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Early Aggressive Nutrition in the Neonate

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OBJECTIVES

After completing this article, readers should be able to:

1. Describe the possible long-term effects of suboptimal nutrition in preterm infants and critically ill term neonates.
2. Explain why the current standard for postnatal nutrition in preterm infants may not be adequate for postnatal growth.
3. List the the lower limit at which to start intravenous protein delivery in very low-birthweight infants.
4. Characterize the commonly used definition for minimal enteral nutrition.
5. List the advantages of minimal enteral nutrition compared with exclusive total parenteral nutrition for the neonate.

Introduction

Nutritional practices vary dramatically among neonatal intensive care units (NICUs) in the United States. In many institutions, nutrition is introduced only gradually over the first weeks of life because of concerns of nutrient intolerance by the very preterm or ill infant who is fed intravenously and the risk of necrotizing enterocolitis (NEC) in preterm infants who are fed enterally. Often this period of nutritional deficiency is accepted as inevitable in this population. However, such a strategy of cautious nutrition might lead to a period of early malnutrition from which the neonate has a prolonged recovery and may have long-term adverse consequences. In many neonates this period of early nutritional deprivation need not be inescapable.

Many neonatologists will consider the early feeding strategies for the NICU population suggested in this article to be somewhat aggressive. The premise for these recommendations for extremely low-birthweight (ELBW) infants is that avoiding early malnutrition has both short- and long-term benefits for the neonate. This strategy involves initiating total parenteral nutrition (TPN) in the first hours after birth and administering it in conjunction with initially small, and then advancing, enteral feedings beginning on the first or second day of life. Use of

TPN is a means to achieve rapid, maximal nutrition, and early enteral feedings are designed to prime the gut and stimulate normal hormonal homeostasis.

As with most practices in neonatology, the rationale for the strategies presented here are based on existing data in neonates and extrapolation from animal data and human studies in older children and adults. There are no well-controlled, prospective investigations of neonates that conclusively validate the approach to nutrition in the very preterm and ill neonate that is presented here. The accompanying article by Premer and Georgieff confirms that there is a paucity of data to guide tailoring of nutrition to specific neonatal disease conditions. This article concludes with a discussion of the potential benefits, but also the potential undesirable consequences, of early aggressive nutrition in ill and very preterm neonates.

The Optimal Nutritional Goal for Preterm Neonates

The current standard for postnatal nutrition in preterm infants is one that duplicates normal in utero fetal growth rates. This recommendation was established by the American Academy of Pediatrics (AAP) in 1985, and it remains the nutritional guideline to which most neonatologists adhere, despite numerous advances in our understanding of

nutritional metabolism in this population.

For ELBW infants, postnatal duplication of normal in utero growth rates may not be a realistic goal for medical, practical, and theoretical reasons, especially for the first several weeks of life. From the medical and practical standpoints, the weight change in an ELBW infant during the first 1 to 2 weeks of life reflects more fluid management than tissue deposition. Fluid administration generally is targeted to cover insensible water losses. Relative fluid restriction usually is practiced to prevent development of patent ductus arteriosus, with some neonatologists advocating allowing weight to decrease as much as 15% to 20% below birthweight in the first days of life. At the same time, because of concerns about intolerance of both intravenous and intragastric feeding during the stresses of birth and intercurrent illness, parenteral and enteral nutrition commonly are introduced only gradually over a period of days, and enteral nutrition generally is withheld in the first week of life. Thus, rates of weight gain in utero would not be expected to be achieved for at least the first 1 to 2 weeks of life. Additionally, postnatal weight gain in ELBW infants has been shown to be affected adversely by intraventricular hemorrhage, diuretic administration, and steroid use. During this period, weight is not indicative of growth and should not be used to assess nutritional status in ELBW infants.

From a theoretical standpoint,

ABBREVIATIONS

CNS:	central nervous system
EFA:	essential fatty acid
ELBW:	extremely low birthweight
MEN:	minimal enteral nutrition
NEC:	necrotizing enterocolitis
NICU:	neonatal intensive care unit
SGA:	small for gestational age
TPN:	total parenteral nutrition
VLBW:	very low birthweight

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achieving in utero body *composition* at comparable gestational age should be the nutritional goal in ELBW infants rather than attaining specific *weight* gains. Because glucose is stored as glycogen, and glycogen stores are limited in all age groups, the body compartments that can change significantly with nutrition are protein mass and fat mass. Increase in protein mass is a measure of true growth, and a protein accretion rate comparable to that of the age-matched fetus should be the primary goal of neonatal nutrition. Unfortunately, measurements of body composition cannot be obtained easily for clinical purposes. However, as will be discussed, good estimates of protein accretion can be made in most infants based on nutritional protein intake.

The rate of increase in fat mass in the ELBW infant is a more complex and controversial issue. Fetal fat accretion occurs primarily by transplacental transport of lipid, and in the human infant this does not occur in significant amounts until the third trimester. A major unanswered question is whether postnatal fat accumulation in the ELBW infant should parallel that of the fetus of the same postconceptional age or that of a more gestationally mature fetus to enhance adaptation to an ex utero environment. There is some evidence that the latter practice may contribute to development of long-term obesity and its associated diseases. The short-term and long-term advantages and disadvantages of increased fat mass relative to in utero fat stores are unknown.

Fetal Nutrition

We administer substrates aggressively from the first day of life, particularly protein, with a goal of providing fetal nutrient delivery rates to the neonate as soon as possible to avoid the period of early neonatal malnutrition. An understanding of fetal nutrition may be helpful in designing postnatal nutrition strategies in very preterm 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 then it 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 pumps amino acids into 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 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 high protein turnover and oxidation rates in the fetus. Infusions of selected amino acids labeled with stable isotopes into the fetus indicate significant amino acid oxidation, which can be as high as 25% for leucine.

In contrast to fetal nutrition, lipid often is used as a significant energy source in the ELBW infant and in amounts that greatly exceed in utero delivery rates. Rates of glucose administration usually exceed that seen in utero, and amino acids are delivered at low rates that are significantly less than fetal accretion. It is worth considering whether high rates of amino acid delivery to the ELBW infant might be more physiologic, comparable to that seen in the fetus. In this scenario, increased concentrations of blood urea nitrogen in the ELBW infant might be evidence of effective use of amino acids as an energy supply (ie, amino acid oxidation releases carbon dioxide as well as ammonia that is converted to urea) rather than protein intolerance.

The marked difference between the nutrient supply that the fetus receives (amino acids and glucose with minimal fat) and that which the ELBW infant is given (high lipid and glucose concentrations plus low levels of protein) provides another perspective from which to estimate nutritional requirements of ELBW infants. It also raises questions regarding the outcomes that current feeding practices may produce. At this time, the safety and efficacy of applying fetal nutrient delivery to an

ELBW neonate essentially are untested.

Amino Acids

As discussed previously, protein accretion more appropriately reflects nutritional status than does weight gain. The neonatal period is characterized by very high rates of protein turnover, synthesis, catabolism, and deposition. Throughout life the greatest weight-specific protein gain occurs prior to 32 weeks' gestation. Several studies have shown that infants who receive only supplemental glucose lose approximately 1% of protein stores daily (or approximately 1.2 g protein loss per kilogram of body weight). Without exogenous protein intake, protein synthesis rates still remain high, but breakdown rates increase. ELBW infants are particularly vulnerable because nitrogen loss with glucose administration alone is greatest in the most immature infants and lessens significantly with increasing gestational age.

Nevertheless, it is common practice in many NICUs to provide intravenous glucose alone for several days and to limit protein administration to ELBW or sick neonates in the early neonatal period because of concerns that these fragile patients may not tolerate protein. Often this practice is based on data from adult studies in which a variety of stresses (surgical, traumatic, infectious) induce a catabolic response that is not ameliorated by protein administration. Whether this strategy is applicable to NICU patients is not clear. It is known that protein metabolism and accretion are influenced by a variety of factors, including protein intake (both quality and quantity), energy intake, underlying disease states, and medications.

In addition to preventing catabolism and promoting anabolism, early protein administration may have several other beneficial effects in the first days of life. These include decreasing the frequency and severity of neonatal hyperglycemia by stimulating endogenous insulin secretion and stimulating growth by enhancing the secretion of insulin and insulin-like growth factors.

PROTEIN QUANTITY AND QUALITY

Neonates are very efficient at using amino acids for protein accretion. If there are no superimposed catabolic influences, protein gain increases linearly with protein intakes over an intake range of approximately 0.5 to 4.0 g/kg per day. In general, 1.5 to 2.0 g/kg per day is sufficient to avoid catabolism and may result in a slightly positive protein balance in most neonates. Several studies have shown that the parenteral intake required to avoid catabolism in ELBW infants may be as low as 1.1 to 1.5 g/kg per day when administered concomitantly with 30 kcal/kg per day of energy. This latter intake should be considered the lower limit at which to start intravenous protein delivery.

In terms of the upper limits of protein intake, if the goal is to achieve intrauterine rates of protein deposition, 3.85 g/kg per day of protein intake have been estimated to cover protein accretion for ELBW infants weighing 700 to 1,000 g. This value may be slightly higher for infants who weigh less than 700 g.

The quality of dietary protein is defined by the content of its nutritionally essential amino acids. The term “essential” does not refer to the physiologic function of these amino acids; all amino acids have important metabolic roles. Rather, the essential amino acids are those that cannot be synthesized by the body in sufficient quantities to sustain protein synthesis or other critical body functions and, therefore, must be ingested through the diet. In the neonate, particularly the ELBW neonate, the traditional list of essential amino acids also includes a number that are considered “conditionally essential”. These are not made in sufficient quantities by the metabolically immature preterm neonate to meet body demands. In general, the higher the quantity of essential (and conditionally essential) amino acids in a protein, the greater its quality.

Many of the concerns about early administration of amino acids and toxicity arose from studies in the 1970s when the source of intravenous protein was casein hydrolysates. Administration of these com-

mercial amino acid solutions often led to acidosis and hyperammonemia, probably because the preparations were of suboptimal quality and resulted in poor utilization. Infant studies in the early 1980s demonstrated that nitrogen retention improved significantly with use of intravenous crystalline amino acid preparations. In the late 1980s, a parenteral mixture of crystalline amino acids for use in preterm infants was developed that was designed to produce plasma amino acid concentrations comparable to those of postprandial breastfed infants of the same gestational age. Trophamine™ (McGaw, Inc, Irvine, CA) improved nitrogen balance and resulted in normal blood urea nitrogen concentrations. Subsequently, several more “pediatric” TPN amino acid preparations have been developed and are in common use today. However, there still is no TPN amino acid mixture designed exclusively for the unique amino acid requirements of ELBW infants.

ENERGY INTAKE AND AMINO ACID METABOLISM

Energy is required for both protein metabolism and deposition. Not only are relative protein accretion rates higher in the ELBW infant, but protein synthesis and breakdown rates, both of which are energy-dependent processes, also are increased. Protein synthesis-to-gain ratios in ELBW infants may be as high as 5:1. Thus, with insufficient energy stores or energy delivery, protein accretion will be impaired.

It has been shown clearly in preterm infants that increasing energy intake raises the protein accretion rate up to a maximal energy intake of 100 to 120 kcal/kg per day. This relationship, however, is curvilinear, with most of the effect of energy on protein gain occurring at less than 50 to 60 kcal/kg per day. In contrast, increasing protein intake (up to an approximate maximum intake of 4.0 to 4.5 g/kg per day) leads to greater protein accretion at nearly all energy intakes above 30 to 50 kcal/kg per day. Such observations support the need for much higher protein intakes than these infants normally receive and indicate

that protein gain will be greatest with protein, not energy, intake. In the first days of life of the ELBW infant, when energy intolerance may be an issue, the minimum energy required to metabolize protein is not known. However, as noted previously, several studies have demonstrated that intake of 1.1 to 1.5 g/kg per day of amino acid at that time can prevent catabolism in parenterally fed ELBW infants who are receiving low energy intakes (30 kcal/kg per day). Most infants will tolerate an energy intake of 25 to 30 kcal/kg per day in the first several days of life.

In a study of short-term administration of full parenteral nutrition (90 kcal/kg per day of energy and 2.5 g/kg per day of protein) to ELBW and term infants in the first days of life, both groups were in a positive nitrogen balance, but this balance was significantly greater in term infants. Although rates of protein synthesis increased to the same degree in ELBW and term infants, rates of protein breakdown remained large in ELBW infants.

In the absence of protein intake, glucose is a more effective energy substrate in preventing protein breakdown than is fat. When amino acids are given, both glucose and lipid are known to be protein-sparing. Studies in older children and adults have shown the positive effect of both glucose and lipid on nitrogen retention. Although it has been known for more than 15 years that the amount and type of energy can affect protein balance in the parenterally fed neonate, controversy remains regarding the impact of the composition and amount of the energy source on protein metabolism. Optimal glucose/lipid intake ratios that maximize protein accretion are yet to be determined in the neonatal population, and it is likely this ratio will vary with gestational age, prior nutrition status, and particularly underlying disease state.

STRESS AND AMINO ACID METABOLISM

The neonatal stress response may differ from the adult response, but there is little information about how it affects protein metabolism in the

infant. In the adult stress response, increased catecholamine, cortisol, and glucagon concentrations are associated with a negative nitrogen balance. With vaginal delivery of term infants, catecholamine concentrations increase 10-fold but return to normal by 2 hours postdelivery. This catecholamine surge is increased markedly with perinatal hypoxia and complicated deliveries, but decreased with cesarean section delivery and in preterm infants. Assuming a relatively short duration of elevated catecholamine concentrations immediately after birth in stable infants, the effect of the perinatal surge in epinephrine and norepinephrine on protein balance is probably minimal. However, this may not be true in infants who have undergone significant perinatal asphyxia or who require dopamine and dobutamine infusions, conditions that have been shown to increase plasma concentrations of endogenous catecholamines significantly.

DRUG EFFECTS

With the exception of corticosteroids, there have been few investigations of the effects of specific medications on metabolism in the ELBW infant. A number of studies have reported decreased somatic growth during dexamethasone therapy for chronic lung disease, and it appears this is mediated by increasing protein catabolism.

Several drugs may have a positive effect on protein balance in ELBW infants. In adults, high-dose fentanyl anesthesia attenuates the stress response to surgery, with a resultant decreased catabolic response. Several investigations indicate this also is true in preterm infants.

The role of insulin on protein metabolism in the ELBW population is not clear. Insulin and insulin-like growth factors generally are considered to be the major fetal growth factors. In the adult, insulin is an anabolic hormone that acts primarily to decrease protein breakdown at both physiologic and pharmacologic concentrations. There are not sufficient data to draw firm conclusions about the possible anabolic role of

insulin in the neonate. In both term and preterm infants, a threefold increase of plasma insulin concentration as a result of glucose infusion had no effect on the rate of protein breakdown, although inhibition of protein breakdown may have been limited by the simultaneous decrease in plasma amino acid concentrations. In a study of ELBW infants receiving glucose alone, euglycemic hyperinsulinemia decreased both proteolysis and protein synthesis to the same degree, resulting in no net anabolic effect. However, this study did not address the potential anabolic effect in ELBW infants who are receiving amino acids. In neonatal animals, the independent effect of insulin (when glucose and amino acid concentrations are maintained at normal concentrations) is to increase utilization of amino acids.

These effects of insulin on protein metabolism fall under the category of metabolic effects. Another unexplored mechanism by which insulin might affect protein balance is via its mitogenic effects. There is evidence that insulin action leads to specific and significant changes in the cellular responses to other growth factors. Thus, insulin may modulate growth (and protein accretion) by amplifying the effects of other growth factors.

EARLY INTRODUCTION OF AMINO ACIDS

At least eight studies in VLBW infants have demonstrated that infusion of amino acids at intakes ranging from 1.0 to 2.2 g/kg per day in the first days of life decreases protein breakdown. Despite these results, there is still hesitation to follow this approach because of concerns that intolerance may produce hyperammonemia, azotemia, and metabolic acidosis. However, none of these studies demonstrated evidence for amino acid intolerance as determined by abnormalities in the appropriate laboratory assessments. Although these are the most common clinical indicators used, it is not known if these are the appropriate markers for assessing protein toxicity. If, as is seen in the fetus, amino acids can serve as a signifi-

cant energy source beyond the requirements for protein accretion in the ELBW infant, an elevated urea concentration may reflect acceptable production of an acceptable metabolic byproduct rather than protein intolerance.

PARENTERAL PROTEIN ADMINISTRATION STRATEGIES

Because recent studies show that early parenteral protein administration is well tolerated in many ELBW infants, amino acid nutrition should be initiated in the first day of life to avoid a catabolic state. The minimal protein intake to prevent protein catabolism is 1.0 to 1.5 g/kg per day in most infants, which appears to be well-tolerated. Protein deposition occurs at intakes above this rate.

The majority of stable ELBW infants can receive 2.0 g/kg per day in the first day of life. At the same time, energy intakes should be increased to 50 to 60 kcal/kg per day as quickly as possible using a combination of glucose and lipid (advanced until serum glucose and triglyceride concentrations exceed 120 mg/dL and 150 mg/dL, respectively). Ideally, this should be achieved by 24 to 48 hours of life. Thereafter, the rate of nutrient advancement is based on monitoring of substrate toxicity, with maximal target intakes optimally reached by the third to fourth postnatal day. Protein intake should be increased to 3.0 g/kg per day in term infants and 3.7 to 4.0 g/kg per day in ELBW infants to achieve in utero protein deposition rates, and simultaneous parenteral energy intake should increase to approximately 100 to 110 kcal/kg per day. This feeding schedule may need to be altered in infants who are critically ill, particularly if the infant has suffered significant hypoxia, has a suspected or proven infection, or is receiving high-dose corticosteroids.

Some experts have advocated even higher initial intakes, but these have not been evaluated prospectively. Further studies are needed to identify more sensitive markers for protein toxicity, to determine if early and higher amino acid intakes are safe and efficacious in these infants,

and to ascertain if early and aggressive protein intake affects long-term growth and development.

Glucose

Glucose is the primary energy substrate for the fetus and for the neonate in early life. The storage form of glucose is glycogen. This is a limited store in the ELBW infant because the fetus does not make glycogen until the third trimester. The 25- to 27-week gestation ELBW infant is born with approximately 200 kcal of energy stores, which is enough to supply energy needs for only 4 to 5 days. Glucose is particularly important as the primary energy source for central nervous system (CNS) energy requirements. Alternate substrates such as ketones have low concentrations in preterm infants because of low fat stores at early gestational ages. The ELBW infant has relatively high energy requirements because of the relatively large body proportions of metabolically active organs (heart, liver, kidney, and especially the brain). Thus, the ELBW infant requires a large and continuous source of glucose for energy metabolism.

MINIMAL GLUCOSE INTAKES

The minimal glucose requirement to provide basal metabolic needs for the ELBW infant can be estimated from endogenous glucose production in the stable infant who has sufficient glycogen stores (ie, approximately 6 mg/min per kilogram). This is a good estimate of the minimum supply rate necessary to maintain adequate energy for the brain. Glucose administration also is required to support protein deposition, and an additional requirement of 25 kcal/kg or about 2 to 3 mg/min per kilogram of glucose per gram of protein intake is necessary.

In practice, glucose administration often is limited in the first days of life by the development of hyperglycemia. Elevated glucose concentrations are common in the NICU, with a reported incidence of 20% to 85% in ELBW infants. This hyperglycemia frequently is attributed to both peripheral and hepatic insulin

resistance and to decreased insulin secretion. Insulin resistance generally is presumed to be due to increased secretion and plasma concentrations of glucagon, catecholamines, and cortisol.

Several strategies are used to manage this early hyperglycemia in ELBW infants: 1) decreasing glucose administration until hyperglycemia resolves (unless the hyperglycemia is so severe that this strategy would require infusion of a hypotonic solution); 2) administering intravenous amino acids, which decrease glucose concentrations in ELBW infants, presumably by enhancing endogenous insulin secretion; 3) initiating exogenous insulin therapy at rates to control hyperglycemia; and 4) using insulin to control hyperglycemia and to increase nutritional uptake. The first three strategies prevent adequate early nutrition, and the safety of the last has been questioned in this population because of the possible development of lactic acidemia.

Several studies have shown that insulin used as a nutritional adjuvant successfully lowers glucose concentrations and increases weight gain in preterm infants without significant risk of causing hypoglycemia. However, little is known about its effects on the quality of weight gain and counterregulatory hormone concentrations. A recent study in which the effect of insulin was examined using a hyperinsulinemic-euglycemic clamp in ELBW infants receiving only glucose who were normoglycemic prior to the initiation of insulin demonstrated a significant elevation in plasma lactate concentrations and the development of significant metabolic acidosis. Although this experimental approach does not replicate the common clinical use of insulin, it does raise safety issues regarding the use of insulin in ELBW infants.

MAXIMAL GLUCOSE INTAKE

The upper limit of glucose delivery should be less than the maximal glucose oxidative capacity. Administration rates above this level result in glucose being delivered in excess of the body's energy needs, and the excess glucose is converted to fat. Glucose conversion to fat is an

energy-inefficient process that results in increased energy expenditure, increased oxygen consumption, and increased carbon dioxide production. The rate of glucose administration that exceeds the maximal glucose oxidative capacity is not known definitively in neonates, but it appears to be approximately 12 to 13 mg/kg per minute (18 g/kg per day). The rate may be lower if lipid is administered concomitantly. Unfortunately, there is no good clinical means to determine if this capacity has been exceeded. The best guidelines are to maintain a high index of suspicion when glucose intake reaches 12 to 13 mg/kg per minute and to monitor for evidence of carbon dioxide retention.

GLUCOSE ADMINISTRATION STRATEGIES

Initial intravenous glucose infusion rates of approximately 6 mg/min per kilogram usually are well-tolerated, and as long as hyperglycemia does not develop, the infusion rate can be advanced over a period of several days to 10 to 12 mg/min per kilogram. If hyperglycemia occurs at glucose infusion rates less than 3 to 4 mg/min per kilogram, insulin can be infused at 0.05 to 0.1 U/kg per hour. The infusion rate then is adjusted based on frequent measurements of plasma glucose concentration to achieve and maintain concentrations between 80 and 120 mg/dL.

Lipid

The ELBW infant is particularly vulnerable to insufficient lipid supply because significant in utero fat accretion does not occur until the third trimester. In the early neonatal period, intravenous lipid is administered to the ELBW infant to prevent essential fatty acid (EFA) deficiency and to serve as an energy substrate. Unfortunately, intravenous fat delivery may be impeded in this population by both an immaturity of mechanisms for fat metabolism and by a number of clinical conditions (eg, infection, surgical stress, malnutrition) that inhibit lipid clearance. Of the major intravenous substrates, lipid is the most controversial in

terms of optimal intakes and potential side effects.

MINIMAL LIPID INTAKE

Minimal intravenous lipid intakes should be targeted to prevent EFA deficiency and to cover metabolic energy costs if intake from other energy substrates is insufficient. Avoiding a deficiency of linoleic and linolenic acids is imperative, especially in view of their critical role in postnatal brain development. In ELBW infants, particularly under conditions of low energy intake where fat may be oxidized to cover energy needs, EFA deficiency can develop within 72 hours if exogenous fat is not administered. EFA deficiency can be prevented with as little as 0.5 to 1.0 g/kg per day of intravenous lipid.

MAXIMAL LIPID INTAKE

Maximal intravenous lipid intake in ELBW infants is limited by an inability to clear the plasma of lipid. Clinical, theoretical, or potential lipid toxicities also affect lipid administration. Infrequently, an upper limit of intake is based on concerns of excessive fat accretion. The AAP Committee on Nutrition has recommended maximal intravenous lipid infusion rates of 0.25 g/kg per hour. However, these recommendations were made in 1985, referred to the low-birthweight (not ELBW) infant receiving 10% intravenous lipid preparations, and were proposed only as a guide to avoid hyperlipemia. A 24-hour intake rate of 0.25 g/kg per hour is equivalent to an intake of 6 g/kg per day, an amount that rarely is used clinically. Minimal intake is fairly well defined as that which prevents EFA deficiency, but ideal upper limits are very controversial. This has resulted in very different lipid administration strategies in NICUs. A number of sources recommend a gradual intake of intravenous lipid to a maximal intake of 3.0 g/kg per day.

Recommendations for maximal plasma triglyceride concentrations range from less than 150 mg/dL to 200 mg/dL. The use of 20% rather than 10% lipid emulsions is recommended because the higher phos-

pholipid content of 10% emulsions interferes with plasma triglyceride clearance, resulting in higher triglyceride and plasma cholesterol concentrations.

Plasma clearance of intravenously administered lipid depends on the activity of lipoprotein lipase, hepatic lipase, and lecithin cholesterol acyltransferase. The activities of these enzymes decrease with decreasing gestational age. Lipoprotein lipase activity is particularly low in infants younger than 26 weeks' gestation. These lipases are the major enzymes for clearance of lipoprotein triglyceride, and their activities can be induced with administration of low-dose heparin. Plasma triglyceride concentrations provide a reasonable guide to lipid clearance rate and need to be monitored closely in more immature infants.

Most ELBW infants receiving intravenous lipid have central venous access and already are receiving heparin to prevent central catheter thromboses. However, heparin administration should be considered in infants younger than 26 weeks' gestation and in ELBW infants who demonstrate lipid intolerance, even those receiving TPN via peripheral vein. Intravenous lipid has a relatively low osmolality, is well tolerated by peripheral vein, and actually can help to maintain venous patency.

Lipid clearance is correlated with the hourly rate of infusion and is maximized when a specific daily volume of lipid is infused over 24 hours. Patients receiving chronic TPN often receive a "lipid rest" for several hours each day to prevent hepatic toxicity, but this is not necessary for the relatively short periods of TPN administration required by most NICU patients. There is no evidence to support the common practice of gradually increasing the daily lipid intake to induce further lipid clearance.

POTENTIAL COMPLICATIONS AND TOXICITIES

Early administration and rapid advancement of lipid emulsions in the preterm infant require caution because of a variety of potential complications and toxicities. These

include lipid intolerance, increased free bilirubin concentrations, impaired pulmonary function or increased risk for developing chronic lung disease, and interference with immune and platelet function.

Intravenous lipids are broken down to free fatty acids, and accumulated free fatty acids can displace bilirubin from albumin. Studies in VLBW and ELBW infants suggest that bilirubin displacement from albumin is not common at infusion rates less than 3.25 g/kg per day. Infusion rates should be increased cautiously in ELBW infants who have moderate-to-high bilirubin levels, low serum albumin concentrations, or conditions that might increase bilirubin toxicity, such as marked acidosis.

Currently, the greatest controversy regarding lipid administration in neonates revolves around concerns of possible lipid-related pulmonary dysfunction, including decreased oxygenation and increased pulmonary vascular resistance. Although this area requires further investigation, it appears that lipid infusions may be administered safely to most infants at infusion rates of 0.2 g/kg per hour or less.

LIPID ADMINISTRATION STRATEGIES

Minimal intake for all infants should be 0.5 g/kg per day beginning on the first day of life. In the majority of stable ELBW infants, lipid can be started at 1.0 to 1.5 g/kg per day, with the lower level indicated for the most immature infants. The infusion rate can be increased by 0.25 to 0.5 g/kg per day up to a maximum of 3.0 g/kg per day when employing lipid intake as an energy source. It is unclear what the ideal intake is in terms of body composition, particularly in the very preterm infant. Intakes above 3.0 g/kg per day can be administered if there are excessive energy requirements or in certain cases of growth failure despite adequate protein and energy intakes.

Triglyceride concentrations should be monitored at each incremental change, particularly if the previous concentration was elevated. Serum triglyceride concentrations

are maintained at 150 mg/dL or less. If the infant is septic, critically ill, has severe respiratory disease, or is approaching bilirubin levels that may require exchange transfusion, lipid intake can be held at 0.5 g/kg per day. Incremental changes in triglyceride concentrations may be important in these infants.

Intravenous heparin is administered to ELBW infants receiving intravenous lipid to enhance lipid metabolism, particularly if the infant is intolerant of higher lipid intakes. Heparin should be used even if TPN is administered by peripheral vein. Total lipid dose for 24 hours should be spread out over the entire 24-hour period.

Minimal Enteral Nutrition (MEN)

Early initiation of MEN is advocated as a supplement to parenteral nutrition in the NICU population. There is no well-established definition for MEN, but it generally refers to enteral feeding of formula, human milk, or both at intakes of 5 to 25 mL/kg per day. Some studies suggest that physiologic benefits occur at volumes as low as less than 1 mL/kg per day. Such volumes are referred to as "priming" feedings because of their role in stimulating many aspects of gut function.

In the 1960s and 1970s, the introduction of gavage feedings allowed for full enteral nutrition in the preterm infant. However, because of very rapid advancement of feeding by this route, a significant number of very preterm infants developed NEC with enteral feedings. This, in combination with the development of complete parenteral nutrition for this age group, led to the common practice of withholding enteral nutrition in preterm infants for the first several weeks of life. Subsequent concerns over TPN toxicity as well as a growing recognition of the importance of enteral feedings in stimulating growth and development of the gastrointestinal tract prompted a number of studies that have demonstrated the benefits and safety of early MEN as a supplement to parenteral nutrition.

SAFETY

Promoting wider use of early MEN required documentation of its safety and specifically that it did not increase the incidence of NEC because most infants who develop NEC have received some enteral feedings. Two studies in the mid-1980s provided good evidence that MEN did not increase the incidence of NEC. One investigation hypothesized that delayed oral feedings would lower the incidence of NEC in "sick" infants at risk for this complication who weighed less than 1,500 g at birth. In a prospective, randomized study in preterm infants whose birthweights ranging from 680 to 1,440 g, one group was given MEN starting in the first week of life and the other group received TPN only for the first 2 weeks of life. Contrary to the original hypothesis, the incidence of NEC was significantly lower in the MEN group. In a second study, "sick" infants whose birthweights ranged from 640 to 1,000 g were randomized prospectively to enteral feedings starting on the first versus the seventh day of life. Those who were fed enterally were started on 1 mL/hr and gradually advanced to full feeds by day 7 of life. There were no differences in the incidence of NEC between the groups.

EFFICACY

Four subsequent prospective, randomized trials demonstrated the efficacy of MEN. Although volume of feedings, day of initiation of feedings, caloric density, and rate of advancement varied, all studies demonstrated the beneficial effects of MEN and no obvious detrimental effects. These advantages of MEN included: shorter time to full enteral feedings, less time under phototherapy, a lower incidence of direct hyperbilirubinemia, smaller gastric residuals and less feeding intolerance, the same or faster weight gain, and no increased incidence of NEC.

PHYSIOLOGIC EFFECTS

Physiologic data also were accumulating regarding the variety of mechanisms by which MEN exerts its benefits. Most of these studies used human milk as the type of feeding,

and it is less clear to what extent formulas exert comparable effects as those described below.

It had long been known that starvation quickly induces atrophy of the gastrointestinal tract, but more recent studies in human and animal neonates have demonstrated the positive direct and indirect trophic effects of MEN, even when administered for brief periods of time. Direct contact of the gut tissue with human milk increases intestinal mass and enhances DNA synthesis rates. The majority of the direct trophic effects induced by human milk appear to be mediated by growth factors, such as epidermal growth factor, trophic peptides, and insulin. Trophic hormones and peptides that are released in response to the presence of intraluminal nutrients mediate indirect trophic effects of enteral feedings. They can have potent trophic effects on the gastrointestinal mucosa and include substances such as gastrin, cholecystokinin, enteroglucagon, motilin, neurotensin, and gastric inhibitory peptide. These gastrointestinal hormones and peptides are released by 20 weeks' gestation, with fasting plasma concentrations of many of these substances being similar in term and preterm infants. Even very preterm infants can increase the level of these hormones and peptides in response to feeding, and plasma concentrations of the hormones are decreased in the absence of enteral feedings in preterm infants. The decreasing concentrations can be reversed with enteral feeding volumes of as little as 0.1 mL/kg per day. In addition to their direct trophic action on the gut mucosa, most of these substances have complex and vital roles in other aspects of gastrointestinal tract function, such as nutrient absorption and digestion.

Using manometric techniques, it has been shown that early enteral feeding enhances maturation of the motor responses of the small intestine of the preterm infant compared with infants receiving exclusively parenteral nutrition. MEN has a positive influence on both mixing and churning of intestinal contents as well as on forward propulsion of enteral feedings. Moreover, maturation of the gastrointestinal tract

motor activity in response to feedings occurs when the intake is as little as 4 mL/kg per day and is enhanced when full-strength rather than dilute formula or sterile water is used.

CONTRAINDICATIONS

No prospective studies have investigated specific contraindications to MEN, but common understanding of normal transitional physiology and clinical conditions associated with the gut suggest situations under which MEN might be withheld or at least not advanced. In the adult, resistance of the splanchnic vascular bed decreases postfeeding, which results in increased intestinal blood flow and oxygen uptake. In healthy term infants, superior mesenteric artery blood flow gradually increases over the first 72 hours of life, and the increase in blood flow in response to feeding is well-established by the third day of life. Comparable information is not available in the very preterm or sick neonate. Any condition that is known to decrease gut blood flow is a contraindication to enteral feeding, including gut hypoxia (eg, after a significant asphyxial episode or associated with ongoing hypoxemia), decreased intestinal blood flow (eg, as in hypotension), diastolic intestinal blood flow “steal” due to a patent ductus arteriosus, or transient decreased superior mesenteric artery blood flow caused by rapid bolus indomethacin therapy.

INITIATING MEN

Data are not sufficient to determine if a minimal enteral feeding that is sufficient in volume to prime the gut but not designed to provide nutritional support is safe to administer to a sick infant. A single prospective study has examined MEN (1 mL/kg per hour) plus TPN starting at 24 hours of life versus exclusive parenteral nutrition in infants who had severe respiratory distress syndrome and weighed approximately 1,000 g at birth. Infants were excluded if they had hypoxemia, respiratory acidosis, severe asphyxia, or hypotension. Despite a relatively brief period of MEN, infants in the early feeding group had a compara-

ble number of episodes of feeding intolerance, took less time to reach full feeds, and had better weight gain at 30 days of age, even though caloric intake was equivalent from days 6 to 30 of life. Additionally, two infants in the parenteral nutrition-only group developed clinical NEC. Although the number of patients enrolled was small, this study suggests that MEN can be started as early as the first day of life in relatively ill, very preterm infants.

It is customary to withhold enteral feeds from severely asphyxiated infants for 48 hours, from all infants during hypoxemia and hypotension, and from those who have a symptomatic patent ductus arteriosus. All enteral nutrition is discontinued in infants who are being evaluated for NEC and in the first 4 to 5 days after diagnosis of significant medical or surgical NEC. MEN may be considered in most other infants. Frequently, extremely small volumes (often as little as 0.1 to 1.0 mL/kg one to four times a day) are initiated, and the volume is not advanced until an infant is clinically very stable. Clearly, these infants are monitored very closely for feeding intolerance, although such monitoring may be difficult at this small volume. Infants in whom we use “MEN without advance” include the majority of ELBW infants beginning the first day of life, after the acute phase of NEC but long before feedings are started for nutritional support, and infants who have stable blood pressure on low-dose pressor support.

In these cases, human milk is the feeding of choice, particularly based on its positive physiologic effects. If human milk is not available, few data support the next enteral feeding choice. In neonatal animal studies, intraluminal protein or lipid increased intestinal oxygen consumption, but glucose did not, suggesting that it was a metabolically less stressful nutrient. The individual efficacy of these three nutrients on priming the gut is unknown, but in a borderline neonate, decreasing the caloric density of administered formula might be advisable in theory.

FEEDING ADVANCES IN THE FIRST WEEK OF LIFE

Clearly, the goal of enteral nutrition in the NICU population is to achieve enteral feedings as quickly as possible without increasing the risk for developing NEC. Sufficient data indicate that human milk feedings are associated with a lower incidence of NEC than commercial formula, making it the nutrition of choice. For very sick or preterm infants, we maintain MEN without advance until the infant is stable. A variety of retrospective and prospective studies cumulatively suggest that volume advances of 15 to 20 mL/kg per day or less of nonhypersmolar feedings do not increase the risk of NEC. There is no clear evidence that dilute formula is protective against the development of NEC, and as noted previously, dilute formulas slow the maturation of the gastrointestinal tract motor responses to feeding when compared with full-strength formula. Therefore, we increase human milk by 20 kcal/oz or formula by 15 to 20 mL/kg per day until full-volume feedings are achieved. Caloric density then may be advanced as needed and tolerated.

A number of issues need to be resolved before optimal recommendations can be made for MEN, including minimal effective volumes to elicit various physiologic responses and safety and efficacy in critically ill infants. However, it has been demonstrated that compared with late enteral feedings, MEN does not increase (and may lessen) the incidence of NEC, shortens the time to full enteral feedings, improves weight gain, produces fewer episodes of feeding intolerance, and has beneficial effects on hyperbilirubinemia and cholestatic jaundice. MEN generates intestinal trophic effects, enhances hormonal and peptide responses, and induces more rapid maturation of gastrointestinal tract motor responses. It also appears to have minimal detrimental effects and significant advantages compared with exclusive TPN in terms of gastrointestinal tract maturation and parenteral nutrient toxicities, even in the ELBW infant.

Potential Benefits of Early Aggressive Nutrition

In humans, the most critical developmental period of brain growth and function occurs during the last trimester of pregnancy and the first 2 years of postnatal life. Both human and animal investigations suggest that malnutrition in the late prenatal and early postnatal period may have long-term developmental consequences. The influence of early diet on later development has been investigated primarily in nonhuman species. Although results have been somewhat inconsistent, both prenatal and early postnatal malnutrition in rats have demonstrated permanent effects on brain structure and function, including a significant loss of brain cell number at autopsy, a brain weight deficit that usually remains after nutritional rehabilitation, and impaired learning performance. These abnormalities are more common in males. The effects of nutritional deprivation are more difficult to reverse in rats if the insult occurs prenatally rather than postnatally. However, it is not known if these findings can be extrapolated to human outcomes.

Most human epidemiologic studies of the impact of early inadequate nutrition on long-term developmental outcome have been performed in economically deprived populations where it has been difficult to distinguish the independent effect of malnutrition from other sociologic factors that might affect outcome.

More recent studies have provided intriguing evidence that even very short-term nutritional strategies instituted very early in life may have a lifelong impact on both mental and motor outcomes. Investigators randomized 926 preterm infants weighing less than 1,850 g at birth (mean birthweight, approximately 1,400 g) to one of two simultaneous dietary trials for the first month of life. The "sole diet" trial compared feeding a standard "term" infant formula with a "preterm" formula that was comparable to currently available commercial formulas designed for use in preterm infants. The preterm formula contained

increased quantity (but not quality) of protein and fat compared with the term formula plus enrichment with sodium, calcium, phosphorus, copper, zinc, and vitamins D, E, and K. The "human milk supplement" trial randomized infants either to term or preterm formula supplemented with human milk. Analysis controlled for a number of medical and socioeconomic factors that might influence outcome. Follow-up data at 18 months of age of the 377 surviving infants in the "sole diet" trial demonstrated that those who had received preterm rather than term formula had "major developmental advantages, more so in motor than mental function." This was particularly evident in small-for-gestational-age (SGA) and male infants. Similarly, developmental scores were significantly higher at 18 months in children who received their own mother's milk.

Although these results are intriguing, developmental status at 18 months does not necessarily predict long-term developmental outcome. Results now have been published of study outcome at 7.5 to 8 years of age, an age at which assessment is likely to correlate with long-term cognitive function. Among 300 children undergoing intelligence quotient (IQ) testing, those who had received human milk in the first weeks of life had significantly higher scores than those who had consumed no maternal milk, even when adjusted for maternal social and educational status. Additionally, there was a dose-dependent correlation between quantity of human milk consumed and IQ score. Of the 360 "sole diet" infants followed up at 7.5 to 8 years of age, those who had received term formula had significantly lower verbal IQ scores than those who received preterm formula, and this difference was most pronounced in males. There also was a higher incidence of cerebral palsy in the term formula group. This was the first human study to demonstrate that even a brief nutritional intervention at a period of critical brain development could demonstrate a long-term developmental effect.

Cost Implications of Early Aggressive Nutrition

Numerous studies have demonstrated that a shorter time to maximal nutritional intake (either enteral, parenteral, or a combination of the two) decreases the duration of hospitalization. MEN lessens the time to full enteral feedings, may decrease the incidence of NEC, and decreases the length of hospital stay. Whether other specific nutritional interventions decrease the incidence of certain morbidities, thereby affecting hospitalization-associated health-care costs, is not clear.

Potential Long-term Detriments of Early Aggressive Nutrition

The majority of nutrition management decisions in neonatology are based on very short-term outcomes because with today's mobile population, long-term outcome studies of early nutritional therapies are difficult to conduct. Additionally, the hospital courses of sick neonates are compounded by so many therapeutic and medical interventions that isolating the effect of a single variable is extremely difficult. Further, few acute clinical tests can indicate if a specific dietary intervention in preterm infants will be associated with a specific long-term outcome. For example, acute protein toxicity that may produce long-term cognitive deficits may be determined best by concentrations of amino acids in CNS tissue (which cannot be measured in human infants), not by blood urea nitrogen or ammonia concentrations.

Most long-term outcome studies in neonates investigate physical and neurologic development. More recently, attention has focused on an increasing body of human epidemiologic and animal experimental investigations that suggest early nutrition may influence susceptibility to chronic diseases in adult life. Numerous human population studies have shown that low birthweight or being asymmetrically SGA at birth predisposes an individual to type 2 diabetes, hyperlipidemia, hypertension, and ischemic heart disease as an adult. A few studies also suggest

that catch-up growth may be an independent risk factor for these disorders. It must be concluded that the potential long-term detriments of early aggressive nutrition are unknown.

Evidence for Current Feeding Practices in NICUs Contributing to Growth Failure

Many ELBW infants are also born SGA. There is growing evidence that both ELBW appropriate size-for-gestational age and ELBW SGA infants acquire a relative growth deficit over the first several weeks of life. Ziegler refers to the practice of withholding protein and energy intake while the ELBW neonate is considered unstable as creating “qualitative malnutrition.”

The most compelling evidence that current nutritional strategies

produce acute growth failure and contribute to a persistent growth delay comes from a recently published large, prospective, multicenter cohort study conducted by the NICHD Neonatal Research Network. The goal of this study was to determine longitudinal growth in VLBW infants (<1,500 g at birth) and to construct postnatal growth curves from this information that could be related to nutritional practices and specific morbidities. Data were collected until the infant weighed 2,000 g, reached 120 days of age, or was discharged, transferred, or died. Infants were placed in 100-g weight cohorts. Among the smallest ELBW infants (501 to 600 g), 53% were SGA. The Figure demonstrates the differences between normal intrauterine growth according to the reference data of Alexander et al and the observed rates of postnatal growth in the NICHD study. For

each gestational age category, the postnatal study growth curve was shifted to the right of the reference curve. It is clear that many of the ELBW infants developed “growth deficiency” during the study. There were no uniformly prescribed feeding schedules, and it is presumed that nutritional practices at these institutions reflected a representative sample of currently acceptable feeding strategies. For infants 501 to 800 g at birth, the approximate mean age at first enteral feeding was 8 to 9 days, with full enteral feeding not achieved until 1 month of age.

The Table provides a rough estimation of the cumulative protein and energy balances over the first 5 days of life based on four theoretical feeding regimens in an infant weighing 1 kg at birth. Protein balance is calculated from protein intake minus an estimated 130 mg/kg per day of nitrogen loss.

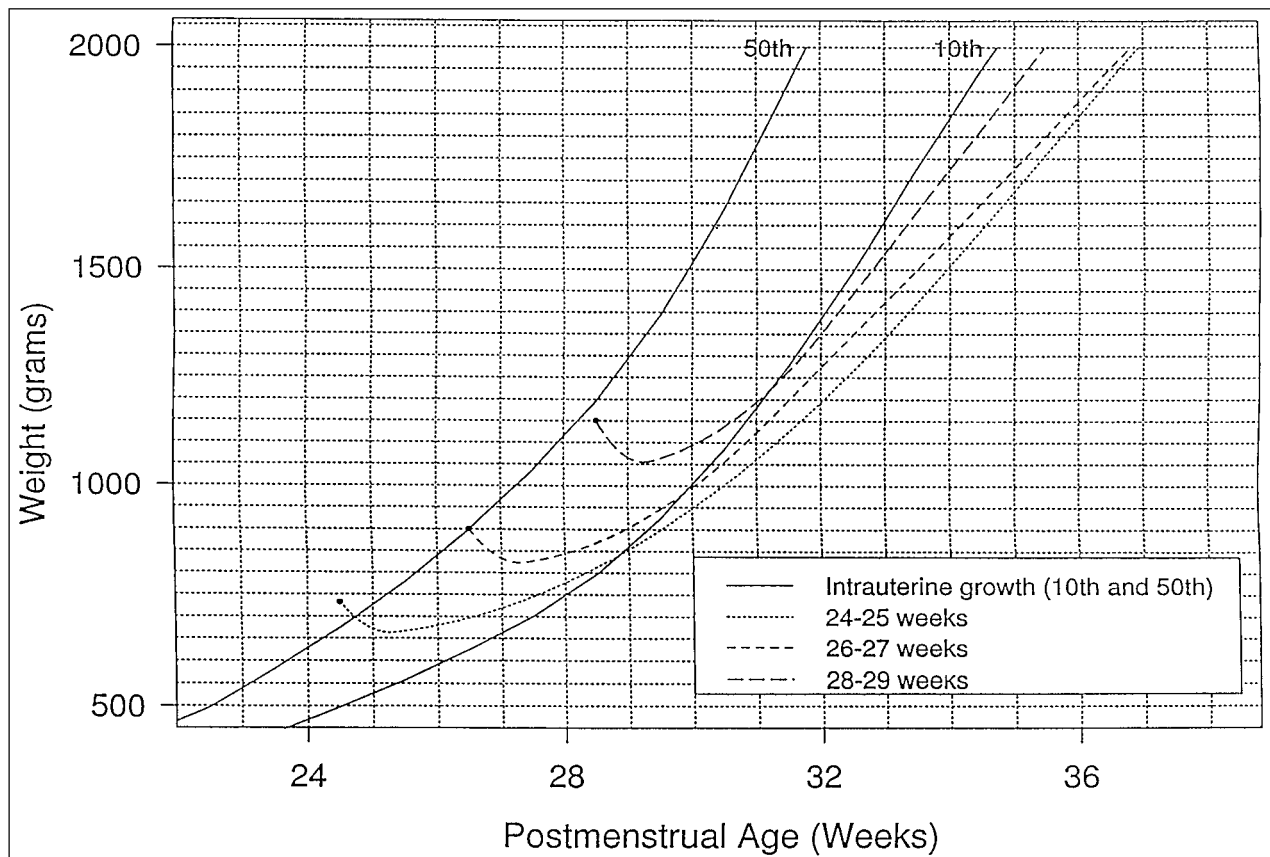


FIGURE. Mean body weight versus gestational age in weeks for all study infants who had gestational ages at birth between 24 and 29 weeks. Reproduced with permission from Ehrenkranz R, Younes N, Lemons J, et al. Longitudinal growth of hospitalized very low birthweight infants. *Pediatrics*. 1999;104:280–289. Reference intrauterine growth curves represent the 10th and 50th percentile birthweight data reported by Alexander et al. (Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol*. 1996;87:163–168.)

TABLE 1. Estimated Protein and Energy Balance Over the First Five Days of Life Using Different Nutrient Regimens in a 1 kg Infant

DAY	GLUCOSE INTAKE (g/dL)	FLUID INTAKE (mL/kg/d)	PROTEIN INTAKE (g/kg/d)	LIPID INTAKE (g/kg/d)	NONPROTEIN ENERGY INTAKE (kcal/kg/d)	CUMULATIVE PROTEIN BALANCE* (g/kg)	CUMULATIVE ENERGY BALANCE* (kcal/kg)
Regimen 1							
1	10	80	0	0	27.2	-0.81	-12.8
2	10	100	0	0	34.0	-1.63	-18.8
3	10	120	0	0	40.8	-2.44	-18.0
4	10	140	0	0	47.6	-3.25	-10.4
5	10	150	0	0	51.0	-4.06	0.6
Regimen 2							
1	10	80	0	0	27.2	-0.81	-12.8
2	10	100	0	0	34.0	-1.63	-18.8
3	10	120	0.5	0	40.8	-1.94	-18.0
4	10	140	1	0	47.6	-1.75	-12.3
5	10	150	1.5	0.5	56.0	-1.06	-3.2
Regimen 3							
1	10	80	0.5	0	27.2	-0.31	-12.8
2	10	100	1	0	34.0	-0.13	-20.7
3	10	120	1.5	0.5	45.8	0.56	-21.8
4	10	140	2	1	57.6	1.75	-16.0
5	10	150	2.5	1.25	63.5	3.44	-9.4
Regimen 4							
1	10	80	2	1	37.2	1.19	-14.7
2	10	100	2	1.5	49.0	2.38	-17.6
3	10	120	2.5	1.5	55.8	4.06	-18.6
4	10	140	2.5	2	67.6	5.75	-7.9
5	10	150	3	2	71.0	7.94	1.2

*Cumulative protein and energy balances are determined by summing the net balance on a specific day and the net balances on all preceding days of the regimen.

The in utero rate of protein deposition in a 1 kg infant is approximately 2 g/kg per day, making the expected in utero cumulative protein balance over 5 days approximately 10 g/kg. Energy balance is the difference between nonprotein energy intake and energy expenditure, and in this instance energy expenditure is calculated as a fixed 40 kcal/kg per day resting energy expenditure plus 10 kcal/kg per day expended for each gram of protein accretion. In general, energy balance should be zero if glucose is the sole energy source and positive if sufficient lipid is delivered to result in fat deposition.

In Regimen 1, protein is not given over the first 5 days of life. This could be due to infant instability or to the intentional decision to withhold protein over this period, which is practiced in some NICUs.

By the fifth day of life, the infant experiences significant catabolism. Note that if glucose intake had been only D₅W because of hyperglycemia, the infant also would have been in a significantly negative energy balance (approximately 100 kcal/kg). Both Regimens 1 and 2 would result in an EFA deficiency by the fifth day of life. Although Regimens 3 and 4 would have resulted in a positive cumulative nitrogen balance, they still lag behind the estimated in utero protein accretion rate.

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Early Aggressive Nutrition in the Neonate

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