Re: RK Whyte, AL Jefferies; Canadian Paediatric Society, Fetus and Newborn Committee. Red blood cell transfusion in newborn infants. Paediatr Child Health 2014;19(4):213-222.

To the Editor;

Many thanks to Drs Whyte and Jefferies for their excellent review of neonatal red blood cell transfusions, published in the April 2014 issue of the *Journal*, and their willingness to address this controversial topic. However, I would like to raise concerns regarding their recommended thresholds for transfusion for anemia of prematurity. The neurodevelopmental outcomes of the Premature Infants in Need of Transfusion (PINT) study, published in 2009 (1), clearly indicate (albeit in the authors' post hoc analysis) a benefit of higher transfusion thresholds in reducing the rate of mild cognitive delay (motor development index [MDI] <85). In the absence of contradictory evidence, this critically important observation cannot be ignored.

This year's updated Canadian Paediatric Society Position Statement recommendation on this matter states that "it would be prudent to maintain hemoglobin levels above the thresholds described in Table 1", which references the lower transfusion thresholds from the PINT study.

In fact, what little evidence has been published on long-term neurodevelopmental outcomes supports the higher transfusion cut-off values. In light of this, the Position Statement should, at the very least, support individual centres'/clinicians' choice to follow either set of thresholds. I have a feeling that many neonatologists around Canada share the same concern.

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REFERENCE

1. Whyte RK, Kirpalani H, Asztalos EV, et al; PINTOS Study Group. Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. Pediatrics 2009;123:207-13.

The author responds;

We thank Dr Gryn for his remarks. He makes an important point, and refers to the recommendations in the Canadian Paediatric Society Position Statement 'Red blood cell transfusion in newborn infants' (1) with respect to the neurodevelopmental outcome of extremely low birthweight infants and hemoglobin transfusion thresholds. He questions our use of the lower rather than higher thresholds of the PINT study (2) in our table of recommended thresholds.

The relationship between transfusion threshold and neurodevelopmental outcome was addressed only in the PINT outcome study (3). These results were incorporated into the Cochrane review (4) and into the Position Statement (1).

At the level of the trial itself, there were three results that have a bearing on neurodevelopment and on the statement recommendations. The primary composite outcome of the PINT study was death or neurodevelopmental disability, occurring in 45% of the low- and 38% of the high-threshold group (adjusted OR 1.45, confidence limits [CL] 0.94, 2.21; P=0.09). The preplanned secondary outcome of cognitive delay in survivors (MDI <70) was 24% versus 18% (adjusted OR 1.74 [CL 0.98, 3.11]); P=0.06. At the request of the journal reviewers and of the scientific community to which these results were presented, a post hoc secondary outcome was re-evaluated using an MDI <85. This yielded rates of 45% versus 34% (OR 1.81 [CL 1.12, 2.93]); P=0.016. No other post hoc outcomes were evaluated. The Cochrane Review reported all of these findings in its own tables, using unadjusted analyses. These analyses yielded similar but less statistically significant summary statistics.

In the statement, we interpreted these findings overall as showing no evidence of a significant difference between the two regimens and, therefore, presented the lower threshold values as our recommendation values for a transfusion threshold. Dr Gryn argues that the best evidence is that there were benefits attributable to the higher threshold and that the higher limits should, therefore, have been recommended in this table.

Dr Gryn makes a fine point and exposes a dilemma appreciated by both PINT investigators and the Canadian Paediatric Society Fetus and Newborn Committee. We argue that the hierarchy of primary outcome, planned secondary outcome and post hoc secondary outcomes lends its own important, although inestimable, weight to our interpretation. Statistical analysis does not take into account which level of outcome is being reported. A numerical adjustment of confidence would not be possible, particularly with respect to post hoc secondary analyses; these results should be considered hypothesis-generating rather than hypothesis-testing. In fact, the hypothesis generated by the post hoc analysis has resulted in a newer and larger trial to address these uncertainties (5).

If we accept that the main finding of the PINT study and of the Cochrane review was of no significant difference in the primary outcome, should the statement advocate the higher or lower hemoglobin threshold? Because the entire concept of threshold is of a lower limit, it makes sense to choose this in the context of no difference. The lower limit is a reflection of a conservative approach to blood transfusion, given the rare but serious complications associated with this therapy.

With respect to Dr Gryn's final point, we agree that all statements should support a clinician's responsibility to provide individualized, evidence-based care in their interpretation of guidelines. Our recommendations with respect to thresholds were categorized as 'weak'. We endorse the recent opinion that as "… real evidence based medicine is as much about when to ignore or over-ride guidelines as how to follow them, those who write guidelines should flag up the need for judgment and informed, shared decision making (6)." We should take this advice to heart.

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Ann Jefferies MD
On behalf of the Fetus and Newborn Committee of the Canadian Paediatric Society

REFERENCES

1. Whyte RK, Jefferies A, Canadian Paediatric Society, Fetus and Newborn Committee. Red blood cell transfusion in newborn infants. Paediatr Child Health 2014;19:213-7.
2. Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: A randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr 2006;149:301-7.
3. Whyte RK, Kirpalani H, Asztalos EV, et al; PINTOS Study Group. Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. Pediatrics 2009;123:207-13.
4. Whyte R, Kirpalani H. Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. Cochrane Database Syst Rev 2011;(11):CD000512.
5. Kirpalani HM, Higgins R; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Transfusion of prematures trial (TOP) NCT01702805 <http://clinicaltrials.gov/ct2/show/record/NCT01702805> (Accessed August 12, 2014).

6. Greenhalgh T, Howick J, Maskrey N, Evidence Based Medicine Renaissance Group. Evidence based medicine: A movement in crisis? BMJ 2014;348:g3725.