Central Manchester University Hospitals NHS
NHS Foundation Trust

What about anaemia in small infants and neonates?

Dr Ruth Gottstein
Consultant Neonatologist
Saint Mary's Hospital, Manchester
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MANCHESTER 1824
The University of Manchester

Overview

1. Background
2. Anaemia of prematurity
3. Top-up Red Cells transfusions RCTs
4. BCSH 2016 Recommendations

Physiology

- Normal Hb @ birth 140 – 200g/L (avg 170g/L)
- Decreases to 110g/L (preterm to 70-80g/L) over 3-4months =

  "*physiological anaemia of infancy*"
- MCV decreases
  - 100-130fl @ birth → 70-85fl @ 1yr
- Lifespan of RBC
  - Adult 100-120 d
  - Term 80-100 d
  - Preterm 60-80 d

Anaemia of Prematurity

- 80% of infants with b.wt <1.5kg are transfused

- Multifactorial
  - Iatrogenic blood loss
  - Low circulating blood volume
  - Relative low intrinsic EPO levels
  - Relative shorter RBC survival
  - Inadequate erythropoesis
  - Haemorrhage
  - Haemolysis

ELSEVIER

SEMINARS IN PERINATOLOGY

International Survey of Transfusion Practices for Extremely Premature Infants

Úrsula Guillén, MD,* James J. Cummings, MD,† Edward F. Bell, MD,‡
Shigerharu Hosono, MD, PhD,§ Axel R. Frantz, MD,¶ Rolf F. Maier, MD,**
Robin K. Whyte, BSc, MBBS,†† Elaine Boyle, MRCP,‡‡ Max Vento, MD, PhD,§§
John A. Widness, MD,‡ and Haresh Kirpalani, BM, MSc¶¶

Semin Perinatol 36:244-247 © 2012

- 1018 neonatologists,
- 11 countries

- scenarios for neonates < 1000g bw and/or < 28 wks gestational age

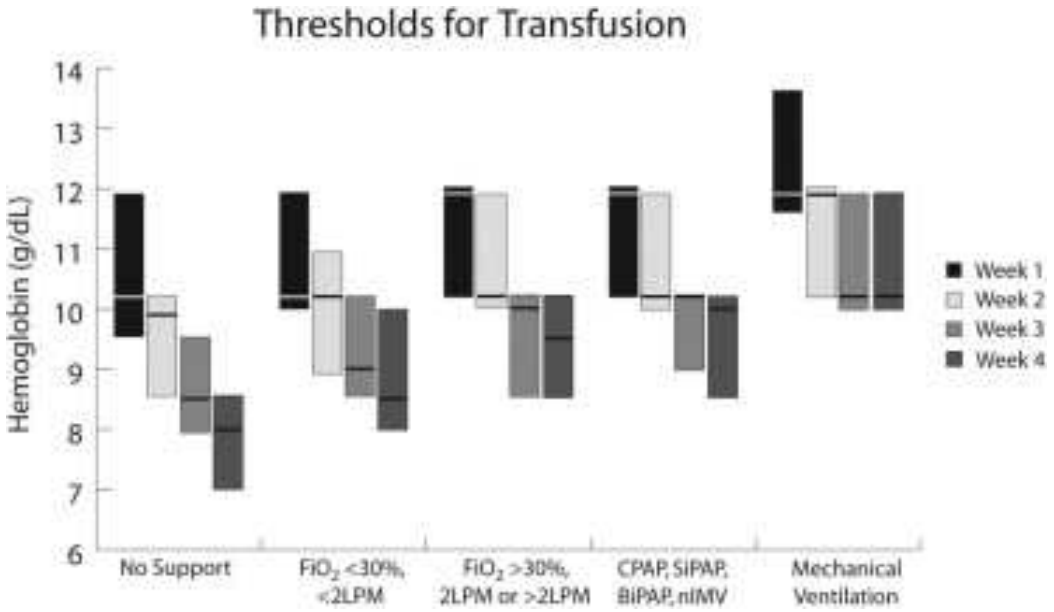


Figure 1 Thresholds for red cell transfusion for infants weighing <1000 g at birth and/or <28-week GA for each of the first 4 weeks of life given 5 different levels of respiratory support. Each box represents the interquartile range (25th-75th percentile). The median value intersects each box.

The RCT evidence

Iowa study

- 100 preterm infants, b.wt. 0.5-1.3kg
- Hb stratification: respiratory status
  - Intubated 113g/l vs 153 g/l
  - O_2 or distending pressure 93g/l vs 127g/l
  - No respiratory support 73g/l vs 99g/l
- Primary endpoint: difference in transfusion number

Bell et al *Pediatrics* 2005:115;1685-1691

The RCT evidence

PINT (Preterm Infants in Need of Tx)

- 451 ELBW infants < 48hrs age (<1kg)
- Hb stratification
  - respiratory status and postnatal age
  - Assisted vent; Postnatal wk 1: 115g/l vs 135
  - . wk 2: 100g/l vs 120g/l
  - . wk 3 until discharge: 85g/l vs 100g/l
- Composite clinical outcome
  - No significant difference in death, CLD, ROP, brain injury, lab outcomes

Kirpilani et al *J Paediatr* 2006:149;301-7

Outcomes

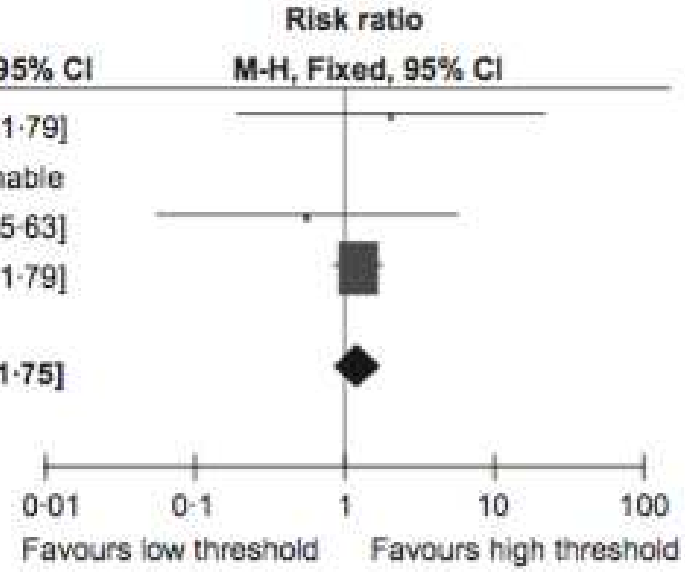
	Iowa (n=100)	PINT (n=451)	
Mean Hb g/dl	8.3 vs 11.0	10.1 vs 11.2	
No transfusion	10% vs 12%	5% vs 11%	p 0.037
Death/brain injury	16% vs 2%	31% vs 31%	
Longer term	Approx 12 yr: Brain volumes in liberally transfused smaller than controls McCoy *et al.*, 2011	18-21 mth -cognitive delay in restrictive group - post hoc Whyte *et al*., 2009	

Mortality

Study or subgroup	Low threshold Events	Total	High threshold Events	Total	Weight(%)	Risk ratio M-H, Fixed, 95% CI
Bell *et al* (2005)	2	49	1	50	2·3	2·04 [0·19, 21·79]
Brooks *et al* (1999)	0	24	0	26		Not estimable
Chen *et al* (2009)	1	17	2	19	4·5	0·56 [0·06, 5·63]
Kirpalani *et al* (2006)	48	223	40	228	93·2	1·23 [0·84, 1·79]
Total (95% CI)		**313**		**323**	**100·0**	**1·22 [0·84, 1·75]**
Total events	51		43			

Heterogeneity: $\chi^2 = 0{\cdot}62$, df = 2 ($P = 0{\cdot}73$); $I^2 = 0\%$

Test for overall effect: $Z = 1{\cdot}05$ ($P = 0{\cdot}30$)



Venkatesh V…... *Stanworth S*. *Br J Haematol*. 2012;**158**, 370-385.

Small volume RBC transfusion RCTs

Iowa study

- 100 preterm infants, b.wt. 500-1300g
- Hb stratification: respiratory status
- Primary endpoint: difference in transfusion number

Bell et al *Pediatrics* 2005:115;1685-1691

PINT

- 451 ELBW infants < 48hrs age (<1000g)
- Hb stratification
  - respiratory status and postnatal age
- Composite clinical outcome

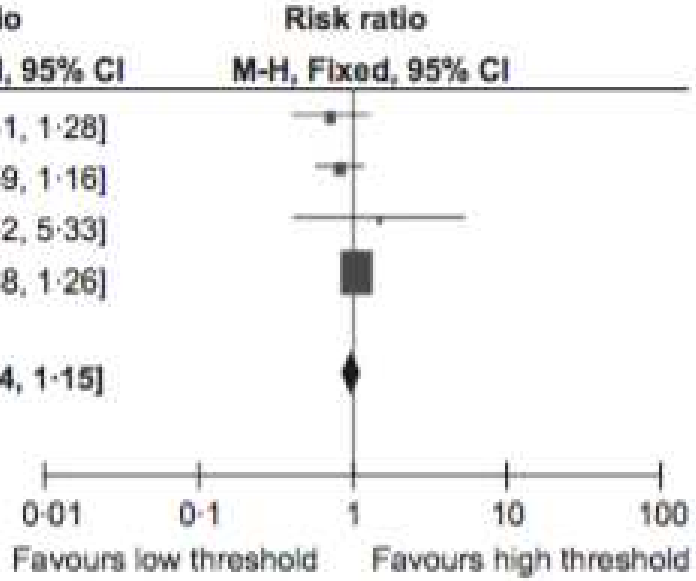
Kirpilani et al *J Paediatr* 2006:149;301-7

Chronic Lung Disease (CLD)

Study or subgroup	Low threshold Events	Total	High threshold Events	Total	Weight(%)	Risk ratio M-H, Fixed, 95% CI
Bell *et al* (2005)	13	45	20	50	13·4	0·72 [0·41, 1·28]
Brooks *et al* (1999)	16	24	21	26	14·2	0·83 [0·59, 1·16]
Chen *et al* (2009)	5	19	3	17	2·2	1·49 [0·42, 5·33]
Kirpalani *et al* (2006)	101	175	103	188	70·1	1·05 [0·88, 1·26]
Total (95% CI)		**263**		**281**	**100·0**	**0·99 [0·84, 1·15]**
Total events	135		147			

Heterogeneity: $\chi^2 = 3{\cdot}11$, $df = 3$ ($P = 0{\cdot}37$); $I^2 = 4\%$

Test for overall effect: $Z = 0{\cdot}17$ ($P = 0{\cdot}86$)



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What's on the horizon?

Effects of Transfusion Thresholds on Neurocognitive Outcome (ETTNO)

- 920 VLBW infants randomised from 2011

- Primary outcome: Incidence of death or major neurodevelopmental impairment @ 24 months CA
- major neurodevelopmental impairment is defined as cognitive delay defined as mental developmental index (MDI) score of the Bayley 2 Scales < 85, cerebral palsy, or severe visual or hearing impairment
- Expected completion of study July 2017

BCSH 2016 recommendations

Postnatal age	Suggested transfusion threshold Hb (g/L)		
	Ventilated	On oxygen /CPAP	Off oxygen
1st 24 hours	< 120	< 120	< 100
≤ week 1 (day 1-7)	< 120	< 100	< 100
week 2 (day 8 - 14)	< 100	< 95	< 75 - 85 depending on clinical situation
≥ week 3 (≥ day 15)		< 85	

Neonatal Transfusions - Key practice points

1. Hospitals should develop policies which help to minimise exposure to multiple donors.

2. Minimise phlebotomy where possible.

Have a local policy on the frequency and types of regular blood tests required, using small samples and small volume laboratory analysers, and near patient testing. Use of cord blood for initial blood tests may be considered (Baer et al, 2013).

Neonatal Transfusions - Key practice points

3.Hospital policies should ensure that paedipacks are available for emergency use by maternity and neonatal units. The laboratory should be notified once they have been used.

How to order blood on the NICU

Minimising blood donor exposure is key to good blood transfusion practice. On ICE request 'neonatal packs' instead of the volume of blood (mls). A single donor unit is split into 6 'neonatal packs', also called 'paedipacks' and have a shelf life of approx. 30 days. Therefore there is no need to send a G&S sample every time a baby needs a transfusion until these have all been used or expired.

Blood transfusion for New Admissions:

1. Take group and save sample in **RED EDTA bottle** (approximately 0.75ml)
2. Handwrite label with **Name, DOB, district number (038..), date, time, sign**
3. Do not send until correct form printed off ICE…
4. On ICE:
   - Select 'Neonatal/Haem Blood transfusion' tab under Neonate requests
   - Click 'provide 'Red cells'
     - **If lb.wt. <900g** – type **6** in the first box (total quantity needed) and select **neonatal pack** from the drop down menu (type of product required)
     - **If lb.wt. >900g** – type **3** in the first box (total quantity needed) and select **neonatal pack** from the drop down menu (type of product required)
   - Enter the patient's birth weight
   - Special Requirements:
     - **CMV negative** (for all aged <1 yr)
     - **Irradiated** only if previous IUT, Exchange Transfusion or ?DiGeorge
5. Print off form, sign and date
6. **Check the EDTA sample is correctly labelled with another health professional who will countersign the form**
7. Send form together with RED EDTA blood sample obtained

Blood transfusion for NICU Inpatients:

1. Ask the Nurse to check on Blood Track to see if neonatal packs are already available – if so, there is no need to contact transfusion lab.
2. If no packs available – order blood as described in the steps above. If a blood sample in the lab is less than 6 days old, it may be used for cross matching and a new sample may not be required. Phone the lab to ask.

Transfusion tips

- blood suitable for neonates:
  - CMV negative
  - Donors have to have donated at least once previously (within 2 years)
- Red cells expire 35 days after donation
  - NHSBT need to test it and might not release it for a few days
- 6 paedipacks from one adult donor unit

Neonatal Transfusions - Recommendations

1. Studies to date support restrictive transfusion thresholds (2B)

2. Transfusion volumes of 15mL/kg are generally recommended for non-bleeding neonates (2C)

3. The routine use of EPO or Darbepoetin is not recommended in preterm infants (1B)

4. Where a term (1B) / preterm (2C) neonate does not require resuscitation, undertake delayed cord clamping

Acknowledgement: BCSH 2016

Writing group:

New HV[1], Berryman J[2], Bolton-Maggs PHB[3], Cantwell C[4], Chalmers E[5], Davies T[6], Gottstein R[7], Hennem S[8], Kelleher A[9], Kumar S[10], Morley SL[11], Stanworth SJ[12]

1. NHSBT/Imperial College London; 2. UCH, 3. NHSBT, Manchester/TTF member; 4. Imperial College London; 5. Glasgow Hospital for Women and Children;

6. NHSBT, Manchester; 7. St. Mary's Hospital, Manchester; 8. GOS, London;

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GRADE - BCSH guidelines

Grading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation.

GRADE nomenclature for

- levels of evidence (A-D)

and

- the strength of recommendations (1 , 2)

GRADE: Strength of Recommendation

Strong (grade 1) recommendations - clinicians are very certain that benefits do, or do not, outweigh risks and burdens. Where words such as “recommend”, “offer” and “should” are appropriate.

Weak (grade 2) recommendations - clinicians believe that benefits, risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks.

GRADE: Levels of Evidence

(A) High: Further research is very unlikely to change our confidence in the estimate of effect.

(B) Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

(C) Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

(D) Very Low: Any estimate of effect is very uncertain.