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# Red Blood Cell Transfusion in the Neonate Clinical Pathway

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# Clinical Pathway

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# Red Blood Cell Transfusion in the Neonate Clinical Pathway

## Rationale

Neonatal Anemia is a common clinical condition encountered in neonatal intensive care and red blood cell (RBC) transfusion is a common therapeutic intervention. This Clinical Pathway provides guidance to conservative transfusion in consideration of the possible adverse effects of RBC transfusion in the neonate.

## Background

The purpose of RBC transfusion is to rapidly increase RBC mass to treat significant acute or chronic anemia and/or to increase oxygen delivery to tissues.

The optimization of RBC mass and oxygen delivery may be considered in the management of neonatal pulmonary disease, hemodynamic instability, and in acute blood loss. Signs of symptomatic chronic anemia in the neonate may include increased resting heart rate, slow feeding, poor weight gain/growth, decreased activity, apnea, need for increased respiratory support, and metabolic acidosis.

Trigger threshold hemoglobin and hematocrit values at which to consider transfusion depend on the pathologic indication for transfusion and remain an area of active investigation. The balance of risks and benefits of transfusion in some conditions remain uncertain.

Possible adverse effects of RBC transfusion include: inhibition of erythropoiesis, infection, graft-versus-host disease, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), and toxic effects of anticoagulants or preservatives.

Historic studies have associated RBC transfusion in neonates with an increased risk of death, necrotizing enterocolitis (NEC), extension of intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and transient increases in respiratory support, but more recent studies do not support a causal relationship with these adverse events.

Indications for RBC transfusions in the neonate should be carefully considered. Every effort should be made to reduce predisposing factors in neonates (minimizing iatrogenic blood losses through blood sampling). Every effort should be made to reduce additional donor exposures in neonates.

## Recent Published Data and Levels of Evidence

PINT Study (Canadian Premature in Need of Transfusion Study, 2006)
Infants weighing <1000 g birth weight were randomly assigned within 48 hours of birth to a transfusion algorithm of either low or high hemoglobin transfusion thresholds. The composite primary outcome was death before home discharge or survival with any of either severe retinopathy, bronchopulmonary dysplasia, or brain injury on cranial ultrasound. Morbidity outcomes were assessed, blinded to allocation. Four hundred fifty-one infants were randomly assigned to low (n=223) or high (n=228) hemoglobin thresholds. Groups were similar, with mean birth weight of 770 g and gestational age of 26 weeks. Fewer infants received one or more transfusions in the low threshold group (89% low versus 95% high, *P* = .037). Rates of the primary outcome were 74.0% in the low threshold group and 69.7% in the high (*P* =.25; risk difference, 2.7%; 95% CI –3.7% to 9.2%). There were no statistically significant differences between groups in any secondary outcome. (Level 1B)

Post hoc analyses (2009) suggested that cognitive impairment may be more common with restrictive transfusion trigger thresholds. Follow-up was performed at 18 to 21 months' corrected age. Erythrocyte transfusion was determined by an algorithm of low (restrictive) or high (liberal) hemoglobin transfusion thresholds, differing by 10 to 20 g/L and maintained until first hospital discharge. The primary composite outcome was death or the presence of cerebral palsy, cognitive delay, or severe visual or hearing impairment. Of 451 enrolled infants, the primary outcome was available in 430. There was no statistically significant difference in the primary outcome, found in 94 (45%) of 208 in the restrictive group and 82 (38%) of 213 in the liberal group. There were no statistically significant differences in preplanned secondary outcomes. However, the difference in cognitive delay (Mental Development Index score < 70) approached statistical significance. A posthoc analysis with cognitive delay redefined (Mental Development Index score < 85) showed a significant difference favoring the liberal threshold group. (Level 1B)

| **PINT STUDY, 2006, Transfusion Criteria** | | | | |
|---|---|---|---|---|
| | High Threshold, Hgb (Hct) | | Low Threshold, Hgb (Hct) | |
| Age (days) | Resp Support | No Resp Support | Resp Support | No Resp Support |
| 1-7 | ≤ 122 g/L (36.6%) | ≤ 109 g/L (32.7%) | ≤ 115 g/L (31%) | ≤ 90 g/L (27%) |
| 8-14 | ≤ 109 g/L (32.7%) | ≤ 90 g/L (27%) | ≤ 90 g/L (27%) | ≤ 77 g/L (23.1%) |
| ≥15 | ≤ 90 g/L (27%) | ≤ 77 g/L (23.1%) | ≤ 77 g/L (23.1%) | ≤ 68 g/L (20.4%) |

Cochrane Review (2011)
Selected randomized controlled trials (RCTs) comparing the effects of early versus late, or restrictive versus liberal erythrocyte transfusion regimes in low birthweight infants applied within three days of birth, with mortality or major morbidity as outcomes, through June 2010 were assessed. Four trials, enrolling a total of 614 infants, compared low (restrictive) to high (liberal)

hemoglobin thresholds. Restrictive thresholds tended to be similar, but one trial used liberal thresholds much higher than the other three. There were no statistically significant differences in the combined outcomes of death or serious morbidity at first hospital discharge (typical risk ratio (RR) 1.19; 95% confidence interval (CI) 0.95 to 1.49) or in component outcomes. Only the largest trial reported follow-up at 18 to 21 months corrected gestational age; in this study there was no statistically significant difference in a composite of death or adverse neurodevelopmental outcome (RR 1.06; 95%CI 0.95 to 1.19). One additional trial comparing transfusion for clinical signs of anemia versus transfusion at a set level of hemoglobin or hematocrit, reported no deaths and did not address disability. (Level 1A, but outdated)

ETTNO Trial (Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants, 2020)

Randomized clinical trial conducted in 36 level III/IV neonatal intensive care units in Europe among 1013 infants with birth weights of 400 g to 999 g at less than 72 hours after birth; enrollment took place between July 14, 2011, and November 14, 2014, and follow-up was completed by January 15, 2018. Infants were randomly assigned to liberal (n = 492) or restrictive (n = 521) red blood cell transfusion thresholds based on infants' postnatal age and current health state. The primary outcome, measured at 24 months of corrected age, was death or disability, defined as any of cognitive deficit, cerebral palsy, or severe visual or hearing impairment. Secondary outcome measures included individual components of the primary outcome, complications of prematurity, and growth. Among 1013 patients who were randomized (median gestational age at birth, 26.3 [interquartile range {IQR}, 24.9-27.6] weeks; 509 [50.2%] females), 928 (91.6%) completed the trial. Among infants in the liberal vs restrictive transfusion thresholds groups, respectively, incidence of any transfusion was 400/492 (81.3%) vs 315/521 (60.5%); median volume transfused was 40mL (IQR, 16-73 mL) vs 19mL (IQR, 0-46 mL); and weekly mean hematocrit was 3 percentage points higher with liberal thresholds. The primary outcome was not significantly different between groups (Liberal threshold 200/450, 44.4%; Restrictive threshold 205/478, 42.9%), nor were the secondary outcomes of death (38/460, 8.3%; 44/491, 9.0%), cognitive deficit (154/410, 37.6%; 148/430, 34.4%), or cerebral palsy (18/419, 4.3%; 25/443, 5.6%). Necrotizing enterocolitis requiring surgical intervention occurred in 20/492 (4.1%) vs 28/518 (5.4%); bronchopulmonary dysplasia occurred in 130/458 (28.4%) vs 126/485 (26.0%); and treatment for retinopathy of prematurity was required in 41/472 (8.7%) vs 38/492 (7.7%). Growth at follow-up was also not significantly different between groups. (Level 1 B)

**ETTNO TRIAL, 2020, Transfusion Criteria**

| | High Threshold, Hct | | Low Threshold, Hct | |
|---|---|---|---|---|
| Postnatal Age (days) | Critical | Non-critical | Critical | Non-critical |
| Up to 7 | < 41% | < 35% | < 34% | < 28% |
| 8-21 | < 37% | < 31% | < 30% | < 24% |
| >21 | < 34 % | < 28% | < 27% | < 21% |

*Critical was defined as an infant having at least 1 of the following criteria: invasive mechanical ventilation, continuous positive airway pressure with fraction of inspired oxygen >0.25 for >12 hours per 24 hours, treatment for patent ductus arteriosus, acute sepsis or necrotizing enterocolitis with circulatory failure requiring inotropic/vasopressor support, >6 nurse-documented apneas requiring intervention per 24 hours, or >4 intermittent hypoxemic episodes with pulse oximetry oxygen saturation <60%.*

TOP Trial (Transfusion of Prematures, NICHD, 2020)

Open, multicenter trial of infants with a birth weight 1000 g or less and a gestational age between 22 0/7 wks and 28 6/7 wks EGA randomly assigned within 48 hours after delivery to receive red-cell transfusions at higher or lower hemoglobin thresholds until 36 weeks of postmenstrual age or discharge, whichever occurred first. The primary outcome was a composite of death or neurodevelopmental impairment (cognitive delay, cerebral palsy, or hearing or vision loss) at 22 to 26 months of age, corrected for prematurity. A total of 1824 infants (mean birth weight, 756 g; mean gestational age, 25.9 weeks) underwent randomization. There was a between-group difference of 1.9 g per deciliter (19 g per liter) in the pretransfusion mean hemoglobin levels throughout the treatment period. Primary outcome data were available for 1692 infants (92.8%). Of 845 infants in the higher-threshold group, 423 (50.1%) died or survived with neurodevelopmental impairment, as compared with 422 of 847 infants (49.8%) in the lower-threshold group (relative risk adjusted for birth-weight stratum and center, 1.00; 95% confidence interval [CI], 0.92 to 1.10; P = 0.93). At 2 years, the higher- and lower-threshold groups had similar incidences of death (16.2% and 15.0%, respectively) and neurodevelopmental impairment (39.6% and 40.3%, respectively). At discharge from the hospital, the incidences of survival without severe complications were 28.5% and 30.9%, respectively. Serious adverse events occurred in 22.7% and 21.7%, respectively. (Level 1B)

| **TOP TRIAL, 2020, Transfusion Criteria** | | | | |
|---|---|---|---|---|
| | High Threshold, Hct | | Low Threshold, Hct | |
| Postnatal Age (days) | Resp Support | No Resp Support | Resp Support | No Resp Support |
| Week 1 | < 38% | < 35% | < 32% | < 29% |
| Week 2 | < 37% | < 32% | < 29% | < 25% |
| ≥Week 3 | < 32% | < 29% | < 25% | < 21% |

## Clinical Management

Indications for RBC Transfusion in Neonates:

RBC transfusion should be considered to achieve an increase in RBC mass to treat significant acute or chronic anemia and/or to increase oxygen delivery to tissues when clinical condition indicates.

Central measurements of hemoglobin or hematocrit are preferred due to accuracy when using hemoglobin or hematocrit trigger threshold levels as indications for transfusion.

Acute Anemia Secondary to Blood Loss:

Assessment of the etiology of acute anemia should be completed as indicated.

Consider acute RBC transfusion in the setting of acute blood volume loss of ≥10% estimated total body blood volume with symptoms of decreased oxygen delivery or when acute blood volume loss is >20% estimated total body blood volume.

In the setting of acute blood volume loss with symptoms of decreased oxygen delivery and critical clinical instability, consideration should be given to the transfusion of emergency-release un-crossmatched RBC product.

Chronic Anemia

Assessment of the etiology of chronic anemia should be completed as indicated.

The following are generalized guidelines to assist in the clinical decision to transfuse RBC product. *Additional consideration may be given to the individual patient's clinical condition and clinical course.*

Every effort should be made to reduce predisposing factors in neonates (minimizing iatrogenic blood losses through blood sampling, optimizing iron intake).

Every effort should be made to reduce additional donor exposures in neonates.

Consider RBC transfusion for chronic anemia based on trigger threshold hematocrit/hemoglobin levels dependent on the infant's clinical stability, need for respiratory support, post-menstrual age, and chronologic age.

- For *critically unstable* infants requiring invasive mechanical ventilation for pulmonary indications with increasing respiratory support and $FiO_2$ > 0.60, and hematocrit < 40% (hemoglobin <13.5 g/dL).
- For *critically unstable* infants with significant hemodynamic instability on >1 pressor, and hematocrit < 40% (hemoglobin <13.5 g/dL).
- For select hypoxic cardiac disease, as recommended by Cardiology consultation, and hematocrit < 40% (hemoglobin <13.5 g/dL).
- For *unstable* infants requiring invasive mechanical ventilation or non-invasive respiratory support for pulmonary indications, with increasing or dynamic respiratory support, with $FiO_2$ < 0.60, and hematocrit < 35% (hemoglobin < 11.5 g/dL).
- For *unstable* infants with hemodynamic instability on pressor support, and hematocrit < 35% (hemoglobin < 11.5 g/dL).
- For *stable* infants (no changes in baseline respiratory status; no hemodynamic instability) requiring chronic invasive mechanical ventilation or chronic non-invasive respiratory support for pulmonary indications, and hematocrit < 30% (hemoglobin < 10 g/dL).
- For *stable* infants with signs attributed to anemia, and not attributable to other causes, and hematocrit <30% (hemoglobin <10 g/dL):
    - Inadequate weight gain over the previous four days while receiving ≥ 120 kcal/kg/day: <10 g/kg/day for <1,000 g infant; <15 g/kg/day for 1,000- 2,000 g infant; <25 g/day for > 2,000 g infant
    - ≥ 24 hours of tachycardia (heart rate persistently > 180 beats per minute) or tachypnea (RR > 70 breaths per minute or persistently increased from baseline)
    - Serum lactate ≥ 2.5 mEq/L or an acute metabolic acidosis (pH < 7.2)
    - If the infant will undergo major surgery within 72 hours
- For *stable* infants born ≤30 0/7 wks and ≤21 days old or PMA ≤30 wks, and hematocrit < 30% (hemoglobin < 10 g/dL).

- For *stable* infants born >30 0/7 wks and ≤21 days old, and hematocrit < 25% (hemoglobin < 8 g/dL).
- For *stable* infants >21 days old and PMA >30wks, and hematocrit < 21% (hemoglobin < 7 g/dL).
- For premature infants without any signs of symptomatic anemia, refer to the Clinical Practice Guideline "Darbepoetin use in the management of Anemia of Prematurity" for recommendations regarding the possible use of darbepoetin in this population.

Approach to RBC Transfusion in Neonates:

Please refer to the JHACH Clinical Policy and Practice Guideline "Blood and Blood Components Administration".

Acute Neonatal Anemia Secondary to Blood Loss:

- Initial volume of PRBC transfusion should be 20 mL/kg.
- Larger initial volumes may be considered if presentation suggests blood losses greater than 20% total body blood volume (Hct < 30% at birth with evidence of acute blood loss, measured surgical or procedural blood loss, or other acute hemorrhaging).

Chronic Neonatal Anemia:

- Initial volume of PRBC transfusion should be 15-20 mL/kg.
- Consider follow-up Hgb/Hct sampling at 12-24 hrs post-transfusion and repeat transfusion at volume of 10-20 mL/kg to achieve Hct > 35-40% to reduce risk for repeated transfusions during hospital course and additional donor exposure.

## Summary

A conservative approach to transfusion should be followed in consideration of the possible adverse effects of RBC transfusion in the neonate.

**Red Blood Cell Transfusion in the Neonate Pathway**

| Guidelines for RBC Transfusion in the Neonate | |
|---|---|
| **Clinical Condition** | **Transfusion Trigger Level (Hct,%)** |
| *Critically Unstable; Select hypoxic cardiac disease | **< 40%** |
| †Unstable | **< 35%** |
| ‡Stable requiring invasive or non-invasive resp support for pulmonary indications | **< 30%** |
| Stable with signs attributed to anemia§ | **< 30%** |
| Stable, born ≤30 0/7 wks and ≤21d old or PMA ≤30 wks | **< 30%** |
| Stable, born >30 0/7 wks and ≤21d old | **< 25%** |
| Stable, >21 days old and PMA >30wks | **< 21%** |

*Critically Unstable: Infants on invasive resp support for pulmonary indications, with increasing respiratory support, oxygen >60%; Significant hemodynamic instability on >1 pressor.

†Unstable: Infants on invasive or non-invasive resp support for pulmonary indications, with increasing or dynamic respiratory support, oxygen <60%; Hemodynamic instability on pressor support

‡Stable: No changes in baseline respiratory status; no hemodynamic instability

§Signs attributed to anemia: persistent tachycardia, increased apnea/bradycardia, inadequate weight gain, or lethargy

## Glossary

Neonate: For the purposes of this CPG, Neonate refers to an infant with a condition arising during the neonatal period resulting in hospitalization up to 6 months corrected gestational age. Used interchangeably with *Infant*.

Neonatal Anemia: For the purposes of this CPG, Neonatal Anemia refers to a reduction in a neonate's red blood cell mass resulting in a decrease in hemoglobin measurement below 11.5 g/dL or hematocrit measurement below 35%.

RBC Transfusion: For the purposes of this CPG, RBC Transfusion refers to the therapeutic administration of RBC product in response to Neonatal Anemia or a hemoglobin or hematocrit measurement below a determined trigger threshold.

## References

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Franz AR, Engel C, Bassler D, et al. Effects of Liberal vs Restrictive Transfusion Thresholds on Survival and Neurocognitive Outcomes in Extremely Low-Birth-Weight Infants: The ETTNO Randomized Clinical Trial. JAMA 2020; 324:560.

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## Outcome Measures

1. CPG compliance, guideline deviations
2. RBC transfusion per patient, assessed by gestational age
3. Total number of donor exposures

Clinical Pathway Team

Red Blood Cell Transfusion in the Neonate Clinical Pathway

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*Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The ultimate judgment regarding care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.*

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