



Highlights from this issue

Ben J Stenson, *Edition Editor*

PROBIOTICS AND THE MICROBIOME

Paul Fleming addresses the question of whether it is time for neonatal units to provide probiotics routinely in the care of preterm infants. This editorial was commissioned in relation to a single centre report of outcomes before and after implementation of probiotics in Newcastle (UK) by Claire Granger and colleagues. Probiotics were implemented in Newcastle in January 2013, initially with a dual strain (*Lactobacillus acidophilus* and *Bifidobacterium bifidum*) and later with a triple strain preparation (*L. acidophilus*, *B. bifidum* and *Bifidobacterium longum* spp *infantis*) from August 2016. Outcomes were compared for infants born <32 weeks gestation before and after implementation. There were around 500 infants eligible for inclusion in each period. Granger and colleagues observed no significant change in necrotising enterocolitis (NEC), late onset sepsis or death between the two periods. In a sub-group analysis by gestation, there was a reduction in the OR for developing NEC observed in infants >28 weeks gestation (OR. 95% C.I. 0.42, 0.2 to 0.99). Although there were numerically more infants at higher gestation, their individual risk of NEC is lower, so cases in more mature infants represented a minority of the total. Paul Fleming discusses the present evidence base, including the evidence quality and the challenge of interpreting a literature that has evolved from single strain to multi-strain products. No single large trial, whatever it may show, will de-rail the present meta-analysis overall, but implementation of pro-biotics is patchy because of unresolved uncertainties, particularly for higher risk infants. Paul calls on the clinical community to learn the lessons from the SARS-CoV-2 Pandemic and the Recovery Trial, which has shown how rapidly it is possible to complete clinical trials when the clinical community engage fully and with urgency. Collaborating on a large scale in this way to evaluate regulated probiotic interventions and other future

new interventions should be possible so that we stop getting stuck in this way.

In a separate review, Emma Wong and colleagues summarise how modern birth practices may contribute to deficiencies in neonatal gut microbiome development and they present emerging concepts of 'microbiome engineering' that are under evaluation, with the aim of enabling the development of the microbiome in the face of these challenges. *See pages F344, F352 and F346*

BENCHMARKING TRANSITION IN EXTREMELY PRETERM INFANTS

Prakesh Shah and colleagues from the International Network for Evaluating Outcomes of Neonates (iNeo) assess associations between 5 min Apgar score and mortality and severe neurological injury (SNI) in infants born at 24–28 weeks of gestation between 2007 and 2016 in 11 high income countries. Among 92412 neonates, as 5 min Apgar score increased from 0 to 10, mortality decreased from 60% to 8%. There was not a similar relationship between Apgar score and severe neurological injury. It is difficult to determine the extent to which this association with mortality reflects higher risk infants transitioning less well vs adverse consequences of initial care that could be improved. The 5 min Apgar score clearly has relevance to outcome in this population and may have value as a measure for benchmarking, quality improvement and clinical studies. It is not being proposed as a marker for individual decision making. The observation is similar to that of Ju Lee Oei and colleagues, who report an individual patient data meta-analysis of 3 randomised clinical trials comparing the effects on a composite of death or disability of initial resuscitation with 30% or 60% oxygen for preterm infants born <32 weeks gestation. Initial FiO₂ had no effect on this outcome measure or its components. Regardless of starting FiO₂, infants who failed to reach a SpO₂ of at least 80% by 5 min had increased risk of death or disability. Larger trials may

be needed to exclude an influence of starting FiO₂ but either the initial risk characteristics of the infant or the quality of the initial care appears to be more important. The SpO₂ at 5 min may be a more objective benchmarking measure than the Apgar score at that time. *See pages F437 and F386*

SURFACTANT IN LATE PRETERM AND TERM INFANTS

Viraraghavan Vadakkencherry Ramaswamy and colleagues performed a systematic review and meta-analysis of studies of surfactant therapy for term and late preterm infants with respiratory distress syndrome. Most of the information in these more mature infants was derived from observational studies so there were issues with the level of certainty of the evidence showing that surfactant therapy decreased mortality, air leak, persistent pulmonary hypertension of the newborn, duration of ventilation and of hospital stay. There is little that can be determined about the balance of risks and benefits of different thresholds for intervention and whether treatment can be directed using diagnostic tests of surfactant deficiency. *See pages F393*

TIMING OF STOMA CLOSURE

As part of a project aimed at determining the feasibility of a trial of the timing of stoma closure in the newborn (ToSCiN) Jonathan Ducey and colleagues performed a survey of practice among neonatal surgical professionals (mostly surgeons and neonatologists) in the UK. They obtained feedback from 166 respondents working in all 27 units where surgery is provided. There was a lot of variation between respondents regarding optimal timing of closure and the factors that might influence it, suggesting the need for more evidence to guide practice. It is to be hoped that a question can be framed that the clinical community will have the equipage to address. Work is in progress. *See page F448*