

For a Change, May the Hare Defeat the Tortoise

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In this issue of *Indian Pediatrics*, Modi and co-workers [1] have published an interesting open-label randomized controlled trial in which they compared an early aggressive enteral feeding strategy with a conservative enteral feeding strategy among neonates weighing 750-1250 grams at birth, for its effect on all-cause mortality during hospital stay. The authors initiated and advanced feeds at 15 or 20 mL/kg/day in the conservative arm; and initiated and advanced feeds at 30 or 40 mL/kg/day in the aggressive arm. They did not detect statistically significant differences between the two groups with respect to all-cause mortality, culture-positive sepsis, survival without major morbidity, feed intolerance, or average daily weight gain during hospital stay. However, the aggressive feeding regimen group reached full feeds significantly earlier than the conservative feeding group.

This research group had published a somewhat similar study [2] on neonates weighing <1250 g at birth, where they had compared enteral feed advancement rates of 15 mL/kg/day and 30 mL/kg/day, with the primary outcome being the time taken to achieve full feeds. Like in their present study, the authors had demonstrated that the fast advancement group had reached full feeds significantly earlier.

The present study population is a microcosm of India, because it belonged to a lower middle- to lower social economic class, which availed healthcare in a public hospital. Fifty-nine percent participants had fetal growth restriction, 26% were born to mothers with gestational hypertension, and 22% had absent or reversed end-diastolic flow. While the need to safely reach full feeds early is felt world over, it is particularly pressing in low- and middle-income countries (LMIC) like India, because of the higher risk of nosocomial sepsis with each extra hour of intravenous cannulation and the lack of parenteral nutrition facilities in many centers. In LMIC, the risk of sepsis and growth failure often overrides the competing risk (real or perceived) of necrotizing enterocolitis (NEC). Sepsis, growth failure and NEC; all contribute to

mortality and/or neuro-developmental impairment.

Modi, *et al.* [1] did well to choose a patient-centric outcome (all-cause mortality before discharge) as the primary short-term outcome in this study, though it would have been ideal to have a long-term patient-centric composite outcome such as survival without neuro-developmental impairment by 18 months. There are several other similar small clinical trials and meta-analyses, many of which the authors have referenced in their article. In another study on extremely low birth weight infants from Cape Town, South Africa, infants receiving higher initial feed volumes and more rapid advancement had more rapid weight gain, with no significant differences in the incidence of NEC, feed intolerance and late-onset sepsis [3]. An updated Cochrane systematic review has been published after the ones referred to by Modi, *et al.* in their article [4]. In this meta-analysis of trials typically comparing daily increments of 15-20 mL/kg/day versus 30-40 mL/kg/day in very preterm or very low birth weight (VLBW) infants, there was no overall effect on the risk of all-cause mortality or NEC, nor was there any effect on the risk of these outcomes in subgroups of extremely low birthweight or small for gestational age infants. In the rapid advancement group, full enteral nutrition was established 1 to 5 days earlier than the slow advancement group. The GRADE quality of evidence of this meta-analysis was rated “moderate” because of the unavoidable lack of blinding.

Modi, *et al.* [1] have administered a slightly higher feed advancement rate (up to 40 mL/kg/day), compared to most other authors, who have typically restricted the fast advancement to 30-35 mL/kg/day in VLBW infants. There are researchers who have gone a step further and started full enteral feeds from the outset. Modi, *et al.* [1] have referred to a feasibility study by Sanghvi, *et al.* [5] in which they observed that it was possible to provide exclusive enteral nutrition to preterm neonates weighing 1200-1500 g from day one, without providing parenteral nutrition. In another randomized controlled trial [6]

conducted in Assam on neonates weighing 1000-1500 g, the authors randomly allocated the neonates to receive either complete enteral feeding (80 mL/kg/day) with expressed breast milk starting at 1 hour of life *versus* minimal enteral feeding. The authors found no statistically significant differences in the incidence of feed intolerance and NEC; however, time to regain birth weight, duration of NICU stay and time to reach 180 kcal/kg/day was significantly shorter in the complete enteral feeding group. Very recently, Nangia, *et al.* [7] published a randomized controlled trial comparing early total enteral feeding *versus* conventional feeding in stable infants who weighed 1000-1500 grams. They too concluded that early total enteral feeding resulted in earlier attainment of full feeds with a shorter duration of hospital stay and no difference in the risk of NEC. All this evidence suggests that it is possible to safely start larger feed volumes upfront and advance faster than what we have been accustomed to doing so far.

Modi, *et al.* [1] have correctly observed that their study was underpowered to detect the desired difference in all-cause mortality and other important outcomes. What is surprising is that the authors had assumed an 80% mortality in the conservative feeding strategy group, based on their pilot observation, a figure that seems rather high in present era. Having assumed such a high mortality, the authors hypothesized that an aggressive enteral feeding regimen would reduce the mortality rate by almost one-third, which again seems too ambitious. The observed mortality of 43% in the control arm also seems high by today's standards. The lack of data on the proportion of usage of preterm formula is another shortcoming in the study.

Authors of a multicenter trial in the UK (the SIFT trial) have planned to enrol 2800 very preterm or very low birth weight infants and randomly allocate them to either a faster (30 mL/kg/day) or slower (18 mL/kg/day) advancement of enteral feeds, with the intention of comparing short-term morbidity, time to reach full feeds and neurodevelopmental outcomes at 24 months of corrected age [8]. The SIFT study has finished recruiting subjects in January 2019, and the follow-up part of the study is currently in progress. The results of the UK-based SIFT study will throw light upon long-term

outcomes but they may not be generalizable to India and other developing countries, as the initial volume and rate are still conservative by Indian standards. An Indian multicenter trial on VLBW infants, which compares an aggressive enteral feeding policy (based upon the local published experience of early complete enteral feeding and/or rapid advancement) *versus* a conservative policy, while assuming a more realistic baseline mortality rate that reflects current-day pooled Indian data, is the need of the hour.

The current study [1] focuses attention on this pressing need. In this modern-day race between the hare and the tortoise, one can only wish that it is the hare that wins.

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