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## Aggressive nutritional support and nutritional adjuncts for premature and critically ill neonates

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### INTRODUCTION

Advances in obstetrics and neonatal intensive care have resulted in a marked increase in the number of very immature and other critically ill infants who survive. Nutrition is becoming a key factor not only for the growth of these infants during their hospital stay but also for life-long well being. The major goal of this review is to provide the reader with an overview of a few recent advances in nutrition that can be applied in the daily care of these patients. In addition, a few emerging concepts about conditionally essential amino acids, long chain polyunsaturated fatty acids and probiotics are presented that are likely to become important modalities in future care of these infants.

### GLUCOSE AND CARBOHYDRATES

Both hyper and hypo-glycemia are common problems in very low birth weight (VLBW) infants. Glucose utilization and production rates in VLBW average from 6-10 mg·kg<sup>-1</sup>·min<sup>-1</sup>[1]. Fetal plasma glucose levels over the second half of gestation are usually greater than 50-55 mg/dL[2]. A 50-55 mg/dL glucose concentration range should be the lower limit for VLBW preterm infants. Because of its critical role in brain metabolism, glucose infusions should start immediately.

### AMINO ACIDS AND PROTEIN

Growth cannot be attained without protein or amino acids. The growth rate of lean body mass of the normally growing human fetus is about 3.6-4.8 g·kg<sup>-1</sup>·d<sup>-1</sup>[13,14]. This is greater than the amount of amino acid or protein intake that these infants usually are fed[3]. With current human milk or formula feeding regimens, it is practically impossible to achieve intakes that are

necessary to achieve and maintain the desired rates of protein intake[3]. This becomes especially critical in sick VLBW infants. If they receive glucose alone, they lose in excess of 1.2 g·kg<sup>-1</sup>·d<sup>-1</sup> of endogenous protein[4]. Unfortunately, many VLBW infants do not receive adequate amino acid or protein intakes during their first several days and weeks of life, thus assuring the development of a catabolic state.

There is a tendency to begin parenteral amino acid intake at only 0.5 g·kg<sup>-1</sup>·d<sup>-1</sup> or less, gradually achieving an intake of 2.5-3.0 g·kg<sup>-1</sup>·d<sup>-1</sup> over a period of 7 to 10 d to avoid protein "intolerance and toxicity." This practice should become obsolete because of recent studies demonstrating that intakes up to 2.9 g·kg<sup>-1</sup>·d<sup>-1</sup> revealed little evidence of complications[5].

### LIPIDS

Lipid requirements are limited to the essential fatty acids (linoleic or linolenic acid). The frequent practice of limiting enteral intake precludes the supply of these essential fatty acids, unless they are provided intravenously. Parenteral lipid emulsions provide these essential fatty acids but their use is often delayed or limited by concerns of adverse effects. Failure to provide essential fatty acids in the ELBW infant results in biochemical signs of deficiency within 72 h[6]. This can be prevented by the administration of as little as 0.5 g·kg<sup>-1</sup>·d<sup>-1</sup> of lipid emulsions. Although these emulsions contain high concentrations of linoleic and linolenic acid, they do not contain the long chain polyunsaturated fatty acids (LC-PUFAs), arachidonic (AA) or docosahexaenoic acid (DHA). These are thought to be critical nutrients for the developing central nervous system.

### ENTERAL FEEDINGS

How quickly should enteral feedings be advanced? Clinical judgement based on available scientific data and experience presently appear to be the best criteria upon which we should base our feeding practices. From the available studies, minimal enteral feedings should be instituted within the first days of life.

The following table summarizes a rational nutritional approach to VLBW infants.

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#### ENTERAL INTAKE

-Begin as soon as possible (day 1 of life, eg) with minimal enteral nutrition while infants are receiving most of their nutrition by the parenteral route.

-Breast milk—preferably from infant's own mother, or premature formula.

-Advance enteral intake as TPN is being decreased.

#### PARENTERAL INTAKE

-Begin glucose infusion immediately after birth at 4-8 mg·kg<sup>-1</sup>·min<sup>-1</sup>.

-Begin amino acid infusion at 2.5-3.0 g·kg<sup>-1</sup>·d<sup>-1</sup> on day one of life.

-Begin intravenous lipids at less than 0.2 g·kg<sup>-1</sup>·h<sup>-1</sup> infusion but greater than 0.5 g·kg<sup>-1</sup>·d<sup>-1</sup> within the first 1-2 d of life.

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#### NUTRITIONAL SUPPLEMENTS

The intestine is a primary origin of the systemic inflammatory response syndrome (SIRS) and is the largest immune organ of the body. It is therefore reasonable that nutritional agents might stabilize the intestinal mucosal barrier, alter the balance of pro- and anti-inflammatory cytokines, and prevent excessive activation of nuclear factor kappa B (NF-κB), a transcription factor that is thought to play a major role in the production of pro-inflammatory mediators.

Some nutrients such as glutamine, arginine, omega-3 fatty acids, and probiotics have been shown to influence intestinal barrier function and immune system.

**Glutamine** Even when high quantities of amino acid or protein are provided, an inadequate intake of certain "conditionally essential" amino acids may exist. Examples of these include glutamine, arginine, glycine, histidine, taurine, and tyrosine. If these are not provided, essential amino acids are diverted away from protein synthesis. One such amino acid that has recently received increasing attention is glutamine. Supplementation in adults has resulted in improved survival; decreased hospital acquired sepsis in bone marrow transplant and trauma patients along with improved nitrogen

balance and decreased costs of hospitalization<sup>[7]</sup>. One study of parenteral glutamine supplementation has shown decreased requirement for mechanical ventilation in neonates with a birthweight less than 800 grams<sup>[8]</sup>. Another study of enteral glutamine supplementation has suggested decreased hospital acquired sepsis, decreased catabolism and/or improved amino acid utilization, improved tolerance to enteral feedings, decreased cost of hospitalization and appeared safe at the doses used<sup>[9]</sup>. In a study of a rat model of endotoxemia, Wischmeyer *et al*<sup>[10]</sup> found glutamine reduced pro-inflammatory cytokine release, organ damage, and mortality. In another study, nine fasted volunteers received either glutamine or saline orally over 6 h. Duodenal biopsies were taken and cultured for 24 h with or without glutamine. This study demonstrated that glutamine pretreatment in vivo and in vitro significantly decreased production of pro-inflammatory cytokines (IL-6 and IL-8) by the human intestinal mucosa<sup>[11]</sup>. Preliminary studies in Caco-2 cells by our group demonstrated that glutamine decreases IL-8 production after LPS stimulation (unpublished results). These studies support the hypothesis that some of glutamine's beneficial effects may be a result of improved gut integrity or immune function and that glutamine could be used to regulate the intestine-mediated inflammatory response.

**Arginine** Another amino acid that some consider as either essential or conditionally essential in the neonate is arginine. This amino acid plays a critical role in immune function, as a stimulant to the production of growth hormone and as a precursor to energy carriers such as creatine. As a precursor for the synthesis of nitric oxide (NO), creatine, polyamines, urea, ornithine, proline, glutamate, and other molecules with enormous biologic importance, and as a stimulant to the production of growth hormone, *L*-arginine plays versatile key roles in nutrition and metabolism<sup>[12]</sup>.

The plasma and intracellular concentration of arginine may be critical not only for tissue growth but also for normal physiological function. It has been shown that premature infants who subsequently developed NEC had a significantly lower plasma concentration of arginine<sup>[13]</sup>. These may due to an increased metabolic demand for arginine or limited endogenous synthesis. One study in VLBW infants demonstrated lower incidence of NEC in arginine supplemented infants<sup>[14]</sup>.

**Probiotics** Probiotics are defined as live microbial food supplements that beneficially affects the host animal by improving its intestinal microbial balance. Probiotics work through a variety of mechanisms to produce several positive clinical effects. Their attachment to the intestinal epithelium can strengthen the host's mucosal defenses through enhancement of secretory

antibody responses, through a tightening of the mucosal physical barrier to microorganism translocation, and by a balance in T helper cell response<sup>[15]</sup>.

Administration of *Bifidobacterium bifidum* to bottle-fed infants results in an increase in fecal counts of bifidobacteria and a decrease in fecal pH, which plays a role in protecting premature infants and other newborns from intestinal disease<sup>[16]</sup>. One study documented a reduction of NEC in premature newborns given an enteral supplement of *Lactobacillus acidophilus* and *Bifidobacterium infantis* daily compared with a historical control group<sup>[17]</sup>.

**Long-chain and omega-3 polyunsaturated fatty acids (PUFAs)** Dietary fatty acids such as linoleic acid (LA; 18:2n-6) and  $\alpha$ -linolenic acid (ALA; 18:3n-3) of the n-6 and n-3 series of PUFA, respectively, are considered "essential" because they must be derived from the diet. Once ingested, the essential fatty acids are converted to longer-chain, more highly unsaturated fatty acids, including arachidonic acid (AA) from LA and eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) from ALA. Modulation of immune and inflammatory responses has been reported with increased intakes of PUFA's of the n-3 series<sup>[18]</sup>. Recently, Caplan *et al*<sup>[19]</sup> indicated dietary PUFA supplementation (AA/DHA ratio of 1.5:1) significantly reduced the incidence of NEC in the neonatal rat model.

Intake of long-chain PUFAs (LC-PUFAs) may be related to structural and functional development of sensory, perceptual, cognitive and motor neural systems and are selectively incorporated, retained, and highly concentrated in the phospholipid bilayer of biologically active brain and retinal neural membranes<sup>[20]</sup>.

## SUMMARY

In this brief overview, the main message is that during critical illness in newborn infants, emphasis should be placed on provision of optimal nutrition. This is necessary for alleviation of not only short-term morbidity, but for optimization of health throughout the individual's lifetime.

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