Nutrition Management of the Very Low-birthweight Infant: I. Total Parenteral Nutrition and Minimal Enteral Nutrition
David H. Adamkin
*NeoReviews* 2006;7:e602-e607
DOI: 10.1542/neo.7-12-e602

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://neoreviews.aappublications.org/cgi/content/full/neoreviews;7/12/e602
Nutrition Management of the Very Low-birthweight Infant.

I. Total Parenteral Nutrition and Minimal Enteral Nutrition

David H. Adamkin, MD*

Author Disclosure
Dr Adamkin did not disclose any financial relationships relevant to this article.

Objectives After completing this article, readers should be able to:

1. Describe the conditions that early amino acid infusions can prevent in neonates.
2. Describe the effects of minimal enteral nutrition on time to full feedings and length of hospitalization.
3. Explain the clinical usefulness of gastric residuals in very low-birthweight infants.
4. Explain the benefits of gut stimulation protocols for extremely low-birthweight infants (500 to 600 g).

Introduction

This review of nutrition management of very low-birthweight (VLBW) infants (<1,500 g) examines two of three important strategies in a timeline configuration (Fig. 1). This covers the first hours and days after birth through the end of the first postnatal year.

The goal of nutrition management in VLBW infants, which is supported by the American Academy of Pediatrics Committee on Nutrition, is the achievement of postnatal growth at a rate that approximates the intrauterine growth of a normal fetus at the same postconceptional age. In reality, however, the growth of VLBW infants lags considerably after birth. Such infants, especially those weighing less than 1,000 g at birth (very, very low-birthweight [VVLBW]), typically do not regain birthweight until 2 to 3 weeks of age. The growth of most VLBW infants proceeds at a slower rate than in utero, often by a large margin. Although many of the smallest VLBW infants are also born small for gestational age (SGA), both appropriate-for-gestational-age VLBW and SGA infants develop extrauterine growth restriction. Figure 2, from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, demonstrates the differences between normal intrauterine growth and the observed rates of postnatal growth in the NICHD study. The postnatal growth curves shifted to the right of the reference curves in each gestational age category. This “growth deficiency” is far too common in VVLBW infants.

Nutrient intakes of VLBW infants are much lower than what the fetus receives in utero, an intake deficit that often persists throughout much of the infants’ stay in the hospital and even after discharge. Although non-nutritional factors (morbidities) are involved in the slow growth of VLBW infants, nutrient intakes are low and critical in explaining their poor growth. Considerable evidence suggests that early growth deficits have long-lasting effects, including short stature and poor neurodevelopmental outcomes. The most convincing data concerning the neurodevelopmental consequences of inadequate early nutrition are those reported by Lucas and associates. They demonstrated that preterm infants fed a preterm formula containing a higher content of protein and other nutrients over the first postnatal month had higher neurodevelopmental indices at both 18 months and 7 to 8 years of age compared with infants fed term formula.

Nutrition management of VLBW infants is marked by a lack of uniformity from one neonatal intensive care unit to the next as well as within individual practices. Such heterogeneity of practice persists from the first hours after birth to hospital discharge and beyond. Diversity of practice thrives where there is uncertainty. Because undernutrition is, by definition, unphysiologic and undesirable, any measure that diminishes it is inherently good, as long as safety is not compromised.

As elusive as the goal is that nutrition should support “postnatal growth” approximat-

*Professor of Pediatrics, University of Louisville, Louisville, Ky.
ing in utero growth of the normal fetus, the fetal model unquestionably is sound, and there is no alternative model or gold standard. Similarly, estimates of required intakes to achieve fetal growth are available.

**Early Parenteral Nutrition (PN)**

Aggressive nutrition theoretically allows the transfer from fetal to extraterrestrial life with minimal, if any, interruption of growth and development, but this requires that the transfer of nutrients to the fetus/infant not be interrupted. When birth occurs, particularly in VVLBW infants, there is some temporary interruption of the transfer of nutrients. Reduction of this interruption to a reasonable minimum is the first goal of aggressive nutrition.

Until recently, the initiation of PN had been delayed by a number of days. Reasons for such a delay have not been clear but probably have been related to the ability of VLBW infants to catabolize amino acids and general concerns about “tolerance” in the first days after birth for critically ill infants. We administer amino acids from the first postnatal hours to avoid the period of early malnutrition.

An understanding of fetal nutrition may be helpful in designing postnatal strategies for VVLBW infants. At 70% of gestation, there is little fetal lipid uptake. Fetal energy metabolism is not dependent on fat until early in the third trimester, and it then increases only gradually toward term. Glucose is delivered to the fetus from the mother at low fetal insulin concentrations, generally at a rate that matches fetal energy expenditure. The human placenta actively transports amino acids to the fetus, and animal studies indicate that fetal amino acid uptake greatly exceeds protein accretion requirements. Approximately 50% of the amino acids taken up by the fetus are oxidized and serve as a significant energy source. Urea

![Figure 1](image1.png)

**Figure 1.** Aggressive nutrition to prevent extrauterine growth restriction. PWL=postnatal weight loss, RTBW=return to birthweight, TPN=total parenteral nutrition, D/C=discharge, IWL=insensible water loss, CAPS=baby hats, ICF=intracellular fluid, AA=amino acids, E/N=energy/nutrition, PTF=preterm formula, H.C.=head circumference. Reprinted with permission from Adamkin DH. J Perinatol. 2005;25(suppl):S7–S11.

![Figure 2](image2.png)

**Figure 2.** Mean body weight versus gestational age in weeks for all study infants who had gestational ages at birth of between 24 and 29 weeks. Reprinted with permission from Ehrenkrantz RA, et al. Pediatrics. 1999;104:280–289.
production is a byproduct of amino acid oxidation. Relatively high rates of fetal urea production are seen in human and animal fetuses compared with the term neonate and adult, suggesting that high protein turnover and oxidation rates occur in the fetus. An increase in blood urea nitrogen, which often is observed after the start of PN, is not an adverse effect or sign of toxicity; rather, it is a normal accompaniment of an increase in the intake of amino acids or protein.

Several controlled studies have demonstrated the efficacy and safety of amino acids initiated within the first 24 hours after birth. No recognizable metabolic derangements, including hyperammonemia, metabolic acidosis, or abnormal aminograms, were observed.

A strong argument for the early aggressive use of amino acids is the prevention of “metabolic shock.” Concentrations of some key amino acids begin to decline in the VLBW infant from the time the cord is cut. Such metabolic shock may trigger the starvation response, of which endogenous glucose production is a prominent feature. Irrepressible glucose production may be the cause of the so-called glucose intolerance that often limits the amount of energy that can be administered to the VLBW infant. It makes more sense to smooth the metabolic transition from fetal to extrauterine life than to withhold PN for days, or even hours, and send the infant unnecessarily into a metabolic emergency. The need for PN may never be more acute than immediately after birth. It is noteworthy that investigators have made the surreptitious observation that glucose tolerance improves substantially in infants receiving early amino acids. Early amino acid administration may stimulate insulin secretion consistent with the concept that forestalling the starvation response improves glucose tolerance.

Finally, without initiation of early parenteral amino acids, plasma concentrations of certain amino acids (eg, arginine and leucine) decrease. Secretion of insulin depends on the plasma concentrations of these amino acids as well as that of glucose. A shortage of amino acids limits glucose transport and energy metabolism via a reduction in insulin and insulin-like growth factors. This scenario leads to a downregulation of glucose transporters at the cellular membrane level, resulting in intracellular energy failure via a decrease in Na\(^+\), K\(^+\) ATPase activity. This directly contributes to leakage of intracellular potassium and is associated with nonoliguric hyperkalemia.

Early PN with amino acids minimizes the abrupt postnatal deprivation of amino acid supply and meets the following goals:

- Prevention of protein catabolism
- Prevention of a decrease in growth-regulating factors such as insulin and downregulation of glucose transporters
- Prevention of hyperglycemia and hyperkalemia

From a practical standpoint, this strategy should be associated with less extreme postnatal weight loss and an earlier return to birthweight (Fig. 1). An earlier return to birthweight means the VLBW infant will be less likely to develop extrauterine growth restriction.

The studies of early PN used doses between 1.0 and 1.5 g/kg per day, an amount that replaces ongoing losses. Our practice currently uses a 4% stock amino acid solution with dextrose 10% concentration and provides approximately 2 g/kg of protein with the first infusion, which is initiated within 24 hours of birth. Ultimate amino acid intake is 3.0 g/kg per day, although intakes of 3.5 g/kg per day for infants weighing less than 1,200 g may be appropriate when enteral feedings are extremely delayed or withheld for prolonged periods.

**Minimal Enteral Nutrition**

The timing of initial feedings for the preterm infant has been debated for nearly a century and remains controversial. As suitable PN solutions designed for neonates became available, many physicians chose to use PN alone in the sick, ventilated, preterm infant because of concerns about enteral feedings and necrotizing enterocolitis (NEC). Total parenteral nutrition (TPN) was believed to be a logical continuation of the transplacental nutrition that infants would have received in utero. However, this view discounts any role that swallowed amniotic fluid may play in nutrition and in the development of the gastrointestinal tract. In fact, by the end of the third trimester, amniotic fluid provides the fetus with the same enteral volume intake and approximately 25% of the enteral protein intake as that of a term, breastfed infant. PN does little to support the function of the gastrointestinal tract. Studies in animals deprived of enteral substrate despite being maintained in an anabolic state with TPN showed that intraluminal nutrition was necessary for normal gastrointestinal structure and functional integrity. Enteral feedings have both direct trophic effects and indirect effects due to the release of intestinal hormones. Lucas and associates demonstrated significant increases in plasma concentrations of enteroglucagon, gastrin, and gastrin-inhibiting polypeptide in preterm infants after milk feedings of as little as 12 mL/kg per day. Similar surges in the trophic hormones were not seen in intravenously nourished infants.

Clearly, one of the important benefits of using PN is...
Regardless of feeding strategy, the advancement of feedings is based on perceived evidence of intolerance because of increased pregavage residuals or greenish aspirates. Gastric residuals are very frequent in the early neonatal period and are virtually always benign (ie, not associated with NEC).

A 2002 study by Mihatsch and associates demonstrated that in VVLBW infants, excessive gastric residual volume (GRV), either determined by percent of the previous feeding or an absolute volume (>2 mL or >3 mL), did not necessarily affect feeding success, as determined by the volume of total feeding on day 14. Similarly, the color of the GRV (green, milky, clear) did not predict feeding intolerance. Nonetheless, the volume of feeding on day 14 correlated with a higher proportion of episodes of no GRVs and with predominantly milky gastric residuals. Thus, isolated findings related to gastric emptying alone should not be the sole criteria to initiate or advance feedings. Stooling pattern, abdominal distention, and the nature of the stools also should be considered.

A 2004 retrospective case-control study comparing gastric residuals among VLBW infants who had proven NEC and controls showed more gastric residuals in those who developed NEC. However, the clinical usefulness of these findings is limited by the overlap in the volumes of gastric residuals with the control infants. The maximum residual volume seems to be the best predictor for NEC. A GRV of less than 1.5 mL or less than 25% of a feeding (the 25th percentile for NEC group) is probably within the range of normal. However, a GRV of more than 3.5 mL or 33% of a feeding (75th percentile for control infants) may be associated with a higher risk for NEC.

The cause of NEC remains unclear. Because NEC occurs rarely in infants who are not being fed, feedings have come to be seen as the cause, but the association between feedings and NEC is likely to be explained by feedings acting as vehicles for the introduction of bacterial or viral pathogens or toxins. They are more likely to survive the gastric barrier because of low acidity against which the immature gut is poorly able to defend itself. Efforts aimed at minimizing the risk of NEC have focused on the time of introduction of feedings, feeding volumes, and the rate of feeding volume increments. Each strategy that had been developed with the aim of reducing the risk of NEC has been shown to be ineffective and unnecessary. These strategies linger today, however, distracting neonatologists from concentrating on the real challenge, which is faltering growth in VLBW infants.

Withholding feedings for prolonged periods of time was one of the primary strategies intended to reduce the risk of NEC. Even though such a strategy never was shown to prevent NEC, forms of this strategy were widely adopted in the 1970s and 1980s. The withholding of feedings eventually came under scrutiny and were compared with early introduction of feedings in a number of controlled trials. A systematic review of the results concluded that early introduction of feedings shortens the time to full feedings as well as the length of hospitalization and did not lead to an increase in the incidence of NEC. A controlled study involving 100 VLBW infants not only confirmed these findings, but also found a significant reduction of serious infections when feedings were introduced early. Thus, delayed introduction of feedings now is known to have no beneficial effects, such as reduction in incidence of NEC, and yet has substantial negative effects.

Gut priming, minimal enteric feedings, hypocaloric feedings, or trophic feedings are all different names for gut stimulation aimed at improving gastrointestinal function. However, this strategy has not prevented NEC. A recent study compared a gut stimulation protocol that involved holding feeding volumes constant for 10 days before advancement with a traditional enteral feeding protocol that used standard rates of volume advancement. The study was closed early because the incidence of NEC in the group randomized to immediate volume advancement was 10% versus 1.4% in those receiving the gut stimulation protocol.

These studies raise several important questions: Is gut stimulation protective? Do early advancing protocols contribute to NEC? The answer to both questions may be “yes.” Regardless, the data reinforce previous conclusions that gut stimulation protocols are beneficial to VLBW infants and should be routine in all NICUs. There are few contraindications to using these protocols, even in infants weighing 500 to 600 g who have indwelling umbilical catheters and are receiving assisted ventilation.

Conclusion
The aggressive strategies for early nutrition described in this review are aimed at minimizing the interruption of nutrient intake that occurs with preterm birth. The two strategies should enhance the overall nutritional health of the extremely low-birthweight infant, as evidenced by
less postnatal weight loss, an earlier return to birth-
weight, and improved overall postnatal growth and out-
come.

Suggested Reading
Adamkin DH. Feeding the preterm infant. In: Bhatia J, ed. Perina-
tal Nutrition: Optimizing Infant Health and Development. New
York, NY: Marcel Dekker; 2004:165–190
Adamkin DH. Pragmatic approach to in-hospital nutrition in high-
Berseth CL, Bisquera JA, Paje VU. Prolonging small feeding vol-
umes early in life decreases the incidence of NEC in very low
Cobb AC, Carlo WA, Ambalavanan N. Gastric residuals and their
relationship to necrotizing enterocolitis in very-low-birth-

Ehrenkranz RA, Younes N, Lemons J, et al. Longitudinal growth of
104:280–289
Jadcherla SR, Kliegman RM. Studies of feeding intolerance in
very-low-birth-weight infants: definition and significance [com-
Lucas A, Morley R, Cole TJ. Randomised trial of early diet in
preterm babies and later intelligence quotient. *BMJ*. 1998;317:
1481–1487
Mihatsch WA, von Schoenaich P, Fahnenstich H, et al. The signif-
icance of gastric residuals in the early enteral feeding advance-
109:457–459
Thureen PJ, Hay WW Jr. Intravenous nutrition and postnatal
Ziegler EE, Thureen PJ, Carlson SJ. Aggressive nutrition of the
NeoReviews Quiz

1. Very low-birthweight (VLBW) neonates are at significant risk of postnatal growth failure. Nutritional management of such infants should be aimed at minimizing this growth failure. Of the following, the most accurate statement regarding nutrition and growth in VLBW infants is that:

A. Early postnatal growth deficit is associated with transient neurodevelopmental abnormalities.
B. Extrauterine growth restriction occurs only in infants born small for gestational age.
C. Non-nutritional factors such as morbidities are not critical components of poor postnatal growth.
D. Nutritional management usually is consistent from one neonatal intensive care unit to the next.
E. The goal of nutrition should be to support postnatal growth that approximates in utero fetal growth.

2. The interruption in the transfer of nutrients from the mother to the fetus that occurs following birth can be minimized by early administration of parenteral nutrition in VLBW neonates. Several controlled studies have examined the safety and efficacy of initiating amino acids within the first 24 hours after birth. Of the following, the most common metabolic consequence of early parenteral nutrition with amino acids is:

A. Hyperammonemia.
B. Hyperglycemia.
C. Hyperkalemia.
D. Increase in blood urea nitrogen values.
E. Metabolic acidosis.

3. Minimal enteral feeding, also called gut priming or trophic feeding, is designed to improve gastrointestinal function and is used frequently in the nutritional management of VLBW neonates. Of the following, the most accurate statement regarding minimal enteral feeding is that it:

A. Increases plasma concentrations of gastrointestinal hormones.
B. Is best avoided in infants weighing 500 to 600 g.
C. Is contraindicated in the presence of assisted ventilation.
D. Is contraindicated in the presence of indwelling umbilical catheters.
E. Prevents necrotizing enterocolitis.
Nutrition Management of the Very Low-birthweight Infant: I. Total Parenteral Nutrition and Minimal Enteral Nutrition

David H. Adamkin

NeoReviews 2006;7:e602-e607
DOI: 10.1542/neo.7-12-e602

Updated Information & Services
including high-resolution figures, can be found at:
http://neoreviews.aappublications.org/cgi/content/full/neoreviews;7/12/e602

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://neoreviews.aappublications.org/misc/Permissions.shtml

Reprints
Information about ordering reprints can be found online:
http://neoreviews.aappublications.org/misc/reprints.shtml