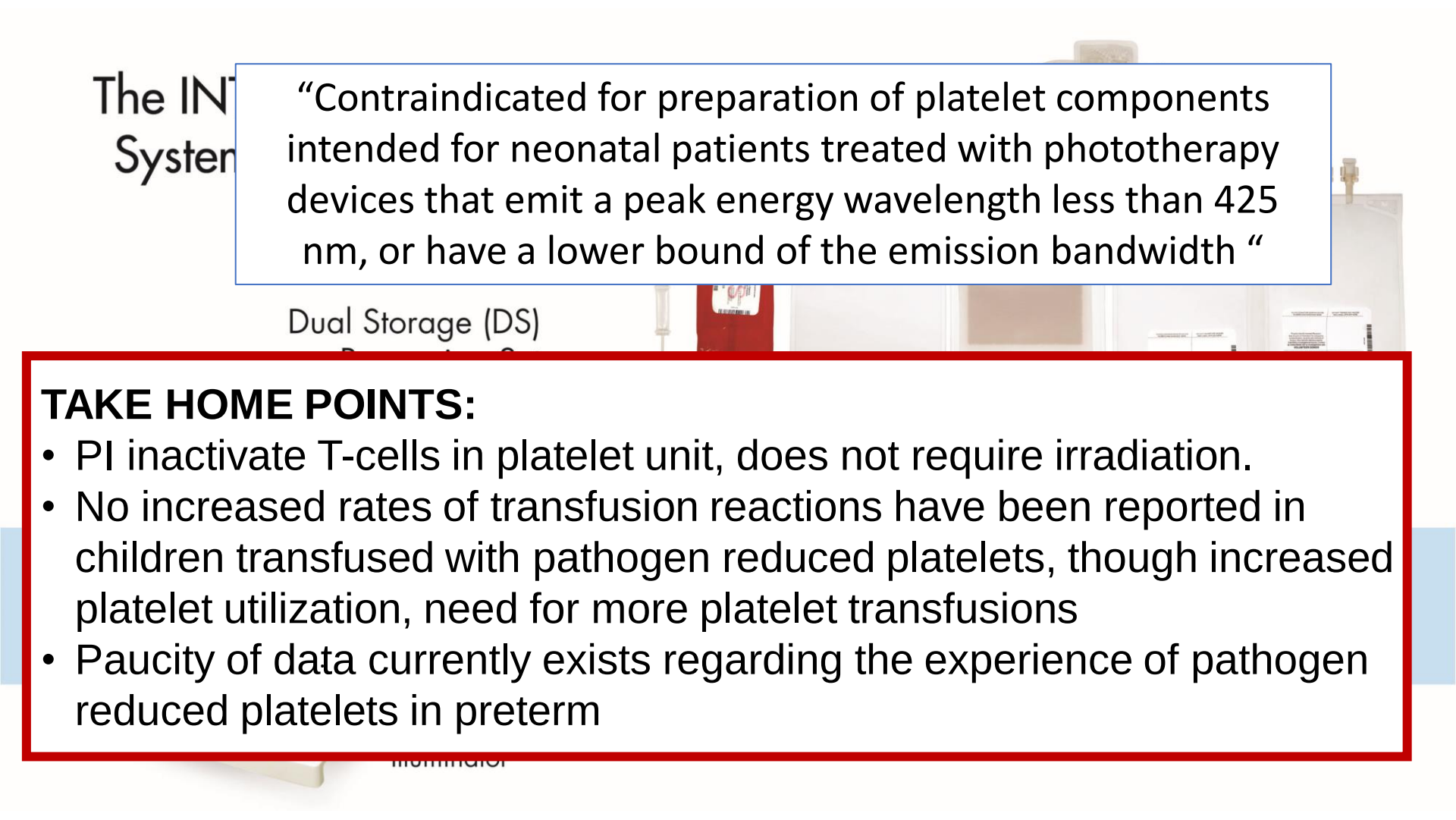
ABO Compatible or Incompatible Platelets



Choices: apheresis or whole blood donors, buffy coat platelets

ABO compatible or identical platelets are ideally selected for transfusion into pediatric patients, in an attempt:

1) to minimize the passive transfer of incompatible plasma
2) to minimize the destruction of platelets expressing incompatible antigens
3) to minimize transfusion reaction rates (including febrile and allergic reactions).

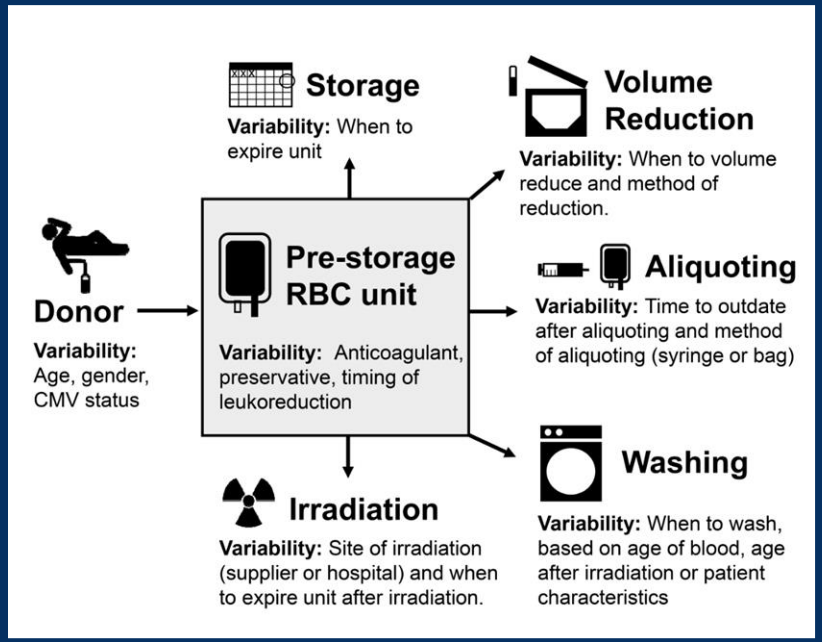


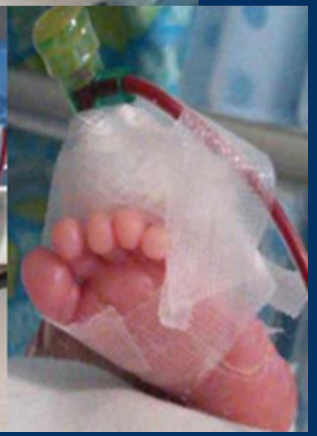
"Contraindicated for preparation of platelet components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth "

TAKE HOME POINTS:

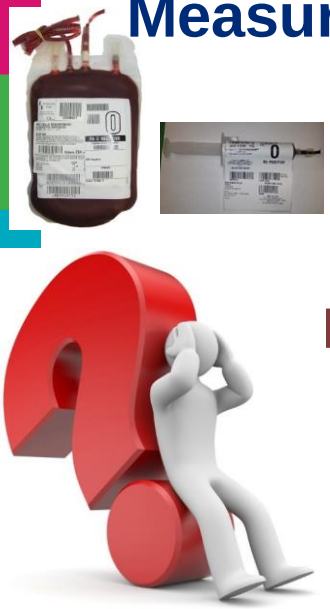
- PI inactivate T-cells in platelet unit, does not require irradiation.
- No increased rates of transfusion reactions have been reported in children transfused with pathogen reduced platelets, though increased platelet utilization, need for more platelet transfusions
- Paucity of data currently exists regarding the experience of pathogen reduced platelets in preterm

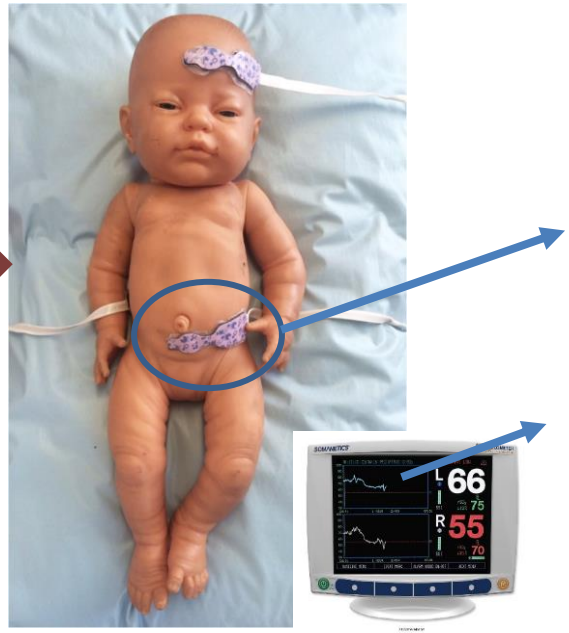
Future RBC


Storage
Variability: When to expire unit
Volume Reduction
Variability: When to volume reduce and method of reduction.
Donor
Variability: Age, gender, CMV status
Pre-storage RBC unit
Variability: Anticoagulant, preservative, timing of leukoreduction
Aliquoting
Variability: Time to outdate after aliquoting and method of aliquoting (syringe or bag)
Irradiation
Variability: Site of irradiation (supplier or hospital) and when to expire unit after irradiation.
Washing
Variability: When to wash, based on age of blood, age after irradiation or patient characteristics



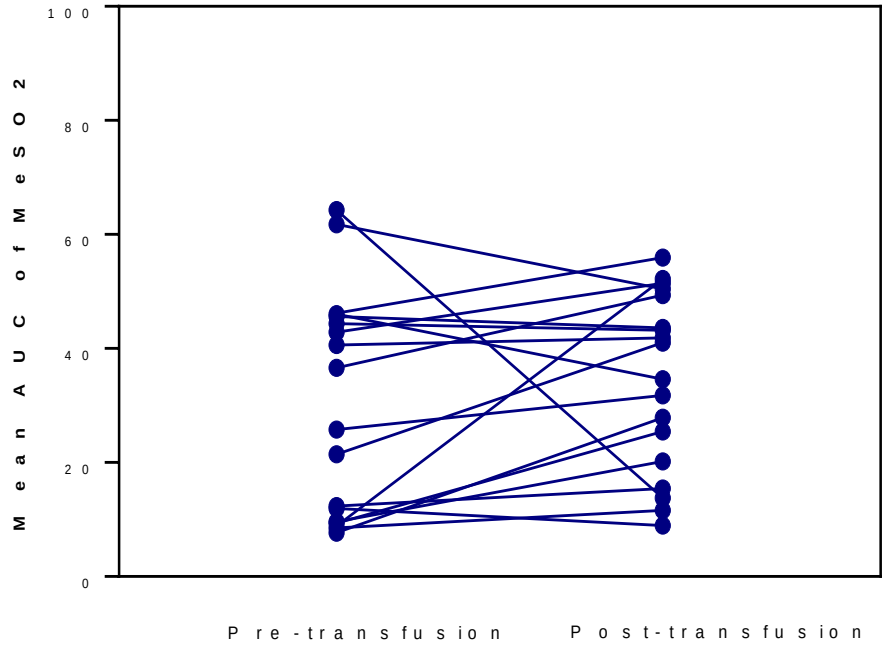
Variability in clinical and physiologic response to RBC transfusion: Focus on Recipient and Not Just Hemoglobin Measurements





Near-Infared spectroscopy (NIRS)

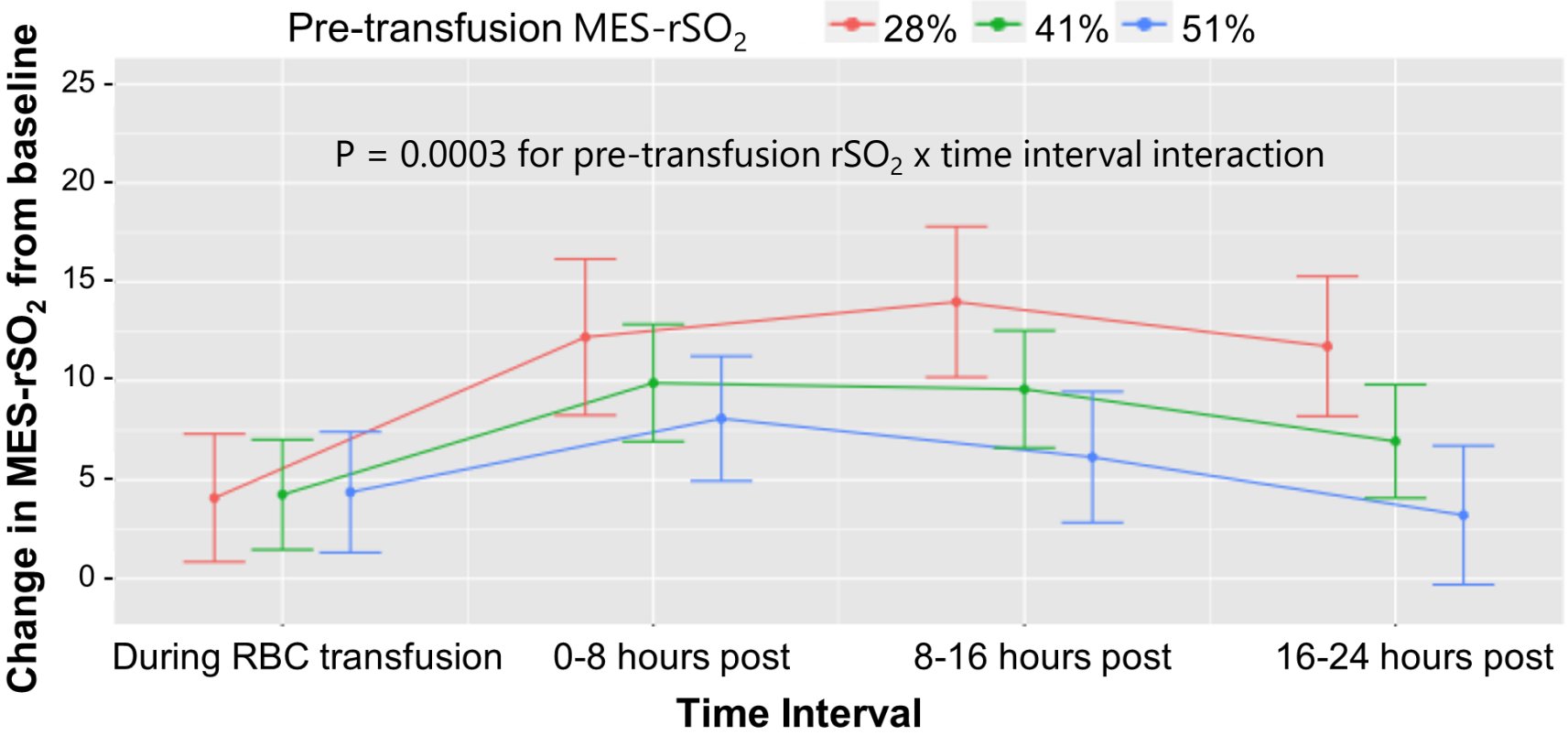
18 RBC transfusions (N=14 infants, mean GA 28 wks)



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

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

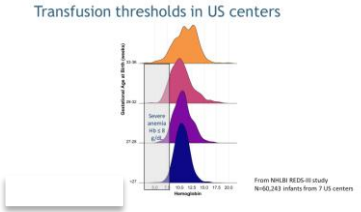
Change in gut oxygenation by baseline rSO_2

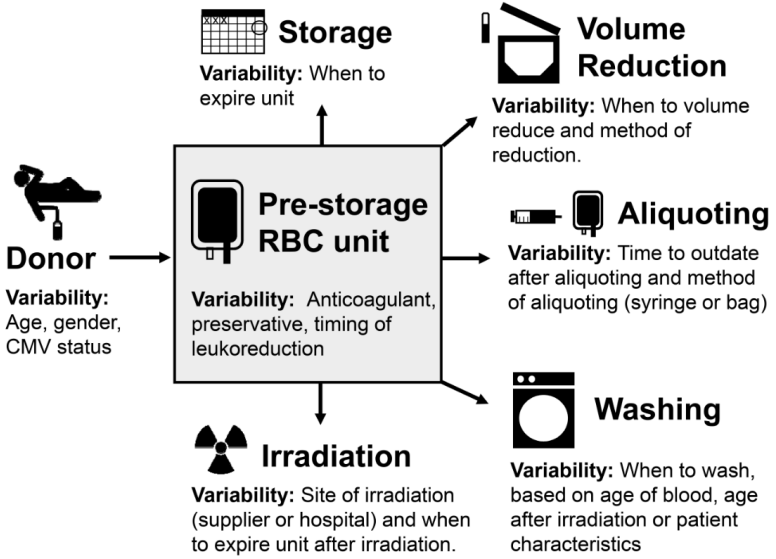


Patel et al. PAS 2021

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

RBC Transfusion in Neonates
Variations can occur at many levels





Research

Original Investigation

Association of Red Blood Cell Transfusion, Anemia, and Necrotizing Enterocolitis in Very Low-Birth-Weight Infants

Ravi M. Patel, MD, MSc; Andrea Knezevic, MS; Neeta Shenvi, MS; Michael Hinkes, MD; Sarah Keene, MD; John D. Roback, MD, PhD; KW

IMPORTANCE Data reg... to necrotizing enterocc... prospectively evaluate...

OBJECTIVE To determ...

DESIGN, SETTING, AND ... cohort study from Janu... infants, within 5 days o... Atlanta, Georgia. Two h... infants received follow... hospital, or death (whi... used, including adjustm... duration of initial antib... severe anemia, and NE...

EXPOSURES The primar... anemia, defined a prior... evaluated as time-vary...

MAIN OUTCOMES AND M... by preplanned adjudica...

RESULTS Of 600 VLBW... developed NEC. Thirty-... received a total of 1430... NEC at week 8 among ... 4.6% (95% CI, 2.6%-8.... RBC transfusion in a gi... cause-specific hazard r... longitudinal measurem... significantly increased ... with those who did not... CI, 2.00-18.0); P = .00...

CONCLUSIONS AND REL... RBC transfusion, was a... to evaluate whether pr... transfusion.

JAMA. 2016;315(9):889-897. doi:10.1001/jama.2016.1204

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Atlanta, Georgia (Roback, Josephson); Center for Transfusion and Cellular Therapies, Emory University School of Medicine, Atlanta, Georgia (Roback, Josephson).

Corresponding Author: Ravi Mangal Patel, MD, MSc, Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University School of Medicine, 2015 Uppergate Dr NE, Third Flr, Atlanta, GA 30322 (rmpatel@emory.edu).

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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)[d]			
Received RBC transfusion in a given week[e]	0.44 (0.17-1.12)	.09	45
Severe anemia in a given week (hemoglobin ≤8 g/dL)[e]	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....Josephson RM et al. *JAMA*. 2016

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

Recipient Sex Differences, Anemia, and Transfusion

ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

Sex Differences in the Association of Pretransfusion Hemoglobin Levels with Brain Structure and Function in the Preterm Infant

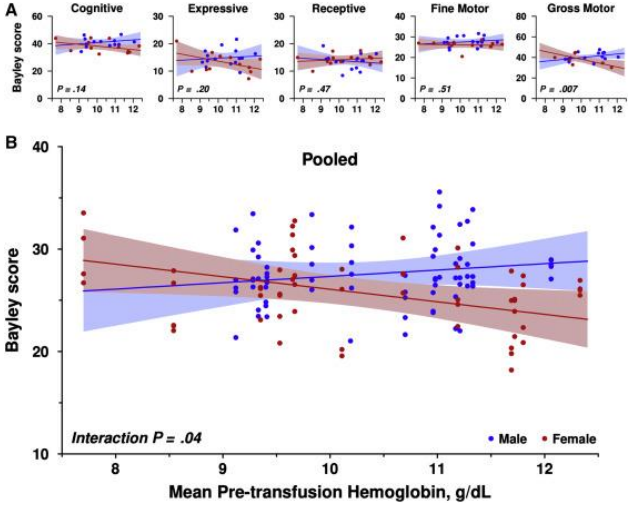
Amanda Benavides, MD, PhD[1], Edward F. Bell, MD[2], Amy L. Conrad, PhD[2], Henry A. Feldman, PhD[3], Michael K. Georgieff, MD[4], Cassandra D. Josephson, MD[5,6], Timothy R. Koscik, PhD[1], Sean R. Stowell, MD, PhD[7], Martha Sola-Visner, MD[3], and Peg Nopoulos, MD[1,2,8]

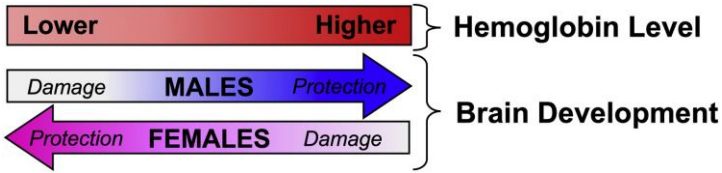
Objective To assess sex-specific differences in early brain structure and function of preterm infants after red blood cell (RBC) transfusions.

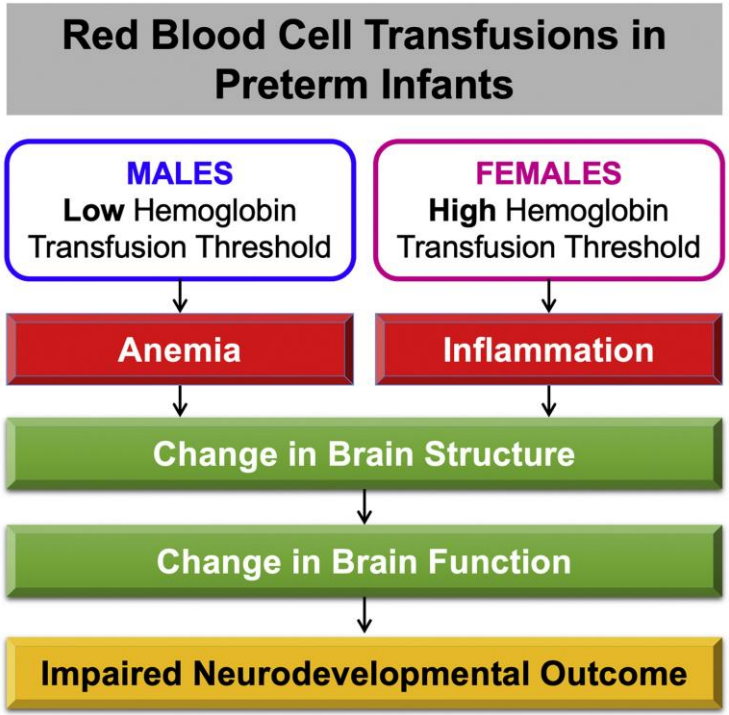
Study design A single-center subset of infants with a birth weight <1000 g and gestational age 22-29 weeks were enrolled from the National Institute of Child Health and Human Development's Neonatal Research Network Transfusion of Prematures Trial. Hemoglobin (Hb) concentration obtained directly before each transfusion (pretransfusion Hb [ptHb]) was obtained longitudinally throughout each infant's neonatal intensive care unit stay and used as a marker of degree of anemia (n = 97). Measures of regional brain volumes using magnetic resonance imaging were obtained at ~40 weeks postmenstrual age or at hospital discharge, if earlier (n = 29). Measures of brain function were obtained at 12 months corrected age using the Bayley Scales of Infant & Toddler Development, 3rd Edition (n = 34).

Results PtHb was positively correlated with neonatal cerebral white matter volume in males (B = +0.283; *P* = .006), but not females (B = −0.099; *P* = .713), resulting in a significant sex interaction (*P* = .010). Bayley-III gross motor scores and a pooled mean score were significantly lower in association with higher ptHb in females (gross motor score: B = −3.758; *P* = .013; pooled mean score: B = −1.225; *P* = .030), but not males (gross motor score: B = +1.758; *P* = .167; pooled mean score: B = +0.621; *P* = .359). Higher ptHb was associated with descriptively lower performance on multiple Bayley-III subscales in females, but not in males.

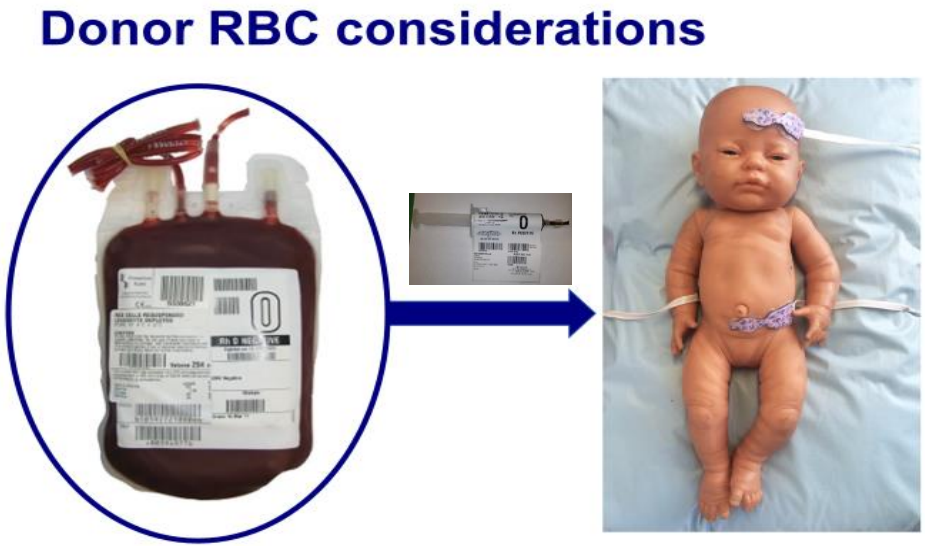
Conclusions This study demonstrates sex-specific associations between an early marker of anemia and RBC transfusion status (ie, ptHb) with both neonatal white matter volume and early cognitive function at age 12 months in preterm infants. *(J Pediatr 2022;243:78-84).*







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



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ORIGINAL ARTICLES

Impact of Blood Donor Sex on Transfusion-Related Outcomes in Preterm Infants

Thomas Murphy, MD[1], Anju Chawla, MD[2], Richard Tucker, BA[1], and Betty Vohr, MD[1]

Objective Explore the role of red blood cell donor sex on preterm infant neonatal outcomes.

Study design In a retrospective, exploratory, cohort study, the hospital blood bank database was queried for units of blood released to neonatal intensive care unit patients in 2009-2010. The state blood center provided donor sex, and a[illegible] for 2 groups: th[illegible]

Results [illegible] analyses, comp[illegible] higher rates of b[illegible]ng enterocolitis[illegible] analyses, fema[illegible]0098). After addi[illegible]ed with bronchopulmonary dysplasia ($P = .0009$), any morbidity ($P = .0001$), and length of stay ($P = .0001$). In subset regressions comparing exclusively female donor blood with male donor blood, there was a significant interaction of female donor blood and number of transfusions for any morbidity (OR 2.6 95% CI 1.2-5.7, $P = .01$).

Conclusions Preliminary findings suggest that female donor blood was associated with preterm vulnerability to neonatal morbidities. *(J Pediatr 2018;201:215-20).*

Retrospective:
Female blood was associated with preterm vulnerability to neonatal morbidities

Received: 6 December 2022 | Revised: 20 March 2023 | Accepted: 5 May 2023

DOI: 10.1111/trf.17417

TRANSFUSION MEDICINE

TRANSFUSION

Associations between blood donor sex and age, and outcomes of transfused newborn infants

Timothy M. Bahr[1,2] | Thomas R. Christensen[3] | Sarah M. Tweddell[2] | Erick Henry[1] | Terry Rees[4] | Mark E. Astin[4] | Walter E. Kelley[5] | Sarah J. Ilstrup[4] | Robin K. Ohls[2] | Robert D. Christensen[1,2]

[1]Obstetric and Neonatal Operations, Intermountain Healthcare, Salt Lake City, Utah, USA

[2]Division of Neonatology, Department of Pediatrics, University of Utah, Salt Lake

Abstract

Background: It is controversial whether the sex or age of red blood cell (RBC) donors affects mortality or morbidities of transfused newborn infants. We assessed these issues using a multi-year, multi-hospital database linking spe-

± SD, $p < .001$). We identified no significant differences in mortality or morbidities associated with the sex or the age of blood donors. Similarly, an analysis of matched vs. mismatched donor/recipient sex revealed no associations with death or neonatal morbidities.

Conclusion: These data support the practice of transfusing newborn infants with RBC obtained from donors of either sex and regardless of donor age.

KEYWORDS

adverse outcomes; blood donor sex, blood donor age; newborn infant; red blood cell; transfusion

Retrospective:
No difference found with outcomes in newborn infants due to donor sex or donor age

JAMA Network Open

Original Investigation | Pediatrics

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

Ravi M. Patel, MD, MSc; Joshua L
John D. Roback, MD, PhD; Ying C

Key Points

Question Is the sex o
donor associated with
mortality in very low-b
infants receiving blooc

Findings In this cohor
low-birth-weight infan
infants receiving red b
transfusion from fema
lower risk of death or s
compared with those
transfusion from male
protective association
donor and adverse ou
with increasing donor
diminished with increa
blood transfusions.

Meaning These findir
characteristics of bloo
sex and age, may be a
recipient outcomes in
weight infants receivir
transfusions.

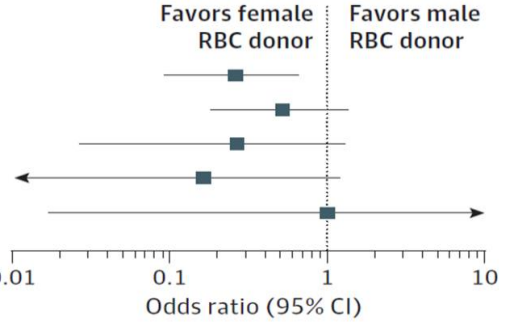
Abstract

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

	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)



- Prospectively collected, retrospectively analyzed
- 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

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BRIEF REPORT

TRANSFUSION

Associations of donor, component, and recipient factors on hemoglobin increments following red blood cell transfusion in very low birth weight infants

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Abstract

Background: Anemia in very low birth weight (VLBW) infants is common and frequently managed with red blood cell (RBC) transfusions. We utilized a linked vein-to-vein database to assess the role of blood donors and component factors on measures of RBC transfusion effectiveness in VLBW infants.

Study Design and Methods: We linked blood donor and component manufacturing data with VLBW infants transfused RBCs between January 1, 2013 and December 31, 2016 in the Recipient Epidemiology Donor Evaluation Study-III (REDS III) database. Using multivariable regression, hemoglobin increments and subsequent transfusion events following single-unit RBC transfusion episodes were examined with consideration of donor, component, and recipient factors.

Results: Data on VLBW infants ($n = 254$) who received one or more single-unit RBC transfusions ($n = 567$ units) were linked to donor demographic and component manufacturing characteristics for analysis. Reduced post-transfusion hemoglobin increments were associated with RBC units donated by female donors (−0.24 g/dL [95% confidence interval (CI) −0.57, −0.02]; $p = .04$) and donors <25 years old (−0.57 g/dL [95% CI −1.02, −0.11]; $p = .02$). For RBC units donated by male donors, reduced donor hemoglobin levels were associated with an increased need for subsequent recipient RBC transfusion (odds ratio 3.0 [95% CI 1.3, 6.7]; $p < .01$). In contrast, component characteristics, storage duration, and time from irradiation to transfusion were not associated with post-transfusion hemoglobin increments.

Conclusion: Donor sex, age, and hemoglobin levels were associated with measures of RBC transfusion effectiveness in VLBW infants. Mechanistic studies are needed to better understand the role of these potential donor factors on other clinical outcomes in VLBW infants.

KEYWORDS
RBC transfusion; transfusion practices (neonatal, pediatrics)

REDS III Database – V2V Study

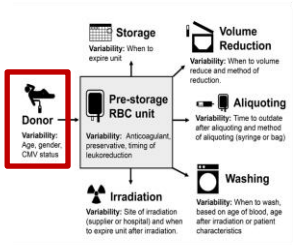


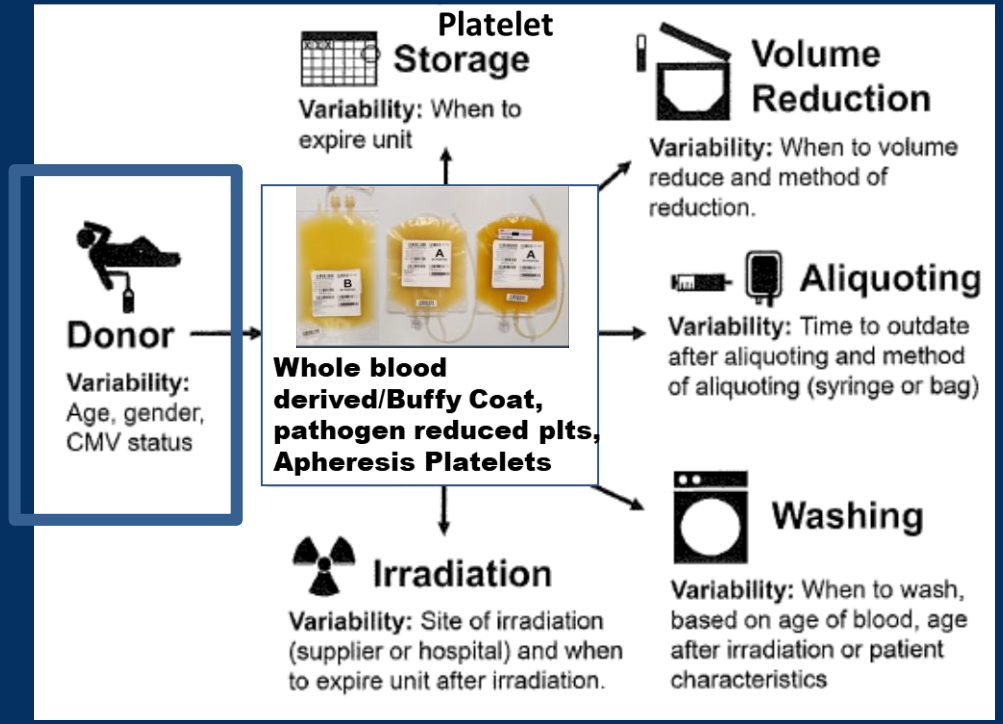
TABLE 2 Regression estimates for hemoglobin increments after red blood cell (RBC) transfusion for very low birth weight (VLBW) infants ($n = 567$)[a]

Characteristic	Hemoglobin increment in g/dL (95% CI)	*p*-value
Female donor	−0.24 (−0.57, −0.02)	.04
Donor age (ref: 46–70 years)		
<25	−0.57 (−1.02, −0.11)	.02
26–45	−0.19 (−0.55, 0.17)	.31
70+	−0.32 (−0.78, 0.13)	.17
Donor Rh positive status	−0.02 (−0.33, 0.28)	.88
Donor hemoglobin	−0.01 (−0.03, 0.01)	.29
Apheresis blood collection	0.45 (−.23, 1.13)	.20
Leukoreduction	−0.60 (−1.49, 0.28)	.18
RBC additive solution (ref: AS-1)		
AS-3	0.37 (−0.21, 0.95)	.21
CPDA	−0.13 (−0.80, 0.53)	.69
Irradiation	−0.20 (−1.00, 1.40)	.74
Days from irradiation to transfusion	−0.01 (−0.04, 0.02)	.47
Storage duration in days	−0.01 (−.03, 0.01)	.53
Aliquot volume in ml/kg	−0.00 (−0.00, 0.00)	.43
Male recipient	−0.36 (0.35, 1.50)	<.001
Recipient weight in kg	0.39 (0.17, 0.61)	<.001
Recipient Rh positive status	0.15 (−0.55, 0.84)	.68
Pre-transfusion hemoglobin level	−0.70 (−0.79, −0.61)	<.001
Concomitant plasma transfusion	−0.64 (−1.06, −0.23)	.003
Concomitant platelet transfusion	−0.08 (−0.43, 0.28)	.67

Abbreviations: Hb, hemoglobin level (g/dL); RBC, red blood cell; Tx, transfusion; VLBW, very low birth weight.
[a]Multivariable regression estimates estimating the mean hemoglobin increment after transfusion accounting for donor, component, and recipient characteristics presented in Table 1.

Future Platelets

Product



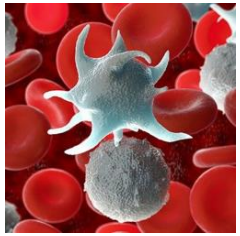
Recipient

Inflammation ???

Bronchopulmonary Dysplasia (BPD)

Bleeding

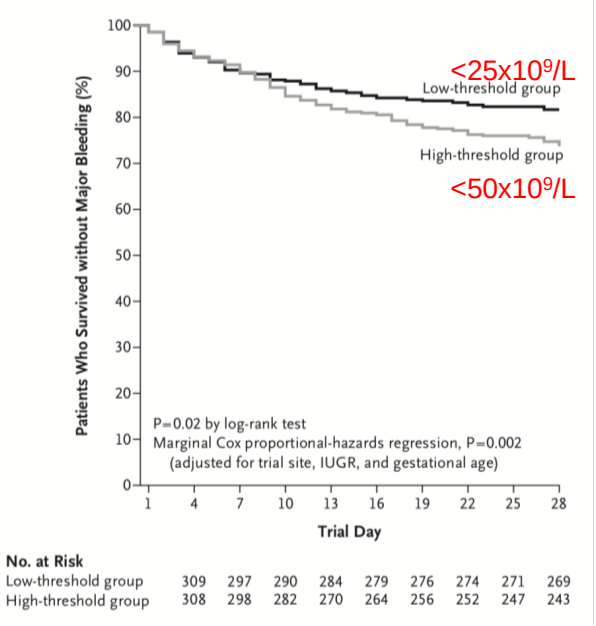
Intraventricular Hemorrhage (IVH)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Platelet-Transfusion Thresholds in Neonates



- Key Questions regarding platelet transfusions:
  - What are the mechanisms underlying the increased mortality and morbidity associated with platelet transfusions in neonates?
  - Do factors related to the donor, product, or recipient influence the effects of platelet transfusions in neonates?
  - What platelet products are we transfusing neonates with and have we really studied the impact?

Death or major bleeding: 26% vs. 19% in high- vs. low threshold group, OR 1.57 (1.06-2.32)

Potential adverse effects of platelet transfusion

- Several observational studies have shown an association between the rate or number of platelet transfusions and higher mortality and morbidity.
  - Studies limited by confounding from illness severity
- Pre-clinical studies suggest adult platelets can tip the unique neonatal primary hemostatic system toward a pro-thrombotic state.
- Platelets are also central mediators of inflammation and contain pro-inflammatory factors that are released during storage.

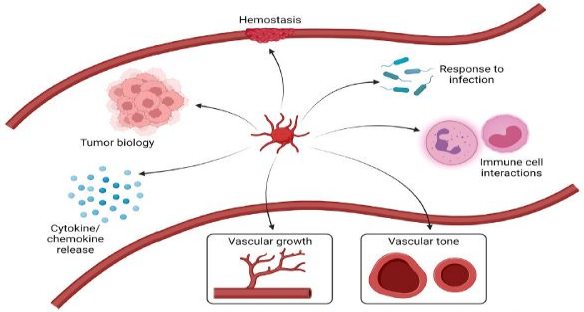


Fig. 1. Platelets have multiple functions beyond their roles in hemostasis, including antimicrobial functions, interactions with immune cells, cytokine/chemokine release, and regulation of vascular tone, vascular growth, and tumor biology.

Davenport et al

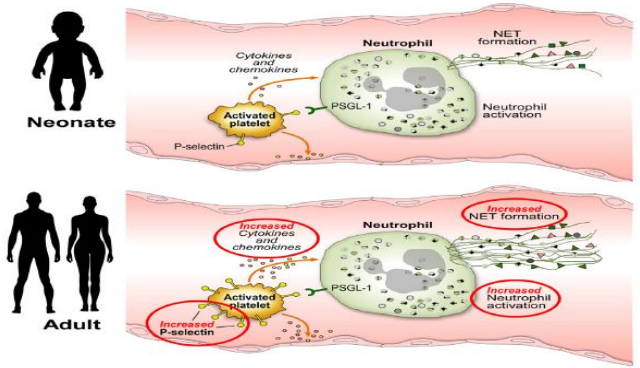
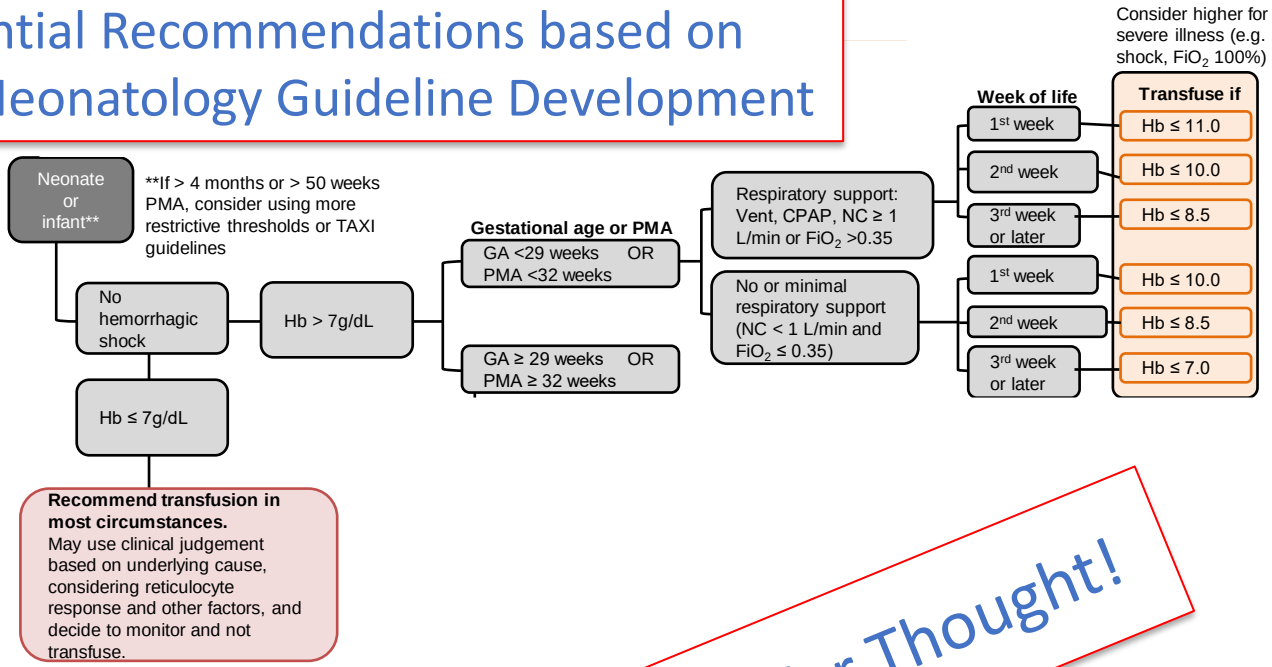


Fig. 2. Schematic representation of key developmental differences between neonatal and adult platelets, and potential effects on immune cells. On activation, human neonatal platelets express less P-selectin and release their alpha granule content (including cytokines and chemokines) less effectively than adult platelets. Decreased P-selectin surface expression results in a reduced ability to interact with and activate immune cells, including neutrophils and monocytes. A neutrophil is shown as an example. The reduced NET formation in neonates is caused by the presence of a placenta-derived NET inhibitor. NET, neutrophil extracellular trap; PSGL-1, P-selectin glycoprotein ligand-1. (*From* Davenport P, Sola-Visner M. Platelets in the neonate: not just a small adult. Res Pract Thromb Haemost 2022;6(3):e12719.)

Patel et al. *Transfusion.* 2019
Kenton et al. *J Perinatol.* 2005
Sola-Visner and Bercovitz. *Trans Med Rev.* 2016
Ferrer-Marin et al. *J Thromb Haemost.* 2011

Potential Recommendations for RBC and PLT Transfusion in Preterm Infants: Food for Thought!

Potential Recommendations based on Emory Neonatology Guideline Development



Food for Thought!

Strong recommendation

Weak recommendation

- Transfuse 15 mL/kg over 3-4 hours for infants not in hemorrhagic shock
- Hemoglobin (Hb) in g/dL

Journal of Perinatology (2021) 41:1487–1494
https://doi.org/10.1038/s41372-021-01033-6

QUALITY IMPROVEMENT ARTICLE

Implementation of a neonatal platelet transfusion guideline to reduce non-indicated transfusions using a quality improvement framework

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Abstract

Objective Variation exists in neonatal platelet transfusion practices. Recent studies found potential harm in liberal platelet transfusion practices, supporting the use of lower transfusion thresholds. Our aim was to reduce non-indicated platelet transfusions through implementation of a restrictive platelet transfusion guideline.

Study design Platelet transfusions from January 2017 to December 2019 were classified as indicated or non-indicated using the new guideline. Interventions included guideline implementation and staff education. Outcomes were evaluated using statistical process control charts. Major bleeding was the balancing measure.

Result During study, 438 platelet transfusions were administered to 105 neonates. The mean number of non-indicated platelet transfusions/month decreased from 7.3 to 1.6. The rate of non-indicated platelet transfusions per 100 patient admissions decreased from 12.5 to 2.9. Rates of major bleeding remained stable.

Conclusions Implementation of a restrictive neonatal platelet transfusion guideline significantly reduced potentially harmful platelet transfusions in our NICU without a change in major bleeding.

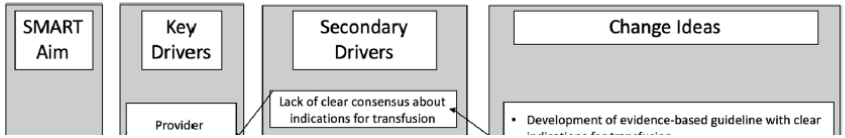

Fig. 1 Key Driver Diagram. Diagram outlining the project-specific aim, key drivers, and change concepts.

Table 1 Neonatal platelet transfusion guidelines before (version 1) and after (version 2) January 2019.

	Platelet transfusion guideline version 1 thresholds[a] ($\times 10^9$/L)	Platelet transfusion guideline version 2 thresholds[a] ($\times 10^9$/L)
Active bleeding	Transfuse	Transfuse
Transfuse all	<30	<25
Clinical instability (i.e., vasopressor requirement, high ventilator settings)	<50	<25
Prematurity		
BW <1500 g and <7 days	<50	N/A
<28 weeks GA and <7 days	N/A	<50
Concurrent coagulopathy	<50	<25
Prior significant hemorrhage	<50 (regardless of time since bleed)	<50 (if bleeding within last 48 h)
Platelet transfusion volume	Unspecified (usually 15 ml/kg)	10 ml/kg
Platelet transfusion rate	Unspecified (usually over 30–60 min)	Over 2–3 h

[a]These recommendations are based on medical evidence and professional expert opinions. Decisions about treatment are the responsibility of the treating clinician and should be tailored to individual circumstances. Platelet volume and transfusion time are provided for reference only. Providers should refer to institutional formulary or guidelines when prescribing.

Table 3 Outcome and process measures.

	Pre-guideline (2017–2018)	Post-guideline (2019)	Ratio, Post: Pre	*p*
Months	24	12		
Admissions	1407	666		
Transfusions	359	79	0.33[a]	0.0001
Indicated	183 (51%)	60 (76%)		
Non-indicated	176 (49%)	19 (24%)		
Transfusions per month	15.0 ± 0.8[b]	6.6 ± 0.7	0.44[c]	<0.0001
Indicated	7.6 ± 0.6	5.0 ± 0.6	0.66	0.005
Non-indicated	7.3 ± 0.6	1.6 ± 0.4	0.22	<0.0001
Transfus				
Indic				
Non-i				
Patients transfus				
Per n				
Per 1				

[a]Odds r

[b]Rate ±

[c]Rate ra

Table 4 Balancing measure: incidence of major bleeding, per site.

	n (%)		*p*[a]
	Pre-intervention January 2017–December 2018	Post-intervention January 2019–December 2019	
Admissions	1388	687	
Intracranial hemorrhage, total	22 (1.6)	9 (1.3)	0.65
Grade I IVH	13 (0.9)	7 (1.0)	
Grade II IVH	3 (0.2)	1 (0.1)	
Grade III IVH	2 (0.1)	0 (0.0)	
Intraparenchymal	4 (0.3)	1 (0.1)	
Other bleeding, total	107 (7.7)	37 (5.5)	0.06
Pulmonary hemorrhage	7 (0.5)	1 (0.1)	
Upper GI bleeding	7 (0.5)	3 (0.4)	
Rectal bleeding	4 (0.3)	2 (0.3)	
Adrenal hemorrhage	1 (0.1)	1 (0.1)	
Non-specified hemorrhage	88 (6.3)	30 (4.4)	

[a]Totals compared by chi-squared test, corroborated by Fisher exact test.

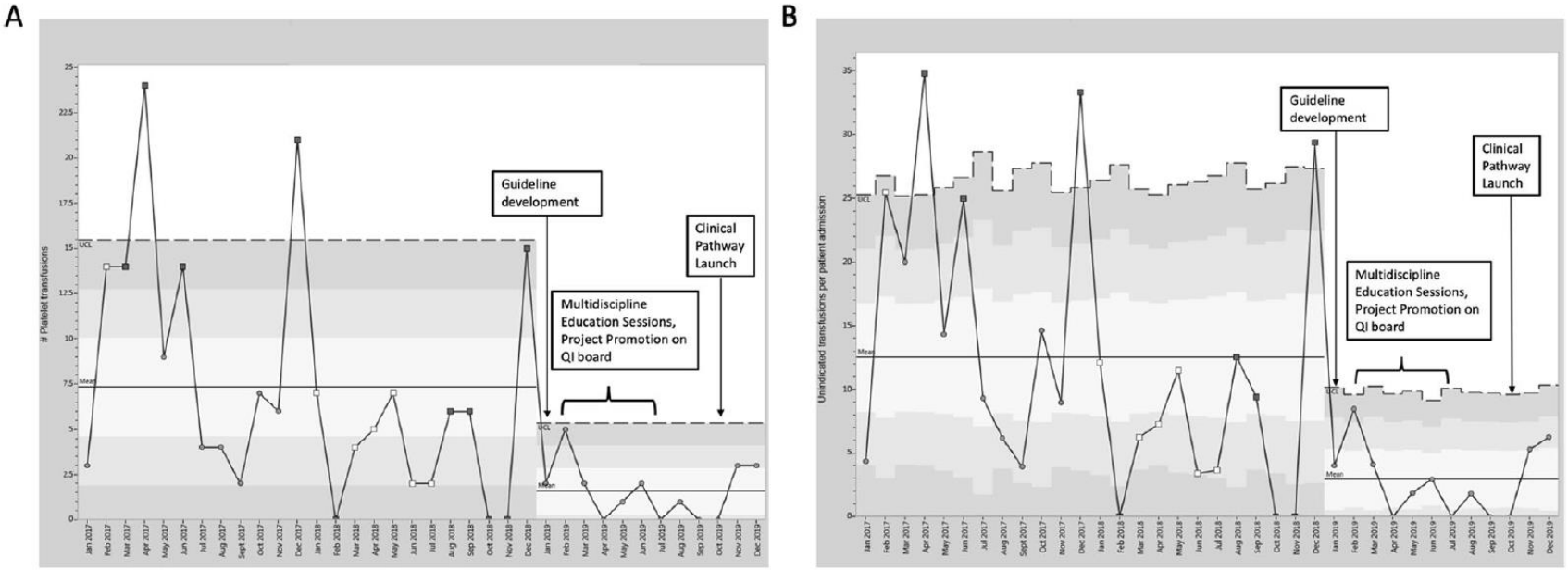

Fig. 2 Significant decreases in non-indicated platelet transfusions after project start on SPC analysis. Special cause variation shows significant change. **A** Decreased number of non-indicated platelet transfusions/month after project start from 7.3 to 1.6 on SPC C-chart analysis. **B** Rate of non-indicated transfusions per 100 patient admissions decreased from 12.5 to 2.9 after project start on U-chart analysis. For both **A** and **B**, the rule used to determine special cause variation was 8 or more points below the centerline.

Conclusions: Coming of Age Party
Neonatal Transfusion Medicine

- Current day evidence for VLBW and ELBW infants has high grade RCTs in RBC and PLTs transfusion practices that can support guidelines.
- However, neonates are not just small children and preterm infants are not just small neonates. **We still have a generalizability problem!!!**
- Even with RCTs many questions remain regarding RBC products and special modification to those products for this population.
- Clinical/physiologic measures need to be investigated to help determine when, how much, and how fast to transfusion RBCs to neonates.
- Platelet products with different additive solutions and chemical treatments for PI must be rigorously tested in this vulnerable population especially as we learn more about the immunologic behavior of platelets.
- More information is needed to know when we should wash, irradiate, aliquot, store, chill platelets for this population.

PAS – Hot Topic Symposia
Toronto, May 4, 2024

Title: Advances in Neonatal Transfusion: New Insights on WHEN and WHAT We should Transfuse.

Speakers: Sola-Visner M, Kirpalani H, Josephson C, Patel R, Davenport P.

Any questions?

Time to Giggle!!

A priest, a minister, and a rabbit walk into a blood bank. The rabbit says, "I think I might be a type O."
—*Submitted by*
VINCENT GOTTSCHALK
Dallas, Texas