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Evidence Supporting Early Nutritional Support with Parenteral Amino Acid Infusion

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Postnatal growth of extremely low birth weight (ELBW) infants remains poor and does not come close to approximating rates of in utero growth. There is good evidence that early deficiencies in protein may be an important contributor to the poor growth outcomes observed in this population. Protein losses are inversely related to gestational age, and ELBW infants lose 1% to 2% of their total endogenous body protein stores each day that they receive glucose alone. It is now abundantly clear from a variety of studies that providing intravenous amino acids to sick premature infants in early postnatal life can improve protein balance and can increase protein accretion, even at low caloric intakes. Provision of approximately 1 g/kg/day of amino acids will result in a net protein balance close to zero, whereas delivery of 3 g/kg/day will accomplish protein accretion. Although data from metabolic studies, observational studies, and even a few randomized clinical trials overwhelmingly support the short-term safety and efficacy of early amino acids in reversing protein loss, there is much less known about the effects of early amino acid administration on longer-term outcomes such as growth and neurodevelopment in extremely premature infants. Based on the sum of currently available evidence presented, providing ELBW infants with 2.5 to 3.5 g/kg/day of intravenous amino acids as soon as possible after birth is a reasonable recommendation. Future studies are required to determine whether provision of 3 to 3.5 g/kg/day of amino acids is "aggressive" enough for optimal growth and neurodevelopmental outcome of ELBW infants.
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Although modern neonatal care has produced dramatic increases in the survival of extremely low birth weight (ELBW; birth weight ≤1000 g) infants, the postnatal growth of these infants remains poor and does not come close to approximating rates of in utero growth. The NICHD Neonatal Research Network has documented that the vast majority of ELBW infants weigh less than the 10th percentile at 36 weeks postmenstrual age (PMA) based on Alexander growth curves.[1] Among ELBW infants born at Network centers between 1995 and 1996, 99% were found to have growth failure at 36 weeks PMA,[2] and there have been only modest improvements in the postnatal growth of these infants over the last 10 years.[3] Information collected from predominately private neonatal intensive care units (Pediatrix Medical Group, Inc.) also documents a high rate of extrauterine growth restriction at the time of hospital discharge among premature (23-34 weeks estimated gestational age) neonates.[4] Figure 1 shows the percentage of infants with weight, length, and head circumference less than or equal to the 10th percentile at the time of discharge based on growth curves published by the same group of investigators for neonates discharged at 33 to 40 weeks estimated gestational age.[5] Not surprisingly, the greatest degree of impaired growth was found at the lowest gestational ages. Given the significant association between in-hospital growth velocity and neurodevelopmental and growth outcomes at 18 to 22 months corrected age,[6] optimizing growth outcomes in the extremely premature population remains a crucial goal.

There is good evidence that early deficiencies in protein may be an important contributor to poor growth outcomes. Berry and colleagues determined that protein intake in the first 2 weeks of life in ELBW infants was an independent positive prognostic determinant of growth.[7] Consistent with these findings is the study by Olsen and coworkers that examined differences in weight gain velocity of extremely pre-

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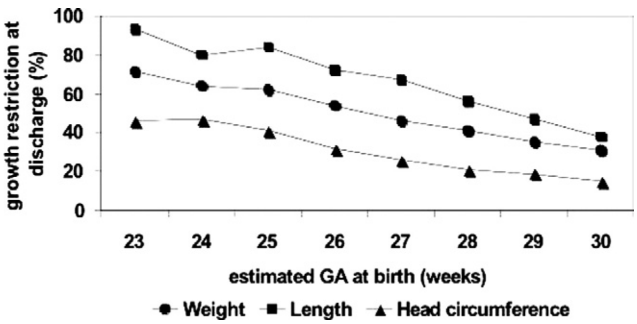

Figure 1 Percentage of infants with growth restriction (weight, length, or head circumference less than the 10th percentile) at time of hospital discharge from the NICU by estimated gestational age at birth. Sample size for each gestational age: 23 weeks ($N = 100$); 24 weeks ($N = 313$); 25 weeks ($N = 509$); 26 weeks ($N = 708$); 27 weeks ($N = 856$); 28 weeks ($N = 1104$); 29 weeks ($N = 1317$); 30 weeks ($N = 1743$).

mature infants among six level III NICUs.[8] Early protein intake was a significant determinant of growth velocity even after adjusting for other potentially confounding variables. These observational studies strongly suggest that preserving existing protein stores and providing for appropriate protein accretion will be critical if improved growth outcomes are to be achieved in ELBW infants.

It is important to understand the magnitude of early protein losses in premature neonates when amino acids are not provided. Historically, intravenous glucose was typically the only nutrient solution provided to neonates on admission to the NICU. In a series of studies, our laboratory has measured protein losses (based on leucine and phenylalanine kinetics using stable isotopic methods) in infants receiving intravenous glucose alone across a wide range of gestational ages.[9-11] Extremely premature (26 weeks gestation, ~850 g birth weight), clinically stable premature (32 weeks gestation; ~1600 g birth weight), and healthy term infants were studied in the first week of life. Rates of protein loss (based on phenylalanine kinetics) from these studies are shown in Figure 2; protein losses are inversely related to gestational age, with losses in extremely premature infants approximately two-fold higher than that in term infants. Other investigators have obtained

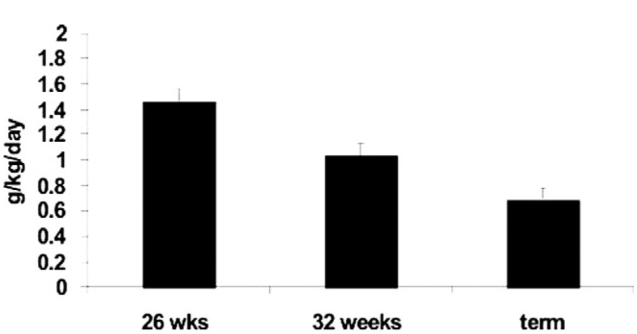

Figure 2 Rates of protein loss (based on phenylalanine kinetics) measured in extremely premature, premature, and term infants during an infusion of intravenous glucose alone in the first week of life.

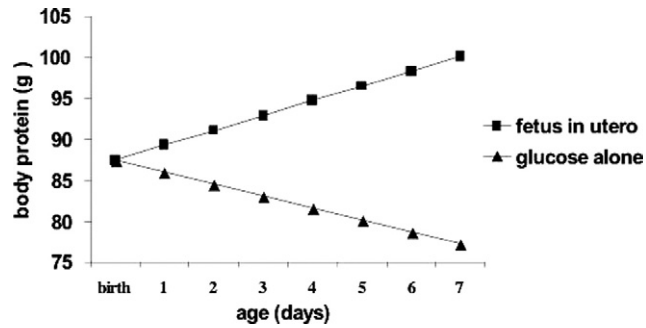

Figure 3 Change in body protein over the first week of postnatal life for a theoretical 1000-g, 26-week gestation infant provided with glucose alone versus protein accretion of the fetus in utero at the same gestational age.

similar results using nitrogen balance techniques.[12,13] Collectively, these data demonstrate that ELBW infants lose 1% to 2% of their total endogenous body protein stores each day that they receive glucose alone. In contrast, protein accretion in the fetus at the same gestational age is approximately 2 g of body protein per day.[14] The change in body protein over the first week of life for an ELBW infant receiving glucose alone versus that of the fetus in utero is depicted in Figure 3. The difference between these two curves is significant and clearly illustrates the magnitude of protein deficit that can rapidly accumulate for each day that glucose is the only nutritional substrate provided. The resultant protein deficit may be difficult if not impossible to recoup and may impact both short and long-term morbidities.

Multiple studies have been performed to determine whether providing intravenous amino acids to sick premature infants in early postnatal life can reverse negative nitrogen balance, even in the face of low caloric intake. Van Goudoever and colleagues studied 18 premature infants (29 weeks gestation, ~1.4 kg birth weight) who required mechanical ventilation and had indwelling arterial and venous catheters.[15] Study subjects were randomized to receive glucose alone or glucose plus 1.1 g/kg/day amino acids (Primene 10%, Clintec, Baxter, Benelux, NV, Brussels, Belgium) beginning on the first day of life. Caloric intake was 26 kcal/kg/day in the glucose alone group and 29 kcal/kg/day in the glucose plus amino acid group. Nitrogen balance was negative in the group of infants who received glucose alone and was essentially zero in the glucose plus amino acid group (Fig. 4). Rivera and colleagues studied 23 premature infants (28.5 weeks gestation, ~1 kg birth weight) with respiratory distress syndrome who were less than 24 hours of age and required mechanically assisted ventilation and indwelling arterial catheters.[16] Study subjects were randomized to receive glucose alone or glucose plus 1.5 g/kg/day of amino acids (Aminosyn PF, Abbott Laboratories, North Chicago, IL) beginning on the first day of life. The caloric intake of the two groups over the first 3 days of life was 32 kcal/kg/day for the glucose alone group and 46 kcal/kg/day for the glucose plus amino acid group. Nitrogen balance was measured in both groups for 24 hours between the second and third days of life. Protein balance was significantly negative in those infants that