



# Highlights from this issue

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## TRANSFUSION THRESHOLDS FOR PRETERM INFANTS

In this review, Edward Bell gives a detailed summary of the findings from and implications of two randomised controlled trials of different transfusion thresholds for preterm infants. Between the two of them the ETTNO (Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants) Trial<sup>1</sup> and the TOP (Transfusion of Prematures) Trial<sup>2</sup> enrolled just over 2800 preterm infants with birthweights 1000 g or less. Dr Bell was one of the investigators of the TOP trial. ETTNO took place in Europe and included a high proportion of infants who had delayed cord clamping (DCC). TOP took place in the USA, where DCC was less frequent. Both trials utilised transfusion protocols that varied the haemoglobin threshold for transfusion, according to disease severity and postnatal age. There was a high level of follow-up to 2 years. Within the range of haemoglobin levels permitted by the protocols there was no difference between groups in either study in the primary outcome of neurodevelopmental impairment at 2 years' corrected age or death before assessment. There was no difference between groups in either study in the components of the primary outcome. There were also no differences between groups in either study in the rates of necrotising enterocolitis (NEC), patent ductus arteriosus, severe retinopathy of prematurity, severe intraventricular haemorrhage, periventricular leucomalacia, or bronchopulmonary dysplasia. In sick infants in the first week of life there was no advantage to transfusing at Hb levels higher than 11 g/dL. It is interesting that in the two trials there were more than 2000 more transfusions in infants targeted to higher haemoglobin levels, but no excess of NEC cases was observed in association with these extra transfusions. These findings will inform evidence-based practice guidelines. See page F126

## EARLY VERSUS LATE PARENTERAL NUTRITION FOR PRETERM INFANTS

Two studies from the same group investigate the balance of risks and benefits of early parenteral nutrition for preterm infants. Trials in older children and adults suggest that there may be harms from early use in critically ill patients, but preterm infants are in a very different nutritional position and are often not critically ill. Both studies analysed routinely collected data from England and Wales, extracted from the UK National Neonatal Research Database. James Webbe *et al* looked at infants born at 30–32+6 weeks in 2012–17. With reasonable exclusion criteria they defined parenteral nutrition as early

if any was given in the first 7 days. Infants who received early parenteral nutrition were compared using propensity matching to those who received no parenteral nutrition. There were around 35 000 infants included in matched pairs. Early parenteral nutrition was associated with slightly higher survival to hospital discharge (absolute difference 0.91%–95% CI 0.53% to 1.3%, but higher absolute rates of complications that might affect later outcome, such as NEC (4.6%), BPD (3.9%), late onset sepsis (1.5%). Sabita Uthaya *et al* studied infants <31 weeks' gestation, defining early parenteral nutrition as having been given in the first two postnatal days and later parenteral nutrition as having been given after this. They too used propensity matching and studied around 16 000 infants born in 2008–19. They found no difference in their primary outcome of survival to discharge without major morbidity. As in the study by James Webbe *et al*, they found higher survival to discharge associated with earlier parenteral nutrition (absolute difference 3.25%, 95% CI 2.68% to 3.82%). Again, they found that early parenteral nutrition was associated with some small increases in absolute rates of morbidities that might affect later outcome, including BPD (1.24%), late onset sepsis (0.84%), ROP treatment 0.5%. These observational studies cannot direct practice, but they are helpful because they highlight an area where there is variation in practice that may have important effects on life outcomes. They show that differences between approaches are not so large as to be obvious anecdotally in day to day care and should support clinicians and families in having the equipoise to allow large scale randomised trials. There is an accompanying editorial by Mark Johnson that gives further explanation of the difference of this situation to that in older children and adults and the need for careful selection of the right comparisons for future studies. See pages F131 and F137

## NON-INVASIVE VENTILATION AND BPD

Two further studies from large patient data systems report trends in non-invasive ventilation. Alejandro Avila-Alvarez *et al* report data from the Spanish SEN1500 network, which captures around two thirds of the very low birth weight infants admitted to neonatal units in Spain. The report covers the years 2010–19 and just under 18 000 infants with birth weight less than 1500 g and gestation <32 weeks. When split into two 5 year periods, the proportion never intubated increased from 39.8% to 49.5%. Use of non-invasive IPPV, high flow nasal cannula treatment and CPAP during the neonatal course all increased but there was no change in survival,

or survival without BPD, or survival without moderate to severe BPD. From the UK, Laura Sand and colleagues report National Neonatal Research Database information on 56 000 infants born <32 weeks gestation in England and Wales from 2010 to 17. There were substantial increases in the use of CPAP and High Flow Nasal Cannula therapy over time, including as primary therapy. Increasing use of high flow therapy was associated with increased risk of BPD. An accompanying editorial by Brett Manley and Kate Hodgson discusses the difficulties with the definition of BPD as a binary outcome. There may be confounding by indication whereby infants who survive to get HFNC may be those who already have BPD. The range of gestations and birthweights included in these studies groups together infants with dramatically different risks and care needs. As with parenteral nutrition, large scale simple trials with samples capable of resolving small differences in outcomes important to families will be required to understand how to gain the most from the available therapies. See pages F143, F150 and F118

## TRAINING PRETERM INFANTS TO FEED

Can we train our preterm babies to achieve oral feeding more quickly? Perhaps we can. In this randomised controlled trial, Ju Sun Heo *et al* studied the effect of direct swallow training and oral sensorimotor stimulation in speeding the progression to full enteral feeding in 186 preterm infants born <32 weeks' gestation. Interventions were masked from the care team by using screens around the incubator. Two 15 min sessions were provided per day until the infants reached full enteral feeds (see supplementary videos). The primary outcome was the time from start of oral feeding to the first day that the infant achieved 100% oral feeds of daily intake without adverse events that did not self-resolve. This took 21 days in control infants, 17 days in infants who received direct swallow training, and 15 days in infants who received both direct swallow training and oral sensorimotor stimulation. There were changes in length of hospital stay that reflected the feeding progress but were not statistically significant. It will be interesting to see further studies. See page F166

## REFERENCES

- 1 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;324:560–70.
- 2 Kirpalani H, Bell EF, Hintz SR, *et al*. Higher or lower hemoglobin transfusion thresholds for preterm infants. *N Engl J Med* 2020;383:2639–51.