in the United States. It is essential that we now design and perform the right trials to determine whether the infusion of inotropic agents, pressor agents, or the use of fluid boluses is helping these patients rather than harming them.

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EARLY POSTNATAL ADMINISTRATION OF INTRAVENOUS AMINO ACIDS TO PRETERM, EXTREMELY LOW BIRTH WEIGHT INFANTS

Over the past 25 years, dramatic improvements in neonatal medicine have resulted in regular survival of prematurely born infants as young as 24 weeks gestational age and as small as 500 to 600 g. Nowadays, these very small, immature infants are relatively common in neonatal intensive care units. Their survival creates a significant dilemma for neonatologists. How do they achieve growth of 2 to 3 kg of healthy body mass in these in preterm infants over a 12- to 16-week postnatal period? Is it possible to meet the goal of the American Academy of Pediatrics to achieve normal intrauterine growth rates in infants born preterm?[1]

Unfortunately, this goal remains elusive. Recent National Institute of Child Health and Development (NICHD) Neonatal Research Network data confirm that these smaller and smaller infants are taking longer and longer to initiate postnatal growth, to achieve "normal" rates of growth (commonly defined as fetal rates of growth), and to attain normal body size for adjusted gestational age after preterm birth.[2] This is not surprising when one observes that early postnatal nutritional state in these very preterm, extremely low birth weight (ELBW) infants often consists of significantly higher energy intake but significantly lower protein intake than the pla-

BUN Blood urea nitrogen
ELBW Extremely low birth weight

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J Pediatr 2006;148:291-94
0022-3476/$ - see front matter

10.1016/j.jpeds.2005.12.011

centa delivers to the fetus of the same gestational age. As a result, many of these very preterm infants develop a relatively greater fat mass, but decreased lean body mass, compared with fetuses growing in utero over the same gestational age period.[3] This decrease in growth of lean body mass occurs despite considerable data showing that increasing amino acid and protein intakes above the relatively low values commonly delivered to these infants results in a greater net protein balance.[4,5] Recent studies also indicate that enhanced amino acid intake can be successful when started during the first day after birth.[6] In this issue of *The Journal of Pediatrics*, Poindexter et al[7] present the effects of early intravenous amino acid feeding on growth, and neurodevelopmental outcomes in a large population of preterm infants from centers in the USA that are part of the NICHD Neonatal Research Network.[8] The results indicate that certain measures of growth are maintained or enhanced later in infancy among the infants that were fed earlier after birth with more amino acids. The results also show that the infants who were more aggressively fed intravenous amino acids had no greater measurable deficits in neurodevelopment than did those ELBW infants started on intravenous amino acid infusions later after birth. If confirmed, this is important information, as it provides evidence that nutrition can play an important, in fact, essential, role in improving growth without worsening the already far less than optimal neurodevelopmental outcome of extremely preterm birth. Why therefore is early postnatal amino acid nutrition of extremely preterm infants an issue at all?

There also are concerns regarding feeding preterm infants too much protein. In general, these concerns derive from early studies in which protein administration in large quantity or of poor "quality" produced metabolic acidosis, hyperammonemia, uremia, hyperaminoacidemia, growth restriction, and worse developmental outcome.[9] The good news is that today even very preterm, ELBW infants are in better physiological condition when nutrition is initiated than they were 30 years ago, and protein mixtures, especially those used intravenously, also are of much higher quality. In the current era, even "high" protein intakes have been demonstrated to be efficacious in terms of enhancing protein accretion, and they are well tolerated in terms of potential side effects.[6] Regarding side effects, many also have worried that higher amino acid/protein intakes in preterm infants would lead to excessive uremia and that uremia will cause harm to these infants. There is no credible evidence, however, that uremia of the degree commonly seen in preterm infants does cause harm. Also, a recent study showed that among a group of preterm infants of highly variable gestational age and birth weight, but including ELBW infants less than 1000 g birth weight and 27 weeks gestational age, there was no correlation between amino acid intake and blood urea nitrogen (BUN), and there were very few BUN values greater than 40 mg/dL.[10] In fact, BUN only increased modestly (~ 5 mg/dL) when amino acid intake was nearly tripled from ~1 to ~3 g/kg/d, which it should do, since amino acids are a normal oxidative substrate.[11] Again, the fear of uremia likely reflects early experience when intravenous and enteral amino acid and protein mixtures were not of appropriate quality or were given in excess quantity. Of course there always is reason for caution, and infants with documented excessive uremia probably should have their energy intakes and cardiovascular and renal systems improved before being fed more than the minimum amount of amino acids (~1.5 g/kg/d) needed to prevent protein breakdown.

It has been questioned whether current intravenous amino acid solutions are "optimal" for very preterm neonates. Current intravenous amino acid solutions that are commonly used in preterm infants were developed from studies in infants who were older and more mature than today's ELBW infant population. These solutions were manipulated to produce plasma aminograms similar to those found in term to 1-month-old, breast-fed infants. The major change in their composition was an increase in the total amount of essential amino acids, as well as their relative fraction versus nonessential amino acids. There also were specific reductions in certain amino acids (eg, glycine, phenylalanine, and methionine) that were considered to be potentially toxic and that might, at higher amino acid infusion rates, produce dangerously high plasma concentrations. Fortunately, clinical trials have shown improved nitrogen balance, growth rates, and lower plasma concentrations of the worrisome amino acids in preterm infants fed current parenteral nutrition solutions compared with those found in infants who were fed the original intravenous amino acid mixtures that were based on egg albumin and which had much lower relative amounts of the essential amino acids.[12] Nevertheless, there still is room for improvement, as concentrations of some essential amino acids (eg, lysine and threonine) are lower than found in normally growing, healthy human fetuses in both the second and third trimesters from umbilical vein samples.[6] It is possible therefore that even further improvement in amino acid quality of intravenous amino acid mixtures will promote better amino acid balance and improved growth.[13]

There is a misconception that increased amino acid/protein intakes must be accompanied by increasing energy intakes or the amino acids/protein will not adequately be incorporated into net protein growth. This is true only at very low nonprotein caloric intakes, below 60 kcal/kg/d. Above that level, increased protein intake is the primary determinant of protein gain, whereas increased non-protein intake, alone or with amino acids and protein, primarily enhances growth of body fat.[13]

There is increasing concern for over growth leading to long-term, later-life disorders of metabolism. This is a reasonable concern, and more and more evidence is accumulating that overgrowth is detrimental.[14] One must distinguish clearly, however, "aggressive" nutrition after birth of very preterm, ELBW infants that is aimed simply at providing the nutrients that they need to achieve normal growth rates and body compositions (more amino acids/protein vs energy) from aggressive nutrition later in the neonatal period that leads to rapid catch-up growth (usually provided as more energy than